LYCASIN® 80/55

SUGARLESS EXCIPIENT
FOR MEDICINAL PREPARATIONS
LYCASIN® 80/55
sugarless excipient
for medicinal preparations

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LYCASIN® 80/55 is a maltitol syrup manufactured according to rigorous specifications and which has unique properties.

LYCASIN® 80/55 was developed after many years of research in collaboration with world renowned dental specialists.

The specific composition of LYCASIN® 80/55 gives very low acid production when in contact with the plaque bacteria: LYCASIN® 80/55 does not induce caries.

LYCASIN® 80/55 is widely used in the food industry in many countries, especially in confectionery applications.

In the pharmaceutical industry, LYCASIN® 80/55 is used to totally replace sucrose in preparations such as sugarless syrups, lozenges and medicated confectionary (gums, gellies...).

LYCASIN® 80/55 is obtained by the hydrogenation of a maltose syrup whose composition is strictly defined and controlled (1, 2).

The maltose syrup is obtained from starch by enzymatic hydrolysis.

The constituents of LYCASIN® 80/55 are the hydrogenated homologues of the oligosaccharides contained in the original syrup.

### Composition of maltose syrup

- **D-Glucose (dextrose)**: 8% maximum
- **Disaccharides**: 50 to 55%
- **Polysaccharides DP* > 20**: 3%

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### Composition of LYCASIN® 80/55

- **D-Sorbitol**: 8% maximum
- **Hydrogenated disaccharides**: 50 to 55%
- **Hydrogenated polysaccharides DP* > 20**: 3% maximum

*DP: degree of polymerization

LYCASIN® 80/55 is a very pure product, it is odourless and has a pleasant sweet taste.
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**Composition**

LYCASIN® 80/55 is a very pure product, it is odourless and has a pleasant sweet taste.
LYCASIN® 80/55 has the following properties:

- Dry matter 75% (W/W),
- Colourless (ICUMSA index less than 20),
- Clear,
- Density 1.36 @ 20°C,
- Refractive index approximately 1.478,
- Ultraviolet spectrum (absorption maximum @ 205 nm)

Viscosity

The viscosity of LYCASIN® 80/55 @ 20°C is about 2000 cps, allowing handling without difficulty (Figs. 3 and 4). The following two diagrams show the changes in viscosity of LYCASIN® 80/55 as a function of dry matter and temperature, in comparison with sucrose.

In order to obtain a viscosity identical to that of sucrose at equal dry matter, LYCASIN® 80/55 is mixed with a defined quantity of NEOSORB® 70/02: (i.e. Roquette's crystallizing liquid sorbitol).
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**General physical properties**

[Graphs and diagrams are not transcribed but are shown in the middle of the page.]

- **Figure 1:** UV spectrum of LYCASIN® 80/55
- **Figure 2:** IR spectrum of LYCASIN® 80/55
- **Figure 3:** LYCASIN® 80/55 - Sucrose Viscosity as a function of dry matter @ 25°C
- **Figure 4:** LYCASIN® 80/55 - Sucrose Viscosity as a function of temperature
- **Figure 5:** Composition of the mixture LYCASIN® 80/55 - NEOSORB® giving the same viscosity as a sucrose solution
Physical stability, absence of crystallization

A decrease in temperature or an increase in concentration of LYCASIN® 80/55 does not cause crystallization. The advantages of this include:

- no crystallization around closures of bottles containing oral solutions (cap-locking),
- no crystallization of pharmaceutical candies, which retain their translucent appearance, and
- no crystallization in storage tanks.

Sweetening power

LYCASIN® 80/55 has a mild, pleasant, sweet taste with a sweetening power approximately 0.75 that of sucrose. This leads to improved taste and flavour perception in products.

For example, the quantity of acidulant usually used in a product (citric acid, lactic acid, etc.) can be reduced by 20 to 30%.

The sweet taste of LYCASIN® 80/55 removes the need to use artificial sweeteners when a sugarless formula is being developed.

LYCASIN® 80/55 is nevertheless compatible and can be combined with the main artificial sweeteners on the market: aspartame, saccharin, etc.

Miscibility

LYCASIN® 80/55 is miscible with the principal solvents used in the formulation of oral solutions.

Hygroscopicity

LYCASIN® 80/55 at 75% DM is not very hygroscopic.

At equal dry matter contents, the equilibrium relative humidity (ERH) of a solution of LYCASIN® 80/55 is similar to that of a sucrose solution (Fig. 6).

Figure 6: Comparison of LYCASIN® 80/55 and sucrose Equilibrium Relative Humidity as a function of dry matter

When dehydrated (lozenges, candies), LYCASIN® 80/55 is more sensitive to ambient humidity: finished products should thus be tightly packaged to prevent the uptake of water.
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Osmolality

The osmolality of LYCASIN® 80/55 is very similar to that of sucrose at equal concentration (Fig. 7).

Figure 7: Osmolarity of LYCASIN® 80/55 and sucrose

General chemical properties

- **Very low reducing power**

The low concentration of free reducing groups confers very high chemical stability on LYCASIN® 80/55, particularly when the product is heated. LYCASIN® 80/55 does not react with nitrogenous compounds: no Maillard reaction.

Principle of the Maillard reaction:

- R-CHO + R'-NH2 → R-CO-NH-R' Yellow colour
- R-CH2-OH + R'-NH2 → No reaction No colour

- **Chemical stability**

  - **Stability with time:**
    Under normal storage conditions, LYCASIN® 80/55 is a very stable product. After two years, no change in appearance or composition can be detected using either thin layer chromatography or UV spectroscopy.

  - **Stability as a function of temperature and pH:**
    - At room temperature, LYCASIN® 80/55 is stable over the pH range 2 to 9. No colour or chemical changes were detected after 3 months of storage under these conditions.
    - At 50°C, stability was examined as a function of pH and time:

      | pH | Slight hydrolysis | Very slight hydrolysis | No hydrolysis |
      |----|-------------------|------------------------|--------------|
      | 2  | 0.5% at 6 weeks   | 0.1% at 6 weeks        |              |
      | 3  | 1.2% at 3 months  | 0.2% at 3 months       |              |

      Yellow colour No colour Very slight yellow colour under basic conditions

Figure 8: Change in reducing power of LYCASIN® 80/55 as a function of time and pH of solution
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(LYCASIN®)

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<tr>
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<th>pH 4 - 9</th>
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Yellow colour | No colour | Very slight yellow colour under basic conditions

Figure 8: Change in reducing power of LYCASIN® 80/55 as a function of time and pH of solution
Incompatibilities

To our knowledge, LYCASIN® 80/55 has never exhibited any incompatibility with other substances.

LYCASIN® 80/55 is compatible with a wide range of active ingredients used in the formulation of syrups:
- dextromethorphan,
- carbocysteine,
- codeine,
- terpin,
- paracetamol (acetaminophen),
- ibuprofen,
- antacid salts,
- guaifenesin, etc.

LYCASIN® 80/55 is compatible with the most commonly used preservatives:
- methyl para-hydroxybenzoates,
- benzoates.

LYCASIN® 80/55 is compatible with polyethylene glycols (PEG) commonly used in oral solutions.

Microbial stability

In order to increase in number, microorganisms have two basic requirements:

- **Substances are required for their nutrition:** this includes carbohydrates. LYCASIN® 80/55 contains no carbohydrates and additionally, the hydrogenated oligosaccharides in LYCASIN® 80/55 are highly resistant to bacterial hydrolysis.

- **Free water:** most bacteria require a water activity between 0.85 - 0.98 for development. As a first approximation, the water activity can be compared with the equilibrium relative humidity of the solution (Aw = EHR/100), and for LYCASIN® 80/55 this is 0.76 @ 20°C. Good microbial stability is therefore assured.

The healthy tooth

**Dental caries**

Dental caries is a very widespread disease and W.H.O. has classed it as the third most serious world health problem.

The etiology of caries is complex although its appearance and development are now well known.

Since the work of KEYES, the factors favouring caries have been divided into three main groups. These factors and their interactions are illustrated in figure 9 (3).

**The host:** factors related to the teeth themselves and to the buccal cavity.

**Microorganisms:** caries does not develop in the absence of bacteria.

**Acid-forming sugars:** bacteria produce acids from these sugars which then attack the dental enamel.

To prevent caries:
- Increase the level of personal dental hygiene (use toothpaste, floss, mouthwashes, fluoridation),
- Change any bad eating habits since they can totally negate the beneficial effect of this prevention program. The effect of sugar eaten between meals is particularly dangerous for the teeth. This is why the consumer should have available not only sugarless candy, but also sugarless medicinal preparations: syrup, lozenges, etc.

A very close correlation has been established between the rate and severity of caries and the frequency of consuming carbohydrates which can be fermented by the microorganisms of the dental plaque.
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The formation of caries: 3 different steps
• bacterial colonization of the surface of the teeth, favoured by polysaccharides (dextran and levan) synthesized from sucrose;
• formation of organic acids by bacteria, in particular lactic acid, from fermentable carbohydrates;
• attack on underlying crystalline structures of the teeth by these acids. This slow solubilization of the enamel culminates in the formation of a cavity.

The relationship between dental plaque pH and caries
A large number of studies have shown that sucrose has the highest caries-forming capacity. For this reason, substitution products which are less aggressive towards the teeth, notably LYCASIN® 80/55 can be used to replace sugar.

A pH of 5.7 is considered to be the critical value below which hard dental tissues are attacked, leading to dissolution of the crystalline enamel structure (4).

A method has been developed in which the pH of the dental plaque can be measured in situ. This is a biotelemetric method involving the implantation of microelectrodes in a false tooth which is placed in the mouth (5).

The pH of the dental plaque after ingestion of LYCASIN® 80/55 was never lower than 5.7, whereas it decreased to pH 4 after ingesting sucrose.
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Composition of LYCASIN® 80/55:
G: Glucose
S: Sorbitol

A complete intestinal hydrolysis of LYCASIN® 80/55 releases glucose and sorbitol (1).

The free glucose is actively transported by intestinal cells and is rapidly absorbed.

The sorbitol is absorbed passively in the small intestine, a process which is less efficient than that for glucose.

When a large quantity of sorbitol is ingested, stagnation of the substance in the intestinal lumen causes water to enter from surrounding tissues by the process of osmosis. This may lead to accelerated transit and cause osmotic diarrhoea.

Sorbitol not absorbed in the intestine is degraded by the colon microflora and may give rise to flatulence.

Digestive tolerance in healthy subjects after the ingestion of sorbitol-based lozenges was studied by FLOURIE et al. (6). In comparison with subjects taking sorbitol on an empty stomach, it was shown that 10 to 20 g of sorbitol consumed during the day in the form of candy did not cause digestive symptoms. The mean dose causing diarrhoea was more than 60 g per day.

The digestion of LYCASIN® 80/55 depends primarily on that of sorbitol and thus digestive tolerance has the same dependence.

In order to fully define the relationship between LYCASIN® 80/55 and sorbitol, it should be noted that LYCASIN® 80/55 releases a maximum of 44 % of its weight as sorbitol after total hydrolysis.

In theory therefore, the threshold digestive tolerance of LYCASIN® 80/55 should be twice that of sorbitol.

What is the situation in reality ?
Several studies have been carried out in humans.

In adult subjects, TACQUET and DEVULDER have shown that no clinical problems occur for doses up to 60 ml per day (7).

KEARSLEY et al. have shown that most individuals can tolerate LYCASIN® 80/55 up to dose levels of 85 g taken over the course of one day (8).

BARR et al. reported that no adverse reaction was observed at a dose level of 1g/kg bodyweight in a population of 27 children between 3 and 17 years of age, eating candy sweetened with LYCASIN® 80/55 over a period of one hour (9).

All these observations lead to the conclusion that LYCASIN® 80/55 taken as an excipient in medicinal preparations will in most cases be well tolerated.
Digestive tolerance

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Schematic representation of the composition* of LYCASIN® 80/55

- DP 1 = sorbitol : 7%
- DP 2 = maltitol : 52.5 G 1-4 S
- DP 3 = maltotriitol : 18 % G 1-4 G 1-4 S
- DP4 =
- DP5 = polyol : 2 % G 1-4 G 1-4 G 1-4 G 1-4 S
- > DP5 =

* this composition is given as a guidance and can not be considered as specification.

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All these observations lead to the conclusion that LYCASIN® 80/55 taken as an excipient in medicinal preparations will in most cases be well tolerated.
A digestive tolerance study was carried out with LYCASIN® HBC, a maltitol syrup with higher viscosity than LYCASIN® 80/55, and suitable for the manufacture of medicated hard boiled candies. The comparative gastrointestinal responses of children (6-9 years old) and adults (18-24 years old) following consumption of sweets formulated with sucrose, isomalt and LYCASIN® HBC showed that consumption of 25 g of LYCASIN® HBC did not provoke an unacceptable laxative effect or gastrointestinal response in adults or children compared to 25 g isomalt which was associated with a mild effect and increase in gastrointestinal responses. (12)
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The Directive of the Council of the European Communities of 24 September 1990 attributed an energy value of 2.4 kcal/g to all polyols, including LYCASIN® 80/55 (10).
**AUTHORIZATIONS**

LYCASIN® 80/55 conforms to main Pharmacopoeias: USP/NF and European Pharmacopoeia.

On the basis of a complete toxicology dossier, LYCASIN® 80/55 has been authorized as a food additive in many countries.

In its 49th report (1997), the international organization J.E.C.F.A.*, a mixed FAO/WHO** committee, attributed a “not specified” Acceptable Daily Intake (A.D.I.) to this product.

This is basically a recognition of the total safety of the product, since the A.D.I. per kilogram of body weight was not limited.

In the pharmaceutical field, LYCASIN® 80/55 is used as an excipient in a large number of preparations marketed throughout the world, including Argentina, Australia, Denmark, Spain, the United States, France, Great Britain, Italy, Mexico, Philippines, Switzerland, Thailand and many others.

LYCASIN® 80/55 is manufactured at our factories in Lestrem, France, as well as Gurnee, Illinois USA.

LYCASIN® 80/55 manufactured at the Roquette factory in Gurnee, USA, is subject to a D.M.F. application with the FDA, registered under N°6611.

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**GLYCAEMIC AND INSULINAEMIC INDEXES IN HEALTHY AND TYPE-2 DIABETES PEOPLE**

Glycaemic index is defined by “the incremental area under the blood glucose response curve of a 50g carbohydrate portion of a test food expressed as a percentage of the response to the same amount of carbohydrate from a standard food taken by the same subject” (FAO 1998). In this definition, carbohydrate usually means available carbohydrate. The standard food mentioned is usually glucose in water or white bread.

The glycaemic response (GR) has been recognized by the 2005 Dietary Guidelines Advisory Committee, as the effects of carbohydrate-containing foods on blood glucose concentration during the time course of digestion. The definition is less standardized than that of the Glycaemic Index where 50g of available carbohydrate has to be administered. That is why GR is often used when the bioavailability of carbohydrates is low.

A review supported by the European Polyols Association compiles all the data about glycaemic and insulinaemic indexes available for polyols in healthy and type 2 diabetes people. (13) Maltitol syrup (LYCASIN®) and maltitol powder (SweetPearl®) were included in this research review.

The glycaemic and insulinaemic indexes of LYCASIN® and SweetPearl® were reported according to the health status of the studied population: healthy or type-2 diabetes. Mean values are reported in the table below:

<table>
<thead>
<tr>
<th>Product</th>
<th>Source (cited in Livesey et al. 2003)</th>
<th>Number of subjects</th>
<th>Intake (g)</th>
<th>Glycaemic response</th>
<th>Insulinaemic response</th>
<th>Subjects health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>SweetPearl®</td>
<td>Slama et al., 1989</td>
<td>6</td>
<td>50</td>
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<td></td>
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<td>6</td>
<td>25</td>
<td>27</td>
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<td>Lycasin®</td>
<td></td>
<td>6</td>
<td>66</td>
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<td>Lycasin®HBC</td>
<td>Rizkalla et al., 2002</td>
<td>6</td>
<td>66</td>
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Maltitol syrups, LYCASIN® and LYCASIN® HBC, as sugar replacers display low glycaemic index, which make them suitable solutions in the management of post-prandial glycaemia.
Glycaemic and insulinaemic indexes in healthy and Type-2 diabetes people

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<table>
<thead>
<tr>
<th>Product</th>
<th>Source (cited in Livesey et al. 2003)</th>
<th>Number of subjects</th>
<th>Intake (g)</th>
<th>Glycaemic response</th>
<th>Insulinaemic response</th>
<th>Subjects health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maltitol</td>
<td>Slama et al., 1989</td>
<td>6</td>
<td>50</td>
<td>29</td>
<td>33</td>
<td>Normal</td>
</tr>
<tr>
<td>Maltitol</td>
<td></td>
<td>6</td>
<td>6</td>
<td>25</td>
<td>27</td>
<td>T2D</td>
</tr>
<tr>
<td>Lycasin®</td>
<td></td>
<td>6</td>
<td>66</td>
<td>34</td>
<td>52</td>
<td>Normal</td>
</tr>
<tr>
<td>Lycasin®</td>
<td></td>
<td></td>
<td></td>
<td>41</td>
<td>64</td>
<td>T2D</td>
</tr>
<tr>
<td>Lycasin® HBC</td>
<td>Rizkalla et al., 2002</td>
<td>6</td>
<td>66</td>
<td>47</td>
<td>23</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25</td>
<td>39</td>
<td>T2D</td>
</tr>
</tbody>
</table>

Maltitol syrups, LYCASIN® and LYCASIN® HBC, as sugar replacers display low glycaemic index, which make them suitable solutions in the management of post-prandial glycaemia.
A number of medicinal preparations involve substantial ingestion of sugars which are very bad for the health of the teeth:
- syrups,
- pharmaceutical candies,
- oral solutions,
- lozenges, etc

When these pharmaceutical forms are absorbed, even in small quantities between meals, they present a high risk factor for the health of the teeth, in the same way as classical candy and sweets.

In addition, patients with xerostomia, either pathological or induced by certain active ingredients, are more sensitive to the caries potential of sugar owing to their reduced salivary secretion.

Series of surveys have investigated the problem of caries potential of pharmaceutical products, especially of syrups for children and syrups for treating chronic disorders.

A number of experts have worked on this subject:

“Reformulation of liquid medicines and changes of dietary habits are needed to reduce dental caries” CRAWFORD (1981).

“Destruction by caries, sometimes even of the entire dentition, by sugar-containing pharmaceutical syrups remains ignored by the pharmaceutical industry”. MÜHLEMANN et al. (1982).

“The fact that some children are affected by sucrose-containing medicines leads us to continue to question the use of sucrose as a sweetening agent in pediatric medications”. FEIGAL et al. (1984).

“Many cough syrups... are consumed by children in the evening just before going to bed. The sugar contained in these pharmaceutical preparations remains in the mouth all night long and is implicated, by a large number of dentists, in the occurrence of dental caries”. ASTIER DUMAS (1984).


“The panel recommends that the government should seek the means to reduce the use of sugared liquid medicines”. COMMITTEE ON MEDICAL ASPECTS OF FOOD POLICY, 1989 (11).

The particular properties of LYCASIN® 80/55 offer a solution to the pharmaceutical industry for the development of sugarless medicinal preparations which will help prevent tooth decay.

Our Pharmaceutical Business Unit is composed essentially of Pharmacists who will be pleased to respond to the needs and questions of the pharmaceutical industry.

In cooperation with research engineers and technicians in the scientific and applications laboratories of Roquette, this team is ready to contribute to the development of new formulae for our customers.

Our customers can also benefit from the wide experience of our specialized development service for the design and installation of materials handling systems.

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