Oral dispersable tablet

The present invention is directed to an oral disintegratable tablet which exhibits oral disintegratability of not more than 60 seconds. The tablet for oral administration, comprises an effective amount of at least one active agent, an amount of at least 50% (w/w) of a water insoluble parts, a surfactant and a disintegrant, such that said tablet is orally disintegretable or dispersable.

Oral dispersable tablets are in principle not different from common immediate release (IR) tablets. They should be mechanically stable, to allow handling during technical operations and handling by the patient or customer. Their disintegration time in aqueous environment should be fast and complete. A softening under the conditions of release, so that weak mechanical stress is sufficient for complete dispersion, is also acceptable.

To improve disintegration properties, several principles are common. For example tablets containing gas-developing mixtures of at least one acid component (like e.g. citric acid) and at least one basic component in form of a carbonate or hydrogen-carbonate. Such a tablet for oral dispersibility is described e.g. in US 2002/0110578. Another common method is the use of rapidly soluble tablet excipients like e.g. sugar alcohols (Mannitol, Sorbitol, Xylitol, Erythritol etc.), sugars or specialized forms of these like Pharmaburst™ or F-Melt™. Rapid disintegration is a result of the dissolution of these excipients.

For tablets, used for disintegration in the oral cavity, some additional properties are desirable. The resulting solution or dispersion after tablet disintegration should be easy to swallow, acceptable in its taste and mouth-feel. Hence often additional measurements for the taste-masking of the active component or components (like micro-encapsulation, coating, salt-formation, ester-formation etc.) are necessary. Furthermore aroma and/or sweeteners are used to improve the taste and the patient acceptance. Sometimes the used excipients also have a pleasant taste (sugars, sugar-alcohols) and by this property improve patient acceptance.

Another difficulty in the rapid disintegration in the oral cavity is the limited amount of liquid that is present. In comparison to water, the liquid inside the oral cavity is of higher viscosity. The amount of liquid and its viscosity is not constant. There is a variation between different subjects and even within one subject depending on the time of the day, the amount of liquid consumed (drinking-status), the consumed food etc. Highly porous tablet structures, into which liquid can easily penetrate are therefore also common in the field of oral dispersable tablets. Several specialized manufacturing technologies ensure highly porous tablet structures. The geometry of the

tablet can also influence the disintegration time. Short ways for liquid penetration are preferred. This prerequisite also influences the tablet shape and geometry. The desired optimal geometry also has to consider mechanical stability, as described already.

In the manufacturing of all tablets, and also for oral dispersable tablets, the costs are important. The manufacturing cost should be as low as possible. This can best be achieved by using established standard technologies and keeping the manufacturing process as lean as possible. Any additional manufacturing step would increase cost and has to be avoided. Also the use of specialized excipients tends to increase the costs, as these are more expensive than standard excipients.

The target group for the application of oral dispersable tablets can be found in patients with difficulties in swallowing tablets or in groups were water for the intake of normal tablets is not readily available. In some markets the convenience of taking tablets without water has a high preference. In all cases, the disintegration time of the tablet should be short and the patient/costumer should get the impression of something happening with the tablet inside his mouth. This perception of disintegrating action helps the patients/costumers expectation of a positive influence of the active principle(s) on his/her state or health.

JP 9071523 describes the formulation of oral dispersable tablet. The use of microcrystalline cellulose (MCC) in combination with low substituted hydroxyl-propyl Cellulose (L-HPC) is described. A certain ratio of the two excipients is found to yield the desired tablet properties.

WO 2004091585 describes the use of Prosolv (silicified microcrystalline Cellulose) for the formulation of oral dispersable tablets. Prosolv is a trademark excipient and further described in the US 6471994 as a new tablet excipient also for the use with oral dispersable tablets.

In the development of a new formulation approach to oral dispersable tablets, the use of surfactants was studied. Surfactants and hydrophilic, wetting polymers, like Poloxamer, are used to aid the wettability of active ingredients (drug substance(s)) or increase their bioavailibilty by enhancing their dissolution. In the field of oral dispersable tablets surfactants can be used to reduce the viscosity of the aqueous media inside the oral cavity, independent of the wettability of the active. This effect can be promoted by the use of one or more sweet tasting substances inside the formulation. Salt (NaCl), acid components or intensive flavour can have a similar effect and would also reduce the viscosity of the aqueous media inside the oral cavity. Combinations of these can be used to increase the effect.

Rapid tablet disintegration was found to by promoted by less hydrophobic lubricant at minimized amount, as the most commonly used Magnesium-stearate tends to slow down tablet disintegration. A potent tablet disintegrant is also advantages in combination with other insoluble substances within the formulation.

The present invention is directed to a non-effervescent tablet for oral administration, comprising an effective amount of at least one active agent, an amount of at least 50% (w/w) of a water insoluble parts, a surfactant and a disintegrant, such that said tablet is orally disintegretable or dispersable. The said tablet exhibits oral disintegratability in not more than 60 seconds. Preferably the tablet exhibits oral disintegratability in not more than 30 seconds. More preferably the tablet exhibits oral disintegratability in not less than 5 seconds. Most preferred the tablet exhibits oral disintegratability in not less than 2 seconds.

The water insoluble carrier in the tablet is selected from the group Cellulose, microcrystalline Cellulose or silicified microcrystalline Cellulose or mixtures thereof. The silicified microcrystalline cellulose is contained in an amount within the range of 20% to 90% preferably within the range of 25% to 60%.

The said silicified microcrystalline cellulose contains 1-5% silicon dioxide. The tablet silicified microcrystalline cellulose in the tablet has an average particle size within the range of 20-300 µm.

The desintegrant in the tablet is selected from the group consisting of low substituted hydroxypropyl cellulose, carboxymethyl cellulose, crosscarmelose sodium, crosspovidone (crosslinked Polyvinylpyrolidone), sodium starch glycolate, starch, and combinations thereof. Preferrability the disintegrant is low substituted hydroxypropyl cellulose or crosspovidone (crosslinked Polyvinylpyrolidone) or combinations thereof. The disintegrant is contained in the tablet in an amount of 0.5% to 50%.

The surfactant in the tablet is selected from the group Sodium dodecylsulfate, Polyoxyethylen Sorbitan fatty acid esters (Tweens), Polyoxyethylene Stearates, Sorbitan fatty acid esters (Spans) .

The tablet according to the invention is one which has a tensile strength of 300 to 2000 kN/m² (calculated as Tensile strength =2*Breakingload / (diameter * thickness *π; observed tensile failure of the measured tablet)

The tablet according to the invention has a friability of less than 1 %. The tablet according to the invention does not contain a water soluble binder.

The tablet according to to the invention may further comprises at least one additional excipient selected from the group consisting of taste masking agents, sweeteners, lubricants, stabilizers, preservatives, and pH-adjustors. The active agent in the tablet according to the invention is selected from the group consisting of pharmaceutical active agents, nutrients, nutriceuticals, and cosmetics. The active agent can be one or more vitamins. The active agent can also be one or more pharmaceutically active agent(s).

The said pharmaceutically active agent can be present in the form of coated particles containing said pharmaceutically active agent. The coating can be an extended release or an enteric coating.

The tablet according to the invention is a tablet, wherein said pharmaceutically active agent is selected from the group consisting of anti-inflammatories, antirheumatics, antiemetics, analgetics, antiepileptics, antipsychotics, antidepressants, hypnotics, antiulcerics, prokinetic, antiasthmatics, antiparkinsonics, cardiovasculars, vasodilators, urologics, hypolipidemics, antidiabetics, and antihistaminics.

The said pharmaceutically active agent can be selected from the group consisting of ibuprofen, acetominophen, piroxicam, leflunomide, ondansetron, granisetron, paracetamol, carbamazepin, lamotrigine, clozapine, olanzapine, risperidone, citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine, zopiclon, zolpidem, cimetidine, ranitidine, omeprazole, metoclopramide, cisapride, domperidon, zafirlukast, montelukast, prarnipexol, selegiline, zolpidem, zopiclon, doxazosin, terazosin, atenolol, bisoprolol, amlodipine, nifedipine, diltiazem, enalapril, captopril, ramipril, losartan, glyceroltrinitrate, alfuzosin, finasteride, pravastatin, atorvastatin, simvastatin, gemfibrozil, metformin, terfenadine, loratadine, celecoxib, rifecoxib, and rivastigmine, as well as a pharmaceutically acceptable salt, ester, hydrate or solvate of the active agent.

According to the invention the pharmaceutical orally disintegratable non-effervescent tablet is one which consists essentially of 20% to 90% silicified microcrystalline cellulose or cellulose or microcrystalline cellulose, 0% to 20% of low substituted hydroxypropyl cellulose, 0% to 20% crosslinked Polyvinylpyrolidone, a lubricant, a surfactant and an effective amount of a pharmaceutically active agent, wherein said tablet exhibits disintegration within 1 to 15 seconds when tested in an in vitro disintegration test.

The tablet can further comprise flavorants, colorants, or both.

The invention is further directed to the use of a surfactant for making an orally disintegratable non-effervescent pharmaceutical tablet.

The present invention provides also a process of rapidly releasing an active agent from a solid tablet, which comprises disintegrating a tablet as described above, by placing the tablet in a water environment. The said water environment is an oral cavity or is a waterfilled container.

The percentage of insoluble parts of the tablet mixture should be above 30% by weight. Insoluble excipients can be either of inorganic origin (like salts e.g. Calcium Phosphate, Calcium sulfate, Magnesium carbonate, Calcium Carbonate, Silicate(s), Oxides like Titanium dioxide, Aluminium oxide, Magnesium oxid or their respective hydrates and/or polymorphic forms) or of organic nature (like natural polymers e.g. Cellulose, Cellulose esters or ethers, Chitin, Chitosan, Starch, Starch esters or ethers, Alginates, synthetic polymers e.g. Polyethylen, Polypropylen, Polyvinylchloride, Polymethacrylate). If the active principle(s) are insoluble or their solubility is low, they would also act as insoluble parts.

Suitable disintegrants in this respect are e.g. swellable polymers, crosslinked swellable polymers, hydrophilic polymers or other substances which take up water and with that increasing their volume. Pharmaceutically common are Crosscarmellose, crosslinked Polyvinylpyrolidone, L-HPC or Sodium starch glycolate. Other soluble excipients, such as sugars (Lactose, Saccarose, Glusose, Fructose, Maltose) sugar alcohols (Mannitol, Sorbitol, Xylitol, Erythritol) or soluble actives can be used, as long as their proportion is not to high and their mean particle size remains above 50µm. The use of this soluble excipients is also common in the field of oral dispersable tablets.

For the incorporation of soluble actives it was found, that their particle size has an influence on tablet disintegration. It is advantageous to have the particles not to small in this case. A particle size of greater than 50µm (mean value of the distribution) was found to yield the desired tablet properties. If solubility of the active(s) is high, or time for dissolution is short, greater mean particle sizes are preferred. The way in which the particle size is increased is not important. Larger crystals work as good as agglomerates made by granulation (wet- or dry-granulation methods can be used).

For the manufacturing of the described formulation, a direct compression manufacturing workflow can be used. Thus manufacturing costs are low and standard technology can be used, which keeps investments low.

Desired tablet properties are sufficient mechanical stability (expressed as tensile strength and friability), rapid disintegration (expressed as disintegration time using the method described in the European Pharmacopia (European Pharmacopia 5th edition 2007 (5.8) Method 2.9.1, using water at 37°C and the disk), acceptable mouth feeling and taste.

With the described formulation principle pharmaceutically active substances (drug substances) of different solubility can be formulated. Drug substances can either be soluble (like e.g. the oral Antidiabetics Acarbose or Miglitol) up to insoluble (like e.g. Nifedipine). In the case of soluble drug substances a special definition (fraction) of the particle size can be advantageous with respect to disintegration time, content uniformity and tablet hardness. The particles of the pharmaceutically active substances could be crystals or agglomerates. The particle size of the pharmaceutically active substances can be 50µm-1000µm, preferably 100µm-800µm, more preferably 125µm-630µm, and most preferably 125µm-800µm. In particular useful in this particle size are the pharmaceutically active substances acarbose, miglitol and voglibose.

Examples :

The tablets can be obtained by mixing the given components (except for the lubricant Na-stearyl-fumerat) in a suitable mixing device (e.g. Turbula mixer or tumble blender) for 10 minutes. Then add the lubricant and mix for another 5 minutes.

This mixture is then compressed into tablets using a 9mm flat-faced beveled edged set of punches to give tablets of the given mass. For double dose tablets use 13mm flat-faced beveled edged punches and compress to the double of the given mass. Tablets should match the given tensile strength range (Breakingloads between 20 to 60 N).

In case of Acarbose as active, the Acarbose is premixed with 0,5% (w/w) Na-stearyl-fumerat and compacted. The compacts are broken and sieved (Dry-granulation or roller-compaction). After sieving the fraction 125µm-800µm is used.

The tablets disintegrate within 5-10 seconds using the described European Pharmacopia Method.

Example 1

Substance	Amount [mg/Tabl.]	Mass [%]
Active *)	50,25	30,15%
Prosolv (SMMC 90)	101,00	60,61%
L-HPC Type B1	13,30	7,98%
Natrium Dodecylsulfat	0,42	0,25%
NaCl	0,50	0,30%
Saccharin-Natrium	0,17	0,10%
Na-Stearyl-Fumarat	1,00	0,60%
Tablet	166,64	100,00%

*) used as 99.5% (m/m) Acarbose and 0.5% (m/m) Sodium stearyl fumerat or Miglitol

Example 2

Substance	Amount [mg/Tabl.]	Mass [%]
Active *)	50,25	30,15%
Prosolv (SMMC 90)	75,00	45,01%
Avicel PH200	26,08	15,65%
L-HPC Type B1	13,30	7,98%
Natrium Dodecylsulfat	0,42	0,25%
NaCl	0,50	0,30%
Saccharin-Natrium	0,09	0,05%
Na-Stearyl-Fumarat	1,00	0,60%
Tablet	166,64	100,00%

*) used as 99.5% (m/m) Acarbose and 0.5% (m/m) Sodium stearyl fumerat or Miglitol

Example 3

Substance	Amount [mg/Tabl.]	Mass [%]
Active *)	50,25	30,21%
Prosolv (SMMC 90)	45,00	27,05%
Avicel PH200	26,08	15,68%
Arbocel P290	25,00	15,03%
L-HPC Type B1	18,00	10,82%
Natrium Dodecylsulfat	0,42	0,25%
NaCl	0,50	0,30%
Saccharin-Natrium	0,09	0,05%
Na-Stearyl-Fumarat	1,00	0,60%
Tablet	166,34	100,00%

*) used as 99.5% (m/m) Acarbose and 0.5% (m/m) Sodium stearyl fumerat or Miglitol

Example 4

Substance	Amount [mg/Tabl.]	Mass [%]
Active *)	50,25	30,21%
Prosolv (SMMC 90)	45,00	27,05%
Arbocel 290	20,00	12,02%
Kollidon CL	49,08	29,51%
Natrium Dodecylsulfat	0,42	0,25%
NaCl	0,50	0,30%
Saccharin-Natrium	0,09	0,05%
Na-Stearyl-Fumarat	1,00	0,60%
Tablet	166,34	100,00%

*) used as 99.5% (m/m) Acarbose and 0.5% (m/m) Sodium stearyl fumerat or Miglitol

Example 5

Substance	Amount [mg/Tabl.]	Mass [%]
Active *)	50,25	30,21%
Prosolv (SMMC 90)	45,00	27,05%
Arbocel 290	30,00	18,04%
Kollidon CL	39,08	23,49%
Natrium Dodecylsulfat	0,42	0,25%
NaCl	0,50	0,30%
Saccharin-Natrium	0,09	0,05%
Na-Stearyl-Fumarat	1,00	0,60%
Tablet	166,34	100,00%

*) used as 99.5% (m/m) Acarbose and 0.5% (m/m) Sodium stearyl fumerat or Miglitol

Example 6

Substance	Amount [mg/Tabl.]	Mass [%]
Active *)	50,25	30,21%
Prosolv (SMMC 90)	45,00	27,05%
Aqualon EC T10	38,00	22,84%
Kollidon CL	15,08	9,07%
L-HPC Type B1	16,00	9,62%
Natrium Dodecylsulfat	0,42	0,25%
NaCl	0,50	0,30%
Saccharin-Natrium	0,09	0,05%
Na-Stearyl-Fumarat	1,00	0,60%
Tablet	166,34	100,00%

*) used as 99.5% (m/m) Acarbose and 0.5% (m/m) Sodium stearyl fumerat or Miglitol

Claims:

1. A non-effervescent tablet for oral administration, comprising an effective amount of at least one active agent, an amount of at least 50% (w/w) of a water insoluble parts, a surfactant and a disintegrant, such that said tablet is orally disintegretable or dispersable.

2. The tablet according to claim 1, wherein said tablet exhibits oral disintegratability in not more than 60 seconds.

3. The tablet according to any of claims 1 to 2, wherein said water insoluble carrier is selected from the group Cellulose, microcrystalline Cellulose or silicified microcrystalline Cellulose or mixtures thereof.

4. The tablet according to claim 6, wherein said silicified microcrystalline cellulose is contained in an amount within the range of 20% to 90%.

5. The tablet according to claims 6-9, wherein said silicified microcrystalline cellulose has an average particle size within the range of 20-300 μm.

6. The tablet according to claim 1 - 5, wherein said desintegrant is selected from the group consisting of low substituted hydroxypropyl cellulose, carboxymethyl cellulose, crosscarmelose sodium, crosspovidone (crosslinked Polyvinylpyrolidone), sodium starch glycolate, starch, and combinations thereof.

7. The tablet according to claim 1 - 6, wherein said surfactant is selected from the group Sodium dodecylsulfate, Polyoxyethylen Sorbitan fatty acid esters (Tweens), Polyoxyethylene Stearates, Sorbitan fatty acid esters (Spans) .

8. The tablet according to claims 1-7, wherein said active agent is selected from the group consisting of pharmaceutical active agents, nutrients, nutriceuticals, and cosmetics.

9. The tablet according to claims 1-8, wherein said pharmaceutically active agent is selected from the group consisting of anti-inflammatories, antirheumatics, antiemetics, analgetics, antiepileptics, antipsychotics, antidepressants, hypnotics, antiulcerics, prokinetic, antiasthmatics, antiparkinsonics, cardiovasculars, vasodilators, urologics, hypolipidemics, antidiabetics, and antihistaminics.

10. The tablet according to claims 1-8, wherein said pharmaceutically active agent is selected from the group consisting of ibuprofen, acetominophen, piroxicam, leflunomide, ondansetron, granisetron, paracetamol, carbamazepin, lamotrigine, clozapine, olanzapine, risperidone, citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine, zopiclon, zolpidem, cimetidine, ranitidine, omeprazole, metoclopramide, cisapride, domperidon, zafirlukast, montelukast, pramipexol, selegiline, zolpidem, zopiclon, doxazosin, terazosin, atenolol, bisoprolol, amlodipine, nifedipine, diltiazem, enalapril, captopril, ramipril, losartan, glyceroltrinitrate, alfuzosin, finasteride, pravastatin, atorvastatin, simvastatin, gemfibrozil, metformin, terfenadine, loratadine, celecoxib, rifecoxib, and rivastigmine, as well as a pharmaceutically acceptable salt, ester, hydrate or solvate of the active agent.

11. Use of a surfactant for making an orally disintegratable non-effervescent pharmaceutical tablet.