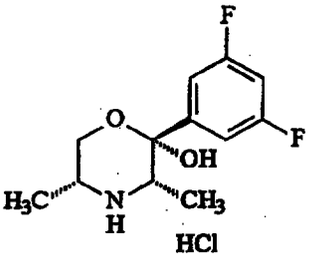
ORAL DOSAGE FORMULATIONS COMPRISING (2S, 3S,5R)-2-(3,5-DIFLUOROPHENYL) -3,5-DIMETHYL-2-MORPHOLINOL AND AN EFFECTIVE STABILIZING AMOUNT OF ALGINIC ACID

This invention relates to discrete oral dosage forms, such as tablets and capsules, comprising (2S,3S,5R)-2-(3,5-difluorophenyl)-3,5-dimethyl-2-morpholinol ("active agent") or salts or solvates thereof.

The compound (2S,3S,5R)-2-(3,5-difluorophenyl)-3,5-dimethyl-2-morpholinol, is most typically prepared and isolated as its hydrochloride salt, which can be depicted as follows:



This compound, along with certain pharmaceutical products prepared therefrom, is described in U.S. Patent No. 5,104,870 (Kelley et al.). In WO99/25355 the use of this compound for the treatment of addiction to nicotine-containing products, and especially tobacco products, is disclosed.

Alginic acid is described in the *Handbook of Pharmaceutical Excipients*, pp. 10-11 (American Pharmaceutical Association 2d Ed. 1994).

Briefly, in one aspect, the present invention provides a discrete oral dosage form comprising a therapeutically effective amount of (2S,3S,5R)-2-(3,5-difluorophenyl)-3,5-dimethyl-2-morpholinol or a physiologically acceptable salt or solvate thereof, or a solvate of said salt, and an effective stabilizing amount of alginic acid.

In another aspect, the present invention provides a method for preventing or treating attention deficit hyperkinetic disorder or depression, comprising administration of a discrete oral dosage form of this invention.

In another aspect, the present invention provides the use of a discrete oral dosage form as defined above in the preparation of a medicament for the prevention or treatment of attention deficit hyperkinetic disorder or depression.

Depression states in the treatment of which the discrete oral dosage form of the present invention is particularly useful are those classified as affective disorders in

the Diagnostic and Statistical Manual of Mental Disorders, Third Edition - Revised, American Psychiatric Association, Washington D.C. (1987) (DSM-III-R), including the mood disorders (DSM-III-R, 296.2X to 296.6X), other specific affective disorders (301.13 and 300.40) and bipolar and depressive disorders not otherwise specified (296.70 and 311.00).

In another aspect, the present invention provides a method for treating addiction to nicotine-containing products, especially tobacco-containing products, comprising administration of a discrete oral dosage form of this invention.

In another aspect, the present invention provides the use of a discrete oral dosage form as defined above in the preparation of a medicament for the treatment of addiction to nicotine-containing products, especially tobacco-containing products.

Nicotine-containing products will include tobacco products (e.g. cigarettes, cigars, pipe tobacco, chewing tobacco etc,) and nicotine replacement products, such as nicotine gums, sprays, patches and inhalers and the like. Treatment of addiction to such nicotine-containing products includes both partial and complete alleviation of addiction. Thus, in respect of tobacco products, as well as the cessation of the activity, for example smoking, this will also include reducing the level or frequency of such activity e.g. reduction of the number of cigarettes smoked in a given period. In respect of other nicotine-containing products, treatment will also involve both cessation of, and a reduction in the level of, usage of such products.

In another aspect, the present invention provides a method for treating other conditions referred to in U.S. Patent No. 5,104,870, comprising administration of a discrete oral dosage form as defined above. Such conditions include the following, with classifications (where indicated) being those adopted in DSM-III-R: anxiety disorders, including phobic neuroses (300.00, 300.21, 300.22, 300.23 and 300.29), anxiety neuroses (300.01, 300.02 and 300.30) and post-traumatic stress disorder (309.89); attention deficit disorders (314.00 and 314.01); eating disorders, including anorexia nervosa (307.10) and bulimia (307.51); personality disorders, including borderline personality disorder (301.83); sexual dysfunctions, including hypoactive sexual desire disorder (302.71), female sexual arousal disorder or male erectile disorder (302.72), inhibited female orgasm (302.73), inhibited male orgasm (302.74), premature ejaculation (302.75), dyspareunia (302.76), vaginismus (306.51) and sexual

dysfunction not otherwise specified (302.70); headaches, including migraine, muscle contraction and mixed (i.e. combination of migraine and muscle contraction) headaches; and narcolepsy-cataplexy syndrome, a condition characterised by excessive sleepiness (narcolepsy) often taking the form of sleep attacks, episodes of a seemingly irresistible need to sleep usually lasting for about fifteen minutes or less, together with brief (often lasting less than a minute) periods of loss of muscle tone (cataplexy) occurring in association with the expression of emotion.

In a preferred aspect, the present invention provides a method for preventing or treating attention deficit hyperkinetic disorder, comprising administration of a discrete oral dosage form of this invention.

In another preferred aspect, the present invention provides the use of a discrete oral dosage form as defined above in the preparation of a medicament for the prevention or treatment of attention deficit hyperkinetic disorder.

In another aspect the discrete oral dosage form may be further used in human medicine: to alleviate symptoms of withdrawal consequent upon the cessation of illicit drug abuse; to potentiate the analgesia induced by morphine or a like opiate analgesic, for example in the care and treatment of terminally-ill cancer patients; to prevent functional impairment and drowsiness following administration of a drowsiness-inducing benzodiazepine tranquillizer - suitable indications for concomitant administration of a said compound or salt and such a benzodiazepine include a) treatment of mixed anxiety and depression in situations where functional impairment or drowsiness is undesirable, and b) treatment of anxiety in situations where functional impairment or drowsiness is undesirable; to prevent memory loss following administration of a benzodiazepine tranquillizer; to restore mental functioning acutely impaired consequent upon ethanol ingestion; to suppress prolactin release or secretion, for example in the suppression of lactation post partum or in the treatment of galactorrhoea, hyperprolactinaemia, amenorrhoea resulting from hyperprolactinaemia and prolactin-sensitive mammary cancer; or to treat memory loss and other memory deficits associated with benign senility.

The discrete oral dosage form of this invention is typically a tablet or capsule and can be prepared by standard methods. For example, tablets of this invention can be prepared by wet granulation or direct compression.

The discrete oral dosage forms of this invention contain a therapeutically effective amount of the active agent or a physiologically acceptable salt or solvate thereof or a solvate of said salt. Generally, the amount needed to be therapeutically effective is calculated based on the weight of the active agent itself and not any associated counter ions or solvent. For example, the active agent is typically prepared as its hydrochloride salt, but the desired amount is usually based on the amount of active agent not including the weight of associated HCl.

The active agent (2S,3S,5R)-2-(3,5-difluorophenyl)-3,5-dimethyl-2-morpholinol, as well as its hydrochloride salt, is known and can be prepared by known techniques, particularly as described in U.S. Patent No. 5,104,870 (Kelley et al.).

Generally, the discrete oral dosage forms of this invention comprise at least 0.1 mg of active agent, or a salt or solvate thereof calculated to give at least 0.1 mg of active agent.

Generally, the discrete oral dosage forms of this invention comprise at least 0.1 % by weight of alginic based on total weight of the tablet or capsule, preferably at least 2 % by weight, and most preferably at least 5 % by weight alginic acid. Particularly preferred alginic acid is alginic acid NF.

As used herein "% by weight", or "weight %", or "wt %", "% w/w", or like terms, means a percentage by weight, based on the total weight of the composition. Unless otherwise indicated, percentages herein are given as percent by weight of the total weight of a discrete oral dosage form.

Alginic acid may be obtained from any suitable source, such as Mendell. In general, the molecular weight is not critical, but is typically from 20,000 to 200,000. Typically the pH of the alginic acid is 1.5 to 3.5 for a 3% weight/volume aqueous dispersion.

Preferably, the discrete oral dosage forms of this invention further comprise standard excipients such as binder, filler, lubricant, disintegrant, or glidant. The discrete oral dosage forms of this invention may also contain stabilizers in addition to the alginic acid.

Filler, sometimes also referred to as carrier, may be any suitable filler. Preferably, the filler is selected from the group consisting of mannitol, sucrose, lactose, and microcrystalline cellulose fillers. Lactose, particularly lactose monohydrate, is most preferred. Preferably the discrete oral dosage forms contain from 40 to 95 % by weight, more preferably from 55 to 90 % by weight, of filler.

Preferably, the discrete oral dosage forms of this invention contain from 1 to 10 percent of a disintegrant. Disintegrants may be any suitable disintegrant. Preferred disintegrants are glucopyranose compounds. Suitable glucopyranose compounds are typically a poly-α- or poly-β-glucopyranose compound in which some of the hydroxyl groups have been converted to carboxy alkyl (*e.g.*, carboxymethyl) ether moieties. Some of the carboxy alkyl ether moieties may be in the form of a pharmaceutically acceptable salt (*e.g.*, a sodium salt). Preferably, the glucopyranose compound is a sodium starch glycolate. Sodium starch glycolate is described in the *Handbook of Pharmaceutical Excipients*, pg. 462-466 (American Pharmaceutical Association 2d Ed. 1994). Most preferably, the glucopyranose compound is a low pH glucopyranose compound. By "low pH" is generally meant that a 3.3% aqueous dispersion of the compound exhibits a pH of from 1 to 5. The molecular weight is not critical, but is typically from 500,000 to 1,000,000. An example of a suitable low pH compound is available as EXPLOTAB® LOW pH from Mendell (a Penwest Company; 2981 Route 22, Patterson, NY, USA 12563-9970). See also, EXPLOTAB® Low pH Sodium Starch Glycolate Product Sheet (Mendell 1996). Other suitable glucopyranose compounds include low pH croscarmellose sodium (see, for example, *Handbook of Pharmaceutical Excipients*, pg. 141).

Preferably, the discrete oral dosage forms of this invention contains from 0.1 to 5 percent of a lubricant. Lubricants that may be employed in carrying out the present invention include, but are not limited to, glyceryl behenate, magnesium stearate, and stearic acid. Glyceryl behenate and magnesium stearate are preferred. Magnesium stearate is particularly preferred.

The discrete oral dosage form may be prepared by any suitable method of pharmacy that includes the step of bringing into association the active agent, the alginic acid, and any other ingredients. Typically a filler or carrier is used and is first mixed with the alginic acid and one or more of the optional ingredients such as lubricant, stabilizer, and/or disintegrant. In general, the formulations of the invention are prepared by uniformly and intimately admixing the active agent hydrochloride salt with solid particulate carrier, alginic acid and optional ingredients, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, with one or more optional ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder. Capsules may be prepared by filling a two piece hard gelatin capsule with the active agent, carrier, and accessory ingredients.

Oral dosage forms of the present invention are useful as antidepressants in the prevention or treatment of depression, obesity, and attention deficit disorder, or aiding in smoking cessation, in subjects, particularly humans, in need thereof, and for all the uses described in U.S. Patent No. 5,104,870.

The present invention is illustrated in the following working examples, in which "NF" means National Formulary grade and "mg" means milligrams.

EXAMPLES

The active agent hydrochloride salt can be prepared as described in the '870 patent.

The active agent, (2S,3S,5R)-2-(3,5-difluorophenyl)-3,5-dimethyl-2-morpholinol, is unstable in the presence of common excipients used in the production of oral dosage forms. The rate of decomposition of the active agent can be unacceptably rapid. Stability was determined by measuring ("assaying") the amount by weight of active ingredient, and the amount of impurities by the amount of area % in an HPLC analysis. The % by weight of active remaining is referred to as "% label

claim" or "LC". Instability is generally indicated by assay values of less than 90% label claim, and impurity levels of 3% or higher. Preferably, formulations will be stable for more than 3 months, and most preferably, for more than 6 months.

Comparative Example C1

Tablets were prepared containing the equivalent of 1 mg of active agent. The active agent hydrochloride salt was weighed so as to give a calculated amount of 1 mg per tablet of free base. The tablets were prepared by sifting each component except magnesium stearate and silicon dioxide through a # 20 mesh screen. The sifted components were added to a V-shell blender and mixed for 15 minutes. The magnesium stearate and silicon dioxide were sifted through a # 20 mesh screen and added to the V-shell blender. The contents were mixed for a period of 5 additional minutes. The blend was compressed on a rotary tablet press fitted with 8.6mm round tooling, uppers scored and lowers, plain, at approximately 250 mg per tablet. The composition of the tablets is summarized below in Table 1.

Table 1

Component	Amount per tablet, wt %
Active agent, HCl	0.463
Anhydrous Lactose	76.9
Microcrystalline Cellulose PH 102	20.0
Magnesium Stearate	0.400
Crospovidone	2.00
Silicon Dioxide	0.200

The tablets were tested for % label claim and impurities initially and after one month at three conditions: 30°C, 40°C with75% relative humidity, and 50°C. The results of the stability testing are summarized below in Table 2.

Table 2

Testing Timepoint	Label Claim, weight %	Total Impurities, area %
Initial	95.7	1.9
30°C	90.8	6.5
40°C/75%RH	76.5	17.7
50°C	78.8	15.0

The data show that the stability of these tablets is unacceptable.

Comparative Examples C2 and C3

Tablets containing 1.25 mg of active agent were prepared as in Comparative Example C1 except stearic acid and sodium starch glycolate were used as the lubricant and disintegrant, respectively and Comparative Example C2 contained 4.8 wt% of ascorbic acid and Comparative Example C3 contained 4.8 wt % of citric acid. The theory was that the pH and/or antioxidant effects of these carboxylic acids would stabilize the formulations. The results of stability testing are summarized below in Table 3.

Table 3

Testing Timepoint	Comparative Example C2		Comparative Example C3	
	Label Claim Weight %	Total Impurities Area%	Label Claim Weight %	Total Impurities Area %
Initial	85.2	2.96	90.1	2.89

As the data show, the stability at the initial test point was poor enough that there was no need to store tablets at acceleratcd conditions. These compositions were actually less stable than the composition with no carboxylic acid.

Examples 1-4

Tablets were made containing 4 different amounts of active agent. The active agent HCl was weighed so as too deliver 0.25 mg, 0.5 mg, 1.25 mg, and 5 mg, of active agent per tablet for Examples 1-4 respectively, based on conversion from active

agent HCl to active agent base. Each of the tablets contained 5% by weight of alginic acid.

The active agent hydrocloride salt ("active agent HCl") was first sieved through a US Standard 30 mesh hand screen to remove any large lumps from the article. Next, the active agent HCl was milled with centrifugal mill fitted with a 0.5 mm screen.

The desired amount of milled active agent HCl was then sieved with a vibratory screener fitted with a US Standard 14-mesh stainless steel screen. The active agent HCl was then charged to V-blender. A 5 cubic foot blender was used in the manufacture of the 1.25 mg tablets, whereas a 3 cubic foot blender was used in the manufacture of the 0.25 mg and 0.5 mg tablets strengths. A one cubic foot blender was used to blend the 5 mg tablets. The desired amounts of lactose monohydrate, modified spray dried, alginic acid and sodium starch glycolate, low pH were also sieved with the vibratory screener fitted with a US Standard 14 mesh stainless steel screen and added to the blender. The V-blender was then rotated for 20 minutes. The proper amount of glyceryl behenate was screened with a vibratory screener fitted with a US Standard 14 mesh stainless steel screen and added to the blender. The V-blender was rotated for an additional 5 minutes.

The active agent HCl tablets were compressed on a rotary tablet press. Round, 5 mm diameter, plain-face, standard concave, tooling was used for the compression. The target compression weight was 75 mg. Finally, the tablets were dedusted. The composition of the tablets is summarized below in Table 4.

Table 4

Component	Example			
	1	2	3	4
Active agent per Tablet (mg)	0.25	0.5	1.25	5
Active agent HCl, Milled (wt %)	0.383	0.767	1.92	7.67
Lactose Monohydrate, NF, Modified Spray Dried (wt %)	87.61	87.23	86.08	80.33
Alginic Acid, NF (wt %)	5	5	5	5
Sodium Starch Glycolate, NF, (Low pH) (wt %)	5	5	5	5
Glyceryl Behenate, NF (wt %)	2	2	2	2

The stability of the tablets was evaluated at three conditions, 25°C with 60% relative humidity ("RH"), 40°C with 75% RH, and 50°C with ambient humidity ("AMB"). The results of the stability evaluation are summarized below in Table 5. In Table 5, the data for L.C. are wt % and the data for Total Impurity are area %.

Table 5

	Example 1		Example 2		Example 3		Example 4	
25°C, 60%RH	Total Impurity	L.C.	Total Impurity	L.C.	Total Impurity	L.C.	Total Impurity	L.C.
Initial	0.53	99.0	0.44	100.0	0.27	98.0	0.18	98.0
1 month	0.73	98.9	NT	NT	0.29	98.5	0.18	98.3
3 month	0.68	98.9	NT	NT	0.30	98.5	0.25	98.3
5 month	NT	NT	NT	NT	0.21	97.8	0.19	98.1
6 month	0.46	99.1	NT	NT	0.25	97.3	0.24	98.7
9 month	0.45	96.9	NT	NT	0.20	97.4	0.18	97.4
40°C, 75%RH								
Initial	0.53	99.0	0.44	100.0	0.27	98.0	0.18	98.0
1 month	0.31	98.5	NT	NT	0.19	97.5	0.15	97.2
3 month	0.28	97.9	NT	NT	0.21	97.7	0.25	99.7
6 month	0.20	99.3	NT	NT	0.30	98.2	0.16	97.7
50°C, AMB								
Initial	0.53	99.0	0.44	100.0	0.27	98.0	0.18	98.0
1 month	0.28	97.7	NT	NT	0.18	96.8	0.47	98.9
3 month	0.22	97.7	NT	NT	0.19	98.2	0.20	98.4

NT = Not Tested

The data show that alginic acid stabilizes the active agent HCl in these tablets at a variety of active agent strengths and at a variety of temperature and humidity conditions.

Examples 5 and 6

Tablets were made containing 2 different amounts of active agent. The active agent HCl was weighed so as to deliver 0.25 mg and 5 mg, of active agent per tablet for Examples 5 and 6 respectively. Each of the tablets contained 10% by weight of alginic acid.

Tablets were prepared as in Examples 1-4 except the tablets were film coated using standard techniques. The film-coating was Opadry, White, YS-1-18034. A tablet weight of 75 mg was used. The composition of the tablets is summarized below in Table 6.

Table 6

Component	Example	
	5	6
Active agent per Tablet (mg)	1.25	5
Active agent HCl, Milled (wt %)	0.383	7.66
Lactose Monohydrate, NF, Modifies Spray Dried (wt %)	87.61	80.84
Alginic Acid, NF (wt %)	10	10
Glyceryl Behenate, NF (wt %)	2	1.5

The stability of the tablets was evaluated initially, after 2 weeks, and after one month, each at 40°C and 75% RH. Both lots were packaged in foil/foil blisters. Stability was assessed by determination of the total impurity levels and active agent content of both formulations. The results of the stability testing are summarized below in Table 7, the data for L.C. are wt % and the data for Total Impurity are area %.

Table 7

	Example 5		Example 6	
40°C/75%RH	Total Impurity	L.C.	Total Impurity	L.C.
Initial	0.21	107	0.19	100
2 weeks	0.60	110	0.26	99
1 month	1.48	105	0.33	99

Examples 7 and 8

Tablets were made containing 2 different amounts of active agent. The active agent HCl was weighed so as to deliver 10 mg and 5 mg, of active agent per tablet for Examples 7 and 8 respectively. Each of the tablets contained 2.5% by weight of alginic acid.

Tablets were manufactured as in Examples 1-4 except the tablet diameter was increased to 6.5 mm, and the tablet weight was increased to 150 mg and 135 mg for formulations 7 and 8, respectively. These tablets were not film-coated. The composition of the tablets is summarized below in Table 8.

Table 8

Component	**Example**	
	7	8
Active agent per Tablet (mg)	10	5
Active agent HCl, Milled (wt %)	7.66	4.26
Lactose Monohydrate, NF, Modifies Spray Dried (wt %)	83.84	57.74
Microcrystalline Cellulose PH 113, NF (wt %)	0	30
Alginic Acid, NF (wt %)	2.5	2.5
Sodium Starch Glycolate, NF, (Low pH) (wt %)	5	5
Magnesium Stearate, NF (wt %)	1	0.5

Tablets were stored in open and closed vials to assess stability in both configurations. Stability results are summarized below in Table 9, the data for L.C. are wt % and the data for Total Impurity are area %..

Table 9

	Example 7, Open		**Example 7, Closed**		**Example 8, Open**		**Example 8, Closed**	
40°C 75%RH	Total Impurity	L.C.	Total Impurity	L.C.	Total Impurity	L.C.	Total Impurity	L.C.
Initial	0.39	100.1	0.39	100.1	0.51	99.7	0.51	99.7
2 weeks	0.34	99.3	0.44	99.3	0.36	99.6	0.48	100.0
1 month	0.31	99.9	0.45	99.8	0.35	99.7	0.53	97.8
3 month	0.35	98.9	0.46	99.7	0.37	99.7	0.64	98.8

Examples 9 and 10

Tablets were made containing 2 different amounts of microcrystalline cellulose. The active agent HCl was weighed so as to deliver 7.5 mg, of active agent per tablet for Examples 9 and 10. Each of the tablets contained 5% by weight of alginic acid.

Tablets were manufactured as listed above the tablet diameter was 6.5 mm and the tablet weight was 135 mg. These tablets were not film-coated. The compositions of the tablets are summarized below in Table 10.

Table 10

Component	Example	
	9	10
Active agent per Tablet (mg)	7.5	7.5
Active agent HCl, Milled (wt %)	6.39	6.39
Lactose Monohydrate, NF, Modifies Spray Dried (wt %)	78.11	73.11
Microcrystalline Cellulose PH 102, NF (wt %)	5	10
Alginic Acid, NF (wt %)	5	5
Sodium Starch Glycolate, NF, (Low pH) (wt %)	5	5
Magnesium Stearate, NF (wt %)	0.5	0.5

Tablets were stored in open and closed vials to assess stability in both configurations. Results of stability testing are summarized below in Table 11, the data for L.C. are wt % and the data for Total Impurity are area %.

Table 11

	Example 9, Open		Example 9, Closed		Example 10, Open		Example 10, Closed	
40°C 75%RH	Total Impurity	L.C.	Total Impurity	L.C.	Total Impurity	L.C.	Total Impurity	L.C.
Initial	0.04	100.9	0.04	100.9	0.06	98.9	0.06	98.9
1 month	0.05	100.0	0.08	100.4	0.05	97.3	0.07	98.7
3 month	0.12	99.5	0.13	100.6	0.14	98.8	0.19	98.5

Examples 11 and 12

Tablets were made containing 2 different amounts of microcrystalline cellulose. The active agent HCl was weighed so as to deliver 1.25 mg, of active agent per tablet for Examples 11 and 12. Each of the tablets contained 5% by weight of alginic acid.

Tablets were manufactured as listed above except the tablet diameter was 6.5 mm and the tablet weight was 135 mg. These tablets were not film-coated. The compositions of the tablets are summarized below in Table 12.

Table 12

Component	Example	
	11	12
Active agent per Tablet (mg)	1.25	1.25
Active agent HCl, Milled (wt %)	1.06	1.06
Lactose Monohydrate, NF, Modifies Spray Dried (wt %)	83.44	78.44
Microcrystalline Cellulose PH 102, NF (wt %)	5	10
Alginic Acid, NF (wt %)	5	5
Sodium Starch Glycolate, NF, (Low pH) (wt %)	5	5
Magnesium Stearate, NF (wt %)	0.5	0.5

Tablets were stored in open and closed vials to assess stability in both configurations. The results of stability testing are summarized below in Table 13, the data for L.C. are wt % and the data for Total Impurity are area %.

Table 13

	Example 11, Open		Example 11, Closed		Example 12, Open		Example 12, Closed	
40°C 75%RH	Total Impurity	L.C.	Total Impurity	L.C.	Total Impurity	L.C.	Total Impurity	L.C.
Initial	0.05	98.0	0.05	98.0	0.05	98.8	0.05	98.8
1 month	0.04	99.3	0.19	98.3	0.06	99.8	0.16	98.4
3 month	0.10	98.2	0.28	97.6	0.11	96.3	0.32	98.6

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

Claims

1. A discrete oral dosage form, comprising a therapeutically effective amount of (2S,3S,5R)-2-(3,5-difluorophenyl)-3,5-dimethyl-2-morpholinol or a physiologically acceptable salt or solvate thereof, or a solvate of said salt, and an effective stabilizing amount of alginic acid.

2. A discrete oral dosage form as claimed in claim 1 wherein said salt is a hydrochloride salt.

3. A discrete oral dosage form as claimed in claim 1 or claim 2 wherein said therapeutically effective amount is at least 0.25 mg.

4. A discrete oral dosage form as claimed in any one of claims 1 to 3 comprising at least 0.2 % by weight of alginic acid.

5. A discrete oral dosage form as claimed in any one of claims 1 to 3 comprising at least 2 % by weight of alginic acid.

6. A discrete oral dosage form as claimed in any one of claims 1 to 3 comprising at least 5 % by weight of alginic acid.

7. A discrete oral dosage form as claimed in any one of claims 1 to 6 further comprising from 40 to 95 weight percent of a filler.

8. A discrete oral dosage form as claimed in claim 7 wherein said filler is selected from the group consisting of mannitol, sucrose, lactose, and microcrystalline cellulose.

9. A discrete oral dosage form as claimed in any one of claims 1 to 8 further comprising from 0.1 to 5 percent of a lubricant.

10. A discrete oral dosage form as claimed in claim 11, wherein said lubricant is selected from the group consisting of gyceryl behenate, magnesium stearate, and stearic acid.

11. A discrete oral dosage form as claimed in any one of claims 1 to 10 further comprising from 1 to 10 percent of a low pH poly α or β glucopyranose compound;

12. A discrete oral dosage form as claimed in claim 11 wherein said glucopyranose compound is sodium starch glycolate, low pH.

13. A discrete oral dosage form as claimed in claim 1, comprising, 0.1 to 25 mg of (2S,3S,5R)-2-(3,5-difluorophenyl)-3,5-dimethyl-2-morpholinol hydrochloride, 40 to 95 weight percent of filler; 0.1 to 15 percent of a low pH poly α or β glucopyranose compound in which some of the hydroxy groups have been converted to carboxy alkyl ethers, 0.1 to 10 percent alginic acid, and 0.1 to 5 weight percent of a lubricant.

14. A discrete oral dosage form as claimed in any one of claims 1 to 13 wherein said form is a tablet.

15. A discrete oral dosage form as claimed in claim 14 wherein said tablet is a film-coated tablet.

16. A discrete oral dosage form as claimed in any one of claims 1 to 13 wherein said form is a capsule.

17. A discrete oral dosage form as claimed in any one of claims 1 to 16 for use in therapy.

18. A method for preventing or treating attention deficit hyperkinetic disorder, or depression, comprising administration of a discrete oral dosage form as claimed in any one of claims 1 to 16.

19. The use of a discrete oral dosage form as claimed in any one of claims 1 to 16 in the preparation of a medicament for the prevention or treatment of attention deficit hyperkinetic disorder or depression.

20. A method for treating addiction to nicotine-containing products, comprising administration of a discrete oral dosage form as claimed in any one of claims 1 to 16.

21. A method as claimed in claim 20 wherein the nicotine-containing product is a tobacco-containing product.

22. The use of a discrete oral dosage form as claimed in any one of claims 1 to 16 in the preparation of a medicament for the treatment of addiction to nicotine-containing products.

23. The use as claimed in claim 22 wherein the nicotine-containing product is a tobacco-containing product.