OPTOELECTRONICS AND ADVANCED MATERIALS – RAPID COMMUNICATIONS Vol. 4, No. 11, November 2010, p. 1916 - 1919

Studies about the generation and characterisation of microdroplets with a controlled content

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The development of bacteria resistance to antibiotic treatment is considered a natural evolution process. A consequence of this resistance is the decrease of the effectiveness of the antibiotics that causes a lower quality of life and the morbidity increase in patients. The same is true for malignant tumors. Since the development of new drugs does not keep the pace with the developed resistance, there is an immediate need to identify new strategies for the improvement of the existing antibiotics efficacy. The reversal of the antibiotics resistance includes not only the treatment against pathogens which directly affect the patient's health but also the fight against the microbes developed in the hospital environment due to repetitive disinfection. The resistance to antibiotic treatment is also signalled as multidrug resistance (MDR) at simultaneous treatment with different drugs. One way to fight MDR can be represented by the use of new vectors to transport the medicines to their targets such as simple droplets of medicines solutions and layered droplets consisting of the active medicine core (Vancomycin in our case), covered by a layer of a oily substance (vitamin A in sunflower oil in this report).

(Received October 1, 2010; accepted November 11, 2010)

Keywords: Micro-droplets, Nano-droplets, Surface tension, Contact angle, Multidrug resistance

1. Introduction

The effects of medicines in multidrug resistance to treatment (MDR) developed by bacteria or malignant tumours can be increased by improving the delivery methods to targets. Such a method is represented by the use of medicines as micro-droplets; it can reduce the active substance consumption by generating drug micro-droplets incorporated in substances that can favour a faster transport of the medicine to target tissue and a more precise accumulation of it in the tissue with respect to the systemic administration [1]. For this purpose the knowledge of the wetting properties of the water solutions of medicines related to the superficial tension of the micro-droplets and their contact angles with hydrophobic and superhydrophobic surfaces is necessary. More detailed data on the contact angles of some medicines solutions in water (such as Doxorubicin or BG1120) are reported in [2] – [4]. In this paper data regarding the contact angle measurements of water with hydrophobic/super-hydrophobic surfaces, only, are shown.

At the same time this paper reports data on the generation and study of simple micro-droplets containing drug solutions. The second topic is dedicated to the generation of micro-droplets with an inner core consisting of medicine solution and a thin layer of oily substance which is immiscible with the core, covering it; these droplets contained a core of water solutions of Vancomycin and an external thin layer of Vitamin A in sunflower oil, and were produced using a double capillary system. The main results were obtained on surface tension at water or Vancomycin solution/air as well as water/oily substance and Vancomycin solution/oil interfaces.

Surface tension is a phenomenon in which the surface of a liquid, at the contact with gas, acts like a thin elastic sheet. This term is typically used only when the liquid surface is in contact with gas (such as the air). If the surface separates two liquids (such as water and oil), it is called "interface tension".

2. Materials and methods

The experiments consisted in the dynamic surface tension (DST) measurements at water/air interface and water/oil interface of Vancomycin and the generation of a droplet of Vancomycin covered with a layer of Vitamin A. The chemical structure of the Vancomycin is shown in Fig. 1.

For this experiment we prepared a stock solution of Vancomycin 5×10^{-4} M and by dilution with ultra-pure water we obtained 10^{-4} M and 10^{-5} M concentrations. For the water/oil measurements, oily Vitamin A and refined sunflower oil were used. The chemical formula and the related structure of the Vitamin A molecule are given in Fig. 2.

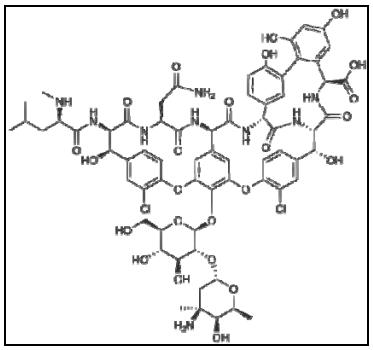

Fig. 1. The chemical structure of Vancomycin.

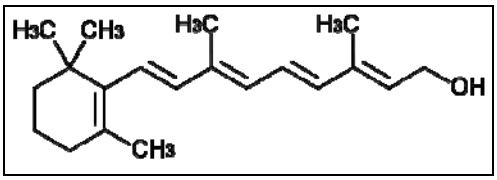

Fig. 2. The chemical structure of Vitamin A.

These experiments were performed using the Drop Profile Analysis Tensiometer (PAT 1 from SINTERFACE) allowing surface or interfacial tension and oscillations measurements over a period of several hours [5]. The experimental set-up is shown in Fig. 3.

The sample cell was kept at room temperature (22°C), carefully protected from environmental dust and kept in an enclosure saturated by water vapour in order to decrease the evaporation effects during the experiments. The high purity grade water was produced by a MilliQ (Millipore) ion-exchange purifier provided with a micro filtration stage, and was used as solvent to prepare the solutions and as reference sample for the measurements. The droplets were obtained by means of a Hamilton programmable dispenser at a slow speed of volume variation in order to ensure a quasistatic measurement.

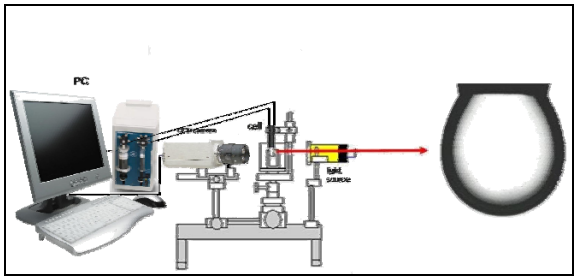

Fig. 3. Experimental set-up.

As for the wetting properties, the contact angles of micro-droplets containing ultra-pure water with hydrophobic and superhydrophobic surfaces were measured; previous measurements [2, 3], have shown that the contact angles of ultra-pure water micro-droplets on one side and micro-droplets containing Doxorubicin or BG1120 in ultra-pure water on the other, are practically the same. That is why in this paper we report our first data on the contact angles measured on micro-droplets of ultra-pure water only. It is expected that the introduction of other medicines in the same class as Doxorubicin in water droplets will do not modify the above mentioned contact angles.

3. Results

Contact angles

The contact angle measurements were performed on superhydrophobic and hydrophobic surfaces; the droplet volume was 5 μl and the temperature of it was constantly kept at 20 ^{o}C.

In Table 1 are presented the obtained values for contact angles at liquid-solid interface, on hydrophobic (Teflon) and superhydrophobic surfaces, respectively for ultrapure water.

Table 1. Contact angles of the micro-droplets with hydrophobic (Teflon) and superhydrophobic (SH) surfaces.

Solvent	Ultrapure water	
Surface	Teflon	Superhydrophobic (SH)
Contact angle (^{o})	135.7±0.8	170.1±0.4

The values represent the respective means between the left and right angles obtained for a set of data corresponding to a particular drug concentration. For our measurements, where the mean values are very close, the small differences obtained between the right and left angles indicate the difference in the local homogeneity of the surface. According to the results reported in [1], the equilibrium values of the contact angles of the micro-droplets on superhydrophobic surfaces do not depend on the doxorubicin or BG1120 concentrations and the small variations of the values are comparable with the accuracy of the method used for the measurements; the micro-droplets have a good compatibility with the surface i.e. with the superhydrophobic materials used for droplets instrumentation [6, 7].

The equilibrium values of the contact angles of the droplets on hydrophobic surfaces do not depend on the solution concentrations either and are nearly as high as for the ultra-pure water.

In general, the measurements about the behavior in time of the contact angles of the samples on hydrophobic and superhydrophobic surfaces have shown that the respective values are constant for time intervals up to 600 s.

Surface tension

For the surface tension measurements of the layered droplets we have used a double dosing system with a double capillary with which we have generated first the exterior droplet then the core through the inner capillary. The total volume of the droplet is kept constant using a built-in camera and the specific software.

In Fig. 4 are shown the DST corresponding to the two Vancomycin concentrations.

The DST equilibrium values for Vancomycin are constant in time and equal for all concentrations. Also, the surface tension (ST) values are close to the pure water value, which means that the drug molecules distribution in the droplet is uniform and remains constant in time. The reason the surface tension of the solution is constant in time is given by the fact that the drug used for these measurements is not a surface active agent, its molecules are not amphiphilic, meaning they don't contain both hydrophobic groups (their *tails*) and hydrophilic groups (their *heads*) and therefore the presence of this medicine do not influence the DST measurements in time.

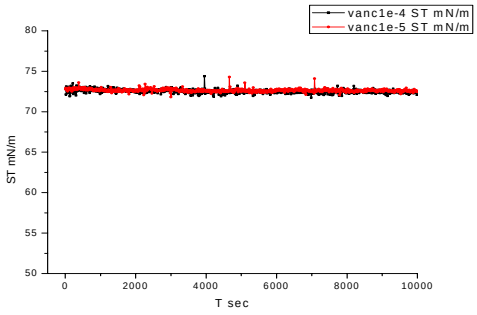

Fig. 4. Surface tension for two different concentrations of Vancomycin.

In Fig. 5 are presented the values of the interfacial tension at the water/oil interface for different systems (the concentration of Vitamin A in sunflower oil is ~8×10^{-2}M): a drop of water in oil; a drop of water in oil plus Vitamin A; a drop of Vancomycin 10^{-4}M in oil; a drop of Vancomycin 10^{-4}M in oil plus Vitamin A.

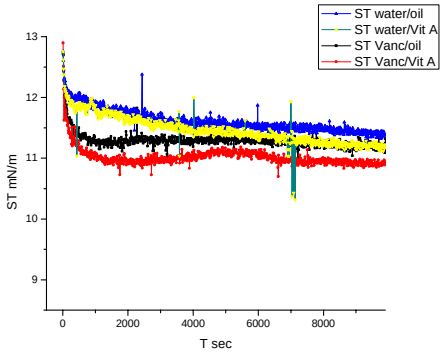

Fig. 5. Interfacial tension.

As may be seen from Fig. 5, there is a small adsorption effect at the water/oil interface – approximately 2 mN/m, too small to have a visible effect at the interface of these two liquids.

Fig. 6 shows the values of surface tension for oil, Vitamin A in sunflower oil at the oil/air interface.

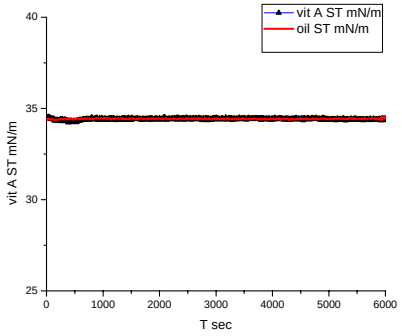

Fig. 6. Surface tension values for oily substances.

The ST values of all the oily substances used in this report are approximately the same.

The final experiments consisted in the generation of a droplet of a Vancomycin solution covered with a layer of Vitamin A. In Fig. 7 the surface tension values are those for a drop of water with a layer of oil, a drop of Vancomycin with a layer of Vitamin A, and the surface tension values for the Vitamin A.

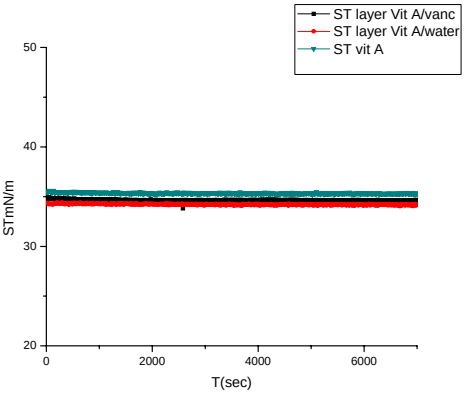

Fig. 7. Surface tension.

These studies revealed the physical properties of the droplets containing medicines (Vancomycin), by showing the adsorption behaviour of the drug molecules at water-air and water-oil interface.

The measurements show that the equilibrium values of the DST for Vancomycin are constant in time and equal for all concentrations; likewise, the values are close to the pure water values, which means that the drug molecules distribution in the droplet is uniform and remains constant in time. The Vancomycin seems to have a better affinity for the water/oil interface than the water/air interface even

if this effect is very low (2mN/m). For the layered droplet case the values of surface tension remain constant in time; the weak adsorption effect at the water/oil interface does not influence the values of the surface tension.

4. Conclusions

Firstly, contact angle measurements were performed for ultra-pure water droplets on superhydrophobic and hydrophobic surfaces for droplets kept at 20 ^{o}C and having a volume of 5 µl. The measurements of the behavior in time of the contact angles of the ultra-pure water droplets on hydrophobic or superhydrophobic surfaces have shown that the respective values are constant for time intervals up to 600 s

Secondly, a systematic set of experiments were performed to monitor the evolution of surface tension values in time.

The experimental results have shown that:

- The equilibrium values of the surface tensions dynamics for Vancomycin are constant in time and equal for all concentrations of the solution; likewise, the values are close to the pure water values, which means that the distribution of drug molecules in the droplet is uniform and remains constant in time
- The drug (Vancomycin) seems to have a better affinity to the water/oil interface than the water/air interface (Fig. 5) even if this effect is very low (2 mN/m)
- For the layered droplet case one may see that the values of surface tension remain constant in time; the weak adsorption effect at the water/oil interface does not influence the surface tension value.

Acknowledgements

The paper reports the results obtained during the STSM (COST-STSM-P21-04703) performed within the COST P21 Action – Physics of droplets, at the Max-Planck-Institute for Colloids and Interfaces Germany.

The research was funded by the PALIRT, 41-018/2007 project of the Romanian CNMP and the ANCS Nucleu Project PN 09 39 01/2009 – 2011.

References

[1] Clement Kleinstreuer, Jie Li, Junemo Koo Microfluidics of nano-drug delivery, International Journal of Heat and Mass Transfer **51**, 5590 (2008).

[2] M. L. Pascu, I. R. Andrei, M. Ferrari, Angela Staicu, Adriana Smarandache, A. Mahamoud, V. Nastasa, L. Liggieri Colloids and Surfaces A: Physicochemical and Engineering Aspects, COLSUA16347, 10.1016/j.colsurfa.2010.02.036, 2010.

[3] I. R. Andrei, M. Ferrari, Silvia Rao, L. Liggieri, M. L. Pascu, P21 COST Action Conference, Capri, May 14-16, 2008.

[4] I. R. Andrei, M. Ferrari, L. Liggieri, Madalina Dicu, V. Nastasa, M. L. Pascu, P21 COST Action Conference, Bucharest, May 4-6, 2009.

[5] L. Del Gaudio, P. Pandolfini, F. Ravera, J. Krägel, E. Santini, A.V. Makievski, B. A. Noskov, L. Liggieri, R. Miller, G. Loglio, Colloids and Surfaces A: Physicochemical and Engineering Aspects- **323**(1-3), (2008).

[6] M. Ferrari, F. Ravera, L. Liggieri, Applied Physics Letters, **88**, 203125 (2006).

[7] Contact Angle, Wettability, Adhesion, Ferrari M. in K. L. Mittal (Ed.), **5**, VSP/Brill, Leiden, The Netherlands, Part 3, (2008).

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