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Research article

Micro-nano particulate compositions of Hypericum perforatum L in ultra high diluted successed solution medicinal products

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ABSTRACT

The fact that many patients all over the world use homeopathic ultra high diluted successed medicinal products, makes very interesting an explanation about the structure of them since until now only unconfirmed hypotheses are made. The present study focuses on the still unanswered questions about what happens with the chemical composition and the physicochemical properties of these products using Hypericum Perforatum L as a representative paradigm. All samples were prepared according to manufacturing procedures described mainly in S. Hahnemann's "Organon" and were examined by SEM, XRD, FTIR, DLS micro Mastersizer, DLS nano Zetasizer, UV-Vis and TEM. Measurements of electrical conductivity and pH were effectuated by the appropriate devices. During trituration of source material in alpha-lactose monohydrate some functional chemical groups present in source material disappeared and some others new ones came in view at the end of the process. A differentiation upon physicochemical properties between the source material and final triturating product was viewed, as well as micro-nanoparticles in colloidal form in all potencies derived trituration or extraction origin were present. The findings showed that the whole preparation process leads to the creation of micro nanoparticles something that for solid origin these products are created by trituration and for extract origin products these nanoparticles exist from the beginning.

1. Introduction

Homeopathy is a logical natural healing method and an experimental science. It exploits one main property of nature, that of self-similarity on a change of scale [1, 2, 3]. According to Article 1 of the Directive 2001/83/EC, of the European Parliament and the European Council a homeopathic medicinal product should not contain more than one part per 10000 of the mother tincture or more than 1/100th of the prescribed smallest dose used by established medicine with respect to active substances. Different studies indicate that the ultra-highly diluted successed medicinal products, derived from solid source materials or liquid stocks, contain, among others, source nanoparticles [4, 5, 6, 7], silicates [8, 9], other less well-characterized structures or nothing [10] beyond 12C potency. Additionally, many hypotheses like water memory [11, 12], epitaxy [13, 14], clathrate formation [15], quantum theory [16] attempt to explain the retention of information of original active materials at ultra-highly diluted successed solution products. With Hypericum perforatum L as example, we will try to support, experimentally and theoretically that only the starting materials in the form of micro-nano particles are present in all ultra-high diluted successed solutions and the homeopathy can now be incorporated into nanomedicine.

2. Materials and methods

2.1. Materials

The source material used was commercial dried Serbian origin Hypericum Perforatum L (Hyperici herba conc.). Different potencies such as 4C, 12C, 30C, 200C, 1M, 10M, 50M in distilled water, derived from the source material (Hyperici herba conc.). Commercial liquid stock of Hypericum Perforatum L (Tinctura Hyperici (70%) 1:5, g 309/2018 Caesar & Loretz GmbH) for the extract solution samples were used. Potencies such as 4C, 12C, 30C, 200C, 1M, 10M, 50M 60% in ethanol 99,8%- distilled water were derived from the same liquid stock. Commercially manufactured crystalline alpha-lactose monohydrate of various particles sizes was obtained from DFM pharma GmbH & Co, KG,

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Gosh, of German origin for pharmaceutical use. Distilled water further purified with ultra filter unit of 200 nm and Ethanol 99,8% anhy Acros Organics were utilized.

2.2. Required equipment

The required equipment for solid sample preparation was a hand mortar and pestle from ceramic, a sterilized scraper (porcelain spoon) and the measuring tiles. A time balance (kern S72, version 4.07-centimeter accuracy 0,00 g) and dark vials for medicinal use, 200 mL also, they were used. For samples characterization Scanning Electron Microscopy (SEM Quanta 200, FEI); Dynamic Light Scattering (DLS-Mastersizer micro, with a size range of 0.3–300 μμ. Malvern instrument 2006 UK) for source material samples up to 3X trituration step); Dynamic Light Scattering (DLS- Zetasizer nano series Nano ZS 173, Malvern instruments LTD with i: Size range 0.6nm to 6μμ. hydrodynamic diameter ii: Size range for Zeta potential 3nm to 10μμ. iii: He–Ne, 4.0mW, 633nm red laser iv: 173° detection optics - Backscatter detection); X-Ray Diffractometer (XRD BRUKER D8 Advance); Fourier Transform Infrared Spectroscopy (FTIR Jasco 4200 with ATR PRO 410-S, TGS detector); Ultraviolet–visible spectroscopy (UV-Vis Varian CARY 1E); Transmission electron microscopy (TEM microscope Jeol 2100, 200 kV); Electrical Conductivity meter (HACH Sension 7 μS/cm) and pH meter (pH CONSORT C532 version 2) were used.

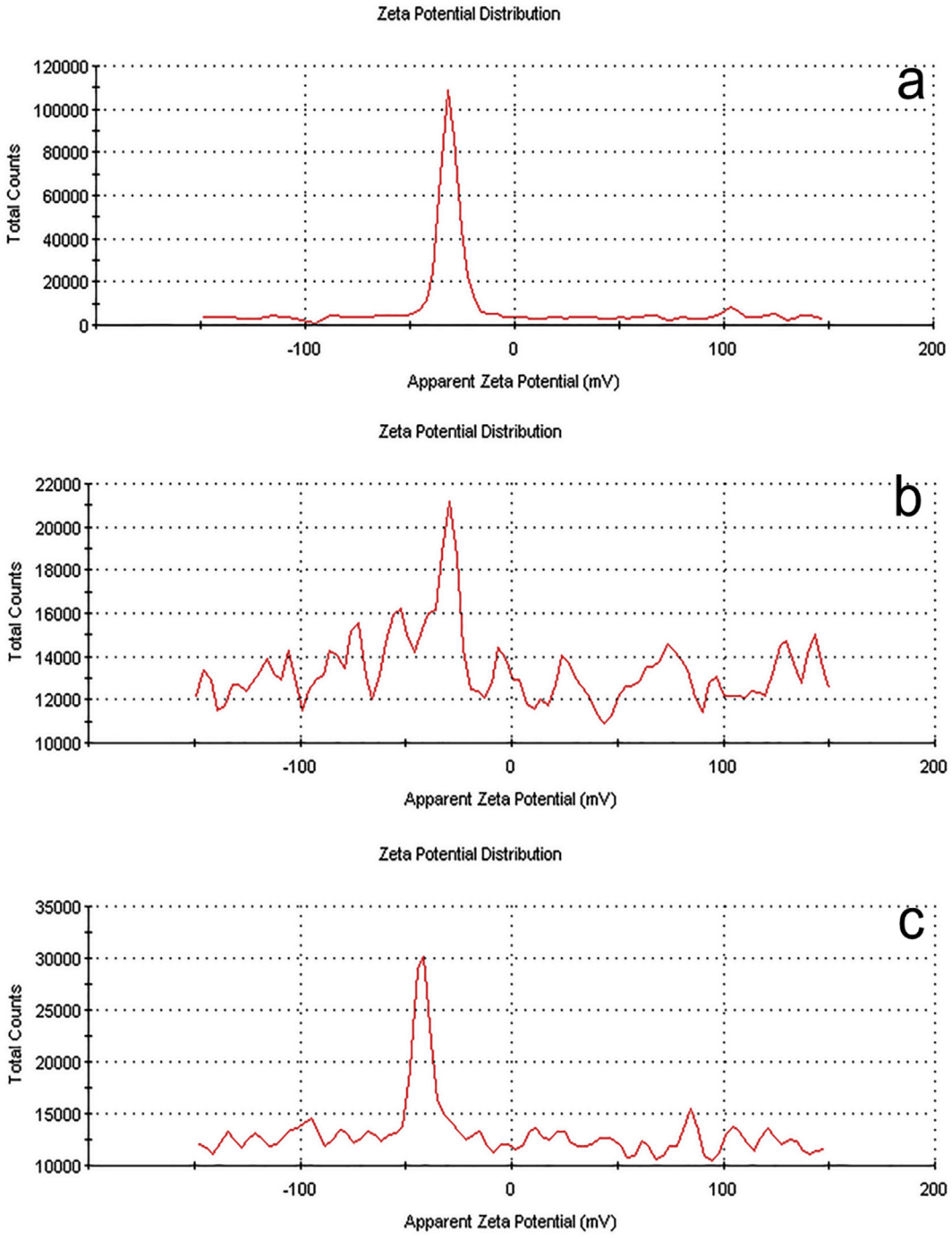

Figure 1. Zeta potential of (a) distilled water further purified with ultra-filter unit of 200 nm, (b) distilled water and (c) ethanol 99,8% anhy - distilled water further purified with ultra-filter unit of 200 nm.

2.3. Preparation procedure

The process proposed by German Homoeopathic Pharmacopoeia [17] and S. Hahnemann's "Organon der Heilkunst" [18] was mainly followed. Hypericum perforatum L source material was selected because we wanted to investigate ultra-high diluted successed medicinal products differently manufactured, but of the same origin. This was possible only if the product was of herbal origin. Also, according to S. Hahnemann's 271 aphorism in "Organon der Heilkunst", when the remedy was of herbal origin, in the case when the mother tincture was not available for any reason, the physician may use the plant after trituration in alpha-lactose monohydrate and prepare the medicinal product. The handmade decimal method of trituration for Hypericum perforatum L source material, was adopted. One part of the previous potency and 9 parts of alpha-lactose monohydrate was taken. The process of trituration for each potency takes 60 min. For a detailed description the readers can look it in this reference [19]. For the preparation of all liquid potencies the centesimal scale was followed, i.e. one drop from the previous potency diluted and successed into 99 drops of solvent. For the preparation of extremely ultra high diluted successed solutions, like 50M potency, S. Hahnemann's 270 aphorism in "Organon der Heilkunst" was followed. Distilled water, further purified using ultra filter of 200 nm, was used to prepare all solutions-potencies of solid origin and ethanol 99,8% diluted in ultra purified distilled water in proportion 60%, was used for potencies prepared from liquid extract origin. For Electrical Conductivity and pH measurements we used 2g from initial up to 6X potency in 100ml distilled water further purified as solvent. The reason why these solvents (Distilled water further purified, Ethanol 99,8% anhy) have been used, was to exclude from our measurements any particle that might be contained in distilled water or ethanol. Therefore, if in our measurements we find particles of z-average size over 200 nm we exclude their origin from solvents. Figure 1 shows the zeta potential of solvents and confirms the absence of colloid structure. The role of alpha-lactose monohydrate as a grinding material during preparation process of ultra high diluted successed solution medicinal products is neutral as we have shown in a previous research [20]. From the initial source material up to 6X potency, 2g are dissolved in distilled water further purified, sequentially, to prepare the samples that have been placed on receptacles to analyze their grain size. For every DLS-Mastersizer micro, DLS-Zetasizer Nano, Zeta Potential Analysis sample, three measurements were done. Here, we present the middle measurement between the lower and higher, so that there is no mismatch between the numerical and graphical results. Also, three samples (three solutions made from the corresponding solid triturated samples from the initial up to 6X potency) were measured from each triturated step and the average of the findings were summarized. The same was done for the ethanol-water liquid stock sample. All the liquid samples from 4C until 50M during preparation process successed. Succussion was a part and necessary procedure in the preparation of ultra high diluted medicinal products after they have been diluted and was done by ten hard strikes against an elastic object.

3. Results

3.1. SEM analysis

In Figures 2a,b,c (SEM examination) a big change of our solid material from initial source material up to 6X trituration can be observed. Figure 2d for comparison reasons, shows the granules' tomahawk shape of 6X triturated alpha-lactose monohydrate that has been used during the preparation process. Figure 2e shows Hypericum perforatum L SEM image Mag 4000x from 6X trituration sample and Figures 2f, g show the

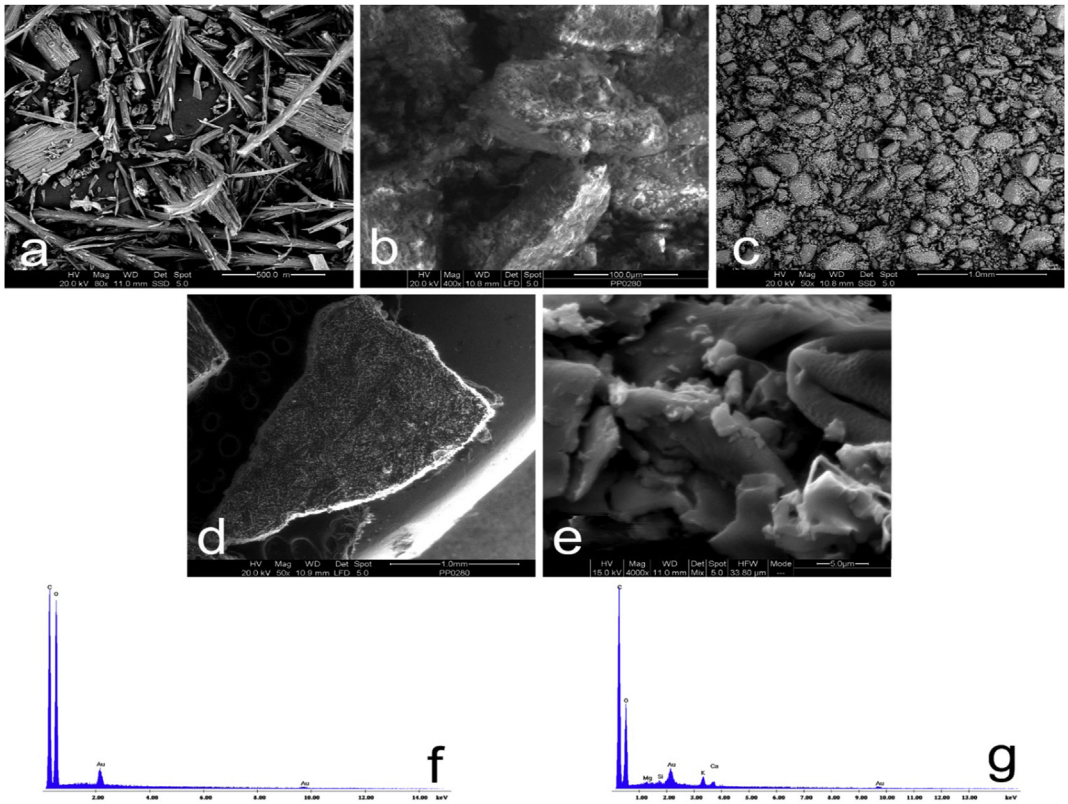

Figure 2. (a) Hypericum perforatum L source material SEM image Mag 50x, (b) 3X triturated in alpha-lactose sample SEM image Mag 400x, (c) 6X triturated in alpha-lactose sample SEM image Mag 100x, (d) alpha-lactose 6X triturated granule SEM image Mag 50x, (e) Hypericum Perforatum L 6X triturated in alpha-lactose sample SEM image Mag 4000x, (f) alpha-lactose SEM-EDAX image and (g) Hypericum Perforatum L SEM -EDAX image.

two EDAX graphs, the one for alpha-lactose monohydrate and the other for Hypericum perforatum L.

3.2. DLS-mastersizer micro granulometry analysis

Figure 3 shows the percent volume size distribution of solid Hypericum perforatum L from source material up to 3X trituration step. In Figure 3e we present, for comparison reasons, the results for alpha-lactose monohydrate DLS-Master Sizer Granulometry in ethanol 99,8% anhy. From DLS Master Sizer it is clear that in 3X, aggregation processes are observed. At 4X, 5X, 6X it was not possible to obtain measurements with this equipment.

3.3. DLS- Zetasizer Nano Analysis

Liquid samples from 4C up to 50M potencies were subjected to granulometric DLS- Zetasizer Nano analysis and their z-Average size and Pdi Distribution were measured. Figure 3f shows the z-average size

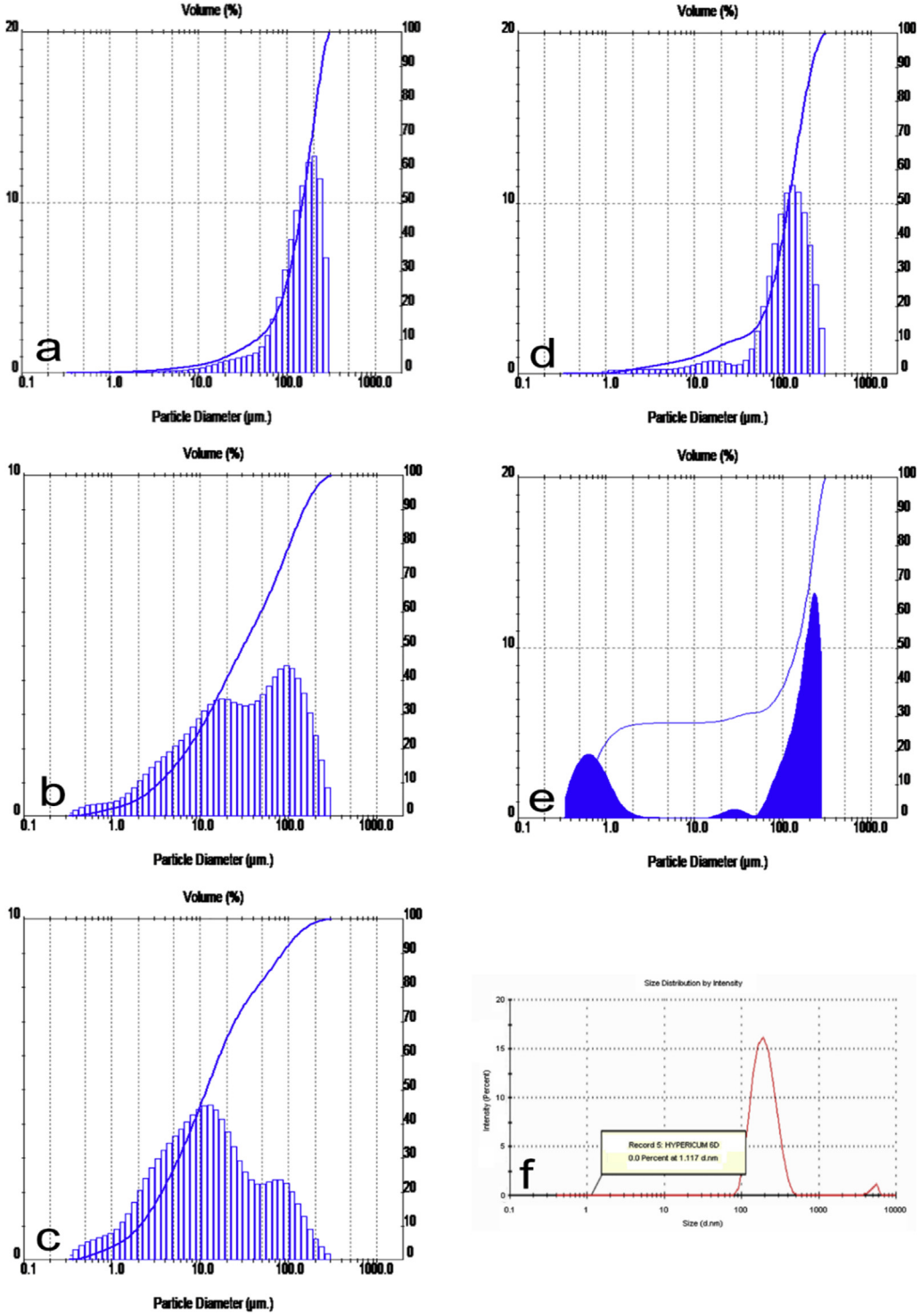

Figure 3. Hypericum perforatum L DLS-Master Sizer Granulometry for (a) initial source material, (b) 1X triturated potency, (c) 2X triturated potency, (d) 3X triturated potency, (e) alpha-lactose monohydrate in ethanol 99,8% anhy and (f) Hypericum perforatum L DLS-Nano Sizer Granulometry for 6X triturated potency.

distribution of Hypericum perforatum L in 6X trituration step while Figures 4a,b,c,d show the results of z-Average size as well as the Pdi Distribution before and after succussion from 4C up to 50M potencies for all solutions in distilled water and ethanol-distilled water.

3.4. Zeta Potential Analysis

The results of zeta potential measurements are present in Figures 4e, f. It is interesting to note that in the water solutions 4C a reverse of z-potential is observed; from a negative scale that was before, it becomes positive after succussion. In the other solutions the polarity of zeta-potential follows its negative course which is lower than the equilibrium states. DLS sizer and Zeta Potential measurements have gained popularity as simple, easy and reproducible tools to ascertain particle sizes and surface charges [21].

3.5. FTIR analysis

Comparing the spectra of alpha-lactose monohydrate and the initial,1X,6X Hypericum perforatum L potencies (Figure 5) we observe that changes have occurred during trituration process for this source material. FTIR analysis is not to show in detail the constituents of the 1X,6X triturated Hypericum perforatum L, but to reveal the probable changes made from the initial up to 6X trituration step before it is turned into solution and become mother tincture of other ultra high diluted succussed solution products. Therefore, we consider that all groups corresponding to the initial wave numbers of raw starting material exist up to 6X trituration.

However, the wavenumber's 2845.45 (=CH/Aldehyde/Stretch medium two peaks) and wavenumber's 1728.87 (C=O/Aldehyde/Stretch/Strong) groups which are found in source material are not present in the 1X and 6X triturated steps. On the contrary, into 1X trituration step the group of wave number 2357.55 ($-C-C\equiv C-C-$ or $H-C\equiv C-$ Alkynes/Monosubstituted/Disubstituted/Amines- Salts Primary/RCN/Nitriles Aliphatic C–N/Amine/Stretch medium-weak) which does not exist in alpha-lactose either in source material, emerge. At 6X trituration step the wavenumber 2316.09 corresponding to the Alkynes Monosubstituted Disubstituted, Amines- Salts, Primary RCN Aliphatic Nitriles, as well as the wavenumber 1171.54 corresponding to C–N/Amine/Stretch Medium-weak are present. On the contrary these wavenumbers do not appear in the case of source material, 1X trituration or alpha-lactose monohydrate.

3.6. UV-Vs analysis

In Figure 6 the results of UV-Vis analysis in distilled water samples are demonstrated. In the inset (Hypericum perforatum L mother tincture 3C), the two characteristics peaks for glucose ≈270 nm and hypericin ≈590 nm are clearly distinguished.

3.7. TEM analysis

In order to confirm the presence of micro-nanoparticles in the samples, TEM characterization was performed before the succussion of the 50M prepared in distilled water (Figure 7a) and ethanol-distilled water (Figure 7b) potencies in 50nm scale.

3.8. XRD analysis

In Figure 8 the XRD graph of source material presents an almost complete lack of crystallinity which is mainly amorphous due to the nature of the sample (mostly cellulose). The other two 1X and 6X samples present perfectly crystallized structures. All the red peaks correspond to alpha-lactose monohydrate which presents a high degree of crystallinity.

3.9. Electrical conductivity – pH analysis

In electrical conductivity (Table 1) a remarkable variation is noticed, from the source material up to the 3X triturated step, then a strong increase in 4X and then a relative reduction on 5X and 6X for solid samples.

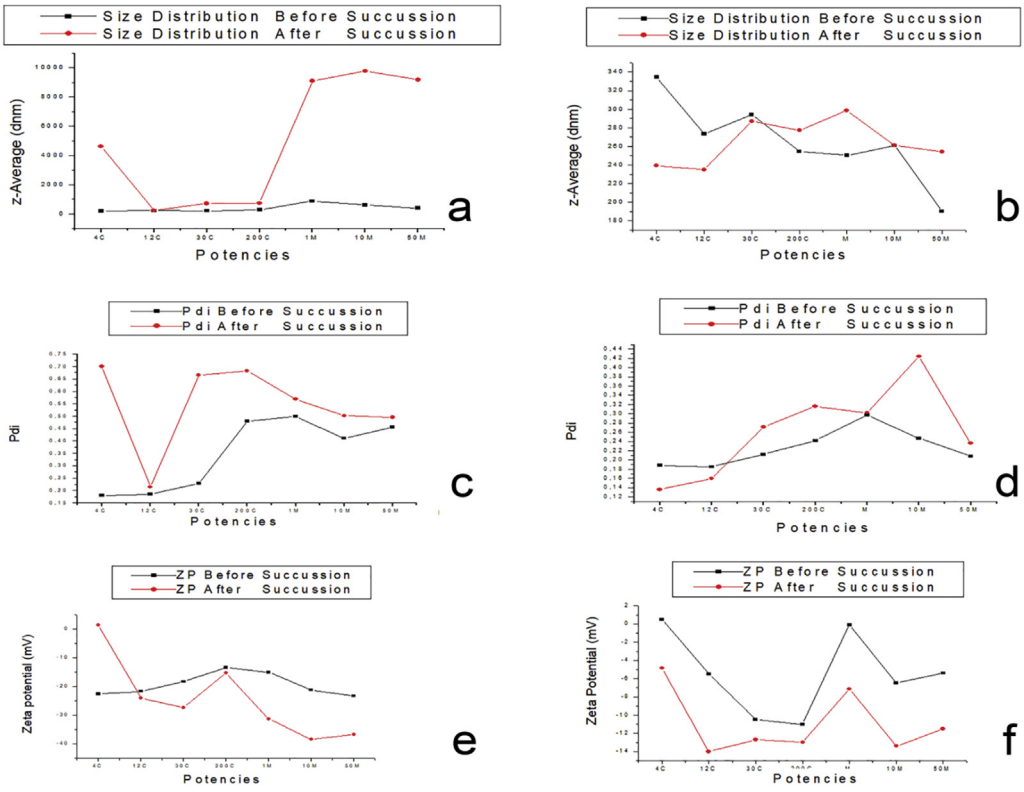

Figure 4. Hypericum perforatum L z-Average Size Distribution prepared (a) in distilled water before and after succussion and (b) prepared in ethanol-distilled water before and after succussion. Pdi Hypericum perforatum L (c) prepared in distilled water before and after succussion and (d) prepared in ethanol-distilled water before and after succussion. Zeta Potential Hypericum perforatum L (e) prepared in distilled water before and after succussion and (f) prepared in ethanol-distilled water before and after succussion.

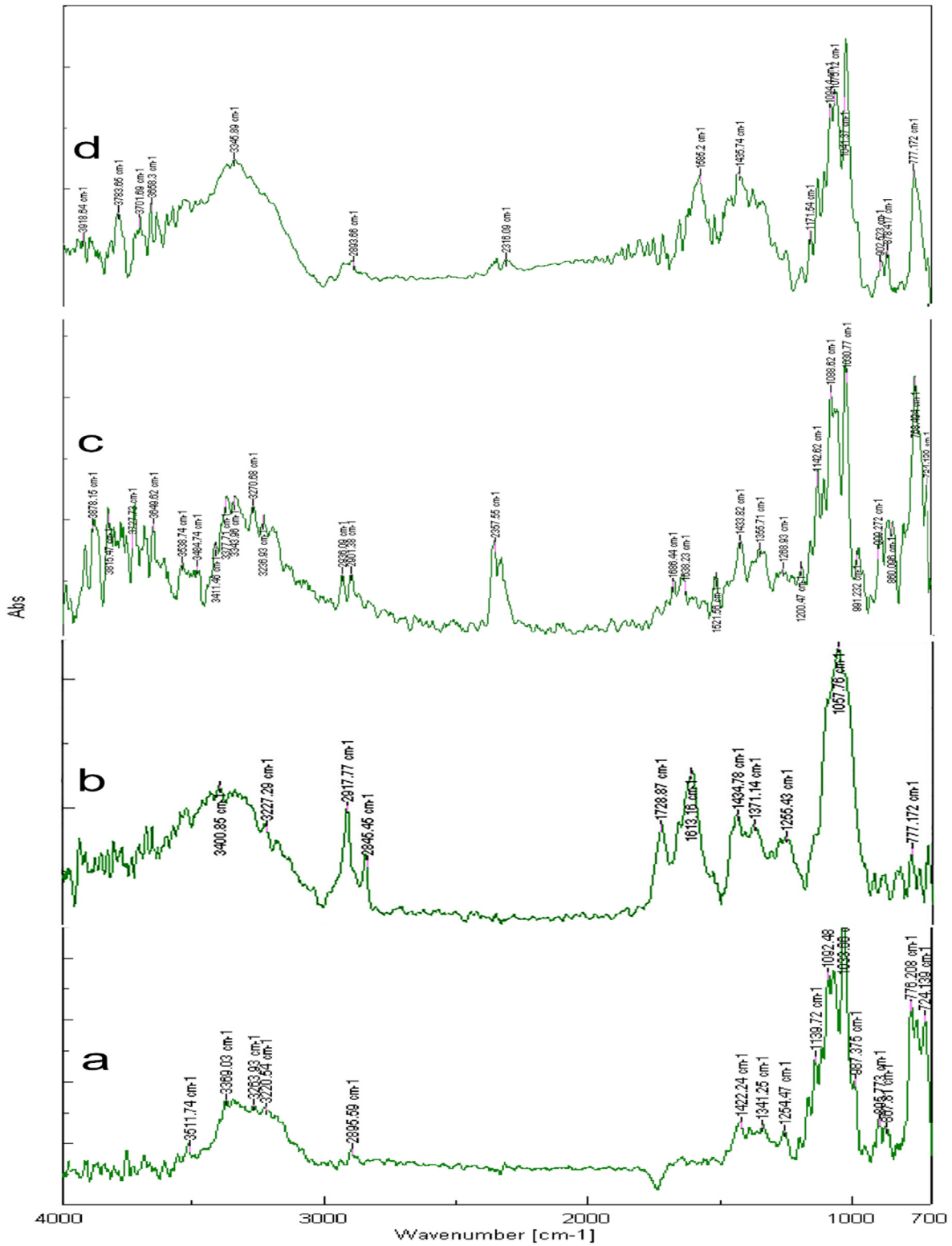

Figure 5. FTIR spectra of (a) alpha-lactose monohydrate, (b) Hypericum perforatum L Initial Source Material, (c) 1X triturated sample and (d) 6X triturated sample.

A similar behavior is observed for the pH. A gradual reduction of the pH up to 3X triturated step, a rise in 4X, 5X and a new small drop in 6X is observed. The change in electrical conductivity is about 96% of the initial average value, and the change of pH about 22% in the final 6X product. Similar measurements were made in the solutions 4C, 12C, 30C, 200C, 1M, 10M, 50M where the indications were the same as those of the solvent, i.e. of distilled water or ethanol-distilled water. This can be attributed to the ultra-high dilutions of the solutions. Similar measurements were also effectuated for liquid stock in ethanol-distilled water.

4. Discussion

Before starting to discuss the results of the investigation methods, it is worth telling about the impact of the mechanical energy mainly imposed

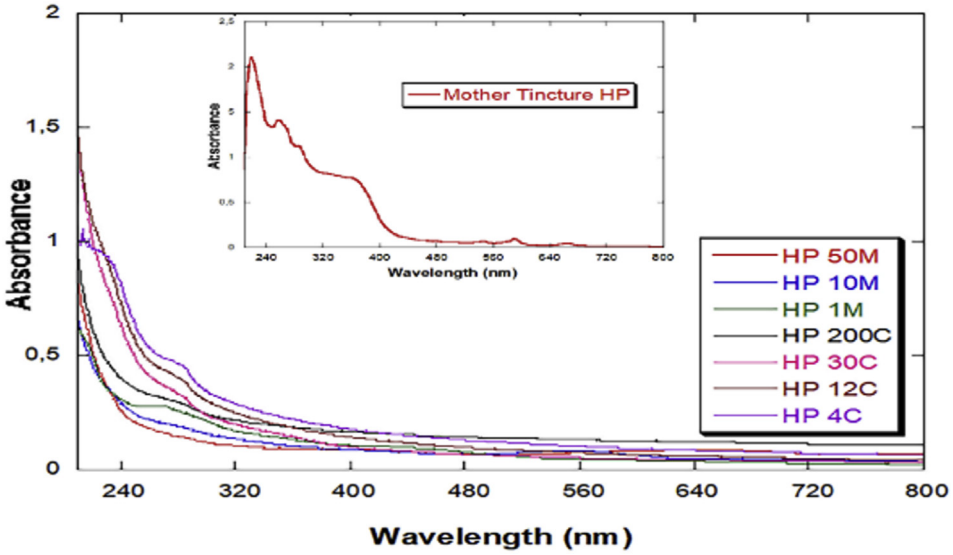

Figure 6. Hypericum perforatum L UV-Vs spectra of all potencies in distilled water further purified with ultra-filter unit of 200 nm prepared samples.

on the solid sample during the preparation procedure. When the sample powder is trapped and crushed between the inner surface of the mortar and the pestle for 6 h, it undergoes plastical deforming, and is repeatedly flattened, cold-welded, fractured and rewelded. The force of the impact acts on the powder particles, leading to broken crystallographic bonds and so new surface is produced. The new surfaces created enable the particles to weld together easily and this leads to an increase in the rate of dissolution of solid material. With continued mechanical deformation, new surface produced of the fragments created by this mechanism may reduce in particle size, and with the increase of surface energy of the material, other profound changes affecting the surface as well as the chemical [22, 23, 24, 25, 26, 27], physico-chemical and structural properties may also take place. This is manifested by the presence of a variety of crystal defects such as increased number of grain boundaries, dislocations, vacancies and interstitial atoms, stacking faults, and deformed and ruptured chemical bonds. For example, the group Alkynes/Monosubstituted/Disubstituted/Amines- Salts Primary/RCN Nitriles/Aliphatic ($-C-C\equiv C-C-H-C\equiv C-$) has FTIR wavenumber 2316.09. In our research this wavenumber is not found in the starting source material nor in alpha-lactose monohydrate. It is appearing during the 1X trituration process and it is found in 6X potency which is the origin of the solutions. In this case the trituration worked as mechanochemistry define. The presence of these defect structures enhances the diffusivity of solute elements. Consequently, grinding a mixture of two or more solid substances results in micro-homogenization of starting components, and sometimes, it induces formation and synthesis of new fine powders [28]. It is now quite clear that all this surface energy (new surfaces, etc.) gives rise to large amounts of the system's (source material and alpha-lactose monohydrate) entropy which are the reason of changes to appear during the whole preparation process of the solid origin ultra-high diluted successed medicinal products. In Figure 2a clearly can be seen the fibrous nature of the source material which from SEM investigation it is evident, and that up to 3X trituration (Figure 2b) the fibrous nature of the sample is no more present. Also, in 6X potency (Figure 2c) cylindrical shapes of the herbal fibers are no longer present. In the same image, alpha-lactose monohydrate particles can be distinguished as tomahawk gray coarse-grained material and on these, small chunks embedded (smaller ones) of the triturated Hypericum perforatum L something that cannot be seen in Figure 2d where a 6X triturated alpha-lactose crystal is distinct. In Figure 2e with mag 4000x the small chunks are clearly observed. The identity of these chunks is revealed by the corresponding EDAX graph. Comparing the two EDAX graphs, the one for alpha-lactose monohydrate (Figure 2f) and the one made on the chunks (Figure 2g), it is obvious that alpha-lactose monohydrate is fully constituted from carbon and oxygen (two high, well-shaped peaks). As it concerns one of the chunks, we have the intense presence of carbon (very high peak) because of the organic nature of the Hypericum perforatum L constituents, another one lower for the oxygen because of its presence in almost all its chemical compounds. In minor quantities other elements, like Mg, Si, K, Ca, are detected (very small peaks) as components of some compounds or soil

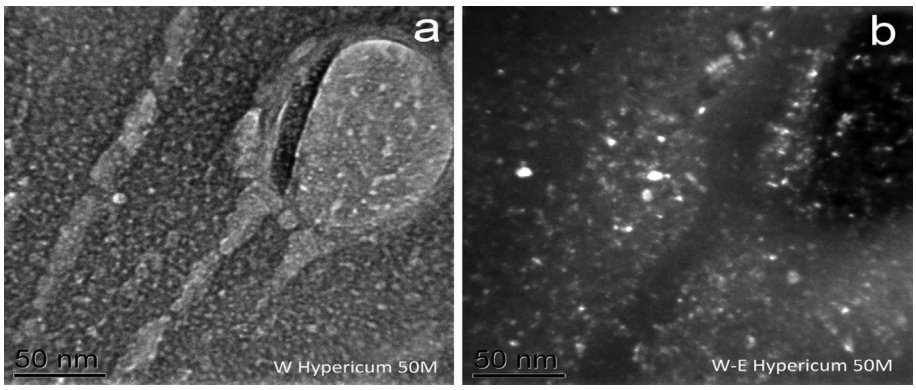

Figure 7. Hypericum perforatum L 50M TEM images in 50nm scale a) in distilled water further purified with ultra-filter unit of 200 nm sample and b) in ethanol-distilled water further purified with ultra-filter unit of 200 nm sample.

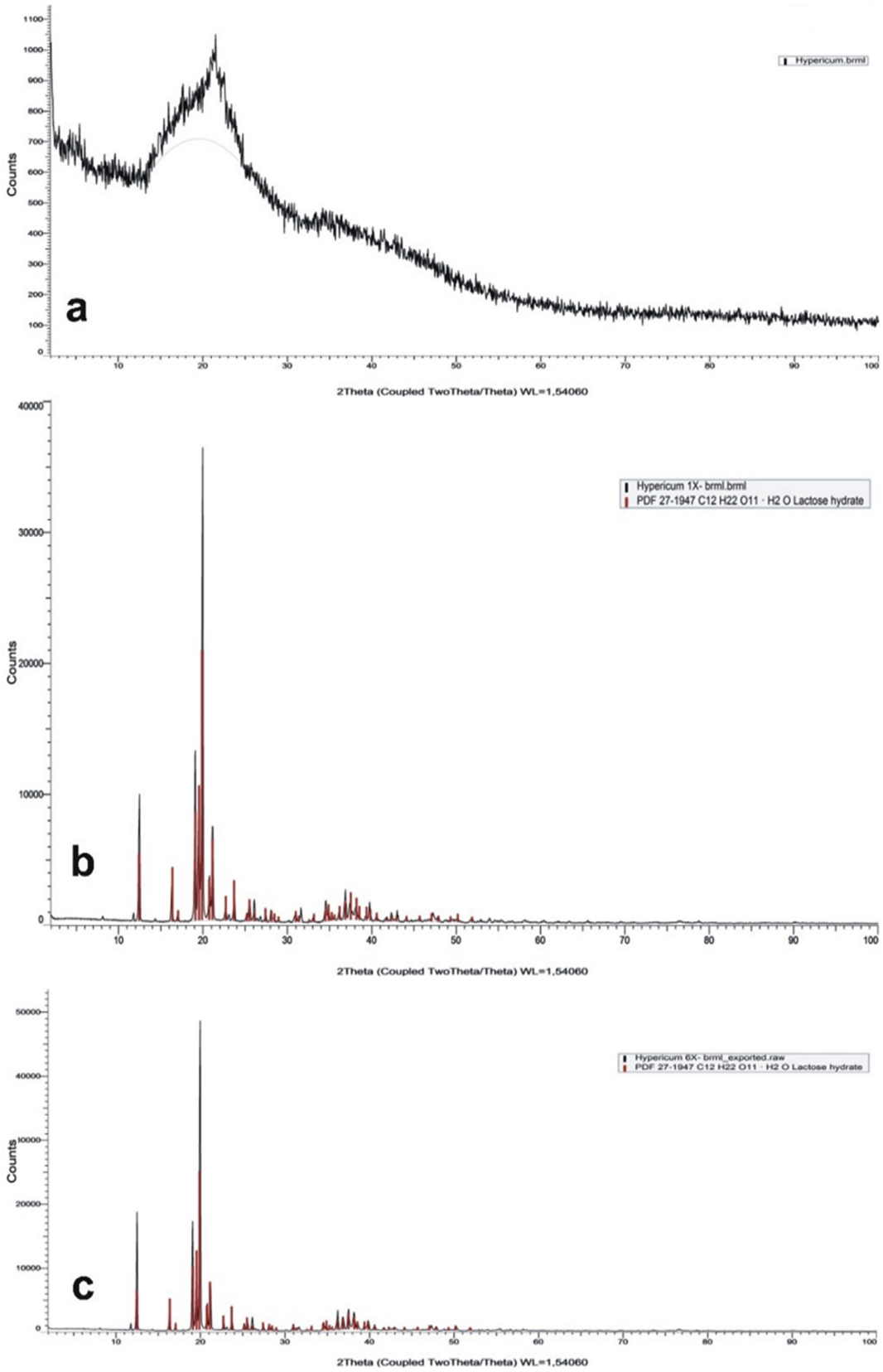

Figure 8. Hypericum perforatum L XRD spectrum (a) Initial Source Material, (b) 1X triturated sample and (c) 6X triturated sample.

Table 1. Hypericum perforatum L Electrical Conductivity-pH from source material up to 6X potency and liquid stock in ethanol-water commercial sample.

Potencies	Electrical Conductivity μS/cm	pH	Temperature °C
Initial	750	4,62	18,3
1X	108,2	4,21	18,8
2X	32,7	3,61	19,3
3X	29,1	3,82	20
4X	136,7	3,59	19,8
5X	45,4	6,49	19,8
6X	30,5	5,98	23,3
Liquid stock in ethanol-water commercial sample	802	4,91	24,16

or/and water salts. The presence of Au is attributed to the fact that the samples were covered with gold before their SEM examination. It is a Sem's technique in order to immobilize the sample upon the microscope slide and do not to sublimate it from the vacuum which is making during processing.

So, undoubtedly the small chunks are particles of Hypericum perforatum L origin. It was not possible to obtain measurements with DLS-Mastersizer beyond the 3X potency. Although we repeated the measurements 4 times, the result was zero. Since alpha-lactose is soluble in water, only the insoluble particles of the origin material remain to be measured. So, we used the DLS- Zetasizer Nano with measuring range 0,6 nm-6μm and the result is shown in Figure 3f, something which was demonstrated in a previous work [29]. Comparing alpha-lactose granulation to ethanol 99,8% solution (Figure 3e) with our results we find no relation between our findings and its existence. For ultra-highly diluted succussed solution extraction-origin products, the measurements of Hypericum perforatum L, showed that the detection of insoluble particles from liquid stock up to 50M potency is present and with succussion the z-average size and Pdi fluctuate. We cannot be absolutely certain about the identity of these particles but we could claim that their origin is only from the extracted plant. From the size distribution by intensity particles prepared from solid sample in distilled water and those prepared from extract in ethanol 99,8% - distilled water before and after succussion, it appears that, the size of particles in all samples is in the range of micro-nanoscale in this research. Similar results have been shown by others as well [30].

In Figure 4 the role of succussion in Hypericum perforatum L solutions prepared in distilled water or ethanol-distilled water is illustrated. As it can be seen in Figures 4a,b,c,d succussion increases or reduces the certainty that any drop from whichever ultra high diluted succussed medicinal product will contain particles something we described in our previous work [31]. It is worth mentioning that before succussion the particles z-average size for 4c solution is ≈ 335 nm and at 50M solution the particle z-average size is found ≈190 nm. In Figure 4b it can also be seen the slight fluctuation of particles' z-average size augmentation which begins for 4C at ≈240 nm and attains a maximum at 1M potency ≈299 nm and then at 50M is found again ≈254 nm. Comparing aquatic solutions (Figure 4a) with ethanol-distilled water solutions (Figure 4b), a totally different outcome is observed, as the form of the plots shows clearly. First the z-average size of the particles in aquatic solutions seem to be quite bigger than the ones in the ethanolic-water solutions. Before succussion there is practically no differentiation in the particle size except a slight augmentation beyond solution 200C. After succussion, a clear augmentation of the particle z-average size is observed ≈4700 nm for 4C solution and ≈9400 nm for 50 M. In Figures 4c,d a different "mathematical" law (schema of graph) governs the distribution and all these differences are due to the succussion and the solvent. For the triturated samples the particles are coarser than in the extracted one, because water cannot break the probable organic polymers or large chains of organic particles present in the extract as its polarity is not the same with the one of ethanol-water. The same reason (difference of polarity) might be responsible for the wider fluctuations of particles size before and after succussion for the extracted solution. The polarity is the essential property for the solvation of a compound as it determines the nature of the intra and inter molecules forces that are present and governs the interactions between solvent and solute.

Also, one of the most popular uses of Zeta Potential data is to relate it with colloid stability. From our measurements all the solutions before succussion seems to form a moderately stable colloid with the more unstable being the 200C. The potencies prepared from extracted in ethanol-water liquid stock, before and after succussion (Figure 4f) seem to be highly unstable compared to relatively stable colloidal dispersions, with the succussed ones being more stable. In both cases (Figure 4e, f) it is worth mentioning that 200C solution seems always to be a turning point. Also, the relation between Zeta Potential and particle concentration is a complex one and usually affected by many factors such as surface charge absorption, the effect of Electrochemical Double Layer (EDL) and its thickness and voltage. When a charged particle is dispersed, an adsorbed double layer often referred as EDL develops on its surface [32]. It is difficult to provide a general guideline for the effect of concentration on Zeta Potential. However, we can state that overall, in dilute conditions like ultra highly diluted succussed solution medicinal products, the surface adsorption phenomenon dominates and hence, the Zeta Potential increases. However, when the thickness of EDL decreases, the opposite effect occurs i.e. decreases in Zeta Potential with less stability of the dispersion is observed [33]. The findings of these methods open new roads to understand/explain the effect of the ultra-highly diluted succussed solution products as DLS-Zetasizer Nano Analysis and Zeta Potential Analysis show that micro-nanoparticles are always present even in potencies 30C, 200C, 1M, 10M, 50M.

There are no rigid rules for interpreting an IR spectrum [34]. According to this, the presence in our spectrum of the 3783.65, 3727.73, 3701.60, 3649.62, 3658.33, 3484, 3411.46 cm-1 peaks are due to O–H bond type. The wavenumbers 3918.64, 3878.45, 3815.47 cm-1 corresponds to Methyl-band C–H stretch. The appearance of $-C-C\equiv C-C-$ group at 2316.09 wavenumber can be attributed to the interaction of alpha-lactose monohydrate with Hypericum perforatum L (some of its substances).

In UV-Vs analysis the glucose [35] is always present in the molecule of alpha-lactose as this disaccharide is constituted from glucose and galactose. In the other potencies' spectra for 4C, 12C and 30C a mild peak at ≈270 nm may be considered as the one of glucose. The same seems to happen for solution 1M. There is nothing seen for 10M, 50M solutions. The spectra for all potencies show a complete lack of peak corresponding to hypericin at ≈590 nm (all the spectra lines are flat). When the excitation spectrum is in accordance with the absorbance spectrum (at least for one chosen emission wavelength), there is a good chance that an absorbance spectrum shows the absorbance properties of one, pure, single compound. The lack of any peak at ≈590nm for the hypericin may be attributed to the following: In Hypericum perforatum L the percentage of naphthodianthrones ranges from 0.05% to 0.30%, which varies depending on the conditions in which the plant grows (altitude, weather, soil composition, sunshine) and harvesting period [36, 37] mainly found in flowers and leaves. Pseudohypericin is found to be greater

(0.03–0.34%) than hypericin (0.03–0.09%), 2 to 4 times more depending on the plant [38]. Other factors affecting the absorption spectrum of hypericin are solvent, pH, ionization and its stochemical state (tautomer). In solutions one tautomer may be converted to another. Also, increasing temperatures disrupt hydrogen bonds by dissolving the hypericin molecules, thereby enhancing the formation of other compounds [39]. The hyperforin and anti-hyperforin compounds are abundantly found in Hypericum perforatum L, however they are difficult to isolate, since they are particularly sensitive molecules and degrade very rapidly in light, air, and organic solvents [40]. Hyperforin ($C_{35}H_{52}O_4$), the main compound, is an isoprenoid volatile compound with 35 carbon atoms due to its β-dicarbonyl isomer. Thus, natural derivatives, in which they were absent, were more stable [41]. From the previous it is clear that it is difficult to have these compounds in ultra high diluted successed solutions, something which justifies from UV-Vis findings. Besides the above reasons for these compounds, there is one more important reason that makes the presence of these compounds impossible in the ultra high diluted successed solutions. This reason is the well-known Avogadro's law which clearly refers to the molecules, atoms or ions contained in the mole, g-atom or g-ion but not any form of micro or nano particles contained in this one. Thus, our findings with regards to absent soluble substances are fully justified, as well as that micro-nano particles are detected in all potencies due to the method of preparation. One mole, g-atom, g-ion of a compound contains 6,23.10 ^{23} molecules or atoms or ions. On the contrary, one cm^3 of any material has a surface area 6 cm^2 while the someone cm^3 when triturated attains the nanoscale and, its surface reaches until 6000 m^2.

As it can be seen from the TEM images in Figure 7a, b the particle sizes range from a few up to many nanometers. Also, there are many forms of agglomerates. The particles are easily distinguished having a lighter color on the surface of the grid. The size range of the particles seen in TEM image, agrees with the z-average size results obtained by DLS method before sample's succussion. According to DLS measurements, the z-average size for the particles in 50 M water potency was found of ≈405,7 nm. In Figure 7a the agglomerate has a size of ≈300 nm (compared with the bar range). As it concerns the ethanolic solution (Figure 7b) the DLS measure resulted to an average size of ≈190,5 nm, and the agglomerate seems to be of the analogous size component.

By comparing the electric conductivity and pH values of solid origin preparations, it is observed that the values of these parameters of the extracted liquid stock are not so close to those of our source solid material sample before trituration. The observed differences must be attributed partly to the presence of alpha-lactose monohydrate in the prepared samples, while the liquid stock manufactured by others do not contain any alpha-lactose monohydrate and partly to the nature of solvent. In the case of our samples the solvent (distilled water) is a polar substance with dielectric constant $\varepsilon = 80$ while for the liquid stock the main solvent is ethanol, a less polar substance with dielectric constant $\varepsilon = 24{,}55$. This difference influences the size of solvation layer and thus the solvated particles in water are much larger and consequently less mobile than the particles in ethanol, which are smaller (less extended solvation layer) and then more mobile.

4.1. The mathematical approach

The mathematical approach is utilized here in order to enhance/reinforce/explain mathematically the experimental findings. Thus, the belief that there is nothing from starting materials but only the solvent in ultra high diluted successed solution products solutions after 12ch potency is not valid. However, these ultra-highly diluted successed medicinal products are manufactured in such a way, that approaches theories which would be capable to interpret/support, fully and deeply, our experimental findings, such as fractal and Shannon information (entropy) theories. The mathematical approach of self-similar sets over the extreme ends of these, there should be a mathematical structure that remains immutable when dimensions change with scale factors. As fractal dimension [42] of a self-similar S set, i.e. an ultra-high diluted successed medicinal product (a set of drops), it is called a number D:

$$D = \frac{\log m}{\log M}$$

Where:

m, the number of equivalent parts subdivided into the S set
M, the magnification factor.

Thus, for the any ultra-high diluted solution medicinal product if:
n, each step of its preparation.
9 or 99, the numbers of equivalent parts subdivided respectively according the decimal or centesimal prepared scale.
10 or 100, the magnification factor.
Then $D_{\text{hom}} = \frac{\log 9^n}{\log 10^n} = 0.954242509\ldots$ or $D_{HOM} = \frac{\log 99^n}{\log 100^n} = 0.997817597\cdots$ are given.

The mathematical formalism of the manufacture of ultra high diluted successed medicinal products, leads to the fact that the diluted particles' dimension depends on decimal or centesimal prepared scale, as it can be seen from the D_{hom} and D_{HOM} values respectively. Because these numbers are irrational ones, so, they include entropy. The main idea of entropy is the randomness, something which is evident during preparation of these medicinal products. Entropy was used to explain how much randomness is to find a single source material or liquid stock particle and so to describe how many of these particles are carried by the drop. A feature key of Shannon information theory is that the term information (in our approach, the source material or liquid stock particle) can often be given by a mathematical meaning, as a numerically measurable quantity, on the basis of a probabilistic model, in such a way that the solutions of many important problems, as the source material or liquid stock particles' existence and storage in a random drop of any potency, can be formulated in terms of this measure. The division of a drop (taken from a mother tincture) is achieved by dilution in order to form a homogenous solution. This is valid during the preparation of the ultra-high diluted successed solution medicinal products. Now, let us consider a homogeneous solution of a potency split into r drops each containing different sizes particles which z-average size is characterized as (k)-dimension. If each drop contains the same number of source material or liquid stock particles (hypothetically), then the number of source material or liquid stock particles present and equally distributed in these drops is given by Eq. (1).

$$M_{(k)} \cdot N_{(k)} = N \tag{1}$$

Where

N, the number of total source material or liquid stock particles of the present
$M_{(k)}$, total drops
$N_{(k)}$, The number of source material particles or liquid stock particles of each drop
(k), The z-average size dimension of particles

Then the local density Π_r is given by Eq. (2).

$$\Pi_r = \frac{N_{(k)}}{N} \tag{2}$$

Where

Π_r, local density of source material or liquid stock particles into solution

This means that:

$$P_r = \lim_{N\to\infty} \frac{N_{(k)}}{N} \text{ or } P_r = \lim_{N\to\infty} \Pi_r \tag{3}$$

Where

P_r, the probability for at least a single source material particle or liquid stock particle to be found into one drop is clearly presented by Eq. (3).

Nevertheless, in the case that an absolute homogeneity is not achieved/established, the Reyni generalized dimension of a set D_q is defined as:

$$D_q = \frac{1}{q-1} \lim_{(k)\to 0} \frac{1n\left(\sum_{r=1}^{M_{(k)}} P_r^q\right)}{1n(\kappa)} \tag{4}$$

Where the q parameter is between $+\infty$ and $-\infty$, but not necessarily an integer. Thus, if for every drop $P_r = \frac{1}{N_{(k)}}$ and for the self-similar of our set we have

$$D_q = D = \frac{\log M_{(k)}}{\log(1/(k))} \tag{5}$$

Something which presented by Eq. (5)where $\frac{1}{(k)}$ symbolizes the inverse of the z-average size dimension of particles which are contained in each r drop. Assuming that we have homogeneity and then $P_r = \frac{N_{(k)}}{N}$ which is necessarily supposed for homogeneous dilutions, then from the fraction numerator which is given by equation [4] we take for q≠1:

$$\sum_{r=1}^{M_{(k)}} \cdot {P_r}^q = \sum_{r=1}^{M_{(k)}} \left(\frac{N_{(k)}}{N}\right)^q = M_{(k)} \left(\frac{N_{(k)}}{N}\right)^q =_{(1)} \left(\frac{N}{N_{(k)}}\right)\left(\frac{N_{(k)}}{N}\right)^q = \left(\frac{N_{(k)}}{N}\right)^{q-1} \Rightarrow$$

$$\Rightarrow \ln \sum_{r=1}^{M_{(k)}} \cdot {P_r}^q = \ln\left(\frac{N_{(k)}}{N}\right)^{q-1} = (q-1)\ln\frac{N_{(k)}}{N}$$

So

$$D_q = \lim_{k\to 0} \frac{\ln \frac{N_{(k)}}{N}}{\ln(k)} = \lim_{(1)k\to 0} \frac{\ln {M_{(k)}}^{-1}}{\ln(k)} = \lim_{k\to 0} \frac{\ln M_{(k)}}{\ln(1/(k))} \tag{6}$$

In Eq. (6) Reyni generalized dimension D_q is defined as the lim ratio of Napier's logarithm of total drops to Napier's logarithm of the inverse of the z-average size particles dimension which are contained in each r drop with k to tend to zero.

In Eq. (7) when the q parameter is zero the numerator of Reyni generalized dimension corresponds to the sum of total drops and then in Eq. (8) Reyni dimension corresponds to Hausdorff-Besicovitch dimension.

For q = 0 we have

$$\sum_{r=1}^{M_{(k)}} \cdot P_r^0 = \sum_{r=1}^{M_{(k)}} \cdot 1 = M_{(k)} \tag{7}$$

And then

$$D_0 = -\lim_{k\to 0} \frac{1nM_{(k)}}{1n(k)} = D_H \text{ (Hausdorff} - \text{Besicovitch dimension)} \tag{8}$$

For q = 1 the Reyni dimension is meaningless, because it results in $\left(\frac{0}{0}\right)$.

For q = 2, it follows $D_2 = D_c$ correlation dimension.

Theoretically the correlation dimension (denoted by q) is a measure of the dimensionality of the space occupied by a set of random points (in our approach particles), often referred to as a type of fractal dimension. For example, if we have a set of particles which size are between minimum-maximum, mathematically between 0 and 1, the correlation dimension will be q = 1, while if they are successed and being agglomerates on say, embedded in three-dimensional space (or m-dimensional space), the correlation dimension will be q = 2. The real utility of the correlation dimension is in determining the (possibly fractional) dimensions of fractal objects.

We assume that q→1 and the resulting dimension according Shannon's theory we are called " active ingredient dimension" which is symbolized with Di: $\sum_r \cdot P_r = 1$ the lim of it is given by Eq. (9)

let be q→1. For q ≈ 1 we set q = 1+δq.

This assumption is true as both our particles and their aggregates coexist in our solutions.

Then

$$P_r^q = P_r^{1+\delta q} = P_r \cdot P_r^{\delta q} = P_r e^{\delta q \ln P_r} = P_r(1 + \delta q \ln P_r + \ldots) \approx P_r + \delta q P_r \ln P_r$$

The Sum

$$\sum_r P_r^q \approx \sum_r P_r + \sum_r \delta q P_r 1nP_r = \sum_r P_r + \delta q \sum_r P_r 1nP_r = 1 + \delta q \sum_r P_r 1nP_r.$$

So, since

$$1n \sum_{r=1}^{M_{(k)}} \cdot P_r^q = 1n\left(\sum_{r=1}^{M_{(k)}} \cdot P_r^q - 1 + 1\right) \approx \sum_{r=1}^{M_{(k)}} \cdot P_r^q - 1.$$

If we set

$$D_i \approx \lim_{r\to 0} \frac{-1n \sum_{r=1}^{M_{(k)}} P_r^q}{1n(k)} \tag{9}$$

For δq→0 we have

$$D_i = \lim_{r\to 0} \frac{-\sum_{r=1}^{M_{(k)}} P_r 1nP_r}{1n(k)} \tag{10}$$

The numerator of Eq. (10) $-\sum_{r=1}^{M_{(k)}} P_r 1nP_r$ is the entropy of the ultra high diluted successed solution itself. In general, what stands is $D_2 \le D_i \le D_0$. Subsequently, from the similarity dimension relationship, if $M = \frac{L_{max}}{\ell}$ Where

L_{max}, a quantity of an ultra high diluted successed solution l, measuring volume unit.

Then $D = \frac{\log(k)}{\log \frac{L_{max}}{\ell}}$ or $\log(k) = D \log L_{max}.\log l^{-1} = \log L_{max}.\log l^{-D} \Rightarrow (k) = L_{max}.l^{-D}$ which means that the z-average size dimension of particles r drop's is an equation-power of the measuring unit l and it is written $(k)_{(l)} = l^{-D}$.

So, since the z-average particle size is a function of measuring volume unit it is means that they are measurable, so they are present. It follows from the above that the particle sizes measured by DLS is described/interpreted by the entropy's change. Therefore, the physicochemical behavior of the particles and hence of the products can be explained. During the mathematical approach of sets over the extreme ends of the set, there should be a mathematical structure that remains immutable when dimensions change with scale factors. The ultra-highly diluted medicinal products generally are the result of a division with a fix ratio,

which explains why it preserves an unchanged mathematical structure -that of its fractal dimension-over the extreme ends of its set. The 0.9542425… or the 0.99781759… are the numbers defining its identity and are related to the dilution. The aim of the mathematical approach is to show that the source materials or liquid stock particles in ultra-high diluted succussed solution products have dimension as an equation-power of the measuring unit l in all potencies, so, they are always present. As it has been shown, in our previous work, the physical features-size and granularity-of solid materials which are using as source materials are strongly affected by trituration in lactose, before turning them into ultra-high diluted succussed medicinal products [29]. During trituration a gradual decrease in grain size of the source materials approaching the micro and nanoscale finally occurs and is related not to the type of material but to its original grain size before grinding. Therefore, Hypericum Perforatum L mother tincture for manufacturing ultra high diluted succussed medicinal products of solid or extract origin, as it is clearly seen is micro-nano solution as well as the subsequent following the initial ones. Thus, the micro-nano structure of source material or liquid stock particles dominates the beginning of these preparations. Contrary to what so far is considered by all about ultra high diluted succussed solution products, that in dilutions above 12C there are no traces of source material or liquid stock particles, our research proves that in all potencies above 12C like 30C, 200C, 1M, 10M, 50M, there are particles with their size to be on the micro-nanoscale. A first physico-chemical explanation for the existence of particles on the micro-nano scale observed for the studied material could be that because of the Brownian motion of soluble materials into solutions and collisions of the particles with the vial's walls during the succussed process, the formation of agglomerates is easier to proceed. The above experimental findings can be enhanced and mathematically supported as presented in the above text. During the preparation of the ultra-highly diluted succussed medicinal products from the beginning up to the final desired potency, a formalism similar to that shown/described in the fractal geometry, i.e., in Cantor set, in Sierpinski triangle, in Koch curve, etc., is followed. In this study we will not discuss in detail the fractal structure of our findings or how the aggregates forming process contributes to this direction. Although the aggregation process determines the fractal dimension, this is not sufficient to characterize the process [43]. Entropy is a concept that is not strictly defined in physics, but in our approach, we will show that it is closely related to the possibility of finding a single source material or liquid stock particle in the r drop, something which is ascertained experimentally by all the above mentioned. Today, there are several definitions for entropy like, Shannon entropy [44], Kullback–Leibler entropy [45], Jaynes entropy [46], Reyni entropy [47], Tsallis entropy [48], Kaniadakis entropy [49], etc. It is interesting that this field has been regarded as one of the most puzzling and controversial parts of the physics for a long period. In our approach Shannon's information theory is used to support our findings [50]. According the mathematical theory, Hausdorff's dimension is a measure of roughness and/or chaos and for a single diluted particle is zero, for a set of single particles is 1, for a set agglomerates is 2, and for the compact of source material or liquid stock is 3. That is, for sets of particles that define smooth agglomerates or one agglomerate that has a small number of corners—the shapes of traditional geometry and science—the Hausdorff dimension is an integer agreeing with the usual sense of dimension, also known as the topological dimension.

5. Conclusion

This research has clearly demonstrated what are the contents of ultra high diluted succussed solution products. Hypericum perforatum L ultra highly diluted succussed solution products provide a good example to show the micro-nano structure of the final solutions independently of whether they are the result of trituration or extraction.

So, this research, which deals with the size of solute particles in ultra-highly diluted succussed solution products, proves, by a mathematical and experimental way, that the source materials are found in all solutions, even in the most diluted ones.

The results are contrary to what is believed up until now, and they clearly mark a new start in basic research in medicine, to understand and explore the action mechanisms of ultra-highly diluted succussed solution products.which are used by homeopaths as remedies. These same research findings can also be used for the standardization of the manufacturing process for ultra-highly diluted solutions.

Trituration is responsible at converting sparingly soluble raw materials into completely soluble, before they are turned into homeopathic solutions. In this research, it was found that beyond the reduction of grains size to a nano dimensional scale up to 6X potency, there is an appearance of functional groups in organic compounds in our mixture that did not exist in initial sample. It seems that in the case of Hypericum Perforatum L the trituration works mechanochemically. Also, there appears to be a change in the basic physicochemical properties such as the change in Electrical Conductivity and pH. The overall change of Electrical Conductivity is 96% and the total pH reduction is 22%, which seems like trituration changes the physical-chemical properties of raw starting material. It is obvious that nano-dimension is the one that predominates in these solutions. Thus, the succussion of the solutions leads the formation of aggregates when the particles are in the nanoscale. On the contrary when aggregates are already present succussion turns them into smaller particles. Also, zeta potential measurements confirm the colloidal nature or not and stability, of the solutions. In all samples the 200C potency seems to have a key role for the preparation and quality of next potencies and must be considered as the one with the maximum entropy, as it presents to be the turning point for the observed changes. The conditions and the quality of the preparation process have a key role for qualitative homeopathic ultra high diluted succussed medicinal products. Because our experimental and theoretical results revise what is believed for ultra high diluted succussed solution products, further research upon this field is an imperative.

Declarations

Author contribution statement

Dimitris Kalliantas: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Meletia Kallianta: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

Konstantinos Kordatos: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Chaido Stefania Karagianni: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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