Flavour improvement of pharmaceutical agents

The invention relates to a method of improving the flavour profile of solid formulations, for example of tablets comprising active substances or mineral substances, that is to say not only the actual flavour itself but also the organoleptic sensation in the mouth.

Polyols and polyol mixtures are used on a large scale as non-cariogenic additives and excipients for, inter alia, pharmaceutically active substances, chewable tablets, lozenges and other products of the pharmaceutical industry, and as compressed articles in the food industry. As a rule, polyols are obtained by hydrogenating the sugars on which they are based. They can be obtained in solid form by crystallization or else by spray-drying. The particular advantage of some polyols is that they are also suitable for direct compression without any further auxiliaries and additives.

While the known polyols mannitol, lactitol, isomaltol and xylitol show a low degree of hygroscopicity, the tableting behaviour is poor, which results in low tablet hardness, scale-off and severe friability of the tablets. In principle, it is desired to achieve high tablet hardness since frequently only a small amount of excipients are employed in solid formulations and the active substances may drastically reduce tablet hardness so that a given pharmaceutical formula is impossible to tablet.

While lactitol, isomaltol and xylitol are less frequently used in the preparation of compressed articles, mannitol is frequently used in pharmaceutical formulations.

However, the use of mannitol entails a more complicated procedure since, as a rule, it has to be subjected to wet granulation together with the remaining ingredients of the pharmaceutical formula prior to compressing. Mannitol which can be tableted directly is also commercially available, but the hardness which can be achieved by using it is only unsatisfactory in comparison with the hardness achieved when using sorbitol.

Sorbitol, in particular sorbitol obtained by spray-drying, results in very good tablet hardness. At the same time, the compressed articles produced have particularly smooth surfaces. A paper by Basedow et al. reveals that tablets comprising calcium carbonate can be prepared by compressing with spray-dried or crystalline sorbitol. However, sorbitol shows a higher degree of hygroscopicity than the other polyols. This means that its uses are limited. In this context, there is also a lack of evidence in the literature that the flavour profile of a formulation may be improved substantially by sorbitol or by another polyol.

When formulating orally administered pharmaceutical preparations, the flavour profile perceived by the user is frequently problematic, not only in the case of liquid dosage forms. A chalky taste, in particular when chewing antacid tablets, is perceived as unpleasant. Attempts to mask this chalky taste by a wide range of additives have been relatively unsuccessful to date. Known antacids, in turn, convey an undesirable chalky, soapy taste in the mouth which can be reduced, albeit only slightly, by conventional additives, but reappears to a large extent upon chewing.

Another problem found in a wide range of active substances is a taste perceived as extremely bitter. Attempts to mask especially bitter or chalky active substances have been unsuccessful to date, even by

adding flavourings or aromas. While there is a possibility of providing tablets comprising such active substances with a coating, this method is unsuitable when the aim is rapid absorption of the active substance which takes place via the mucous membrane of the mouth even while the tablets are being chewed.

The surface of tablets which are intended to be sucked, for example tablets for sore throats, also have to meet specific requirements. What is desired here is a smooth surface of the actual tablet which is retained during the sucking process and does not roughen up gradually.

Moreover, lozenges and, especially, chewable tablets are offered currently in the field of food supplements (vitamin and mineral supplements). In particular in the case of tablets for supplying minerals, the excipient amounts are very little, so that the flavour profile depends largely on the mineral in question.

It is furthermore attempted, in the production of solid formulations, increasingly to employ directly compressible active substances (DC active substances), in order to lower production costs.

It is therefore an object of the present invention to provide a method which, on the one hand, improves the flavour profile of solid formulations but which simultaneously positively affects the organoleptic sensation in the mouth of the resulting products.

It has now been found that the flavour profile of solid formulations can be improved by preparing a composition - which comprises one or more active substances and which can be obtained by concomitant spray-drying or fluidized-bed granulation with at least one polyol - in a solid dosage form by means of compressing.

The invention therefore relates to a method for the preparation of DC active substances which contribute to improving the flavour profile of solid formulations which comprise one or more active substances, characterized in that a composition - which comprises one or more active substances and can be obtained by concomitant spray-drying or fluidized-bed granulation with at least one polyol - is prepared in a solid dosage form by means of compressing. The total amount of polyol employed is to be chosen in such a way that it amounts to 10 to 90% by weight, in particular 25 to 75% by weight, of the pulverulent substance mixture prepared by the method according to the invention.

The composition which is essential to the invention can be obtained by dissolving at least one polyol in water and dissolving or suspending at least one active substance in a solvent and spraying the resulting aqueous mixture in a stream of air at a temperature of 120 to 300°C, preferably 140 to 190°C. Alternatively, it is possible to fluidize the resulting aqueous mixture in a stream of air at a temperature of 40 to 120°C.

Prior to the concomitant spray-drying or fluidized-bed granulation, flavour improvers and, if appropriate, colours may be added to the aqueous mixture. Suitable flavour improvers are, inter alia, natural or synthetic sweeteners from the group consisting of saccharin, Aspartame®, acesulfam K, neohesperidin DC, sucralose, thaumatin or stevioside. Polyols which can be employed are those from the group consisting of sorbitol, mannitol, lactitol, isomaltol, maltitol, erythritol or xylitol. These may amount to 10 to 90% by weight, in particular 25 to 75% by weight, in the resulting product.

The invention therefore also relates to the solid formulations with improved flavour profile which are

produced by the method according to the invention. These formulations may comprise, on the one hand, minerals from the group of the physiologically acceptable Ca, Mg, Na, K, Fe and Zn salts in an amount of from 0.1 to 90% by weight, in particular 25 to 75% by weight, if appropriate trace elements, and one or more vitamin(s) and, if appropriate, one or more active substances which may taste bitter.

The formulations produced by the method according to the invention may comprise one or more pharmaceutically active substances. Such active substances may be, inter alia, antacids, antiallergics, analgesics, hormones, steroids, oestrogens, contraceptives, nasal decongestants, H_1 and H_2 antagonists, β_2 stimulants, vasodilators, antihypertensives, anti-infective agents, laxatives, antitussives, bronchodilators, agents against sore throats, bismuth and its salts, fungicides, antibiotics, stimulants (such as, for example, amphetamines) alkaloids, oral hypogylcaemics, diuretics, cholesterol-lowering agents, combinations of various pharmaceutically active agents or others. These active substances may amount to 0.1 to 70% by weight.

The active substances can be present as coated particles, liposomes or microparticles. Customary substances used in pharmacy can serve as a coating. The particle size of the active substances is preferably 0.1 to 800 µm with a bulk density of 0.15 to 1 g/cm^3.

The percentages by weight given in the above text are, of course, to be understood in such a way that the chosen percentages of the substances employed do not exceed a total of 100.

The term polyol is to be understood as meaning sugar alcohols of the general formula
$CH_2OH-(CHOH)_n-CH_2OH$,
n being 2 to 6, preferably 3 to 4,

and the dimeric anhydrides thereof, in particular $C_{12}H_{24}O_{11}$.

The term polyols is to be understood as meaning, in particular, hexitols such as sorbitol and mannitol, pentitols such as xylitol, but may also be C_4-polyalcohols such as erythritol or C_{12}-polyalcohols such as lactitol or maltitol. However, the term polyols is also to be understood as meaning suitable carbohydrates.

The mixture used for spray-drying is an aqueous solution of at least one polyol. Beforehand, the solids content is preferably brought to approximately 10-90% by weight, in particular 50 to 72% by weight, by mixing at least one polyol solution with one or more solutions or suspensions of the desired active substance(s) in the desired ratio at a temperature of up to 80°C. Spraying is carried out by means of atomizing using nozzles, preferably by means of a centrifugal atomizer, in a dry stream of air which is introduced centrifugally and which has been heated to a temperature of 120 to 300°C, preferably 140 to 190°C. The amount of polyol solution charged and of hot air introduced is matched in such a way that the resulting pulverulent substance mixture is dried down to a water content of approximately 0.1 to approximately 1% by weight, if appropriate in a fluidized bed. In any case, the water content should be below 1% by weight.

The fluidized-bed granulation is carried out for example as described in P. Grassmann, F. Widmer, "Einführung in die thermische Verfahrenstechnik" [Introduction to Thermal Process Technology].

The specific production process, in which an aqueous solution is sprayed, allows water-soluble additives, but also additives which are not soluble in water, for example citric acid, sweeteners, in particular

acesulfam K, Aspartame®, saccharin, cyclamate, sucralose, neohesperidin DC, colours and pharmaceutically active substances, for example analgesics, antacids and the like, vitamins and, if appropriate, trace elements, to be distributed homogeneously in the solid formulation or compositions according to the invention and in the tablets prepared therefrom.

The binders which are optionally to be added are known to those skilled in the art and used to improve the hardness of the composition. Preferred binders are cellulose derivatives, in particular hydroxypropylmethylcellulose, carboxymethylcellulose or starch.

The polyol compositions characterized in this way have a series of properties which are advantageous for tableting:

Surprisingly, it is observed that solid formulations, in particular tablets, with a considerably improved flavour profile and organoleptic sensation in the mouth can be obtained by the method according to the invention with the use of the compositions according to the invention. These advantageous properties are simultaneously linked to the possibility of directly compressing the compositions obtained by concomitant spray-drying or fluidized-bed granulation. These are therefore directly compressible active substance formulations (DC active substances).

When using formulations with a high mineral content of up to 90% by weight results in dramatically improved tableting properties on the one hand and, on the other hand, the tablets produced are characterized by a considerably lower degree of friability during the packaging process. Moreover, when using the compositions according to the invention, the same

pressure as is applied to known polyol-comprising formulations results in harder tablets with smoother surfaces. This improved organoleptic sensation in the mouth, which is perceived at the beginning, is also perceived during chewing or sucking since the normal chalky or even soapy flavour is masked to a high degree. Surprisingly, it is not only the flavour profile of these mineral tablets which is improved. Formulations into which extremely bitter active compounds are incorporated are perceived as considerably better tasting, since the bitter flavour is not quite so perceptible.

The examples which follow are intended to illustrate in greater detail the above invention which is described and claimed but are not suitable for restricting the scope of protection thereto.

Examples

Example 1

Antacid tablet

Composition of the tableting mixture:

Calcium carbonate	65.50%
Karion Instant	28.19%
Karion Powder P300	4.70%
Chlorophyllin 100%	0.01%
Neohesperidin DC	0.10%
Peppermint aroma Naefco (by Firmenich)	0.30%
Magnesium stearate	1.00%

Mechanical production of the mixture:

Calcium carbonate and sorbitol (Karion Instant and Karion Powder P300) are mixed for 5 minutes in a Turbula mixer. Chlorophyllin, neohesperidin DC and the peppermint aroma are subsequently added and mixing is continued for 5 minutes. The mixture is passed through a screen of mesh size 1 mm. Magnesium stearate is passed through a screen of mesh size 250 µm onto the screened mixture, and mixing is continued for a further 5 minutes. The resulting mixture is tableted.

Production of the mixture by concomitant spraying:

Calcium carbonate, sorbitol, neohesperidin DC and chlorophyllin are sprayed concomitantly in the manner mentioned above. The concomitantly sprayed material and the aroma are placed into a Turbula mixer, magnesium stearate is passed through a screen of mesh size 250 µm onto the mixture and everything is mixed for 5 minutes. The resulting mixture is tableted.

Results:

	Mechanical mixture	Concomitantly sprayed material
Tableting (qualitative)	flowability of the mixture very poor, mould not always filled completely, tablets show scale-off	perfect tableting
Flow inclination angle	37.5°	32.6°
Tablet hardness	40 N at 19 KN (maximum tablet hardness obtainable)	129 N at approx. 8 KN
$V_{rel.}$ Tablet weight	not determinable	0.19%
Friability (Roche)	not determinable	0.37%
Organoleptic sensation	strong chalky flavour, strong chalky sensation in the mouth, very dull, weak aroma since masked by chalky flavour	readily chewable tablets, no chalky sensation in the mouth, very little chalky flavour, aroma readily recognizable
Active Substance Distribution		
Mean value (in % of the theoretical value)	98.2	99.9
Deviation (min/max)	96.0 - 99.8	99.6 - 100.2
Deviation	3.8%	0.6%

Example 2

Analgesic tablet

Composition of the tableting material:

Acetyl salicylic acid (ASA)	74.0%
Sorbitol content	24.5%
(Instant quality admixed, or sprayed with ASA)	
Acesulfam K	0.5%
Magnesium stearate	1.0%

Tableting and flavour comparison

Preparation of a mechanical mixture:

ASA is finely powdered by grinding and triturated with sorbitol Instant in a Turbula shaking mixer including the micronized sweetener ASK. This is followed by screening for deagglomeration using a 1 mm screen and remixing with magnesium stearate and then tableting.

Preparation of concomitantly sprayed tablet material:

Finely powdered, ground ASA is partly (about 5%) introduced into the fluidized bed and the remainder is dispersed in sorbitol solution in a ratio of about 1 : 1. The dispersion is maintained by stirring and sprayed directly into the fluidized bed with the sweetener ASK, with simultaneous evaporation of water.

1% magnesium stearate is admixed as lubricant to the relatively fine spray granules thus formed. The mixture obtained is directly tableted.

Results:

	Mechanical mixture	Concomitantly sprayed material
Appearance	only slightly flowable mixture, both main components of which are recognizable	homogeneous, readily flowable tableting granules
Tableting: 500 mg Press force 10 kN		
Tablet hardness:	90 N	210 N
Friability	0.6%	0.3%
Organoleptic sensation	acid-dominant flavour, high surface roughness of the tablet	corrected sweetly acidic flavour, pleasant chewing behaviour (smooth, not very absorptive surface)

Example 3

Vitamin C tablet

Ascorbic acid	87.7%
Sorbitol	10.0%
Orange aroma (powdered)	0.7%
Acesulfam K	0.6%
Magnesium stearate	1.0%

Preparation of a mechanical mixture:

The finely crystalline ascorbic acid is intimately triturated in a Turbula shaking mixer with sorbitol Instant (granulation under 0.3 mm), sweetener and

aroma. The lubricant magnesium stearate is then screened and mixed in.

Preparation of concomitantly sprayed tableting material:

Ascorbic acid, sorbitol and sweetener are dissolved in water at 40°C at about 40% solids content and sprayed onto an identically composed bed of crystal seeds (proportion of the total mass about 15%) in a fluidizing apparatus. The spray granules are mixed with the same aroma and magnesium stearate before tableting.

Results:

	Mechanical mixture	Concomitantly sprayed material
Appearance	sorbitol particles are sporadically recognizable	homogeneous, readily flowable tableting granules
Tableting: Amount: 500 mg Press force 20 kN		
Tablet hardness:	20 N	160 N
Friability	22%	0.2%
Organoleptic sensation	tablets too soft, rough surface, (unacceptable results)	sweetly acidic vitamin C tablet having a smooth surface and pleasant chewing properties

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Patent Claims

1. Method of improving the flavour profile of solid formulations which comprise one or more active substances, characterized in that a composition - which comprises one or more active substances and can be obtained by concomitant spray-drying or fluidized-bed granulation with at least one polyol or carbohydrate - is prepared in a solid dosage form by means of compressing.

2. Method according to Claim 1 characterized in that the compositions obtained by concomitant spray-drying or fluidized-bed granulation are directly compressible active substance formulations.

3. Method according to Claims 1-2 characterized in that a composition is used which comprises flavour improvers and, if appropriate, colours.

4. Composition according to Claims 1-3, which can be obtained by dissolving at least one polyol in water and dissolving or suspending at least one active substance in a solvent and spraying the resulting aqueous mixture in a stream of air at a temperature of 120 to 300°C, in particular 140 to 190°C.

5. Composition according to Claims 1-4, which can be obtained by dissolving at least one polyol in water and dissolving or suspending at least one active substance in a solvent and fluidizing the resulting aqueous mixture in a stream of air at a temperature of 40 to 120°C.

6. Composition according to one or more of Claims 1-5, characterized in that it comprises at least
a) an active substance,
b) a polyol,

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c) if appropriate a natural or synthetic sweetener and
if appropriate a colour.

7. Composition according to Claim 6, characterized in that it comprises a sweetener from the group consisting of saccharin, Aspartame®, acesulfam K, neohesperidin DC, sucralose, thaumatin or stevioside.

8. Composition according to one or more of Claims 1-7, characterized in that it comprises at least one or more polyol(s) from the group consisting of sorbitol, mannitol, lactitol, isomaltol, maltitol, erythritol or xylitol.

9. Solid formulation with improved flavour profile produced by a method according to Claims 1-3.

10. Solid formulation according to Claim 9, characterized in that it comprises 10 to 90% by weight, in particular 25 to 75% by weight, of minerals from the group of the physiologically acceptable Ca, Mg, Na, K, Fe and Zn salts, if appropriate trace elements and if appropriate one or more vitamins, and also, if appropriate, one or more active substances which may taste bitter.

11. Solid formulation according to Claim 9, characterized in that it comprises one or more active substances from the group consisting of analgesics, antacids, antiallergics, hormones, steroids, oestrogens, contraceptives, nasal decongestants, H_1 and H_2 antagonists, β_2 stimulants, vasodilators, antihypertensives, anti-infective agents, laxatives, antitussives, bronchodilators, agents against sore throats, bismuth and its salts, fungicides, antibiotics,

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alkaloids, oral hypoglycaemics, diuretics, cholesterol-lowering agents.

12. Solid formulation according to Claim 9, characterized in that it comprises one or more pharmaceutical agents in an amount of 0.1 to 70% by weight.

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