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# Study of the formation of micro and nano-droplets containing immiscible solutions

V. Nastasa[a,*], K. Samaras[b], I.R. Andrei[a], M.L. Pascu[a], T. Karapantsios[b]

[a] National Institute for Laser, Plasma and Radiation Physics Bucharest, Bucharest, Romania
[b] Department of Chemistry, Aristolte University of Thessaloniki, Thessaloniki, Greece

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ABSTRACT

There is currently significant interest in the multiple resistance to treatment using drugs (MDR), developed by bacteria and malignant tumors. One of the alternatives to the existing medicines and treatment procedures in fighting MDR is strengthening the effects of cytostatics by improving their delivery methods. Such a method is represented by the generation, transport and use of micro-/nano-droplets which contain medicines. This approach can reduce the medicines consumption by generating micro-droplets which contain drugs incorporated in solvents substances; the micro-/nano-droplets can favour a faster delivery to the targets and a higher drug concentration in them. This paper reports first, results concerning the generation of single micro-droplets containing an inner core (medicine solution in water) and a thin layer of oily liquid covering it. This generation is made one by one and it is, at the moment, not conceived as a method for mass production, or in other words for high population of such droplets. We have generated and measured stratified micro-droplets, each of them containing a solution of Vancomycin in ultrapure water as a core and a surrounding layer of Vitamin A in sunflower oil; the micro-droplets generation was made using a double capillary system. Secondly, micro-/nano-droplets were produced by mixing two immiscible solutions in particular conditions (high rotating speed and/or high pressure difference). For this we have studied the generation of emulsions of Vitamin A diluted in sunflower oil and a solution of Tween 80 surfactant in distilled water. The concentration of surfactant in water was, typically, $4 \times 10^{-5}$ M. We have studied the dependence of the droplets dimensions in emulsion on the mixing rotation speed, agitation time and components ratio. The droplets diameters were measured using a light scattering method. It is found that at high enough energy input (high rotation speed, large pressure drop) and relatively small oil/water ratio, droplets diameters smaller than 100 nm were obtained.



## 1. Introduction

Interest in nano/submicron droplets dimensions in emulsions recently increased in the pharmaceutical, cosmetic and food domains, in parallel with the development of better performing emulsification technologies. Droplets with diameters lower than 1 μm can be used as transport vectors of medicines in parenteral, oral, ophthalmic or transdermal delivery systems which are related to therapeutic applications. The systems using droplets allow substances poorly soluble in water, but oil-soluble, such as vitamins or drugs to be incorporated in a lipophilic phase, so that the increase of their local bioavailability takes place; this also stabilizes components sensitive to enzymatic degradation, allows a slower, controlled release of components to the targets over a prolonged period of time and reduces the side effects of drugs. Based on small particles use in systemic treatments, one predicts that micro-/nano-emulsions uptake improves efficiency of lipophilic substances. Emulsions are the dispersions of an immiscible or partially miscible liquid (dispersed phase) in another liquid (continuous phase). These liquids are immiscible or are mutually only slightly soluble. The dispersed phase is present in the form of droplets in the continuous phase. Usually, in order to stabilize the dispersed phase against coalescence, the presence of a surfactant is essential as the droplets are thermodynamically metastable. An emulsion is characterized by the mean size and the size distribution of the droplets; these characteristics can be controlled by a proper choice of the dispersing apparatus and the process conditions [1–3].

Compound droplets of millimeter or sub-millimeter diameters have been reported to be related to a wide and disperse range of applications. For instance, droplets (~2.7 mm) containing emulsions of oil in water sprayed on a moving steel strip or on a rotating roll have been used for cooling the strip/roll by the water whereas efficient lubrication of the sprayed areas was achieved by the oil [4]. Stratified capsules, including immiscible liquids, were produced

* Corresponding author at: National Institute for Laser, Plasma and Radiation Physics, Laser Department, Str. Atomistilor nr. 409, Magurele, Ilfov, 077125 Bucharest, Romania. Tel.: +40 214 574 53940/722 939 894; fax: +40 212 575 739.
*E-mail address:* viorel.nastasa@inflpr.ro (V. Nastasa).

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by electrohydrodynamic forces using coaxial electrified jets in the micrometer and submicrometer ranges [5]. Capsules of 0.150 μm diameter corresponded to a sphere of water of 0.1 μm in the core surrounded by a 0.025 μm thick layer of olive oil. Compound drops composed of a core water sphere encased to a diesel oil shell of diameters between 740 μm and 1 mm were generated by a double capillary coaxial system, as reported recently [6]. One of the most recent reports deals with a double emulsion (oil in water in oil) obtained from a compound drop of diameter of about 2 mm permanently bouncing onto a vibrated liquid surface [7].

Micro-/nano-droplets may be produced by mixing two immiscible solutions at high rotating speed and/or high pressure difference. It is generally accepted that the emulsification is based on two opposite processes: drop breakup resulting in the production of several smaller droplets from a larger drop, and droplet–droplet coalescence leading to the formation of a larger drop from two smaller ones [8,9]. Generally, the evolution of the drop-size distribution during emulsification is determined by the competition between these two processes. At high surfactant concentrations, the contribution of the droplet–droplet coalescence is negligible so that the process of drop breakup determines the evolution of the drop-size distribution in the formed emulsion [9,10]. After a long enough emulsification time, a "steady-state" is reached, which is characterized by a relatively slow change of the drop-size distribution in the formed emulsions [11,12].

This paper reports first, results concerning the generation of single micro-droplets containing an inner core (medicine solution in water) and a thin layer of oily layer surrounding it. These droplets were produced by using a double dosing system (coaxial capillaries). These experiments allowed assessment of the adsorption phenomena between the liquid layers of the examined droplets. The above evidence combined with information from literature on how water/oil viscosity, interfacial tension, and rate of energy dissipation affects the maximum droplet diameter, e.g., [13–22], have been used to select emulsification parameters.

Next, this work reports on the massive production of micro-/nano-droplets realized by mixing relatively large quantities of two immiscible solutions at particular conditions (high rotating speed and/or high pressure difference). We have generated emulsions of sunflower oil droplets containing Vitamin A dispersed in a solution of a surfactant in distilled water. Using a batch stirred tank system we examined the dependence of oil droplets dimensions on the rotation speed of the impeller, and components ratio. The diameter of stable droplets is measured after a sufficiently long period of emulsification, when the steady-state drop size distribution is reached. The droplet diameters were measured by light scattering. The experiments were performed using a surfactant concentration above the CMC of the surfactant in water in order to avoid droplet–droplet coalescence during emulsification.

The scope of this work is dual: first to check the interfacial stability of individual compound droplets related to drug delivery systems and second to check whether intense bulk mixing devices can create high populations of nano-sized droplets with a narrow size distribution. Whether it is possible to use intense bulk mixing of two immiscible liquids in order to create high populations of compound nano-droplets will be the topic of a subsequent study. This is of paramount significance since conventional devices (e.g., coaxial capillaries) for making individual compound droplets are not suitable to create nano-sized droplets.

## 2. Materials and methods

The first part of the work was devoted to the measurement of the dynamic interfacial tension of Vitamin A solutions in sunflower oil and to the generation of a droplet of Vancomycin in ultrapure water covered with a layer of Vitamin A. These experiments were performed using the Drop Profile Analysis Tensiometer (PAT1, SINTERFACE) which generates pendant droplets and allows surface or interfacial tension and viscoelasticity (oscillation) measurements over a period of several hours [23,24]. For the generation and measurement of interfacial tension of the obtained compound pendant droplets we have employed a specific double dosing module of PAT1 furnished with a double capillary with which we have generated first the exterior droplet and then the core through the inner capillary. The total volume of the droplet (10 μL) was kept constant by a built-in control loop based on streaming video images analyzed by a dedicated software.

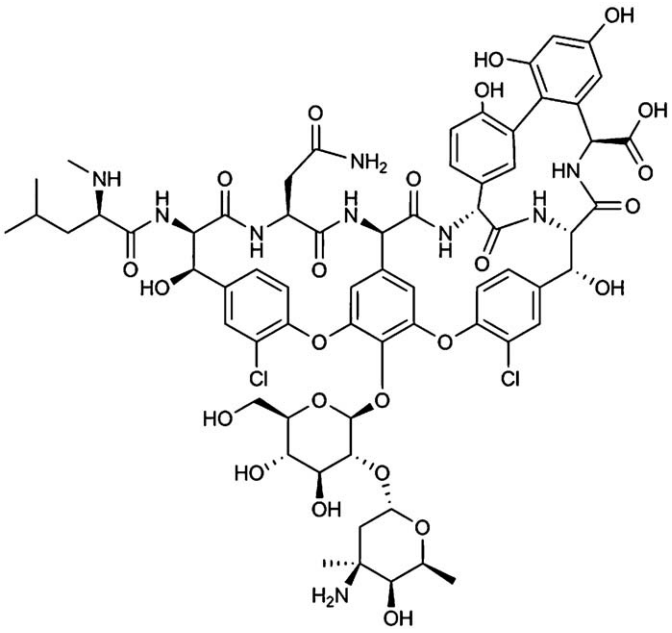

**Fig. 1.** The chemical structure of Vancomycin.

Vancomycin is a glycopeptide antibiotic used in the prophylaxis and treatment of infections caused by Gram-positive bacteria; the chemical structure of Vancomycin is given in Fig. 1. The experiment was conducted to check whether the adsorption of the Vancomycin at the water/oil interface is strong enough to modify the properties of a layered droplet [23].

The Vancomycin solutions were made in high purity grade water and the concentration range used was $10^{-4}$ M to $10^{-5}$ M. The oily Vitamin A (retinol diluted in sunflower oil) used for these measurements is a commercial product found in pharmacies; the chemical formula/structure of it is given in Fig. 2 [23].

In the second part, the micro-/nano-droplets were produced by mixing two immiscible solutions at particular conditions (high rotating speed and/or high pressure difference). The measurements were meant for studying the droplet dimensions dependence on different conditions. First, we have studied the variation of droplets diameter as a function of rotating speed for the same oil/water volume ratio. This allowed us to choose the proper rotating speed for further measurements. Afterwards, in order to study the dependence of droplets dimensions on the oil/water ratio, we kept the

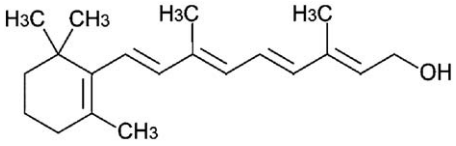

**Fig. 2.** The chemical structure of Vitamin A.