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(54) Titre : SYSTEMES EFFERVESCENTS UTILISANT DES AGENTS D'ENDUCTION FORMES PAR LA REACTION DES ELEMENTS CONSTITUANTS
(54) Title: EFFERVESCENT SYSTEMS USING REACTION DOPING AGENTS

(57) Abrégé/Abstract:

An effervescent tablet is based on an effervescent system composed of carrier crystals of at least one solid, edible organic acid, of one or more components which form gas by reacting with the acid and producing salts, and of one or more salts produced from the acid and the gas-forming component. The carrier crystals are coated firstly with a layer of a different acid and secondly with a layer of a (preferably acid) salt derived from at least one of the two acids. Between ten and forty, and in particular between ten and twenty percent by weight of the total quantity of acids and gas-forming components used are in the form of the salts (preferably acidic salts). Carrier crystals consist in particular of zitric, malic, or tartaric acid, monosodium zitrate, and/or ascorbic acid. The first layer can contain d-gluconic acid-delta lactone and should be coated with nitric acid, malic acid and/or tartaric acid. This is covered with a layer of a monosalt formed by the reaction between part of the total quantity of gas-forming component and at least one of the acids used.

ABSTRACT OF THE DISCLOSURE

An effervescent tablet is based on an effervescent system composed of carrier crystals of at least one solid, edible organic acid, of one or more components which form gas by reacting with the acid and producing salts, and of one or more salts produced from the acid and the gas-forming component. The carrier crystals are coated firstly with a layer of a different acid and secondly with a layer of a (preferably acid) salt derived from at least one of the two acids. Between ten and forty, and in particular between ten and twenty percent by weight of the total quantity of acids and gas-forming components used are in the form of the salts (preferably acidic salts). Carrier crystals consist in particular of zitric, malic, or tartaric acid, monosodium zitrate, and/or ascorbic acid. The first layer can contain d-gluconic acid-delta lactone and should be coated with zitric acid, malic acid and/or tartaric acid. This is covered with a layer of a monosalt formed by the reaction between part of the total quantity of gas-forming component and at least one of the acids used.

EFFERVESCENT SYSTEMS USING REACTION DOPING AGENTS

The invention relates to an effervescent tablet according to the preamble of claim 1, as can be prepared, for example, by the process according to WO 88/00009. The composition and preparation of effervescent systems known to date are based on a mixture of organic, edible acids with carbon dioxide-forming alkalis and/or alkaline earths which are granulated together or reacted together, dried and compressed with active substances. In this process, all substances are present in more or less powdered or finely crystalline form, the properties of the resulting product corresponding to the statistical cross-section of the components of the mixture.

In the known effervescent system stated at the outset, the carrier crystal has a reactive core of, for example, citric acid on the inside but monosodium citrate on the outside, as formed ad hoc by the individual reaction. The particle thus has the chemical properties of monosodium citrate on the outside; on the inside, however, it still consists of citric acid. Thus, when the first layer of monosodium citrate is dissolved away on contact with water, there is a vigorous reaction with the natural citric acid present within the core.

For various reasons, it is desirable to put pharmaceutical formulations on the market in the form of effervescent tablets: on the one hand, many patients have difficulties in swallowing, particularly in the case of large tablets; on the other hand, many active substances should be taken with at least some water, even if only a modest amount, so that they do

not come into contact in concentrated form with the gastric mucus membrane. There have been two problems with effervescent tablets to date:
On the one hand, there are many active substances which are themselves moisture-sensitive or react with one of the components of the effervescent system when moisture is present and thus cannot be readily stored, particularly because the citric acid generally used virtually always has a small residual moisture content of 0.2-0.4%. It has therefore been necessary to date to rely in general on very expensive, moisture-resistant packagings.

Even very readily soluble active substances present problems because they rapidly form concentrated solutions when they begin to dissolve in water and thus hinder or slow down the reaction of the effervescent components with one another.

On the other hand, very large effervescent tablets having a total weight of in general 3-4 g have been required to date, particularly for large active substance doses of, for example, 1 g per dose, for achieving acceptable dissolution times, which tablets in turn require large amounts of liquid for dissolution; however, many patients do not readily consume such large amounts of liquid. Moreover, they are expensive with regard to both material required and packaging and may introduce large amounts of undesirable sodium ions into the patient's body. Finally, large effervescent tablets often have a buffer capacity or acid-consuming capacity which is undesirably high for certain applications.

A further difficulty arises from the necessity of using binders in order in the first place to be able to compress the effervescent mixtures to give stable, sufficiently hard tablets. Such binders, such as, for example, sorbitol, polyvinylpyrrolidone, etc., increase the hardness of effervescent tablets but considerably slow down the disintegration and make the tablets additionally moisture-sensitive.

Attempts have already been made to increase the shelf life of sensitive active substances in effervescent tablets by using, for example, anhydrous potassium carbonate (U.S. Patent 3,136,692) as the gas-forming component or monosodium citrate (DE-A1 3920626 or U.S. Patent 4,689,218) as the acidic component; however, such tablets then require a very long time for dissolution because potassium carbonate itself reacts with citric acid much more slowly than, for example, sodium bicarbonate, or the latter reacts much more slowly with monosodium citrate than with citric acid.

For freely soluble active substances, a combination of disintegration agents with the effervescent system had also been proposed (WO 91/07174), because a concentrated active substance solution formed on initial contact of the table with water without disintegration agents hinders the reaction of the effervescent components with one another. This also permits the production of smaller total tablet weights; unfortunately, here too there is the undesirable effect that the solutions become cloudy owing to the disintegration agent.

The WO 88/00009 stated at the outset has already proposed improving the shelf life and reactivity of an effervescent tablet by inducing a slight initial reaction of the acidic and the carbonate components of the effervescent system, resulting - as mentioned - in an effervescent tablet according to the preamble of claim 1. However, it has been found that the problems just described are only very inadequately solved in this way.

It is therefore the object of the invention to provide an effervescent tablet which has a good shelf life even with pharmaceutical active substances which are moisture-sensitive and/or tend to react with at least one of the components of the effervescent system and/or are freely soluble, and which permits the preparation of smaller effervescent tablets, for example of only 1.5 to 2 gram for up to 1 gram of pharmaceutical active substance, which dissolve in as short a time as possible, the resulting solution being very clear. Finally, the system should also be capable of being readily compressed without the use of dissolution-inhibiting binders and, for certain applications, it should be possible to provide effervescent tablets having a very low acid-consuming capacity.

These objects are satisfactorily achieved in a surprising manner, according to the invention, by the measures described in the defining clause of claim 1. Further and improved embodiments of the invention are described in the defining clauses of the dependent claims.

The present invention relates to the preparation of effervescent particles having an individual structure, where the internal and external properties of the effervescent particles can be quasi-programmed by means of various novel measures.

The basic requirement for this novel technology is the use of carrier crystals of edible, organic acids, because these crystallize in regular form, are available in suitable crystal sizes and, owing to their physical properties, are particularly suitable for doping. The more freely soluble an acid, the more readily can the crystals be wet and subsequently covered or passivated. However, the acid must in each case be present in excess and in suitable particle size so that actually only the surface is wet and the formation of any pasty mass, which could not be further processed according to the invention, is avoided.

Carbonates and bicarbonates are not suitable carrier crystals because they cannot be doped; they repel water.

In one aspect, the invention provides an effervescent tablet containing at least one pharmaceutically active substance and an effervescent system. The effervescent system comprises at least one solid, edible, organic acid, at least one alkali metal carbonate or bicarbonate as a gas-forming component, and at least one alkali metal salt of the acid. There are at least two layers applied to carrier crystals comprising the at least one acid. The first layer contains at least one solid, edible, organic acid different from the crystal acid, or contains the alkali metal salt of the different acid, or contains both. The second layer contains at least one alkali metal salt of the at least one acid, or of the different acid, or of both.

In another aspect, the invention provides a process for the preparation of an effervescent system comprising the steps of: (i) wetting carrier crystals of at least one solid, edible, organic acid with a liquid selected from the group consisting of water, a solution of an acidic component of the effervescent system, and a solution of gluconic acid delta lactone; (ii) admixing the wet carrier crystals with at least one compound in finely divided form to cover the surface of the carrier crystals, wherein the at least one compound is selected from the group consisting of an edible organic acid different from the carrier crystal acid and a gas-forming component, the gas-forming component being allowed to partially react to a salt of an edible organic acid; (iii) further adding at least one solid, gas-forming component, at least part of which gets anchored by partial reaction to the surface of the wet carrier crystals; and (iv) drying the covered carrier crystals to yield effervescent granules.

The simplest case is when defined citric acid crystals, having a crystal size of 0.1 to 0.6 mm, in particular 0.2 to 0.4 mm, are wet with water or with a buffer solution (WO 88/00009) or with a concentrated gluconic acid delta-lactone solution (US-A-4678661, Example 4) and allowed to react with alkaline earth metal carbonates, and this reaction is stopped at a certain time. This gives individual, effervescent particles which are already relatively resistant to moisture but are not suitable for all active substances or for all possible variations. If in fact the reaction is continued too far, i.e. if, for example, more than 5 or 10% of the acid surface is converted into alkali metal salts, the effervescent system becomes too slow.

Example 4 of the stated US-A-4678661 relates to a different object (it is intended to prepare a low-sodium effervescent tablet - and not a particularly small one), to a different technical measure for achieving this object (the first layer of a gas-forming component applied always comprises calcium carbonate which is absent in the present invention) and to a different result (standard effervescent tablets of 3.5 or 4 g - and not of about 2 gram or even less, according to the invention - are prepared).

According to the invention, it has now been found that the system can be accelerated in the reaction if foreign acids are simultaneously incorporated in the surface. Thus, for example, alkali metal salts of a plurality of acids are formed in a plurality of layers, preferably 10 to 40% of the effervescent system reacting to form the salt - in particular only the monosalt.

Finally, owing to the possibility of preparing small effervescent tablets, the invention also makes it possible to keep the content of sodium ions low and to prepare effervescent tablets having only a very low acid-consuming capacity of, for example, ≤ 5 meq.

Thus, malic acid, tartaric acid or gluconic acid delta-lactone can be incorporated, for example, into a citric acid crystal surface, preferably heated to temperatures between 50 and 60°C, by means of, in particular, very concentrated, aqueous, alcoholic or aqueous alcoholic solutions, and this crystal surface doped with foreign acids can then be allowed to react with alkali metal carbonates and/or alkali metal bicarbonates and optionally - in particular in the case of gluconic acid delta-lactone - with further acids having a different pK value.

The way in which these systems are prepared, whether, for example, malic acid and citric acid - both as carrier crystals - are used and either a citric acid solution or gluconic acid delta-lactone solution is then applied and the bicarbonate is then allowed to react, depends on the physical and chemical properties of the active substances to be processed. However, the doping with a foreign acid or with the gluconic acid delta-lactone and the conversion to the monosalt always remain. The ratios of the acids to one another are usually, for example in the case of citric acid to malic acid, about 8:1 but may also be 3:1.

Such systems dissolve substantially more rapidly because, owing to the different pH and pK values of the two or more acids, the formation of a reaction-retarding buffer solution during the dissolution is continuously disturbed locally and thus prevented. In the case of the effervescent particles according to the invention, the lattice defect which causes this is already present and does not have to form, as would be the case, for example, with mixtures of two different acids, occasionally used in the past.

For example, an equilibrium pK of 3.14 is established at the boundary layer of a citric acid crystal; if, however, another acid having a higher or lower pK is present there in the lattice, the equilibrium is disturbed; no stable buffer forms, and the individual particles - and hence the tablet - dissolve more rapidly. However, both acids must have partially reacted; if this is the case for only one acid, then the tablet may not have a sufficiently long shelf life.

In the case of a tribasic, moderately weak acid, the pH depends on the pK according to a fourth degree equation; in this case, different pH values or buffers form at various points.

The system can be further changed if, for example, it is desired to incorporate active substances which are sensitive to alkalis. In this case, the alkaline surface formed by reaction of the carrier crystal with alkali metal or alkaline earth metal carbonates can be further acidified by applying, in a further step, acid solutions or at least powdered acid, in particular the slightly soluble fumaric acid. In this case too, an intermediate layer of gluconic acid delta-lactone may improve coherent layer formation of the acid.

Since carrier systems prepared in this manner are as such extremely stable, they are also very moisture-insensitive because the acid surface is quasi-passivated; they do not react with atmospheric humidity but react only when water is present.

While systems of the prior art begin to react substantially with effervescence at 90% atmospheric humidity after only 5 to 10 minutes, systems having the composition according to the invention are stable for up to 10 hours at 90% atmospheric humidity, without exhibiting bubbles or reaction.

The gluconic acid delta-lactone is particularly readily soluble (1 part of gluconic acid delta-lactone in 0.5 part of water), especially at relatively high temperatures. This lactone is hydrolysed by water to form gluconic acid, probably particularly when it comes into contact with alkalis in aqueous solution. It also acts as a neutral granulating aid for precoated carrier crystals, for example when mixed with sodium carbonate; in contact with water, in particular in the presence of alkalis, it is converted into reactive gluconic acid.

If the reaction of the components of the effervescent system is now continued in the above-mentioned manner (particularly when the salt being formed, for example monosodium citrate, is produced in anhydrous form, as occurs, for example, when the reaction takes place in vacuo), the passivation results in a long shelf life, not only owing to the masking of the citric acid but also due to the "internal" moisture consuming capacity of the resulting anhydrous salt.

In the process according to the invention, alkali metal carbonates or alkali metal bicarbonates are allowed to react on the surface of the carrier particles to a considerable extent, preferably to an order of magnitude of 10 to 40%. In the preparation of the effervescent base, a reaction loss of 5 to 10%, but not more than 15%, may be expected, the resulting CO_2 and water being removed by means of a vacuum. This reaction loss of 5 or 10% of the total amount of citric acid, bicarbonate and carbonate used means that, at a reaction loss of 5%, 16.8% and, at a reaction loss of 10%, 33.5% of the total amount of effervescent components used are present as monocitrate. In fact, this would in general lead to slowly dissolving effervescent tablets, since the sodium salt formed as a result acts as a buffer system and slows down the dissolution, but not when, according to the invention, foreign acids have been incorporated.

If, for example, a concentrated solution of 100 parts by weight of malic acid is applied to 900 parts by weight of a citric acid carrier, preferably to citric acid crystals having a particle size of 0.1 to 0.6 mm, and this malic acid solution is allowed to penetrate into the surface of the citric acid at elevated temperatures, for example at 60°C, and if 10 to 20 parts by weight of sodium bicarbonate powder are then applied to this surface and are allowed to react until gas evolution ceases, then the remaining amount of sodium bicarbonate, for example 400 parts by weight, can furthermore be allowed to undergo partial reaction with still moist and accordingly tacky material and can be dried.

If this system is compressed to give tablets, hardnesses of 12 to 20 kp are obtained at a tablet diameter of 18 to 20 mm, the dissolution rate being about 30 to 40 seconds.

The achievable unusual hardnesses have a physical explanation: the crystal lattice of the carrier acid is disturbed at the surface by the applied concentrated second acid, a surface melting point depression resulting. This crystal defect is further increased if alkali metal ions are introduced into this surface mixture by reaction. It has been found that carrier acid crystals treated in this manner at the surface have extremely high binding forces on compression of the tablets, said forces also making it possible to compress active substances which are difficult to press and to achieve sufficient tablet hardnesses even without further binders. In such a system, it is therefore possible to dispense with every binder. On the other hand, this system nevertheless permits the use of pharmaceutical fillers or excipients, such as, for example, sucrose, sorbitol, mannitol or the like, if they are desired for certain reasons, for example also for reducing the moisture sensitivity of the effervescent tablets, without substantially increasing the dissolution times of the tablets as a result. Finally, the inert filler prevents the generally undesired interaction of the active substance with reactive components of the effervescent system.

The rapid dissolution of such systems arises for two reasons:

1.) The alkali metal bicarbonate or carbonate particles are closely associated with the reacted surface of the acid crystals, so that, after drying, a transition layer from pure acid crystals through the reaction layer to the pure alkali metal carbonate or bicarbonate forms. If such a system enters water, the formation of a buffer system will occur in the case of the presence of particularly large particles of an acid in the binding layer alone, said buffer system retarding the further reaction between inner and outer layers. In many commercial effervescent tablets, it is possible to observe that, after the initial dissolution of the tablet, a core remains which now reacts further only very slowly. This is because the resulting salt solution, for example sodium citrate solution, acts as a buffer between the particles of the effervescent tablet and hinders their further reaction.

2.) The resulting buffer solution is always disturbed by virtue of the fact that carrier particles of different sizes dissolve at different rates and/or different acids having different pH or pK values hinder the formation of a static buffer. The pH in the boundary layers is continuously changed and disturbed since two or more acids having different pK values influence one another.

The system can be further improved if, after moistening by means of, for example, malic acid solution, the citric acid is additionally covered with a powdered third acid, preferably with at least one less moisture-sensitive compound, such as, for example, tartaric acid, fumaric acid or adipic acid. This structure, too, is then allowed partially to react with alkali metal carbonates or alkali metal bicarbonates, sodium citrates, sodium maleates, etc. forming in the interior of the system, while sodium fumarate, sodium adipate or sodium tartrate, which are generally very particularly insensitive to atmospheric humidity, form on the outer shell of the particle. These systems, too, exhibit rapid disintegration after a short time in water and are therefore extremely suitable for mixing with various active substances.

It is true that in principle any solid, edible, organic acid can be used as a carrier crystal. However, citric acid is preferred; to use predominantly tartaric acid would be too expensive; malic acid alone as carrier crystals requires cooling of the granules before further processing, which means an additional step in production.

This structure consisting of two or three edible acids is then caused to undergo a partial reaction with alkali metal carbonates and then covered with further amounts of alkali metal carbonate and/or alkali metal bicarbonates. In this procedure, only some of the sodium bicarbonate, for example, is added and is reacted to give monosodium citrate until no further gas is evolved. Only then is the remaining sodium bicarbonate and/or potassium bicarbonate added and bound to the surface by partial reaction (partial conversion into the monocitrate or monomaleate or monotartrate). This results in a very wide range of alkali metal salts of two or three different organic acids, accounting for 5 to 15% of the total effervescent system.

Although it is not essential to apply the bicarbonate in two parts, this facilitates the process since, by using a certain amount of sodium bicarbonate which is allowed to react completely to form monosodium citrate, the reaction can be more easily controlled and can be allowed to take place in a more defined manner than is possible with the use of the total amount of the alkalis by means of a partial reaction only. The amount of the alkali metal bicarbonate or carbonate reacted with acid is between 2 and 20%, calculated in relation to the total amount of the alkalis used. On average, 5 to 10% of the alkalis used are reacted in a first step. In contrast, only 2% of the alkalis used are reacted in the first step in the subsequent Example 8 (paracetamol), owing to the fact that a very large amount of sodium bicarbonate is used here, whereas almost 20% are reacted in the subsequent Example 5 (minoxidil). This is due to the active substance on the one hand and to the pH on the other. However, it is also entirely possible to double the amount of bicarbonate in the first step in the paracetamol example.

More alkalis than are required for the formation of the monosalt are anyway preferably present, especially in those cases where the pH is to be above that of monosodium citrate, which is 3.9 to 4.15; in solution, effervescent tablets should have a pH of 4.3 to 4.5 or even more.

Finally, in the case of alkali-sensitive active substances, the granules may furthermore be moistened by means of a gluconic acid delta-lactone solution and then covered with either citric acid or fumaric acid in order to obtain an acidic layer on the outside. In other cases, granulation is finally effected with gluconic acid delta-lactone and anhydrous sodium carbonate. In the case of substances which are not alkali-sensitive, the latter step, the addition of gluconic acid delta-lactone solution and the final covering with citric acid, can be omitted.

The Examples which follow relate to three systems which differ fundamentally from one another. Either the active substance is alkali-sensitive and the sodium bicarbonate must be very firmly bound to the citric acid by partial reaction (these include acetylcysteine, captopril (where the base is additionally covered with citric acid) and minoxidil) or the active substances are especially moisture-sensitive (these include ambroxol, ranitidine and cimetidine). Active substances which have to be present in a small tablet in very large amounts are sucralfate, ascorbic acid, arginine aspartate and mesna.

Effervescent systems for arginine aspartate and sucralfate, which are neutral substances, do of course have a slightly different composition compared with paracetamol, which is alkaline. Aspirin™, which has an acidic pH, is in contrast to this.

Particularly with the use of vacuum mixing or granulating drums, the process according to the invention makes it possible exactly to tailor or even to preprogram effervescent systems to the particular active substance and its amount and optionally even to allow the individual steps to take place under computer control.

Example 1 (Acetylcysteine):

200 mg of the active substance acetylcysteine are included in a 1.3 g tablet. The acetylcysteine is sensitive to alkalis and is converted by alkaline oxidation (interaction with, for example, sodium bicarbonate; it is relatively stable to sodium carbonate) into the unstable dimer. In order to prevent this, the sodium bicarbonate is very strongly bound to the citric acid by reaction and partial conversion into sodium citrate, in order to ensure that free sodium bicarbonate, which may interact with the acidic acetylcysteine, is present in as small amount as possible.

Parts:	379	Crystallized citric acid
	100	Malic acid
	105	Citric acid powder
	20	Sodium bicarbonate I
	180	Sodium bicarbonate II
	100	Sodium carbonate
	6	Gluconic acid delta-lactone for solution
	884	
	200	Acetycysteine
	156	Additives
	1240	

Process: Heat citric acid and malic acid to 60°C and moisten with 6 ml of a gluconic acid delta-lactone solution (10 parts of gluconic acid delta-lactone, 5 parts of water). Add sodium bicarbonate I and allow to react to give monosodium citrate; then allow sodium bicarbonate II to undergo partial reaction (partial conversion to the citrate). Add citric acid powder and cover the surface by partial reaction. Add sodium carbonate and allow to undergo partial reaction and finally dry in vacuo. This effervescent base is mixed with 200 parts of acetylcysteine and with corresponding fillers, aromas and sweeteners.

Example 2 (Acetylcysteine):

Parts	
275	Crystallized citric acid
45	Tartaric acid
75	Citric acid powder
20	Sodium bicarbonate I
240	Sodium bicarbonate II
138	Sodium carbonate
12	Monosodium citrate in 30% aqueous solution
805	
600	Acetylcysteine
215	Additives
1620	

Process: Heat crystallized citric acid and tartaric acid to 50°C; allow monosodium citrate solution to penetrate, and cover with citric acid powder; then add sodium bicarbonate I and react to give monosodium citrate; then add the remaining sodium bicarbonate and allow to undergo partial reaction (partial conversion to the citrate); finally add sodium carbonate and allow to undergo partial reaction. 600 parts of acetylcysteine and additives, aromas and sweeteners are added to these base granules.

Example 3 (Ambroxol):

The heat-sensitive and moisture-sensitive ambroxol is bound by means of gluconic acid delta-lactone solution to a highly passivated and hence insensitive base comprising carrier crystals of citric acid and tartaric acid.

Parts	
515	Crystallized citric acid
170	Tartaric acid
25	Sodium bicarbonate I
325	Sodium bicarbonate II
60	Sodium carbonate
6	Malic acid for solution I
1101	
30	Ambroxol HCl
244	Additives to
1375	

Process: Heat crystallized citric acid and tartaric acid to 60°C and moisten with 8 ml of 60% malic acid solution. Allow sodium bicarbonate I to react until monosodium citrate is formed, and then allow sodium bicarbonate II to undergo partial reaction (partial conversion to citrate). Add sodium carbonate, allow to undergo partial reaction and dry in vacuo. Mix the resulting granules with ambroxol HCl and the additives (sweetener, aroma) and compress to give tablets.

Example 4 (Captopril):

Owing to is chemical structure, captopril is even more highly sensitive than acetylcysteine to alkaline substances, under the influence of which it forms the unstable dimer. Here, binding the bicarbonates to the citric acid is not in itself sufficient, and the effervescent base must also be passivated by a layer of powdered citric acid or by means of citric acid solution or gluconic acid delta-lactone solution.

Parts	
250	Crystallized citric acid
55	Monosodium citrate
67	Malic acid
63	Fumaric acid
11	Sodium bicarbonate I
173	Calcium carbonate
36	Sodium carbonate
10	Gluconic acid delta-lactone
665	
25	Captopril
110	Additives
800	

Process: Heat crystallized citric acid, monosodium citrate and malic acid to 60°C. Moisten with 10 ml of gluconic acid delta-lactone solution (10 parts of gluconic acid delta-lactone, 5 parts of water). Add sodium bicarbonate I and allow to react until monosodium citrate forms; then add sodium carbonate and calcium carbonate and allow to react; then add fumaric acid powder and cover the surface by partial reaction; then dry in vacuo. This base is mixed with 25 parts of captopril and the additives, such as, for example, sweeteners, aromas and any fillers.

Example 5 (Minoxidil):

Parts	
243	Crystallized citric acid
80	Malic acid
120	Citric acid powder
39	Sodium bicarbonate I
61	Sodium bicarbonate II
79	Potassium bicarbonate
70	Sodium carbonate
10	Gluconic acid delta-lactone for solution
702	
10	Minoxidil
38	Additives
750	

Process: Heat crystallized citric acid and malic acid to 60°C and moisten with 10 ml of gluconic acid delta-lactone solution (10 parts of gluconic acid delta-lactone to 5 parts of water); add sodium bicarbonate I and allow to react until monosodium citrate forms. Then add sodium bicarbonate II and potassium bicarbonate and allow to under partial reaction (partial conversion to the citrate). Then add citric acid powder and cover the surface by partial reaction. Finally add sodium carbonate and allow to undergo partial reaction and finally dry in vacuo. This effervescent base is mixed with 10 parts of minoxidil and with the additives (for example, sweeteners and aroma).

Example 6 (Ranitidine):

Parts	630	Crystallized citric acid
	210	Tartaric acid
	210	Citric acid powder
	370	Monosodium citrate
	40	Sodium bicarbonate I
	460	Sodium bicarbonate II
	100	Sodium carbonate
	16	Gluconic acid delta-lactone for solution
	2036	
	170	Ranitidine HCl
	294	Additives
	2500	

Process: Heat crystallized citric acid, tartaric acid and monosodium citrate to 60°C. Moisten with 16 ml of a gluconic acid delta-lactone solution (10 parts of gluconic acid delta-lactone, 5 parts of water). Add sodium bicarbonate I, which is converted completely into monosodium citrate.

Then allow sodium bicarbonate II to undergo partial reaction (partial conversion to the citrate). Add citric acid powder and cover the surface by partial reaction. Finally allow sodium carbonate to undergo partial reaction and dry in vacuo. This effervescent base is mixed with 170 parts of ranitidine HCl and corresponding additives, such as sweetener and aroma.

Example 7 (Cimetidine):

200 mg of active substance are included in a 2.3 g tablet:

Parts	
706	Crystallized citric acid
200	Malic acid
250	Citric acid powder
16	Sodium bicarbonate I
462	Sodium bicarbonate II
102	Sodium carbonate
6	Citric acid in 50% aqueous solution
1742	
200	Cimetidine
368	Additives
2310	

Process: Heat crystallized citric acid and malic acid to 60°C, moisten with 6 ml of 50% citric acid solution, add sodium bicarbonate I and allow to react to give monosodium citrate. Then allow sodium bicarbonate II to undergo partial reaction (partial conversion to the citrate). Cover the surface by partial reaction with citric acid powder; finally allow sodium carbonate to undergo partial reaction and dry in vacuo. This effervescent base is mixed with 200 parts of cimetidine and corresponding additives (fillers, aromas and sweeteners).

Example 8 (Paracetamol):
500 mg of paracetamol can be incorporated, according to the invention, in a 2.74 g tablet with good dissolution properties.

The problem in the case of the paracetamol effervescent tablet is that the paracetamol is alkaline and the preferred pH of the ready-to-drink solution is about 6, so that an excess of alkaline substance, such as bicarbonate or carbonate, prevents rapid dissolution, since a relatively small amount of citric acid is present and hence the formation of an active substance core which is poorly soluble is promoted. By means of the novel granulating principle, it is possible to overcome these disadvantages.

Variant I

Parts	
765	Crystallized citric acid
150	Malic acid
20	Sodium bicarbonate I
913	Sodium bicarbonate II
150	Sodium carbonate
25	Gluconic acid delta-lactone for solution I
2023	
500	Paracetamol
50	Gluconic acid delta-lactone for solution II
167	Additives
2740	

Variant II

Parts	
415	Malic acid
500	Crystallized citric acid
20	Sodium bicarbonate I
913	Sodium bicarbonate II
150	Sodium carbonate
25	GDL for solution I
2023	
500	Paracetamol
50	GDL for solution II
167	Additives
2740	

Process: Heat crystallized citric acid and malic acid to 50°C and moisten with 25 ml of gluconic acid delta-lactone solution (10 parts of gluconic acid delta-lactone to 5 parts of water) (the citric acid is doped); allow sodium bicarbonate I to react to give monosodium citrate; then allow sodium bicarbonate II to undergo partial reaction (partial conversion to the citrate); then allow sodium carbonate to undergo slight partial reaction. Then add paracetamol. Granulate with 50 ml of gluconic acid delta-lactone solution (10 parts of gluconic acid delta-lactone to 5 parts of water). Then dry in vacuo. Mix the base granules obtained with corresponding additives, such as sweeteners and aromas.

Example 9 (Acetylsalicylic acid):

A 2.6 g tablet contains 500 mg of acetylsalicylic acid and, in order to achieve a reduced sodium content, also potassium salts and calcium salts as alkalis. Since the acidic aspirin tends to interact with the alkali metal carbonates, the base was covered with citric acid.

Parts	
259	Crystallized citric acid
130	Crystallized malic acid
264	Citric acid powder
15	Sodium bicarbonate I
466	Sodium bicarbonate II
46	Calcium carbonate
137	Potassium bicarbonate
132	Potassium carbonate
42	Sodium carbonate
27	Gluconic acid delta-lactone for solution
1518	
500	Aspirin
47	Additives
2065	

Process: Apply crystallized citric acid, then heat to 60°C and wet with 36 ml of gluconic acid delta-lactone solution (10 parts of gluconic acid delta-lactone to 5 parts of water); apply malic acid, then allow sodium bicarbonate I to react to give monosodium citrate and malate and then allow sodium bicarbonate II, calcium carbonate and potassium bicarbonate to undergo partial reaction (partial conversion to the citrate). Then cover the surface with citric acid powder. Finally allow sodium carbonate to undergo partial reaction, and dry in vacuo. This effervescent base is mixed with 500 parts of aspirin and with corresponding additives.

Example 10 (Arginine aspartate):

Arginine aspartate is particularly freely soluble and, in conventional effervescent systems, by the formation of concentrated solutions, prevents the rapid effervescence of the tablet.

Parts	
384	Crystallized citric acid
53	Sodium bicarbonate I
144	Sodium bicarbonate II
88	Potassium bicarbonate
61	Sodium carbonate
6	Malic acid for solution I
736	
1000	Arginine aspartate
41	Additives
1777	

Process: Heat citric acid to 60°C and moisten with 8 ml of 60% malic acid solution. Allow sodium bicarbonate I to react to give monosodium citrate and malate; then allow sodium bicarbonate II and potassium bicarbonate to undergo partial reaction. Add sodium carbonate and allow to undergo partial reaction, and then dry in vacuo. Mix the resulting granules with arginine aspartate and the additives (Sweetener, aroma) and compress to give tablets.

Example 11 (Sucralfate):

In the preparation of a sucralfate tablet, a very small amount of sodium bicarbonate is available. It must therefore be granulated together with the second bicarbonate by means of gluconic acid delta-lactone solution.

Parts	
394	Crystallized citric acid
42	Sodium bicarbonate I
158	Sodium bicarbonate II
6	Malic acid for solution
200	Gluconic acid delta-lactone for solution
800	
1000	Sucralfate
100	Additives
1900	

Process: Heat crystallized citric acid to 60°C and wet with 8 ml of 60% malic acid solution. Allow sodium bicarbonate I to react to give monosodium citrate, add sucralfate and sodium bicarbonate II and granulate with 280 ml of gluconic acid delta-lactone solution (10 parts of gluconic acid delta-lactone/3 parts of water/3 parts of ethanol) and then dry in vacuo. Mix the granules with the additives (sweetener, aroma).

Example 12 (Mesna):

Parts	
610	Crystallized citric acid
40	Tartaric acid
34	Sodium bicarbonate I
236	Sodium bicarbonate II
68	Sodium carbonate
12	Malic acid for solution I
1000	
1000	Mesna
78	Additives
2078	

Process: Heat crystallized citric acid to 60°C, wet with 14 ml of 70% malic acid solution, apply tartaric acid and allow to penetrate. Allow sodium bicarbonate I to react to give monosodium citrate and malate; add sodium bicarbonate II and allow to undergo partial reaction (partial conversion to the citrate). Add sodium carbonate and dry in vacuo. Mesna is granulated with a 30% sorbitol solution in 1:1 alcohol/water, dried, sieved and mixed with the effervescent base prepared according to the Example and with any desired additives and compressed to give tablets.

Example 13 (Vitamin C):

Parts	
1020	Ascorbic acid
588	Crystallized citric acid
50	Sodium bicarbonate I
350	Sodium bicarbonate II
140	Sodium carbonate
12	Malic acid for solution
2160	
40	Additives
2200	

Process: Heat crystallized citric acid and ascorbic acid to 60°C. Moisten with 16 ml of 60% malic acid solution. Allow sodium bicarbonate I to react to give monosodium citrate and malate; then allow sodium bicarbonate II to undergo partial reaction. Add sodium carbonate and allow to undergo partial reaction. Then dry in vacuo. Mix the resulting granules with the additives (sweetener, aroma).

Examples 1 to 13 are clearly summarized in the Table below. The meanings are as follows:

CA Citric acid (in carrier crystals as fine particles, in the layers as powder)
MA Malic acid
FA Fumaric acid
TA Tartaric acid
CC Calcium carbonate
SC Sodium carbonate
KH Potassium bicarbonate
MNC Monosodium citrate
GDL Gluconic acid delta-lactone (67% solution)
BC1 Sodium bicarbonate, 1st part (reacted to give the monosalt)
BC2 Sodium bicarbonate, 2nd part (anchored to the preceding layers only by partial reaction)

Layer on the carrier crystals		1	2	3	4	5	6	7
Example	Carrier crystals						Active substance	
1	CA,MA	GDL	BC1	BC2	CA	SC	Acetylcysteine	
2	CA,TA	MNC	CA	BC1	BC2	SC	Acetylcysteine	
3	CA,TA	MA	BC1	BC2	SC		Ambroxol	
4	CA,MNC,MA	GDL	BC	CC	FA	SC	Captopril	
5	CA,MA	GDL	BC1	BC2 KH	CA	SC	Minoxidil	
6	CA,TA,MNC	GDL	BC1	BC2	CA	SC	Ranitidine	
7	CA,MA	CA	BC1	BC2	CA	SC	Cimetidine	
8	CA,MA	GDL	BC1	BC2	SC		Paracetamol	GDL
9	CA	GDL	MA	BC1	BC2 CC,KH	CA SC	Acetylsalicylic acid	
10	CA	MA	BC1	BC2	KH	SC	Arginine aspartate	
11	CA,MA	BC1	BC2	GDL			Sucralfate	
12	CA,MA	TA	BC1	BC2	SC		Mesna	
13	CA Vit.C,MA	BC1	BC2	SC				

Except in Examples 10, 11 and 13, the active substance is mixed with the prepared effervescent base and compressed to give tablets. In Examples 10 and 11, the active substance is mixed with one or more other layer component(s) and applied as a layer; in Example 13, the active substance (vitamin C = ascorbic acid) is taken with citric acid as the carrier crystal.

Example 14 (Arginine aspartate and acetylcysteine):

A Table showing the variation of the different effervescent bases appears below. The following five effervescent bases were prepared by the principle according to the invention:

Effervescent base	a	b	c	d	e
Citric acid, fine particles	900				900
Citric acid for solution		19	19	19	24
Tartaric acid type 2V		900	100		
Tartaric acid powder	100				
$NaHCO_3$ (BC1)	50	50	50	50	
$NaHCO_3$ (BC2)	350	350	350	350	
Na_2CO_3	100	100	120	270	100
Malic acid, fine particles		100	900	900	
Malic acid for solution	19				
Adipic acid				100	
Fumaric acid					100
$KHCO_3$					150
K_2CO_3					250

These five effervescent bases a to e were each mixed in alternating amounts with 1000 mg of arginine aspartate or with 1000 mg of acetylcysteine and 290 mg of Na_2CO_3 and compressed to give tablets. The resulting tablet hardnesses, dissolution times in only 50 ml of water and pH achieved are shown:

	1000 mg of arginine aspartate			1000 mg of acetylcysteine	
Effervescent base	500 mg	750 mg	1000 mg	460 mg	710 mg
a Hardness	5.9	6.3	6.5	6-7	6-7
Dissolution time	50"	50"	60"	70"	75"
pH	4.5	4.45	4.35	4.3	4.4
b Hardness	6.1	5.9	7.6	7.1	7.5
Dissolution time	50"	70"	100"	100"	115"
pH	4.3	4.1	4.1	4.01	4.1
c Hardness	6.0	6.2	7.2	6-7	6-7
Dissolution time	50"	50"	75"	90"	80"
pH	4.5	4.4	4.3	4.1	4.3
d Hardness	5.9	7.2	6.2	6-7	6-7
Dissolution time	60"	80"	70"	75"	85"
pH	4.99	4.86	4.9	5.1	5.1
e Hardness	5.9	6.9	6.2	6-7	6-7
Dissolution time	80"	75"	60"	50"	60"
pH	4.55	4.5	4.39	4.4	4.35

Example 15:

Dimeticon (dimethylpolysiloxane) is usually used as an antifoam for suspensions, for example during tablet coating, or in some cases also for creams and effervescent tablet formulae. Dimeticon has also been used to date to reduce the moisture sensitivity of effervescent tablets. According to the invention, however, it is now possible to increase the reaction rate of the effervescent tablet by 20 to 30%, i.e. accelerate the dissolution, by adding dimeticon applied to a carrier in small amounts. The dimeticon evidently results in an improvement in the contact between the effervescent reactants during the reaction, this being achieved by applying small amounts of dimeticon to a neutral carrier and mixing the latter with the effervescent base.

The procedure is as follows: 100 parts by weight of neutral fillers, such as, for example, mannitol, sorbitol, lactose, maltodextrin or Aerosil™, are heated to 40°C. A solution of 0.1 to 0.8 parts by weight of dimeticon in organic solvents is sucked into a vacuum drum containing this carrier. The solvent is evaporated during thorough stirring, in order to obtain an appropriate uniform distribution. The product thus obtained is added to the effervescent tablet in an amount between 0.1 and 0.6 mg per tablet, depending on the active substance, whose hydrophobic or hydrophilic character also plays a role here. For example, a dissolution time of 80 sec is achieved for a cimetidine effervescent tablet without dimeticon whereas a dissolution time of 55 sec is achieved with the same hardness in the presence of dimeticon.

In the case of ambroxol, the dissolution time can be decreased from 120 sec to 70-80 sec by adding 100 mg of mannitol to which 0.4 mg of dimeticon has been applied.

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

1. An effervescent tablet containing:
at least one pharmaceutically active substance; and
an effervescent system comprising:
at least one solid, edible, organic acid,
at least one alkali metal carbonate or bicarbonate as a gas-forming component, and
at least one alkali metal salt of the acid;
wherein there are at least two layers applied to carrier crystals comprising the said at least one acid;
wherein the first layer contains at least one solid, edible, organic acid different from said crystal acid, or contains the alkali metal salt of said different acid, or contains both; and
wherein the second layer contains at least one alkali metal salt of said at least one acid or of said different acid or of both.

2. The effervescent tablet as claimed in claim 1, wherein at least one of said alkali metal salts is acidic.

3. The effervescent tablet as claimed in claim 1 or 2, wherein, of the total amount of the acid and of the gas-forming component, 10 to 40 percent by weight is present in the form of salts.

4. The effervescent tablet as claimed in claim 3, wherein 10 to 20 percent by weight of the total amount of the acid

and of the gas-forming component is present in the form of salts.

5. The effervescent tablet as claimed in any one of claims 1 to 4, wherein at least part of the salt or of the gas-forming component is present in essentially anhydrous form.

6. The effervescent tablet as claimed in claim 5, wherein the anhydrous gas-forming component forms the outermost layer of the carrier crystal.

7. The effervescent tablet as claimed in any one of claims 1 to 6, wherein the effervescent system has an acid-consuming capacity of not more than 5 meq.

8. The effervescent tablet as claimed in any one of claims 1 to 7, further comprising 0.1 to 0.6 mg of dimethicone in combination with a neutral excipient or carrier.

9. The effervescent tablet as claimed in claim 8, wherein the neutral excipient or carrier is selected from the group consisting of mannitol, sorbitol, lactose, maltodextrin, and silica.

10. The effervescent tablet as claimed in any one of claims 1 to 9, further comprising fifteen to thirty parts by weight of fillers or excipients, per 100 parts by weight of the effervescent system.

11. The effervescent tablet as claimed in any one of claims 1 to 6, comprising at least two edible organic acids having different pK values.

12. The effervescent tablet as claimed in claim 11, wherein the two edible organic acids are citric acid and malic acid, present in a ratio of 20:1 to 3:1.

13. The effervescent tablet as claimed in claim 12, in which the ratio is 12:1 to 8:1.

14. The effervescent tablet as claimed in any one of claims 1 to 7, wherein the gas-forming component is present in a substoichiometric amount relative to the total of the acid and metal salt components of the effervescent system.

15. The effervescent tablet as claimed in claim 14, wherein the gas-forming component is present in an amount which forms only the monosalt.

16. The effervescent tablet as claimed in any one of claims 1 to 15, wherein 5 to 20 percent by weight of the total amount of the gas-forming component has reacted with the carrier crystals to give a layer of the monosalt of said at least one acid around said carrier crystals, while another portion of said gas-forming components is present in the form of an additional layer on the carrier crystals over said monosalt layer.

17. The effervescent tablet as claimed in claim 16, wherein 10 to 15 percent by weight of the total amount of the gas-forming component has reacted to give the monosalts which form the second or a third layer.

18. The effervescent tablet as claimed in any one of claims 1 to 17, wherein in the sequence citric acid-malic acid-tartaric acid-adipic acid, a first acid is present in the carrier crystal, on whose surface at least one subsequent acid or its salt is anchored and is further at least partly covered with at least part of the gas-forming component and an intermediate layer consisting of its salt formed upon reaction with the gas-forming component.

19. The effervescent tablet as claimed in claim 18, wherein the at least one subsequent acid or salt is monosodium citrate and is diffused in the crystal lattice of the carrier crystal.

20. The effervescent tablet as claimed in any one of claims 1 to 19, wherein a mixture of citric acid with at least one of the following compounds is present as carrier crystals: malic acid, tartaric acid, and monosodium citrate.

21. The effervescent tablet as claimed in any one of claims 1 to 20, wherein said first layer contains malic acid, unless the carrier crystals consist exclusively of malic acid.

22. The effervescent tablet as claimed in any one of claims 1 to 21, wherein the first layer contains gluconic acid delta-lactone, said first layer being covered with at least one of the following acids or alkali metal salts thereof: citric acid, malic acid, and tartaric acid.

23. The effervescent tablet as claimed in claim 22, in which the first layer is covered with an acid or alkali metal salt thereof.

24. The effervescent tablet as claimed in any one of claims 1 to 23, wherein the first layer comprises the different acid and the alkali metal salt thereof, and the second layer comprises a monosalt of the different acid, said tablet comprising a further layer comprising a layer containing at least one gas-forming component.

25. The effervescent tablet as claimed in any one of claims 1 to 24, wherein the pharmaceutically active substance is alkali-sensitive, and wherein the outermost layer applied to the carrier crystals consists essentially of an edible organic acid or an acidic salt thereof.

26. The effervescent tablet as claimed in claim 25, wherein said acid in said outermost layer is citric acid or fumaric acid.

27. The effervescent tablet as claimed in any one of claims 1 to 26, further comprising - based on 100 parts by weight of the effervescent system - at least 50 parts by

weight of said pharmaceutically active substance and the active substance being incorporated in a layer containing the gas-forming components in anhydrous form.

28. The effervescent tablet as claimed in claim 27, comprising at least 100 parts by weight of said pharmaceutically active substance incorporated in the layer containing the gas-forming component, the composition further comprising anhydrous sodium carbonate.

29. The effervescent tablet as claimed in claim 27 or 28, wherein the alkali metal salts are monosalts, and wherein the carrier crystals covered with said first and second layers are present as a mixture with gluconic acid delta-lactone or sodium carbonate or both, in the form of granules.

30. The effervescent tablet of any one of claims 1 to 29, wherein the gas-forming component is selected from the group consisting of sodium bicarbonate, sodium carbonate, potassium bicarbonate, and potassium carbonate.

31. The effervescent tablet as claimed in any one of claims 1 to 30, wherein said at least one pharmaceutically active substance is selected from the group consisting of ambroxol, ranitidine, cimetidine, acetylcysteine, captopril, minoxidil, sucralfate, paracetamol, arginine aspartate, mesna, acetylsalicylic acid, and vitamin C.

32. A process for the preparation of an effervescent system comprising the steps:

(i) wetting carrier crystals of at least one solid, edible, organic acid with a liquid selected from the group consisting of water, a solution of an acidic component of the effervescent system and a solution of gluconic acid delta lactone;

(ii) admixing said wet carrier crystals with at least one compound in finely divided form to cover the surface of said carrier crystals, wherein said at least one compound is selected from the group consisting of an edible organic acid different from said carrier crystal acid and a gas-forming component, the gas-forming component being allowed to partially react to a salt of an edible organic acid;

(iii) further adding at least one solid, gas-forming component, at least part of which gets anchored by partial reaction to the surface of the wet carrier crystals; and

(iv) drying the covered carrier crystals to yield effervescent granules.

33. The process as claimed in claim 32, wherein dimethicone is combined with the effervescent system.

34. The process as claimed in claim 32 or 33, further comprising the addition of an edible organic acid between steps (ii) and (iii).

35. The process as claimed in claim 32, 33, or 34, wherein the gas-forming component is applied in a substoichiometric

amount relative to the acidic components, to yield an acid consuming capacity of not more than 5 meq.

36. The process as claimed in any one of claims 32 to 35, wherein the effervescent granules are further mixed with at least one component selected from the group consisting of a pharmaceutically active substance, a sweetener, an aroma and a filler; and pressed into tablets.

37. A process for the preparation of an effervescent system comprising at least one solid, edible, organic acid, at least one component which forms a gas by reaction with the acid with salt formation, and at least one salt formed from the acid and the gas-forming component, the surface of the crystals of the one or more acids which are present in a bed being wet with water or with the solution of a component intended for the effervescent system and being at least partially reacted and being at most partially dried, and a further component present in finely divided form then being anchored on the surface and, optionally after partial reaction, the material being dried, wherein another acid and then at least a part of the gas-forming component are anchored to the surface of the wet acid crystals.

38. A process as claimed in claim 37, wherein dimethicone is combined with the effervescent system.