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Graphene Impurity in Biotechnological Products: Particle Size, Hydrophilic Properties and Technological Implications: HYPOTHESIS OF WORK

Luisetto M[1*], Edbey K[2], Cipelli RB[3], Hamid GA[4], Rasool MG[5], Cabianca L[6], Cyress GGP[7] and Latyshev OY[8]

[1]IMA Acdemy Marijnskaya, Applied Pharmacologist, Ship Toxicology, Applied and Industrial Chemistry Branch, Italy

[2]Professor of Phisical Chemistry, Libyan Authority for Scientific Research

[3]IMA Marijnskaya Academy, Italy

[4]Professor Hematology Oncology, University of Aden, Yemen

[5]Professor, Department of Medical & Health Sciences for Woman, Peoples University of Medical and Health Sciences for Women, Pakistan

[6]Bio-medical Laboratory Turin Italy Citta' Della Salute

[7]University Malawi

[8]PRESIDENT IMA Academy RU

[*]Corresponding author:

Luisetto M,
IMA Acdemy Marijnskaya, Applied Pharmacologist, Ship Toxicology, Applied and Industrial Chemistry Branch, 29121, Italy

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1. Abstract

Based on the fact that if present graphene in vials of nanolipids of biopharmaceutical the aspects must to be coloured the reported findings by some independet researcher of graphene like particle in viasl of m Rna covid-19 vaccine seem to suggest that this impurity can be present only inside the nanolipids.

The production fo this encapulated biotecnological product imply the mixing of an acqueos phases (mRna) with an lipidic phases (nanolipids).

The graphene finded as reported , probably due by purification steps, because idrofilic it must to be encapsulated .

The Raman spectra of registrated m RNA C19 vaccine not revealed graphene particle , but in literature it is reported that the direct tecchnique is no the best way to to detect well the nanolipids payload : so a negative results not imply this it not present inside the nanoparticle.

Aim of this work is to investigate the manifacturing process of this biotechnological products submitting to the reseacrher an hypothesis of work than can explain all this pheneomena: the possible segregation of graphene inside the nanolipids.

Great enphasys is given to the size, the chemico physical property like hydrophilicity of the graphene particle versus the nanolipids used in some m RNA C19 vaccine, and the property of inside / outside this particles.

2. Introduction

In order to start this research it is of interest to introduce some concepts related chemico - physical properties of graphene materials like the SIZE and hydrophilic – hydophobic charcateristics and then to verify the matrix effect played by nanolipids in detecting the raman spectra if present as impurity in sample of biotechnological products:

About the size it is possible to verify that : Particle Graphene NANOPLATELETS Dimension 25 µm SIGMA ALDRIC CAS:7782-42-5

Form https://www.ottokemi.com/graphene/graphene-98-gr-522.aspx Graphene SIize >50 µm CAS 1034343-98-0

Novoselov and Geim in 2004 where an adhesive tape was used to detach graphene from graphite crystals From http://www.graphenesq.com/whatis/how.asp

"This year's winners of the physics prize, Andre Geim and K.Novoselov, from Manchester University, UK, extracted graphene from the common material known as graphite - widely used as the «lead» in pencils." IN 2010 Nobel price for Physics

Journal of Science: Advanced Materials and Devices Dec 2017

Effects of initial graphite particle size and shape on oxidation time in graphene oxide prepared by Hummers' method

Seyyedeh Saadat Shojaeenezhad, M. Farbod, Iraj Kazeminezhad

"The average particle size of the first, second , third samples were 18, 6, and 25 µm, respectively."(1) (Figure 2).

From January 10, 2022 by Michael Ducharme

Dr Andreas Noack's Warning to the World about Covid Jabs

"These graphene structures (AKA monolayer carbon or monolayer graphite) are so stable, every chemist knows this. They are not degradable. The structure is 50 nm long and 0.1 nm thick" (Figure 3).

According Meenu Mehta et al "Liposomes can be synthesized into unilamellar or multilamellar vesicles, with sizes varying from 20 to 1000 nm and Solid lipid nanoparticles were initially formulated as small spherical particles with a solid lipid core at room temperature, and subsequent advancements have led to the development of flat ellipsoidal or disc-like shapes, exhibiting sizes between 50 and 100 nm. "

Sci Rep. 2023; doi: 10.1038/s41598-023-42274-z

Quantitative size-resolved characterization of mRNA nanoparticles by in-line coupling of asymmetrical-flow field-flow fractionation with small angle X-ray scattering

Melissa A. Graewert et al

"The success of mRNA nanoparticles for vaccination against Covid-19 has highlighted the potential of RNA nanomedicines as well as of nano-scaled pharmaceutical products in general. In mRNA vaccines, so-named lipid nanoparticles (LNPs), which are characterized by a specific lipid composition and manufacturing

process, are used for mRNA delivery. There is a wealth of different other nano-scaled pharmaceuticals which have reached various stages of clinical and preclinical development.

The particles may be based on organic (lipids, polymers, polypeptides, proteins) or inorganic materials (metals, metal oxides, silica).

The majority of these products are intended for parenteral application with particle sizes typically below 200 nm (the limit for the sterile filtration): LNPs measure 100 nm or less, and certain particle formats (for targeting tumors or crossing the blood–brain barrier BBB) are in the range of tens of nanometers. With dimensions of a few or few tens of Angstroms, other types of drug formats like as biologics (therapeutic proteins, antibodies) or soluble polymers may be included for this category of nano-sized drugs. The characteristics of these systems are dominated by their colloidal nature, where particle size and size-related attributes are of fundamental importance for quality, biological efficacy, and safety." (2) (Figure 4).

(200 Nanometer = 0, 2 micrometer)

In PREPRINT REVIEW ON ANALYTICAL METHODS FOR THE CHARACTERIZATION OF GRAPHENE STRUCTURES AND TOXICITY PROFILES

Amedeo Cinosi , L. Bolgan and Carlo Martelli Is reported :

"the potential spectral contributions from nanostructures within the matrix, such as graphene sheets

10 exponent – 2 (0,01 micrometer) and 10 exponent- 3 µm (0,0001 micrometer), are masked by other compounds in the matrix." And " The structures observed in the P. vaccine by TEM are described by Young as clusters/aggregates of graphene, but both the morphological characteristics and t**he dimensions (50 µm**) are not correlated with graphene phases known from the literature or studied in a clinical context. The presence of suspended solid particulate in a colorless liquid (water or organic solvent) imparts a characteristic color, according to Lambert-Beer's law. Iron imparts a red color, and the intensity is proportional to the concentration and the path of light through the medium. The presence of even a few parts per million (ppm = µg/ml) of graphene nanoparticles in the preparations should give a straw-yellow coloration. This is not observed in the doses of sera analyzed, as they appear colorless or milky-white;" [3].

(0,01 micrometer = 10 nanometer) (Figure 5).

Some independent researcher finded particles similar to graphene into some vials of c19 vaccine or in blood of vaccinated with size about.

(It is also to be considered to self asselbling properties of graphene particle).

It was finded 19- 114 micrometers or more size in blood of vaccinated (Ki-Yeob Jeon et al), or voluminoses particle of about 329.14µm by 137.74µm five week after vaccination (graphene particles?) Benzi Cipelli et al.

Form Nanotechnology Nanomaterials AUGUST 18, 2015

Is graphene hydrophobic or hydrophilic? by National Physical Laboratory

"the findings indicate that the graphene hydrophobicity is strongly thickness-dependent, **with single-layer graphene being significantly more hydrophilic than its thicker counterparts."**

And in Dissertation: Understanding the intrinsic water wettability of graphite

Kozbial, Andrew (2016) Understanding the intrinsic water wettability of graphite. Doctoral Dissertation, University of Pittsburgh.

"This work unequivocally shows that fresh graphitic surfaces are mildly hydrophilic."

J Chem Phys. 2015 Oct 21; doi: 10.1063/1.4933011.

Hydrophilic behavior of graphene and graphene-based materials

Sebastián R Accordino , Joan M. Montes de Oca , J Ariel Rodriguez Fris , Gustavo A Appignanesi

"Our molecular dynamics studies will demonstrate that parallel graphene sheets present strong tendency to remain fully hydrated for a moderately long times (even when the equilibrium state is indeed the collapse of the plates), they are less prone to self-assembly than the model hydrophobic surfaces we shall employ as control which readily undergo a hydrophobic collapse. Potential of mean force calculations will indeed make evident that the solvent exerts a repulsive contribution on the self-assembly of graphene surfaces"

Figure 1: From http://www.graphenesq.com/whatis/how.asp

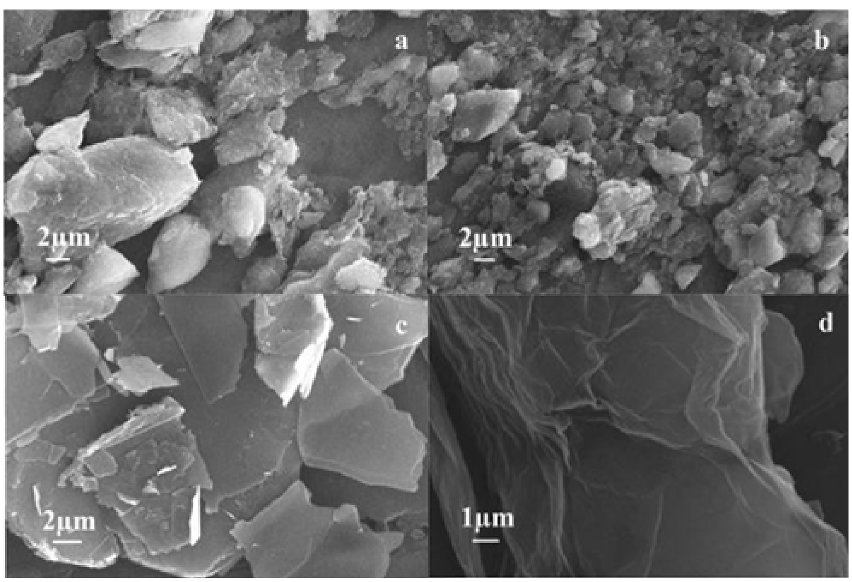

Figure 2: SEM images of the initial graphite a) the unmilled sample, b) the 5 h milled sample, c) the flake sample, and d) graphene oxide. From ref n 1

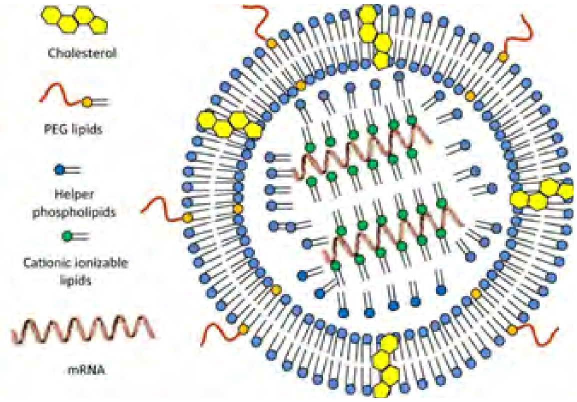

Figure 3: Schematic representation of components of lipid nanoparticles (LNPs). PEG polyethylene glycol From doi.org/10.1007/s40290-021-00417-5

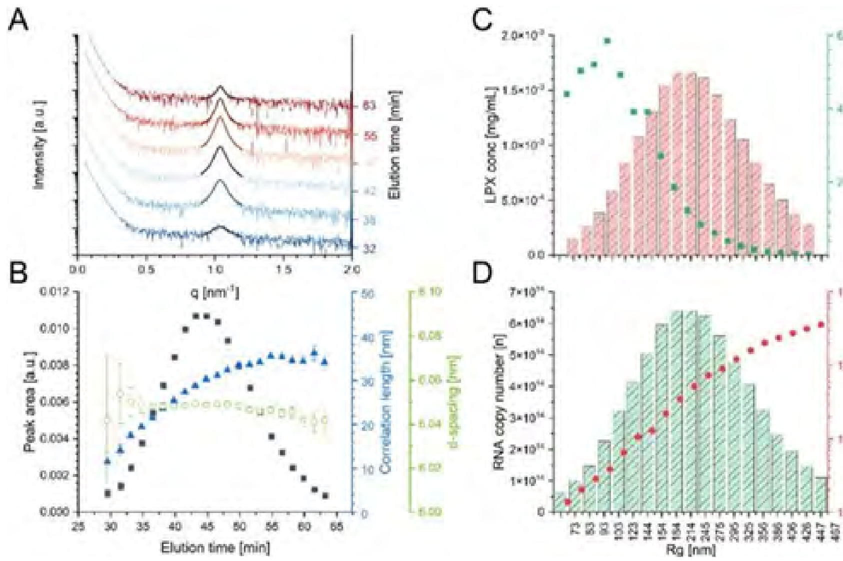

Figure 4: (C) Absolute material concentration (LPX conc. in mg/mL) derived from SAXS signal for LPX peak (red bars) and the calculated absolute n. of particles as a function of radius of gyration (Rg) derived from MALS (green dots). From doi: 10.1038/s41598-023-42274-z

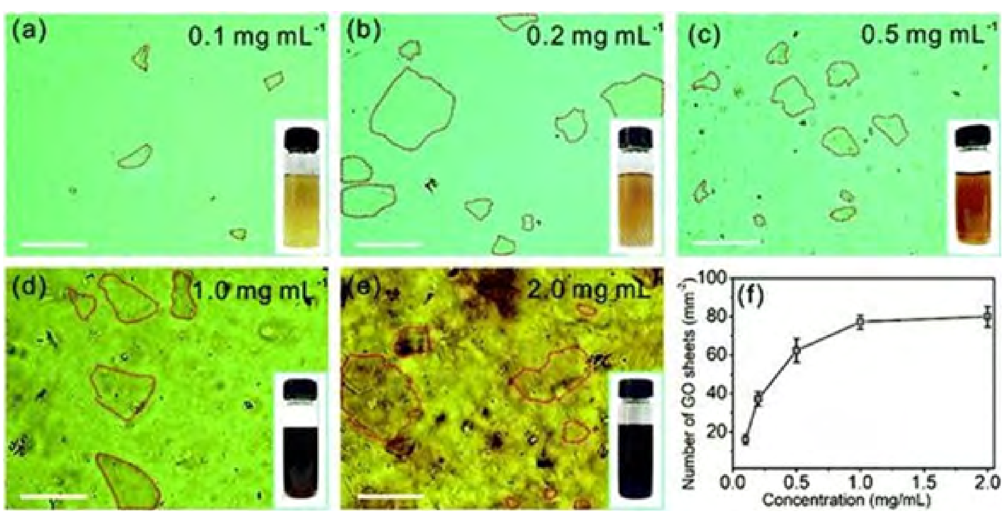

Figure 5: a)–(e) OM images of GO suspensions in water at conc. in the range of 0.1 to 2.0 mg mL−1. The GO sheets are marked by red dashed lines. The insets in images (a)–(e) show photographs of the GO
suspensions in 20 mL vials. Scale bars: 100 μm. (f) The number of GO sheets calculated by counting the GO sheets in the OM images as a function of the GO concentrations. From
https://doi.org/10.1039/C9RA02076D

3. Materials and Methods

With an observational point of view various concepts of phisycal chemistry relates Size and idorphilic properties are reported.

Relevant literature is analysed (from 4 to 13) and figure reported (from 1 to 15) help in clarify the concepts related the hypothesis Submitted.

An experimental project hypothesis is provided to test this process. Finally a global conclusion make possible to resume all.

4. Results

Form literature

Lee, Y. M. et al (2022). Foreign materials in blood samples of recipientsof COVID-19 vaccines. International Journal of Vaccine Theory, Practice, and Research, 2(1), 249–265.

"they also found components that the CDC had claimed were not used — including reduced graphene oxide (rGO), or graphene hydroxide (GH), in the M. vaccine.

The diameter they observed at 100μm was apparently the same as the one we have pictured above in Figure reported. We also showed a slightly smaller very similar structure. [4] (Figure 6-9).

From Is Graphene Hydrophilic or Hydrophobic? Posted by MSE Supplies Admin on May 11, 2020

"Materials scientist in the Netherlands furthered this study work by measuring the contact angle of water on the graphene and several other kind of materials. They found that with water the graphene surface was smooth and clean meaning the graphene material was indeed hydrophilic"

Amedeo Cinosi et al

"The presence of even a few ppm (ppm = µg/ml) of graphene nanoparticles in the preparations should give a straw-yellow coloration.

This is not observed in the doses of sera analyzed, as they appear colorless or milky-white"

Regulatory agency allow use of direct (non-sample destructive) RAMAN spettroscopy in PAT: but according literature this method without pretreat the sample with solvent is not adeguate to measure nanolipids payload [5].

According Karen A. Esmonde- et al

"Raman spectroscopy RS has been used since 2006 to provide analytical -quality control of compounded formulations stored in vials or directly through polymeric infusion pumps in hospital setting" [6].

In the light of this recent investigation, does the Commission intend to have an independent analytical chemical laboratory perform a careful analysis to check for the presence of graphene in the C-19 vaccines?"

Last updated: 27 Jan 2022 Parliamentary question - P-000303/2022(ASW) European Parliament

Answer given by Ms Kyriakides on behalf of the European Commission 8.3.2022

Written question

"EMA has analysed reports describing the analysis of several vials of C-19 vaccines suggesting the presence of graphene and concluded that the currently available data do not show presence of graphene in the

vaccines concerned. The analysis by EMA's working party for biological medicines included an input on the

Raman- spectroscopy RS from the European Directorate for Quality of Medicines and the independent national testing lab responsible for the batch release (OMCLs).

Quality control testing and quality assurance review, by the vaccine manufacturers and OMCLs responsible for batch release, confirm that each batch met all quality standards prior the release. "

Analytical and Bioanalytical Chemistry

Raman spectroscopy as a process analytical technology for pharmaceutical manufacturing and bioprocessing

04 August 2016

"Since the 1980s, Raman spectroscopy RS has been used to study active pharmaceutical ingredients (API)" [7].

Luisetto M et al

"In European pharmacopeia's EP last edition it is allowed to use direct nondestructive methods " [8].

20 January 2016, Strasbourg, France Council of Europe

Revised General Chapter on Raman Spectroscopy in the European Pharmacopoeia: inclusion of handheld devices, adaption to PAT purposes

"Hand-held instruments are now available on the market, which are suitable for identification purposes even though requiring different tolerances for the wavenumber scale verification than benchtop models."

How Raman Spectroscopy RS is adapting to European Pharmacopoeia regulations Sponsored Content by Metrohm Middle East FZC Feb 15 2022

"Raman spectrometers, especially portable and handheld instruments, are being used predominantly for the QC of raw materials and medicines. Requiring less technical skill, instrument interfaces are easy to use. For several samples with rapid, non-destructive measurements, they also offer flexible sampling options."

European Pharmacopoeia adopts revised Raman spectroscopy chapter may 2021 By Hannah Balfour (EP Review)13 May 2021

"Ph. Eur. Explained that Raman spectrometers RS are increasingly being deployed in the pharmaceutical environment because of the essential information they can provide via rapid, non-destructive measurements."

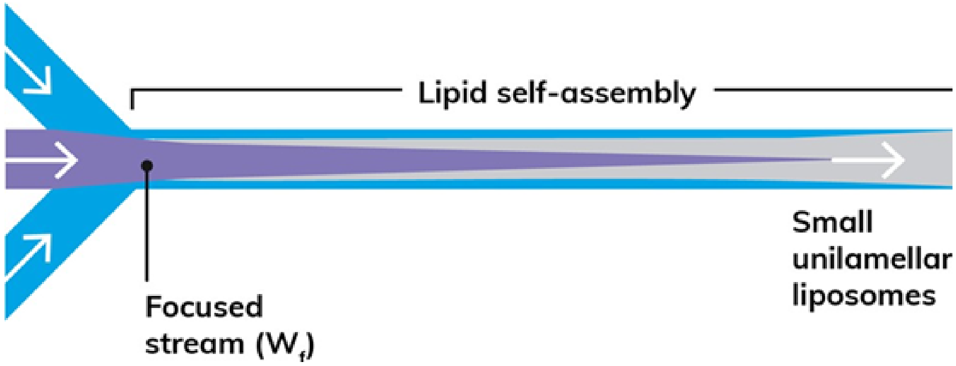

Figure 6: from https://www.ondrugdelivery.com/automated-lipid-nanoparticle-production-from-protocol- development-to-gmp-manufacture/

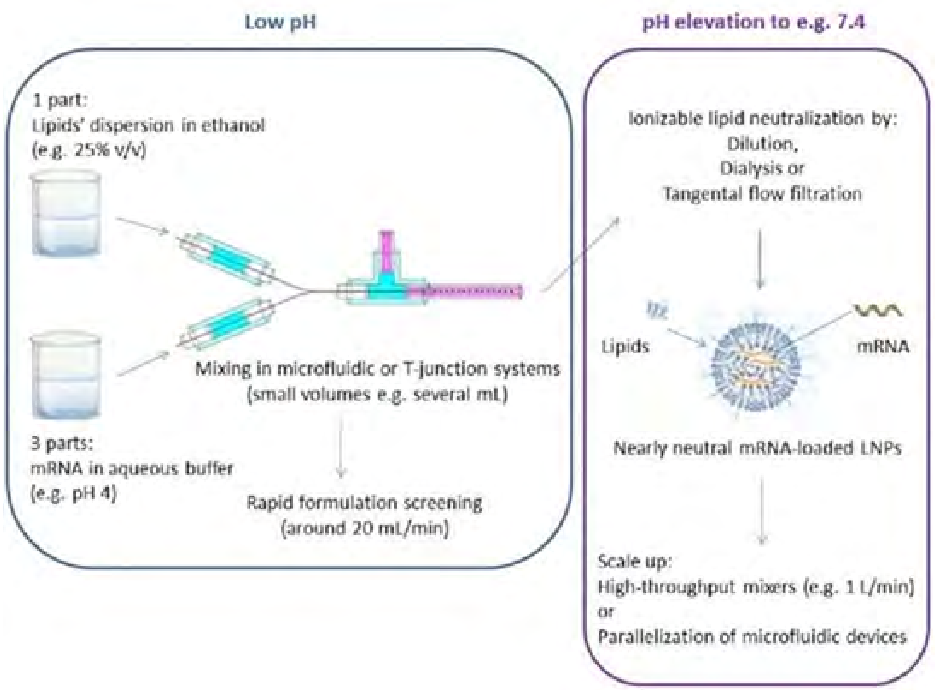

Figure 7: Schematic presentation of a manufacturing approach to obtaining mRNA encapsulated lipid nanoparticles as potent vaccines for COVID-19 prevention. From Lipid nanoparticles employed in mRNA- based COVID-19 vaccines: An overview of materials and processes used for development and production
Jan 2022 Arhiv Za Farmaciju DOI: 10.5937/arhfarm72-33660

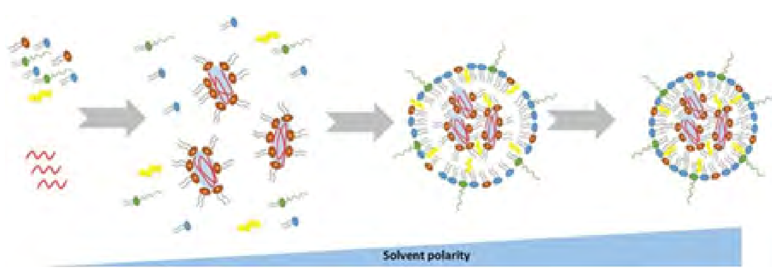

Figure 8: Schematic representation of the mechanism driving the self-assembly of mRNA-loaded lipid-based nanoparticles

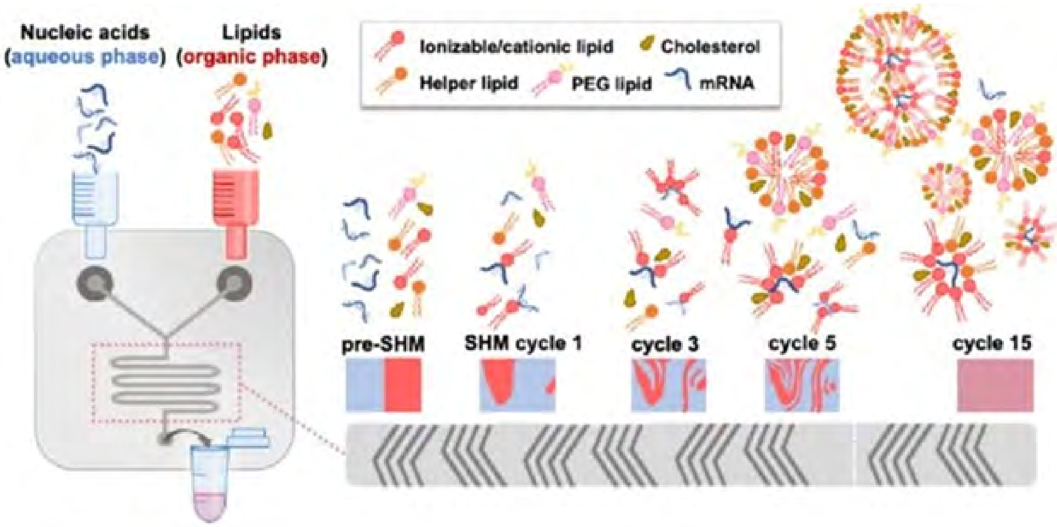

Figure 9: Lipid nano-particle formation utilizing a microfluidic platform with a staggered herringbone micromixer. Within the microfluidic channels, the SHM allows the aqueous phase (containing the nucleic acids, mRNA, under an acidic pH) and the water-miscible organic phase (containing the lipids and cholesterol) to proceed from laminar flow (pre-SHM) through several cycles of chaotic mixing until complete mixing of the phases has occurred (cycle 15).From Emily Pilkingtonab et al.

Afroditi Ntziouni et al

"According the IUPAC Gold Book, sample is a portion of material selected from a larger quantity of material, the term needs to be qualified (bulk sample and representative sample) and implies the existence of a sampling error (otherwise the correct term would be test portion, aliquot, specimen)." [9].

Kevin Buckley et al

"Sampling Factors Affecting Raman Measurements

Raman spectroscopy RS is considered as a vibrational technique with advantages such as little or no sample preparation and direct and nondestructive analysis"and "The other major, complicating factor in the use of Raman spectroscopy RS for biopharma is the fact that many of the aqueous solution samples (the cell culture media and spent bioreactor broths), and the biogenic molecules themselves, can have extremely complex compositions/ structure. [10].

Zai-Qing Wen et al

"The detection limit of 10 ppb in raw material dissolved in 30:70% water/acetonitrile is equivalent to 0.5 ppm in solid raw material. It has excellent linearity in the conc. range measured. The detection of melamine using the SERS technique is rapid (within 3 minutes), convenient, and requires no extraction procedure, offering an alternative method for screening melamine in raw materials RM at biopharmaceutical manufacture sites [11].

From AGILENT website: Raw Material Identification of Mrna Lipid Nanoparticle Components with the Agilent Vaya Raman Spectrometer

"Lipids are the building blocks of LNPs. Figure reported shows the overlay of Raman spectra rs and how the Vaya can easily discriminate the PEGylated, ionic, and sterol lipids from each other. Raman band assignments confirm the presence of the long hydrocarbon chains present in lipids. The band at 1,440 cm–1 is attributed to the deformation vibrations of CH2 and CH3,the band at 1,673 cm–1 is a result of the stretching vibrations of C=C present in the cholesterol. In DSPC, the band at 949 cm–1 corresponds to PO stretching.

The band at 1,700 cm–1 is attributed to C=O stretching in both DSPC and DMG-PEG 2000 lipids." (Figure 10-15).

Sally Vanden-Hehir,et al.

"When incubated with HeLa cells, the nanoparticles were observed by Raman imaging to localize in the cytoplasm. The spontaneous Raman spectra RS show a strong, sharp alkyne peak at 2200 cm−1, along with the characteristic cellular peaks CP. Shows that the alkyne signal co-localizes with the cellular lipids (2850 cm−1), there is an absence of signal in the cell-silent region at 2170 cm−1, confirming that the signal in the on-resonance image is due to TAT-PPE nanoparticles." [5].

Exeperimental project hypothesis

Verify of segregation phenomena of graphene particle into the nanolipis:

In order to test if the hypothesis is correct is to add in artificial way to 50 Mrna sample particles of graphene in significative amount before to add into the lipids phase for encapsluation (group A)

The control it is done without adding this artificial substantia. (group B).

After this: it must to be detected using Raman spectroscopy whit pretreating the nanolipids with solvents to make possible to avoid the matrix interference.

The test will be positive, confirming the hypothesis , if graphene is finded in the group A .

It must to be collected the colour of the vials (group A and B)

In the results it must to be indicated what kind of monoliths was used in the purification steps (carbon composite materials or silica resin or other): this make possibile to verify the impurity profile when using different materials).

The results must to be divided in subclasses according th kind of monoliths used.

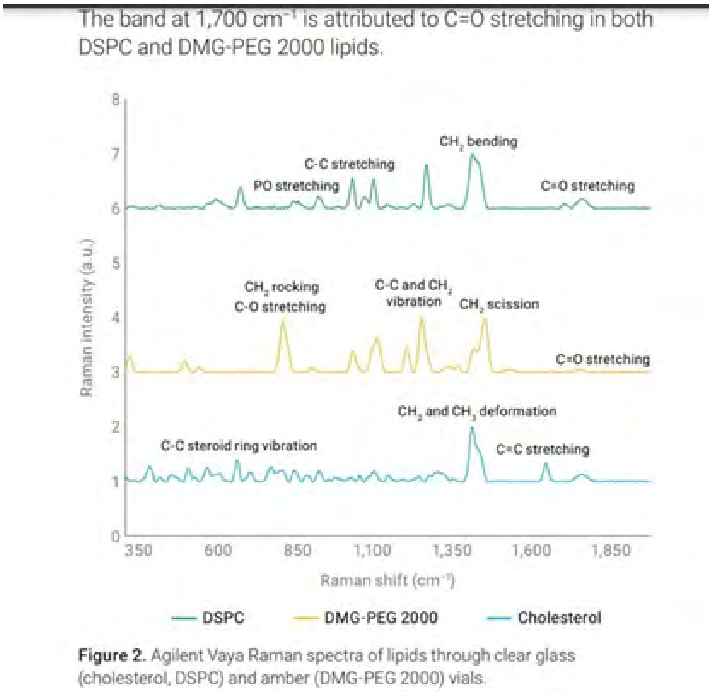

Figure 10:

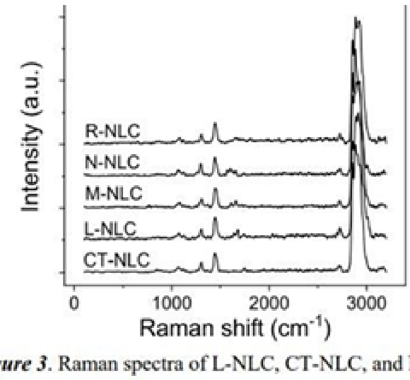

Figure 11: The most intense bands in the spectra of molecules including alkanes and lipids with alkyl groups are the CH stretching modes. NLC nanostructured lipid carriers From C . CIMINO thesis

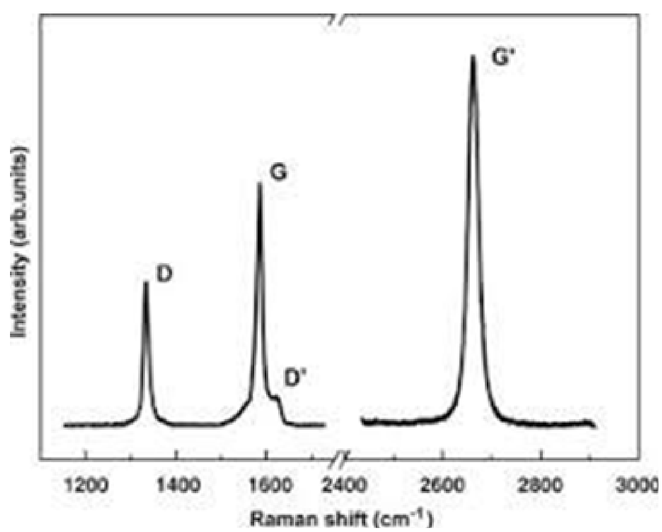

Figure 12: From https://doi.org/10.1016/j.physrep.2009.02.003T he most prominent features in the Raman spectra of monolayer graphene are the so-called G band appearing at 1582 cm−1 (graphite) and the
G' band at about 2700 cm−1 using laser excitation at 2.41 eV

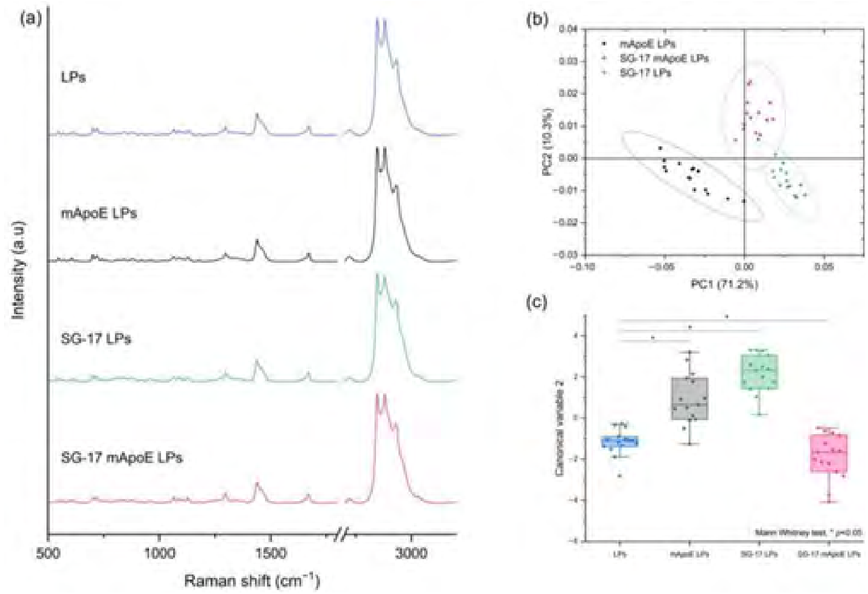

Figure 13: form doi: 10.3390/nano13040699

Francesca Rodà et al. "peaks at 596, 944, 1008, 1199, 1339 and 1550 cm−1" (13)

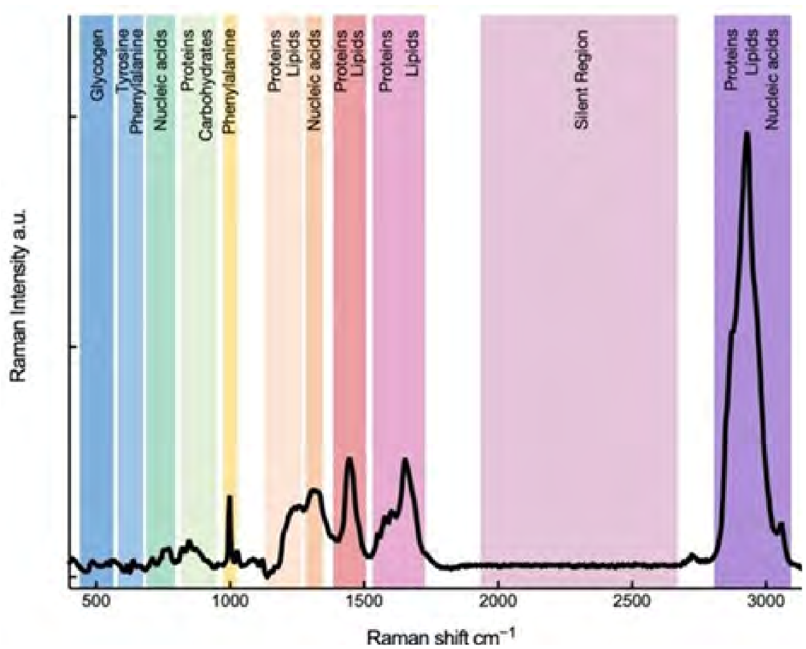

Figure 14: from DOI: 10.3390/cancers13071718

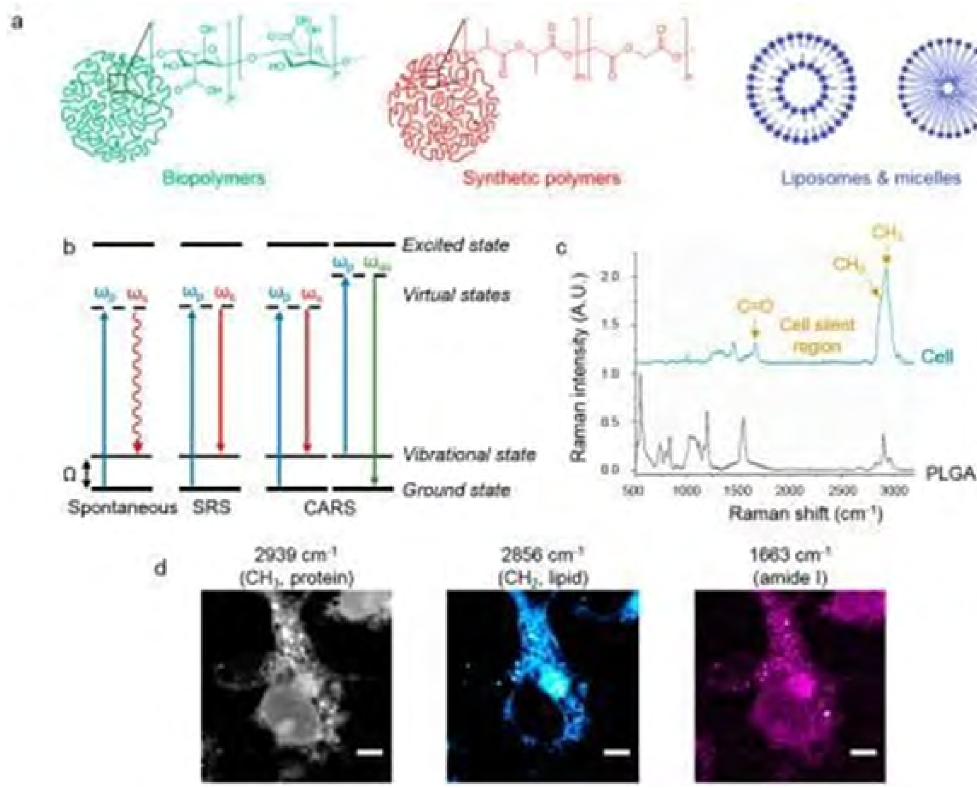

Figure 15: Raman imaging of nanocarriers. (a) Representation of different materials which can be fabricated into nanocarriers, such as biopolymers , synthetic polymers (PLGA), and lipids (as liposomes and micelles).
(b) Energy level diagrams showing the processes of spontaneous Raman, stimulated Raman scattering , and coherent anti-Stokes Raman scattering (CARS). (c) Spontaneous Raman spectra showing the characteristic peaks in microglia (top, green spectrum) and PLGA, a common polymer for drug delivery (bottom, black spectrum). From doi: 10.3390/nano9030341

5. Discussion

The findings of graphene like particles in vials of some C19 vaccine by independent researcher imply a great effort in order to clear this report vs the regulatory requirements.

Related the official question to the European parliament to investigate about this impurity in the answer

Raman- spectroscopy RS from the European Directorate for Quality of Medicines and the independent national testing lab responsible for the batch release (OMCLs).

Quality control testing and quality assurance review, by the vaccine manufacturers and OMCLs responsible for batch release, confirm that each batch met all quality standards prior the release" the sample is adeguate as allowed by regulatory rules?

As seen in fig n 9 From Emily Pilkingtonab et al in the manifacturing of encapsulated m RNA the acqueous phases is fisrt mixed with the lipids phases.

Because Graphene is an hydrophilic, if present in the purification steps of the m RNA it must to be finded in the acquesous phases.

Literature reported: NANOLIPIDIS SIZE about 200 nanometer and some GRAPHENE SHEETS SIZE also about 0,01 MICROMETER.

Young finded di 50 micrometer particle, and other finded particle similar graphenic with size from 19 to 319 micrometers in blood of vaccinated.

(Graphene materials are subjected of self assembling properties.)

Indepented researcher or authorities not finded abnormal coloured vials of m RNA VACCINE.

The peack of raman spectra of graphene , Nanoparticles are very informative to verify the interference.

The effect played by syntetic polimer PLGA nanocarrier on raman signal is clear: reduced versus the cell signal.

In literature is reported that Raman spettroscopy is not the best technique to detect payload of nanoparticles.

Base on this fact it is submitted to the producers of biotechnological products with nanoparticles to test for graphene impurities taking in consideration that it must to be necessary to use analytical technique with preteratement of the sample with solvent in order to destroy the nanoparticle and make free their content.

increase the quality of the separation procedure without impurity release making more safe this manifacturing steps.

6. Conclusion

The chemico -physical properties of graphene particle like idrofilicity and size make possible to think that:

- the nanolipids of some biotechnological products can in theory contain graphene particles due by their specific size (in example if impuriy of the purification steps)

- the manifacturign process imply the mixing of an acqueous phase (with the m RNA) with the lipids phase

- the process is then concluded increasing the polarity of the enviroment

- if presente graphene impurity it must to be encluded into the nanolipids because its hydrophilic properties.

- because encapsulated, the Raman direct technique cannot adeguately detec because matrix effects

(this techniqye is not efficacy for test the payload) :see the peak of RAMAN spectra of the graphene and the Nanolipids.

In this way the vials can appare not coloured ? (if the graphene is only encapsulated).(to be verified) Performing the experimental project submitted is possible to test if this hypothesis is real or not.

It is opinion of the authors that the process reported can explain what was finded by some independent researcher and what not was finded using Direct Raman spettroscopy by producers and regulatory Body.

In some cases the reality can show different perpective depending by what approach and vision method is used.

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