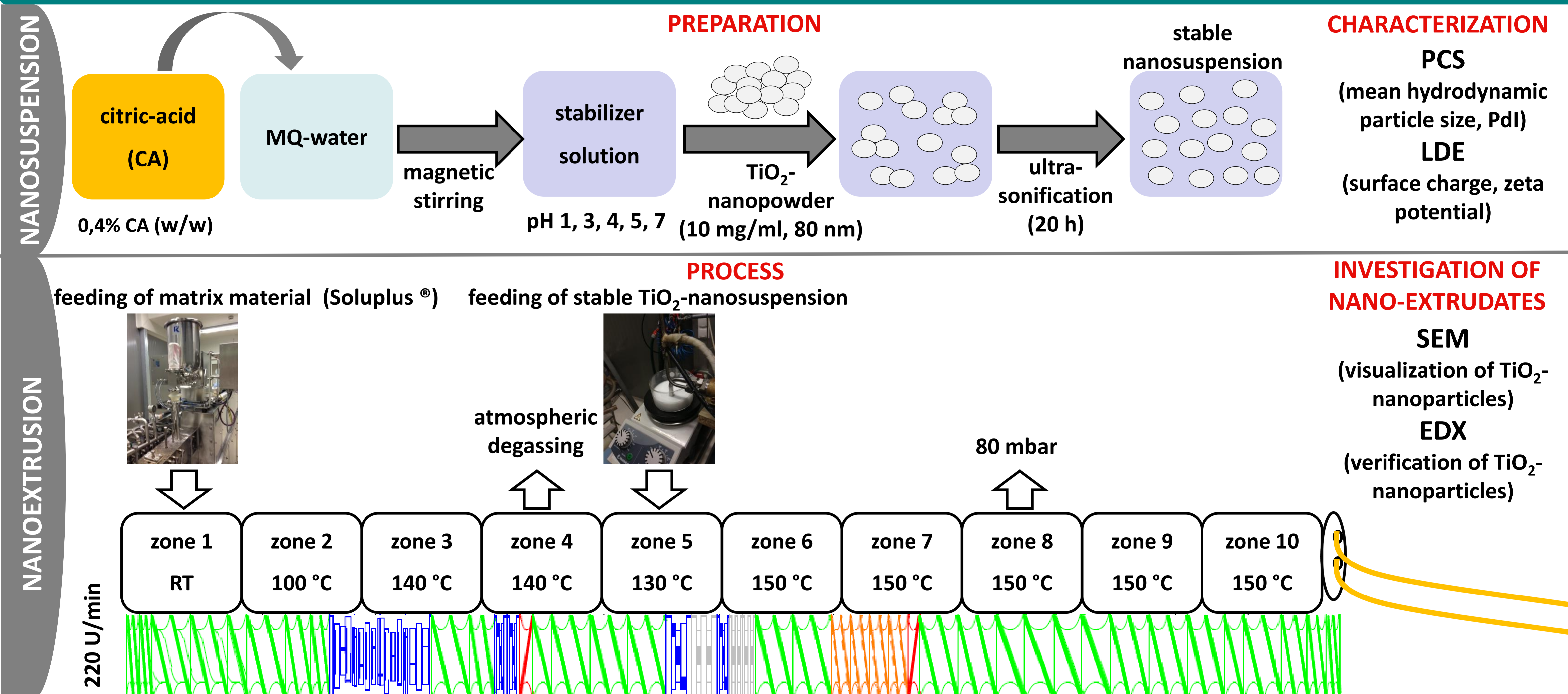


Nano-Extrusion (NANEX): Manufacturing of Solid-Nanoparticle Formulations Directly from the Liquid Phase via Hot-Melt Extrusion

Introduction

Given the increasing number of active pharmaceutical ingredients (APIs) that have poor solubility and thus poor oral bioavailability, pharmaceutical scientists are constantly seeking innovative formulation approaches in order to achieve satisfiable dissolution properties. The emerging field of nanoscience, in particular the application of nanosuspensions, offers novel possibilities. However, nanosuspensions, i.e., colloidal stabilized nanosuspended drugs in aqueous medium, suffer from stability problems. Since they are typically delivered parenterally, patient compliance also must be considered. Thus, in order to develop a preferred solid dosage form for oral administration, the nanosuspension must be transformed into a solid product. However, the manufacturing of solid-nanoparticle formulations requires several time-consuming and challenging steps [1]. Therefore, there is an enormous need for new one-step process technologies that transfer a nano-suspension into a solid dosage form while avoiding any agglomeration. In the present study, a one-step nano-extrusion (NANEX) process was developed where the nanosuspension is directly fed to a hot-melt extruder. The goal was to obtain extrudates that contain homogeneously distributed and de-aggregated embedded nano-crystals in a polymer matrix.

Materials and Methods



Results

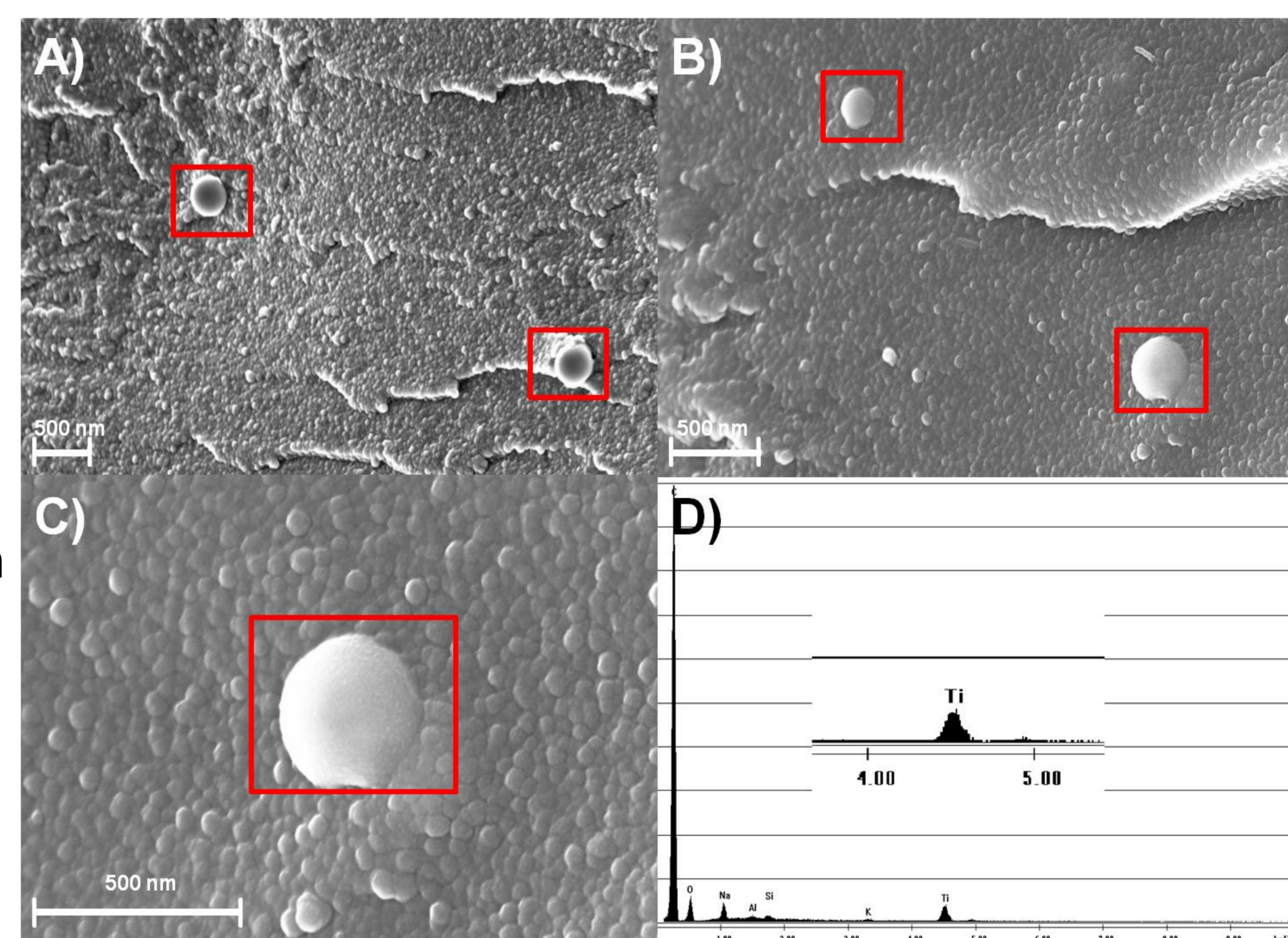
EVALUATION OF APPROPRIATE pH-VALUE OF STABILIZER-SOLUTION

pH	duration of storage [d]	ϕ-hydrodynamic size ± SD [nm]	ϕ-Pdl ± SD	ϕ-zeta potential ± SD [mV]
1	1	2236.3 ± 519.5	0.924 ± 0.127	-5.8 ± 1.9
	14	1853.7 ± 410.2	0.834 ± 0.148	-27.7 ± 0.5
3	1	572.1 ± 28.0	0.439 ± 0.070	28.9 ± 3.9
	14	267.7 ± 17.2	0.282 ± 0.033	-44.5 ± 0.9
4	1	519.3 ± 77.8	0.429 ± 0.034	-35.1 ± 1.3
	14	197.7 ± 10.6	0.248 ± 0.022	-44.5 ± 0.5
5*	1	557.5 ± 52,2	0.443 ± 0.075	-44.2 ± 0.8
	14	156.6 ± 7.1	0.239 ± 0.013	-53.9 ± 0.4
7	1	525.4 ± 59.8	0.429 ± 0.053	-45.1 ± 0.8
	14	224.1 ± 31.2	0.319 ± 0.082	-52.7 ± 0.9

→ (A, B) 210 - 340 nm TiO₂ particles embedded in Soluplus® in de-aggregated form

→ (C, D) verification of a TiO₂ nanoparticle (340 nm) via elemental analysis (EDX)

INVESTIGATION OF NANO-EXTRUDATES



Summary

Stable TiO₂-nanosuspensions were obtained after 14 days of storage at 5°C at pH 5. These suspensions were processed via NANEX. SEM-data confirm that the TiO₂-nanoparticles were embedded in the matrix in a de-aggregated form. Therefore, the current study demonstrates that this novel process based on hot-melt extrusion of a nano-suspension is an appropriate continuous technology for producing solid nano-formulations. This one-step process helps to eliminate problems associated with stabilization of nanosuspensions, parenteral delivery and the conversion of nanoparticles into a (dry) solid dosage form.

References

[1] Van Eerdenbrugh B, Van den Mooter G, Augustijns P. Top-down production of drug nanocrystals: nanosuspension stabilization, miniaturization and transformation into solid products. Int J Pharm. 2008;364:64–75.