AGGLOMERATION OF A CALCIUM-CONTAINING COMPOUND BY ROLLER COMPACTION

Field of the invention

The present invention relates to a particulate material and a solid dosage form notably tablets comprising a regularly shaped calcium-containing compound such as a calcium salt as a therapeutically and/or prophylactically active substance and a pharmaceutically acceptable sugar alcohol such as, e.g., sorbitol and/or isomalt that has a micro structure as evidenced by SEM. The invention also relates to a process for the preparation of the particulate material and solid dosage form. The process involves agglomeration of the calcium-containing compound and the pharmaceutically acceptable sugar alcohol by means of roller compaction. The particulate material obtained by roller compaction is suitable for use in the further processing of the particulate material into e.g. tablets such as chewing tablets.

The present invention is based on the findings that the result of an agglomeration process by which a calcium-containing compound is agglomerated depends on the particular shape of the calcium-containing compound and the micro structure of the material used as a binder in the agglomeration process.

Background

Calcium is essential for a number of key functions in the body, both as ionized calcium and a calcium complex (Campell AK.Clin Sci 1987; 72:1-10). Cell behaviour and growth are regulated by calcium. In association with troponin, calcium controls muscle contraction and relaxation (Ebashi S. Proc R Soc Lond 1980; 207:259-86).

Calcium selected channels are a universal feature of the cell membrane and the electrical activity of nerve tissue and the discharge of neurosecretory granules are a function of the balance between intracellular and extra cellular calcium levels (Burgoyne RD. Biochim Biophys Acta 1984;779:201-16). The secretion of hormones and the activity of key enzymes and proteins are dependent on calcium. Finally calcium as a calcium phosphate complex confers rigidity and strength on the skeleton (Boskey AL. Springer, 1988:171-26). Because bone contains over 99% of the total body calcium, skeletal calcium also serves as the major long-term calcium reservoir.

Calcium salts such as, e.g., calcium carbonate is used as a source of calcium especially for patients suffering from or at risk of osteoporosis. Moreover, calcium carbonate is used as an acid-neutralizing agent in antacid tablets.

Furthermore, calcium may have anticancer actions within the colon. Several preliminary studies have shown high calcium diets or intake of calcium supplementation is associated with reduced colon rectal cancer. There is increasing evidence that calcium in combination with acetylsalicylic acid (ASA) and other non-steroidal anti-inflammatory drugs (NSAIDS) reduce the risk the risk of colorectal cancer.

Recent research studies suggest that calcium might relieve premenstrual syndrome (PMS). Some researchers believe that disruptions in calcium regulation are an underlying factor in the development of PMS symptoms. In one study, half the women of a 466 person group of pre-menopausal women from across the U.S. were tracked for three menstrual cycles and were given 1200 mg of calcium supplements daily throughout the cycle. The final results showed that 48% of the women who took placebo had PMS related symptoms. Only 30% of those receiving calcium tablet did.

Calcium salts like e.g. calcium carbonate is used in tablets and due to the high dose of calcium required, such tablets are often in the form of chewable tablets. It is a challenge to formulate chewable tablets containing a calcium salt, which tablets have a pleasant taste and an acceptable mouthfeel without the characteristic dominating taste or feeling of chalk.

Furthermore, i) the high dose of calcium carbonate (normally 300-600 mg of elemental calcium twice daily, corresponding to 750 - 1500 mg of calcium carbonate twice daily), ii) the inherent poor properties of regular shaped calcium carbonate with respect to tabletting properties like compressibility, which accordingly calls for the need of adding one or more pharmaceutically acceptable excipients in order to obtain a suitable compressibility, and iii) the extremely bad taste or mouthfeel of a calcium salt itself especially with respect to chalkiness make it very difficult to prepare a tablet that has a suitable small size, which is conveniently small for a patient. Sufficient taste masking is another major challenge when formulating chewable tablets.

The present inventors have found an easy way for producing e.g. chewable tablets containing a physiologically tolerable calcium-containing compound by using a granulate comprising agglomerates of the calcium-containing compound. The granulate is obtained without use of any solvent (e.g. water), but involves the technique of roller compaction of the calcium-containing compound to form agglomerates having suitable properties for further processing into a solid dosage form such as, e.g., tablets.

EP 0 054 333 (Stauffer Chemical Company) describes a process of compacting fine particles of calcium phosphate by means of roller compacting to obtain a powder. The powder obtained has a larger bulk density than the starting material, which makes it suitable for use as an excipient in producing pharmaceutical tablets. In contrast to EP 0 054 333 the present invention does not employ roller compaction with the aim of increasing the bulk density of a pharmaceutically acceptable excipient, but as a novel method for agglomeration, i.e. for building up agglomerates of particles in order to increase the mean particle size to a size that is suitable for further processing of the material into e.g. tablets such as, e.g., chewable tablets that have an acceptable taste and/or mouthfeel.

Previously it has been described that the quality of the calcium-containing compound as well as the method for preparation of a pharmaceutical composition containing the calcium-containing compound are of great importance in order to obtain acceptable taste and mouthfeel of a chewable tablet (WO 00/28973). In contrast to WO 00/28973 the method according to the invention does not employ a step of binding the particles together by a wet granulation process, which means that the method according to the invention advantageously can be employed when it is desired to incorporate substances that are sensitive towards humidity. An example of such a substance is vitamin D that often is included together with a calcium salt in a pharmaceutically dosage form. The present invention provides a simple and cost-effective alternative method to obtain such a dosage form without the need of a step e.g. involving wet granulation.

Description of the invention

It has surprisingly been found that roller compaction of a calcium-containing compound together with a pharmaceutically acceptable sugar alcohol that has binding properties improves the properties for pharmaceutical use of the compacts obtained thereby.

As mentioned above, in the present context the process of roller compacting of a powder is applied as an alternative method to known granulation or agglomeration methods, i.e. wet granulation or – when tablets are prepared – direct compression using dry binders. The present inventors have found that the process of roller compacting is a very mild method that does not destroy the possibility of obtaining products that have an acceptable mouthfeel and at the same time are without a dominating chalk-like taste or feel. Normally, roller compaction is employed with the purpose of increasing the bulk density of a particular substance or composition e.g. in order to transform a bulky material to a less voluminous material that is easier to use in the manufacturing of pharmaceutical compositions. To the best of the present inventor's knowledge, roller compaction has not been employed as a gentle granulation process that maintains or do not destroy important properties of the material (i.e. the calcium-containing compound) so that an acceptable taste, mouthfeel etc. can be obtained.

With an aim of preparing a smaller tablet that still has acceptable taste and mouthfeel, the present inventors have found that the use pharmaceutically acceptable sugar alcohols as binding material in the agglomeration process is particularly suitable. However, in order to obtain suitable properties of a roller compacted composition containing a calcium-containing compound, two major factors are important, namely the properties of the calcium-containing compound itself and the choice of sugar alcohol used as a binder in the agglomeration process. To this end the present inventors have found that when a regularly shaped calcium-containing compound is used, which has very poor compressibility properties itself, then - in order to obtain an acceptable end result - it is very important that the sugar alcohol used has a micro structure, i.e. a structure that enables a certain deformation and sufficient distribution throughout the tablet during the roller compaction process in order to establish sufficient bonding between the individual calcium (and sugar alcohol) particles.

In the present context, the term "regularly shaped" in connection with a calcium-containing compound is intended to denote that the individual particles as evidenced by SEM have a rounded or smooth-like surface like e.g. the cubic-formed crystals shown in Figure 15 herein. The regular shape results in a relatively low specific surface area, that is below 1.5 m^2/g

In the present context, the term "micro structure" used in connection with sugar alcohols is intended to denote that a single crystal of the sugar alcohol is a polycrystal such as multiple crystals or fiber crystals comprising smaller units, i.e. the crystals have an identifiable substructure that is detectable by SEM (e.g. see Figure 16 herein). The micro structure enables a certain deformation and sufficient distribution throughout the tablet during the roller compaction process in order to establish sufficient bonding between the individual calcium (and sugar alcohol) particles. Furthermore, a sufficient compressibility is required, cf. the examples herein.

Moreover, in contrast to what is general knowledge within the field of pharmaceutical formulation, the present inventors have found that a sugar alcohol like sorbitol is not suitable for use in the standard quality generally recommended. This quality has a mean particle size of about 300 μm, but as demonstrated in the examples herein such a mean particle size is too large in order to enable a sufficient distribution of sorbitol particles around the particles of the calcium-containing compound resulting in tablets having unacceptable properties with respect to crushing strength. The particle size of e.g. sorbitol must be much smaller in order to obtain good and acceptable results with respect to crushing strength.

Accordingly, the pharmaceutically acceptable sugar alcohol employed according to the invention has a mean particle size of at the most about 150 μm such as, e.g., at the most about 110 μm, at the most about 100 μm, at the most about 90 μm, at the most about 80 μm, at the most about 70 μm, at the most about 60 μm, at the most about 50 μm, at the most about 40 μm, at the most about 30 μm, at the most about 20 μm or about 10 μm.

In specific embodiments, the pharmaceutically acceptable sugar alcohol employed has a mean particle size in a range of from about 5 to about 150 μm such as, e.g., from about 5 to about 110 μm or from about 5 to about 80 μm.

Furthermore, it would have been expected that use of e.g. sorbitol in a much smaller particle size would lead to stability problems as it is known that sorbitol is hygroscopic and a smaller particle size increases the surface area and thereby the risk of adsorbing moisture e.g. from the surroundings. However, as demonstrated herein, tablets prepared using a granulate obtained by roller compaction of a composition containing the calcium-containing compound and e.g. sorbitol having a mean particle size well

below 300 μm are stable with respect to crushing strength, i.e. the crushing strength of the tablets when stored in open petri dishes at 25 °C and 60% RH changes at the most 50% such as, e.g. at the most about 40%, at the most about 30%, at the most about 20%, at the most about 15%, at the most about 10% during a time period that starts 5 days after manufacture and runs during the remaining storage period e.g. 1 month, 3 months etc. The crushing strengths of tablets of the invention should be in a range of from about 70 to about 140 N.

Such improved stability indicates that products obtained as described herein are suitable for so-called zone 3 or 4 countries (as defined in ICH Q1F), i.e. countries that have a relatively high average temperature and relative humidity.

In one aspect, the invention relates to a process for the preparation of a particulate material or a solid dosage form comprising one or more regularly shaped calcium-containing compound as an active substance and one or more pharmaceutically acceptable sugar alcohols having a micro structure, the process involving roller compaction of a composition containing the calcium-containing compound and the sugar alcohol. The invention also relates to the particulate material as such as well as to a solid dosage form based on the particulate material. The sugar alcohols employed have binding properties and - as in the case of sorbitol and isomalt - preferably sweetening properties.

In order to achieve satisfactory results, the sugar alcohol (binder) must be present in the particulate material in a concentration of at least about 5% w/w such as, e.g., at least about 10% w/w, at least about 15% w/w or at least about 20% w/w.

Use of roller compaction as a means for agglomeration of a calcium-containing compounds to obtain a particulate material that is suitable for use in the preparation of e.g. chewable tablets having an acceptable taste and mouthfeel, has two critical parameters, namely the shape of the calcium carbonate crystals and the structure of the sugar alcohol crystal. Moreover, the pharmaceutically acceptable sugar alcohol (binder) is normally present in a minimum concentration of about 5% w/w or about 10% w/w.

Furthermore, it has been also been observed that when a calcium-containing compound is employed that has a bulk density of at least about 0.7 g/ml (such as e.g.

calcium carbonate in the form of Scoralite) then the bulk density of the composition (containing the calcium-containing compound and the sugar alcohol) subjected to roller compaction is not remarkably higher than the bulk density of the calcium-containing compound itself (i.e. before roller compaction). Thus, when such a calcium carbonate quality is used, the bulk density before and after roller compaction may not change much, i.e. the change in bulk density between the particulate material obtained and the calcium-containing compound used is at the most about 40% such as, e.g., at the most about 30% or at the most about 20% calculated as $[(d_{particulate\ material} - d_{calcium\text{-}containing\ compound})/d_{particulate\ material}] \times 100\%$.

As mentioned above, the present invention relates to a particulate material comprising one or more regularly shaped calcium-containing compounds as an active substance and one or more pharmaceutically acceptable sugar alcohols having a micro structure. Normally, such a particulate material is further processed into a convenient dosage form such as tablets and such tablets must have suitable technical properties in order to withstand normal handling etc. Furthermore, when chewable tablets are prepared, the tablets must not be so hard, i.e. have an unacceptable high crushing strength, so that it becomes difficult for a patient to chew. Accordingly, it is important to balance the crushing strength to an acceptable level. As shown in the example herein, it is possible to determine whether a specific sugar alcohol is suitable for use in the preparation of a particulate material according to the invention by subjecting the sugar alcohol to two tests, namely i) a SEM photo showing that the sugar alcohol has a micro structure and ii) a test showing the compressibility properties of the sugar alcohol itself. To this end, the pharmaceutically acceptable sugar alcohol - when compressed into tablets containing 100% w/w of the sugar alcohol using 11,29 mm flat faced punches and a max compression force of 25kN - has a slope of correlation between crushing strength (measured in N) and compression pressure (measured in (N) of 7×10^{-3} or more, when tested using a Schleuniger Hardness Autotester 4 or Schleuniger Tablet tester 6D and a tablet placed with the longest dimension orthogonal to the jaws of the crushing strength apparatus.

The inventors have found that it is of great advantage in the roller compaction process to use a pharmaceutically acceptable sugar alcohol that has binding and sweetening properties. Examples of suitable binders or sweeteners include sorbitol, maltitol, xylitol, fructose, lactitol, isomalt, tagatose and manitol. Sorbitol has a sweetening effect

(compared to sucrose) of 0.55; maltitol that has a sweetening effect of <1; xylitol that has a sweetening effect of 1, isomalt that has a sweetening effect of <0.5, etc.

In order to ensure a sufficient distribution of the pharmaceutically acceptable sugar alcohol between the individual particles of the calcium-containing compound during the roller compaction, the inventors have found that the binder suitably have a mean particle size of at the most about 110 μm such as, e.g., at the most about 100 μm, at the most about 90 μm, at the most about 80 μm, at the most about 70 μm, at the most about 60 μm, at the most about 50 μm, at the most about 40 µm, at the most about 30 µm, at the most about 20 µm or about 10 µm. Examples of such materials are sorbitol and isomalt.

In the literature (see Pharmaceutical Technology, volume 1 (tabletting technology), Michael H. Rubinstein (ed.), Ellis Horwood Ltd, 1987) it has been stated that sorbitol has good tabletting properties and that the admixing of this excipient will increase the tablet strength. However, it has also been stated that in order to get this effect the sorbitol should be of the "instant" quality that is manufactured by spray-drying. The optimal particle size of sorbitol "instant" has been described as having 60 – 90% between 212 – 500 µm when determined by sieve analysis. The recommended concentration in the tablet is 30 – 80%. However, in the context of the present invention, sorbitol can be used as a binder (having sweetening properties) in tablets based on roller compaction and important deviations from the reported use of sorbitol are necessary:

1. Sorbitol should be finely dispersed or distributed between the particles of the calcium-containing compound in order to secure an optimal or a good as possible binding; this leads to limitations with respect to the particle size of sorbitol.

2. A particle size of sorbitol corresponding to $D_{0.5}$ < 100 µm seems to be suitable. The particle size is measured employing Malvern Mastersizer and the size is given as D(v;0.5).

3. The concentration of sorbitol should exceed that of 5% w/w and approx 20% w/w seems to be fine.

4. Sorbitol of the "instant" quality mentioned above would fail completely if the above described and relatively large particle size distribution was used.

Especially two sugar alcohols have proved to be suitable for use in the roller compaction process, namely sorbitol and isomalt. However, it is contemplated that other sugar alcohols also may be available in a quality that fulfils the above-mentioned criteria, and such sugar alcohols are envisaged to be suitable for use according to the invention. Below is mentioned other sugar alcohols, that may fulfil the above-mentioned criteria.

In a specific embodiment, the sugar alcohol is sorbitol, notable a sorbitol that has a mean particle size in a range of from about 25 to about 50 μm such as, e.g., from about 35 to about 45 μm or from about 30 to about 45 μm.

In another embodiment, the sugar alcohol is isomalt, notably an isomalt that has a mean particle size in a range of from about 20 to about 50 μm such as, e.g., from about 25 to about 35 μm or from about 20 to about 35 μm.

Provided that a sugar alcohol is employed that fulfils the above-mentioned criteria it is possible to use one or more sugar alcohols that not necessarily fulfils these criteria, but has other functions e.g. as a sweetener. Such sugar alcohols are typically selected from the group consisting of mannitol, xylitol, maltitol, inositol, and lactitol, and mixtures thereof. Examples are Sorbitols, Neosorb P100T, Sorbidex P1666B0 and Sorbogem Fines Crystalline Sorbitol available from Roquette Freres, Cerestar and SPI Polyols Inc. respectively. Maltisorb P90 (maltitol) available from Roquette Freres, Xylitol CM50, Fructofin CM (fructose) and Lactitol CM50 available from Danisco Sweeteners, Isomalt ST-PF, Isomalt DC100, Gaio Tagatose and Manitol available from Palatinit, Arla Foods and Roquette, Freres respectively. Further examples of suitable saccharide-based binders/sweeteners include sucrose, dextrose. Specific qualities of sorbitol and isomalt that do not fulfil the above-mentioned criteria may of course also be added.

In a specific embodiment, a particulate material according to the invention may comprise a mixture of sorbitol and xylitol. In such cases, the weight ratio between sorbitol and xylitol is normally in a range of from about 1:0.1 to about 1:1.5 such as, e.g., about 1:1. A mixture of isomalt and xylitol is also suitable and in such cases, the

weight ratio between isomalt and xylitol is normally in a range of from about 1:0.1 to about 1:1.5 such as, e.g., about 1:1.

In a paragraph given in the following, a description of calcium-containing compounds is given. However, as mentioned herein before, the calcium-containing compound for use in the roller compaction process according to the invention has a regular shape such as a calcium salt like calcium carbonate in specific qualities. In preferred aspect, the calcium salt is calcium carbonate and notably with a shape and a mean particle size corresponding to that of Scoralite 1B or Merck 2064. In a specific embodiment, the calcium carbonate is Scoralite 1B or Merck 2064.

However, the above-mentioned calcium carbonate may be used in admixture with other calcium-containing compounds such as, e.g., those mentioned herein in the following paragraph, especially calcium citrate, calcium lactate, calcium phosphate including tricalcium phosphate, calcium gluconate, bisglycino calcium, calcium citrate maleate, hydroxyapatite including solvates, and mixtures thereof.

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Normally, the content of the regularly shaped calcium-containing compound in the particulate material is in a range of from about 40% to about 100% w/w such as, e.g., from about 45% to about 98% w/w, from about 50% to about 95% w/w, from about 55% to about 90% w/w or at least about 60% w/w, at least about 65% w/w, at least about 70% w/w or at least about 75% w/w.

The particulate material obtained by roller compaction may comprise 100% w/w of the calcium-containing compound or it may comprise from about 50% to about 90% w/w such as, e.g., from about 70 to about 80% w/w of the total amount of calcium-containing compound contained in the tablet. Accordingly, a part of the total amount of calcium-containing compound may be added after roller compaction.

As mentioned above, during the roller compaction process, the calcium carbonate and the sugar alcohol are brought in close contact and due to the micro structure of the crystal of the sugar alcohol, the sugar alcohol crystals are squeezed between the calcium carbonate crystal. Accordingly, a SEM photo of the particulate material - when compressed into a tablet - shows that a surface of a deformed particle of the pharmaceutically acceptable sugar alcohol is in close contact with surfaces of the crystals of the one or more calcium-containing compound.

A particulate material according to the invention may further comprise one or more pharmaceutically acceptable excipients or additives, or one or more therapeutically, prophylactically and/or diagnostically active substances. A description of pharmaceutically acceptable excipients suitable for use in the present context is given herein.

A particular active substance of interest is a vitamin D.

Furthermore, roller compaction of a composition containing a calcium-containing compound and a sugar alcohol to obtain a particulate material according to the invention leads to a particulate material that has such a flowability that - when tablets are prepared from the particulate material optionally admixed with at the most 10% w/w such as, e.g. at the most about 7.5% w/w or at the most about 5% w/w of a glidant using a tabletting machine operating at at least 300 tablets per min - the mass variation of the tablets obtained fulfils the requirements given in Ph. Eur. The tabletting machine may be operating at e.g. 1000 tablets/min or even higher such as, e.g., 2000 tablets/min, 3000 tablets/min, 4000 tablets/min, 5000 tablets/min, 6500 tablets/min etc. The dwell time during the preparation of the tablets is at the most about 1 sec.

In a specific embodiment a particulate material according to the invention contains from about 60 to about 95% w/w of the calcium-containing compound and from about 5 to about 40% w/w of the pharmaceutically acceptable sugar alcohol, provided that the sum does not exceed 100% w/w.

In another specific embodiment a particulate material according to the invention contains from about 60 to about 94% w/w such as, e.g., from about 65% to about 80% w/w of the calcium-containing compound, from about 5 to about 35% w/w such as, e.g., from about 15 to about 30% w/w of the pharmaceutically acceptable sugar alcohol and from about 1 to about 15% w/w of one or more pharmaceutically acceptable excipients and/or active substances, provided that the sum of ingredients amounts to 100% w/w.

More specifically, a particulate material according to the invention preferably contains from about 65% to about 80% w/w such as, e.g., from about 70% to about 75% w/w of the calcium-containing compound and from about 15% to about 25% w/w such as, e.g., from about 20 to about 25% w/w of sorbitol or isomalt or mixtures thereof.

A particulate material according to the invention may be used as such, but normally it is manufactured into a suitable solid dosage form. One or more pharmaceutically acceptable excipients may be added in order to prepare the dosage form. The dosage form is intended for oral administration e.g. in the form of a single unit or a multiple unit dosage form such as, e.g., in the form of tablets, capsules, sachets, beads, pellets or the like.

In a preferred embodiment, the solid dosage form according to the invention is in the form of tablets.

In a specific embodiment the tablets have a shape and dimensions essentially as shown in Figure 24 herein. This shape is especially designed to easily break the tablet into two halves of essentially the same size, i.e. essentially containing the same amount of calcium. The breakage is provided by placing the tablet on a flat surface e.g. a table and then by use of e.g. two fingers pressing simultaneously on each end of the tablet. Due to the fact that the tablet is in contact with the table only in one point this is possible.

A solid dosage form according to the invention may contain an amount of the one or more calcium-containing compounds corresponding to from about 300 to about 1200 mg calcium such as, e.g., from about 400 to about 600 mg calcium. Normally, the total concentration of the one or more calcium-containing compound in the dosage form is in a range of from about 40% to about 99% w/w such as, e.g., from about 45% to about 98% w/w, from about 50% to about 95% w/w, from about 55% to about 90% w/w or at least about 60% w/w, at least about 65% w/w, at least about 70% w/w.

In a specific embodiment, the total concentration of the particulate material contained in the dosage form is from about 65% to about 100% w/w such as, e.g., from about 70% to about 98% w/w, from about 75% to about 95% w/w, from about 80% to about 95% or from about 85% to about 95% w/w.

In another specific embodiment, a solid dosage form according to the invention contains from about 60% to about 95% w/w of the calcium-containing compound and from about 5% to about 40% w/w of the pharmaceutically acceptable sugar alcohol, provided that the sum does not exceed 100% w/w. Alternatively, a solid dosage form

contains from about 60 to about 94% w/w such as, e.g., from about 65% to about 80% w/w of the calcium-containing compound, from about 5 to about 35% w/w such as, e.g., from about 15 to about 30% w/w of the pharmaceutically acceptable sugar alcohol and from about 1 to about 15% w/w of one or more pharmaceutically acceptable excipients and/or active substances, provided that the sum of ingredients amounts to 100% w/w.

A SEM photo of a fractured surface of the solid dosage form shows that a surface of a deformed particle of sugar alcohol is in close contact with surfaces of the one or more calcium-containing compound.

As mentioned herein before, a solid dosage form according to the invention is stable. Accordingly, the crushing strength of the tablets when stored in open petri dishes at 25 °C and 60% RH at the most changes 50% such as, e.g. at the most about 40%, at the most about 30%, at the most about 20%, at the most about 15%, at the most about 10% during a time period that starts 5 days after manufacture and runs during the remaining storage period. Acceptable stability is obtained if a tablet during the whole storage period (e.g. 1 month, 3 moths) in open Petri dishes has a crushing strength in a range of from about 70 to about 140 N.

In a preferred aspect, a solid dosage form is in the form of a chewable, suckable and/or swallowable tablet. Importantly for chewable tablets is the taste and such tablets of the invention must have an acceptable taste with respect to sweetness, flavour and chalkiness when tested by a professional/skilled sensory test panel of at least 6 persons.

A solid dosage form according to the invention may comprise a sweetener selected from the group consisting of dextrose, fructose, glycerin, glucose, isomalt, lactitol, lactose, maltitol, maltose, mannitol, sorbitol, sucrose, tagatose, trehalose, xylitol, alitame, aspartame, acesulfam potassium, cyclamic acid, cyclamate salt (e.g. calcium cyclamate, sodium cyclamate), neohesperidine dihydrochalcone, thaumatin, saccharin, saccharin salt (e.g. ammonium saccharin, calcium saccharin, potassium saccharin, sodium saccharin), and mixtures thereof.

The invention also relates to a process for the preparation of a particulate material as defined above, the process comprises roller compaction of a composition comprising the regularly shaped calcium-containing compound and one or more pharmaceutically

acceptable sugar alcohols having a micro structure. Details concerning this aspect appear from the appended claims and from the description above relating to the particulate material apply *mutatis mutandis* to this and other aspects of the invention.

A further aspect of the invention is to combine the manufacture of a particulate material and the manufacture of tablets. By use of pocket rollers on the roller compactor a powder mixture can be transformed directly into a solid dosage form, that is a tablet.

A further aspect of the invention is a process for preparing a tablet comprising a calcium-containing compound, the process comprises

i) preparing a particulate material as defined herein,

ii) optionally admixing one or more pharmaceutically acceptable excipients or additive and/or one or more active substances, and

iii) compressing the material into tablets.

Normally, the compression in step iii) is performed at a compression force that is adjusted with respect to the diameter and the desired height of the tablet so that the compression force applied is at the most about 80 kN such as, e.g., at the most 70 kN, at the most 60 kN, at the most 50 kN, at the most about 40 kN, at the most about 30 kN or at the most about 20 kN when tablets having a a diameter of about 16 mm or is capsule shaped (9.4 x 18.9 mm) and a resulting height of at the most about 10 mm such as, e.g., about 9 mm, about 8 mm or about 7 mm or about 6 mm are obtained.

Specifically, the invention relates to a process according for the preparation of a tablet comprising

i) calcium carbonate

ii) sorbitol and/or isomalt,

iii) a vitamin D, and

iv) optionally one or more pharmaceutically acceptable excipients.

The tablet may comprise

i) from about 50% to about 90% w/w of calcium carbonate,

ii) from about 5 to about 30% w/w of sorbitol and/or isomalt,

iii) from about 0.01 to about 1% w/w of a vitamin D, and

iv) optionally one or more pharmaceutically acceptable excipients

with the proviso that the total amount of ingredients corresponds to about 100% w/w.

Calcium-containing compound

The calcium-containing compound contained in a particulate material made according to the invention is a physiologically tolerable calcium-containing compound that is therapeutically and/or prophylactically active.

Calcium is essential for a number of key functions in the body, both as ionized calcium and a calcium complex (Campell AK.Clin Sci 1987; 72:1-10). Cell behaviour and growth are regulated by calcium. In association with troponin, calcium controls muscle contraction and relaxation (Ebashi S. Proc R Soc Lond 1980; 207:259-86).

Calcium selected channels are a universal feature of the cell membrane and the electrical activity of nerve tissue and the discharge of neurosecretory granules are a function of the balance between intracellular and extra cellular calcium levels (Burgoyne RD. Biochim Biophys Acta 1984;779:201-16). The secretion of hormones and the activity of key enzymes and proteins are dependent on calcium. Finally calcium as a calcium phosphate complex confers rigidity and strength on the skeleton (Boskey AL. Springer, 1988:171-26). Because bone contains over 99% of the total body calcium, skeletal calcium also serves as the major long-term calcium reservoir.

Calcium salts such as, e.g., calcium carbonate is used as a source of calcium especially for patients suffering from or at risk of osteoporosis. Moreover, calcium carbonate is used as an acid-neutralizing agent in antacid tablets.

As mentioned above, calcium has a number of important functions within the mammalian body in particular in humans. Furthermore, in many animal models, chronic low calcium intake produces osteopenia. The osteopenia affects cancellous bone more than cortical bone and may not be completely reversible with calcium supplementation. If the animal is growing reduced calcium intake leads to stunting. In the premature human neonate the higher the calcium intake, the greater the increase in skeletal calcium accretion which, if high enough, can equal gestational calcium retention. During growth chronic calcium deficiency causes rickets. Calcium supplements in both pre- and postpubertal healthy children leads to increased bone mass. In adolescents the higher the calcium intake, the greater the calcium retention, with the highest retention occurring just after menarche. Taken together, these data suggest that in children and adolescents considered to be taking an adequate intake of calcium, peak

bone mass can be optimized by supplementing the diet with calcium. The mechanisms involved in optimizing deposition of calcium in the skeleton during growth are unknown. They are probably innate properties of the mineralization process that ensures optimal calcification of the osteoid if calcium supplies are high. The factors responsible for stunting of growth in states of calcium deficiency are also unknown but clearly involve growth factors regulating skeletal size.

In adults calcium supplementation reduces the rate of age-related bone loss (Dawson-Hughes B. Am J Clin Nut 1991;54:S274-80). Calcium supplements are important for individuals who cannot or will nor achieve optimal calcium intakes from food. Furthermore, calcium supplement is important in the prevention and treatment of osteoporosis etc.

Furthermore, calcium may have anticancer actions within the colon. Several preliminary studies have shown high calcium diets or intake of calcium supplementation is associated with reduced colon rectal cancer. There is increasing evidence that calcium in combination with acetylsalicylic acid (ASA) and other non-steroidal anti-inflammatory drugs (NSAIDS) reduce the risk the risk of colorectal cancer.

Recent research studies suggest that calcium might relieve premenstrual syndrome (PMS). Some researchers believe that disruptions in calcium regulation are an underlying factor in the development of PMS symptoms. In one study, half the women of a 466 person group of pre-menopausal women from across the U.S. were tracked for three menstrual cycles and were given 1200 mg of calcium supplements daily throughout the cycle. The final results showed that 48% of the women who took placebo had PMS related symptoms. Only 30% of those receiving calcium tablets did.

Calcium salts like e.g. calcium carbonate is used in tablets and due to the high dose of calcium required, such tablets are often in the form of chewable tablets. It is a challenge to formulate e.g. chewable tablets containing a calcium salt, which tablets have a pleasant taste and an acceptable mouth feel without the characteristic dominating taste or feeling of chalk.

A calcium-containing compound for use according to the invention may be e.g. bisglycino calcium, calcium acetate, calcium carbonate, calcium chloride, calcium

citrate, calcium citrate malate, calcium cornate, calcium fluoride, calcium glubionate, calcium gluconate, calcium glycerophosphate, calcium hydrogen phosphate, calcium hydroxyapatite, calcium lactate, calcium lactobionate, calcium lactogluconate, calcium phosphate, calcium pidolate, calcium stearate and tricalcium phosphate. Other calcium sources may be water-soluble calcium salts, or complexes like e.g. calcium alginate, calcium-EDTA and the like or organic compounds containing calcium like e.g. calcium organophosphates. Use of bone meal, dolomite and other unrefined calcium sources is discouraged because these sources may contain lead and other toxic contaminants. However, such sources may be relevant if they are purified to a desired degree.

The calcium-containing compound may be used alone or in combination with other calcium-containing compounds.

Of specific interest is bisglycino calcium, calcium acetate, calcium carbonate, calcium chloride, calcium citrate, calcium citrate malate, calcium cornate, calcium fluoride, calcium glubionate, calcium gluconate, calcium glycerophosphate, calcium hydrogen phosphate, calcium hydroxyapatite, calcium lactate, calcium lactobionate, calcium lactogluconate, calcium phosphate, calcium pidolate, calcium stearate and tricalcium phosphate. Mixtures of different calcium-containing compounds may also be used. As appears from the examples herein, calcium carbonate is especially suitable for use as a calcium-containing compound and calcium carbonate has a high content of calcium.

Of particular interest is calcium carbonate.

Normally, a tablet made according to the invention contains an amount of the calcium-containing compound corresponding to from about 100 to about 1000 mg Ca such as, e.g., from about 150 to about 800 mg, from about 200 to about 700 mg, from about 200 to about 600 mg or from about 200 to about 500 mg Ca.

Calcium carbonate

Calcium carbonate can be in three different crystal structures: calcite, aragonite and vaterite. Mineralogically, these are specific mineral phases, which relate to the distinct arrangement of the calcium, carbon and oxygen atoms in the crystal structure. These distinct phases influence the shape and symmetry of the crystal forms. For example, calcite is available in four different shapes: scalenohedral, prismatic, spherical and rhombohedral, and aragonit crystals can be obtained as e.g. discrete or clustered

needle-like shapes. Other shapes are also available such as, e.g., cubic shapes (Scoralite 1A + B from Scora).

As shown in the examples herein, a particular suitable quality of calcium carbonate is calcium carbonate having a mean particle size of 60 μm or less such as, e.g., 50 μm or less or 40 μm or less.

Furthermore, an interesting quality of calcium carbonate has a bulk density below 2 g/mL.

Calcium carbonate 2064 Merck (available from Merck, Darmstadt, Germany) that has a mean particle size of 10 – 30 µm, an apparent bulk density of 0.4 to 0.7 g/mL, and a specific surface area of 0.3 m^2/g;

Calcium carbonate 2069 Merck (available from Merck, Darmstadt, Germany) that has a mean particle size of approx. 3.9 µm, and an apparent bulk density of 0.4 to 0.7 g/mL;

Scoralite 1A (available from Scora Watrigant SA, France) has a mean particle size of 5 to 20 µm, an apparent bulk density of 0.7 to 1.0 g/mL, and a specific surface area of 0.6 m^2/g;

Scoralite 1B (available from Scora Watrigant SA, France) has a mean particle size of 10 –25 µm, an apparent bulk density of 0.9 to 1.2 g/mL, and a specific surface area of 0.4 to 0.6 m^2/g;

Scoralite 1A + B (available from Scora Watrigant SA, France) have a mean particle size of 7 – 25 µm, an apparent bulk density of 0.7 to 1.2 g/mL, and a specific surface area of 0.35 to 0.8 m^2/g;

Pharmacarb LL (available from Chr. Hansen, Mahawah New Jersie) L has a mean particle size of 12 – 16 µm, an apparent bulk density of 1.0 to 1.5 g/mL, and a specific surface area of 0.7 m^2/g;

Sturcal H has a mean particle size of approx. 4 µm, an apparent bulk density of 0.48 to 0.61 g/mL;

Sturcal F has a mean particle size of approx. 2.5 µm, an apparent bulk density of 0.32 to 0.43 g/mL;

Sturcal M has a mean particle size of 7 µm, an apparent bulk density of 0.7 to 1.0 g/mL, and a specific surface area of 1.0 m^2/g;
Mikhart 10, SPL, 15, 40 and 65 (available from Provencale, Provencale, France);
Mikhart 10 has a mean particle size of 10 µm,
Mikhart SPL has a mean particle size of 20 µm,
Mikhart 15 has a mean particle size of 17 µm,
Mikhart 40 has a mean particle size of 30 µm, an apparent bulk density of 1.1 to 1.5 g/mL;
Mikhart 65 has a mean particle size of 60 µm, an apparent bulk density of 1.25 to 1.7 g/mL;

Omyapure 35, (available from Omya S.A.S, Paris, France) has a mean particle size of 5 - 30 µm, and a specific surface area of 2.9 m^2/g;

Socal P2PHV (available from Solvay, Brussels, Belgium) has a mean particle size of 1.5 µm, an apparent bulk density of 0.28 g/mL, and a specific surface area of 7.0 m^2/g;

Calci Pure 250 Heavy, Calci Pure 250 Extra Heavy and Calci Pure GCC HD 212 with a mean particle size of 10-30µm, an apparent bulk density of 0.9 – 1.2 g/ml, and a specific surface area of 0.7 m^2/g (available from Particle Dynamic Inc., St. Louis Montana).

The content of the calcium-containing compound in a tablet made according to the present invention is in a range from about 40% to about 100% w/w such as, e.g., from about 45% to about 98% w/w, from about 50% to about 95% w/w, from about 55% to about 90% w/w or at least about 60% w/w, at least about 65% w/w, at least about 70% w/w or at least about 75% w/w.

Normally, the dose of calcium for therapeutic or prophylactic purposes is from about 350 mg (e.g. newborn) to about 1200 mg (lactating women) daily. The amount of the calcium-containing compound in the tablets can be adjusted to that the tablets are suitable for administration 1-4 times daily, preferably once or twice daily.

As mentioned above, the granulate obtained by the method according to the invention may be used as such, but it is also very suitable for further manufacturing into solid dosage forms like e.g. tablets, capsules or sachets.

A person skilled in the art will know how to adjust the composition and the various process parameters in order to obtain a desired calcium-containing product.

In one embodiment of the invention, the granulate obtained by the present method is intended to be manufactured into tablets. Often it is necessary to add one or more pharmaceutically acceptable excipients (e.g. lubricants) in order to avoid adherence and/or increase flowability of the granulate obtained. Accordingly, the method may also comprise a step of mixing the granulate obtained with one or more pharmaceutically acceptable excipients.

In the event that it is desired to include other active substances than the calcium-containing compound, the method may also comprise a step of adding one or more therapeutically, prophylactically and/or diagnostically active substance to the granulate obtained.

Such substances include one or more nutrients such as, e.g., one or more vitamins or minerals. In a specific embodiment, the further active substance is a D-vitamin such as, e.g., D_3 vitamin, D_2 vitamin or derivatives thereof.

D vitamin or other active substances

A particulate material as well as a tablet obtained according to the invention may comprise a further therapeutically and/or prophylactically active substance. Of particular interest are one or more D-vitamin compounds. Non-limitating examples are dry vitamin D3, 100 CWS available from Roche and dry vitamin D3 100 GFP available from BASF.

A particulate material or tablet made according to the invention may comprise a further therapeutically and/or prophylactically active substance, or it may contain one or more nutrients such as, e.g. one or more vitamins or minerals. Of specific interest are e.g. vitamin B, vitamin C, vitamin D and/or vitamin K and minerals like e.g. zink, magnesium, selenium etc.

Of particular interest are one or more D-vitamin compounds such as, e.g., Vitamin D_2 (ergocalciferol) and Vitamin D_3 (cholecalciferol) including dry vitamin D_3, 100 CWS available from Roche and dry vitamin D_3 100 GFP available from BASF.

In addition to its action on calcium and skeletal homeostasis, vitamin D is involved in the regulation of several major systems in the body. The actions of vitamin D are medicated at the genome by a complex formed by 1,25-$(OH)_2$ vitamin D mainly produced in the kidney, with the vitamin D receptor (VDR). The latter is widely distributed in many cell types. The 1,25-$(OH)_2$ vitamin D/VDR complex has important regulatory roles in cell differentiation and in the immune system. Some of these actions are probably dependant on the ability of certain tissues other than the kidney to produce 1,25-$(OH)_2$ vitamin D locally and act as a paracrine (Adams JS et al. Endocrinology 1996;137:4514-7).

In humans, deficiency of vitamin D results in rickets in children and osteomalacia in adults. The basic abnormality is a delay in the rate of mineralization off osteoid as it is laid down by the osteoblast (Peacock M. London Livingstone, 1993:83-118). It is not clear whether this delay is due to a failure of a 1,25-$(OH)_2$ vitamin D–dependant mechanism in the osteoblast or to reduced supplies of calcium and phosphate secondary to malabsorption or a combination of both. Accompanying the mineralization delay, there is reduced supply of calcium and phosphate, severe secondary hyperparathyroidism with hypocalcaemia and hypophosphatemia and increased bone turnover.

Vitamin D insufficiency, the preclinical phase of vitamin D deficiency, also causes a reduced calcium supply and secondary hyperparathyroidism, albeit of a milder degree than found with deficiency. If this state remains chronic, osteopenia results. The biochemical process underlying this state of calcium insufficiency is probably inappropriate level of 1,25-$(OH)_2$ vitamin D due to a reduction in its substrate 25-OHD (Francis RM et al. Eur J Clin Invest 1983; 13:391-6). The state of vitamin D insufficiency is most commonly found in the elderly. With age there is a decrease in serum 25-OH vitamin D due to decreased sunlight exposure and possible to decreased skin synthesis. Furthermore, in the elderly the condition is exacerbated by a decrease in calcium intake and a paradoxical decrease in calcium absorption. The reduction in renal function with age giving rise to reduced renal 1,25-$(OH)_2$ vitamin D production may be a contributing factor. There are a number of studies of the effects of vitamin D

supplementation on bone loss in the elderly. Some are without calcium supplementation and others are with calcium supplementation. It appears from the studies that although vitamin D supplementation is necessary to reverse deficiency and insufficiency, it is even more important as far as the skeleton is concerned to provide calcium supplementation since the major skeletal defect is calcium deficiency. In literature based on clinical trials, recent findings suggest trends of need for higher doses of vitamin D for the elderly patients (Compston JE. BMJ 1998;317:1466-67). An open quasi-randomised study of annual injections of 150.000-300.000 IU of vitamin D (corresponding to approx. 400-800 IU/day) showed a significant reduction in overall fracture rate but not in the rate of hip fracture in treated patients (Heikinheimo RJ et al. Calcif Tissue Int 1992; 51:105-110).

As it appears from above, a combination of calcium and vitamin D is of interest. The recommended Daily Allowance (RDA) of calcium and vitamin D_3 are as follows (European Commission. Report on osteoporosis in the European Community. Action for prevention. Office for official Publications of the European Communities, Luxembourg 1998):

Group	Age (years)	Calcium (mg)*	Vitamin D_3 (µg)
Newborn	0-0.5	400	10-25
	0.5-1.0	360-400	10-25
Children	1.0-3.0	400-600	10
	4.0-7.0	450-600	0-10
	8.0-10	550-700	0-10
Men	11-17	900-1000	0-10
	18-24	900-1000	0-15
	25-65	700-800	0-10
	65+	700-800	10
Women	11-17	900-1000	0-15
	18-24	900-1000	0-10
	25-50	700-800	0-10
	51-65	800	0-10
	65+	700-800	10

Pregnant	700-900	10
Lactating	1200	10

* RDA of calcium varies from country to country and is being re-evaluated in many countries.

Vitamin D is very sensitive towards humidity and is subject to degradation. Therefore, vitamin D is often administered in a protective matrix. Accordingly, when tablets are prepared containing a vitamin D it is of utmost importance that the compression forces applied during the tabletting step do not decrease the protective effect of the matrix and thereby impair the stability of vitamin D. To this end, the combination of the various ingredients in a granulate or tablet made according to the invention has proved to be very suitable in those cases where vitamin D also is incorporated into the composition as it is possible to employ a relatively low compression force during tabletting and still achieve a tablet with suitable mechanical strength (crushing strength, friability etc.).

As indicated above, a tablet containing vitamin D is contemplated to fulfil the following requirements with respect to stability:

After storage in a closed container at 25 °C at 60% relative humidity (RH) for at least 6 month such as, e.g., at least 1 year, at least 1.5 years, at least 2 years or at least 5 years, there is a decrease in the content of D vitamin of at the most about 15% w/w such as, e.g., at the most about 10% w/w or at the most about 5% w/w.

After storage in a closed container at 40 °C at 75% relative humidity (RH) for at least 1 month such as, e.g., at least 2 months, at least 4 months or at least 6 months, there is a decrease in the content of D vitamin of at the most about 15% w/w such as, e.g., at the most about 10% w/w or at the most about 5% w/w.

In a specific embodiment, the invention provides a tablet comprising
i) a calcium-containing compound as an active substance,
ii) a vitamin D, and
iii) optionally one or more pharmaceutically acceptable excipients or actives.

More specifically, the tablet may comprise
i) at least 200 mg of the calcium-containing compound (normal range 200-1500 mg),

ii) at least 5 μg of vitamin D (normal range 5-100 μg - 1 μg = 40 IU), and
iii) optionally one or more pharmaceutically acceptable excipients or actives.

In a specific embodiment, the invention provides a tablet comprising
i) from about 50% to about 90% w/w of the calcium-containing compound,
ii) from about 0.00029%o about 0.0122% w/w of a vitamin D, and
iii) optionally one or more pharmaceutically acceptable excipients or actives
with the proviso that the total amount of ingredients corresponds to about 100% w/w.

In particular, the tablet may comprise
i) from about 50% to about 90% w/w of the calcium-containing compound,
ii) from about 5 to about 40% w/w of a sweetening agent,
iii) from about 0.12% to about 4.9 % w/w of a vitamin D including a protective matrix,
iv) optionally one or more pharmaceutically acceptable excipients or actives
with the proviso that the total amount of ingredients corresponds to about 100% w/w.

Pharmaceutically acceptable excipients

In the present context, the term "pharmaceutically acceptable excipient" is intended to denote any material, which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect per se. A pharmaceutically acceptable excipient may be added to the active drug substance with the purpose of making it possible to obtain a pharmaceutical composition, which has acceptable technical properties. Although a pharmaceutically acceptable excipient may have some influence on the release of the active drug substance, materials useful for obtaining modified release are not included in this definition.

The calcium-containing compound and the sugar alcohol may also be admixed with one or more pharmaceutically acceptable excipients before or after roller compaction. Such excipients include those normally used in formulation of solid dosage forms such as, e.g. fillers, binders, disintegrants, lubricants, flavouring agents, colouring agents, including sweeteners, pH adjusting agents, stabilizing agents, etc.

Typically, a disintegrant is selected from the group consisting of: croscarmellose sodium (a cross-linked polymer of carboxymethylcellulose sodium), crospovidone,

starch NF; polacrilin sodium or potassium and sodium starch glycolate. Those skilled in the art will appreciate that it is desirable for compressible tablets to disintegrate within 30 minutes, more desirable within 10 min, most desirable within 5 min; therefore, the disintegrant used preferably results in the disintegration of the tablet within 30 minutes, more preferable within 10 min, most preferable within 5 min.

Examples of disintegrants that may be used are e.g. cellulose derivatives, including microcrystalline cellulose, low-substituted hydroxypropyl cellulose (e.g. LH 22, LH 21, LH 20, LH 32, LH 31, LH30); starches, including potato starch; croscarmellose sodium (i.e. cross-linked carboxymethylcellulose sodium salt; e.g. Ac-Di-Sol®); alginic acid or alginates; insoluble polyvinylpyrrolidone (e.g. Polyvidon® CL, Polyvidon® CL-M, Kollidon® CL, Polyplasdone® XL, Polyplasdone® XL-10); sodium carboxymethyl starch (e.g. Primogel® and Explotab®).

Fillers/diluents/binders may be incorporated such as polyols, sucrose, sorbitol, mannitol, Erythritol®, Tagatose®, lactose (e.g., spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose or Fast-Floc®), microcrystalline cellulose (e.g., various grades of Avicel®, such as Avicel® PH101, Avicel® PH102 or Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tai® and Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low-substituted) (e.g. L-HPC-CH31, L-HPC-LH11, LH 22, LH 21, LH 20, LH 32, LH 31, LH30), dextrins, maltodextrins (e.g. Lodex® 5 and Lodex® 10), starches or modified starches (including potato starch, maize starch and rice starch), sodium chloride, sodium phosphate, calcium sulfate, calcium carbonate.

In pharmaceutical compositions made according to the present invention, especially microcrystalline cellulose, L-hydroxypropylcellulose, dextrins, maltodextrins, starches and modified starches have proved to be well suited.

In a specific embodiment of the invention, the calcium-containing compound may be roller compacted together with one or more pharmaceutically acceptable binders, or a binder may be added after roller compaction. Suitable binders include those normally used within the pharmaceutical field although binders usually employed in wet granulation processes are not likely to be able to function to the same extent as essentially no liquid is present in during the agglomeration.

More specifically, examples include
cellulose derivates including methylcellulose, hydroxypropylcellulose (HPC, L-HPC), hydroxypropylmethylcellulose (HPMC), microcrystalline cellulose (MCC), sodium carboxymethylcellulose (Na-CMC), etc.;

mono- di-, oligo-, polysaccharides including dextrose, fructose, glucose, isomalt, lactose, maltose, sucrose, tagatose, trehalose, inulin and maltodextrin;

polyols including sugar alcohols such as, e.g, lactitol, maltitol, mannitol, sorbitol, xylitol and inositol;

polyvinylpyrrolidone including Kollidon K30, Kollidon 90F or Kollidon VA64
and

proteins including casein.

Glidants and lubricants may be incorporated such as stearic acid, metallic stearates, talc, waxes and glycerides with high melting temperatures, colloidal silica, sodium stearyl fumarate, polyethylenglycols and alkyl sulphates.

Surfactants may be employed such as non-ionic (e.g., polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, polysorbate 120, sorbitane monoisostearate, sorbitanmonolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, glyceryl monooleate and polyvinylalkohol), anionic (e.g., docusate sodium and sodium lauryl sulphate) and cationic (e.g., benzalkonium chloride, benzethonium chloride and cetrimide) or mixtures thereof.

Other appropriate pharmaceutically acceptable excipients may include colorants, flavouring agents, and buffering agents.

As appears from the claims, the present invention also provides a method comprising the step of processing the particulate material obtained by roller compaction into a solid dosage form. Such dosage forms may be provided with a coating provided that the

coating does not substantially retard the release of the active drug substance from the composition. Typically, a film coating may be employed.

Suitable lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and the like. Preferably, magnesium stearate is used.

Suitable bulking agents include xylitol, mannitol, compressible sugars, lactose, calcium phosphate and microcrystalline celluloses.

Suitable artificial sweeteners include dextrose, fructose, glycerin, glucose, isomalt, lactitol, lactose, maltitol, maltose, mannitol, sorbitol, sucrose, tagatose, trehalose, xylitol, alitame, aspartame, acesulfam potassium, cyclamic acid, cyclamate salt (e.g. calcium cyclamate, sodium cyclamate), neohesperidine dihydrochalcone, thaumatin, saccharin, saccharin salt (e.g. ammonium saccharin, calcium saccharin, potassium saccharin, sodium saccharin), and mixtures thereof.

If desired known flavourants and known FD & C colorants can be added to the composition.

Specific aspect relating to tablets designed for dose dispensing machines

In today's world the global healthcare area faces major changes. The future holds further medical advancement with an increasing elderly population demanding extended care. To improve compliance for e.g. the elderly population, packing of medicine in daily unit/multiple dose packages ("dose dispensing") is implemented in more and more countries such as, e.g., European countries. Typically the medicine is dosed for a two weeks period of time and the daily dose package contains e.g. packages/bags for the morning, noon, evening and night medication. On each bag information about the person and the medicine are printed.

Development of tablets that are sufficiently robust to be dispensed via a dose-dispensing machine is a particular challenge when the tablets are formulated as chewable tablets. Normally, chewable tablets do not have sufficient technical properties, which are required for a dose-dispensing machine (e.g. the tablets are too fragile and when exposed to the filling equipment they afford dust which makes the filling difficult or impossible). Today no product is available on the market containing a calcium-containing compound as a therapeutically and/or prophylactically active

substance and being chewable, i.e. having an acceptable taste and mouthfeel, and at the same time having sufficient technical properties to enable dispensing via a dose-dispensing machine. Accordingly, it is not possible for patients to obtain a daily dose package packed by a dose-dispensing machine, which package includes one or more calcium-containing chewable tablets. The present inventors address this issue by providing a tablet that is sufficient robust to withstand packaging by a dose-dispensing machine and at the same time gives the patient or the user the liberty of choosing whether she wants to chew, suck and/or swallow the tablet, i.e. the improved technical properties do not impair an acceptable taste and mouthfeel.

As appears from the above, the present invention solves the problem of providing chewing tablets with an acceptable taste (which tablets also may be sucked or swallowed) and with mechanical properties and a size that are suitable for use when the tablets are dispensed by a dose-dispensing machine.

In general, improved outcomes and reduced costs are some of the advantages in applying a dose-dispensing machine, which may be achieved by, e.g.,

i) reduced distribution time, which increases staff efficiency and releases staff to other functions,
ii) reduced incidence of prescribing, dispensing and/or administration errors,
iii) improved patient care by clearly labelled unit/multi dose packages, which help patients receiving the right medication at the right time, and/or
iv) reduced waste of medicine.

As mentioned above, the regulatory requirements for tablets dispensed by a dose-dispensing machine are relative high, and they may be different from country to country with regard to the application, type of medicine, stability etc.

Currently, there are three important types of dose-dispensing machines on the market, namely a Tosho machine type Main-Topra 2441 CE. This machine doses in small plastic bags and doses up to 244 different compositions. Another type Main-Topra 4001 CE doses up to 400 different compositions with the same speed as Main-Topra 2441 CE (45 bags/min).

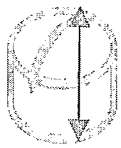
Automed Technologies Inc, USA, has e.g. the type ATC 212 on the European market. This machine doses in small plastic bags and doses up to 212 different compositions. The machine packs 25 bags/min. Other recent types are improved with respect to number of different compositions to be packed (330 or 520) and the speed is increased to 60 bags/min.

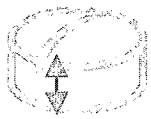
Hyupshin Medical co. Ltd has a dose-dispensing machine, ATDPS, which doses in small plastic bags and doses up to 352 different compositions. The speed is 60 bags/min. Furthermore, new machines have been developed (ATDPS JV-500SL and ATDPS JV-352SL), which doses up to 500 different compositions with the same speed (60 bags/min).

Due to the different size and shapes of tablets and capsules, the machines are supplied with different types of cassettes and rotary parts, which ensure that only one tablet or capsule is dosed at the same time. The main body of the cassettes is well shielded from light, it is dust-tight and damp-proof, so the cassettes are well-suited to store the medicine. Misplacing the cassettes is not possible because of a safety lock. Tablets and capsules will not be stored in the cassettes for more than a defined period of time to ensure the quality of the compositions. The machines will make a notice when a composition has been stored in the cassettes for more than this period of time.

With respect to the size of the tablets, the following requirements should be met in order to ensure that the tablets can be packed with a dose-dispensing machine: The requirements are dynamic and may change over time.

Round tablet





Length/Diameter Thickness

Distributor	Interval	Length (mm)	Thickness (mm)
Tosho	Minimum		
	Maximum	14.0	9.4
Hyupshin	Minimum	5.5	1.5
	Maximum	13.2	6.7
Automed Tech.	Minimum	4.6	2.2
	Maximum	14.0	7.0

Oval tablet







Length Thickness Width

Distributor	Interval	Length (mm)	Thickness (mm)	Width (mm)
Tosho	Minimum			
	Maximum	21.5	7.5	7.5
Hyupshin	Minimum	8.5	2.7	4.0
	Maximum	20.0	7.7	10.0
Automed Tech.	Minimum	6.9	2.2	4.6
	Maximum	21.0	7.5	11.7

The above-mentioned dimension for a round or an oval tablet may be changed and still fit into the specified dose-dispensing machine. Experiments performed by the present

inventors have shown that a variation in a range of ± 20% is acceptable, preferable ± 10%. With respect to the size, one of the major problems, the inventors were faced with was to reduce the thickness of the tablets. This was solved by using a proper combination of active ingredient(s) and pharmaceutically acceptable excipients and by a careful selection of a suitable particle size and/or crystal form of the calcium-containing compound, the properties of the excipients and the preparation method.

It is of importance that the tablets do not create dust and as mentioned above, the tablets must be sufficiently robust to withstand the mechanical stress employed by using a dose-dispensing machine.

The present inventors have found that it is possible to apply a thin film coating on the tablets in order e.g. to increase the swallowability or in order to minimize any dust problems or problems relating to crushing strength or friability. To this end it should be noted that application of a film coating cannot repair substantial problems with respect to crushing strength or friability, but it can just give the final push in the right direction. Furthermore, only a thin film coating must be applied in order to maintain an acceptable mouthfeel, i.e. the coating may be applied in an amount that corresponds to an increase in weight of the tablet of at the most about 2% w/w such as, e.g., at the most about 1.5% w/w, at the most about 1% w/w or in a range of from about 0.25% to 0.75% w/w based on the weight of the uncoated tablets.

In the following are given dimensions of marketed tablets containing calcium carbonate
Dimensions of calcium carbonate containing tablet

	Length [mm]	Height [mm]	Width [mm]
Calcipos-D swallowable (oval/capsule)	19.3	5.6	8.7
Calcipos-D chewing tablet (round)	17.2	7.0	--
Calcichew chewing tablet (round)	16.1	7.0	--
Ideos chewing tablet (quadratic)	19.6	4.8	19.6

The following non-limiting examples are meant to illustrate the present invention.

Legends to figures

Figure 1 shows the use of intra granular, extra granular sorbitol or no sorbitol as binder. Investigation of tablet hardness as a function of compression pressure.

Figure 2 shows the impact of compaction force on particle size distribution.

Figure 3 shows the impact on tablet hardness of variations in particle size distribution of granulate.

Figure 4 shows the variation in particle size of sorbitol. Investigation of tablet hardness as a function of compression pressure.

Figure 5 shows the variation in amount of sorbitol and addition of microcrystalline cellulose. Investigation of tablet hardness as a function of compression pressure.

Figure 6 shows the impact of moisture content of surrounding air on tablet hardness.

Figure 7 shows the impact on tablet hardness of addition of other sugar alcohols, that is maltitol.

Figure 8 shows the impact on tablet hardness of omitting lumb breaking of 38 μm sorbitol.

Figure 9 shows the variation in granulate pad. Investigation of impact on vitamin D_3 Vitamin assay in samples drawn during tabletting.

Figure 10 shows the impact on tablet hardness of admixing of Povidone K 30.

Figure 11 shows the impact of type and particle size of sugar alcohol. Scoralite is used as calcium source.

Figure 12 shows the impact of type and particle size of sugar alcohol. Merck 2064 is used as calcium source.

Figure 13 shows the impact of extra granular admixture of sortitol in different particle sizes. Scoralite is used as calcium source.

Figure 14 shows the impact of granular particle size of intra or extra granular admixture of sorbitol. Scoralite is used as calcium source.

Figure 15. SEM photos of regularly shaped calcium carbonate crystals (Merck 2064 and Scoralite, respectively)

Figure 16. SEM photos of sugar alcohols having a micro structure (isomalt and sorbitol, respecitvely)

Figure 17. SEM photos of sugar alcohols that do not have a micro structure (maltitol, xylitol and mannitol, respectively)

Figure 18. SEM photos of roller compacted material consisting of Scoralite and sorbitol and Merck 2064 and xylitol, respectively.

Figure 19. Compaction properties of sugar alcohols.

Figure 20. Stability using Scoralite 1B.

Figure 21. Stability using Merck 2064.

Figure 22. Impact of mixing time on crushing strength stability

Figure 23. DVS Mass plot showing the water up-take in the presence and absence of a superdisintegrant.

Figure 24 shows suitable design and dimensions of a tablet according to the invention.

Figure 25 shows how to break a tablet into two parts of essentially the same size by providing a pressure at both ends. The tablet has a design as shown in Figure 24.

List of materials

Raw material	Trade name	Vendor
Calcium carbonate	Scoralite 1B	Scora Watrigant, SA, France
	Merck 2064	Merck, Darmstadt, Germany

Sorbitol	Neosorb P100T Mean particle size: 110µm (coarse)	Roquette Freres, France
	Sorbidex P1666BO Mean particle size: 38µm (fine)	Cerestar
	Sorbidex P16656 Mean particle size: 300µm	
Xylitol	Xylitol CM50	Danisco Sweeteners
Isomalt	Isomalt ST-PF: 28 µm (fine)	Palatinit GmbH, Mannheim, Germany
	Isomalt DC100: 137µm (coarse)	
Mannitol	Mannitol 60	Roquette Freres, France
Maltitol	Maltisorb P90	Roquette Freres, France
Povidone K 30	Povidone K 30	BASF
Povidone K 90	Povidone K 90	BASF
Cellulose Microcrystalline Type M101	Cellulose Microcrystalline Type M101	Mingtai Chemical, Taiwan
Pregelatinized Maize Starch	Starch 1500	Colorcon
Crosscarmellose Sodium	Primellose	DMV International
Acesulfame Potassium	SweetMaster Ace Fine Grade	Brøste A/S, Denmark
Flavour lemon	Flavour Lemon Powder	Firmenich, Schwitzerland
Flavour granulate lemon		Nycomed
Flavour granulate orange		Nycomed
Aspartame	Ajinomoto powder	Multi Chem Wallinco (Norway)
D3 vitamin	D3-vitamin, Cholecalciferol 100	Roche
Magnesium Stearate	Magnesium stearate	Peter Greven, Netherlands
Hypromellose 15	Methocel E15	Dow
Talc	Talc	Luzenac, Italy
Propylene glycol	Propylene glycol	Lyondell Chemie, France

Glycerol distearat Type I EP	Precirol ATO 5	Gattefossé, France

Examples

Example 1

Investigation of the influence on tablet strength of intra-granular admixing of sorbitol

The investigations were based on the following formulation:

Table 1. Formulation

1	Calcium Carbonate (Scoralite)	71.40%
2	Sorbitol (110µm)	22.28%
3	Povidone K30	2.08%
4	Aspartame	0.06%
5	Cholecalciferol - sieved 250 µm (Vitamin D_3)	0.25%
6	Flavour granulate orange	3.60%
7	Magnesium Stearate	0.34%

Sorbitol was lump breaked in a Cone Mill (Quadro U20) and afterwards premixed with Calcium Carbonate in a high-shear mixer (Diosna P250 at low impeller speed and no chopper) for 60 sec.

The premix was granulated on a roller compactor (Gerteis 3W-Polygran), and the compacted granules was then mixed with Povidone K30, Aspartame, D_3 Vitamin and Flavour in a high-shear mixer (Diosna P250 at low impeller speed and no chopper) for 60 sec. Finally, lubrication with Magnesium Stearate was done a high-shear mixer (Diosna P250 at low impeller speed and no chopper) for 25 sec.

The roller compaction was based on a setup with knurled rollers and control. The key set up parameters are: Gap Width (GW), Force (F), Roller Speed (RS) and screen size.

The particulate material obtained was a granulate that was tabletted on a Fette PT1090 fully instrumented tablet press with a 16 mm round standard concave tablet design. Tablet weight was approximately 1,750 mg. All in-process weight and hardness data are obtained using a Schleuniger AT4.

In this example conditions for the roller compaction was the following:

Table 1: Roller compaction conditions

	H310001 sb. 10	H314301 sb. 02	H314301 sb. 08
GW, mm	3.5	2.0	3.0
F, kN/cm	12	8	20
RS, rpm	10	5	5
Screen size, mm	1.5	1.5	1.5
Sorbitol admixed	Intra granular	Extra granular	Extra granular

The impact on tablet hardness of having admixed sorbitol (having a mean particle size, determined by use of a Malvern laser sizer, of approx 110 µm) compared to not admixing the sorbitol is shown in Figure 1.

In Figure 1 it is shown that the presence of sorbitol leads to increased tablet hardness values when compared to tablets consisting solely of calcium carbonate. Furthermore, it is illustrated that admixing the sorbitol 110 µm intra- or extra granular has the same impact on tablet hardness.

Example 2

Impact on tablet strength of variation in roller compaction force

This experiment was carried out according to Example 1 with the variations as described in Table 2.

Table 2: The actual values for GW, F, RS and screen size

	H326501 sb. 3	H326501 sb. 07	H326501 sb. 11
GW, mm	4.0	4.0	4.0
F, kN/cm	4	8	12
RS, rpm	15	15	15
Screen size, mm	1.5	1.5	1.5

Furthermore, the sorbitol had a mean particle size around 38 µm.

The resulting particle size distribution and hardness profiles are shown in Figure 2 and 3.

From Figures 2 and 3 it is illustrated that even though a variation in roller compaction force leads to a variation in particle size, the tablet hardness profiles remain unaltered. However, an increase in compaction force will improve flowability of the granulate due to a reduction in the fraction below 125 µm.

Example 3

Impact on tablet strength of variation in particle size of sorbitol

This experiment was carried out according to Example 1 with the following variations:

The actual values for GW, F, RS and screen size were the following:

GW 3.5 mm,
F 12 kN/cm,
RS 10 rpm,
Screen size 1.5 mm.

Three qualities of sorbitol was used, having mean particle sizes around 11 µm or 38 µm or 110 µm. The 11 µm and 38 µm qualities were obtained by milling the 110 µm quality.

The tablet design was 14 mm round concave with double radius.

The impact of the variations in particle size of sorbitol is shown in Figure 4.

From Figure 4 it is seen that decreasing the size of sorbitol leads to markedly increased tablet hardness for fixed compression force.

Example 4

Impact on tablet strength of variation in intra-granular concentration of sorbitol and presence of microcrystalline cellulose

This experiment was carried out according to Example 1 with the following variations as described in Table 3 and Table 4. The roller compaction were in all cases carried out on calcium carbonate and sorbitol alone, where after the other excipients listed were admixed.

Table 3. The formulation used

	H335528	H404302	H407504
Calcium carbonate, Scoralite	67.5%	71.4%	80.1%
Sorbitol, 38 µm	21.1%	22.3%	15.5%
Mixing ratio - Calcium:Sorbitol	3.2:1	3.2:1	5.2:1
Cellulose Microcrystalline Type M101	6.6%		
Starch 1500	4.2%		3.4%
Acesulfam Potassium	0.1%		0.1%
Flavour Lemon	0.3%		0.5%
Povidone K30		2.1%	
Aspartame		0.1%	
Vitamin D3		0.3%	
Flavour granulate orange		3.6%	
Magnesium stearate	0.3%	0.3%	0.4%

Table 4: The actual values for GW, F, RS and screen size

	H335528	H404302	H407504
GW, mm	3.5	4.0	3.5
F, kN/cm	12	12	12
RS, rpm	15	15	3
Screen size, mm	1.5	1.5	1.5

Figure 5, which includes batch H310001 sb10 from Example 1 shows the impact on tablet hardness when the amount and particle size of sorbitol used are varied. This illustrates that it is important to have sorbitol distributed as completely as possible between the calcium particles. Inappropriate distribution will be the result of too large a particle size or too low a concentration. Furthermore, Figure 5 illustrates that the impact of cellulose microcrystalline (mcc) on tablet hardness is minor compared to the influence of sorbitol.

Example 5

Impact on tablet strength of moisture content in the surrounding air when using sorbitol as binder

This experiment was carried out according to Example 1 with the following variations as described in Table 5.

Table 5. The actual values for GW, F, RS and screen size

	H310001 sb. 11	H315501 sb. 02	H322801 sb. 02 dried
GW, mm	3.5	3.5	3.5
F, kN/cm	12	16	12
RS, rpm	10	10	10
Screen size, mm	1.5	1.5	1.5

Further, the tablet design was 14 mm round concave with double radius.

The manufacturing was carried out during winter and summer conditions. During winter condition RH in the surrounding air was below 50%, whereas in the summer period the RH was above 70 %.

The impact on tablet hardness of variation in moisture content in the surrounding air is shown in Figure 6.

Figure 6 shows that the granulate is very sensitive to moisture, when sorbitol having a mean particle size of 110 µm is used.

Tablets based on sorbitol having a mean particle size of approx. 38 µm did not show sensitivity towards the time of the year at which the tabletting was carried out.

Example 6

Bulk density of roller compacted formulations containing a calcium salt

Changes in bulk density as a consequence of roller compaction are shown in Table 6.

Table 6. Changes in bulk density

Density mixture (g/cm^3)	Density roller compacted granulate (g/cm^3)
0.99	1.08

Based on data in the table above it is clear that the increase in density caused by the roller compaction process is minimal.

This experiment was carried out according to Example 1 with the following variations:

- Only the granulate was produced. The admixing of povidone 30, aspartame, D3 vitamin and flavour was omitted.
- The actual values for GW, F, RS and screen size were the following

GW,mm	3.5
F, kN/cm	12
RS, rpm	10
Screen size, mm	1.5

Example 7

Influence of variations in the type of binder used on tablet hardness

This experiment was carried out according to Example 1 with the following variations as described in Table 7 and Table 8. The roller compaction was in all cases carried out on calcium carbonate and either sorbitol or maltitol, where after the other excipients listed were admixed.

Table 7. The formulation used

	H335525	H335528
Calcium carbonate, (Scorallite)	75.3%	67.5%
Sorbitol, 38 µm		21.1%
Maltitol	13.3%	
Cellulose microcrystalline, type M101	6.6%	6.6%
Starch 1500	4.2%	4.2%
Acesulfame Potassium	0.1%	0.1%
Lemon flavour	0.3%	0.3%
Magnesium stearate	0.3%	0.3%

Table 8. The actual values for GW, F, RS and screen size

	H335525	H335528
GW, mm	3.5	3.5
F, kN/cm	12	12
RS, rpm	3	15
Screen size, mm	1.5	1.5

Further, the tablet design was capsule shaped 9.4 mm * 18.9 mm.

The resulting hardness profiles are shown in Figure 7.

From Figure 7 it is seen that the use of maltitol as binder does not impart as good binding properties as that obtained when sorbitol is employed.

Example 8

Impact on tablet hardness of non-optimal admixing of sorbitol

This experiment was carried out according to Example 1 with the variations as described in Table 9.

Table 9. The actual values for GW, F, RS and screen size were the following:

	H326501 sb. 11	G334701-a	G/H404301	G/H404302
GW, mm	4.0	3.5	4.0	4.0
F, kN/cm	12	12	12	12
RS, rpm	15	15	15	15
Screen size, mm	1.5	1.5	1.5	1.5
Sorbitol lump breaked	Yes	No	Yes	Yes

Sorbitol had a mean particle size about 38 µm.

Figure 8 shows the impact on tablet hardness of adding sorbitol that has not been lumb breaked before the admixture.

From Figure 8 it is seen that lump breaking is important. Furthermore, this illustrates the importance of getting an optimal distribution of sorbitol particles between the calcium particles.

Having an optimal distribution, the tablet hardness is very reproducible as also shown in Figure 8.

Example 9

Investigation of D_3 vitamin assay of tablets based on intra-granular admixing of fine particle sized sorbitol

This experiment was carried out according to Example 1 with the variations as described in Table 10.

Table 10: The actual values for GW, F, RS and screen size

	H328001 sb. 01	H328001 sb. 02
GW, mm	4.0	4.0
F, kN/cm	8	12
RS, rpm	15	15
Screen size, mm	1.25	1.5

Sorbitol had a mean particle size around 38 µm.

In Figure 9 the D3 vitamin assay results from sampling over 2 hours of compression has been illustrated. It can be seen that the admixing of a small amount of D3 vitamin is possible in production scale. The slopes of the trend lines are close to 0 and almost identical for the 2 batches tested in this example.

Example 10

Impact on tablet hardness of the admixing of the binder Povidone K 30, a typical example of a wet binder

This experiment was carried out according to Example 1 with the variations as described in Table 11 and Table12.

Table 11. The actual values for GW, F, RS and screen size

	H310002 sb. 17	H310002 sb. 19	H310003 sb 17	H310003 sb 19
GW, mm	3.5	3.5	3.5	3.5
F, kN/cm	8	8	8	8
RS, rpm	10	10	10	10
Screen size, mm	1.5	1.5	1.5	1.5

Table 12. Changes of the composition and tabletting

	H310002 sb. 17	H310002 sb. 19	H310003 sb 17	H310003 sb 19

+/- Povidone K 30	+	+	-	-
Tablet design	16 mm round, concave	14 mm round, concave double radius	16 mm round, concave	14 mm round, concave double radius

Figure 10 shows that the admixing of dry Povidone K 30 has no beneficial impact on the tablet hardness.

Example 11

Impact on tablet hardness of variation in type of calcium carbonate and type and particle size of sugar alcohol

This experiment has been carried out as described below:

In all the below described experiments 1 - 24 the amount of calcium salt is 76.22 % w/w of the final tablet mass, the amount of sugar alcohol is 23.78% w/w, with the exception of experiments 4 and 20 at which the 23.78% w/w of sugar alcohol is replaced with 14.63% w/w of sugar alcohol and 9.15% w/w of Precirol. The actual type of calcium source and the type of sugar alcohol is described in Table 13.

Table 13, types of calcium and sugar alcohol source

Experiment no.:	Calcium salt Source	Sugar alcohol, source and ps*	Sugar alcohol Figure legend
1	Scoralite	Sorbitol, 38 µm	Sorb38
2	Scoralite	Sorbitol, 110 µm	Sorb110
3	Scoralite	Xylitol, 34 µm	Xyli34
4	Scoralite	Xylitol, 34 µm and Precirol	Xyli34P
5	Scoralite	Isomalt, 28 µm	Isom28
6	Scoralite	Isomalt, 137 µm	Isom137
7	Scoralite	Mannitol, 48 µm	Mann48
8	Scoralite	Maltitol, 31µm	Malt31
17	Merck 2064	Sorbitol, 38 µm	Sorb38
18	Merck 2064	Sorbitol, 110 µm	Sorb110

19	Merck 2064	Xylitol, 34 µm	Xyli34
20	Merck 2064	Xylitol, 34 µm and Precirol	Xyli34P
21	Merck 2064	Isomalt, 28 µm	Isom28
22	Merck 2064	Isomalt, 137 µm	Isom137
23	Merck 2064	Mannitol, 48 µm	Mann48
24	Merck 2064	Maltitol, 31 µm	Malt31
25	Scoralite	Sorbitol, approx. 300 µm	Sorb300
26	Scoralite	Sorbitol, 38 µm	Sorb38

*: ps: mean particle size (d(v;0.5) determined by use of a Malvern Mastersizer)

The calcium salt and the sugar alcohol are mixed in a total amount of 6 kg in a Fielder high shear mixer. The sugar alcohol is sieved through sieve size 300 µm prior to mixing. The mixing of 6 kg is done twice and the total yield of 12 kg is mixed in a planetary mixer. Thereafter, the mixtures are roller compacted (intra granular sugar alcohol) using the following values for GW, F, RS and screen size. (For the experiments 25 – 26 the sugar alcohol is admixed by hand *after* roller compaction has been carried out (extra granular sugar alcohol)).

GW:	3.5 mm
F:	12 kN/cm
RS:	5 rpm
Screen size	1.5 mm

The compactate is admixed with 0.34 % w/w of magnesium stearate.

Compression is carried out on a Fette 1090 using a 18.9 mm x 9.4 mm capsule shaped punch design and a theoretical tablet mass of 1683 mg. For each experiment a correlation between tablet compression force and crushing strength is found. The crushing strength has been measured by use of a Schleuniger Autotest 4 and n = 20. The resulting hardness profiles are shown in Figures 11–13.

From Figures 11–12 it is seen that for both the Scoralite and Merck 2064 calcium carbonates intra granular admixed fine particular sorbitol or isomalt results in tablets with a much higher crushing strength than can be obtained with xylitol, mannitol, maltitol or coarse particular sorbitol and isomalt. Furthermore it was observed during

the experiment that the use of mannitol, xylitol or maltitol leads to tablets with a tendency of capping.

Without being bound by theory the impact of different sugar alcohols on tablet crushing strength can be described as being dependent on their binding properties and distribution throughout the tablet. The distribution of the sugar alcohol throughout the tablet is crucial, as regular shaped calcium carbonate crystals, see Figure 15, are not likely to establish the adherence necessary for obtaining a coherent tablet. Sugar alcohols capable of obtaining a homogeneous distribution throughout the tablet are especially suitable. Examples of such sugar alcohols are sorbitol and isomalt as illustrated in Figure 16 where it is shown that the individual crystals of sorbitol and isomalt have a micro structure or a non-compact micro structure, i.e. the individual crystals have some deformation capacity to be squeezed between other kinds of particles. This is in contrast to the crystals of mannitol, maltitol and xylitol where the same kind of micro structure cannot be found, as illustrated in Figure 17. This micro structure is assumed facilitate a further distribution throughout the tablet by breakage during the tablet compression. The distribution of sugar alcohol made possible by this micro structure is shown in Figure 18. Therefore, calcium carbonate containing tablet comprising sugar alcohols with the described micro structure are much more likely to be coherent tablets, with a satisfactory crushing strength, than tablet based on sugar alcohols without the described micro structure.

However, even if a micro structure is present it is required that the particles of the sugar alcohols are sufficiently small which is illustrated in Figure 11 and 12 where it can be seen that fine particular sorbitol and isomalt results in tablets with a much higher crushing strength than can be obtained with coarser particles.

Based on the above discussions of the importance of particle size and micro structure of sugar alcohols the results shown in Figure 13 can easily be explained. Even though tablets illustrated by the curve Sorb300 are based on the teaching of Pharmaceutical Technology Vol 1 (Tabletting technology, editor M. H. Rubinstein), where instant sorbitol having a particle size distribution of 60 – 90% between 212 – 500 µm is admixed as extra granular sugar alcohol, the crushing strength is extremely low even at high compression forces. Crushing strength can be markedly increased by the use of sorbitol with a finer particle size, see Figure 13 (curve Sorb38). Even though the different punch design of Example 1 makes a direct comparison difficult it is illustrated

than when using sorbitol of a 110 µm quality there is no difference between intra and extra granular admixture of sorbitol. Therefore, when using sorbitol as extra granular sugar alcohol the particle size is very critical. This also applies for other sugar alcohols.

However, the compaction of pure calcium carbonate results in a granulate with a very low binding capacity, as illustrated by the very large fraction below 125 µm seen in Figure 14. This means that by adding sugar alcohol extra granularly instead of intra granularly the final mixture for tabletting will have extremely poor flow properties which will make tabletting in production scale very difficult.

Furthermore it can be seen from Figure 11 that the addition of Precirol increases the crushing strength without changing the sensitivity of the crushing strength to changes in main compression force, that is Precirol is less optimal as a binder.

Example 12

Test of compactability of different sugar alcohols

Tablets comprising sorbitol 110 µm, sorbitol 38 µm, isomalt 27µm, maltitol, mannitol or xylitol were compressed on an instrumented Fette Exacta 1/F single punch tablet press, only maximum compression force on the upper punch was recorded.

Before the compression of each tablet the punch tips and the die bore were lubricated with a 5% suspension of magnesium stearate in acetone. The acetone was allowed to evaporate before compression of the tablet.

The sugar alcohol was weighed, transferred to the die bore and then compressed, see Table 14. Immediately after ejection the tablet was tested for crushing strength.

Table 14

Sugar alcohol	Trade name	Tablet weight
Sorbitol	Neosorb P100T	530 mg
	Sorbidex P1666BO	400 mg
Isomalt	Isomalt ST-PF	400 mg
Maltitol	Maltisorb P90	400 mg
Mannitol	Mannitol 60	400 mg

Xylitol	Xylitol CM50	400 mg

It was assumed that the obtained tablet crushing strengths of the sugar alcohols are substantially independent of particle size and this was tested using sorbitol having two different mean particle sizes, 38 µm and 110 µm. From Figure 19 (each point is the average of three measurements) it is seen that the assumption was correct. Therefore, test of particle size was not repeated for the other sugar alcohols.

From Figure 19 it can be seen that sorbitol has the best compactability resulting in the steepest slope of the correlation between compression force and crushing strength. Sorbitol is followed by isomalt whereas maltitol, mannitol and xylitol have a very poor compactability. These results support the results discussed in Example 11 and Figures 17–18. Therefore, it can be concluded that sugar alcohols having a polycrystal structure results in stronger tablets when compressed than sugar alcohols without a polycrystal structure.

Example 13

Impact on tablet crushing strength stability of variation of calcium carbonate and type and particle size of sugar alcohol

Tablets according to Example 11 were manufactured. Tablets with an initial crushing strength between 70 N to 100 N were stability tested. The conditions for the stability testing were storage in open petri dishes at 25 °C/60 % (25/60) relative humidity (RH) for 14 days. The crushing strength was tested just before the stability test was started and after 2 days, 7 days and 14 days. The crushing strength was measured by use of a Schleuniger-2E Hardness tester, n = 10.

Crushing strength stability is shown in Figures 20-21.

From Figures 20 and 21 it is seen that for both the Scoralite and Merck 2064 calcium carbonates intra granularly admixed fine particular sorbitol or isomalt (both fine and coarse) results in tablets with a satisfactory stability of crushing strength. However the use of coarse sorbitol results in tablets with a decrease in crushing strength during storage in open petri dishes at 25 °C/60% RH.

Possible explanations for the observed differences in stability of tablets containing coarse sorbitol or either fine sorbitol or isomalt (both fine and coarse) could be the

following: In order to obtain sorbitol containing tablets with the desired initial crushing strength a considerably higher main compression force was needed for tablets containing coarse sorbitol compared to fine. Even though the tablets based on coarse sorbitol were less porous, the crushing strength declined considerably during the first two days of stability testing. This could be caused by a much less homogeneous distribution of the coarse sorbitol in the tablet.

For isomalt the use of either fine or coarse particles in both cases leads to tablets with satisfactory crushing strength stability. This could be caused by the fact that isomalt is considerably less hygroscopic compared to sorbitol.

Example 14

Manufacture of calcium carbonate containing tablets

Tablets were manufactured according to Example 1 with the below described exceptions. The roller compaction was in all cases carried out on calcium carbonate and sorbitol, where after the other excipients listed were admixed. The film liquid was applied at described below.

Tablet formulation:

Table 15

	Amount per tablet			
Raw material	**2 [mg]**	**[%]**	**3 [mg]**	**[%]**
Calcium carbonate Scoralite	1250	72.2	1250.0	71.9
Sorbitol P 1666B0	385.5	22.3	385.5	22.2
Cellulose microcryst Type 101	75	4.3	75	4.3
Acesulfam Potassium	1	0.1	1	0.1
Flav. Lemon Powder			7.5	0.4
Magnesium stearate	6	0.3	6	0.3
Tablet weight [mg]	1717.5		1725.0	
Film liquid *				
Hypromellose 15	7.16	0.4	7.19	0.4
Talc	4.30	0.2	4.31	0.2
Propylene glycol	1.43	0.1	1.44	0.1
Water, purified	130.28		130.81	

The granulate was compressed on a Fette PT1090 using capsule shaped punches (9.4 mm x 18.9 mm).

The film liquid were applied on the tablets in an Accella Coater 150 (Manesty Inc.), by use of the following parameters:

* Inlet air temperature 50 °C
* Outlet air temperature 45 °C
* Pan rpm 2.2
* batch size 75 kg

The obtained tablets had a crushing strength of 133 N and a disintegration time below 12 minutes.

Example 15

Manufacture of calcium carbonate containing tablets

A granulate was manufactured according to Example 14 with the following exceptions:

Table 16

Raw material	**Amount per tablet [mg]**	**Amount per tablet [%]**
Calcium carbonate, Scoralite	1250.0	72.26
Sorbitol 38µm	385.0	22.26
Cellulose microcryst. Type 101	56.0	3.24
Croscarmellose sodium	20.0	1.16
Magnesium stearate	6.0	0.35
Acesulfame Potassium	1.0	0.06
Flavour lemon powder	7.5	0.43
D3-vitamin	4.4	0.25
Total	**1729.9**	100.00
Coating liquid		
Hypromellose 15	7.2	
Talc	4.3	
Propylene glycol	1.4	

Water, purified	131.2	
Total	**1742.9**	

The granulate was compressed on a Fette PT 2090 using capsule shaped punches (9.4 mm x 18.9 mm).

The tablets were coated in an O´Hara FC-660 (O´Hara), by use of the following parameters:

* Inlet air temperature 50 °C
* Product temperature 45 °C
* Pan rpm 2.0
* Process air flow 8000 m^3
* Liquid flow rate 300 g/min
* batch size 600 kg

The obtained tablets had a crushing strength of 135 N and a disintegration time below 2 minutes.

Example 16

Impact on sensoric properties of the use of sugar alcohols and flavours

Kalcipos®-D

Ingredients according to the manufacturer:

- Calcium carbonate
- Vitamin D_3
- Maltodextrin
- Crosscarmellose sodium
- Gelatine
- Sucrose
- Maize starch
- Colloidal silicium dioxide
- Magnesium stearate
- Hypromellose
- Macrogol 6000
- Parafin

- Hydrated soya bean oil
- Hydrated cottonseed oil

Sensorial comparison has been performed between the above described Kalcipos®-D and tablets manufactured as described in Example 15.

The test has been performed as a paired comparison test in accordance with ISO – 5495, by use of 8 trained persons. This will show whether there is a significant difference between the reference (Kalcipos®-D) and the tablets of Example 15, at a five % level.

The products have been compared with respect to the following properties:

* Sweetness
* Lemon flavour
* Chalkiness

The results conformed a significant difference with respect to all three properties showing more sweetness, more lemon flavour and less chalkiness for the tablets of Example 15 when compared to Kalcipos®-D.

Example 17

Manufacture of calcium carbonate containing tablets

Tablets were manufactured according to Example 14 with the following formulations:

Table 17

Raw material	**[% w/w]**
Calcium carbonate, Scoralite	60 - 94
Sorbitol 38µm or Isomalt 27µm	5 - 30
Cellulose microcryst Type 101	0 – 10
Crosscarmellose sodium	0 - 5
Acesulfam Potassium	0.1
Flav. Lemon Powder 501162	0 – 2
Magnesium stearate	0.3 - 1

The individual amounts are adjusted so that each composition contains 1250 mg calcium carbonate and that the total amount does not exceed 100%. Tablets are compressed by use of punch design like:

* Round shallow concave 16 mm
* Round compound cup 14 mm
* Capsule shaped 9.4 x 18.9 mm
* Capsule shaped 8.6 x18.9 mm

on a Fette PT 2090 achieving tablets with a crushing strength above 70 N and a disintegration time below 15 minutes for tablets containing croscarmellose sodium in an amount of approximately 0.5 % or more (such tablets are meant for the oral route by swallowing). Optionally a standard water soluble coat (such as a traditional coating known by a person skilled in the art) can be applied to the tablets, in which case the disintegration time should be below 30 minutes.

If tablets only are meant for chewing the disintegration time is not relevant.

Example 18

Investigation of the impact of different production methods on the size of calcium carbonate tablets

This experiment was carried out in large production with a batch size of approx. 40.000 tablets. The experiment was performed in order to investigate whether the technique used for manufacturing granulate for the product had any impact on tablet dimensions especially the tablet height.

The techniques in question were:

i) Fluid bed granulation, and

ii) Roller compaction.

	Raw material	Fluid bed	Roller compaction
		Batch 1 per 1000 tabl. [g]	Batch 2 per 1000 tabl. [g]
I	Calcium carbonate Scoralite	1250.0	1250.0
II	Sorbitol 38µm	-	385.5

III	Sorbitol 110µm	390.0	-
IV	Povidone K 90	36.4	-
V	Cellulose microcrystalline Type 101	-	75.0
VI	Acesulfam Potassium	-	1.0
VII	Aspartame	1.0	
VIII	Flavour lemon	-	7.5
IX	Flavour granulate lemon	50.68	-
X	Magnesium stearate	6.0	6.0
XI	Purified water	73.0	-
	Tablet weight	1734.08	1725.0

Manufacture of batch 1:

The granulating fluid is manufactured by dissolving IV in XI. III is passed through a suitable screen and mixed with I in a Glatt fluid bed granulator. The powder mixture is granulated by spraying the granulating fluid on the powder bed while the fluidizing process is ongoing. The remaining parts of the excipients VII, IX and X are admixed to granulate and tablets are compressed by use of a Fette PT1090 and capsule shaped punch design (9.4 x 18.9 mm).

Manufacture of batch 2

II is passed through a suitable screen and mixed together with I in a 220 l high shear mixer for 1 min at impeller speed 110 rpm and chopper speed 1500 rpm.

The powder mixture is granulated using a roller compactor according to example 1.

The remaining excipients V, VI, VIII and X are admixed by use a high shear mixer (Diosna P250) with low impeller speed no chopper for 60 seconds and finally tablets are compressed by use of a Fette PT1090 and capsule shaped punch design (9.4 x 18.9 mm).

	Compression force [kN]	Tablet height [mm]	Tablet length [mm]
Batch 1	19.9	7.40	19.04
Batch 2	20.9	7.16	19.07

Comparison of batch 1 and 2 shows that the lowest tablet height is obtained by roller compaction.

Example 19

Stability of calcium carbonate tablets

This experiment was carried out in large production with a batch size of approx. 693,000 tablets. 3 batches were manufactured.

The experiment was performed in order to investigate the stability of coated tablets in open petri dishes and the reproducibility of crushing strength for three mixing intervals.

Composition: Amounts per tablet

Table 18

Raw material	**[mg]**	**[%]**
Calcium carbonate, Scoralite	1250	72.26
Sorbitol 38µm	385	22.26
Cellulose microcrystalline, type M101	56.0	3.24
Crosscarmellose sodium	20.0	1.16
Acesulfam Potassium	1.0	0.06
Flavour Lemon	7.5	0.43
D3 vitamin	4.4	0.25
Magnesium stearate	6.0	0.35
Tablet weight [mg]	1729.9	
Coating		
Hypromellose 15	7.2	
Talc	4.3	
Propylene glycol	1.4	
Water, purified	131.2	
Total weight [mg]	1742.9	

The batch was manufactured according to the following description:

Premixing and roller compaction

Calcium Carbonate is added to a tumble mixer.

Sorbitol is sieved through screen size 2.0 mm and is transferred to the tumble mixer

Calcium carbonate and sorbitol are premixed in the tumble mixer. Mixing time 15 minutes, speed 6 rpm.

The pre-mix is roller compacted with knurled rollers, screen size 1.5 mm. Settings: Gap 3.5 mm, Force 12 kN/cm, Roller speed 15 rpm.

Mixing

The rest of the excipients, with the exception of magnesium stearate were admixed to the granulate in a tumble mixer using speed 6 rpm and mixing time for the 3 batches were according to Table 19.

Table 19: Mixing intervals

	Batch 1	**Batch 2**	**Batch 3**
Mixing time	20 minutes	30 minutes	40 minutes

Magnesium stearate were admixed for 5 minutes, speed 6 rpm.

Tabletting

The granulate is compressed on a Fette 2090 tablet press by use of a capsule shaped punch design (18.9 x 9.4mm) achieving a crushing strength of 110 N.

Coating

Coating parameters is as described in Example 15.

The amount of film applied is corresponding to a theoretical weight gain of 0.75 %.

Stability studies in open petri dishes stored at 25 °C/60 % RH have been performed. The results are shown in Figure 22. Even though sorbitol having a mean particle size of 38 µm has been used a decrease is seen. This decrease is similar to that of tablets based on sorbitol 110 µm from Example 13. The decrease is due to the addition of extra excipients. However, the crushing strength is still sufficiently high to allow handling and therefore acceptable.

Example 20

Impact of super disintegrant on water absorption

A mixture of 72.26 % calcium carbonate (Scoralite) and 22.26 % sorbitol (38 µm) were Roller compacted as described in Example 18.

The roller compacted granulate was admixed the following ingredients:

Table 20. Composition of test 1 and 2 based on content of single tablets:

	Excipients	Test 1	Test 2
I	Roller compacted granulate from example 18	1635.5 mg	1635.5 mg
II	Cellulose microcrystalline Type 101	75.0 mg	75.0 mg
III	Croscarmellose sodium	17.3 mg	
VI	Magnesium stearate	6.0 mg	6.0 mg
	Tablet Weight:	1733.8 mg	1716.5 mg

.

Tablets are compressed by use of capsule shaped punch design (9.4 x 18.9 mm)

Coating of the tablets is carried out based on the following composition

	Excipients	% (w/w)
I	Hypromellose 15	2.5
II	Talkum	1.5
III	Propylene Glycol	0.5
IV	Purified water	95.5

Coating is carried out in a lab scale coater (Combi Cota, Niro, Denmark) using the following parameters:

Inlet air temperature: 48 - 50°C

Liquid flow rate 3 – 4 gram/min

Spray pressure: 2 bar

The tablets were tested in a DVS (Dynamic Vapour Sorption) equipment (Surface Measurement System, UK) at 25°C and 60% RH. Each test was based on 5 tablets. The result is shown in Figure 23. From Figure 23 it can be seen that the addition of a superdisintegant only results in a minor increase in water absorption meaning that only minor impact on stability of tablet technical properties is to be expected from the addition of a superdisintegrant.

CLAIMS

1. A particulate material comprising a compact of one or more regularly shaped calcium-containing compounds as an active substance and one or more pharmaceutically acceptable sugar alcohols having a micro structure, wherein the one or more sugar alcohols have a mean particle size of at the most about 150 µm such as, e.g., at the most about 110 µm, at the most about 100 µm, at the most about 90 µm, at the most about 80 µm, at the most about 70 µm, at the most about 60 µm, at the most about 50 µm, at the most about 40 µm, at the most about 30 µm, at the most about 20 µm or about 10 µm.

2. A particulate material according to claim 1, wherein the pharmaceutically acceptable sugar alcohol - when compressed into tablets containing 100% w/w of the sugar alcohol - has a slope of correlation between crushing strength (measured in N) and compression pressure (measured in N) of 7×10^{-3} or more such as, e.g., in a range of from about 10×10^{-3} to about 30×10^{-3}.

3. A particulate material according to claim 1 or 2, wherein the pharmaceutically acceptable sugar alcohol has binding properties.

4. A particulate material according to any of the preceding claims, wherein the one or more calcium-containing compound is in the form of crystals having a specific surface area below 1.5 m^2/h such as, e.g., 1.3 m^2/h or less, 1.1 m^2/h or less, 0.9 m^2/h or less, 0.7 m^2/h or less.

5. A particulate material according to any of the preceding claims, wherein the concentration of the pharmaceutically acceptable sugar alcohol in the particulate material is at least about 5% w/w such as, e.g., at least about 10% w/w, at least about 15% w/w or at least about 20% w/w.

6. A particulate material according to any of the preceding claims, wherein the pharmaceutically acceptable sugar alcohol employed has a mean particle size in a range of from about 5 to about 150 µm such as, e.g., from about 5 to about 110 µm or from about 5 to about 80 µm.

7. A particulate material according to any of the preceding claims, wherein the sugar alcohol is sorbitol or isomalt or mixtures thereof.

8. A particulate material according to claim 7, wherein the sugar alcohol is sorbitol.

9. A particulate material according to claim 8, wherein the mean particle size is in a range of from about 25 to about 50 µm such as, e.g., from about 35 to about 45 µm or from about 30 to about 45 µm.

10. A particulate material according to claim 7, wherein the sugar alcohol is isomalt.

11. A particulate material according to claim 10, wherein the mean particle size is in a range of from about 20 to about 50 µm such as, e.g., from about 25 to about 35 µm or from about 20 to about 35 µm.

12. A particulate material according to any of the preceding claims comprising a sugar alcohol selected from the group consisting of mannitol, xylitol, maltitol, inositol, lactitol, and mixtures thereof.

13. A particulate material according to any of the preceding claims comprising a mixture of sorbitol and xylitol.

14. A particulate material according to claim 14, wherein the weight ratio between sorbitol and xylitol is in a range of from about 1:0.1 to about 1:1.5 such as, e.g., about 1:1.

15. A particulate material according to any of the preceding claims comprising a mixture of isomalt and xylitol.

16. A particulate material according to claim 15, wherein the weight ratio between isomalt and xylitol is in a range of from about 1:0.1 to about 1:1.5 such as, e.g., about 1:1.

17. A particulate material according to any of the preceding claims, wherein the calcium-containing compound is a calcium salt.

18. A particulate material according to any of the preceding claims, wherein the calcium salt is calcium carbonate.

19. A particulate material according to claim 18, wherein calcium carbonate has a shape and a mean particle size corresponding to that of Scoralite 1B or Merck 2064.

20. A particulate material according to claim 19, wherein calcium carbonate is Scoralite 1B or Merck 2064.

21. A particulate material according to any of the preceding claims, wherein the content of the calcium-containing compound in the particulate material is in a range of from about 40% to about 100% w/w such as, e.g., from about 45% to about 98% w/w, from about 50% to about 95% w/w, from about 55% to about 90% w/w or at least about 60% w/w, at least about 65% w/w, at least about 70% w/w or at least about 75% w/w.

22. A particulate material according to any of the preceding claims, wherein a SEM photo of the particulate material - when compressed into a tablet - shows that a surface of a deformed particle of the pharmaceutically acceptable sugar alcohol is in close contact with surfaces of the crystals of the one or more calcium-containing compound.

23. A particulate material according to any of the preceding claims further comprising one or more pharmaceutically acceptable excipients or additives, or one or more therapeutically, prophylactically and/or diagnostically active substances.

24. A particulate material according to any of the preceding claims further comprising vitamins or minerals such as vitamin D or a vitamin K or Magnesium.

25. A particulate material according to any of the preceding claims comprising one or more second calcium-containing compounds selected from the group consisting of calcium citrate, calcium lactate, calcium phosphate including tricalcium phosphate, calcium gluconate, bisglycino calcium, calcium citrate maleate, hydroxyapatite including solvates, and mixtures thereof.

26. A particulate material according to any of the preceding claims that has such a flowability that - when tablets are prepared from the particulate material optionally admixed with at the most 10% w/w such as, e.g. at the most about 7.5% w/w or at the most about 5% w/w of a glidant using a tabletting machine operating at at least 300

tablets per min - the mass variation of the tablets obtained fulfils the requirements given in Ph. Eur.

27. A particulate material according to claim 26, wherein the dwell time during the preparation of the tablets is at the most about 1 sec.

28. A particulate material according to any of the preceding claims containing from about 60 to about 95% w/w of the calcium-containing compound and from about 5 to about 40% w/w of the pharmaceutically acceptable sugar alcohol, provided that the sum does not exceed 100% w/w.

29. A particulate material according to any of the preceding claims containing from about 60 to about 94% w/w such as, e.g., from about 65% to about 80% w/w of the calcium-containing compound, from about 5 to about 35% w/w such as, e.g., from about 15 to about 30% w/w of the pharmaceutically acceptable sugar alcohol and from about 1 to about 15% w/w of one or more pharmaceutically acceptable excipients and/or active substances, provided that the sum of ingredients amounts to 100% w/w.

30. A particulate material according to claim 29 containing from about 65% to about 80% w/w such as, e.g., from about 70% to about 75% w/w of the calcium-containing compound and from about 15% to about 25% w/w such as, e.g., from about 20 to about 25% w/w of sorbitol or isomalt or mixtures thereof.

31. A solid dosage form comprising a particulate material defined in any of claims 1-30 and, optionally, one or more pharmaceutically acceptable excipients or additives.

32. A solid dosage form according to claim 31 for oral administration.

33. A solid dosage form according to claim 31 or 32 in the form of a single unit or a multiple unit dosage form.

34. A solid dosage form according to claim 33 in the form of tablets, capsules, sachets, beads, pellets or the like.

35. A solid dosage form according to claim 34 in the form of tablets.

36. A solid dosage form according to claim 35, wherein the tablets have a shape and dimensions essentially as shown in Figure 24 herein.

37. A solid dosage form according to any of claims 31-36 containing an amount of the one or more calcium-containing compounds corresponding to from about 250 to about 1000 mg calcium.

38. A solid dosage form according to any of claims 31-37, wherein the amount of the one or more calcium-containing compounds corresponds to from about 400 to about 600 mg calcium.

39. A solid dosage form according to any of claims 31-38, wherein the total concentration of the one or more calcium-containing compound in the dosage form is in a range of from about 40% to about 99% w/w such as, e.g., from about 45% to about 98% w/w, from about 50% to about 95% w/w, from about 55% to about 90% w/w or at least about 60% w/w, at least about 65% w/w, at least about 70% w/w.

40. A solid dosage form according to any of claims 31-39, wherein the total concentration of the particulate material contained in the dosage form is from about 65% to about 100% w/w such as, e.g., from about 70% to about 98% w/w, from about 75% to about 95% w/w, from about 80% to about 95% or from about 85% to about 95% w/w.

41. A solid dosage form according to any of claims 31-40 containing from about 60% to about 95% w/w of the calcium-containing compound and from about 5% to about 40% w/w of the pharmaceutically acceptable sugar alcohol, provided that the sum does not exceed 100% w/w.

42. A solid dosage form according to any of claims 31-41 containing from about 60 to about 94% w/w such as, e.g., from about 65% to about 80% w/w of the calcium-containing compound, from about 5 to about 35% w/w such as, e.g., from about 15 to about 30% w/w of the pharmaceutically acceptable sugar alcohol and from about 1 to about 15% w/w of one or more pharmaceutically acceptable excipients and/or active substances, provided that the sum of ingredients amounts to 100% w/w.

43. A solid dosage form according to any of claims 31-42, wherein a SEM photo of a fractured surface of the solid dosage form shows that a surface of a deformed particle of sugar alcohol is in close contact with surfaces of the crystals of the one or more calcium-containing compound.

44. A solid dosage form according to any of claims 31-43 in the form of tablets, wherein the crushing strength of the tablets when stored in open petri dishes at 25 °C and 60% RH at the most changes 50% such as, e.g. at the most about 40%, at the most about 30%, at the most about 20%, at the most about 15%, at the most about 10% during a time period that starts 5 days after manufacture and runs during the remaining storage period one month preferable 3 months.

45. A solid dosage form according to any of claims 31-44 in the form of a chewable, suckable and/or swallowable tablet.

46. A solid dosage form according to claim 45, which has an acceptable taste with respect to sweetness, flavour and chalkiness when tested by a professional/skilled sensory test panel of at least 6 persons.

47. A solid dosage form according to any of claims 31-46 comprising a sweetener selected from the group consisting of dextrose, fructose, glycerin, glucose, isomalt, lactitol, lactose, maltitol, maltose, mannitol, sorbitol, sucrose, tagatose, trehalose, xylitol, alitame, aspartame, acesulfam potassium, cyclamic acid, cyclamate salt (e.g. calcium cyclamate, sodium cyclamate), neohesperidine dihydrochalcone, thaumatin, saccharin, saccharin salt (e.g. ammonium saccharin, calcium saccharin, potassium saccharin, sodium saccharin), and mixtures thereof.

48. A process for the preparation of a particulate material as defined in any of claims 1-30, the process comprises roller compaction of a composition comprising a regularly shaped calcium-containing compound and one or more pharmaceutically acceptable sugar alcohols having a micro structure.

49. A process according to claim 48, wherein the pharmaceutically acceptable sugar alcohol - when compressed into tablets containing 100% w/w of the sugar alcohol - has a slope of correlation between crushing strength (measured in N) and compression

pressure (measured in N) of 7×10^{-3} or more such as, e.g., in a range of from about 10×10^{-3} to about 30×10^{-3}.

50. A process according to claim 48 or 49, wherein the pharmaceutically acceptable sugar alcohol has binding properties.

51. A process according to any of claims 48-50, wherein the one or more calcium-containing compound is in the form of crystals having a rounded or a cubic shape.

52. A process according to any of claims 48-51, wherein the calcium-containing compound is a calcium salt.

53. A process according to any of claims 48-52, wherein the calcium salt is calcium carbonate.

54. A process according to claim 53, wherein calcium carbonate has a shape and a mean particle size corresponding to that of Scoralite 1B or Merck 2064.

55. A process according to claim 54, wherein calcium carbonate is Scoralite 1B or Merck 2064.

56. A process according to any of claims 48-55, wherein the concentration of the pharmaceutically acceptable sugar alcohol in composition that is subject to roller compaction is at least about 5% w/w such as, e.g., at least about 10% w/w, at least about 15% w/w or at least about 20% w/w.

57. A process according to any of claims 48-56, wherein the pharmaceutically acceptable sugar alcohol employed has a mean particle size of at the most about 150 µm such as, e.g., at the most about 110 µm, at the most about 100 µm, at the most about 90 µm, at the most about 80 µm, at the most about 70 µm, at the most about 60 µm, at the most about 50 µm such as, e.g. about 40 µm.

58. A process according to any of claims 48-57, wherein the pharmaceutically acceptable sugar alcohol employed has a mean particle size in a range of from about 5 to about 150 µm such as, e.g., from about 5 to about 110 µm or from about 5 to about 80 µm.

59. A process according to any of claims 48-58, wherein the sugar alcohol is sorbitol or isomalt or mixtures thereof.

60. A process according to claim 59, wherein the sugar alcohol is sorbitol.

61. A process according to claim 60, wherein the mean particle size of sorbitol is in a range of from about 25 to about 50 µm such as, e.g., from about 35 to about 45 µm.

62. A process according to claim 59, wherein the sugar alcohol is isomalt.

63. A process according to claim 62, wherein the mean particle size of isomalt is in a range of from about 20 to about 50 µm such as, e.g., from about 25 to about 35 µm.

64. A process according to any of claims 48-63, wherein the composition that is subjected to roller compaction contains from about 60 to about 95% w/w of the calcium-containing compound and from about 5 to about 40% w/w of the pharmaceutically acceptable sugar alcohol, provided that the sum does not exceed 100% w/w.

65. A process according to any of claims 48-64, wherein the composition that is roller compacted contains from about 60 to about 94% w/w such as, e.g, from about 65% to about 80% w/w of the calcium-containing compound, from about 5 to about 35% w/w such as, e.g., from about 15 to about 30% w/w of the pharmaceutically acceptable sugar alcohol and from about 1 to about 15% w/w of one or more pharmaceutically acceptable excipients and/or active substances, provided that the sum of ingredients amounts to 100% w/w.

66. A process according to claim 65, wherein the composition contains from about 65% to about 80% w/w such as, e.g., from about 70% to about 75% w/w of the calcium-containing compound and from about 15% to about 25% w/w such as, e.g., from about 20 to about 25% w/w of sorbitol or isomalt or mixtures thereof.

67. A process according to any of claims 48-66, wherein the pharmaceutically acceptable sugar alcohol employed is lump breaked before admixing it with the calcium-containing compound.

68. A process according to any of claims 48-67 further comprising a step of admixing to the composition that has been subjected to roller compaction one or more pharmaceutically acceptable excipients or additive and/or one or more active substance.

69. A process according to any of claims 48-68 further comprising a step of shaping the particulate material obtained into a solid dosage form.

70. A process according to claim 69, wherein the solid dosage form is as defined in any of claims 31-47.

71. A process for preparing a tablet comprising a calcium-containing compound, the process comprises
i) preparing a particulate material as defined in any of claims 1-30 or 48-70,
ii) optionally admixing one or more pharmaceutically acceptable excipients or additive and/or one or more active substances, and
iii) compressing the material into tablets.

72. A process according to claim 71, wherein the compression in step iii) is performed at a compression force that is adjusted with respect to the diameter and the desired height of the tablet so that the compression force applied is at the most about 80 kN such as, e.g., at the most about 70 kN, at the most 60 kN, at the most 50 kN, at the most about 40 kN, at the most about 30 kN or at the most about 20 kN when tablets having a diameter of about 16 mm and a resulting height of at the most about 10 mm such as, e.g., about 9 mm, about 8 mm or about 7 mm are obtained.

73. A process according to claims 71 or 72 for the preparation of a tablet comprising
i) calcium carbonate
ii) sorbitol and/or isomalt,
iii) a vitamin D, and
iv) optionally one or more pharmaceutically acceptable excipients.

74. A process according to claim 73, wherein the tablet comprises
i) from about 50% to about 90% w/w of calcium carbonate,
ii) from about 5 to about 30% w/w of sorbitol and/or isomalt,

iii) from about 0.01 to about 1% w/w of a vitamin D, and

iv) optionally one or more pharmaceutically acceptable excipients

with the proviso that the total amount of ingredients corresponds to about 100% w/w.