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ORIGINAL ARTICLE

Development of nanostructured lipid carrier (NLC) assisted with polysorbate nonionic surfactants as a carrier for L-ascorbic acid and Gold Tri.E 30

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Abstract Lipid nanocarrier displays the advantages over conventional drug carriers as they are formulated with biodegradable and non-irritant lipids. However, the main drawbacks are the agglomeration of lipid particles, instability over storage, low drug loading, and the burst release of active ingredients. In this study, we investigated the effects of various polysorbate nonionic surfactants namely Tween 20, 40, 60, or 80 on the nanostructured lipid carrier (NLC). NLC incorporated with polysorbate nonionic surfactant was prepared by using high-pressure homogenization technique. The average size was reduced to 139.9 ± 15.8 nm in the presence of Tween 80 and remained stable in nano-size even incubated for 28 days. Encapsulation of L-ascorbic acid or Gold Tri.E 30 showed a high encapsulation efficiency of more than 75%, where the highest was Gold Tri.E in the presence of Tween 60 at 99.7%. In vitro release study showed that the release of both L-ascorbic acid and Gold Tri.E was significantly reduced in NLC with Tween as compared to bare active ingredients and NLC without Tween. In conclusion, the incorporation of Tween successfully produced a lipid nanocarrier that has the potential to be developed as a carrier of various active ingredients such as nutrients, extracts, and drugs.

Keywords Nanostructured lipid carrier · Polysorbate nonionic surfactant · TWEEN · Vitamin · In-vitro release

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Introduction

Lipids are biomolecules that are widely used as food ingredients. Lipid can be categorized as fatty acids, glycerolipids, phospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids, and polyketides. Fundamental understanding of the chemistry and physicochemical properties of the amphiphilic properties of lipids enabled scientists to formulate various lipid-based carriers such as nano and microemulsion (Abbasi and Radi 2016; Raikos 2017), liposome (Amiri et al. 2018), and lipid nanocarriers such as solid lipid nanoparticles (SLN) (Weber et al. 2014) and nanostructured lipid carrier (NLC) (Han et al. 2016; Pardeike et al. 2016; Pornputtapitak et al. 2018). NLC is a second generation of lipid nanocarriers, which developed to overcome disadvantages of traditional lipid carriers such as short shelf life, poor stability, low encapsulation efficacy, and solvent dependent (Czajkowska-Kośnik et al. 2019; Ling et al. 2019). NLC is characterized by a less organized structure, which allows for higher loading capacity and more active ingredients stability during storage (Han et al. 2016; Müller et al. 2016; Czajkowska-Kośnik et al. 2019) and can be used for oral delivery (Talegaonkar and Bhattacharyya 2019). Many research had been done to encapsulate lipophilic nutrients such as vitamin A (Pezeshki et al. 2014), vitamin D (Sabzichi et al. 2017), and vitamin E (Vaz et al. 2019).

NLC can be prepared by using high-pressure homogenization (HPH) technique (Czajkowska-Kośnik et al. 2019) due to the ease in preparation and short production period (Mitri et al. 2011) with the aim of future scaling up. NLC is formulated from the mixture of solid and liquid lipids, dispersed in the aqueous phase. However, the particles tend to agglomerate and less stable. The surfactant such as lecithin (Woo et al. 2014), poloxamers (Yu et al. 2018),

and polysorbates (Akbari et al. 2015; Wei et al. 2018) are alternative for stabilizing the NLC dispersion. In this study, NLC was prepared from the mixture of oleic acid and stearic acid, then stabilized with polysorbate nonionic surfactants, namely Tween 20, 40, 60, or 80, which widely used as an emulsifier in the food industry. The physicochemical properties of NLC affected by the presence of each Tween were analyzed.

Hydrophilic nutrient, namely L-ascorbic acid, and lipophilic nutrient, namely Gold Tri.E 30, were used as a model for encapsulating and delivering the nutrients to the body. This also aims to protect the nutrients from degradation, simultaneously enhancing the stability of nutrients that sensitive to light, oxidation, and hydrolysis as well as enabling modulation of nutrients release. L-ascorbic acid is in the vitamin C family, which is an essential nutrient involved in the repair of tissue and the enzymatic production of certain neurotransmitters. Gold Tri.E 30 is a tocotrienol in Vitamin E family that extracted from palm fruit (*Elaeis Guineensis*) by Sime Darby Plantation Sdn. Bhd. It is usually used to reduce arterial blockage, lowering bad cholesterols, poses anti-aging effect, and protect from ultraviolet (UV) light, radiation, ozone and other forms of pollution from the environment. Information on the preparation, development, and physicochemical properties of NLC can be used as a model for the for delivering the other nutrients, plant extracts (Pornputtapitak et al. 2018; Wei et al. 2018), anti microbes (Ling et al. 2019), or drugs for gene therapy (Han et al. 2016).

Materials and methods

Material

Technical grade oleic acid (*cis*-9-octadecenoic acid) (Belgium) and Tween® 20 (Switzerland) were purchased from Fluka. Reagent grade stearic acid (Malaysia), Tween® 40 (USA), Tween® 60 (USA), and Tween® 80 (France) were purchased from Sigma-Aldrich. L-ascorbic acid FCC (vitamin C) (Germany) was purchased from SAFC™, while Gold Tri.E 30 Powder (vitamin E) was provided by Sime Darby Plantation Sdn. Bhd., Malaysia. Phosphate buffered saline tablets (USA) was purchased from Spectrum Chemical MFG. and ethanol absolute for analysis EMSURE (United Kingdom) was purchased from Merck. All solutions were prepared at 30 ± 1 °C using 18.2 MΩ cm deionized water Barnstead NANO pure® Diamond™ ultrapure water system.

Preparation of nanostructured lipid carrier (NLC)

NLC was prepared by a hot homogenization method paired with high-pressure homogenization (HPH) (Woo et al. 2014; Czajkowska-Kośnik et al. 2019). Lipid phase, which is stearic acid and oleic acid were heated separately from an aqueous phase which was the Tween solution, for 15 min at 80 °C using Lauda E2000 water bath (USA) until the mixture became a clear gel. The aqueous phase was added slowly into the lipid phase under strong agitation of 15,000 rpm at 80 °C for 5 min by using Heidolph Silent Crusher homogenizer (Germany). The hot emulsion solution was solidified in cold water at 2 °C under magnetic stirring by Harmony Hot Plate stirrer HTS1003 (Japan). The NLC dispersions were incubated at 8 °C in LCF402-30 Linden Refrigerator (USA).

Optical polarizing microscope (OPM)

The size, dispersity, and morphology of NLC were observed using Leica DM RXP light polarizing microscope (Germany) in the Colloid Laboratory, Department of Chemistry, UM. The NLC was spiked on a clean glass slide, covered with a coverslip, and followed with a drop of immersion oil on the coverslip. Three replications have been done to observed the distribution of the particles. The presence of NLC was observed at 50 × magnification using Leica QWin image analysis software.

Field emission scanning electron microscopy (FESEM)

Micrographs were taken and analyzed using FESEM-EDX model SU8220 (Hitachi, Japan). Two hundred µl of sample is carefully dropped on the 400 mesh copper-coated carbon grid and the excess solution was discarded with a clean filter paper. The samples were then dried in a desiccator for 24 h. The copper-coated carbon grid with the samples was carefully placed on the conductive adhesive tape at the specimen stub and viewed at 2.0 kV.

Average particle size and zeta potential

The average particle size and zeta potential of NLC were measured using Malvern Zetasizer NanoZS (United Kingdom). NLC solution was diluted by the factor of 50 to avoid multiple scatterings of the light caused by a high concentration of particles (Almeida et al. 2017). The sample was carefully introduced into the gold plated U-shape capillary cells using disposable Pasteur pipettes. The average particle size and zeta potential of NLC dispersion were measured using the pre-set SOP at 25 ± 1 °C in triplicates. The storage stability curves of NLC stored at 8 °C was observed by measuring the particle size and zeta potential of dispersion every 7 days for 28 days.

Encapsulation efficiency (%)

The encapsulation efficiency of NLC was quantified by using the Sartorius Stedim 10 kDa Molecular Weight Cut-off (MWCO) Vivaspin (Belgium). The solution of L-ascorbic acid or Gold Tri.E 30 was added to the emulsion before the cold emulsification steps. The free L-ascorbic acid or Gold Tri.E 30 was eliminated from the solution with the aid of Dynamica Scientific Velocity 18R refrigerated centrifuge at 8000 rpm 25 ± 1 °C for 30 min (Woo et al. 2014; Boakye et al. 2015). The UV absorbance of the free L-ascorbic acid at 268 nm or Gold Tri.E 30 at 227 nm was measured using an Agilent UV–VIS spectrophotometer (USA) in triplicates at room temperature. The encapsulation efficiency (%EE) of NLC was calculated using the equation $\%EE = [100 - (100F/T)]$, where F is the amount of free L-ascorbic acid or Gold Tri.E 30, and T is the total amount of L-ascorbic acid or Gold Tri.E 30 added into the formulation.

Determination of in vitro release

In-vitro release of L-ascorbic acid or Gold Tri.E 30 from NLC was determined by using an automated Hanson Research Franz Diffusion Cell System (USA). Five kDa MWCO Cellulose dialysis membranes was then placed on top of the receptor chamber. One mL of NLC encapsulating L-ascorbic acid or Gold Tri.E 30 was introduced into the donor chambers. The media were collected at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, and 24 h, with stirring of 400 rpm at 37 °C. The absorbance of the eluent was quantified by UV–VIS spectrophotometer and compared to the calibration curve. In-vitro release mechanisms were then analyzed by using the add-in program for modeling and comparison of dissolution profiles, namely DDSolver (Zhang et al. 2010).

Results and discussion

Morphological observation

Light phase OPM was used due to the NLC was optically inactive in dark phase OPM (Placzek and Kosela 2016) while FESEM was further used due to its ability to provide topographical and elemental information with unlimited depth of field.

The OPM of one-day-old NLC revealed the presence of spherical particles in the dispersions (Fig. 1). Without the presence of Tween, the particles were large and agglomerated. Incorporation of Tween induced the crystallization that promoted self-assembly properties and reduced the agglomeration of NLC, where more single particles of NLC were observed (Ariyaprakai et al. 2013; Uvanesh et al. 2016). The formation of individual particles NLC was significantly increased in the presence of Tween 40 and 60. However, the micrograph of NLC with Tween 80 displayed agglomeration of NLC particles that may promote the fusion of the particles to form larger NLC particles. This explains the significant increase of size upon the incubation period as shown in Fig. 3 due to the bulky long-chain of Tween 80 induced the agglomeration of NLC.

Further observation via FESEM confirms the formation of less organized spherical particles, which allows higher loading capacity and more active ingredients stability during storage as depicted in Fig. 2. Incorporation of the Tween series promoted the formation of more individually spherical shape particles. Agglomeration of particles in the presence of Tween 80 was observed, which was agreeable with the OPM micrograph.

Zeta potential and average particle size

The surfactant has proved to be critical in stabilizing the NLC (Wei et al. 2019). The zeta potential of NLC without Tween was measured to be a negative surface charge with the potential of −36.9 ± 2.9 mV. Incorporation of Tween in the formulations affected the zeta potential of NLC by providing the shielding effect to the particles, where the lowest zeta potential was found in Tween 40 at −43.2 ± 0.8 mV (Sazalee et al. 2017) as shown in Table 1. Comparing to all formulation, Tween 80 gave the less negative zeta potential, which might explain the agglomeration of the particle as shown in Figs. 1 and 2.

The average particle size of NLC was measured by using a dynamic light scattering technique as they undergo Brownian motion (Anderson et al. 2013). The average particle size of one-day-old NLC without the Tween was 289.5 ± 24.7 nm and decrease gradually with the addition of Tween in the formulation as surfactant will reduce the interfacial tension between oil/water, hence promote the formation of smaller droplets (Ariyaprakai et al. 2013) as presented in Fig. 3. The average particle size for formulation incorporated with Tween 20, 40, 60, and 80 were 277.1 ± 97.8, 190.2 ± 53.2, 149.6 ± 42.8, and 139.9 ± 15.8, respectively. The average particle size was reduced the most, when Tween 80 was used, which was 51.7%. This was maybe due to the bend and kink at the double bond of monooleate in Tween 80, which increase the curvature of the NLC particles (Teo et al. 2011). Through the 28 days of the incubation period, all NLC formulations showed an increase in the average particle size. This is maybe due to the sedimentation, aggregation or flocculation of the particles (Li et al. 2015). Without Tween, the average particle size of NLC was 474.5% increased to 1663.2 ± 320.1 nm. A high standard deviation was observed may be due to the rupture of the

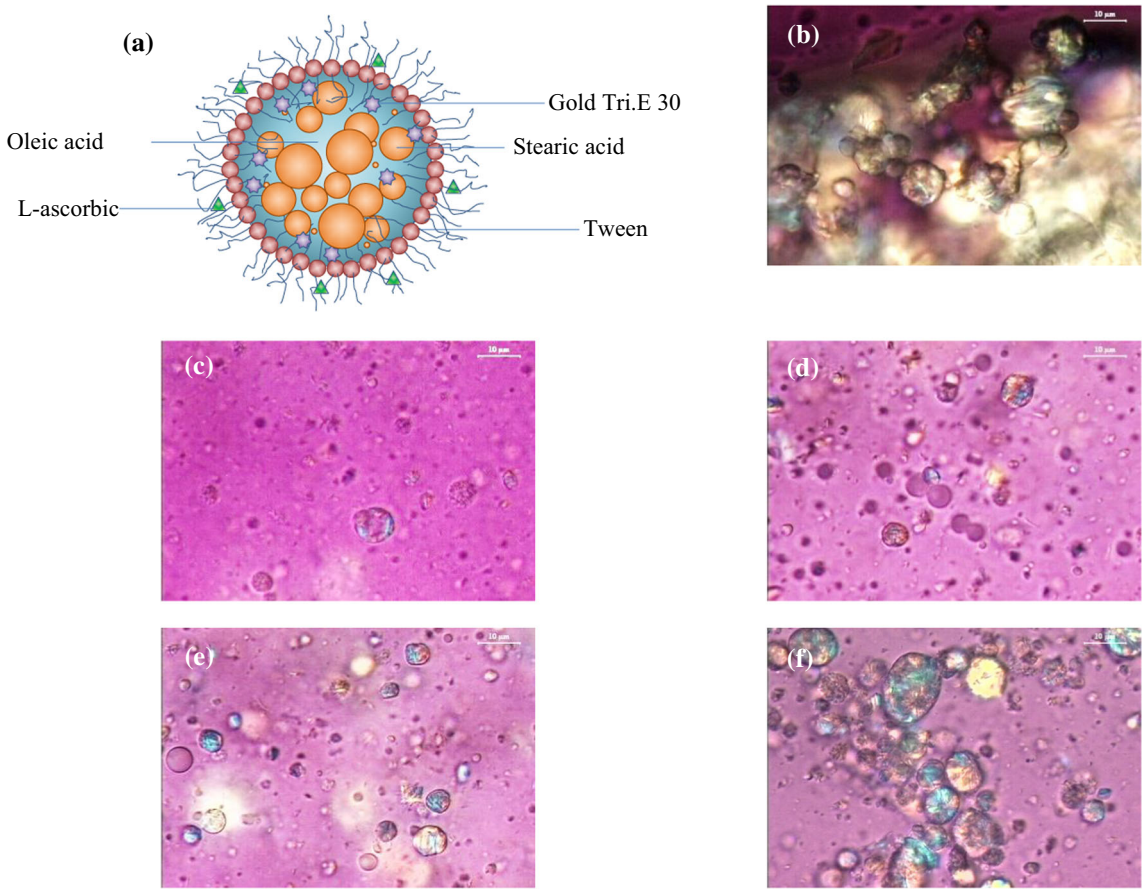

Fig. 1 Schematic diagram of nanostructured lipid carrier (**a**) and light phase optical polarizing micrograph with a scale of 20 μm at room temperature of nanostructured lipid carrier without (**b**) and with Tween 20 (**c**), 40 (**d**), 60 (**e**), or 80 (**f**)

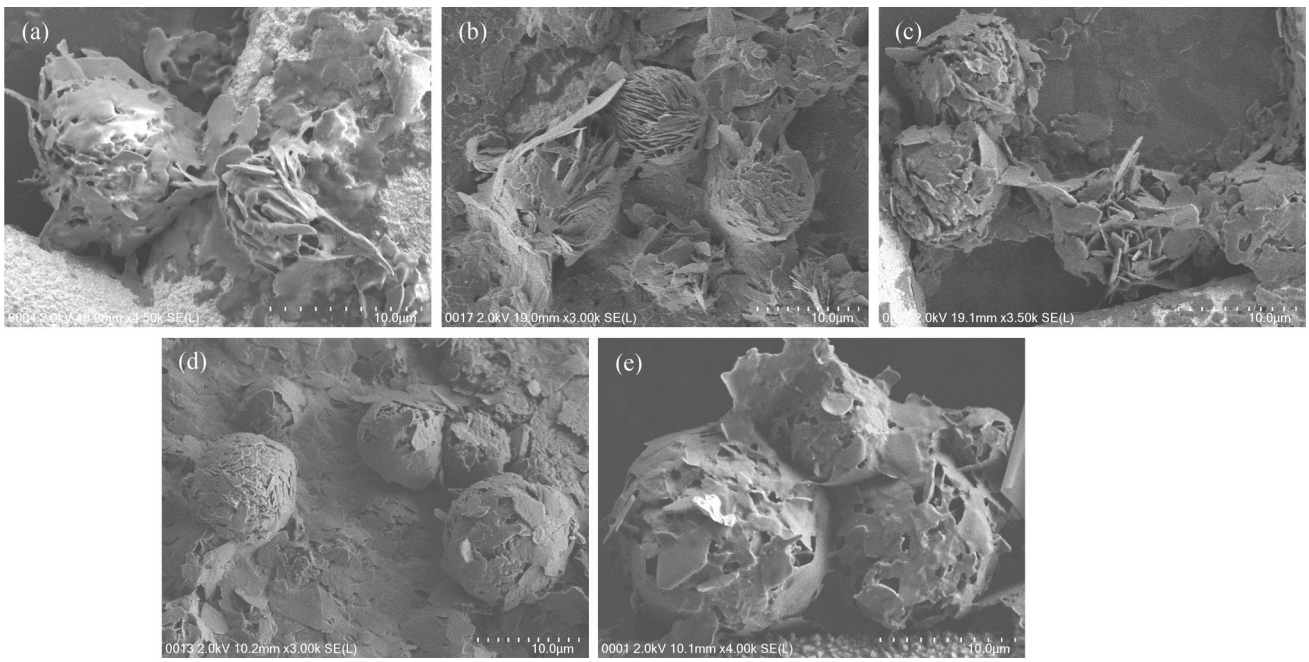

Fig. 2 Field emission scanning electron microscopy (FESEM) micrograph of nanostructured lipid carrier without (**a**) and with Tween 20 (**b**), 40 (**c**), 60 (**d**), or 80 (**e**) at room temperature. The scale was 10.0 μm

Table 1 Average data from the triplicates measurement of zeta potential, mobility, and conductivity of one-day-old nanostructured lipid carrier (NLC) at 25 °C

Nanostructured lipid carrier (NLC)	Zeta potential (mV)	Mobility (μmcm Vs^{-1})	Conductivity (mS cm^{-1})
No Tween	− 36.9 ± 2.9	− 2.9 ± 0.2	0.02 ± 0.01
Tween 20	− 34.5 ± 0.5	− 2.7 ± 0.0	0.01 ± 0.01
Tween 40	− 43.2 ± 0.8	− 3.4 ± 0.1	0.02 ± 0.01
Tween 60	− 37.5 ± 1.1	− 2.9 ± 0.1	0.01 ± 0.01
Tween 80	− 31.9 ± 1.9	− 2.5 ± 0.2	0.01 ± 0.00

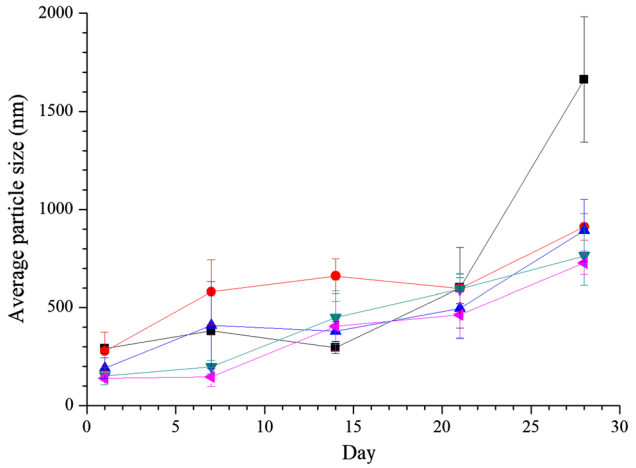

Fig. 3 Average particle size of nanostructured lipid carrier without Tween (■) and nanostructured lipid carrier incorporated with Tween 20 (●), 40 (▲), 60 (▼), or 80 (◀). The data is the average of triplicates (colour figure online)

aggregated particle and producing particles of varied size. The percentage of increase in the average particle size of NLC was lowest in Tween 20 at 228.8% and highest in Tween 80 at 420.0%. The increment was 369.5% in Tween 40 and 410.2% in Tween 60. This showed that the stability of NLC has improved with the incorporation of Tween because the surfactant will protect the droplets from aggregated and fused (Ariyaprakai et al. 2013). However, the stability was reduced gradually from Tween 20 to Tween 40, 60, and 80, which may be due to the increase in the polymeric chain that induced the flocculation through their strong van der Waals interactions (Tolpekin et al. 2004).

Encapsulation efficiency (%EE)

More than 70% of L-ascorbic acid and Gold Tri.E 30 have been encapsulated in NLC as shown in Fig. 4. Without the presence of Tween, the %EE of L-ascorbic acid was 70.5%

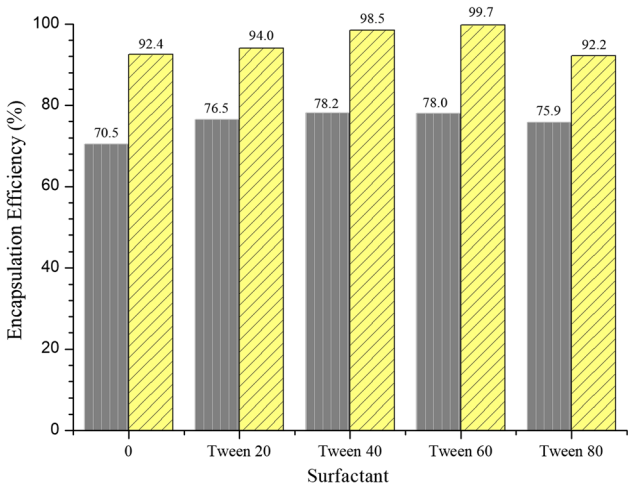

Fig. 4 Encapsulation Efficiency of L-ascorbic acid ( ) and Gold Tri.E 30 ( ) in nanostructured lipid carrier (NLC). The data is the average of triplicates with a standard deviation of less than 1 (colour figure online)

and Gold Tri.E 30 at 92.4%. The %EE was enhanced with the incorporation of Tween. The %EE of L-ascorbic acid was highest in Tween 40, which was 78.2%, followed by Tween 60, 20, and 80 at 77.9, 76.6, and 75.9%, respectively. The %EE of Gold Tri.E 30 was increased by 7.8% to the highest %EE in Tween 60 of 99.7%. However, the %EE in formulation with Tween 80 showed a drop of 0.3%, maybe due to their small particle size that limits the loading of active ingredients. Generally, the %EE of Gold Tri.E 30 was higher as compared to L-ascorbic acid in all formulations, showing that NLC was more suitable for lipophilic active ingredients because lipophilic active ingredients will be strongly trapped in the core of NLC (Beloqui et al. 2016).

In vitro release

Evaluation of the in vitro release of active ingredients provides the information on the efficacy of the engineered carrier. The in vitro release of L-ascorbic acid and Gold Tri.E 30 in the media for 24 h was reported in Fig. 5. The release of bare hydrophilic L-ascorbic acid was higher as compared to bare lipophilic Gold Tri.E 30, which was 67.4 and 60.0%, respectively. The release curve showed that the bare L-ascorbic acid was gradually released and the magnitude of release was reduced after the 12th hours. However, bare lipophilic Gold Tri.E 30 displayed a gradual release, followed by a sudden increase after the 8th hours.

Incorporation of L-ascorbic acid or Gold Tri.E 30 in the NLC has significantly reduced the cumulative release after 24 h for both active ingredients. Without Tween, the cumulative in vitro release for L-ascorbic acid or Gold Tri.E 30 was 18.7 and 3.7%, respectively. Incorporation of

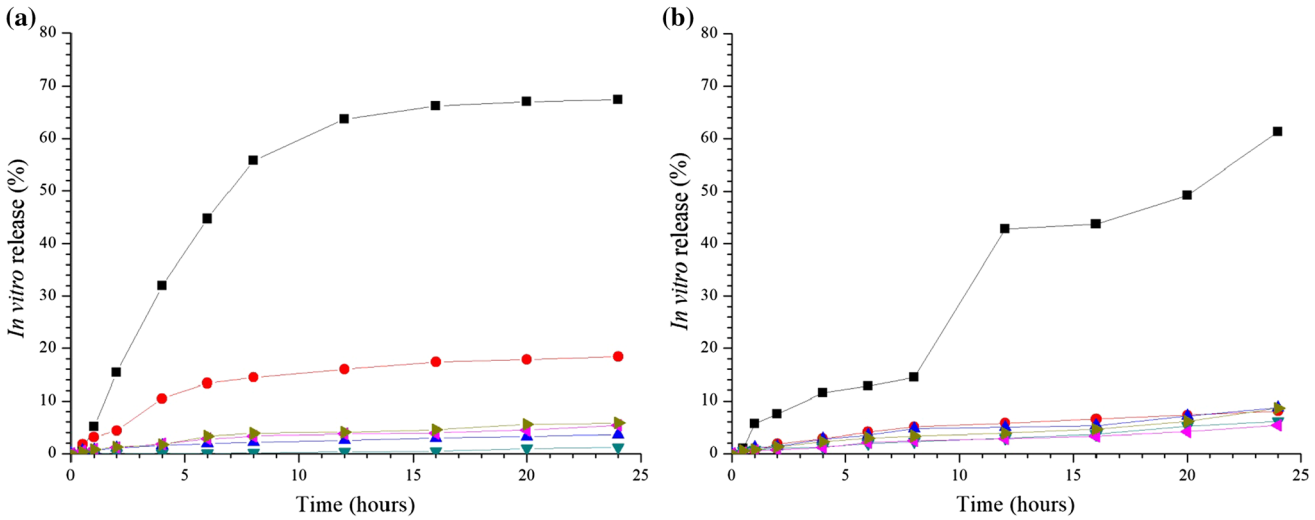

Fig. 5 In vitro release of L-ascorbic acid (**a**) and Gold Tri.E 30 (**b**) from nanostructured lipid carrier without Tween ( ), nanostructured lipid carrier incorporated with Tween 20 ( ), 40 ( ), 60 ( ), or 80 ( ), and bare active ingredient ( ) at 37 °C. The data is the average of triplicates with a standard deviation of less than 1 (colour figure online)

Tween further suppressed the release of both active ingredients, which the lowest was in Tween 40 for L-ascorbic acid and Tween 60 for Gold Tri.E 30, at 1.2 and 0.8%, respectively. This showed that the presence of Tween in the formulations enhance the controlled release properties of NLC by producing the highly ordered and compacted nanostructures (Wei et al. 2019).

The release kinetics, drug diffusion coefficient, and model fitting of L-ascorbic acid or Gold Tri.E 30 from NLC were determined by using mathematical modeling, namely DDSolver (Dash et al. 2010; Zhang et al. 2010). Table 2

Table 2 Average release constant (k), regression coefficient (R_{sqr}), and mean squared error (MSE) of the in vitro release of L-ascorbic acid and Gold Tri.E 30 fitted to drug dissolution model by DDSolver. AI is the bare active ingredient. The measurements were done in triplicates

Drug dissolution model		L-ascorbic acid						Gold Tri.E 30					
		AI	No Tween	Tween 20	Tween 40	Tween 60	Tween 80	AI	No Tween	Tween 20	Tween 40	Tween 60	Tween 80
Zero order	k_0	3.78	1.01	0.18	0.04	0.25	0.29	2.62	0.40	0.38	0.26	0.23	0.34
	R_{sqr}	0.62	0.45	0.62	0.88	0.73	0.78	0.95	0.81	0.88	0.97	0.93	0.92
	MSE	274.11	22.57	0.43	0.02	0.73	0.85	23.39	1.44	0.89	0.11	0.18	0.48
First order	k_1	0.07	0.01	0.00	0.00	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.00
	R_{sqr}	0.90	0.53	0.63	0.88	0.74	0.79	0.94	0.83	0.89	0.97	0.94	0.93
	MSE	70.78	19.17	0.41	0.02	0.70	0.81	26.59	1.31	0.82	0.11	0.17	0.47
Higuchi	k_H	15.77	4.28	0.75	0.15	1.05	1.18	10.22	1.63	1.54	1.01	0.90	1.35
	R_{sqr}	0.90	0.91	1.00	0.63	0.97	0.96	0.82	0.96	0.93	0.88	0.92	0.88
	MSE	70.29	3.65	0.00	0.06	0.07	0.16	83.36	0.28	0.51	0.43	0.22	0.75
Korsmeyer-Peppas	k_{KP}	15.48	4.98	0.80	0.00	0.98	1.00	3.11	1.30	1.01	0.39	0.49	0.64
	R_{sqr}	0.90	0.92	1.00	0.98	0.97	0.97	0.95	0.98	0.96	0.98	0.98	0.95
	MSE	79.00	3.67	0.00	0.00	0.08	0.15	25.55	0.21	0.30	0.08	0.07	0.37
Hixson-Crowel	k_{HC}	0.02	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00
	R_{sqr}	0.84	0.51	0.63	0.88	0.73	0.79	0.95	0.82	0.89	0.97	0.94	0.93
	MSE	115.52	20.27	0.42	0.02	0.71	0.82	23.43	1.35	0.84	0.11	0.17	0.47
Gompertz	α	2.83	3.18	4.91	14.26	4.76	4.79	10.17	4.57	4.86	6.13	5.66	5.42
	β	1.59	0.49	0.28	0.85	0.34	0.38	2.12	0.44	0.47	0.55	0.45	0.53
	R_{sqr}	0.89	0.96	1.00	0.97	0.98	0.98	0.94	0.99	0.96	0.96	0.97	0.93
	MSE	10.24	2.04	0.00	0.01	0.06	0.11	31.52	0.09	0.32	0.17	0.09	0.54

shows the release constant (k), regression coefficient (R_{sqr}), and mean squared error (MSE) of L-ascorbic acid and Gold Tri.E 30 generated by DDSolver. The R_{sqr} of L-ascorbic acid was at 0.90 in the first order, Higuchi, and Korsmeyer-Peppas, dissolution model. However, it is most suitable for the first order dissolution model, which is normally used to describe the release of the water-soluble molecule (Costa and Lobo 2001). Gold Tri.E 30 gave out the highest R_{sqr} of 0.95 in zero-order, Korsmeyer-Peppas, and Hixson-Crowell dissolution model, but the zero-order dissolution model is most suitable as it is used to explain the release of molecules that less soluble and released slowly. Upon incorporation in NLC, the R_{sqr} was more than 0.93 in Gompertz and Korsmeyer-Peppas dissolution model. This model was normally used to describe the release of molecules from polymeric molecules that having an intermediate release rate or involved many steps of release (Dash et al. 2010). This shows that the release of L-ascorbic acid and Gold Tri.E 30 were controlled by the NLC and fitted to the Gompertz and Korsmeyer-Peppas dissolution model.

Conclusion

This work demonstrates the effect of polysorbate nonionic surfactants namely Tween 20, 40, 60, or 80 on the physicochemical properties of nanostructured lipid carriers (NLC). Incorporation of Tween improved the self-assembly of NLC, where Tween 60 appears as the best surfactant for stabilizing oleic acid-stearic acid NLC, with the average particle size of 149.6 ± 42.8 nm and stable over 28 days. Encapsulation of Gold Tri.E 30 yielded a higher %EE of 99.7% as compared to L-ascorbic acid at 78.0%. In vitro release of Gold Tri.E 30 and L-ascorbic acid was significantly reduced in the presence of Tween. We anticipate that this work will contribute to the development of the carrier that prolongs the shelf-life and enhances the delivery of the essential nutrients, as well as potentially produced in a large scale production.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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