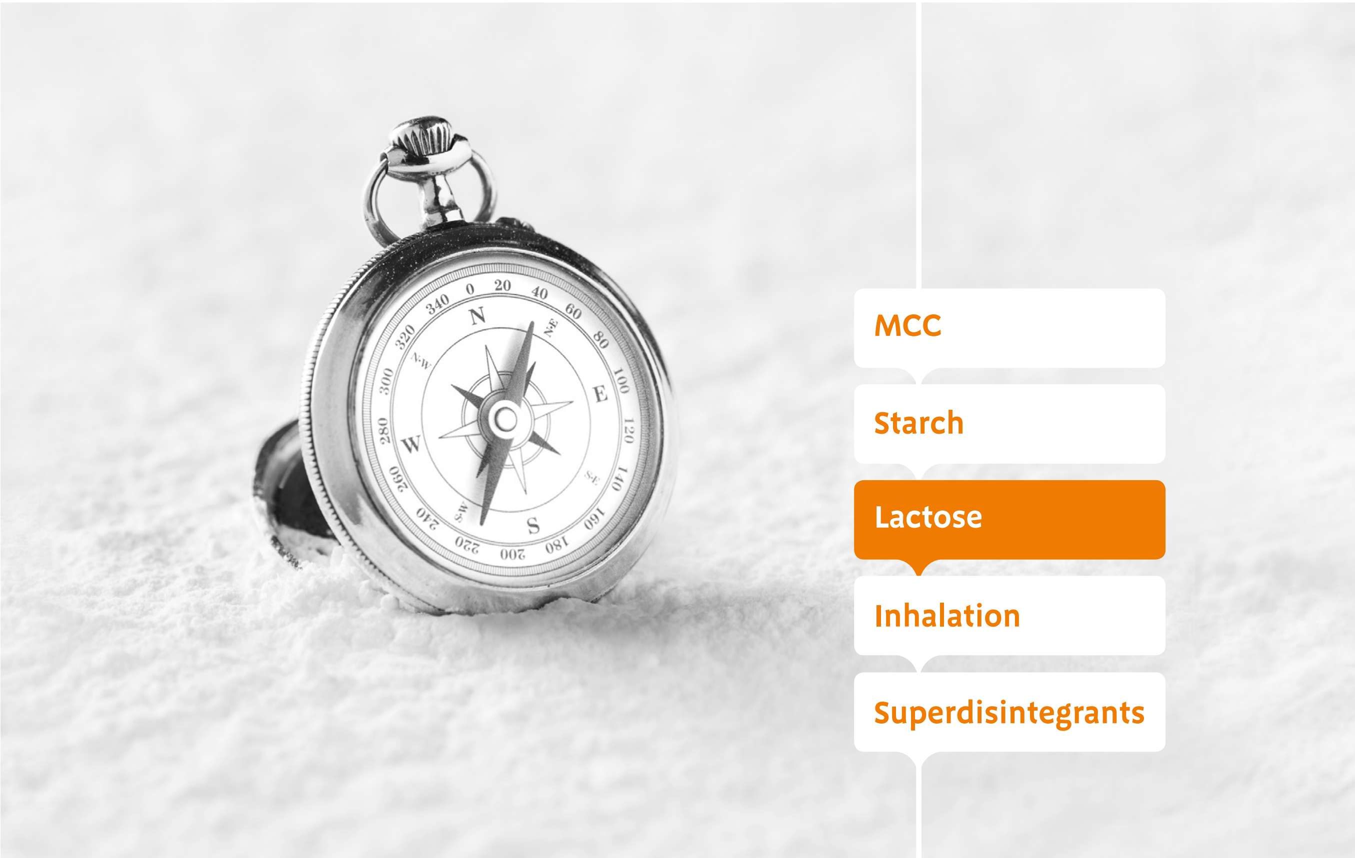
DFE pharma

Lactose

Some basic properties and characteristics

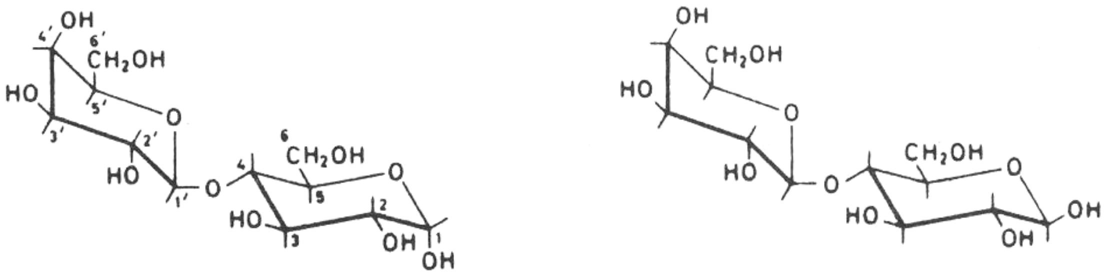


The pursuit of excipient excellence

1 Introduction

Lactose is the most important carbohydrate of the milk of most species. Its biosynthesis takes place in the mammary gland. Concentrations in milk vary strongly with species. Lactose is the first and only carbohydrate every newborn mammal (including human) consumes in significant amounts. Bovine milk contains 45 – 50 grams lactose per liter. Industrially lactose is produced from bovine milk exclusively, or rather from milk derivatives like cheese whey or ultra filtration permeate. Lactose is also known as milk sugar.

Lactose is a carbohydrate, and as such a disaccharide. One molecule of lactose is built from one molecule each of two other carbohydrates, galactose and glucose.The galactose and glucose moieties are linked together through a so called beta-(1,4) glucosidic linkage. The molecular structure of lactose is depicted in figure 1.



(a) α-lactose

(b) β-lactose

***Figure1:** Molecular structure of lactose*

The official chemical name of lactose, which is frequently encountered in regulatory documents is4-O-β-D-galactopyranosyl, D-glucopyranose.

2 Isomeric forms

In milk, lactose exists in two isomeric forms, called α- and β- lactose respectively. The molecular structures of α- and β -lactose differ in the orientation of a hydrogen- and a hydroxyl group on carbon atom no.1 in the glucose moiety, as is shown in figure 1. Both forms change into one another continuously. This phenomenon is called mutarotation. The velocity of mutarotation is determined by factors like temperature, concentration and pH (acidity) of the solution.Lactose solutions strive after a state of equilibrium between theα andβ form. At room temperature the equilibrium results in a ratio of about 40% α-lactoseand 60% β-lactose. The fact that two forms of lactose exist which differ in molecular structure, has profound effects on various properties of lactose such as crystallization behaviour, crystal morphology, solid state properties and solubility.

3 Lactose in the solid state

Lactose in solid form can either be in a crystalline state or in an amorphous state.Crystalline lactose can exist in a number of distinct forms. Most well known are α-lactose monohydrate and β-lactose. Also, two crystalline anhydrous α-lactose types are known, a stable and an unstable (hygroscopic) form. Furthermore,a so-called mixed crystalline form is reported, containing both α- and β- lactose in a special crystal lattice. Crystallinity is the result of a highly ordered arrangement of the lactose molecules. Amorphous lactose lacks crystallinity and the arrangement of the lactose molecules is more or less random. The most frequently encountered forms of solid lactose are described below.

3.1 α-Lactose monohydrate

The most common way to obtain lactose in solid form is crystallizing from solution.When crystallization is performed at temperatures below 93.5°C, exclusively α-lactose monohydrate is obtained. α-Lactose has the peculiarity that in the crystalline state each lactose molecule is associated with 1 molecule of water. In other words, α-lactose crystallizes as monohydrate. The water is incorporated in the crystal lattice and forms an integral part of it. It is not removed by normal drying processes. Due to this water of crystallization the normal water content of α-lactose monohydrate is around 5%. Only at temperatures as high as 140°C, the crystal water will be removedcompletely. Crystals of α-lactose monohydrate possess a characteristic tomahawk-like shape, as shown in figure 2. These crystals are very hard and brittle. On an industrial scale, α-lactose monohydrate is obtained by crystallizing highly concentrated lactose solutions at low temperatures, separating the crystals from the mother liquor by centrifugation and subsequently drying off the adhering moisture from the crystal mass.

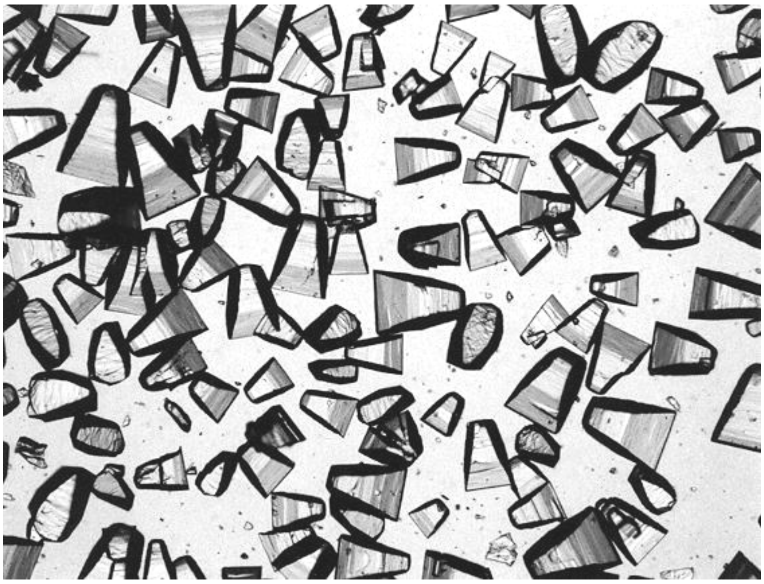


Figure 2: *Lactose monohydrate crystals*

In the pharmaceutical industry this type of lactose is used mainly as an excipient in the production of solid dosage forms, e.g. tabletsvia wet granulation processes and direct compression, and for capsule filling. In dry powder inhalers α-lactose monohydrate is used as a carrier.

3.2 B-Lactose

When a highly concentrated solution of lactose is crystallized at temperatures above 93.5°C, crystals of β-lactose are exclusively formed. Crystals of pure β-lactose have a characteristic kite-like form as shown in figure 3. Particles with crystalline β-lactose are more brittle than α–lactose monohydrate crystals andthey do not contain crystal water. B-Lactose is often referred to as anhydrous lactose. Industrially, β-lactose is produced by roller drying highly concentrated lactose solutions. The isomeric purity is approximately 80% β-lactose, the remaining 20% being anhydrous α-lactose. Crystals of β-lactose in this product are very small and the kite form is rarely encountered, as can be seen in figure 4.This type of lactose is used mainly as filler-binder for tablet production via direct compression processes.

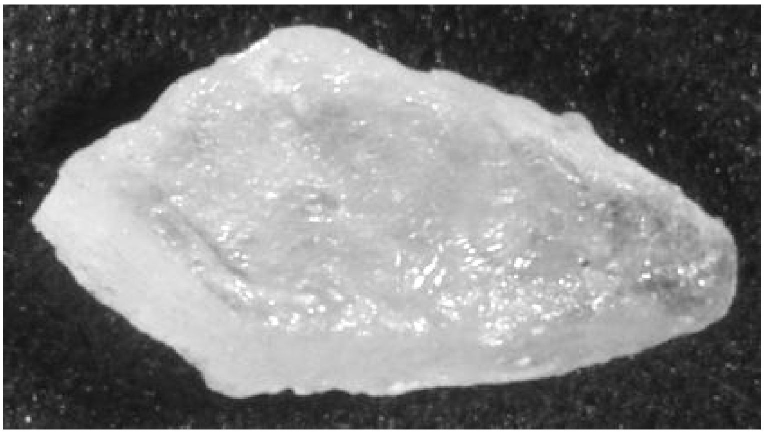


Figure 3: Microscopic picture of a typical β-lactose crystal

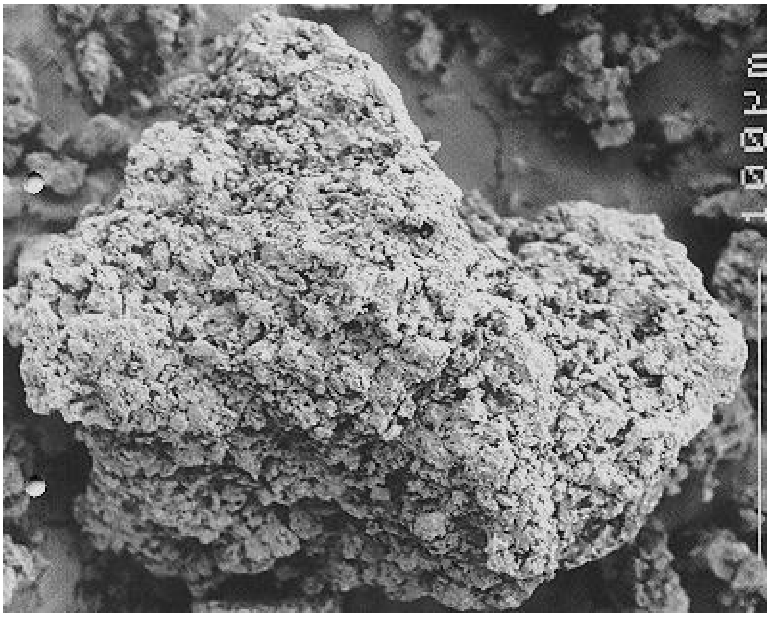


Figure 4: Electron microscope picture of β-lactose crystals in roller dried lactose

3.3 Amorphous lactose and spray dried lactose

When a highly concentrated lactose solution is dried very quickly, for instance by spray drying, a glassy lactose mass is obtained. This lactose glass is a form of amorphous lactose. This amorphous lactose contains both α- and β-lactose, the ratio being approximately the same as the equilibrium ratio of the original lactose solution at the drying temperature. Lactose glass is very hygroscopic (see under paragraph 4. Physical properties).
Although dry lactose glass can appear very hard, it lacks the brittleness of crystalline α-lactose monohydrate and anhydrous lactose. The material is plastically deformable under high pressure.
On an industrial scale, lactose products with amorphous lactose are produced by spray drying a suspension of fine lactose crystals in a concentrated lactose solution. The resulting product consists of a matrix of lactose glass in which lactose monohydrate crystals are embedded. Figure 5 shows an electron microscope picture of spray dried lactose particles. A typical ratio crystalline/amorphous lactose is around 85/15.
Spray dried lactose is used mainly for tablet manufacture by direct compression processes. To improve the tableting properties, the size of the lactose crystals suspended in the lactose solution can be decreased.

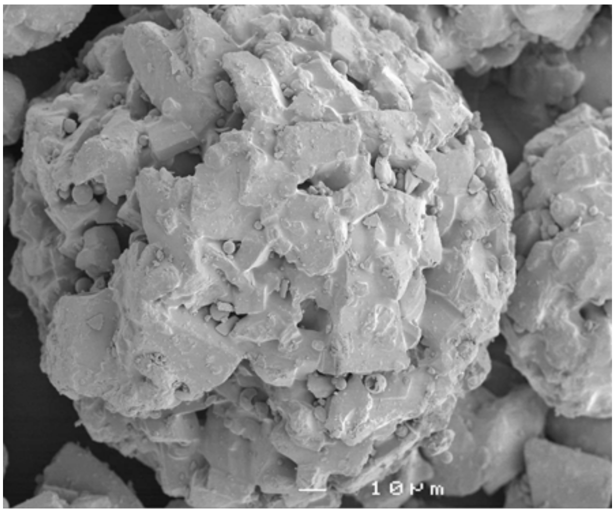


Figure 5:*Electron microscope picture of spray dried lactose.*

4 Some physical properties

4.1 Stability, moisture sorption and hygroscopicity

The stability towards moisture and the hygroscopicity of products used as excipient, are important physical characteristies. These properties can be studied best by measuring the moisture sorption isotherms of these products. Figure 6 illustrates the moisture sorption behaviour of different lactose products, characterised by their moisture sorption isotherms at room temperature and expressed as the relation between moisture content and relative humidity of the air surrounding it.
In a moisture sorption isotherm, the steeper the curve, the more hygroscopic the product. From these curves it can be seen that the α-lactose monohydrate products have a very low affinity to humid air over an extensive range of relative humidities and so they are very stable products in this respect. The same conclusion can be drawn for the anhydrousβ-lactose. This behaviour can be considered as a very favourable aspect of these lactose types.

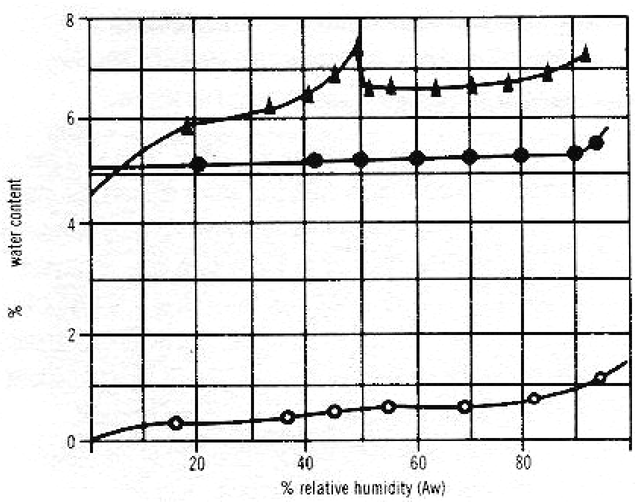


Figure 6: Sorption isotherms of various lactose products at room temperature(● α- lactose monohydrate, ○ anhydrous β-lactose,▲ spray-dried lactose)

The moisture adsorption behaviour of spray dried lactose differs from that of the other lactose types. The peak in the curve at about 50% relative humidity is the result of the transition of amorphous lactose into the crystalline α-lactose monohydrate form. When a certain amount of moisture is taken up by the product (about 1%), at conditions at or over 50% relative humidity, this transition occurs.
Since a certain amount of amorphous lactose is needed for the good binding properties of spray dried lactose, it is clear that this transition is unwanted. So, during storage and handling of spray dried lactose, uptake of too much moisture has to be avoided in order to retain the optimum functionality.

4.2 Powder rheology (properties of powder flow)

4.2.1 Powder density

The specific weight of α-lactose monohydrate is 1.54 kg/l (at 20ºC). Pure β-lactoseis somewhat heavier (1.59 kg/l at 20ºC).The density of lactose powder is much lower than the values cited above because of the presence of air between the individual lactose particles in the powder.Powder density is not as well defined a characteristic as is the true density (specific weight). It heavily depends on the granulometry (particle size distribution) of the powder. In general, coarse powders have a higher powder density than fine powders.
Powders tend to compact spontaneously over time which will cause the apparent powder density to increase. It is therefore common to give 2 values for the density of a powder:

- the bulk density, which is the powder density of fresh, loosely discharged powder.
- the tapped density, which is the density after compacting the powder by tapping it in a well defined way.

Powder density is an important characteristic for e.g. calculating the capacity of packaging materials, containers, hoppers, bins, silos, and also for filling of the die of tableting machines and for capsule filling. The ratio of the tapped density and bulk density is called the Hausner ratio. This ratio is strongly related to the flow properties of lactose powder. A slightly different way of calculating gives the Carr's Index, which also is used to indicate flow properties.

4.2.2 Powder flow

The laws governing powder flow have been extensively studied and described in technical literature. We will here take a more qualitative view on the subject. The ability of a lactose product to flow freely is determined by factors like mean particle size, particle size distribution and particle shape. As a measure for flowability the Hausner ratio is determined by these factors.

A number of general *rules of thumb* apply and are useful for lactose as well:

- powders consisting of regularly shaped particles flow better than those consisting ofirregular shaped particles.
- the more the particles in a powder resemble spheres the better the powder flows.
- coarse powders in general have better flow properties than fine powders.
- powders with narrow particle size distributions flow better than powders with wide particle size distributions.
- powders with a low Hausner ratio (or low Carr's Index) flow better than powders with a high Hausner ratio (or high Carr's Index).

In spray dried lactose most particles have shapes closely resembling spheres. The flow properties are therefore excellent. α-Lactose monohydrate products, consisting of regularly shaped, undamaged crystals also show good flow properties. In milled lactose powders damaged crystals and irregularly shaped crystal fragments are predominant. Therefore flow properties are not as good as for un-milled lactose products. Micronised lactose has poor flow properties.

4.3 Solubility

Lactose is freely soluble in water. However, the solubility of lactose is much less than that of other common sugars. Solubility increases with increasing temperature.β-Lactose dissolves more readily than α-lactose as is apparent from their very different initial solubilities. Final solubility is the same for α- and β-lactose because of the mutarotation equilibrium which is eventually reached in solution.The particle size of the lactose influences the dissolution speed. Coarse lactose crystals dissolve much slower than fine lactose particles. Dissolution speed, and hence particle size, does not alter the final solubility. Figure7 shows the final solubility of lactose as a function of temperature.

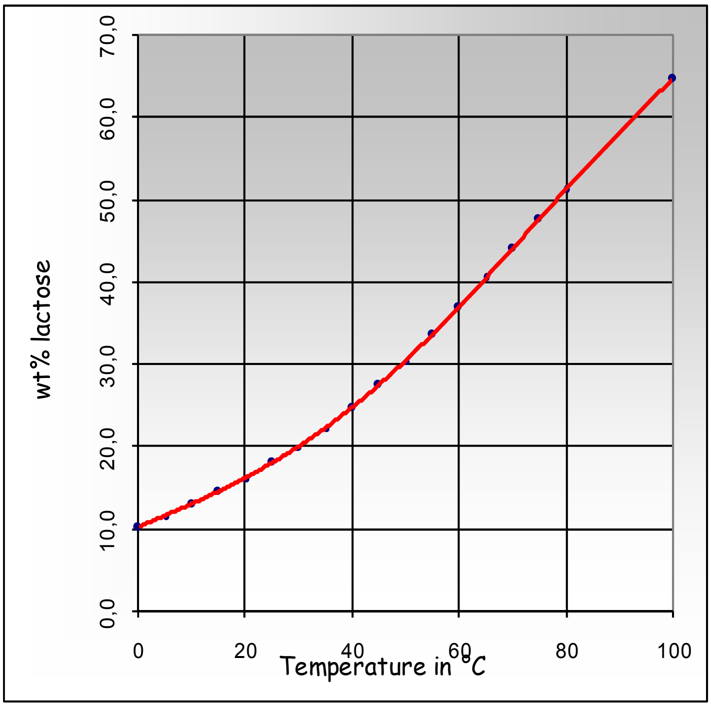


Figure 7: Final solubility of lactose as a function of temperature.

5 Chemical and biochemical properties

Lactose is very stable and inert from a chemical point of view. It has, apart from some special cases, no significant tendency to react with the drug or other components of a formulation.Some remarks on the chemical properties of lactose are useful however.The low hygroscopicity of crystalline lactose supports its virtual chemical inertness. Most chemical reactions of lactose occur noticeably only in aqueous environment. Because lactose has a very low tendency to attract moisture, water in dry lactose preparations is normally not present in amounts sufficient for chemical reactions to proceed at a noticeable speed. The water of crystallisation is bound so tightly in the crystal lattice of the lactose that it is chemically inert.

5.1 Dehydration and pyrolysis

At temperatures above 100ºC, α-lactose monohydrate gradually loses its water of crystallisation. At 140ºC, the loss of crystal water is completed. The loss of water of crystallisation is accompanied by a change of the crystalline structure of the lactose. The lactose becomes anhydrous. Further heating of lactose to higher temperatures causes the lactose to decompose. This process is called pyrolysis. The primary reaction products of pyrolysis tend to polymerize, resulting in brown and black coloured macromolecules. Eventually the lactose becomes black on heating.

5.2 Maillard reaction

In aqueous solution, lactose, as all reducing sugars (e.g. glucose, galactose, maltose, maltodextrines), tends to react with compounds possessing primary- and secondary amino-groups, such as proteins and peptides. This reaction is called the Maillard reaction. The chemical pathways of the Maillard reaction are very complicated and will not be dealt with further. High temperature and alkaline pH promote the reaction. In an advanced stage, yellow and brown polymers are formed, which ultimately turn the reaction mixture black.Purified lactose, even of pharmaceutical grade, still contains traces of proteinaceous matter. These are the reason why the Maillard reaction cannot be completely excuded, even from some dry lactose preparations. However, the Maillard reaction requires some free water, although very little may suffice. Here again the low hygroscopicity of lactose proves favourable.α-Lactose monohydrate and roller dried lactose have a very low tendency to adsorb moisture. Furthermore, they have a moisture content which is sufficiently low to prevent the Maillard reaction to occur noticeably. Even over periods of years significant changes in colour are normally not observed.Spray dried lactose, being somewhat hygroscopic, may have some tendency to become slightly coloured at long storage times when moisture adsorption occurs. In this respect dry storage in an adequate packing is important. Formulating lactose with drugs of a protein or peptide character, in general, should pose no problems of drug stability, provided that free moisture content of the formulation can be kept very low. Examples on the market are Levothyroxin andAlendronic acid.

5.3 Fermentation

Lactose is a carbohydrate and as such an easy substrate for microorgamisms, like bacteria, yeasts and moulds. Controlled use of this is made in several industrial fermentation processes where lactose is used as the carbon source.Uncontrolled fermentation of lactose, i.e. microbial spoilage of the lactose product, is of course highly undesirable.Here again the low hygroscopicity of lactose adds to its microbial stability as well. Microorganisms require a certain water activity (Aw) to grow. Storage of lactose under dry and cool conditions will prevent microbial growth to occur.

6 Physiological properties

6.1 Taste, palatability, sweetness

Lactose has a clean sweet taste, without any aftertaste. The sweetness profile resembles that of sucrose. However, the relative sweetness of lactose is low, only about 30% compared to sucrose. β-Lactose appears to be somewhat sweeter than α-lactose. The latter probably is also due to the fact that β-lactose dissolves somewhat quicker in the saliva of the mouth than α-lactose, hence reaching a higher concentration in the same time and thus giving rise to a higher sweetness sensation.

6.2 Lactose tolerance

Lactose is not actively absorbed by the intestine unless it is split into its two monosaccharide components, i.e. glucose and galactose. This hydrolysis of lactose is affected by the enzyme lactase which is produced by the epithelium cells in the brush-border of the small intestine. Thus the capacity of mammals to digest lactose is dependent on the lactase activity in the intestine. The maximum activity of the enzyme occurs shortly after birth and declines during the weaning period, after which it remains at a relatively constant level. Genetically determined factors governing residual lactase activity also exist. Individuals having low lactase activity are called lactose malabsorbers. They may not be able to digest all the lactose ingested. Consequently remnants of lactose remain in the intestine. In the small intestine this may lead to disturbed water resorption. Lactose reaching the the large intestine (colon) will be fermented by the microbial flora residing there, yielding lactic and other organic acids, hydrogen, carbon dioxide, etc. This causes increased moisture retention in the colon which, in combination with the gas produced, cause symptoms like diarrheoea, abdominal pain and flatulence.
Various studies have shown that 80 to 90% of individuals clinically diagnosed as lactose malabsorbers can tolerate 250 ml of milk without any symptoms. This percentage is even greater amongst children and adolescents. Thus the intake of regular small or medium quantities of milk or corresponding amounts of lactose would give rise to little concern amongst the majority of consumers, Particularly when, as is more normal, milk or lactose is taken in combination with other foods, thus slowing down in gastric emptying and intestinal passage.
Some individuals are extremely sensitive to even small amounts of lactose. As little as 3 g portions have been reported to cause complaints in some cases. However, in the majority of cases the amount of lactose in a tablet or a capsule does not exceed 1 g. Therefore no problems with ingestion of lactose after taken a tablet or a capsule are to be expected, even with individuals who are very sensitive to lactose.

6.3 Diabetes

In modern treatment of diabetes mellitus strictly sugar free diets are no longer advised. The aim of the diet is to obtain normal blood glucose levels throughout the day (and night). This can perfectly be attained by normal diet provided it is restricted in energy and the meals are spread evenly throughout the day. A daily basic diet for a diabetes mellitustype I patient may contain up till 255 g of carbohydrates, accounting for 50% of the total energy consumed. Compared to this amount of dietary sugars the amount of lactose ingested when taking medicines is very small. Furthermore lactose is resorbed and digested slowly when compared to sucrose and glucose. Hence, their will generally be no restrictions for diabetes patients to take lactose containing medicines.

6.4 Cariogenicity

Milk sugar is hardly cariogenic when compared to sucrose. To explain this it is important to recognise the factors which promote dental caries. The etiology of dental caries lies in the presence of bacteria of Steptococcus species in the oral cave. These bacteria synthesize adhesive extracellular polymers which assist the bacteria in sticking to the tooth and thus promoting the colonisation of the tooth. On top of that these difficult to remove bacteria ferment carbohydrates, resulting in the formation of organic acids which are capable of destroying the surface layer of the tooth. The increased acidity in the oral cave causes calcium from the enamel layer of the tooth to dissolve. Biosynthesis of the adhesive substances occurs largely by the action of microbial enzymes which are highly specific for dietary sucrose. These enzymes are much less capable of using other dietary sugars than sucrose. Therefor other sugars, including lactose, are relatively safe with respect to dental caries.In addition to this, tablets and capsules are commonly swallowed with water. The rinsing effect of this leaves hardly any residues of lactose in the oral cave.However, it is recommended to rinse the mouth with water after using a dry powder inhaler, especially when inhaling took place shortly before going to sleep.

Literature for further reading

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DFE pharma

Head Office
Klever Strasse 187
P.O. Box 20 21 20
47568 Goch, Germany
T. +49 2823 9288 770
F. +49 2823 9288 7799
pharma@dfepharma.com

www.dfepharma.com

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