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Solid, rapidly disintegrating cetirizine formulations

The present invention relates to solid, rapidly disintegrating effervescent cetirizine formulations in the form of soluble tablets, dispersible tablets or soluble granules.

Cetirizine, a 4-(diphenylmethyl)piperizinoalkoxyacetic acid derivative having antiallergic and spasmolytic action, is described in EP 058 146. EP 294 993, WO 92/02212 and EP 357 369 claim cetirizine formulations for the controlled or continuous release of cetirizine in the form of tablets and capsules. Oral or nasal formulations, for example in the form of cough syrup, are disclosed in WO 94/08551.

Cetirizine solutions for administration at the eye and in the nose are described in EP 605 203. Oral administration forms coated with at least one layer of a volatile aroma, such as menthol (WO 94/25009), and freeze-dried dosage forms having a taste-masking matrix (EP 636 365) can be found in the patent literature.

EP 548 356 claims multiparticulate tablets having a disintegration rate in the oral cavity or on the tongue of less than 60 seconds which comprise the active ingredient in the form of coated microcrystals or microgranules in particular for masking the taste.

WO 95/07070 discloses effervescent granules for producing a pharmaceutical preparation based on calcium carbonate and citric acid, where 5-20 parts by weight of the citric acid are replaced by at least one other edible acid, such as malic acid.

EP 636 364 describes a dosage which dissolves very quickly and which comprises active ingredient particles

which are coated with a taste-masking substance, a water soluble combinable carbohydrate and a binder. After oral administration, the tablet disintegrates in the mouth within 30 seconds, so that the coated active ingredient particles can be swallowed by the patient before the active ingredient is released.
Carbohydrates that are employed are, for example, mannitol, dextrose or lactose, and the taste-masking substance employed is, for example, cellulose acetate or hydroxypropylmethylcellulose.

EP 525 388 claims lozenges or chewable tablets which essentially consist of the dibasic alkali metal and/or alkaline earth metal salt of a tribasic edible organic acid, in particular citric acid, and preferably an edible organic acid, in particular malic acid, which is only partly converted into the alkali metal and/or alkaline earth metal salt, and further auxiliaries. Thus, it is intended to avoid the stale aftertaste of hitherto known lozenges or chewable tablets. In particular the prevention of the chalky taste of lozenges or chewable tablets containing mineral substances is described. However, a reduction of bitter taste was not observed.

The active ingredient cetirizine hydrochloride has a very bitter taste and is not particularly suitable for rapidly disintegrating, solid preparations.
Consequently, effervescent cetirizine formulations are also not known in the prior art.

However, for various reasons there is a need to introduce on the market effervescent pharmaceutical preparations in the form of soluble and dispersible tablets based, in particular, on a calcium-containing base. On the one hand, in particular elderly people may have problems with taking tablets, on the other hand, there are many patients who have difficulties swallowing.

Certain rapidly disintegrating effervescent formulations have the additional advantage that they can conveniently be taken away from home, without fluid intake.

The simultaneous intake of the mineral calcium with antihistamines has great advantages in the treatment of allergies.

Masking the bitter taste of cetirizine causes particular problems. Thus, an aqueous solution of cetirizine hydrochloride has an unpleasant bitter taste.

By adding suitable taste-masking substances, as described, for example, in EP 636 364 or US 5,178,878, the preparation process becomes more complicated. In addition, the dispersibility of microencapsulated active ingredients is considerably reduced.

It is a further disadvantage that, in addition to the actual active ingredient, a large number of auxiliaries are required for preparing such a formulation.

Hitherto, film-coated tablets and oral solutions have been marketed. Here, the film layer serves to mask the bitter taste. The solutions contain large amounts of sorbitol (450 mg of sorbitol per mg of cetirizine).

It is the object of the present invention to provide novel and therapeutically advantageous solid, rapidly disintegrating effervescent formulations of cetirizine.

This object is achieved by the present invention which provides solid, rapidly disintegrating effervescent formulations for oral administration which comprise cetirizine or its pharmaceutically acceptable salts, an effervescent base comprising at least one organic edible acid and/or its salts, alkali metal and/or alkaline earth metal carbonates or bicarbonates and, if appropriate, pharmaceutically acceptable auxiliaries.

By adding water to the soluble or dispersible tablets or soluble granules according to the invention, a solution or suspension is formed, with evolution of CO_2 gas, which can be taken very easily, even by patients who have difficulties swallowing.

Surprisingly, this solution already has a pleasant taste. This becomes evident in particular in the case of calcium-containing effervescent preparations in soluble form.

The rapidly disintegrating tablet can also be administered directly disintegrating in the mouth.

A rapid release of the active ingredient is of particular importance here, to ensure a rapid onset of action.

Effervescent preparations of various active ingredients and vitamins are known in the prior art. These effervescent preparations 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 employed are alkali metal carbonates or alkali metal bicarbonates, such as sodium carbonate or sodium bicarbonate. 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.
Possible 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 monosodium or disodium citrate.
Surprisingly, it has now been found that the sole use of an effervescent system, in particular a system based on calcium, leads to a masking of the taste of the active ingredient cetirizine.

The described complicated coating of the individual crystals of the active ingredient for masking the bitter taste of cetirizine is therefore not necessary. Thus, it is possible, for the first time, to provide effervescent preparations of the substance cetirizine, which is very effective for allergic disorders.

For a person skilled in the art, it was not obvious to develop such solid, rapidly disintegrating cetirizine formulations, since this was rather disencouraged by the bitter taste of cetirizine.
Our own investigations have shown, for example, that 10 mg of cetirizine, dissolved in 60 ml of water, have a bitter taste (Figure 1).
If the formulation according to the invention is dissolved in the same amount of water, the solution has a pleasant taste and can be taken by the patient without any problems, thus considerably improving compliance.

The chemical structure of cetirizine is that of an organic acid, which can lead to stimulation of the H_2 receptors and consequently to an increase in the secretion of gastric juices. The buffer action of the effervescent formulation according to the invention could help to avoid resulting side-effects.

The invention preferably provides effervescent cetirizine formulations having an effervescent base comprising:

a) a mixture of calcium carbonate with an organic edible acid

b) a mixture of calcium carbonate, sodium carbonate, sodium bicarbonate and an edible organic acid

c) a mixture of sodium bicarbonates, sodium carbonate and an edible organic acid.

The soluble or dispersible cetirizine tablet or the soluble granules comprise(s) from 5 mg to 20 mg of cetirizine and 50-5000 mg, preferably 500-3000 mg, of an effervescent base.
The effervescent base preferably comprises 100-500 mg of calcium ions, in the form of calcium carbonate, and 20-1500 mg of citric acid and/or its salts.
In a further preferred embodiment, the effervescent base comprises 50-2000 mg of sodium bicarbonate, 20-200 mg of sodium carbonate and 20-1500 mg of citric acid and/or 20-500 mg of tartaric acid.
A further preferred composition of the effervescent base comprises 50-500 mg of sodium bicarbonate, 20-100 mg of sodium carbonate and 50-750 mg of calcium carbonate and 100-1500 mg of citric acid.

When dispersing the dispersible cetirizine tablet according to the invention, there is likewise the formation of CO_2 which accelerates the disintegration of the tablet even more. However, compared with the soluble tablet, a reduced effervescent activity is observed here.

The soluble/dispersible tablet can be prepared by known processes for preparing effervescent bases. In the segregated-bed process, the acidic components are granulated with a solution of, for example, citric acid in water or polyvinylpyrrolidone in water or alcohol. For the calcium component, it is also possible to admix directly tablettable calcium carbonate. Sodium carbonate/bicarbonate and alkaline earth metal carbonate components can also be granulated separately. The other tabletting auxiliaries are incorporated

homogeneously and the material is tabletted using an appropriate press.
However, it is also possible to obtain the appropriate product by other processes, such as alcoholic granulation of acidic and alkaline components with binder solutions, for example PVP or sugar alcohols. Other granulation processes, such as, for example, topogranulation, have also been described in several instances.

The cetirizine formulations according to the invention may additionally comprise aromas and sweeteners and also known pharmaceutical auxiliaries, such as polyethylene glycol, sodium benzoate, adipic acid and silica.

The formulations according to the invention are to be illustrated in more detail by means of examples, but without limiting them.

Example 1	mg	**EFFERVESCENT TABLET**
Cetirizine HCl	10	
Effervescent base	890	
Mannitol FG	60	
Pharmatose DCL 21	70	
Peppermint aroma	10	
	1040	

The effervescent base comprising:

Citric acid	558.5
Sodium bicarbonate	200
Sodium carbonate	100
Sodium citrate	0.5
Ascorbic acid	25
Saccharin sodium	6
	890

Example 2	mg	**SOLUBLE TABLET**
Cetirizine	10	
Sodium bicarbonate	200	
Citric acid	443	
Ascorbic acid	25	
Sodium carbonate	100	
Saccharin sodium	6	
Mannitol	60	
Lactose	70	
	914	

Example 3	mg	**SOLUBLE GRANULES**
Cetirizine	10	
Sodium bicarbonate	200	
Citric acid	730	
Calcium carbonate	230	
Ascorbic acid	25	
Sodium carbonate	50	
Saccharin sodium	4	
Mannitol	60	
Lactose	70	
	1379	

Example 4	mg	**SOLUBLE TABLET**
Cetirizine	5	
Sodium bicarbonate	200	
Tartaric acid	454	
Sodium carbonate	100	
Saccharin sodium	6	
Mannitol	100	
Lactose	40	
	905	

Example 5	mg	**SOLUBLE TABLET**
Cetirizine	10	
Sodium bicarbonate	186	
Citric acid	491	
Calcium carbonate	130	
Aspartame	6	
Sodium carbonate	35	
Mannitol	120	
	978	

Example 6	mg	**SOLUBLE GRANULES**
Cetirizine	10	
Calcium carbonate	750	
Citric acid	805	
Avicel	42	
Mannitol	625	
Maltodextrin	15	
Aspartame	3	
Aroma	20	
	2270	

Example 7	mg	**DISPERSIBLE TABLET**
Cetirizine	5	
Calcium carbonate	500	
Polyvinylpyrrolidone	20	
Citric acid	270	
Avicel	20	
Maltodextrin	18	
Xylitol	500	
Aspartame	2	
Saccharin sodium	1	
Aroma	15	
Maize starch	60	
	1411	

Example 8	mg	**DISPERSIBLE TABLET**
Cetirizine	10	
Calcium carbonate	500	
Polyvinylpyrrolidone	17	
Citric acid	160	
Avicel	15	
Mannitol	430	
Maltodextrin	18	
Aspartame	2	
Aroma	15	
	1167	

Example 9	mg	**DISPERSIBLE TABLET**
Cetirizine	10	
Calcium carbonate	300	
Citric acid	32	
Avicel	17	
Mannitol	250	
Maltodextrin	6	
Aspartame	1	
Hydrogenated castor oil	21	
Aroma	8	
	645	

Example 10	mg	Chewable **DISPERSIBLE TABLET**
Cetirizine	5	
Calcium carbonate	750	
Ethocel	37	
Aerosil	100	
Mannitol	1130	
Citric acid	123	
Maltodextrin	23	
Avicel	87	
Aspartame	5	
Peppermint aroma	8	
Orange aroma	70	
	2338	

Example 11	mg	Chewable **DISPERSIBLE TABLET**
Cetirizine	10	
Calcium carbonate	750	
Ethocel	37	
Aerosil	100	
Mannitol	1130	
Citric acid	123	
Maltodextrin	23	
Avicel	87	
Aspartame	5	
Peppermint aroma	8	
Orange aroma	70	
	2343	

Example 12	mg	Chewable **DISPERSIBLE TABLET**
Cetirizine	5	
Calcium carbonate	750	
Eudragit E	37	
Aerosil	100	
Mannitol	1130	
Citric acid	123	
Maltodextrin	23	
Avicel	87	
Aspartame	5	
Peppermint aroma	8	
Orange aroma	70	
	2338	

Example 13	mg	Chewable **DISPERSIBLE TABLET**
Cetirizine	10	
Calcium carbonate	750	
Ethocel	37	
Aerosil	100	
Mannitol	1130	
Citric acid	123	
Maltodextrin	23	
Avicel	87	
Aspartame	5	
Peppermint aroma	8	
Orange aroma	70	
	2343	

Patent Claims

1. Solid, rapidly disintegrating effervescent formulations for oral administration which comprise cetirizine or its pharmaceutically acceptable salts, an effervescent base comprising at least one organic edible acid and/or its salts, alkali metal and/or alkaline earth metal carbonates or bicarbonates and, if appropriate, pharmaceutically acceptable auxiliaries.

2. Effervescent formulations according to Claim 1 in the form of soluble tablets, dispersible tablets or soluble granules.

3. Effervescent formulations according to Claims 1 and 2 comprising from 5 mg to 20 mg of cetirizine or its pharmaceutically effective salts and 50-5000 mg, preferably 500-3000 mg, of an effervescent base.

4. Effervescent formulations according to Claims 1 to 3, characterized in that the effervescent base comprises a mixture of sodium bicarbonate, sodium carbonate and an edible organic acid.

5. Effervescent formulations according to Claim 4, characterized in that the effervescent base preferably comprises 50-2000 mg of sodium bicarbonate, 20-200 mg of sodium carbonate and 20-1500 mg of citric acid and/or 20-500 mg of tartaric acid.

6. Effervescent formulations according to Claims 1 to 3, characterized in that the effervescent base comprises a mixture of calcium carbonate and an edible organic acid.

7. Effervescent formulations according to Claim 6, characterized in that the effervescent base preferably comprises 100-500 mg of calcium ions in the form of calcium carbonate and 20-1500 mg of citric acid and/or its salts.

8. Effervescent formulations according to Claims 1 to 3, characterized in that the effervescent base comprises a mixture of calcium carbonate, sodium bicarbonate, sodium carbonate and an organic edible acid.

9. Effervescent formulations according to Claim 8, characterized in that the effervescent base preferably comprises 50-500 mg of sodium bicarbonate, 20-100 mg of sodium carbonate, 50-750 mg of calcium carbonate and 100-1500 mg of citric acid and/or its salts.

10. Effervescent formulations according to claim 1, characterized in that the edible organic acids used are tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, ascorbic acid, maleic acid or citric acid.

11. Effervescent formulations according to Claim 10, characterized in that citric acid is preferably used.

12. Effervescent formulations according to Claim 1, characterized in that said formulations may additionally comprise aromas and sweeteners and also known pharmaceutical auxiliaries, such as polyethylene glycol, sodium benzoate, adipic acid, silica.

Abstract

The present invention relates to rapidly disintegrating effervescent formulations for oral administration which comprise cetirizine or its pharmaceutically acceptable salts, an effervescent base comprising at least one organic edible acid and/or its salts, alkali metal and/or alkaline earth metal carbonates or bicarbonates and, if appropriate, pharmaceutically acceptable auxiliaries.