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(54) **Title:** ORALLY DISINTEGRATING TABLET FORMULATIONS OF DONEPEZIL AND PROCESS FOR PREPARING THE SAME

(57) **Abstract:** The present invention relates to surfactant agent free orally disintegrating tablet formulations of donepezil hydrochloride comprising mannitol, crospovidone, sucralose and one or more pharmaceutically acceptable excipient and process for preparing such a formulation.

ORALLY DISINTEGRATING TABLET FORMULATIONS OF DONEPEZIL AND PROCESS FOR PREPARING THE SAME

Technical Field of the Invention

5 The present invention relates to surfactant agent free orally disintegrating tablet formulations of donepezil hydrochloride comprising mannitol, crospovidone, sucralose and one or more pharmaceutically acceptable excipient and process for preparing such a formulation.

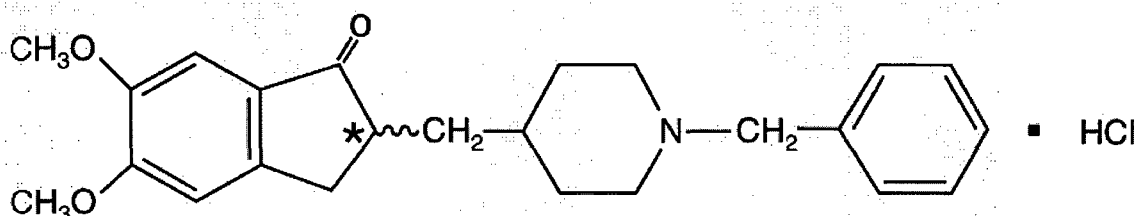
10 More specifically, the invention relates to the orally disintegrating tablet formulations of donepezil hydrochloride comprising mannitol in an amount of between 50.0 and 95.0 % by weight, crospovidone (cross-linked polyvinylpyrrolidone) in an amount of between 5.0 to 30.0 % by weight and sucralose in an amount of between 0.01 and 2.00 % by weight of the total tablet formulation, further not comprising a silicon dioxide.

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Background of the Invention

Donepezil hydrochloride is a reversible inhibitor of the enzyme acetylcholinesterase, which is known as (\pm)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidiny]methyl]-1*H*-inden-1-one hydrochloride and its chemical structure is shown in the Formula I.

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Formula 1

25 Donepezil hydrochloride is available for oral administration in conventional tablet formulations and orally disintegrating tablet formulations containing 5 or 10 mg of donepezil hydrochloride and indicated for the treatment of dementia and Alzheimer's Disease.

30 Various formulations and methods are already known for the preparation of orally disintegrating formulations of donepezil or pharmaceutically acceptable salts thereof. However, orally disintegrating formulations are becoming an increasingly important issue in the area of better patient compliance comparative to the conventional solid dosage forms for oral administration such as capsules and tablets, which are the most commonly

used. In particular pediatric and geriatric patients, and patients with mental problems such as dementia and Alzheimer's disease, often experience difficulties in swallowing solid dosage forms. Besides, conventional solid dosage forms are not suitable for bedridden or busy and travelling patients, in case the patient may not have easy access to water. Thus, orally disintegrating compositions represent an alternative for such patients and provide for a better patient compliance with recommended pharmaceutical therapies.

Additionally oral administration of the drugs is difficult in patients having concomitant vomiting, nausea or diarrhoea. The orally disintegrating dosage form is one of the advantageous methods to deliver the drugs to such patients. By administering the orally disintegrating dosage forms, faster absorption of the drug occurs through buccal mucosa and it may reduce the first pass metabolism leading to better efficacy of the drug. This dosage form enhances the clinical effects of some drugs by leading to an increase in bioavailability and a reduction in side effects because of avoidance of first-pass liver metabolism.

It is known that, to develop orally disintegrating compositions are difficult because of several different reasons. A satisfied orally disintegrating dosage form needs to meet number of requirements. Firstly, it has to disintegrate in the oral cavity rapidly. Moreover, a premature release in the mouth could also lead to problems due to the often unpleasant taste of the active ingredient. Besides, these compositions should be very porous and should not be very hard. These porous compositions tend to be very sensitive to humidity. As a consequence, they may have some stability problems. Finally, any orally disintegrating composition with suitable organoleptic and pharmacokinetic properties must also be manufactured at commercially useful rates and yields.

To fulfill all these requirements the formulation for a specific drug needs to be adapted in particular by a careful selection of the excipients used. However, the excipients selected may lead to formulations which are not bioavailable to the corresponding conventional dosage forms. Thus, they have to be chosen very carefully. Additionally, precautions have to be taken at the preparation, packaging, handling and storing of the finished dosage forms of orally disintegrating compositions since they tend to be both hygroscopic and friable.

Thus, various technologies have been developed which enable the preparation of compositions that disintegrate quickly in the oral cavity. These technologies are including

spray drying, freeze drying, floss formation and wet granulation. However, all these technologies have their own limitations.

5 The spray drying technique involves spraying the drug and excipients into a chamber maintained at a high temperature. As a result this technique is not suitable for application to thermo- labile drugs. Additionally, the spray drying technology leads only to a very poor output and is very expensive.

10 Freeze drying on a large scale has not been found to be very effective. Moreover, it has limitations due to factors such as time, costly equipment and processing conditions. Besides, the Zydis[®] tablets prepared by this technique are so fragile that the formation of the matrix material has to take place in a specific container. Tablets manufactured by this technology require a special type of packaging and careful handling during dispensing and administration to the patients, since they are prone to breakage. Such US Patents
15 which disclose these formulations are US 4 642 903, 5 188 825, 5 631 023, 5 827 541 and 5 976 577.

20 The floss formation technique includes compressing micro- particles of a drug and a cotton candy-like fibrous saccharide matrix, such as sucrose, dextrose, lactose and fructose. It is also known as Flash Dose technology (Fuisz) and requires specific equipment for making the specific matrix, which is sensitive to moisture, and generally results in tablets of high friability.

25 EP 1 120 109 A2 discloses highly-porous, rapidly-disintegrating and fast-dissolving dosage forms produced from steam extruded polymers. Such polymers are in particular high amylase starch or derivatived products. However, it is a disadvantage that the preparation of these specific polymers requires special equipment and processes.

30 The wet granulation technique results in cores of a high hardness which make it difficult to obtain fast dissolving and fast disintegrating tablets. Moreover, tablets prepared thereby often lead to coarse dispersions in the oral cavity resulting in a poor patient compliance. The use of solvents and the additional drying step required in this technique may lead to a change of the polymorphic or pseudopolymorphic form of the drug or to its degradation.
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Finally, many of these techniques have proved to be successful only for specific drugs and are often not transferable to other active ingredients.

Thus, a need rises for orally disintegrating tablet formulations of donepezil hydrochloride and a process for preparing such formulation which overcomes the above described problems in prior art and having additive advantages over them. Further advantages and
5 embodiments of the present invention will become apparent from the following description.

Detailed Description of the Invention

The main object of the present invention is to provide an improved orally disintegrating
10 tablet formulation of donepezil hydrochloride which overcomes above described problems with using adequate excipients and which further provide the advantageous property of allowing the active medicament to disintegrate rapidly in the oral cavity without remaining substantial amounts of the active ingredient and which have a pleasant mouth feel.

Another object of the present invention is to provide a simple, cost-effective and time
15 saving process for the preparation of orally disintegrating tablet formulation of donepezil hydrochloride.

Yet another object of the present invention is to provide an orally disintegrating tablet
20 formulation of donepezil hydrochloride which has good mechanical strength enough to be processed in high speed tableting machines and shipped in low cost packages.

A further object of the present invention is to provide bioavailable and stable orally
25 disintegrating tablet formulation of donepezil hydrochloride throughout the shelf-life. According to this object, in this invention an orally disintegrating tablet formulation of donepezil hydrochloride which is comparable with the existing conventional solid dosage forms is provided, however unexpected benefits are found with oral disintegration. Because, presentation of donepezil hydrochloride in conventional solid or liquid oral dosage forms, having their own limitations, are not ideal for use in pediatric or geriatric
30 patients or in patients suffering from dementia or Alzheimer's disease.

According to this object the present invention is directed to a surfactant agent free orally
35 disintegrating tablet formulation of donepezil hydrochloride comprising mannitol in an amount of between 50.0 to 95.0 % by weight, crospovidone (cross-linked polyvinylpyrrolidone) in an amount of between 5.0 to 30.0 % by weight, sucralose in an amount of between 0.01 to 2.00 % by weight of the total tablet formulation and one or more pharmaceutically acceptable excipient.

Another object of the invention is an orally disintegrating tablet formulation of donepezil hydrochloride which does not comprise a silicon dioxide. It is known that an improved orally disintegrating tablet formulation should have minimum grit or sandy effect, and to provide this effect silicon dioxide is mostly used. However, silicon dioxides, especially colloidal silicon dioxide is very hygroscopic and this cause problems when preparing the orally disintegrating tablet formulations. Thus, precautions have to be taken at the preparation, packaging, handling and storing of the finished dosage forms of orally disintegrating formulations since they tend to be both hygroscopic and friable. We have surprisingly obtained good and improved results despite not using silicon dioxide, especially colloidal silicon dioxide. Thus, this is achieved by the adequate selection of excipients which will be further detailed below.

According to the present invention, said "surfactant agents" which are not used in this orally disintegrating tablet formulation may comprise but not limited to sodium lauryl sulfate, magnesium lauryl sulfate, dioctyl sulfosuccinate, polysorbates, especially polysorbate 80, polyoxyethylene alkyl esters and ethers, glyceryl monolaurate saponins (e.g. quillaja saponins), sorbitan laurate and and the like and their mixtures thereof; preferably it is sodium lauryl sulfate.

Without using surfactant agent in an orally disintegrating tablet formulation, the selection of excipients has more importance to obtain the ideal disintegrating time. Thus, crospovidone has physical and chemical properties that make it ideal for constituting the appropriate disintegrant for this invention. Because crospovidone particles have a very different appearance from those of the other disintegrants. Crospovidone particles seem to consist of aggregates of smaller particles that are fused together. This aggregation gives crospovidone a spongy, highly porous appearance and it swells very little, yet takes water into its network quite rapidly. This helps crospovidone to dissolve easily and quickly in a little amount of water or saliva and makes its disintegrating rate much faster than other related excipients.

According to this embodiment of the invention, crospovidone is present in an amount of between 5.0 to 30.0 % by weight, preferably in an amount of 8.0 to 15.0 % by weight of the total formulation and the formulation disintegrates in oral cavity in less than 60 seconds, preferably in less than 30 seconds, more preferably in less than 25 seconds.

Another embodiment of the invention is to provide a sodium lauryl sulfate free orally disintegrating tablet formulation of donepezil hydrochloride comprising, mannitol in an amount of between 50.0 to 95 % by weight, crospovidone in an amount of between 5.0 to 30.0 % by weight, sucralose in an amount of between 0.01 to 1.00 % by weight of total tablet formulation and one or more pharmaceutically acceptable excipient, further not comprising a silicon dioxide, preferably not comprising colloidal silicon dioxide.

In another embodiment, the orally disintegrating tablet formulation comprises donepezil hydrochloride in an amount of 0.5 to 10.0 % by weight, preferably it is 1.0 to 5.0 % by weight of total tablet formulation.

In contrast to prior art formulations it is not necessary to use a highly-compressible quality, such as spray-dried mannitol which is also more expensive than the mannitol. According to this embodiment of the invention, the orally disintegrating tablet formulation of donepezil hydrochloride comprises mannitol, wherein it is present in an amount of between 50.0 to 95.0 % by weight, preferably it is 60.0 to 90.0 % by weight, more preferably it is 70.0 to 90.0 % by weight of total formulation.

Another object of the present invention is to develop orally disintegrating compositions having optimal mechanical strength. The present invention addresses this need and discloses formulations that rapidly disintegrate in the oral cavity. These tablet compositions have a pleasant mouth feel and good mechanical strength. These tablets are robust (e.g., low friability, adequate hardness) enough to be processed in high speed tableting machines and shipped in low cost packages, and at the same time retain rapid disintegration or dissolution properties. These orally disintegrating compositions are bioavailable in correspondence with the conventional solid dosage formulations and stable throughout the shelf-life.

It has surprisingly been found that the specific combination of mannitol and crospovidone with the active ingredient donepezil hydrochloride results a synergistic effect over the disintegration time and mechanical strength (such as; hardness and friability) of the orally disintegrating tablet formulation.

According to this embodiment, the weight ratio of mannitol to crospovidone is in the range of between 1:1 and 30:1 (w/w), preferably it is in the range of between 1:1 and 15:1 (w/w).; said amount makes it possible to significantly improve compressibility, reduce friability and achieve a substantial reduction in disintegration time. Higher quantities may

have negative mechanical strength of the formulation and lower quantities may worsen the disintegration time.

5 According to this object of the present invention, the hardness of the orally disintegrating tablet is between 5 N to 100 N, preferably it is between 20 N to 50 N; and the friability of the orally disintegrating tablet is less than 1.0%.

10 The orally disintegrating compositions of this invention also comprise sucralose as a sweetener to improve patient compliance. In prior art, it is known that aspartame is used mostly as sweetener but contradictory to the prior art we have found that the effect of sucralose as a sweetener in this formulation, not only helped to improve its taste but also increased the efficacy and the convenience of the formulation because of its positive effects over the glycemic index. There are lots of disadvantages about aspartame and it has a limited usage if you have to use it every day and also there are several incompatibilities reported in literature and safety problems (*Handbook of Pharmaceutical Excipients, Raymond C Rowe, Paul J Sheskey, Marian E Quinn, sixth edition, pages 48-50*). Thus, sucralose has an important role in this aspect and even if it is used in low amounts it has a synergistic taste improvement with mannitol which is also very important issue in orally disintegrating tablet formulations. According to this object of the present invention sucralose is present in an amount of between 0.01 to 2.00 % by weight, preferably it is 0.05 to 1.00 % by weight, more preferably it is 0.10 to 0.50 % by weight of total formulation.

25 In a further embodiment the orally disintegrating tablet formulation of donepezil hydrochloride comprises one or more pharmaceutically acceptable excipients other than mannitol, crospovidone and sucralose wherein the one or more pharmaceutically acceptable excipients are selected from the group comprising lubricants, flavouring agents, coloring agents and preservatives.

30 Suitable lubricants may comprise but not limited to sodium stearyl fumarate, magnesium stearate, polyethylene glycol, stearic acid, metal stearates, boric acid, sodium chloride benzoate and acetate and the like and mixtures thereof, preferably the lubricant is sodium stearyl fumarate. In one aspect, sodium stearyl fumarate is present in an amount of from 0.10 to 10.0 % by weight, preferably it is from 1.0 to 5.0 % by weight of the total tablet formulation.

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Suitable flavouring agents may comprise but not limited to fruit flavours such as orange, banana, strawberry, cherry, wild cherry, lemon; and other flavours such as cardamom, anise, peppermint, menthol, vanillin and ethyl vanillin and the like and mixtures thereof; preferably the flavouring agent is fruit flavour such as orange or banana. In one aspect, flavouring agent content is present in an amount of from 0.1 to 5.0%, preferably from 0.5 to 2.0% by weight of total composition.

Suitable coloring agents are selected from the group comprising iron oxides (such as; iron oxide yellow, red or black), Food, Drug & Cosmetic (FD&C) dyes, poncau, indigo blue, indigotine blue, carmoisine indigotine, quinoline yellow, flaming red, carmine, carmoisine, sunset yellow and the like and mixtures thereof; preferably the coloring agent is iron oxide yellow. In one aspect, coloring agent is used optionally and may present in an amount of from 0.01 to 1.00 % by weight of the total tablet formulation.

Suitable preservatives may comprise but not limited to methyl paraben and propyl paraben and their salts (such as sodium, potassium), sodium benzoate, citric acid, benzoic acid, butylated hydroxytoluene and butylated hydroxyanisole and the like and mixtures thereof. In one aspect, the preservative content may present in an amount of about from 0,01 to 5.0%, preferably about from 0.5 to 2.0% by weight of total composition.

As it is mentioned above, to develop orally disintegrating compositions are difficult because of several different reasons. A satisfied orally disintegrating dosage form needs to meet number of requirements. Firstly, it has to disintegrate in the oral cavity rapidly. Moreover, a premature release in the mouth could also lead to problems due to the often unpleasant taste of the active ingredient. Besides, these compositions should be very porous and should not be very hard. These porous compositions tend to be very sensitive to humidity. As a consequence, they may have some stability problems.

However, in order to be pharmacologically acceptable, orally disintegrating compositions must be palatable, e.g. have acceptable organoleptic properties such as good taste and mouthfeel, because orally disintegrating compositions are designed to disintegrate in the oral cavity of the patient rapidly without remaning substantial amounts of the active ingredient. In addition, the orally disintegrating formulations must also provide acceptable pharmacokinetics and bioavailability to provide the desired therapeutic effect. Conversely, components of the formulation that promote rapid release may result in undesirable taste or mouthfeel properties. Finally, any orally disintegrating composition with suitable

organoleptic and pharmacokinetic properties must also be manufactured at commercially useful rates and yields.

5 To fulfill all these requirements the formulation for a specific drug needs to be adapted in particular by a careful selection of the excipients used. However, the excipients selected may lead to formulations which are not bioavailable to the corresponding conventional dosage forms. Thus, they have to be chosen very carefully.

10 In this present invention, to minimize the disintegration time and maximise the mechanical resistance of the tablets of this invention, this orally disintegrating tablet formulaiton has been designed, consisting the followings:

- a. 0.5 to 10.0% by weight of donepezil hydrochloride,
- b. 50.0 to 95.0% by weight of mannitol,
- c. 0.5 to 30.0% by weight of crospovidone,
- 15 d. 0.01 to 2.00% by weight of sucralose,
- e. 0.1 to 5.0% by weight of flavouring agent,
- f. 0.1 to 10.0 % by weight of sodium stearyl fumarate,
- g. optionally 0.01 to 1.00 % by weight coloring agent.

20 According to further object of the invention, the preferred process of the present invention for preparing the orally disintegrating tablet formulation of donepezil hydrochloride is direct compression which comprises the following steps;

- a. sieving donepezil hydrochloride, mannitol, crospovidone, sucralose, flavouring agent and coloring agent and mixing them until having homogenous mixture,
- 25 b. adding the sieved sodium stearyl fumarate to this mixture and blending for a short time,
- c. compressing the blended mixture to form tablets.

30 In a further aspect, the present invention shows that it is possible to have a significant influence on the disintegration rate of the tablet by modifying the dimensions and shape of the tablet. In general, as the tablet becomes thinner and have higher porosity, the orally disintegrating composition will be weakened faster when it contacts with saliva, because the disintegration process is produced after wetting all the surface of the tablet via capillary action. Also, any shape which maximizes the contact surface with the saliva
35 may produce a significant reduction in disintegration time.

The preferred shape of the orally disintegrating tablet composition of this invention may have a shape of a disk, circle, round, sphere, donut, bar, polygon, ellipse and the like. The preferred shape of the tablet is a flat round shape.

5 This invention is further defined by reference to the following examples. Although the examples are not intended to limit the scope of the present invention, it should be considered in the light of the description detailed above. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

10 **Examples**

Example 1 – Orally disintegrating donepezil hydrochloride tablets

Ingredients	Amount (mg)
Donepezil hydrochloride	5.00
Mannitol (Pearlitol SD-100)	237.48
Crospovidone (Kollidon CL-SF)	28.00
Sucralose	0.56
Orange-banana flavour	3.36
Sodium stearyl fumarate	5.60
Total tablet weight	280.00

15 This formulation is prepared by direct compression as described in detail above. Firstly, donepezil hydrochloride, mannitol, crospovidone, sucralose and orange-banana flavour is sieved and then blended together until having a homogenous mixture. Sodium stearyl fumarate is then sieved and added to this mixture and blending all together for a short time. This blended mixture is compressed to form tablets.

Example 2 - Orally disintegrating donepezil hydrochloride tablets

Ingredients	Amount (mg)
Donepezil hydrochloride	10.00
Mannitol (Pearlitol SD-100)	232.24
Crospovidone (Kollidon CL-SF)	28.00
Sucralose	0.56
Orange-banana flavour	3.36
Yellow iron oxide	0.24
Sodium stearyl fumarate	5.60
Total tablet weight	280.00

This formulation is prepared by direct compression as described in detail above. Firstly, donepezil hydrochloride, mannitol, crospovidone, sucralose, orange-banana flavour and yellow iron oxide is sieved and then blended together until having a homogenous mixture. Sodium stearyl fumarate is then sieved and added to this mixture and blending all together for a short time. This blended mixture is compressed to form tablets.

Example 3

According to standardized methods and equipment for testing friability, hardness and disintegrating time have been provided in European Pharmacopeia. These orally disintegrating tablet formulations of the invention (Ex.1 and 2) are tested according to these methods. As it is seen in the Table 1, the hardness of the tablets is quite sufficient to allow easy and convenient removal from the package without breaking the dose unit. These orally disintegrating tablets are hard enough to be handled and packaged like conventional tablets. They are compressed to a hardness of 20-50 Newton and possess a friability of less than 1%. The disintegrating times are acceptable and the taste and mouthfeel of the tablets are good.

Table 1

Harndness (Newton)	20-30	30-50
Friability (%)	0,67	0,51
Disintegration time (sec)	20	22

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Claims

1. A surfactant agent free orally disintegrating tablet formulation of donepezil hydrochloride comprising;
5 a. mannitol in an amount of between 50.0 to 95.0 % by weight,
 b. crospovidone in an amount of between 5.0 to 30.0 % by weight,
 c. sucralose in an amount of between 0.01 to 2.00 % by weight of total tablet formulation and one or more pharmaceutically acceptable excipient.
- 10 2. The orally disintegrating tablet formulation of donepezil hydrochloride according to claim 1, further not comprising a silicon dioxide.
3. The orally disintegrating tablet formulation of donepezil hydrochloride according to claims 1 to 2, wherein donepezil hydrochloride is present in an amount of 0.5 to
15 10.0 % by weight, preferably it is 1.0 to 5.0 % by weight of total formulation.
4. Sodium lauryl sulfate free orally disintegrating tablet formulation of donepezil hydrochloride according to claims 1 to 3 comprising;
 a. mannitol in an amount of between 50.0 to 95.0 % by weight,
20 b. crospovidone in an amount of between 5.0 to 30.0 % by weight,
 c. sucralose in an amount of between 0.01 to 2.00 % by weight of total tablet formulation and one or more pharmaceutically acceptable excipient.
5. The orally disintegrating tablet formulation of donepezil hydrochloride according to
25 claim 4, further not comprising a silicon dioxide.
6. The orally disintegrating tablet formulation of donepezil hydrochloride according to claims 1 to 5, wherein mannitol is preferably present in an amount of between 60.0 to 90.0 % by weight, more preferably it is 70.0 to 90.0 % by weight of total
30 formulation.
7. The orally disintegrating tablet formulation of donepezil hydrochloride according to claims 1 to 5, wherein sucralose is preferably present in an amount of between 0.05 to 1.00 % by weight, more preferably it is 0.10 to 0.50 % by weight of total
35 formulation.

8. The orally disintegrating tablet formulation of donepezil hydrochloride according to claims 1 to 5, wherein crospovidone is preferably present in an amount of between 8.0 to 15.0 % by weight of the total formulation.
- 5 9. The orally disintegrating tablet formulation of donepezil hydrochloride according to claims 1 to 8, wherein the weight ratio of mannitol to crospovidone is in the range of between 1:1 and 30:1 (w/w), preferably it is in the range of between 1:1 and 15:1 (w/w).
- 10 10. The orally disintegrating tablet formulation of donepezil hydrochloride according to any preceding claims, wherein the composition disintegrates in oral cavity in less than 60 seconds, preferably in less than 30 seconds.
- 15 11. The orally disintegrating tablet formulation of donepezil hydrochloride according to any preceding claims, wherein the hardness of the tablet is between 5 N to 100 N, preferably it is between 20 N to 50 N.
- 20 12. The orally disintegrating tablet formulation of donepezil hydrochloride according to any preceding claims, wherein the friabilite of the tablet is less than 1.0%.
- 25 13. The orally disintegrating tablet formulation of donepezil hydrochloride according to claims 1 to 5, wherein the one or more pharmaceutically acceptable excipients are selected from the group comprising lubricants, flavouring agents, coloring agents and preservatives.
- 30 14. The orally disintegrating tablet formulation of donepezil hydrochloride according to claim 13, wherein the lubricants are selected from the group comprising sodium stearyl fumarate, magnesium stearate, polyethylene glycol, stearic acid, metal stearates, boric acid, sodium chloride benzoate and acetate and the like and mixtures thereof, preferably the lubricant is sodium stearyl fumarate.
- 35 15. The orally disintegrating tablet formulation of donepezil hydrochloride according to any preceding claim consisting;
- a. 0.5 to 10.0% by weight of donepezil hydrochloride,
 - b. 50.0 to 95.0% by weight of mannitol,
 - c. 0.5 to 30.0% by weight of crospovidone,
 - d. 0.01 to 2.00% by weight of sucralose,

- e. 0.1 to 5.0% by weight of flavouring agent,
- f. 0.1 to 10.0 % by weight of sodium stearyl fumarate,
- g. optionally 0.01 to 1.00 % by weight coloring agent.

5 16.A process for preparing orally disintegrating tablet formulation of donepezil hydrochloride according to any preceding claim comprising;

a. sieving donepezil hydrochloride, mannitol, crospovidone, sucralose, flavouring agent and coloring agent and mixing them until having homogenous mixture,

10 b. adding the sieved sodium stearyl fumarate to this mixture and blending for a short time,

c. compressing the blended mixture to form tablets.

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