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STABILISED PHARMACEUTICAL

The present invention relates to pharmaceutical compositions comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser and methods of stabilising bupropion hydrochloride in a pharmaceutical composition.

Bupropion hydrochloride is a known antidepressant sold in instant release tablet form under the brand name WELLBUTRIN^{R}. (Also see U.S. Patents 3,819,706 and 3,885,046; 1993 Physicians Desk Reference and the Merck Index, Eleventh Edition, Entry No. 1488. Bupropion hydrochloride is also useful as an anticholesterol agent, in suppressing prolactin secretion, in preventing functional impairment and drowsiness seen upon administration of benzodiazepine, in the treatment of minimal brain dysfunction, tardive dyskinesia, impaired mental alertness upon ingestion of ethanol and psychosexual dysfunction. While the instant release tablets currently sold are quite suitable for the indicated use, the method of manufacturing these is less than desirable based on cost as well as process conditions.

The object of the present invention is to prevent (inhibit) the degradation of bupropion hydrochloride, using stabiliser ingredients, thus allowing the preparation of pharmaceutical compositions such as instant and sustained release tablets and capsules which, from a cost of manufacture and processing standpoint, are much improved over those achievable in the past.

Thus the present invention provides a pharmaceutical composition in solid form comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser in an effective stabilising amount, in which the composition contains at least about 80% w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 40°C and 75% relative humidity and in which an aqueous solution of the stabiliser in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid, an acid salt of an amino acid and sodium metabisulphite.

Alternatively, the present invention also provides a pharmaceutical composition in solid form comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser in an effective stabilising amount, in which the composition contains at least about 80%

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w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 50°C and 27% relative humidity and in which an aqueous solution of the stabiliser in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid other than ascorbic acid and isoascorbic acid, an acid salt of an amino acid and sodium metabisulphite.

The preferred pH of the aqueous solution of the stabiliser is 0.9 to about 2 and most preferably 1.

Preferably the pharmaceutical composition according to the present invention contains at least about 90% w/w of undegraded bupropion hydrochloride after storage for 6 weeks under the above conditions and more preferably 95% or even 98%. In an additional aspect, the amount of undegraded bupropion hydrochloride is greater than 80% of its labelled strength, and more preferably greater than 90% percent of the labelled strength after one year of storage under the humidity and temperature conditions usually encountered in pharmacies and medicine cabinets i.e. room temperature and 35-60% humidity. Thus, when used in a pharmaceutical preparation for example, a tablet will still retain at least 80% of its potency and preferably at least 90% after one year of storage at room temperature (15-25°C (59-77°F)) at 35-60% humidity. For example if the tablet initially contains 100mg bupropion hydrochloride (labelled amount) at time of preparation, after one year storage at least 80mg of undegraded bupropion hydrochloride will remain in the tablet.

The amount of the stabiliser which may be used with the present invention may vary but preferably is about 2.7% to 27%, most preferably about 5% to 16.2% based on the label strength of bupropion hydrochloride in the pharmaceutical formulation (composition) in solid form. For example if a formulation contains 100mg of bupropion hydrochloride it would preferably contain about 2.7 to 27g of stabiliser.

Stabilisers of use in this invention include organic acids, carboxylic acids, acid salts of amino acids and sodium metabisulphite. Preferably, the acid salts of amino acids are hydrochloride salts such as cysteine hydrochloride, glycine hydrochloride or cystine dihydrochloride. Other preferred examples of stabilisers according to the present invention include: ascorbic acid, malic acid, isoascorbic acid, citric acid and tartaric

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acid. L-cysteine hydrochloride and glycine hydrochloride are the most preferred stabilisers.

In the examples the cysteine hydrochloride is in the L form and NF and USP are designations for standards published in the National Formulary and US Pharmacopeia, respectively.

The present invention extends to the use of combinations of stabilisers especially combinations of the aforementioned stabilisers.

The pH of the aqueous solution of the stabilisers may be determined as follows:

The stabiliser is weighed out to provide 3.75 grams thereof, (except for 3.34 grams of L-cystine dihydrochloride) and is then added to 60 grams of distilled water in a glass Pyrex^{R} beaker. The resulting mixture is stirred for approximately 5 minutes, using a stir plate and magnetic stir bar. The resulting solution or dispersion is examined using either a Orion Model 701A Ionalyzer^{R}, or an Accumet pH Meter Model 915. Solutions are stirred with a magnetic stir bar during analysis. Measurements of pH are performed in triplicate and the average thereof is used.

Examples of forms of preferred solid pharmaceutical composition include a tablet or capsule. Such forms are prepared using standard procedures known in the art which involve admixing buproprion hydrochloride and the stabiliser with the tablet or capsule excipients. Such excipients may include, for example, microcrystalline cellulose, sodium starch glycolate and/or corn starch, talc, magnesium stearate and colloidal silicon dioxide. Caplets are tablets generally shaped in the form of capsules. Capsules of this invention are generally prepared by mixing the stabiliser with bupropion hydrochloride and other excipients and placing same in, e.g., a two-part hard gelatin capsule.

Preferably the weight of the inactive ingredients is greater than about 1 ½ times that of bupropion hydrochloride but less than about 4 times that of bupropion hydrochloride. The tablets or capsules of this invention generally contain 25mg to 500mg of bupropion hydrochloride and usually contain 50mg, 75mg, 100mg or 150mg of bupropion hydrochloride. The amount of bupropion hydrochloride in solid form pharmaceutical

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compositions e.g. tablets after storage, may be determined using standard procedures such as high performance liquid chromatography (HPLC).

This invention is also directed to a new and improved method for stabilising the antidepressant bupropion hydrochloride to prevent the degradation thereof by admixing the stabiliser with bupropion hydrochloride. In this way a pharmaceutical composition is produced in which the bupropion hydrochloride is inhibited from degrading thus facilitating the storage of the composition over a prolonged period of time at room temperature i.e. under humidity and temperature conditions usually encountered in pharmacies and in medicine cabinets.

The compositions according to the present invention include those suitable for oral, rectal, topical (including buccal and sublingual) or transdermal administration.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing bupropion hydrochloride and the stabiliser into association with a carrier which constitutes one or more accessory ingredients. In general, the composistions are prepared by uniformly and intimately bringing bupropion hydrochloride and the stabiliser into association with a finely divided solid carrier and then, if necessary, shaping the product.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of bupropion hydrochloride and the stabiliser; as a powder or granules including microencapsulated or time-release forms.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, bupropion hydrochloride and the pharmaceutically acceptable stabiliser in a free-flowing form such as a powder or granules optionally mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets comprising a mixture of the powdered bupropion hydrochloride and the stabiliser with any suitable carrier may be made by molding in a suitable machine.

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Compositions suitable for rectal administration may be presented as a suppository with a conventional carrier such as cocoa butter, hydrogenated fats or hydrogenated fatty carboxylic acids.

Compositions suitable for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising bupropion hydrochloride and the stabiliser in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active compound in a basis such as gelatin and glycerin or sucrose and acacia.

In addition to the aforementioned ingredients, the compositions of this invention may further include one or more accessory ingredient(s) selected as appropriate from diluents, buffers, flavouring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

The following examples are representative of the invention.

In the examples, cysteine hydrochloride means L-cysteine hydrochloride.

EXAMPLE 1

The formulation contained the following ingredients in the following amounts:

Ingredient	100 mg potency Weight (mg) per tablet	75 mg potency
Bupropion hydrochloride	100.00	75.0
Microcrystalline cellulose, NF	91.3	68.5
Sodium starch glycolate, NF	9.2	6.9
L-Cysteine hydrochloride, NF	5.0	3.8
Talc, USP	23.0	17.3
Magnesium stearate, NF	1.2	0.9
Colloidal silicon dioxide, NF	0.3	0.2
TOTAL	230.0mg	172.6mg

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The powder ingredients were weighed out for a 120,000 tablet batch size for the 100mg potency and a 160,000 tablet batch size for the 75mg potency.

The bupropion hydrochloride, microcystalline cellulose and sodium starch glycolate were sifted through a 30 mesh Russell-Finex sifter.

The sifted ingredients were blended for 15 minutes in a 3 cu. ft. slant-cone blender.

The blended ingredients were granulated as follows:

The cysteine hydrochloride was dissolved in 1.28kg of purified water using a Lightnin'R Mixer. This cysteine hydrochloride solution was added to 5.12 kg of SD3A alcohol (anhydrous) and mixed thoroughly using a Lightnin'R Mixer. The blended ingredients were placed in a 3 cu. ft. Littleford Lodige granulator and ganulated using the cysteine hydrochloride solution. Mixing time was 3 to 5 minutes and chopper time was 3 to 5 minutes. Wetness was checked and additional 80% w/w SD3A alcohol (aqueous) solution was added to achieve appropriate massing.

Clumps of wet granule were broken up by hand.

Granule was dried in a WST-30 Glatt fluid-bed dryer until loss on drying (by Compu-Trac^R, 90°C) of granule was between 1 to 2%. Fluid-bed dryer parameters were set as follows:

Inlet air temperature: 60°C.
Air volume: 200-800 cu meter/hr
Pre-heat temperature: 25°C.
Dew point: 10°C.
By-pass flap: 50%
Shaker interval: 5 seconds every 2 minutes

Dried granule was sifted through a 20 mesh Russell-Finex sifter.

Talc (pre-sifted 60 mesh) was added to a small amount of dried granule, sifted through a 20 mesh Russell Finex sifter, added to a 3 cu. ft. slant-cone blender and blended with

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the remainder of the granule for 5 minutes. Magnesium stearate and colloidal silicon dioxide was sifted together through a 30 mesh Russell-Finex sifter and blended in a table-top v-shell blender for 20 minutes. This magnesium stearate/colloidal silicon dioxide blend was then added to the dried granule in the 3 cu. ft. slant-cone blender and blended an additional 5 minutes.

The lubricated granule was compressed on a rotary-type Manesty Betapress^R in a controlled humidity environment of less than 30% relative humidity. Tablets were compressed at a compression weight of about 230mg for the 100mg potency and about 172.6mg for the 75mg potency. Round, 7.8 mm, concave, plain punches were used for the 100mg potency and round, 7.0 mm, concave, plain punches were used for the 75mg potency.

Tablets were dedusted using a Manesty Tablet Deduster.

A portion of tablets was film-coated using a compu-lab Acella - Cota^R film-coater. The aqueous film coat Opadry^R Red YS-1-1846 was used for the 100mg potency and Opadry^R Yellow YS-1-2186 for the 75mg potency (supplied by Colocon, Inc. of 415 Moyer Blvd, West Point, PA 19486. The Accela - Cota^R parameters were:

Inlet air temperature:	50-80°C.
Inlet air volume:	100-500 cfm
Exhaust air temperature:	50-60°C.

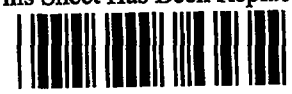
Tablets were coated to a weight gain of 1-5% based on the core tablet weight to achieve an acceptable color intensity.

EXAMPLE 2

The procedure of Example 1 was repeated except that lubricant levels were changed, resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0

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Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
L-Cysteine hydrochloride	5.0
Talc, USP	23.0
Magnesium stearate, NF	2.4
.Colloidal silicon dioxide, NF	0.6
TOTAL	231.5

EXAMPLE 3

The procedure of Example 2 was repeated except;

In order to achieve a 75mg potency, the tablets were compressed using 7.0mm, round, concave, plain punches and were not film-coated. Tablets had the resulting formulation:

Ingredient	75mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	75.0
Microcrystalline cellulose, NF	68.5
Sodium starch glycolate, NF	6.9
L-Cysteine hydrochloride	3.8
Talc, USP	17.3
Magnesium stearate, NF	1.8
Colloidal silicon dioxide, NF	0.5
TOTAL	173.8

EXAMPLE 4

Tablets are manufactured according to the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet

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Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
Glycine hydrochloride	5.0
Talc, USP	23.0
Magnesium stearate, NF	1.2
Colloidal silicon dioxide, NF	0.32
TOTAL	230.0MG

Sufficient powder ingredients were weighed out to make approximately 24,000 tablets.

The bupropion hydrochloride, microcrystalline cellulose and sodium starch glycolate were sifted through a 30 mesh Russell-Finex sifter.

The sifted ingredients were blended for 15 minutes in a Patterson-Kelly (PK) v-shell blender.

The blended ingredients were granulated as follows:

A quantity of purified water, USP that equals approximately 25% of the total weight of granulating solvent needed to impart the desired granule wetness was weighed out. The glycine hydrochloride was dissolved in the purified water using a Lightnin'R Mixer. The glycine hydrochloride solution was added to a quantity of SD3A alcohol, anhydrous, equal to the remaining 75% of the total weight of solvent needed to impart the desired granule wetness and mixed thoroughly using a Lightnin'R Mixer. The blended ingredients were placed in a Hobart planetary mixer and granulated using the glycine hydrochloride solution. Mixing and time was approximately 3 to 5 minutes. Granulation wetness was checked and additional 75% w/w SD3A alcohol (aqueous) solution was added to achieve appropriate massing.

Any clumps of wet granule were broken up by hand.

Granule was dried in a Despatch Tray Oven to 50°C for approximately 4 hours until loss on drying (by Compu-TracR, 90°C) of granule was 1 to 2%.

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Dried granule was sifted through a 20 mesh Russell-Finex sifter.

Talc (pre-sifted 60 mesh) was added to a small amount of dried granule and sifted through a 20 mesh hand screen. This was added to the remainder of the granule and blended in a PK v-shell blender for 5 minutes. Magnesium stearate and colloidal silicon dioxide was sifted together through a 30 mesh hand screen, and blended in a PK v-shell blender for 15-20 minutes. This magnesium stearate/colloidal silicon dioxide blend was then added to the granule/talc blend in the PK v-shell blender and blended an additional 5 minutes.

The lubricated granule was compressed on a rotary-type Manesty Betapress^{R} in a controlled humidity environment of less than 30% relative humidity. Tablets were compressed at a compression weight of 230mg, using 7.8mm, round, concave, plain punches.

EXAMPLE 5

The procedure of Example 4 is repeated except that the lubricant levels are changed resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
Glycine hydrochloride	5.0
Talc, USP	22.9
Magnesium stearate, NF	0.7
Colloidal silicon dioxide, NF	0.2
TOTAL	229.3mg

Tablets are compressed at approximately 229.3mg.

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EXAMPLE 6

The procedure of Example 4 is repeated except that the lubricant levels are changed resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
Glycine hydrochloride	5.0
Talc, USP	10.9
Magnesium stearate, NF	1.1
Colloidal.silicon dioxide, NF	0.2
TOTAL	217.7mg

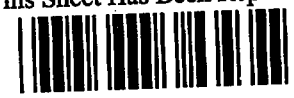
Tablets are compressed at approximately 217.7mg.

EXAMPLE 7

The procedure of Example 4 was repeated except that the lubricant levels were changed resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
Glycine hydrochloride	5.0
Talc, USP	10.9
Magnesium stearate, NF	0.7
Colloidal silicon dioxide, NF	0.2
TOTAL	217.3mg

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Tablets are compressed at approximately 217.3mg

EXAMPLE 8

The procedure of Example 4 was repeated except magnesium stearate and colloidal silicon dioxide were replaced with sodium stearyl fumarate resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
Glycine hydrochloride	5.0
Talc, USP	10.9
Sodium stearyl fumarate	3.3
TOTAL	219.7mg

Tablets are compressed at approximately 219.7mg

EXAMPLE 9

The procedure of Example 4 was repeated except that the formulation is changed as follows:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	68.8
Corn starch, NF	23.0
Sodium starch glycolate, NF	9.2

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Glycine hydrochloride	5.0
Talc, USP	23.0
Magnesium stearate, NF	0.8
Colloidal silicon dioxide, NF	0.2
TOTAL	230.0mg

Tablets are compressed at approximately 230.0mg.

EXAMPLE 10

The procedure of Example 4 is repeated except sodium starch glycolate is replaced with crospovidone, resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	95.9
Crospovidone	4.6
Glycine hydrochloride	5.0
Talc, USP	23.0
Magnesium stearate, NF	1.2
Colloidal silicon dioxide, NF	0.3
TOTAL	230.0mg

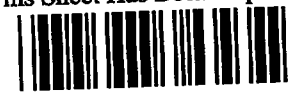
Tablets are compressed at approximately 230.0mg

EXAMPLE 11

The procedure of Example 4 is repeated except that the formulation is changed as follows:

Ingredient	100mg potency tablet

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	Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	68.8
Corn starch, NF	23.0
Sodium starch glycolate, NF	9.2
L-Cysteine hydrochloride	5.0
Talc, USP	23.0
Magnesium stearate, NF	1.2
Colloidal silicon dioxide, NF	0.3
TOTAL	230.5mg

Tablets were compressed at approximately 230.5mg

EXAMPLE 12

The procedure of Example 11 is repeated except that L-cysteine hydrochloride is replaced with glycine hydrochloride.

EXAMPLE 13

The procedure of Example 4 is repeated except that the sodium starch glycolate and colloidal silicon dioxide are removed and the formulation follows:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	71.0
Corn starch, NF	22.0
L-Cysteine hydrochloride	5.0
Talc, USP	22.0
Magnesium stearate, NF	1.1

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TOTAL 221.1mg

Tablets were compressed at approximately 221.1mg

EXAMPLE 14

The procedure of Example 4 was repeated except that the sodium starch glycolate was removed and the formulation follows:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	71.0
Corn starch, NF	22.0
L-Cysteine hydrochloride	5.0
Talc, USP	22.0
Magnesium stearate, NF	1.1
Colloidal silicon dioxide, NF	0.2

TOTAL 221.3mg

Tablets were compressed at approximately 221.3mg.
A portion of tablets was film-coated using a Compu-Lab Accela-Cota^R film-coater. The aqueous film coat Opadry Red YS-1-1846 was used for the 100mg potency. The Acella-Cota^R parameters were:
Inlet air temperature: 50-80°C.
Inlet air volume: 200-1000 cfm
Exhaust air temperature: 40-60°C.
Exhaust air volume: 200-1000 cfm
Tablets were coated to a weight gain of 1-5% over the core tablet weight to achieve an acceptable color intensity.

150MG CAPSULES

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EXAMPLE 15

150mg capsules were prepared according to the following formulation and procedure:

Ingredient	Weight (mg) per capsule
Bupropion hydrochloride	150.0
Microcrystalline cellulose, NF	106.5
Corn starch, NF	33.00
Talc, USP	33.00
L-Cystein hydrochloride	7.500
TOTAL	330.0mg

A stock blend of bupropion hydrochloride, corn starch (purity 826) and microcrystalline cellulose (MCC) was prepared as follows:

The above ingredients were sifted by hand through a 30 mesh screen. They were then blended in an Patterson-Kelly (P-K) v- shell blender for 10 minutes.

The proper amount of cysteine hydrochloride was weighed out and added to 85% w/w SD3A alcohol (aqueous) solution. This mixture was vigorously mixed for approximately 5 minutes. It was then immediately added to the proper amount of the above mentioned stock blend and wet-granulated in a table-top Hobart mixer.

The resulting wet granulation was screened by hand through a 16 mesh screen.

The wet granule was dried in a tray oven at 50°C for 4 hours to obtain a loss on drying (LOD) of below 2% using a CompuTrac^{R} moisture analyser 90°C. (Upon standing the batches re-equilibrated to 2-3% LOD).

The dried granule was sifted through a 16 or 30 mesh hand screen.

The granule was lubricated with talc (sifted 60 mesh), in a P-K v-shell blender for 5 minutes.

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Finished granule is encapsulated on a Chemi-Pharm manual capsule-filling machine Model No. 201, using size No. 1, white, opaque two part hard gelatin capsules.

EXAMPLE 16

The procedure of Example 15 is repeated except cysteine hydrochloride was replaced with glycine hydrochloride.

EXAMPLE 17

The procedure of Example 15 is repeated except cysteine hydrochloride was replaced with L-cystine dihydrochloride.

EXAMPLE 18

The procedure of Example 15 is repeated except cysteine hydrochloride was replaced with tartaric acid.

EXAMPLE 19

The procedure of Example 15 is repeated except cysteine hydrochloride was replaced with citric acid.

EXAMPLE 20

The procedure of Example 15 is repeated except cysteine hydrochloride was replaced with malic acid.

EXAMPLE 21

The procedure of Example 15 is repeated except cysteine hydrochloride is replaced with isoascorbic (erythorbic) acid.

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The procedure of Example 15 is repeated except cysteine hydrochloride is replaced with ascorbic acid.

EXAMPLE 23

The procedure of Example 15 is repeated except cysteine hydrochloride is replaced with sodium metabisulfite.

CAPLETS

EXAMPLE 24

The caplets were manufactured according to the following formulation:

Ingredient	100mg potency caplet
(Core)	Weight (mg) per caplet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	274.0
Sodium starch glycolate, NF	15.00
L-Cysteine hydrochloride, USP	9.00
Talc, USP	12.00
Magnesium stearate, NF	4.00
CORE WEIGHT	414.0MG
(Coating)	
Opadry^{R} Red, YS-1-1846	12.00
Carnauba Wax, NF	0.04
TOTAL WEIGHT	426.0

Sufficient powder ingredients were weighed out to make a batch size of approximately 60,000 caplets.

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The bupropion hydrochloride, microcrystalline cellulose and sodium starch glycolate were sifted through a 20 or 30 mesh Russell Finex sifter.

The sifted ingredients were blended for 15 minutes in a 3 cu.ft. slant-cone blender.

The blended ingredients were granulated as follows:

A quantity of purified water, USP that equals approximately no more than 20% of the total weight of granulating solution needed to impart the desired granule wetness was weighed out. The cysteine hydrochloride was dissolved in the purified water using a mixer. The cysteine hydrochloride solution was added to a quantity of SD3A alcohol, anhydrous, equal to the remaining ~80% (no less than) of the total weight of solution needed to impart the desired granule wetness and mixed thoroughly using a mixer. The blended ingredients were placed in a 3 cu.ft. Littleford Lodige^{R} granulator and granulated using the hydroalcoholic cysteine hydrochloride solution. Mixing and chopper time was approximately 5-10 minutes. Wetness was checked and additional 80% w/w SD3A alcohol (aqueous) solution was added to achieve appropriate massing.

Any clumps of wet granule were broken up by hand.

Granule was dried in a WST-30 Glatt fluid-bed dryer until loss on drying (by Compu-Trac^{R}, 90°C) of granule was 0.8-2.0%. Fluid-bed drying parameters were set as follows:
Inlet air temperature: 60°C
Air volume: 200-1200 cu meter/hr

Dried granule was milled using a Comil^{R} and appropriately sized screen.

Talc (pre-sifted 60 mesh) was added to small amount of dried granule and mixed by hand. Magnesium stearate (pre-sifted) was added to a small amount of dried granule and mixed by hand. Both mixtures were sifted through a 16 mesh screen in a Russell Finex sifter. This sifted mixture was added to the remainder of the granule and blended in the 3 cu.ft slant-cone blender for 5 minutes.

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The lubricated granule was compressed on a rotary-type Manesty Betapress^R. Caplets were compressed at a compression weight of approximately 414 gm. using 6.5 x 14.5 mm concave, caplet punches containing a partial score-bar on the upper and lower punches.

Caplets were dedusted using a Manesty Tablet Deduster.

A portion of tablets was film-coated using a Compu-Lab Accela-Cota^R film-coater. The aqueous film coat Opadry Red^R YS-1-1846 was used. The Accela-Cota^R parameters were:
Inlet air temperature: 50-80°C.
Inlet air volume: 100-500 cfm
Exhaust air temperature: 40-60°C.

Caplets were coated to a weight gain of 1-5% over the core tablet weight to achieve an acceptable color intensity.

Caplets were coated with carnauba wax to assist in packaging. Carnauba wax was added to the film-coated caplets which were rotated in the coating drum for approximately 5 minutes to distribute the wax.

EXAMPLE 25

The procedure of Example 24 is repeated except:
In order to achieve a 75mg potency, the caplets are compressed at a compression weight of approximately 310.5mg, using 5.9 x 13.1mm concave, caplet punches containing a partial score-bar on the upper and lower punches. The aqueous film coat Opadry^R Yellow-Gold YS-1-2186 is for the 75mg potency.
Caplets have the resulting composition:

Ingredient (Core)	75mg potency caplet Weight (mg) per caplet
Bupropion hydrochloride	75.00
Microcrystalline cellulose, NF	205.5

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Sodium starch glycolate, NF	11.25
Cysteine hydrochloride, USP	6.750
Talc, USP	9.00
Magnesium stearate, NF	3.00
CORE WEIGHT	310.5mg
(Coating)	
Opadry Yellow, YS--1-2186	9.00
Carnauba Wax, NF	0.03
TOTAL WEIGHT	319.5.0mg

EXAMPLE 26

The procedure of Example 24 is repeated except:
In order to achieve a 50mg potency, the caplets are compressed at a compression weight of approximately 207mg, using 5.1 x 11.4mm concave, caplet punches containing a partial scorebar on the upper and lower punches. The aqueous film coat Opadry^{R} White YS-1-7059 is used for the 50mg potency. Caplets have the resulting composition:

Ingredient	50mg potency caplet
(Core)	Weight (mg) per caplet
Bupropion hydrochloride	50.00
Microcrystalline cellulose, NF	137.0
Sodium starch glycolate, NF	7.50
Cysteine hydrochloride, USP	4.50
Talc, USP	6.00
Magnesium stearate, NF	2.00
CORE WEIGHT	207.0mg
(Coating)	
Opadry White^{R}, YS-1-7059	6.00
Carnauba Wax, NF	0.02

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TOTAL WEIGHT 213.0mg

EXAMPLE 27

The procedure of Example 24 is repeated except:
The blended powders are granulated with 100% SD3A Alcohol.

EXAMPLE 28

The procedure of Example 27 is repeated except:
The cysteine hydrochloride is blended in dry with the other ingredients rather than adding it to the granulating solution.

The level of cysteine hydrochloride is increased giving the caplets the following composition:

Ingredient	100mg potency caplet
(Core)	Weight (mg) per caplet
Bupropion hydrochloride	100.00
Microcrystalline cellulose, NF	274.0
Sodium starch glycolate, NF	15.00
Cysteine hydrochloride, USP	18.00
Talc, USP	12.00
Magnesium stearate, NF	4.00
CORE WEIGHT	423.0mg
(Coating)	
Opadry Red^{R}, YS-1-1846	12.00
Carnauba Wax, NF	0.040
TOTAL WEIGHT	435.0mg

EXAMPLE 29

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The procedure of Example 24 was followed except:
Glycine hydrochloride is used as the Stabiliser, giving the caplets the following composition:

Ingredient	100mg potency caplet
(Core)	Weight (mg) per caplet
Bupropion hydrochloride	100.00
Microcrystalline cellulose, NF	274.0
Sodium starch glycolate, NF	15.00
Glycine hydrochloride, USP	9.00
Talc, USP	12.00
Magnesium stearate, NF	4.00
CORE WEIGHT	414.0mg
(Coating)	
Opadry Red^{R}, YS-1-1846	12.00
Carnauba Wax, NF	0.04
TOTAL WEIGHT	426.0mg

EXAMPLE 30

The procedure of Example 24 was repeated except:
The blended powders were granulated with 100% Isopropyl alcohol.

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CLAIMS

1. A pharmaceutical composition in solid form comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser in an effective stabilising amount, in which the composition contains at least about 80% w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 40°C and 75% relative humidity and in which an aqueous solution of the stabiliser in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid, an acid salt of an amino acid and sodium metabisulphite.

2. A pharmaceutical composition in solid form comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser in an effective stabilising amount, in which the composition contains at least about 80% w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 50°C and 27% relative humidity and in which an aqueous solution of the stabiliser in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid other than ascorbic acid and isoascorbic acid, an acid salt of an amino acid and sodium metabisulphite.

3. A pharmaceutical composition according to claim 1 or 2, wherein the aqueous solution of the stabiliser has a pH of about 0.9 to 2.

4. A pharmaceutical composition according to claims 1, 2 or 3, wherein the aqueous solution of the stabiliser has a pH of around 1.

5. A pharmaceutical composition according to any of the preceding claims which contains at least about 90% w/w of undegraded buproprion hydrochloride after storage for 6 weeks.

6. A pharmaceutical composition according to any of the preceding claims which contains at least 95% w/w of undegraded bupropion hydrochloride.

7. A pharmaceutical composition according to any of the preceding claims which contains at least 98% w/w of undegraded bupropion hydrochloride.



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8. A pharmaceutical composition according to any of the preceding claims, wherein the amount of stabiliser is 2.7% to 27% of the weight of bupropion hydrochloride in the composition.

9. A pharmaceutical composition according to claim 8, wherein the amount of stabiliser is 5% to 16.2% of the weight of bupropion hydrochloride in the composition.

10. A pharmaceutical composition according to any of the preceding claims, wherein the acid salt of the amino acid is a hydrochloride salt.

11. A pharmaceutical composition according to claim 10, wherein the salt is cysteine hydrochloride, glycine hydrochloride or cystine dihydrochloride.

12. A pharmaceutical composition according to any of claims 1 to 9, wherein the organic acid is tartaric acid, citric acid or malic acid.

13. A pharmaceutical composition according to any of claims 1, 3, 4, 5, 6, 7, 8 or 9 wherein the carboxylic acid is ascorbic or isoascorbic acid.

14. A tablet or capsule according to any of the preceding claims, wherein the amount of bupropion hydrochloride is 25 to 500mg.

15. A tablet or capsule according to claim 14, wherein the amount of bupropion hydrochloride is 25 to 300mg.

16. A tablet or capsule according to claim 14 or 15, wherein the amount of bupropion hydrochloride is 50, 75, 100 or 150mg.

17. A method of stabilising bupropion hydrochloride in a solid pharmaceutical composition so that at least about 80% w/w of bupropion hydrochloride is present in the undegraded form after storage for 6 weeks at about 40°C and 75% relative humidity, wherein said method comprises mixing bupropion hydrochloride with a stabiliser of which an aqueous solution in a concentration

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of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid, an acid salt of an amino acid and sodium metabisulfite.

18. A method of stabilising bupropion hydrochloride in a solid pharmaceutical composition so that at least about 80% w/w of bupropion hydrochloride is present in the undegraded from after storage for 6 weeks at about 50°C and 27% relative humidity, wherein said method comprises mixing bupropion hydrochloride with a stabiliser of which an aqueous solution in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid other than ascrobic acid or isoascrobic acid, an acid salt of an amino acid and sodium metabisulfite.

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ABSTRACT

This application discloses a method of inhibiting degradation of the antidepressant bupropion hydrochloride in a solid pharmaceutical formulation, so that the pharmaceutical formulation will maintain at least 80% of its initial bupropion potency after one year.

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STABILISED PHARMACEUTICAL

The present invention relates to pharmaceutical compositions comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser and methods of stabilising bupropion hydrochloride in a pharmaceutical composition.

Bupropion hydrochloride is a known antidepressant sold in instant release tablet form under the brand name WELLBUTRIN^{R}. (Also see U.S. Patents 3,819,706 and 3,885,046; 1993 Physicians Desk Reference and the Merck Index, Eleventh Edition, Entry No. 1488. Bupropion hydrochloride is also useful as an anticholesterol agent, in suppressing prolactin secretion, in preventing functional impairment and drowsiness seen upon administration of benzodiazepine, in the treatment of minimal brain dysfunction, tardive dyskinesia, impaired mental alertness upon ingestion of ethanol and psychosexual dysfunction. While the instant release tablets currently sold are quite suitable for the indicated use, the method of manufacturing these is less than desirable based on cost as well as process conditions.

The object of the present invention is to prevent (inhibit) the degradation of bupropion hydrochloride, using stabiliser ingredients, thus allowing the preparation of pharmaceutical compositions such as instant and sustained release tablets and capsules which, from a cost of manufacture and processing standpoint, are much improved over those achievable in the past.

Thus the present invention provides a pharmaceutical composition in solid form comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser in an effective stabilising amount, in which the composition contains at least about 80% w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 40°C and 75% relative humidity and in which an aqueous solution of the stabiliser in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid, an acid salt of an amino acid and sodium metabisulphite.

Alternatively, the present invention also provides a pharmaceutical composition in solid form comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser in an effective stabilising amount, in which the composition contains at least about 80%

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w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 50°C and 27% relative humidity and in which an aqueous solution of the stabiliser in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid other than ascorbic acid and isoascorbic acid, an acid salt of an amino acid and sodium metabisulphite.

The preferred pH of the aqueous solution of the stabiliser is 0.9 to about 2 and most preferably 1.

Preferably the pharmaceutical composition according to the present invention contains at least about 90% w/w of undegraded bupropion hydrochloride after storage for 6 weeks under the above conditions and more preferably 95% or even 98%. In an additional aspect, the amount of undegraded bupropion hydrochloride is greater than 80% of its labelled strength, and more preferably greater than 90% percent of the labelled strength after one year of storage under the humidity and temperature conditions usually encountered in pharmacies and medicine cabinets i.e. room temperature and 35-60% humidity. Thus, when used in a pharmaceutical preparation for example, a tablet will still retain at least 80% of its potency and preferably at least 90% after one year of storage at room temperature (15-25°C (59-77°F)) at 35-60% humidity. For example if the tablet initially contains 100mg bupropion hydrochloride (labelled amount) at time of preparation, after one year storage at least 80mg of undegraded bupropion hydrochloride will remain in the tablet.

The amount of the stabiliser which may be used with the present invention may vary but preferably is about 2.7% to 27%, most preferably about 5% to 16.2% based on the label strength of bupropion hydrochloride in the pharmaceutical formulation (composition) in solid form. For example if a formulation contains 100mg of bupropion hydrochloride it would preferably contain about 2.7 to 27g of stabiliser.

Stabilisers of use in this invention include organic acids, carboxylic acids, acid salts of amino acids and sodium metabisulphite. Preferably, the acid salts of amino acids are hydrochloride salts such as cysteine hydrochloride, glycine hydrochloride or cystine dihydrochloride. Other preferred examples of stabilisers according to the present invention include: ascorbic acid, malic acid, isoascorbic acid, citric acid and tartaric

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acid. L-cysteine hydrochloride and glycine hydrochloride are the most preferred stabilisers.

In the examples the cysteine hydrochloride is in the L form and NF and USP are designations for standards published in the National Formulary and US Pharmacopeia, respectively.

The present invention extends to the use of combinations of stabilisers especially combinations of the aforementioned stabilisers.

The pH of the aqueous solution of the stabilisers may be determined as follows:

The stabiliser is weighed out to provide 3.75 grams thereof, (except for 3.34 grams of L-cystine dihydrochloride) and is then added to 60 grams of distilled water in a glass Pyrex^{R} beaker. The resulting mixture is stirred for approximately 5 minutes, using a stir plate and magnetic stir bar. The resulting solution or dispersion is examined using either a Orion Model 701A Ionalyzer^{R}, or an Accumet pH Meter Model 915. Solutions are stirred with a magnetic stir bar during analysis. Measurements of pH are performed in triplicate and the average thereof is used.

Examples of forms of preferred solid pharmaceutical composition include a tablet or capsule. Such forms are prepared using standard procedures known in the art which involve admixing buproprion hydrochloride and the stabiliser with the tablet or capsule excipients. Such excipients may include, for example, microcrystalline cellulose, sodium starch glycolate and/or corn starch, talc, magnesium stearate and colloidal silicon dioxide. Caplets are tablets generally shaped in the form of capsules. Capsules of this invention are generally prepared by mixing the stabiliser with bupropion hydrochloride and other excipients and placing same in, e.g., a two-part hard gelatin capsule.

Preferably the weight of the inactive ingredients is greater than about 1 ½ times that of bupropion hydrochloride but less than about 4 times that of bupropion hydrochloride. The tablets or capsules of this invention generally contain 25mg to 500mg of bupropion hydrochloride and usually contain 50mg, 75mg, 100mg or 150mg of bupropion hydrochloride. The amount of bupropion hydrochloride in solid form pharmaceutical

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compositions e.g. tablets after storage, may be determined using standard procedures such as high performance liquid chromatography (HPLC).

This invention is also directed to a new and improved method for stabilising the antidepressant bupropion hydrochloride to prevent the degradation thereof by admixing the stabiliser with bupropion hydrochloride. In this way a pharmaceutical composition is produced in which the bupropion hydrochloride is inhibited from degrading thus facilitating the storage of the composition over a prolonged period of time at room temperature i.e. under humidity and temperature conditions usually encountered in pharmacies and in medicine cabinets.

The compositions according to the present invention include those suitable for oral, rectal, topical (including buccal and sublingual) or transdermal administration.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing bupropion hydrochloride and the stabiliser into association with a carrier which constitutes one or more accessory ingredients. In general, the composistions are prepared by uniformly and intimately bringing bupropion hydrochloride and the stabiliser into association with a finely divided solid carrier and then, if necessary, shaping the product.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of bupropion hydrochloride and the stabiliser; as a powder or granules including microencapsulated or time-release forms.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, bupropion hydrochloride and the pharmaceutically acceptable stabiliser in a free-flowing form such as a powder or granules optionally mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets comprising a mixture of the powdered bupropion hydrochloride and the stabiliser with any suitable carrier may be made by molding in a suitable machine.

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Compositions suitable for rectal administration may be presented as a suppository with a conventional carrier such as cocoa butter, hydrogenated fats or hydrogenated fatty carboxylic acids.

Compositions suitable for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising bupropion hydrochloride and the stabiliser in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active compound in a basis such as gelatin and glycerin or sucrose and acacia.

In addition to the aforementioned ingredients, the compositions of this invention may further include one or more accessory ingredient(s) selected as appropriate from diluents, buffers, flavouring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

The following examples are representative of the invention.

In the examples, cysteine hydrochloride means L-cysteine hydrochloride.

EXAMPLE 1

The formulation contained the following ingredients in the following amounts:

Ingredient	100 mg potency Weight (mg) per tablet	75 mg potency
Bupropion hydrochloride	100.00	75.0
Microcrystalline cellulose, NF	91.3	68.5
Sodium starch glycolate, NF	9.2	6.9
L-Cysteine hydrochloride, NF	5.0	3.8
Talc, USP	23.0	17.3
Magnesium stearate, NF	1.2	0.9
Colloidal silicon dioxide, NF	0.3	0.2
TOTAL	230.0mg	172.6mg

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The powder ingredients were weighed out for a 120,000 tablet batch size for the 100mg potency and a 160,000 tablet batch size for the 75mg potency.

The bupropion hydrochloride, microcystalline cellulose and sodium starch glycolate were sifted through a 30 mesh Russell-Finex sifter.

The sifted ingredients were blended for 15 minutes in a 3 cu. ft. slant-cone blender.

The blended ingredients were granulated as follows:

The cysteine hydrochloride was dissolved in 1.28kg of purified water using a Lightnin'^{R} Mixer. This cysteine hydrochloride solution was added to 5.12 kg of SD3A alcohol (anhydrous) and mixed thoroughly using a Lightnin'^{R} Mixer. The blended ingredients were placed in a 3 cu. ft. Littleford Lodige granulator and ganulated using the cysteine hydrochloride solution. Mixing time was 3 to 5 minutes and chopper time was 3 to 5 minutes. Wetness was checked and additional 80% w/w SD3A alcohol (aqueous) solution was added to achieve appropriate massing.

Clumps of wet granule were broken up by hand.

Granule was dried in a WST-30 Glatt fluid-bed dryer until loss on drying (by Compu-Trac^{R}, 90°C) of granule was between 1 to 2%. Fluid-bed dryer parameters were set as follows:

Inlet air temperature: 60°C.
Air volume: 200-800 cu meter/hr
Pre-heat temperature: 25°C.
Dew point: 10°C.
By-pass flap: 50%
Shaker interval: 5 seconds every 2 minutes

Dried granule was sifted through a 20 mesh Russell-Finex sifter.

Talc (pre-sifted 60 mesh) was added to a small amount of dried granule, sifted through a 20 mesh Russell Finex sifter, added to a 3 cu. ft. slant-cone blender and blended with

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the remainder of the granule for 5 minutes. Magnesium stearate and colloidal silicon dioxide was sifted together through a 30 mesh Russell-Finex sifter and blended in a table-top v-shell blender for 20 minutes. This magnesium stearate/colloidal silicon dioxide blend was then added to the dried granule in the 3 cu. ft. slant-cone blender and blended an additional 5 minutes.

The lubricated granule was compressed on a rotary-type Manesty Betapress^R in a controlled humidity environment of less than 30% relative humidity. Tablets were compressed at a compression weight of about 230mg for the 100mg potency and about 172.6mg for the 75mg potency. Round, 7.8 mm, concave, plain punches were used for the 100mg potency and round, 7.0 mm, concave, plain punches were used for the 75mg potency.

Tablets were dedusted using a Manesty Tablet Deduster.

A portion of tablets was film-coated using a compu-lab Acella - Cota^R film-coater. The aqueous film coat Opadry^R Red YS-1-1846 was used for the 100mg potency and Opadry^R Yellow YS-1-2186 for the 75mg potency (supplied by Colocon, Inc. of 415 Moyer Blvd, West Point, PA 19486. The Accela - Cota^R parameters were:

Inlet air temperature:	50-80°C.
Inlet air volume:	100-500 cfm
Exhaust air temperature:	50-60°C.

Tablets were coated to a weight gain of 1-5% based on the core tablet weight to achieve an acceptable color intensity.

EXAMPLE 2

The procedure of Example 1 was repeated except that lubricant levels were changed, resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0

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Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
L-Cysteine hydrochloride	5.0
Talc, USP	23.0
Magnesium stearate, NF	2.4
Colloidal silicon dioxide, NF	0.6
TOTAL	231.5

EXAMPLE 3

The procedure of Example 2 was repeated except;

In order to achieve a 75mg potency, the tablets were compressed using 7.0mm, round, concave, plain punches and were not film-coated. Tablets had the resulting formulation:

Ingredient	75mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	75.0
Microcrystalline cellulose, NF	68.5
Sodium starch glycolate, NF	6.9
L-Cysteine hydrochloride	3.8
Talc, USP	17.3
Magnesium stearate, NF	1.8
Colloidal silicon dioxide, NF	0.5
TOTAL	173.8

EXAMPLE 4

Tablets are manufactured according to the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet

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Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
Glycine hydrochloride	5.0
Talc, USP	23.0
Magnesium stearate, NF	1.2
Colloidal silicon dioxide, NF	0.32
TOTAL	230.0MG

Sufficient powder ingredients were weighed out to make approximately 24,000 tablets.

The bupropion hydrochloride, microcrystalline cellulose and sodium starch glycolate were sifted through a 30 mesh Russell-Finex sifter.

The sifted ingredients were blended for 15 minutes in a Patterson-Kelly (PK) v-shell blender.

The blended ingredients were granulated as follows:

A quantity of purified water, USP that equals approximately 25% of the total weight of granulating solvent needed to impart the desired granule wetness was weighed out. The glycine hydrochloride was dissolved in the purified water using a Lightnin'^{R} Mixer. The glycine hydrochloride solution was added to a quantity of SD3A alcohol, anhydrous, equal to the remaining 75% of the total weight of solvent needed to impart the desired granule wetness and mixed thoroughly using a Lightnin'^{R} Mixer. The blended ingredients were placed in a Hobart planetary mixer and granulated using the glycine hydrochloride solution. Mixing and time was approximately 3 to 5 minutes. Granulation wetness was checked and additional 75% w/w SD3A alcohol (aqueous) solution was added to achieve appropriate massing.

Any clumps of wet granule were broken up by hand.

Granule was dried in a Despatch Tray Oven to 50°C for approximately 4 hours until loss on drying (by Compu-Trac^{R}, 90°C) of granule was 1 to 2%.

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Dried granule was sifted through a 20 mesh Russell-Finex sifter.

Talc (pre-sifted 60 mesh) was added to a small amount of dried granule and sifted through a 20 mesh hand screen. This was added to the remainder of the granule and blended in a PK v-shell blender for 5 minutes. Magnesium stearate and colloidal silicon dioxide was sifted together through a 30 mesh hand screen, and blended in a PK v-shell blender for 15-20 minutes. This magnesium stearate/colloidal silicon dioxide blend was then added to the granule/talc blend in the PK v-shell blender and blended an additional 5 minutes.

The lubricated granule was compressed on a rotary-type Manesty Betapress^{R} in a controlled humidity environment of less than 30% relative humidity. Tablets were compressed at a compression weight of 230mg, using 7.8mm, round, concave, plain punches.

EXAMPLE 5

The procedure of Example 4 is repeated except that the lubricant levels are changed resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
Glycine hydrochloride	5.0
Talc, USP	22.9
Magnesium stearate, NF	0.7
Colloidal silicon dioxide, NF	0.2
TOTAL	229.3mg

Tablets are compressed at approximately 229.3mg.

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EXAMPLE 6

The procedure of Example 4 is repeated except that the lubricant levels are changed resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
Glycine hydrochloride	5.0
Talc, USP	10.9
Magnesium stearate, NF	1.1
Colloidal silicon dioxide, NF	0.2
TOTAL	217.7mg

Tablets are compressed at approximately 217.7mg.

EXAMPLE 7

The procedure of Example 4 was repeated except that the lubricant levels were changed resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
Glycine hydrochloride	5.0
Talc, USP	10.9
Magnesium stearate, NF	0.7
Colloidal silicon dioxide, NF	0.2
TOTAL	217.3mg

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Tablets are compressed at approximately 217.3mg

EXAMPLE 8

The procedure of Example 4 was repeated except magnesium stearate and colloidal silicon dioxide were replaced with sodium stearyl fumarate resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	91.3
Sodium starch glycolate, NF	9.2
Glycine hydrochloride	5.0
Talc, USP	10.9
Sodium stearyl fumarate	3.3
TOTAL	219.7mg

Tablets are compressed at approximately 219.7mg

EXAMPLE 9

The procedure of Example 4 was repeated except that the formulation is changed as follows:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	68.8
Corn starch, NF	23.0
Sodium starch glycolate, NF	9.2

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Glycine hydrochloride	5.0
Talc, USP	23.0
Magnesium stearate, NF	0.8
Colloidal silicon dioxide, NF	0.2
TOTAL	230.0mg

Tablets are compressed at approximately 230.0mg.

EXAMPLE 10

The procedure of Example 4 is repeated except sodium starch glycolate is replaced with crospovidone, resulting in the following formulation:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	95.9
Crospovidone	4.6
Glycine hydrochloride	5.0
Talc, USP	23.0
Magnesium stearate, NF	1.2
Colloidal silicon dioxide, NF	0.3
TOTAL	230.0mg

Tablets are compressed at approximately 230.0mg

EXAMPLE 11

The procedure of Example 4 is repeated except that the formulation is changed as follows:

Ingredient	100mg potency tablet

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	Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	68.8
Corn starch, NF	23.0
Sodium starch glycolate, NF	9.2
L-Cysteine hydrochloride	5.0
Talc, USP	23.0
Magnesium stearate, NF	1.2
Colloidal silicon dioxide, NF	0.3
TOTAL	230.5mg

Tablets were compressed at approximately 230.5mg

EXAMPLE 12

The procedure of Example 11 is repeated except that L-cysteine hydrochloride is replaced with glycine hydrochloride.

EXAMPLE 13

The procedure of Example 4 is repeated except that the sodium starch glycolate and colloidal silicon dioxide are removed and the formulation follows:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	71.0
Corn starch, NF	22.0
L-Cysteine hydrochloride	5.0
Talc, USP	22.0
Magnesium stearate, NF	1.1

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TOTAL	221.1mg

Tablets were compressed at approximately 221.1mg

EXAMPLE 14

The procedure of Example 4 was repeated except that the sodium starch glycolate was removed and the formulation follows:

Ingredient	100mg potency tablet Weight (mg) per tablet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	71.0
Corn starch, NF	22.0
L-Cysteine hydrochloride	5.0
Talc, USP	22.0
Magnesium stearate, NF	1.1
Colloidal silicon dioxide, NF	0.2
TOTAL	221.3mg

Tablets were compressed at approximately 221.3mg.
A portion of tablets was film-coated using a Compu-Lab Accela-Cota^R film-coater. The aqueous film coat Opadry Red YS-1-1846 was used for the 100mg potency. The Acella-Cota^R parameters were:
Inlet air temperature: 50-80°C.
Inlet air volume: 200-1000 cfm
Exhaust air temperature: 40-60°C.
Exhaust air volume: 200-1000 cfm
Tablets were coated to a weight gain of 1-5% over the core tablet weight to achieve an acceptable color intensity.

150MG CAPSULES

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EXAMPLE 15

150mg capsules were prepared according to the following formulation and procedure:

Ingredient	Weight (mg) per capsule
Bupropion hydrochloride	150.0
Microcrystalline cellulose, NF	106.5
Corn starch, NF	33.00
Talc, USP	33.00
L-Cystein hydrochloride	7.500
TOTAL	330.0mg

A stock blend of bupropion hydrochloride, corn starch (purity 826) and microcrystalline cellulose (MCC) was prepared as follows:

The above ingredients were sifted by hand through a 30 mesh screen. They were then blended in an Patterson-Kelly (P-K) v- shell blender for 10 minutes.

The proper amount of cysteine hydrochloride was weighed out and added to 85% w/w SD3A alcohol (aqueous) solution. This mixture was vigorously mixed for approximately 5 minutes. It was then immediately added to the proper amount of the above mentioned stock blend and wet-granulated in a table-top Hobart mixer.

The resulting wet granulation was screened by hand through a 16 mesh screen.

The wet granule was dried in a tray oven at 50°C for 4 hours to obtain a loss on drying (LOD) of below 2% using a CompuTrac^{R} moisture analyser 90°C. (Upon standing the batches re-equilibrated to 2-3% LOD).

The dried granule was sifted through a 16 or 30 mesh hand screen.

The granule was lubricated with talc (sifted 60 mesh), in a P-K v-shell blender for 5 minutes.

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Finished granule is encapsulated on a Chemi-Pharm manual capsule-filling machine Model No. 201, using size No. 1, white, opaque two part hard gelatin capsules.

EXAMPLE 16

The procedure of Example 15 is repeated except cysteine hydrochloride was replaced with glycine hydrochloride.

EXAMPLE 17

The procedure of Example 15 is repeated except cysteine hydrochloride was replaced with L-cystine dihydrochloride.

EXAMPLE 18

The procedure of Example 15 is repeated except cysteine hydrochloride was replaced with tartaric acid.

EXAMPLE 19

The procedure of Example 15 is repeated except cysteine hydrochloride was replaced with citric acid.

EXAMPLE 20

The procedure of Example 15 is repeated except cysteine hydrochloride was replaced with malic acid.

EXAMPLE 21

The procedure of Example 15 is repeated except cysteine hydrochloride is replaced with isoascorbic (erythorbic) acid.

EXAMPLE 22

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The procedure of Example 15 is repeated except cysteine hydrochloride is replaced with ascorbic acid.

EXAMPLE 23

The procedure of Example 15 is repeated except cysteine hydrochloride is replaced with sodium metabisulfite.

CAPLETS

EXAMPLE 24

The caplets were manufactured according to the following formulation:

Ingredient	100mg potency caplet
(Core)	Weight (mg) per caplet
Bupropion hydrochloride	100.0
Microcrystalline cellulose, NF	274.0
Sodium starch glycolate, NF	15.00
L-Cysteine hydrochloride, USP	9.00
Talc, USP	12.00
Magnesium stearate, NF	4.00
CORE WEIGHT	414.0MG
(Coating)	
Opadry^{R} Red, YS-1-1846	12.00
Carnauba Wax, NF	0.04
TOTAL WEIGHT	426.0

Sufficient powder ingredients were weighed out to make a batch size of approximately 60,000 caplets.

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The bupropion hydrochloride, microcrystalline cellulose and sodium starch glycolate were sifted through a 20 or 30 mesh Russell Finex sifter.

The sifted ingredients were blended for 15 minutes in a 3 cu.ft. slant-cone blender.

The blended ingredients were granulated as follows:

A quantity of purified water, USP that equals approximately no more than 20% of the total weight of granulating solution needed to impart the desired granule wetness was weighed out. The cysteine hydrochloride was dissolved in the purified water using a mixer. The cysteine hydrochloride solution was added to a quantity of SD3A alcohol, anhydrous, equal to the remaining 80% (no less than) of the total weight of solution needed to impart the desired granule wetness and mixed thoroughly using a mixer. The blended ingredients were placed in a 3 cu.ft. Littleford Lodige^{R} granulator and granulated using the hydroalcoholic cysteine hydrochloride solution. Mixing and chopper time was approximately 5-10 minutes. Wetness was checked and additional 80% w/w SD3A alcohol (aqueous) solution was added to achieve appropriate massing.

Any clumps of wet granule were broken up by hand.

Granule was dried in a WST-30 Glatt fluid-bed dryer until loss on drying (by Compu-Trac^{R}, 90°C) of granule was 0.8-2.0%. Fluid-bed drying parameters were set as follows:
Inlet air temperature: 60°C
Air volume: 200-1200 cu meter/hr

Dried granule was milled using a Comil^{R} and appropriately sized screen.

Talc (pre-sifted 60 mesh) was added to small amount of dried granule and mixed by hand. Magnesium stearate (pre-sifted) was added to a small amount of dried granule and mixed by hand. Both mixtures were sifted through a 16 mesh screen in a Russell Finex sifter. This sifted mixture was added to the remainder of the granule and blended in the 3 cu.ft slant-cone blender for 5 minutes.

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The lubricated granule was compressed on a rotary-type Manesty Betapress^{R}. Caplets were compressed at a compression weight of approximately 414 gm. using 6.5 x 14.5 mm concave, caplet punches containing a partial score-bar on the upper and lower punches.

Caplets were dedusted using a Manesty Tablet Deduster.

A portion of tablets was film-coated using a Compu-Lab Accela-Cota^{R} film-coater. The aqueous film coat Opadry Red^{R} YS-1-1846 was used. The Accela-Cota^{R} parameters were:
Inlet air temperature: 50-80°C.
Inlet air volume: 100-500 cfm
Exhaust air temperature: 40-60°C.

Caplets were coated to a weight gain of 1-5% over the core tablet weight to achieve an acceptable color intensity.

Caplets were coated with carnauba wax to assist in packaging. Carnauba wax was added to the film-coated caplets which were rotated in the coating drum for approximately 5 minutes to distribute the wax.

EXAMPLE 25

The procedure of Example 24 is repeated except:
In order to achieve a 75mg potency, the caplets are compressed at a compression weight of approximately 310.5mg, using 5.9 x 13.1mm concave, caplet punches containing a partial score-bar on the upper and lower punches. The aqueous film coat Opadry^{R} Yellow-Gold YS-1-2186 is for the 75mg potency.
Caplets have the resulting composition:

Ingredient (Core)	75mg potency caplet Weight (mg) per caplet
Bupropion hydrochloride	75.00
Microcrystalline cellulose, NF	205.5

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Sodium starch glycolate, NF	11.25
Cysteine hydrochloride, USP	6.750
Talc, USP	9.00
Magnesium stearate, NF	3.00
CORE WEIGHT	310.5mg
(Coating)	
Opadry Yellow, YS--1-2186	9.00
Carnauba Wax, NF	0.03
TOTAL WEIGHT	319.5.0mg

EXAMPLE 26

The procedure of Example 24 is repeated except:
In order to achieve a 50mg potency, the caplets are compressed at a compression weight of approximately 207mg, using 5.1 x 11.4mm concave, caplet punches containing a partial scorebar on the upper and lower punches. The aqueous film coat Opadry^{R} White YS-1-7059 is used for the 50mg potency. Caplets have the resulting composition:

Ingredient	50mg potency caplet
(Core)	Weight (mg) per caplet
Bupropion hydrochloride	50.00
Microcrystalline cellulose, NF	137.0
Sodium starch glycolate, NF	7.50
Cysteine hydrochloride, USP	4.50
Talc, USP	6.00
Magnesium stearate, NF	2.00
CORE WEIGHT	207.0mg
(Coating)	
Opadry White^{R}, YS-1-7059	6.00
Carnauba Wax, NF	0.02

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TOTAL WEIGHT	213.0mg

EXAMPLE 27

The procedure of Example 24 is repeated except:
The blended powders are granulated with 100% SD3A Alcohol.

EXAMPLE 28

The procedure of Example 27 is repeated except:
The cysteine hydrochloride is blended in dry with the other ingredients rather than adding it to the granulating solution.

The level of cysteine hydrochloride is increased giving the caplets the following composition:

Ingredient	100mg potency caplet
(Core)	Weight (mg) per caplet
Bupropion hydrochloride	100.00
Microcrystalline cellulose, NF	274.0
Sodium starch glycolate, NF	15.00
Cysteine hydrochloride, USP	18.00
Talc, USP	12.00
Magnesium stearate, NF	4.00
CORE WEIGHT	423.0mg
(Coating)	
Opadry Red^{R}, YS-1-1846	12.00
Carnauba Wax, NF	0.040
TOTAL WEIGHT	435.0mg

EXAMPLE 29

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The procedure of Example 24 was followed except:
Glycine hydrochloride is used as the Stabiliser, giving the caplets the following composition:

Ingredient	100mg potency caplet
(Core)	Weight (mg) per caplet
Bupropion hydrochloride	100.00
Microcrystalline cellulose, NF	274.0
Sodium starch glycolate, NF	15.00
Glycine hydrochloride, USP	9.00
Talc, USP	12.00
Magnesium stearate, NF	4.00
CORE WEIGHT	414.0mg
(Coating)	
Opadry Red^{R}, YS-1-1846	12.00
Carnauba Wax, NF	0.04
TOTAL WEIGHT	426.0mg

EXAMPLE 30

The procedure of Example 24 was repeated except:
The blended powders were granulated with 100% Isopropyl alcohol.

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CLAIMS

1. A pharmaceutical composition in solid form comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser in an effective stabilising amount, in which the composition contains at least about 80% w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 40°C and 75% relative humidity and in which an aqueous solution of the stabiliser in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid, an acid salt of an amino acid and sodium metabisulphite.

2. A pharmaceutical composition in solid form comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser in an effective stabilising amount, in which the composition contains at least about 80% w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 50°C and 27% relative humidity and in which an aqueous solution of the stabiliser in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid other than ascorbic acid and isoascorbic acid, an acid salt of an amino acid and sodium metabisulphite.

3. A pharmaceutical composition according to claim 1 or 2, wherein the aqueous solution of the stabiliser has a pH of about 0.9 to 2.

4. A pharmaceutical composition according to claims 1, 2 or 3, wherein the aqueous solution of the stabiliser has a pH of around 1.

5. A pharmaceutical composition according to any of the preceding claims which contains at least about 90% w/w of undegraded buproprion hydrochloride after storage for 6 weeks.

6. A pharmaceutical composition according to any of the preceding claims which contains at least 95% w/w of undegraded bupropion hydrochloride.

7. A pharmaceutical composition according to any of the preceding claims which contains at least 98% w/w of undegraded bupropion hydrochloride.



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8. A pharmaceutical composition according to any of the preceding claims, wherein the amount of stabiliser is 2.7% to 27% of the weight of bupropion hydrochloride in the composition.

9. A pharmaceutical composition according to claim 8, wherein the amount of stabiliser is 5% to 16.2% of the weight of bupropion hydrochloride in the composition.

10. A pharmaceutical composition according to any of the preceding claims, wherein the acid salt of the amino acid is a hydrochloride salt.

11. A pharmaceutical composition according to claim 10, wherein the salt is cysteine hydrochloride, glycine hydrochloride or cystine dihydrochloride.

12. A pharmaceutical composition according to any of claims 1 to 9, wherein the organic acid is tartaric acid, citric acid or malic acid.

13. A pharmaceutical composition according to any of claims 1, 3, 4, 5, 6, 7, 8 or 9 wherein the carboxylic acid is ascorbic or isoascorbic acid.

14. A tablet or capsule according to any of the preceding claims, wherein the amount of bupropion hydrochloride is 25 to 500mg.

15. A tablet or capsule according to claim 14, wherein the amount of bupropion hydrochloride is 25 to 300mg.

16. A tablet or capsule according to claim 14 or 15, wherein the amount of bupropion hydrochloride is 50, 75, 100 or 150mg.

17. A method of stabilising bupropion hydrochloride in a solid pharmaceutical composition so that at least about 80% w/w of bupropion hydrochloride is present in the undegraded form after storage for 6 weeks at about 40°C and 75% relative humidity, wherein said method comprises mixing bupropion hydrochloride with a stabiliser of which an aqueous solution in a concentration

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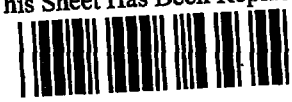
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of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid, an acid salt of an amino acid and sodium metabisulfite.

18. A method of stabilising bupropion hydrochloride in a solid pharmaceutical composition so that at least about 80% w/w of bupropion hydrochloride is present in the undegraded from after storage for 6 weeks at about 50°C and 27% relative humidity, wherein said method comprises mixing bupropion hydrochloride with a stabiliser of which an aqueous solution in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid other than ascrobic acid or isoascrobic acid, an acid salt of an amino acid and sodium metabisulfite.

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STABILISED PHARMACEUTICAL

ABSTRACT

This application discloses a method of inhibiting degradation of the antidepressant bupropion hydrochloride in a solid pharmaceutical formulation, so that the pharmaceutical formulation will maintain at least 80% of its initial bupropion potency after one year.

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w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 50°C and 27% relative humidity and in which an aqueous solution of the stabiliser in a concentration of about 6% w/w has a pH of about 0.9 to about 4, the stabiliser being selected from an organic acid, a carboxylic acid other than ascorbic acid and isoascorbic acid, an acid salt of an amino acid and sodium metabisulphite.

The preferred pH of the aqueous solution of the stabiliser is 0.9 to about 2 and most preferably 1.

Preferably the pharmaceutical composition according to the present invention contains at least about 90% w/w of undegraded bupropion hydrochloride after storage for 6 weeks under the above conditions and more preferably 95% or even 98%. In an additional aspect, the amount of undegraded bupropion hydrochloride is greater than 80% of its labelled strength, and more preferably greater than 90% percent of the labelled strength after one year of storage under the humidity and temperature conditions usually encountered in pharmacies and medicine cabinets i.e. room temperature and 35-60% humidity. Thus, when used in a pharmaceutical preparation for example, a tablet will still retain at least 80% of its potency and preferably at least 90% after one year of storage at room temperature (15-25°C (59-77°F)) at 35-60% humidity. For example if the tablet initially contains 100mg bupropion hydrochloride (labelled amount) at time of preparation, after one year storage at least 80mg of undegraded bupropion hydrochloride will remain in the tablet.

The amount of the stabiliser which may be used with the present invention may vary but preferably is about 2.7% to 27%, most preferably about 5% to 16.2% based on the label strength of bupropion hydrochloride in the pharmaceutical formulation (composition) in solid form. For example if a formulation contains 100mg of bupropion hydrochloride it would preferably contain about 2.7 to 27mg of stabiliser.

Stabilisers of use in this invention include organic acids, carboxylic acids, acid salts of amino acids and sodium metabisulphite. Preferably, the acid salts of amino acids are hydrochloride salts such as cysteine hydrochloride, glycine hydrochloride or cystine dihydrochloride. Other preferred examples of stabilisers according to the present invention include: ascorbic acid, malic acid, isoascorbic acid, citric acid and tartaric

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CLAIMS

1. A pharmaceutical composition in solid form comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser or a combination of stabilisers in an effective stabilising amount, in which the composition contains at least about 80% w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 40°C and 75% relative humidity, an aqueous solution of the stabiliser(s) in a concentration of about 6% w/w having a pH of about 0.9 to about 4, and the stabiliser(s) being selected from an organic acid, a carboxylic acid, an acid salt of an amino acid and sodium metabisulphite;

   with the proviso that a sustained release tablet comprising (i) bupropion hydrochloride and hydroxypropyl methylcellulose, the amount of hydroxypropyl methylcellulose to the amount of bupropion hydrochloride being from 0.19 : 1 to 1.1 : 1, and (ii) glycine hydrochloride or cysteine hydrochloride, is excluded.

2. A pharmaceutical composition according to claim 1 wherein the carboxylic acid is ascorbic or isoascorbic acid.

3. A pharmaceutical composition in solid form comprising bupropion hydrochloride and a pharmaceutically acceptable stabiliser or a combination of stabilisers in an effective stabilising amount, in which the composition contains at least about 80% w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 50°C and 27% relative humidity, an aqueous solution of the stabiliser(s) in a concentration of about 6% w/w having a pH of about 0.9 to about 4, and the stabiliser(s) being selected from an organic acid, a carboxylic acid other than ascorbic acid and isoascorbic acid, an acid salt of an amino acid and sodium metabisulphite;

   with the proviso that a sustained release tablet comprising (i) bupropion hydrochloride and hydroxypropyl methylcellulose, the amount of hydroxypropyl methylcellulose to the amount of bupropion hydrochloride being from 0.19 : 1 to 1.1 : 1, and (ii) glycine hydrochloride or cysteine hydrochloride, is excluded.

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4. A pharmaceutical composition according to any one of claims 1 to 3, wherein the amount of stabiliser(s) is about 2.7% to 27% of the weight of bupropion hydrochloride in the composition.

5. A pharmaceutical composition according to claim 4, wherein the amount of stabiliser(s) is about 5% to 16.2% of the weight of bupropion hydrochloride in the composition.

6. A pharmaceutical composition according to any one of claims 1 and 3 to 5, wherein the acid salt of the amino acid is a hydrochloride salt.

7. A pharmaceutical composition according to claim 6, wherein the salt is cysteine hydrochloride, glycine hydrochloride or cystine dihydrochloride.

8. A pharmaceutical composition according to claim 7, wherein the salt is L-cysteine hydrochloride or glycine hydrochloride.

9. A pharmaceutical composition according to any one of claims 1, 3, 4 and 5, wherein the organic acid is tartaric acid, citric acid or malic acid.

10. A tablet or capsule comprising a composition according to any one of the preceding claims, wherein the amount of bupropion hydrochloride is 25 to 500mg.

11. A tablet or capsule according to claim 10, wherein the amount of bupropion hydrochloride is 25 to 300mg.

12. A tablet or capsule according to claim 10 or claim 11, wherein the amount of bupropion hydrochloride is 50, 75, 100 or 150mg.

13. A method of stabilising bupropion hydrochloride in a solid pharmaceutical composition, so that at least about 80% w/w of bupropion hydrochloride is present in the undegraded form after storage for 6 weeks at about 40°C and 75% relative humidity, wherein said method comprises mixing bupropion

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hydrochloride with a stabiliser or a combination of stabilisers, an aqueous solution of the stabiliser(s) in a concentration of about 6% w/w having a pH of about 0.9 to about 4, and the stabiliser(s) being selected from an organic acid, a carboxylic acid, an acid salt of an amino acid and sodium metabisulfite.

14. A method as claimed in claim 13 wherein the carboxylic acid is ascorbic or isoascorbic acid.

15. A method of stabilising bupropion hydrochloride in a solid pharmaceutical composition, so that at least about 80% w/w of bupropion hydrochloride is present in the undegraded form after storage for 6 weeks at about 50°C and 27% relative humidity, wherein said method comprises mixing bupropion hydrochloride with a stabiliser or a combination of stabilisers, an aqueous solution of the stabiliser(s) in a concentration of about 6% w/w having a pH of about 0.9 to about 4, and the stabiliser(s) being selected from an organic acid, a carboxylic acid other than ascorbic acid or isoascorbic acid, an acid salt of an amino acid and sodium metabisulfite.

16. A method as claimed in claim 13 or claim 15 wherein the acid salt of an amino acid or the organic acid is as defined in any one of claims 6 to 9.

17. A method as claimed in any one of claims 13 to 16 wherein the amount of stabiliser(s) is as defined in claim 4 or claim 5.

18. A method as claimed in any one of claims 13 to 17 wherein the amount of bupropion hydrochloride is as defined in any one of claims 10 to 12.

19. The use, either alone or in combination, of compounds selected from an organic acid, a carboxylic acid, an acid salt of an amino acid and sodium metabisulfite, an aqueous solution of the compound in a concentration of about 6% w/w having a pH of about 0.9 to about 4, as a stabiliser in the preparation of a pharmaceutical composition containing bupropion hydrochloride, and the composition containing at least about 80% w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 40°C and 75% relative humidity.

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20. The use as claimed in claim 19 wherein the carboxylic acid is ascorbic or isoascorbic acid.

21. The use, either alone or in combination, of compounds selected from an organic acid, a carboxylic acid other than ascorbic acid or isoascorbic acid, an acid salt of an amino acid and sodium metabisulfite, an aqueous solution of the compound in a concentration of about 6% w/w having a pH of about 0.9 to about 4, as a stabiliser in the preparation of a pharmaceutical composition containing bupropion hydrochloride, and the composition containing at least about 80% w/w of undegraded bupropion hydrochloride after storage for 6 weeks at about 50°C and 27% relative humidity.

22. The use as claimed in claim 19 or claim 21 wherein the acid salt of an amino acid or the organic acid is as defined in any one of claims 6 to 9.

23. The use as claimed in any one of claims 19 to 22 in which the amount of stabiliser(s) in the composition is as defined in claim 4 or claim 5.

24. A method as claimed in any one of claims 19 to 23 in which the amount of bupropion hydrochloride in the composition is as defined in any one of claims 10 to 12.

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STABILISED PHARMACEUTICAL

ABSTRACT

This application discloses a method of inhibiting degradation of the antidepressant bupropion hydrochloride in a solid pharmaceutical formulation, so that the pharmaceutical formulation will maintain at least 80% of its initial bupropion potency after one year.