Evidence on the Stability of Nanoparticles of Comirnarty® in Syringes

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Short Report

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Abstract

Moving towards a real mass vaccination in the context of COVID-19, healthcare professionals are required to face some criticisms limiting the storage and transport of Comirnaty® as diluted dose in 1mL-syringe. Here, the physical stability of lipid nanoparticles in “real-world” conditions was evaluated, comparing the effects of different syringe materials, temperature and mechanical stress on number and particle size distribution. the positive results of such proof-of-concept can support the preparation and transport of doses to hospitals or vaccination settings.

Main Text

The first vaccine approved for the prevention of COVID19 caused by SARS-CoV-2 virus is mRNA containing lipid nanoparticles (LN) in aqueous cryoprotectant buffer, commercialized as a deep-frozen concentrate for dispersion (Pfizer-BioNTech COVID-19 Vaccine in the US or Comirnaty® in EU) which is diluted after thawing and before injecting of a 0.3-mL dose intramuscularly into the upper arm. The vaccination campaign is hard testing the operativity of healthcare systems as after thawing the vaccine concentrate should be diluted (or maintained at 2-8 °C for maximum 5 days) and administrated within 6 hours [1,2]. The syringe has to be prepared immediately before use. Moreover, in consideration of the innovation of both the active ingredient (i.e., mRNA) and drug delivery system (i.e., lipid nanoparticles) little information about the finished product stability can be retrieved in the SPC or literature [3]. Instead, everyday experience has tough that there is a clear need for a comprehensive overview of all information on the stability of mRNA vaccines. Indeed, during a pandemic that is still increasing, it is critical that no doses are discarded due to a wrong handling or delay in administration to implement mass vaccination. As a matter of fact, to pick its own pace in the further weeks, vaccine doses would be also reasonably transported from hospitals, where vaccine vials are stored -90/-60 °C, to other health care settings and vaccination locations. And again, the road transportation needs special care to ensure that the vaccine quality is not impaired by environmental conditions, such as temperature and shocking [4]. The undiluted product can be transported at 2-8 °C either in two trips each up to 6 hours or for a maximum of 12 hours in one sitting [5]. However, as far as known transport of the diluted vaccine is not currently supported by relevant stability data [6].

Finally, the compatibility “*with commonly used commercially available administration components*” is quoted in the EMA or FDA assessment report [1,2], even if no information on the quality attributes controlling and limiting stability, is available as of the writing of this correspondence.

In attempt to fill the gap of background information which would help to rationalize handling (i.e. administration components and timing) and transport, we investigated the maintenance of the number and particle size distribution of LN of two baches of Comirnaty® in vials and diluted doses in 1mL-syringes made of poly(propylene) or poly(carbonate) and stored in cold chain (i.e. 2-8 °C), and 25 °C over 5 hours. The impact of transport by road in suburban area for 30 km using temperature stabilizing

medium, was a matter of interest. Stress conditions were also applied, namely storage at 25 and 40 °C for 24 and 5 hours, respectively.

LN were characterized in terms of size and polydispersity by dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA), which are complementary techniques proving evidence on the presence of aggregates which change drastically the formulation features, including the dose-to-dose reproducibility, the fate and the biodistribution of the particles once injected *in vivo* [3,7,8].

Indeed, DLS derives hydrodynamic diameters (D_H) from the fluctuation of scattered light caused by Brownian motions (intensity-based diameters) and, in case of polydisperse samples, the population representing the smaller particles is under-represented. Using a microscope NTA takes videos of moving nanoparticles and converts their speed into the particle's translational diffusion coefficient: this feature allows NTA to provide number-based particle size distribution (i.e., mean diameter and D_{90}) and particle concentration in the medium.

Results obtained by the proposed orthogonal approach evidenced that the particles are physically stable, regardless of the syringe materials, storage temperature, and road transportation. DLS results showed that physical features of LN did not significantly change when stored in syringes for 24 h between 2 and 25 °C (**Table 1**).

Road transportation did not affect both particle size and polydispersity of the LN dispersions. NTA results agree with DLS data since the particle size distribution and the nanoparticle concentration did not change significantly ($p>0.05$) after storage in syringes at both storage temperatures over 24 hours as well as after road transportation. The unmodified value of nanoparticle concentration demonstrated both the physical stability of particles that do not undergo aggregation during storage in syringes (or vial transportation) and the lack of absorption phenomena between particles and syringe barrel wall. It is worthy of note that prolonging the storage period up to 10 days from dilution did not affect the physical stability of LN. In fact, although a slight but significant increase of the particle counts was found (**Table 1**), the mean particle diameter and D_{90} remained unvaried ($p>0.05$), ruling out the hypothesis of particle aggregation during storage.

The effect of important shocking and vibrations need to be carefully considered since vortexing and syringe mechanical stress caused a significant increase of the polydispersity, due to the formation of aggregates (**Table 1**).

These favorable observations on physical stability and storage can support the preparation of the doses in hospital pharmacies or other healthcare settings where aseptic conditions are guarantee, before being distributed at vaccination locations.

Declarations

Ethics approval and consent to participate: not applicable

Consent for publication: not applicable

Availability of data and materials: not applicable

Competing interests: not applicable

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Tables

Table 1 - Impact of storage and mechanical stress on the particle size distribution of LN expressed as ratio of hydrodynamic diameter (D), which is calculated based on the main peak of DLS data, and polydispersity index (PDI) before and after the applied experimental condition. DLS: Legend of symbols expressing a variation < 10% (=); 10-25% (+); > 25% (++); NTA: P-values of Student's t-test of particles before and after the applied experimental condition. n.d.: not determined.

Conditions of thawed vaccine		D_f/D_i	PDI_f/PDI_i	LN/mL
In-use	Stored in syringe at 2-8 °C for 5 h	=	=	p=0.86
	Stored in syringe at 25 °C for 5 h	=	=	p=0.17
	Road transportation of syringe at 2-8 °C	=	=	p=0.14
Stressed	Stored in vial at 2-8 °C for 10 days after thawing	=	=	p<0.01
	Stored in syringe at 2-8 °C for 24 h	=	=	p=0.36
	Stored in syringe at 25 °C for 24 h	=	=	p=0.09
	Stored in syringe at 40 °C for 5 h	=	+	n.d.
	Mixing different vial overfill	=	+	n.d.
	Mixing by vortex for 2 min	+	++	n.d.
	Syringe mechanical stress (40 cycles)	++	++	n.d.