



The Impact of ‘Succession’ during preparation of ultra-high diluted solution medicinal products

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Abstract

Objective: Ultra high diluted medicinal products are made by serial dilutions which are always followed by “succussion”. The aim of this work is to investigate the impact of the succussion on the nature of these solutions, when a source material is triturated up to micro and nanoscale particles and then used to prepare ultra-high diluted medicinal products.

Methods: Hence, five source materials, which were used to prepare ultra-high diluted succussed solutions were studied from their initial stage up to 50M potencies with methods approved by chemical science.

Results: The results were that “succussion” contributed to the self-organization of the micro- nano particles present even in the most diluted solution.

Conclusion: This will help to fundamentally redefine basic pharmaceutical research of these ultra-high diluted succussed solution products as well as to highlight their nano character.

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Keywords: Succussion; Dynamization; Medicinal products; Self-organization; Micro-nano particles; Dilutions

Introduction

The idea of using extremely low doses of diluted and potentiated substances for medicinal purposes was originally proposed by S. Hahnemann, the founder of homeopathy, in the eighteenth century. From the eighteenth century to the present, only complex hypotheses were formulated for the role of succussion and not only in the preparation of ultra-high diluted succussed solution products [1]. High dilutions have been reported as having specific effects in many basic research experiments, but most of the results await independent confirmations. There is only a small data set to support special effects unique to high di-

lutions, and not observed with low dilutions in basic research [2-4]. Further research is needed to clarify this aspect. Because of these aspects, it was considered necessary to investigate specific materials used as source materials with analytical control methods widely used by the scientific community and without any doubt as to these methods results. German Pharmacopeia adopted mainly the decimal or centesimal dynamization as the standard scales of attenuation, in either liquid or solid form, by which each successive attenuation or trituration is mainly prepared using 1/10th or 1/100th of the preceding attenuation or



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trituration. Sequentially the dynamizations are presented as a number correspondings and showings the number of successive triturations (for source materials) or dilutions (for liquid stock). The number is always followed by the letters X, C, and M which indicates the decimal, the centesimal and thousandth (1/100)⁻¹⁰⁰⁰ dilution, respectively.

Materials and methods

Preparation

Five different source materials were used after successive trituration in lactose. Afterwards, they were turned into ultra-high diluted succussed solutions. The preparation process for 1X to 6X, triturated solid samples was the same as the one described in our previous works [5,6]. From 6X potency, we prepared the initial 3C potency (1 g of substance was dissolved in 99 mL of distilled water filtered through a 200 nm syringe filter), which it was utilized for making the 4C, 12C, 30C, 200C, 1M, 10M and 50M potencies according to German Pharmacopoeia guidelines. The reason that this solvent was further purified was to exclude from our measurements any particle that could be contained in the initial distilled water.

The materials included were

Sodium chloride, Sulfur, Calcium phosphate, Calcium carbonate in powder from Sigma-Aldrich GmbH Germany (purity 99%). Benzoic acid, in granules from Alfa Aesar GmbH Germany (purity 99%). Crystalline α -lactose monohydrate, from DFM Pharma GmbH & Co, Germany. Distilled water filtered through a 200 nm syringe filter.

The equipment required were

A hand mortar and pestle made from porcelain. Five measuring tiles. A timer. A balance (Mettler Toledo, version AB204-S/FACT- accuracy 0.0000 g). Dynamic Light Scattering Zetasizer Nano series (Nano ZS 173, Malvern instruments LTD) Dark vials, 200 mL

Results and discussion

Three random samples from every potency (4C up to 50M) were investigated. Figure 1 shows the middle in size measurement of three taken in every potency, so that, there is no any mismatch between the numerical and graphical results.

We can see for sodium chloride (Figure 1a, a') that, the Z-average size of the particles at the 4C potency started at 637.5 nm and after succussion was 362.3 nm. For the 12C and 30C potencies, after succussion, particles with larger Z-average sizes were present. At 200C and 1M the reverse occurred. At the 10M potency, dynamization appeared to result in the formation of agglomerates, while at 50M the dimensions were roughly equal. In addition, the polydispersity index followed the same course with a difference at 50M where in the resting state, it was higher than the succussion state. In the resting state, complete heterogeneity in our sample dominated as a possible result of remaining on the shelf for a period of approximately 15 days.

The behavior of benzoic acid (Figure 1b, b') for all potencies was similar to sodium chloride, as it can be observed in the same Figure. We observed that in the 4C and 1M potencies, the differences in the mean Z-average size was relatively small, and the polydispersity index suggested almost complete homogeneity of the samples. With succussion, the polydisper-

sity index became disproportionately large. At the 1M potency, the sample was also characterized by complete heterogeneity. This could primarily be attributed to the reduction in the size of the material agglomerates during succussion and secondarily to random sampling.

For sulfur (Figure 1c, c') at the 4C mother tincture, after the succussion, there was a significant increase in the Z-average particle size, while Pdi almost completely dominated the homogeneity in our samples. In 12C and 30C dilutions, there were lower increases in the mean Z-average size before the succussion state, and a decrease to 200C was observed. In the 1M, 10M and 50M dilutions, the particles' Z-average sizes remained in the order of the nanoscale before succussion. Afterward, the diameter increased considerably. As the polydispersity index increases, the Z-average size at 1M, 10M, 50M was greatly diminished, indicating the tendency for more uniform source particles.

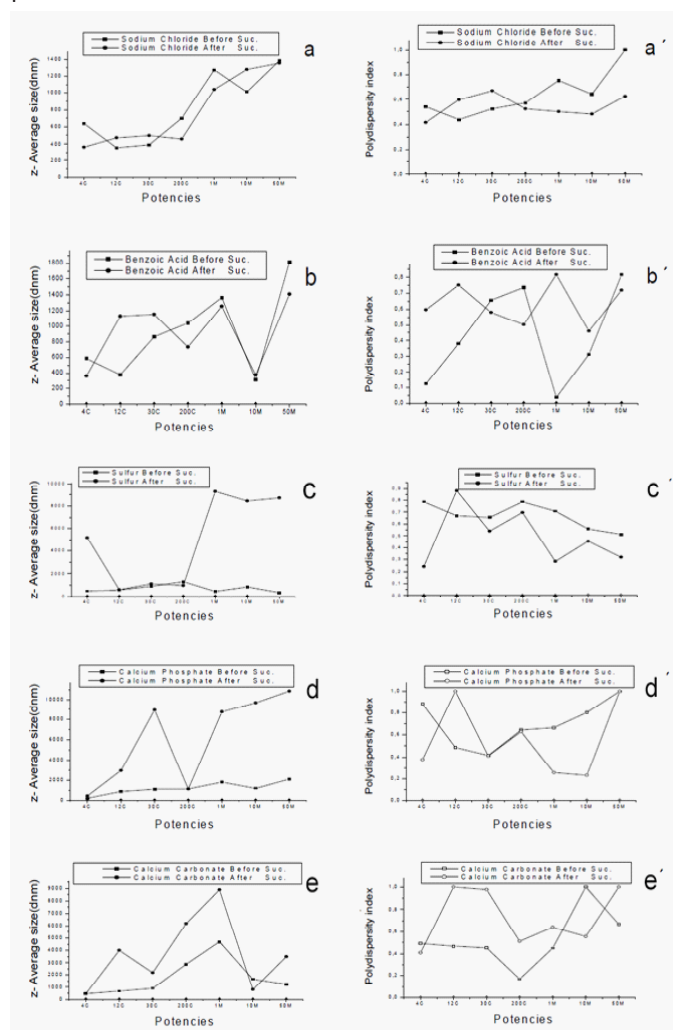


Figure 1: Z- Average size (dnm) and Polydispersity index of a, a' Sodium chloride, b, b' Benzoic acid, c, c' Sulfur, d, d' Calcium phosphate, e, e' Calcium carbonate in all potencies.

In the case of (Figure 1d, d') calcium phosphate it was observed that, although at 4C the Z-average size of the source particles was in nanoscale, during the succussion phase, there was a sufficiently large increase in the average diameter up to the 50M potency. The exception was in the 200C potency, where there was an increase in the Z-average size of 0.001 nm. Additionally, with succussion, a decrease in the polydispersity index was observed related to the resting state, except for 12C, where it almost doubled.

For calcium carbonate (Figure 1e, e'), we observed that from 4C to 1M and 50M potencies, the average diameter of the source particles during the succussion phase showed an increase with the highest value attributed to 1M potency. An exception of this finding was the 10M potency, where a decrease in the Z-average size of source particles was observed. In 12C potency after succussion, there was a large increase in the Z-average size and complete heterogeneity as a result of the particle collisions. An analogous result was observed in the 30C potency. In 1M in the resting state (i.e., before succussion), relative uniformity of the excessively large particles was measured and appeared to be above the measurement limits of the instrument. This issue seemed to be corrected with succussion. In 10M before succussion and 50M after succussion, full heterogeneity was present in our samples.

All these results are justified and clearly explained by the following informations. It is important to note that the Z-average size is the size to be used if a quantitative variable is required for quality control purposes. For sample with slightly increased width, the Z-average size and polydispersity index will give values that can be used for comparative purposes. The Z-average size can only be used to compare results with samples measured in the same dispersant by the same technique, i.e., Dynamic Light Scattering [7]. The polydispersity index is a dimensionless size. It characterizes the distribution breadth resulting from the analysis of pooled data for particulate matter. It is a statistical size that represents the measure of homogeneity or heterogeneity of particles size and has a value from 0 (full homogeneity, monodisperse particles) to 1 (full heterogeneity, multi-size particles). The index is mathematically defined as $Pdi = (\sigma)^2 / d$, where σ is the standard deviation and d is the particle size. Under normal circumstances, it is encountered in particles that follow latex standards or mono-solvent samples ($Pdi < 0.05$). The calculations for these parameters are defined in the ISO standard document 13321:1996 E [8].

According to Brownian diffusion, solvent molecules are much smaller and lighter than solute molecules [9]. Furthermore, this observation has been shown in a previous work [10]. As Brownian motion theory supports, a particle with a mass, m , immersed in a fluid environment, undergoes a jittering movement [11-13].

During succussion, an external force is exerted on the solution molecules, both the solute and the solvent. This power is considered to be a necessary condition to form agglomerates or to further dissolve existing species. In our research this theory is the basis on which the formation of larger agglomerates is justified. These forces also permit the flouting of the species all over the volume of the solution from the top to the bottom of the vial, in which they are contained.

Mathematical details about succussion will not be mentioned in this research. It is to be noted, however, that when suspended particles in a homogeneous solution within a well-defined space, such as the space of a vial, receive forces that alter their kinetic state, their trajectories converge [14]. This detail may justify both the formation of agglomerates from the nanoparticles present in the resting state as well as the breakdown of agglomerates during succussion.

Dispersion stability is an important problem for many applications of colloidal and nanoparticle systems. Colloidal particles with sizes smaller than approximately $5 \mu\text{m}$ are subjected to significant Brownian motion in a liquid dispersion medium.

As a result, the particles will eventually collide with each other. These collisions can cause the particles to "stick" together, that is, irreversibly aggregate or coagulate.

Additional collisions lead to the formation of ever larger aggregates, which either settle or float when they become sufficiently large [15]. This is depicted in Figure 2 of the 200C samples, which were left immovable after their preparation on a shelf in a room for a six-month period. Because these sediments were very small, elemental control was impossible.

Lu and Wang [16] investigated the chaotic behavior of ordinary differential equations with a homoclinic orbit to a saddle fixed point under an unbounded random force driven by a Brownian motion. They proved that, for almost all sample paths of Brownian motion in the classical Wiener space, the forced equation yielded a topological horseshoe of infinitely many branches. This result was then applied to the randomly forced Duffing equation and the pendulum equation.

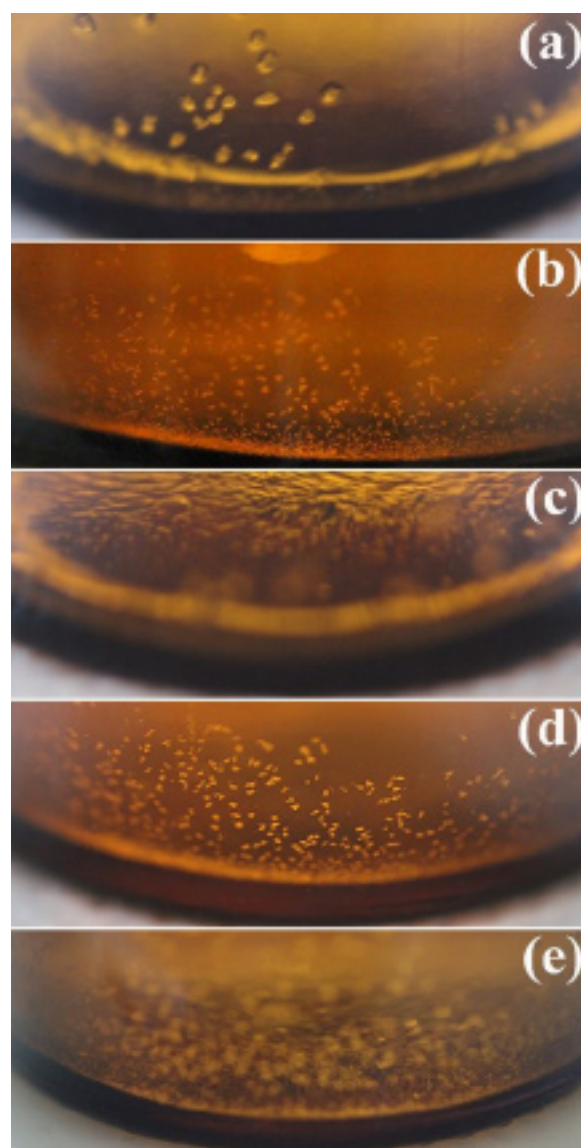


Figure 2: Material agglomerates at the bottoms and the side wall of the vials for (a) Sodium chloride, (b) Benzoic acid, (c) Sulfur, (d) Calcium phosphate, (e) Calcium carbonate at a potentiation of 200C.

Conclusions

'Succussion' is a necessary procedure in the preparation of ultra-high diluted medicinal products. Out of 35 samples, which were analyzed before and after succussion, 24 were found to

have agglomerate formations and no further dissolution of the source particles. In contrast, for the remaining 11 samples, potentiation acted as a factor for further dissolution of active ingredients which have particles with an average dimension over the micro scale. Additionally, ultra-high diluted solutions appear to be active even in the resting state. This feature was probably due to Brownian motion, to the form of the source particles after trituration in the solutions or to changes of their physicochemical properties. All samples in 12C and 30C dynamizations showed the same behavior, namely, the formation of aggregates. From the aforementioned results, it is clear that particles before and after succussion have colloidal dimensions. In future work, the properties of colloidal dispersion for ultra-high diluted succussed solution medicinal products could be revealed.

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