

## Validation of techniques and methods for the impregnation of homeopathic globules

### Introduction

Homeopathy is a medical and pharmaceutical specialty accredited by Federal Boards of Medicine and Pharmacy. It has a well-determined scientific system whose research methodology is backed by the effects of drugs tested upon healthy individuals in clinical experiments. The homeopathic practitioner aims at prescribing a remedy which best matches the totality of symptoms presented by the patient. For that purpose, the patient is given some substance that, in the experiment with healthy individuals, has produced symptoms resembling those the practitioner wants to eliminate; therefore, the organism is stimulated to react against the disease (TEIXEIRA, 1998). The greater the similarity between the patient's symptoms and the experimental clinical pattern of the medication, the stronger its therapeutic effect (BASTIDE & BOUDARD, 1994). However, in order to avoid the toxic effects of the original substance, and to increase its healing potential, the homeopathic pharmacist will transform this drug into a homeopathic medication by using a special technique called dynamization (MARTINEZ, 1983).

The homeopathic medications are prepared and dispensed in different pharmaceutical forms. Whereas the liquid pharmaceutical forms are represented by drops, only one liquid oral dosage, and liquid formulations, the solid pharmaceutical forms are represented by pills, globules, powders, tablets, only one solid oral dosage, and solid formulations (BRAZILIAN HOMEOPATHIC PHARMACOPOEIA, 1997).

One of the homeopathic pharmaceutical forms most prescribed in Brazil is the dosage form intended for internal use called globule. Such form is obtained from the impregnation of inert globules with homeopathic dilutions. Inert globules are small spherical grains which are homogenous and regular, white and practically scentless, and which have a sweet flavor; they are made up of 100% of sucrose or a mixture of sucrose and lactose. They serve as vehicles for the fixation of homeopathic dilutions. (AMERICAN INSTITUTE OF HOMEOPATHY, 1988; SYNDICAT DES PHARMACIES ET LABORATOIRES HOMÉOPATHIQUES, 1981). They are designated and marketed in Brazil according to their average weight of 30 mg (globules #3, 50 mg (globules #5), and 70 mg (globules #7), and they are manufactured from sugar particles by means of multiple coatings (FONTES, 2001).

Hahnemann recommended a certain amount of drops of the homeopathic dilution (stock preparation) to moisten all the inert globules. Nevertheless, he did not determine an exact proportion between the volume of the stock preparation and the weight of the globules (HAHNEMANN, 1984). According to research carried out by the Associação Brasileira de Farmacêuticos Homeopatas (ABFH, for Brazilian Association of Homeopathic Pharmacists), most of the homeopathic pharmacies in the State of São Paulo currently perform single impregnations in proportions from 2% to 5% (w/v) and, more rarely, triple impregnations at 10% (w/V), adopted by the Brazilian Homeopathic Pharmacopoeia, 2<sup>nd</sup> Edition (ABFH, 2001).

Although homeopathic pharmacopoeias and manuals present different methods and techniques devised for the impregnation of inert globules, they do not describe validating procedures. Based mostly on tradition, some authors have suggested the use of a Methylene Blue coloring solution as a visual indicator for the validation of methods of globule impregnation; however, they have not provided any detailed studies on that issue (FONTES, 2001; POZETTI et al., 2002).

### Materials and methods

#### Material

The following equipment, utensils, glasswares and raw materials were used for carrying out the experiments:

#### Equipment and Utensils

Mettler/Micronal PB 303 precision electronic balance (with resolution 0,001g and maximum load 200g); Shimadzu 1601 PC spectrophotometer; manual chronometer; micropipettes; disposable tips; automated dispensers; alcoholometer; picnometer; higrometer; scalpel; paper filter.

#### Glasswares

Flat bottom volumetric flasks; Petri dishes; graduated cylinders; glass rods; amber glass flasks of 30mg; Erlenmeyer flasks; funnels; beakers; mortar and glass pestle.

#### Raw materials

Inert globules, average weight 30mg (#3) and 70mg (#7); analytical grade ethanol (96 v/v); water purified by distillation; colorings (Picric Acid, Methylene Blue, Basic Fuchsin, Safranin, Gentian Violet).

### Methods

#### Coloring Solutions

The coloring solutions were prepared in different concentrations of the raw materials previously chosen; they were dissolved in ethanol (70% and 90% w/w). In order to carry out the experiments to validate methods and techniques for the preparation of homeopathic medicines in the form of globules, experimenters chose color solutions whose densities were more similar to those of the homeopathic dilutions normally used in the homeopathic pharmacies in the State of São Paulo; here they are represented by the hydroethanolic solutions at 70% and 90% (controls). Among the different coloring solutions which were chosen, the ones used (solutions A and B) were the two which behaved similarly to the hydroethanolic solutions at 70% and 90% (w/w), respectively. The color contrast caused by treating the inert globules with the coloring solutions was considered.

The densities of the coloring solutions prepared in different concentrations, determined by the picnometer, were compared to the densities of the homeopathic dilutions (70% and 90% ethanol). The selected coloring solutions were the following: Methylene Blue 0,2%, Safranin 0,2%, Gentian Violet 0,3%, prepared in 70% ethanol; and Methylene Blue 0,2, Safranin 0,2%, Gentian Violet 0,2%, prepared in 90% ethanol.

The colorings Picric Acid and Basic Fuchsin were not used for, whereas the use of the former is controlled by the Army because it is part of the composition of explosives, the latter is insoluble in ethanol.

#### The impregnation of the globules

To prove how the coloring solutions act on inert globules in order to pick the one that most accurately reproduced the behavior of homeopathic dilutions in relation to these vehicles as regards weight loss, we carried out impregnations with standard hydroethanolic solutions (70% and 90%) and with coloring solutions previously selected in the proportions of 2% and 5% (v/w) in relation to the quantity of globules. That is, the volume of the solution was calculated according to the weight of the analyzed globule sampling. Therefore, for each 15 g of inert globules, 0,3 mL and 0,75 mL were used, respectively. As for the impregnations, we used 30 mL amber glass vials containing 15 g of inert globules with average

weight of 30 mg and 70 mg (inert globules numbers 3 and 5, respectively). The coloring solutions were distributed along the sides of the vials. The vials were then sealed with caps featuring sealing rings. Globules were homogeneized by means of lateral shaking together with rotation of the vials for 3 minutes. Time was measured by using a chronometer. Globule drying was done on Petri dishes at ambient temperature and humidity.

Those experiments were carried out in duplicate; the groups were divided according to the size of the globules (globules numbers 3 and 7). Such groups were subdivided according to the ethanolic grade of the coloring solution (70% and 90%), which were subdivided again according to the amount of coloring solution added in the impregnation procedure (2% and 5% v/w)

#### Drying time

To determine the drying time, the homeopathic globules were weighed on an electronic balance after single impregnations (2% and 5% w/v) were carried out into inert globules numbers 3 and 7, by using ethanol graded 70% and 90%. Drying times were recorded from the moment of the stabilization of globule weight. This experiment was done in duplicate and at ambient temperature and humidity.

#### Choosing the coloring solution

To choose the solutions A and B, that is, the solutions that would provide the best color contrast, single impregnations at 2% and 5% were performed with the following dyes: Methylene Blue, Safranin, Gentian Violet, and with the standard solutions.

### Results and discussions

**TABLE 1:** Dilutions of the dyes whose densities are similar to those of the control homeopathic dilutions, prepared with 70% ethanol (w/w).

Solutions	Density 1	Density 2	Density average (D1 and D2)
70% EtOH (control)	0,892	0,894	0,893
METHYLENE BLUE 0,2%	0,893	0,893	0,893
SAFRANIN 0,2%	0,893	0,892	0,8925
GENTIAN VIOLET 0,3%	0,891	0,894	0,8925

Measurement was taken in duplicate (density 1 and density 2) in the afternoon of one single day, at ambient temperature ranging from 29,1°C to 28,6°C, and relative humidity of air

**TABLE 2:** Dilutions of dyes whose densities are similar to those of the control homeopathic dilutions, prepared with 90% ethanol (w/w).

Solutions	Density 1	Density 2	Density average (D1 and D2)
<b>90% EtOH (control)</b>	0,832	0,833	0,8325
<b>METHYLENE BLUE 0,2%</b>	0,833	0,833	0,833
<b>SAFRANIN 0,2%</b>	0,833	0,834	0,8335
<b>GENTIAN VIOLET 0,2%</b>	0,833	0,834	0,8335

Measurement was taken in duplicate (density 1 and density 2) in the afternoon of one single day, at ambient temperature of 26,9°C, and relative humidity of air varying from 57% to 56%.

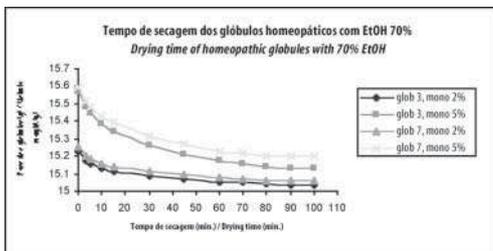


Figure 1: Drying time of inert globules of different sizes (numbers 3 and 7), subjected to single impregnations at 5% and 7% with 70% ethanol (w/w), done at ambient temperature ranging from 25,9°C to 26,3°C and ambient humidity at 59%.

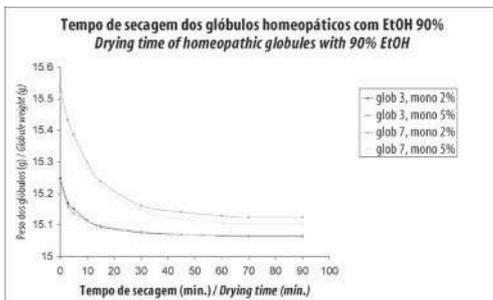


Figure 2: Drying time of inert globules of different sizes (numbers 3 and 7), subjected to single homeopathic impregnations at 2% e 5% with 90% ethanol (w/w), done at ambient temperature ranging from 25,8(C to 26,9(C and ambient humidity varying from 71% to 77%.

**Conclusions**

Among the analyzed coloring solutions, the most appropriate for validating the methods and techniques for the preparation of homeopathic globules were the Gentian Violet solutions at 0,3% (w/V) and 0,2% (w/V), which were prepared respectively in ethanol graded 70% and 90% (w/w).

Based on the data obtained, we concluded that the stabilization of the weight of the globules, after their im-

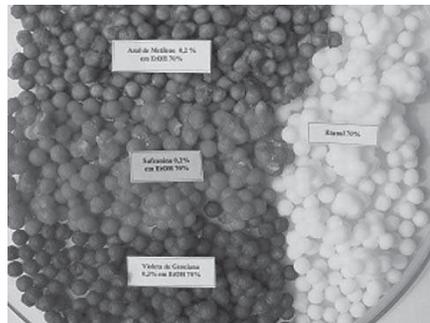


Figure 3: Color contrast and uniformity of the dye dilutions whose densities are similar to those of the homeopathic dilutions with 70% ethanol (w/w).

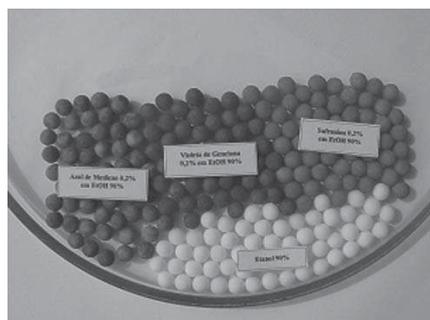


Figure 4: Color contrast and uniformity of the dye dilutions whose densities are similar to those of the homeopathic dilutions with 90% ethanol (w/w).

pregnation with homeopathic dilutions, takes a considerable amount of time, which is different from the length of time routinely taken at homeopathic pharmacies. Using artificial heat at a temperature lower than 40° C may help hasten the drying of the impregnated globules. The results have shown the importance of the validation of pattern operational procedures (POP 's) by pharmacies, including time and ideal drying method for the homeopathic globules.

*The method of triple impregnation at 10% (V/w) with dilution prepared in 90% ethanol (w/w) has been proven to impregnate globules homogeneously and to make them evenly colored and integral. However, such method has been proven unfeasible for dilutions prepared in 70% ethanol (w/w).*

*Studies must proceed further, comparing the triple impregnation at 5% (V/w) and at 10% (V/w) in the 90%*

*alcoholature (w/w), trying to identify the ideal technique for impregnating homeopathic globules.*

*While that has not been ascertained scientifically, that is, whether different amounts of medicine incorporated by the globules are relevant or not for the preservation of the medicine quality, the technical criteria for validating the impregnation methods and techniques must ensure the evenness of impregnation and integrity of the globules.*

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