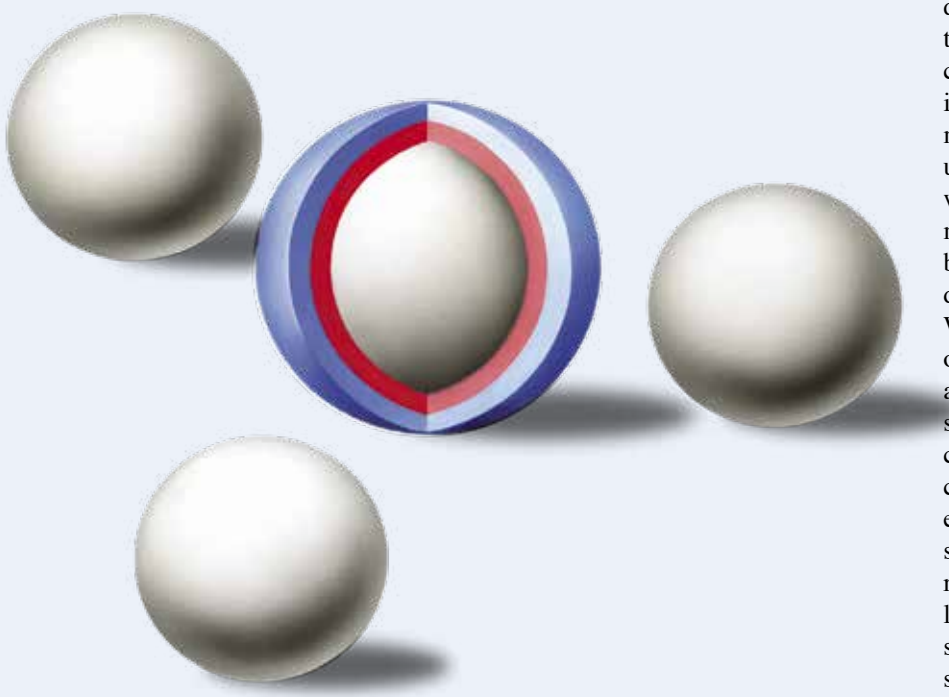
Globuli sacchari

A homoeopathic drug form

Von Dr. Detlef Werner, Tornesch

In homoeopathy a number of different drug forms is known, among which pillules or globuli are outstandingly unique. Hahnemann, the founder of homoeopathy, even preferred them as exclusive form of administering. The little spheres of sucrose (also called globuli sacchari), described as "non-medicinal", neutral, or inert, can be used to prepare almost any homoeopathic drug with various potencies. This is done by impregnation with liquid ethanolic dilutions (globuli sacchari[1]) or by encasing with liquid or solid preparations and sugar syrup (globuli velati[2]). Other related forms of therapy such as anthroposophical medicine also use this drug form. This article deals with globuli sacchari as starting material and the specific characteristics of its preparation and testing from a manufacturer's point of view[3].



Permitted starting materials – various forms of therapy and its different requirements

In Hahnemann's "Organon of Medicine", a description for the preparation of globuli can be found:

"They are prepared under supervision by the confectioner from starch and sugar ...".[4]

From this wording some homoeopaths conclude that globuli must consist of these two starting materials – in a ratio of about 5:1 ("globuli according to the description by Hahnemann"). This hypothesis is confirmed by examination of still existing globuli from Hahnemann's bequest[5,6]. Strictly interpreted, only raw materials which were commonly used by the confectioners at Hahnemann's times, i.e. wheat and rye starch, and cane sugar, may be used. The type of starch can be unambiguously identified by microscope, whereas the distinction between sugars made from sugar cane or from sugar beet is difficult because of the high degree of refining of officinal sucrose. While for more impure types the ratio of potassium/sodium in the ash allowed an evaluation[7], in the case of highly pure sucrose only a $^{13}C/^{12}C$ isotopic analysis can reveal the origin definitely[8]. Since it can not be assumed that Hahnemann has established the formulations to delimitate starches and sugars of other provenance rather than for reasons of general availability, other food starches such as corn starch and cane sugar instead of beet sugar are considered permissible as well. However, based on the 6th edition of the "Organon of Medicine", the mentioned

Tab. 1: Tests based on the monograph "Sucrose" of the Ph.Eur. 2002

Parameter	Method
Identification	IR spectroscopy [1]
Appearance of solution	Colorimetry
Acidity or alkalinity	Limit test using phenolphthalein
Conductivity	Conductometry [2]
Specific optical rotation	Polarimetry
Glucose and invert sugar	Limit test using methylene blue [3]
Sulfites	Limit test using Schiff's reagent [4]
Lead	Atomic absorption spectroscopy
Loss on drying	Thermogravimetry [5]

Remarks

[1] With the corresponding equipment in the testing laboratory, this identity test is more rapid than the alternatively stipulated thin-layer chromatography plus Fehling's reaction after hydrolysis.

[2] The measurement of conductivity replaces the former sulphated ash method which has shown methodical problems caused by the low ash contents of refined sugar. Besides, the "conductometric ash determination" is since long a reliable method in sugar analyses[12].

[3] With regard to this requirement, certain concessions to the preparation technique must be made. Depending on the procedure, sucrose is subjected to a thermal treatment during which glucose and fructose may be formed in trace amounts as inversion products. If necessary, wider tolerances have to be set, e.g. by increasing the concentration of the used methylene blue solution to 0.5%.

[4] Sulphite may arise from the sulphitation processing stage in sugar production[13].

[5] The water content is an important quality parameter particularly for the sugar globuli. Depending on temperature variations, too much water might cause agglomerations[14] and the dull globuli may turn "glassy". In face of the usually low contents, we prefer a Karl Fischer titration (solution in formamide/ethanol and titration at 50 °C) instead of the determination of the weight loss in the drying oven.

conclusion is not undisputed. Earlier editions lack this information for the preparation and Hahnemann constantly used the term sugar globuli. Based on corresponding formulations in the homoeopathic pharmacopoeias[9,10] ("globuli sacchari"), the opinion that sugar globuli have to consist exclusively of sucrose has succeeded. The most far-reaching ideas in this direction even demand that globuli sacchari have to comply with the monograph "Sucrose" of the European Pharmacopoeia (Ph.Eur.)[11]. In addition to the globuli-specific examinations to be discussed later, this results in the following scope of tests (table 1).
The preparation of globuli exclusively from sucrose is a challenge to process engineering. The use of low portions of binding agents would not only simplify the production process, but would also allow for a higher porosity of the globuli and thus an increased absorptivity during the following impregnation. Either humectants such as glucose syrup or invert sugar or thickening agents such as gum arabic or gelatine would be possible. But there is a general agreement that use of such additives is not permitted.
In the French Pharmacopoeia[15], apart from sucrose, lactose ("milk sugar") or a mixture of both sugars is permitted. Because an identification reaction is required for both starting materials, only globuli made from a mixture of both are permitted according to a strict interpretation. Lactose is a common starting material in homoeopathy which is used particularly for the preparation of triturations. Therefore, globuli of this composition are used in the French homoeopathy (by the way without any added binding agents as well).
The way of administering globuli brings the teeth into contact with the cariogenic sucrose. Some homoeopaths consider this as critical and demand "sugar-free" globuli, especially if children are the consumers. Globuli made of xylitol or a mixture of xylitol and calcium carbonate, which do not contain sucrose any more, have therefore been developed. Their use, however, is limited to specific applications.
For the sake of completeness, it shall be mentioned that for the preparation of globuli water is always required (for the preparation of sugar solutions) and thus, al-though being removed during the production process, is considered to be a starting material.
It is obvious that all mentioned substances must comply with the requirements of the respective pharmacopoeias.

The size of the globuli - an assortment of large diversity for a distinct therapy

In Hahnemann's writings, information on the size of the globuli can be found in several passages. First it is said:

"It is most convenient to employ fine sugar globuli of the size of poppy seeds ...".[16]

Due to the variability of poppy seed's size and mass, this guideline is quite vague (thousand grain weight: 0.3 - 0.6 g)[17]. More precise data will follow[18,19,20] later. It shall be clarified that the number of globuli was related to the weight unit "grain" which was in use at that time (1 apothecaries' pound = 12 ounces = 96 drachms = 288 scruples = 5760 grains). It is a problem that depending on the region and time, the apothecaries' pound had different real weights. Simplifying calculated as 60 mg, the Nuremberg apothecaries' weight used by Hahnemann was equal to 357.8436 g per pound and, hence, one grain equal to 62 mg[21]. Table 2 shows a summary on the globuli's sizes. For a better comparison with the globuli in use today, the table also contains the values calculated in g.
For the LM potencies[22,23], Hahnemann preferred globuli corresponding to the size of 100 globuli per grain.
The German Pharmacopoeia of Homoeopathy (HAB) distinguishes ten sizes which are mainly larger than Hahnemann's sizes (table 3).

In Germany, the sizes 3 and 5 are preferred for the decimal and centesimal potencies; size 1 is preferred for LM potencies[24].
The French Pharmacopoeia, on the other hand, distinguishes only two sizes (table 4).
It is a general problem that when determining the globuli's size by the number of globuli per g, the mass of the individual globulus and especially the mass distribution can not be determined. When counting one gram, the same number of globuli can have either a wide or narrow mass distribution. For this reason it is required to determine the deviation by applying e.g. sieve analysis and by requesting certain minimum sizes in a nominal fraction (e.g. at least 90% between 2,500 and 3,150 μm).
The already mentioned French Pharmacopoeia demands tests for uniformity of weight ("Uniformité de masse") to be realized as follows: Twenty globuli are

Tab. 2: Sizes of globuli according to Hahnemann

Number of globuli per grain	Number of globuli per g (calculated)	Mass of one globulus in mg
300	4,839	0.21
200	3,226	0.31
100	1,613	0.62
50	806	1.24
20	323	3.10
10	161	6.20

Tab. 3: Globule sizes according to the German HAB 2001

Size	Globuli per 1 g	Average mass of one globulus
1	470 - 530	2.0 mg
2	220 - 280	4.0 mg
3	110 - 130	8.3 mg
4	70 - 90	12.5 mg
5	40 - 50	22.2 mg
6	22 - 28	40.0 mg
7	10	100.0 mg
8	5	200.0 mg
9	3	333.3 mg
10	2	500.0 mg

Tab. 4: Globuli of the French Pharmacopoeia

Type	Mass of one globulus	Globuli per g
Granules inertes	50 mg	20
Globules inertes´	3 - 5 mg	200 - 333

weighed individually. From the mean value calculated thereof, a maximum number of 5 single weights may differ for more than 10%, but none for more than 20%. As twenty globuli are not really representative for a larger batch, the following standards must also be fulfilled:

- ☐ Homogeneity of the batch
- ☐ Number of tests adapted to the batch size
- ☐ Selection of single globuli strictly by random.

Tab. 5: Properties of globuli depending on the preparation method

Preparation method	Granulation	Pan-coating
Porosity	high	low
Hardness	low	high
Surface structure	rough	even
Way of liquid absorption in impregnating	Wicking into pores by capillary forces	Stays near the surface, encasing

Shape, structure and surface of the globuli as parameters for a uniform impregnation

The ideal spherical shape of the globuli is the aim. However, it must not be forgotten that due to restricted technical possibilities in Hahnemann's times, the shapes of the globuli were quite irregular[25]. But the spherical uniformity is an important condition for achieving a sufficient uniformity in content in the preparation of medicinal globuli which has come into the focus of interest in recent years[26,27]. In the impregnation with alcoholic potencies, each globulus is wetted according to its surface area. The distribution is uniform over all globuli only if they have the same, reproducible surface area.

Additionally because of hygienic reasons, single globuli are increasingly administered by use of dispensers with different mechanisms; all of them requiring a uniform size and shape of the globuli. Besides misshapen, e.g. oval or broken globuli, especially globuli adhering to each other (depending on the size ratio called "twin formations" or "riders") are undesirable. Therefore, many specifications establish limiting values for the amount of such differing globuli. Another important quality parameter in this connection is the structure of the mass and surface, because they determine the globuli's absorptivity. Depending on the preparation method, two basic types of sugar globuli can be distinguished (table 5):

It must however been taken into consideration that in practice often certain states between these extremes can be achieved (e.g. through a directed post processing). Scanning electron micro-scope images demonstrate the crystalline structures of the globuli's surface before and after impregnation[28].

The globuli's behaviour during the impregnation can be determined experimentally. The instructions are often proven "in-house methods", such as the colouring with methylene blue or red-beet juice. The procedure shall correspond to the posterior impregnation as exactly as possible. The uniformity of absorption can be evaluated immediately through the applied colourant's inherent colour. The French Pharmacopoeia requires a more complex but better quantifiable method (Imprégnation): The globuli are impregnated with an ethanolic picric acid solution. Subsequently, the content of 10 samples of 5 g is verified spectrophotometrically. The mean value of the results must not be less than 90% of the theoretical value. Thus, the loss of active agent at the walls of the equipment used for preparation is taken into account and limited at the same time. No requirements are established with regard to the deviation of the individual values.

Production of medicinal globuli - chances for the pharmacist's formulation

Today, medicinal globuli are mainly produced industrially and several manufacturers provide a wide assortment of active agents and potencies. However, the homoeopathic healing art distinguishes itself by the individual and case-specific therapy. For this reason, there is a demand for drug formulations based on prescriptions - this is a chance for the pharmacy. The impregnation of globuli sacchari is possible by simple means in the pharmacy and there are corresponding instructions available in the relevant literature.[29]

Dr. Detlef Werner, PhD
Hanns G. Werner GmbH + Co. KG
Hafenstrasse 9, D-25436 Tornesch

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The entire text of Hahnemann's "Organon of Medicine" in English language is available on the Internet
http://www.homeopathyhome.com/reference/organon/organon.html
or as download in Word format under
http://www.homeopathyhome.com/reference/books_download.shtml

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