Effervescent formulations

The invention relates to solid, rapidly disintegrating administration forms in the form of effervescent formulations for alkali-sensitive active ingredients, in particular selegiline, and processes for their preparation.

Selegiline (= L-N-(1-phenylisopropyl)-N-methyl-2-propynyl-amine) or its pharmaceutically acceptable salts are used in the form of tablets in the therapy of Parkinson's disease.

A large number of administration forms for selegiline have been described in the patent literature. Transdermal administration forms including, for example, patches, are claimed in EP 404 807, EP 406 488, EP 509 761, EP 591 432, EP 593 807, EP 617 515, WO 94/23707, EP 647 137, EP 683 668, WO 95/18603, EP 655 900 and WO 96/02239.

Drug forms for the controlled release of selegiline, for example in the form of tablets, are described in EP 582 186, WO 96/01612 and US 5,484,608, osmotically acting release systems are described in US 5,128,145 and normal-release oral formulations are described in WO 96/22435.
Subject-matter of the patent application WO 96/12472 is a liposomal composition which comprises the active ingredient selegiline.
Buccal and sublingual administration forms are claimed in WO 97/17067.

WO 95/07070 describes effervescent formulations which, to avoid the insoluble residues of tricalcium citrate which can be formed when effervescent formulations are dissolved, comprise at least two different edible acids.

WO 93/00886 describes effervescent tablets having good storage stability, for example alkali-sensitive active ingredients such as acetylcystein, captopril and minoxidil, and said tablets comprise an effervescent base containing a solid edible organic acid as carrier crystals, an alkali metal carbonate or bicarbonate and an alkali metal salt of the acid. Two layers are applied onto the carrier crystals. The first layer consists of a different acid than the carrier crystals, and the second layer consists of the alkali metal salt of one of the two acids.

Selegiline is unstable in alkali-containing effervescent formulations. Even a multi-layer construction is not sufficient for stabilization. Alkali carbonates and bicarbonates are more basic than alkaline earth carbonates, such as calcium carbonate. Up to now, there are no suitable effervescent formulations for selegiline, an alkali-sensitive active ingredient. This may partly be due to the fact that hitherto such formulations were unsuccessful owing to the instability of selegiline, as shown in Figure 1.

The therapeutic treatment of various disorders requires, in particular in elderly people, a very frequent and in some cases even life-long taking of pharmaceutics.
Owing to strong tremor, Parkinson patients usually have, when taking tablets, problems with the subsequent drinking of fluid. Likewise, taking of tablets is very difficult for patients having difficulties swallowing.

There is therefore a demand for novel solid, rapidly disintegrating administration forms, in particular effervescent formulations in the form of soluble tablets, buccal tablets or soluble granules which ensure easy administration, even for, for example, elderly people.

It is an object of the present invention to provide novel and therapeutically advantageous effervescent formulations for selegiline and other alkali-sensitive active ingredients.

The soluble-tablet-formulations are also suitable, in particular, for the combined use with other soluble tablets, such as L-dopa and benzerazide according to EP 521 388.

This object is achieved by the present invention which provides rapidly disintegrating administration forms for oral administration with or without water in the form of effervescent formulations comprising an alkali-sensitive active ingredient and an effervescent base consisting of one or more alkaline earth metal carbonates, an organic edible acid and/or an alkali metal salt of citric acid and, if appropriate, pharmaceutically acceptable auxiliaries.

The invention provides effervescent formulations in the form of granules, tablets or sachets. The tablets can also be buccal tablets.

A particular embodiment of the invention relates to effervescent formulations which comprise selegiline or its pharmaceutically acceptable salts.

By addition of water to or contact of saliva with such effervescent formulations, a suspension or solution is formed with evolution of CO_2 gas, and said suspension or solution has a pleasant taste during taking. Here, a rapid release of the active ingredient is of particular importance to ensure a rapid onset of action. This applies in particular to buccal tablets.

Effervescent formulations for various active ingredients and vitamins are known in the prior art. These effervescent formulations generally comprise an

agent which is capable of releasing CO_2, and an agent which induces the release of CO_2. Agents capable of releasing CO_2 which are preferably used are alkali metal carbonates or alkali metal bicarbonates, such as sodium carbonate or sodium bicarbonate. Alkaline earth metal carbonate formulations mainly relate to mineral preparations. Agents for inducing CO_2 release which are employed are edible organic acids, or their acidic salts, which are present in solid form and which can be formulated with the active ingredient and the other auxiliaries to give granules or tablets, without premature evolution of CO_2.

Suitable edible organic acids are, for example, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, ascorbic acid, maleic acid or citric acid.

Pharmaceutically acceptable acidic salts are, for example, salts of polybasic acids which are present in solid form and in which at least one acid function is still present, such as sodium dihydrogen or disodium hydrogen phosphate or the corresponding citrates.

The active ingredients are either present in the effervescent formulation as readily soluble compounds, or they are solubilized by salt formation during the dissolution process. However, it is also possible to disperse poorly soluble active ingredients.

Selegiline hydrochloride is extremely sensitive towards the customary effervescent bases such as sodium bicarbonate, sodium carbonate or sodium hydrogen citrate in combination with organic edible acids, such as citric acid or tartaric acid.

In these customary effervescent formulations, the active ingredient selegiline is degraded to amphetamine, metamphetamine and demethylselegiline, and the active ingredient undergoes sublimation. It should be noted that degradation to the abovementioned metabolites occurs only partly. The main fraction of selegiline sublimes in the presence of alkali metal

compounds, in particular alkali metal carbonates, so that, surprisingly, loss of active ingredient occurs even in the case of only slight metabolization. As can be seen from Figure 2, the required purity and quantity are no longer met after storage of these effervescent selegiline formulations.
Surprisingly, effervescent formulations based on alkaline earth metals in accordance with the present invention are very stable.

Here, a preferred embodiment is the use of calcium carbonate and citric acid as effervescent base.
It may be advantageous if some of the calcium carbonate has reacted with citric acid to give calcium citrate.
Small amounts of sodium citrate do not cause instabilities. However, these amounts may not be more than 15% of the total weight of the effervescent formulation.

At room temperature and even in the stress test at 40°C and 75% relative atmospheric humidity, the effervescent selegiline formulations according to the invention show no relevant loss of quality (Figure 3).

This is of particular importance since effervescent formulations have to be protected well against atmospheric humidity during production, filling and storage, owing to which preparation is generally only carried out in rooms with low atmospheric humidity (Ritschel, Bio Tablette, Echtio Cauher KG 1966, p. 115 f). As discussed by Wells in "Pharmaceutical Preformulation" (John Wiley 1988), basic catalysis is, in a large number of medicaments, a decisive mechanism for instabilities.

In effervescent tablets, calcium carbonate is usually only employed for calcium therapy, and not as medicinal excipient for active ingredient groups in which calcium does not contribute to the therapy.

Calcium-containing effervescent tablets are generally employed for treating mineral metabolism.
WO 95/07070 describes effervescent granules based on calcium carbonate and citric acid for producing a pharmaceutical preparation, where 5-20 parts by weight of the citric acid are replaced by at least one other edible acid, such as malic acid.

Calcium carbonate is also employed as additional auxiliary in pharmaceutical technology, for example as auxiliary for sugar coating or as extender (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, 1989).

The present effervescent formulations according to the invention permit the preparation of a ready-to-drink solution or suspension with pleasant taste, preferably in a volume of from 40 to 80 ml of water, which can be drunk easily in cases of tremor. This also applies to geriatric patients. Buccal or sublingual effervescent preparations are administered directly at the mucosa of the mouth.

Effervescent minitablets for example, contain from 5 to 10 mg of selegiline HCl and approximately 1200 mg of an effervescent base, "normal" effervescent tablets contain from 2000 mg to 7000 mg and buccal preparations from 50 to 500 mg of an effervescent base. The dose in the buccal preparation can be considerably lower, for example 1-5 mg of selegiline.
In the case of low-dose active ingredients, the effervescent formulations according to the invention may comprise up to 90%, and in the case of high-dose active ingredients, from 30% to 70% of an effervescent base.

The effervescent formulations also permit combined taking together with other active ingredients, as is frequently required in the case of selegiline in Parkinson treatment.

Thus, effervescent selegiline formulations can be administered in combination with other soluble tablets, in particular L-dopa/benzerazide combinations or soluble amantadine tablets.

A cocktail treatment, as described in EP 521 388 is also possible. Here, at least two different active ingredients are dissolved or suspended together in an amount of water and then administered together.

Selegiline can also be administered together with vitamin E in the form of effervescent formulations.

According to the invention, these effervescent preparations can also be employed for other alkali-sensitive active ingredients, such as erythromycin, clarithromycin, diazepam, ampicillin or phenobarbital.

The effervescent formulations according to the invention can be prepared by customary processes known from the prior art. The acids and carbonates are, for example, granulated separately (wet granulation), where the active ingredients are preferably added to the acidic granules. After mixing of the carefully dried granules, soluble lubricants, such as sodium benzoate or polyethylene glycols, are added, and the mixture is compressed.

According to the other method, all acids, carbonates and active ingredients are mixed together and heated in a reactor until the citric acid, for example, releases its water of crystallization and granules are formed (WO 95/13130). Repeated stirring is required to obtain a uniform material. This is then sieved rapidly and dried carefully. Efficient drying is absolutely necessary to avoid gradual disintegration of the tablets by reaction of the acids with the carbonates.

To achieve rapid drying, use is made of vacuum drying cabinets, for example.

In another preparation variant, the acid is partially reacted with the basic components, followed by drying under reduced pressure. Before compression, a soluble

lubricant is admixed to the dry granules. However, tableting can also be carried out using external lubrication.

The effervescent granules according to the invention that are obtained are then compressed to tablets or filled into sachets.

The alkali-sensitive active ingredient, such as selegiline, is preferably bound to neutral carrier substances to obtain good homogeneity. Suitable neutral carrier substances for the effervescent formulations according to the invention are lactose, sucrose, sorbitol, mannitol, starch, pectins or cellulose. Other auxiliaries, such as colorants, sugars or sweeteners, can improve the appearance and/or the taste of the aqueous solutions or suspensions obtainable by disintegration of the effervescent tablet.

The use of colorants can serve both for improving the appearance and for identifying the preparation. Suitable colorants which are approved for use in pharmacy are, for example, carotenoids or chlorophylls.

Suitable for use as sugars or sweeteners are sucrose, xylitol, D-glucose, sorbitol, mannitol, lactose, aspartame and saccharin-Na, acelsulfam or sodium cyclamate.

The following examples are intended to illustrate the invention in more detail, but without limiting it:

Example 1	mg	**SOLUBLE TABLET**
Selegiline HCL [sic]	10	
$MgCO_3$	96	
$CaCO_3$	248	
Citric acid	522	
Aspartame	4	
Lactose	100	
Aroma	15	
	995	

Example 2	mg	**SOLUBLE TABLET**
Selegiline HCL [sic]	10	
Calcium carbonate	310	
Citric acid	620	
Aspartame	7	
Aroma	10	
Sodium citrate	53	
	1010	

Example 3	mg	**SOLUBLE TABLET**
Selegiline HCl	10	
$CaCO_3$	380	
Citric acid	500	
Sodium cyclamate	7	
Saccharin sodium	1	
Aroma	15	
Yellow 6	1	
	914	

Example 4	mg	**SOLUBLE TABLET**
Selegiline	5	
Calcium carbonate	331	
Citric acid	625	
Aspartame	10	
Aroma	10	
Sodium citrate	19	
	1000	

Example 5	mg	**EFFERVESCENT GRANULES**
Selegiline HCl	5	
$CaCO_3$	410	
Citric acid	600	
Sodium cyclamate	5	
Saccharin sodium	1	
Aroma	20	
Mannitol	152	
Aerosil	2	
Kollidon	3	
Aspartame	2	
	1200	

Example 6	mg	**EFFERVESCENT GRANULES**
Selegiline HCl	10	
$CaCO_3$	357	
Citric acid	522	
Sodium cyclamate	5.7	
Saccharin sodium	0.9	
Aroma	15	
Mannitol	187	
Aerosil	2	
Kollidon	2	
Aspartame	2	
Yellow 6	1	
Sodium citrate	100	
	1204.6	

Example 7	mg	**SOLUBLE TABLET**
Selegiline HCl	5	
$MgCO_3$	100	
$CaCO_3$	320	
Citric acid	450	
Aspartame	3	
Lactose	50	
Aroma	15	
	943	

Example 8	mg	**BUCCAL TABLET**
Selegiline HCl	5	
Calcium carbonate	250	
Citric acid	112	
Aspartame	4	
Aroma	10	
Sodium citrate	30	
	411	

Example 9	mg	**BUCCAL TABLET**
Selegiline HCL [sic]	5	
Calcium carbonate	205	
Citric acid	200	
Sodium cyclamate	2	
Saccharin sodium	0.5	
Aroma	7	
Mannitol	71	
Aerosil	1	
Kollidon	1.3	
Aspartame	1	
	493.8	

Example 10	mg	**EFFERVESCENT GRANULES**
Erythromycin	500	
$CaCO_3$	520	
Citric acid	720	
Sodium cyclamate	7	
Saccharin sodium	1	
Aroma	15	
Maize starch	60	
Yellow 6	1	
	1824	

Example 11	mg	**EFFERVESCENT GRANULES**
Diazepam	5	
$MgCO_3$	100	
$CaCO_3$	320	
Citric acid	450	
Aspartame	3	
Lactose	50	
Aroma	15	
	943	

Patent claims:

1. Solid, rapidly disintegrating administration forms for oral administration in the form of effervescent formulations which comprise an alkali-sensitive active ingredient and an effervescent base consisting of one or more alkaline earth metal carbonates, an organic edible acid and/or an alkali metal salt of citric acid and, if appropriate, pharmaceutically acceptable auxiliaries.

2. Effervescent formulations according to Claim 1 in the form of soluble tablets, granules and sachets which are dissolved in suitable amounts of water before being taken.

3. Effervescent formulations according to Claim 1 in the form of buccal or sublingual tablets which are administered directly into the oral cavity.

4. Effervescent formulations according to Claims 1-3, characterized in that the alkali-sensitive active ingredients which can be used are selegiline, erythromycin, clarithromycin, diazepam, ampicillin and phenobarbital or corresponding pharmaceutically acceptable salts.

5. Effervescent formulations according to Claims 1-4, characterized in that the active ingredient used is preferably selegiline or its pharmaceutically effective salts.

6. Effervescent formulations according to Claim 1, characterized in that the effervescent base used is calcium carbonate and/or magnesium carbonate and citric acid.

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7. Effervescent formulations according to Claims 1 and 6, characterized in that the effervescent base used is preferably calcium carbonate and citric acid.

8. Effervescent formulations according to Claims 1 and 6, characterized in that the effervescent base may comprise up to 15% of sodium citrate.

9. Effervescent formulations according to Claim 1, characterized in that they may comprise vitamin E.

10. Effervescent formulations according to Claim 1, characterized in that, in the case of low-dose alkali-sensitive active ingredients, they may comprise up to 90% of an effervescent base.

11. Effervescent formulations according to Claim 1, characterized in that, in the case of high-dose alkali-sensitive active ingredients, they may comprise from 30% to 70% of an effervescent base.

12. Effervescent formulations according to Claims 1 and 5, characterized in that effervescent minitablets comprise from 5 mg to 10 mg of selegiline HCl and 1200 mg of an effervescent base.

13. Effervescent formulations according to Claims 1 and 5, characterized in that buccal preparations comprise 1-10 mg, in particular from 5 mg to 10 mg, of selegiline HCL [sic] and from 50 to 500 mg of an effervescent base.

14. Effervescent formulations according to Claim 1, characterized in that it may comprise, as additional auxiliaries, colorants, sugars and sweeteners, such as sucrose, xylitol, D-glucose,

sorbitol, mannitol, lactose, aspartame, saccharin-Na, acesulfam or sodium cyclamate.

15. Process for preparing effervescent formulations according to Claim 1, characterized in that calcium carbonate and/or magnesium carbonate and the organic edible acid are granulated separately, where the alkali-sensitive active ingredient is preferably added to the acidic granules and the dried granules are subsequently mixed, or all components of the effervescent formulations are mixed together.

16. Process for preparing effervescent formulations according to Claim 15, characterized in that, to obtain good homogeneity, the alkali-sensitive active ingredient is bound to a neutral carrier substance.

17. Process for preparing effervescent formulations according to Claim 16, characterized in that the carrier substances used are lactose, sucrose, sorbitol, mannitol, starch, pectins or cellulose.

18. Process for preparing effervescent formulations according to Claim 15, characterized in that some of the calcium carbonate has been partially reacted with citric acid to give calcium citrate.

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