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(72) Inventeurs/Inventors:
TRITTHART, WOLFRAM, AT;
PISKERNIG, MARIO ANDRE, AT

(73) Propriétaire/Owner:
MEDA PHARMA GMBH & CO. KG, DE

(74) Agent: MARKS & CLERK

(54) Titre : FORMULATIONS SOLIDES ET A DECOMPOSITION RAPIDE CONTENANT DE LA CETIRIZINE
(54) Title: SOLID, QUICK DISSOLVING CETIRIZINE FORMULATIONS

(57) Abrégé/Abstract:
The invention relates to quick dissolving fizzy formulations for oral applications, containing cetirizine or its pharmaceutically compatible salts, a fizzy base consisting of at least one organic, edible acid and/or the salts thereof, alkali or alkaline earth carbonates or hydrogen carbonates and optionally pharmaceutically tolerable adjuvants.

Abstract

The invention relates to quick dissolving fizzy formulations for oral applications, containing cetirizine or its pharmaceutically compatible salts, a fizzy base consisting of at least one organic, edible acid and/or the salts thereof, alkali or alkaline earth carbonates or hydrogen carbonates and optionally pharmaceutically tolerable adjuvants.

Solid, Quick-Dissolving Cetirizine Formulations

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

Cetirizine, a 4-(diphenylmethyl)-piperizino-alkoxy-acetic acid derivative having an antiallergenic and spasmolytic effect is described in EP 058 146. Cetirizine formulations for the controlled or continuous release of cetirizine in the form of tablets and capsules as claimed in EP 294 993, WO 92/02212 and EP 357 369. Oral or nasal formulations, for example in the form of cough syrup, are described in WO 94/08551.

Cetirizine solutions for application to the eye and in the nose are described in EP 605 203. Oral forms of application coated with at least one layer of a volatile flavoring substance such as menthol (WO 94/25009) as well as freezer-dried dosage forms having a taste-masked matrix (EP 636 365) can be found in the patent literature.

In EP 548 356, multiparticular tablets are claimed which have a dissolving rate in the oral cavity or on the tongue of less than 60 seconds which contain the active substance in the form of coated microcrystals or microgranules, in particular to mask the taste.

Effervescent granules for producing a pharmaceutical preparation based on calcium carbonate and citric acid are described in WO 95/07070, wherein 5 - 20 parts by weight of the citric acid are replaced by at least one other edible acid, e.g. malic acid.

A very quickly dissolving dosage form consisting of active substance particles that are coated with a taste-masked substance, a water-soluble combinable carbohydrate and a binder, is described

in EP 636 364.

The tablet dissolves within 30 seconds after the oral application in the mouth, so that the coated active substance particles can be swallowed by the patient before the active substance is released. Mannitol, dextrose or lactose are used, for example, as carbohydrates and cellulose acetate or hydropropyl methyl cellulose as taste-masked substance.

Sucking or chewing tablets are claimed in EP 525 388 which essentially contain the dibasic alkali and/or alkaline earth salt of a tribasic edible organic acid, in particular citric acid, as well as preferably an edible organic acid, in particular malic acid, reacted only partially to form the alkali and/or alkaline earth salt, and other adjuvants. This is to avoid the flat aftertaste of already known sucking or chewing tablets. Especially the prevention of the chalky taste of mineral sucking or chewing tablets is described. However, a decrease in the bitter taste was not observed.

Cetirizine hydrochloride has a very bitter taste as active substance and is not well-suited for quick-dissolving, solid preparations.
Cetirizine effervescent formulations are therefore also not known in the prior art.

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

Certain quick-dissolving effervescent formulations also have the advantage that they can be conveniently taken on the road without the addition of liquid.

The simultaneous addition of the mineral calcium with antihistamines is of great advantage when treating allergies.

Masking the bitter taste of cetirizine causes special problems. Thus, an aqueous solution of cetirizine hydrochloride exhibits an unpleasant bitter taste.
Adding suitable taste-masked substances, as described e.g. in EP 636 364 or US 5,178,878, makes the manufacturing process more complicated. In addition, the dispersibility of micro-encapsulated active substances is clearly rendered more difficult.
It is also disadvantageous that, in addition to the actual active substance, a number of adjuvants are required for the preparation of a formulation of this type.

Currently, film tablets and oral solutions can be found on the market. The film layer is used to mask the bitter taste. The solutions contain large amounts of sorbitol (450 mg sorbitol for 1 mg cetirizine).

The object of the present invention is to provide novel and therapeutically advantageous solid, quick-dissolving effervescent formulations for cetirizine.

This object is solved by the present invention, the object of which is solid, quick-dissolving effervescent formulations for oral application, containing cetirizine or its pharmaceutically tolerable salts, an effervescent base consisting of at least one organically edible acid and/or the salts thereof, alkali and/or alkaline earth carbonates or hydrogen carbonates and optionally

pharmaceutically tolerable adjuvants.

By adding water to the soluble or dispersible tablets or soluble granules of the invention, a solution or suspension is produced while developing CO_2 gas which can be taken very easily, also for patients having difficulties in swallowing.

Surprisingly, this solution already has a pleasant taste. This is especially evident in calcium-containing effervescent preparations in soluble form.

The quick-dissolving tablet can also be dissolved directly in the mouth.

A quick release of the active substance is of special significance in this case in order to ensure a quick onset of the effect.

Effervescent formulations for various active substances and vitamins are known in the prior art. These effervescent forumulations usually contain a CO_2 releasable agent as well as an agent which induces the release of CO_2. Preferably, alkali carbonates or alkali hydrogen carbonatess such as sodium or sodium hydrogen carbonate are used as CO_2 releasable agents.

Edible organic acids or the salts thereof are used as agents to induce the release of CO_2, said acids or salts being present in solid form and capable of being formulated with the active substance and the other adjuvants to form granules or tablets without a premature development of CO_2.
For example, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, ascorbic acid, maleic acid or citric acid are used as edible organic acids.

Pharmaceutically tolerable acidic salts are, for example, salts of polybasic acids present in solid form in which at least one more acid function is present, such as sodium hydrogen or dibasic sodium phosphate or monosodium or disodium citrate.

Surprisingly, it was found that the sole use of an effervescing system, in particular on a calcium base, results in a taste masking of the active substance cetirizine.

Thus, the described, expensive coating of the individual active substance crystals is not required to mask the bitter taste of the cetirizine. As a result, it is for the first time possible to provide effervescent preparations for the substance cetirizine which is especially effective in allergic diseases.

It was not obvious to one skilled in the art to develop solid, quick-dissolving cetirizine formulations of this type since the bitter taste of the cetirizine more likely made this impossible. Our own tests showed, for exmaple, that 10 mg cetirizine, dissolved in 60 ml water, exhibited a bitter taste (Fig. 1).

If the formulation of the invention is dissolved in the same amount of water, the solution is tasty and can be taken by the patient without difficulty, as a result of which the compliance is clearly improved.

With respect to the chemical structure, cetirizine is an organic acid which can lead to a stimulation of the H_2 receptors and thus to an increase in the secretion of gastric juices. The buffer effect of the effervescent formulation of the invention could prevent side-effects resulting therefrom.

According to one aspect of the invention there is provided a solid, effervescent formulation, in rapidly dissolving dosage form for oral administration, which comprises:

(a) cetirizine or a pharmaceutically acceptable salt thereof;

(b) an effervescent base comprising:

(i) at least one of (1) an organic edible acid and (2) a salt thereof,

(ii) at least one of an alkali metal and an alkaline earth metal carbonate and bicarbonate; and

(c) optionally a pharmaceutically acceptable auxiliary ingredient.

Preferably, the invention relates to cetirizine effervescent formulations having an effervescent base consisting of:

a) a mixture of calcium carbonate with an organic edible acid
b) a mixture of calcium carbonate, sodium carbonate, sodium hydrogen carbonate and an organically edible acid
c) a mixture of sodium hydrogen carbonate, sodium carbonate and an organically edible acid.

The cetirizine soluble or dispersible tablet or the soluble granules contain 5 mg to 20 mg cetirizine and 50 - 5000 mg, preferably 500 - 3000 mg, of an effervescent base.

Preferably, the effervescent base contains 100 - 500 mg calcium ions, in the form of calcium carbonate and 20 - 1500 mg citric acid and/or the salts thereof. In a further preferred embodiment, the effervescent base contains 50 - 2000 mg sodium hydrogen carbonate, 20 - 200 mg sodium carbonate and 20 - 1500 mg citric acid and/or 20 - 500 mg tartaric acid.
Another preferred composition of the effervescent base consists of 50 - 500 mg sodium hydrogen carbonate, 20 - 100 mg sodium carbonate and 50 - 750 mg calcium carbonate and 100 - 1500 mg citric acid.

When the cetirizine dispersible tablet of the invention disperses, it also results in a CO_2 formation which accelerates the dissolution of the tablet even more. However, when compared to the soluble tablet, a reduced effervescent activity can be observed.

The soluble/dispersible tablet can be produced according to known methods for producing effervescent bases. In the separate bed process, the acidic components are granulated with a solution consisting, for example, of citric acid in water or polyvinyl pyrrolidone in water or alcohol. Pelletable calcium carbonate can also be added directly for the calcium component. Sodium carbonate/hydrogen carbonate and alkaline earth carbonate components can also be granulated separately. The other pelleting

adjuvants are worked in homogeneously and the mass pelleted on an appropriate press.
However, other processes such as the alcoholic granulation of acidic and alkaline components with binding solutions, e.g. PVP or sugar alcohols, can also result in a corresponding product. Other granulating processes, e.g. topogranulation, have also been repeatedly described.

The cetirizine formulations of the invention can, in addition, contain flavoring agents and sweetening agents as well as known pharmaceutical adjuvants such as polyethylene glycol, sodium benzoate, adipic acid and silicon dioxide.

The formulations of the invention are to be described in greater detail with reference to examples without, however, restricting them.

Example 1	mg	EFFERVESCENT TABLET
Cetirizine HCL	10	
Effervescent base	890	
Mannitol FG	60	
Pharmatose DCL 21	70	
Peppermint flavour	10	
	1,040	

The effervescent base consisting of:

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

Example 2	mg	SOLUBLE TABLET
Cetirizine	10	
Sodium hydrogen carbonate	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 hydrogen carbonate	200	
Citric acid	730	
Calcium carbonate	230	
Ascorbic acid	25	
Sodium carbonate	50	
Saccharin sodium	4	
Mannitol	60	
Lactose	70	
	1,379	

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

Example 5	mg	SOLUBLE TABLET
Cetirizine	10	
Sodium hydrogen carbonate	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	
Flavour	20	
	2,270	

Example 7	mg	DISPERSIBLE TABLET
Cetirizine	5	
Calcium carbonate	500	
Polyvinyl pyrrolidone	20	
Citric acid	270	
Avicel	20	
Maltodextrin	18	
Xylitol	500	
Aspartame	2	
Saccharin sodium	1	
Flavour	15	
Corn starch	60	
	1,411	

Example 8	mg	DISPERSIBLE TABLET
Cetirizine	10	
Calcium carbonate	500	
Polyvinyl pyrrolidone	17	
Citric acid	160	
Avicel	15	
Mannitol	430	
Maltodextrin	18	
Aspartame	2	
Flavour	15	
	1,167	

Example 9	mg	DISPERSIBLE TABLETS
Cetirizine	10	
Calcium carbonate	300	
Citric acid	32	
Avicel	17	
Mannitol	250	
Maltodextrin	6	
Aspartame	1	
Hardened castor oil	21	
Flavour	8	
	645	

Example 10	mg	chewable DISPERSIBLE TABLET
Cetirizine	5	
Calcium carbonate	750	
Ethocel	37	
Aerosil	100	
Mannite	1,130	
Citric acid	123	
Maltodextrin	23	
Avicel	87	
Aspartame	5	
Flavour - Peppermint	8	
Flavour - Orange	70	
	2,338	

Example 11	mg	chewable DISPERSIBLE TABLET
Cetirizine	10	
Calcium carbonate	750	
Ethocel	37	
Aerosil	100	
Mannite	1,130	
Citric acid	123	
Maltodextrin	23	
Avicel	87	
Aspartame	5	
Flavour - Peppermint	8	
Flavour - Orange	70	
	2,343	

Example 12	mg	chewable DISPERSIBLE TABLET
Cetirizine	5	
Calcium carbonate	750	
Eudragit E	37	
Aerosil	100	
Mannite	1,130	
Citric acid	123	
Maltodextrin	23	
Avicel	87	
Aspartame	5	
Flavour - Peppermint	8	
Flavour - Orange	70	
	2,338	

Example 13	mg	chewable DISPERSIBLE TABLET
Cetirizine	5	
Calcium carbonate	750	
Ethocel	37	
Aerosil	100	
Mannite	1,130	
Citric acid	123	
Maltodextrin	23	
Avicel	87	
Aspartame	5	
Flavour - Peppermint	8	
Flavour - Orange	70	
	2,343	

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A solid, effervescent formulation, in rapidly dissolving dosage form for oral administration, which comprises:

(a) cetirizine or a pharmaceutically acceptable salt thereof;

(b) an effervescent base comprising:

(i) at least one of (1) an organic edible acid and (2) a salt thereof,

(ii) at least one of an alkali metal and an alkaline earth metal carbonate and bicarbonate; and

(c) optionally a pharmaceutically acceptable auxiliary ingredient.

2. An effervescent formulation according to claim 1 in the form of soluble tablets, dispersible tablets or soluble granules.

3. An effervescent formulation according to claim 1 or 2, containing 5 mg to 20 mg cetirizine or the pharmaceutically effective salts thereof and 50 - 5000 mg of the effervescent base.

4. An effervescent formulation according to claim 3, containing 500 - 3000 mg of the effervescent base.

5. An effervescent formulation according to any one of claims 1 to 4, wherein the effervescent base comprises sodium hydrogen carbonate, sodium carbonate, or the organic edible acid, or any combination thereof.

6. An effervescent formulation according to claim 5, wherein the effervescent base consists of 50 - 2000 mg sodium hydrogen carbonate, 20 - 200 mg sodium carbonate, 20 - 1500 mg citric acid, or 20 - 500 mg tartaric acid, or any combination thereof.

7. An effervescent formulation according to any one of claims 1 to 4, wherein the effervescent base comprises calcium carbonate or the organic edible acid, or both.

8. An effervescent formulation according to claim 6, wherein the effervescent base contains 100 - 500 mg calcium ions in the form of calcium carbonate, 20 - 1500 mg citric acid, or a salt thereof, or any combination thereof.

9. An effervescent formulation according to any one of claims 1 to 4, wherein the effervescent base comprises calcium carbonate, sodium hydrogen carbonate, sodium carbonate, or the organic edible acid, or any combination thereof.

10. An effervescent formulation according to claim 8, wherein the effervescent base contains 50 - 500 mg sodium hydrogen carbonate, 20 - 100 mg sodium carbonate, 50 - 750 mg calcium carbonate, 100 - 1500 mg citric acid, or a salt thereof, or any combination thereof.

11. An effervescent formulation according to any one of claims 1 to 10, wherein the organic edible acid is tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, ascorbic acid, maleic acid or citric acid, or any combination thereof.

12. An effervescent formulation according to claim 11, wherein the organic edible acid is citric acid.

13. An effervescent formulation according to any one of claims 1 to 12, further containing a flavoring agent, a sweetening agent or a known pharmaceutical adjuvants such as polyethlyene glycol, sodium benzoate, adipic acid, or silicon dioxide, or any combination thereof.

14. An effervescent formulation according to claim 7, wherein said effervescent base comprises from about 100 mg to about 500 mg calcium ions in the form of calcium carbonate, and at least one of (i) from about 20 mg to about 1500 mg citric acid, and (ii) at least one citrate.

15. An effervescent formulation according to claim 14, wherein said effervescent base comprises a mixture of calcium carbonate, sodium bicarbonate, sodium carbonate, or the organic edible acid, or any combination thereof.

16. An effervescent formulation according to claim 15, wherein said effervescent base comprises from about 50 mg to about 500 mg sodium bicarbonate, from about 20 mg to about 100 mg sodium carbonate, from about 50 mg to about 750 mg calcium carbonate, and at least one of (i) from about 100 mg to about 1500 mg citric acid and (ii) at least one citrate.

17. An effervescent formulation according to claim 1 or 2, wherein said effervescent base comprises at least one of (i) an organic edible acid and (ii) a salt thereof, said acid being at least one of tartaric acid, malic acid,

fumaric acid, adipic acid, succinic acid, ascorbic acid, maleic acid, and citric acid.

18. An effervescent formulation according to claim 1 or 2, wherein said effervescent base comprises an organic edible acid or a salt thereof, wherein said organic acid is citric acid.

19. An effervescent formulation according to any one of claims 1 to 12, further comprising one or more of an aroma, sweetener, and a pharmaceutical auxiliary ingredient.

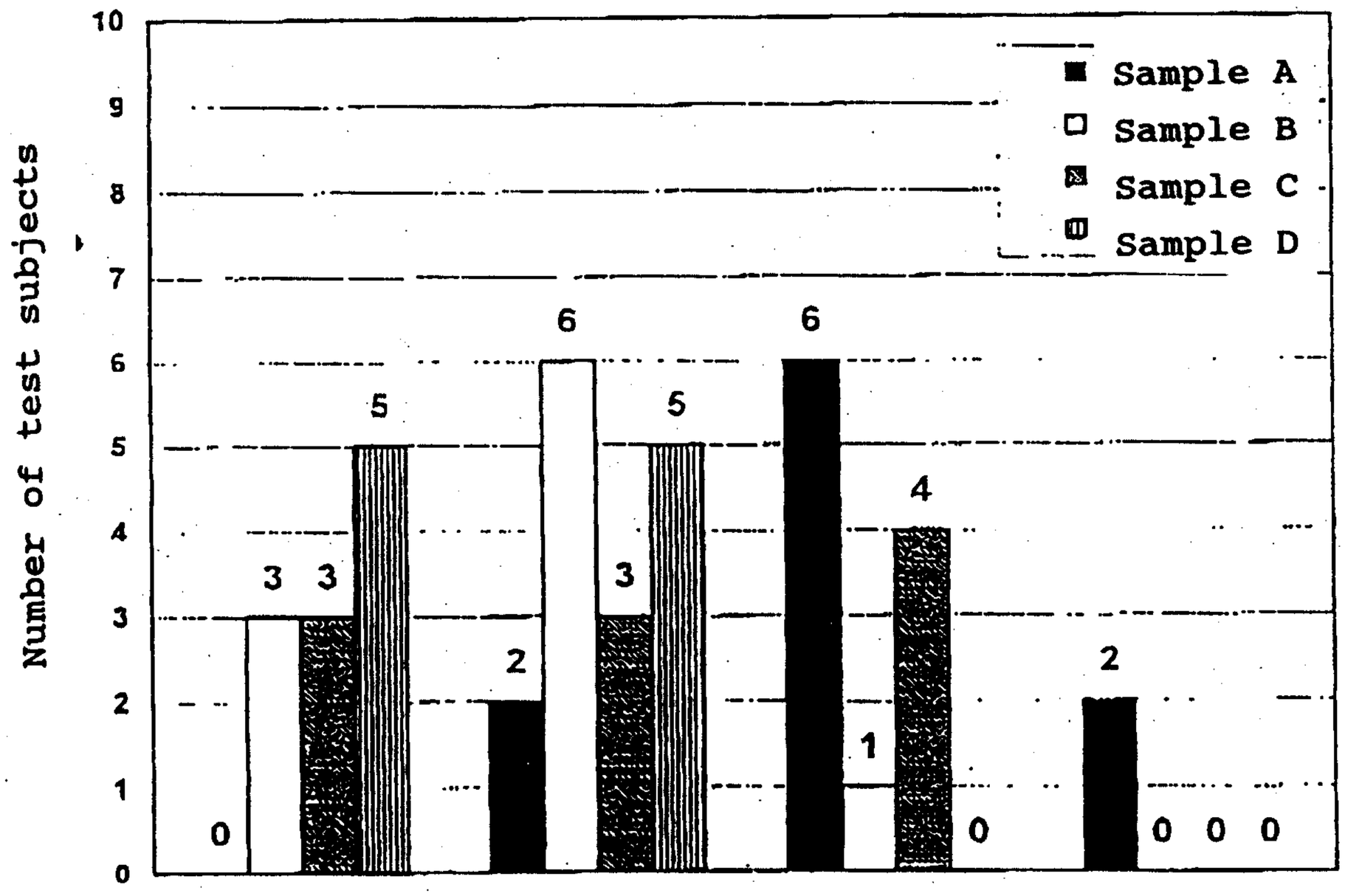
20. An effervescent formulation according to claim 19, wherein said auxiliary ingredient is polyethylene glycol, sodium benzoate, adipic acid, or silica, or any combination thereof.

Figure 1

CONSUMER TASTE TEST
CETIRIZINE Formulations

Formulations tested:

Sample A = 10 mg cetirizine + 60 ml water
Sample B = 10 mg cetirizine + "sodium base" + 60 ml water
Sample C = 10 mg cetirizine + "calcium base" (flavour 1) + 60 ml water
Sample D = 10 mg cetirizine + "calcium base" (flavour 2) + 60 ml water



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