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Lipid-based nanosystems as carriers increasing the potential of selected berry polyphenol representatives

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Abstract
The aim of the study was to obtain stable systems of lipid-based nanocarriers (SLN, NLC, HA-NLC, liposomes) with a selected berry polyphenol – quercetin as an active ingredient. Lipid-based nanosystems were obtained using ultrasonification technique. The stability was assessed by macro- and microscopic observation and viscosity measurements. The physicochemical properties of both incorporated and non-incorporated carriers were examined with dynamic light scattering technique (DLS). In vitro release studies of quercetin were performed using cellulose membrane and the mixture of PBS/ethanol as an acceptor solution. The lowest average particle size was achieved for the traditional NLC formulation and ranged between 126.5 ± 1.6 nm for unloaded and 138.7 ± 1.0 nm for NLC with quercetin. Release study of the active ingredient from optimal lipid-based nanocarriers indicated its prolonged and controlled release profile. On this basis, a mathematical model that best describes the kinetics of the active substance release from the tested carriers was fitted. According to the results, the best fit of quercetin release from examined nanocarriers was obtained for the Higuchi model. The conducted research gave promising results allowing to conclude that the obtained lipid-based nanosystems may be potential carriers for quercetin which possess a therapeutic effect in the treatment of skin disorders.

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1. INTRODUCTION

Polyphenols are naturally occurring phytochemicals from a group of secondary metabolites found in all vascular plants and establish a large unit of at least 10,000 unique compounds, which from the structural point of view are characterized by an aromatic ring with one or more hydroxyl groups. According to chemical structure, polyphenols are classified as flavonoids (flavonols, flavones, flavonones, anthocyanidins, catechins, chalcones), phenolic acids, stilbenes, lignans, curcuminoids and tanins (Li et al., 2014; Brglez Mojzer et al., 2016).

Up to date, polyphenols have gained remarkable attention among pharmaceutical, food and cosmetic industries due to their beneficial effects in the protection and prevention of several diseases, which is the result of numerous studies of their health-promoting properties (Pimentel-Moral et al., 2018). While their use in cosmetic industries is largely documented, several environmental conditions such as light, temperature or oxygen may affect the physicochemical stability of polyphenols. Furthermore, their incorporation into traditional cosmetic products may cause quality issues like browning reactions resulting in undesirable colour changes or complexation reaction with other cosmetic ingredients (Munin and Edwards-Lévy, 2011; Pimentel-Moral et al., 2018). To overcome these limitations, the loading of polyphenols into appropriately structured carriers has been proposed aiming at both increasing their bioavailability and reducing possible side effects.

There are a wide variety of delivery systems for encapsulation of polyphenolic ingredients that have been largely described and among them lipid-based nanosystems take a special place (Forbes-Hernández, 2020). Lipid-based nanosystems offer several advantages, like the possibility of improving the stability of the incorporated compounds and their interaction with the skin, enabling a modulated release action, increasing bioavailability of active, especially hydrophobic, labile molecules. These systems may also improve organoleptic and functional properties, and in addition to this, they consist of compounds with GRAS (Generally Recognized as Safe) status for topical administration (Brugè, 2015). Lipid nanocarriers used so far for encapsulation of polyphenols include emulsions, liposomes, phytosomes, solid lipid nanoparticles (SLN), nanostructured lipid carrier (NLC) and hybrid/grafted lipid nanoparticles (Pimentel-Moral et al., 2018).

The cosmetic and pharmaceutical industries have recognized cutaneous delivery of berry polyphenols as one of the most promising distribution routes. This way of polyphenol administration provides continuous and gradual release at the site of action, which alleviates some of the disadvantages associated with oral drug delivery, including poor bioavailability, metabolic interactions, and cytotoxicity (Farhan, 2024). It also has to be considered that healthy skin has a strong defence against drug penetration, thanks to its unique lipid composition and stratum corneum tissue (Liu et al., 2023). That is the way in order to increase the solubility and bioavailability

of berry polyphenols and to provide site-specific drug delivery with improved pharmacokinetic properties, taking skin structure into account. The development of nanoengineered lipid-based delivery systems is urgently required.

Topical and transdermal delivery of berry polyphenols may provide clinical benefits for certain skin diseases and conditions such as various types of inflammation, wounds, burns, premature skin ageing and even skin cancer (Nagula and Wairkar, 2019). Quercetin (QC) is considered one of the most important berry polyphenols with broad therapeutic potential and is found in numerous plants (de Barros et al., 2022). The basic structure of quercetin consists of two aromatic rings – A and B – and a heterocyclic ring connecting both rings (Figure 1) (Eid and Haddad, 2017). Various studies have stated that the presence of multiple hydroxyl groups, placed at the C 3-,3-',4-',5-, and 7-positions in quercetin may be responsible for its biological activity (Wadhwa et al., 2022).

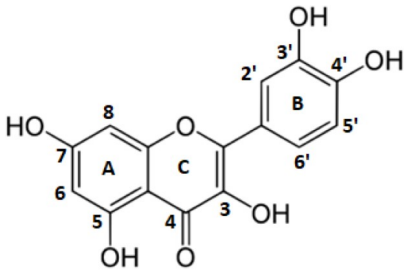


Figure 1. Chemical structure of quercetin.

Quercetin possesses a variety of physiological properties, including antioxidant and anti-inflammatory effects attributed to its ability to neutralize free radicals and block inflammatory mediators, antiaging and antibacterial action as well as anticancer promising therapeutic application (Mallya and Patil, 2021; Nguyen and Bhattacharya, 2022; Yang et al., 2020). In addition, quercetin has also achieved GRAS status by the United States Food and Drug Administration (Magar and Sohng, 2020).

The principal aim of this study was to prepare QC-loaded lipid-based nanosystems (SLN, NLC, and liposome) as long-term stable carriers for the quercetin topical delivery. The applicability of the QC-loaded formulations was illustrated by comprehensive characterization of the carriers. The release profile of the active agent was investigated along with the physicochemical properties of QC-nanocarriers.

2. MATERIALS AND METHODS

2.1. Materials

The active ingredient quercetin (QC) was purchased from Pol-Aura Chemical Reagents, Poland. Tribehinin PEG-20 Esters (Emulium®22) used as solid lipid and medium chain triglyceryde (Myritol®312) chosen as liquid lipid were delivered by Gattefossé GmbH, Germany and BASF Chem Trade GmbH, Burgbenheim, Germany, respectively. All lipid nanocarriers were stabilized by alkylpolyglucoside surfactant (PlantaCare®2000UP), which was supplied by BASF Chem Trade GmbH, Burgbenheim, Germany. Sodium hyaluronate (Hyaluronic acid HMW) for NLC formulation modification was purchased from ECOSPA S.C., Poland. Liposome precursor, Hydrogenated Lecithin (Emulmetik™ 950), was kindly supplied by Lucas Meyer Cosmetics, France. A laboratory purified cholesterol (95%) in powder form was purchased from Alfa Aesar and 96% ethanol was purchased from P.P.H Stanlab. All reagents and solvents were of analytical grade. The ultra-purified water was freshly prepared by a MiliQ®System (Millipore, Schwalbach, Germany).

2.2. Lipid-based nanosystem preparation

All types of empty and QC-loaded lipid nanosystems (NLC, HA-NLC, SLN, liposomes) in accordance with the composition presented in Tables 1 and 2 were prepared with ultrasound homogenization method (t = 30 s, max. amplitude 89%, power 40 W) using a probe-type sonicator (Hielscher UP200Ht).

Firstly, 4 types of lipid nanosystem pre-emulsions were obtained according to the following procedures. For QC-loaded formulations the active agent was added to the lipid phase, ensuring its complete dissolution. In case of NLC pre-emulsion, the lipid phase consisting of solid and liquid lipid (in a mass ratio of 7:3) was heated to a temperature of 70 °C, which is 5 °C higher than the melting point of the solid lipid. The aqueous phase with an adequate concentration of the surfactant was heated to the same temperature and added to the melted oil phase, under magnetic stirring, with 400 rpm, for 5 min (IKA®C-MAG HS 7). For NLC modified with hyaluronic acid (HA), samples were prepared by introducing a 0.1% (w/w) hyaluronic acid solution, previously prepared by dissolving sodium hyaluronate in deionized water, into ready-made NLC dispersions. SLN pre-emulsion was prepared in a similar manner to NLC with the difference that lipid phase consisted of the solid lipid only. In case of liposomes, the lipid phase consisting of lecithin and cholesterol was dissolved in ethanol and heated to 50 °C and next combined with the surfactant aqueous solution at the same temperature under stirring continuously (5 min, 400 rpm).

2.3. Characterization of lipid-based nanosystems

2.3.1. Stability study

The stability of all formulations was firstly evaluated by macroscopic observation which allowed to determine the occurrence of destabilization processes such as coalescence or creaming. Coalescence occurs when separate oil droplets merge into a single larger oil droplet because surfactant monolayers fuse

Table 1. The composition of loaded and unloaded lipid-based nanosystems (NLC, modified NLC and SLN).

Sample name	Solid lipid	Liquid lipid	Surfactant	0.1% HA solution [% wt.]	Active compound	Water [%wt.]
	Emulium®22 [% wt.]	Myritol® 318 [% wt.]	Plantacare® 2000 UP [% wt.]		Quercetin [% wt.]	
NLC1	7.0	3.0	4.0	–	–	q.s.
NLC5	7.0	3.0	4.0	25.0	–	q.s.
SLN1	10.0	–	4.0	–	–	q.s.
NLCQ1	7.0	3.0	4.0	–	0.05	q.s.
NLCQ5	7.0	3.0	4.0	25.0	0.05	q.s.
SLNQ1	10.0	–	4.0	–	0.05	q.s.

Table 2. The composition of loaded and unloaded liposomes.

Sample name	Lectin	Cholesterol [% wt.]	Ethanol [% wt.]	Surfactant	Active compound	Water [%wt.]
	Emulmetik™ 950 [% wt.]			Plantacare® 2000 UP [% wt.]	Quercetin [% wt.]	
L3	3.6	0.4	6.0	4.0	–	q.s.
NLC5LQ3	3.6	0.4	6.0	4.0	0.05	q.s.

together. Co-joined droplets form clusters that precipitate with enough time, produce creaming and later on they lead to complete phase separation. The samples were checked during storage at room temperature for 30 days. Light microscopy is an important procedure to know if the relatively larger moieties detected during particle size analysis by dynamic light scattering technique (DLS) are really particles or agglomerates of nanosized particles as well as solid lipid crystal formations. A Motic B1 Series optical microscope, equipped with a camera was used to observe structural changes of the formulations during storage time.

2.3.2. Particle size and polydispersity index

Following macro- and microscopic stability studies, the most promising formulations were selected and further investigated. The particle size (Z-ave) and polydispersity index (PDI) for optimal nanosystems were determined using dynamic light scattering technique (Zetasizer Nano ZS, Malvern Instruments Ltd., UK), at a fixed angle of 173°, and a temperature of 25 °C. The formulation samples were analysed after appropriate dilution with double-distilled water to generate a suitable scattering intensity. For each sample the measurements were carried out in triplicate and average values of the parameters and standard deviation were calculated.

2.3.3. Rheological measurement

Viscosity measurements of NLC, SLN and liposome samples were performed using a Brookfield Rheometer Model – R/S plus, equipped with a cone and plate type measuring system (cone C75-1). The measurements were carried out three times for each formulation, in the shear rate range of 1–1000 s^{-1}, at 25 °C, for 60 seconds. Each time, a 2 cm^3 sample of the formulation was placed on the measuring plate.

2.4. In vitro release study

In vitro release behaviour of QC from lipid-based nanosystems was performed by dialysis bag method (Hanson, 1982) using Spectra/Por®Dialysis Membrane made of regenerated cellulose, of molecular weight of 6–8 kDa. Three repetitions were made for each sample. An appropriate amount of QC-loaded carrier was filled into the dialysis bag which next was placed into thermostatic dialysis chamber, containing 200 cm^3 of acceptor solution (mixture of PBS (pH = 7.4) with ethanol in a volume ratio of 65:35), maintained at 37 °C ±0.5 °C, and stirred at 200 rpm. Sink conditions were accomplished for quercetin during the performance of the dialysis. At the predetermined intervals of time, 1 cm^3 of the acceptor solution with the released active was withdrawn, and the same volume of fresh acceptor solution

was added to maintain a constant volume. The study was conducted for 24 hours. The concentration of the released QC was analyzed spectrophotometrically using a UV-VIS NanoColor Spectrophotometer (Machery–Nagel), at $\lambda = 367$ nm (Pinheiro et.al., 2020) on the basis of the previously prepared calibration curve. The amount of released quercetin from the formulation was expressed as the ratio of the amount of released substance to the total amount of incorporated active compound (0.05%wt.), as a function of time.

2.5. Kinetic release investigation

Kinetic assessment of quercetin release profiles was performed by fitting the experimental data to equations describing different kinetic orders and plotting them as the percentage of released quercetin as a function of time (zero-order equation), log percentage of the active released as a function of time (first-order equation), the percentage of released active substance as a function of the square root of time (according to the Higuchi equation) and as log of the drug released percentage as a function of the log of time (according to the Korsmeyer–Peppas equation). To determine the mechanism of the active release, the diffusional release exponent (n) was calculated (Cojocaru et al., 2015; Dash et al., 2010; Petropoulos et al., 2012). The best-fitting kinetic model was selected based on the comparison of the determination coefficient (R^2).

3. RESULTS AND DISCUSSION

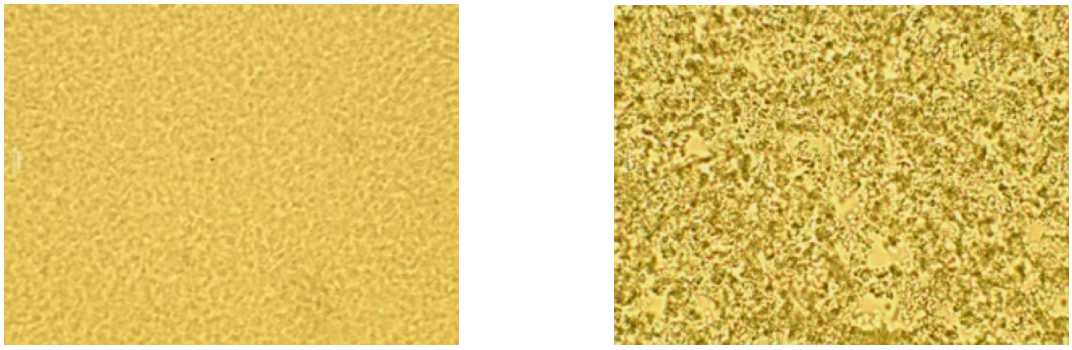
3.1. Preparation and physicochemical characterization of lipid-based nonosystems

In this research work, over a dozen unloaded lipid-based nanocarriers (NLC, SLN and liposomes) were prepared in order to find the optimal formulation for quercetin incorporation. In each of the NLC and SLN samples, the total lipid content was 10%. In case of liposomes, the ratio of lecithin to cholesterol was 90:10. Nanosystems chosen as suitable carriers for QC were formulated from biocompatible and skin-friendly materials. All dispersions appeared as milky systems, bluish after dilution.

Macroscopic observation lasting 30 days confirmed the presence of destabilization processes in some of the obtained formulations and also allowed the selection of four stable types of nanosystems (NLC, NLC modified with hyaluronic acid, SLN and liposomes). The macroscopic assessment of optimal, previously selected samples with the active was also carried out, and after 14 days, the LQ3 liposomal carrier proved to be unstable. Creaming phenomena with further phase separation appeared in the sample. In case of other samples with quercetin, no destabilization processes occurred over time.

The obtained QC loaded lipid-based nanocarriers were also examined using optical microscopy (OM) to detect roughly any presence of agglomerates or crystals. Figure 2 shows the example micrographs of stable NLC with the active (a) which is homogeneous in particle size and contain no crystals, and unstable formulation of SLN (b).

The mean particle size and PDI of empty and QC loaded lipid-based nanosystems are shown in Table 3. The particle size was statistically significant for the samples without the active and with quercetin. The lowest average particle size was achieved for the traditional NLC formulation and ranged between 126.5 ± 1.6 nm for NLC1 and 138.7 ± 1.0 nm for NLCQ1 after preparation ($T = 0$). For most samples, PDI remained at an acceptable range (<0.5) which indicated a narrow size distribution. In case of NLC modified with HA (NLC5 and NLCQ5), the PDI value after 14 days increased slightly and was above 0.5. Hyaluronic acid can increase the viscosity of the medium, which can hinder the uniform dispersion of nanoparticles and promote their agglomeration over time, leading to increased polydispersity. Similarly, larger particle size of the lipid-based systems could be attributed to the increasing viscosity, which means that more energy is needed to disintegrate the particles (Huang et al., 2017).



(a) (b)

Figure 2. Comparison of OM photographs showing the stable NLCQ1 formulation (a) after 30 days of storage with no crystals and agglomerates detected and example of unstable SLN formulation (b) after 30 days of storage, excluded from further study, with solid lipid crystals formation (magnification 100×10).

Table 3. Particle size and polydispersity index (PDI) of NLC, SLN and liposome formulations freshly prepared ($T = 0$) and after 14 days.

Sample name	$T = 0$		$T = 14$ days	
	Z-ave [nm]	PDI	Z-ave [nm]	PDI
NLC1	126.5 ± 1.6	0.186 ± 0.02	128.5 ± 1.3	0.189 ± 0.02
NLCQ1	138.7 ± 1.0	0.151 ± 0.01	140.4 ± 0.5	0.168 ± 0.01
NLC5	221.3 ± 2.3	0.445 ± 0.03	252.4 ± 6.8	0.501 ± 0.02
NLCQ5	220.8 ± 0.9	0.496 ± 0.02	261.4 ± 4.2	0.582 ± 0.01
SLN1	176.4 ± 1.4	0.375 ± 0.01	177.1 ± 2.1	0.407 ± 0.06
SLNQ1	189.0 ± 2.4	0.318 ± 0.05	195.6 ± 1.1	0.370 ± 0.01
L3	197.7 ± 0.7	0.238 ± 0.06	198.8 ± 1.2	0.247 ± 0.01
LQ3	235.68 ± 0.4	0.392 ± 0.01	unstable	

In general, nanoparticles ranging between 20 and 250 nm could assemble on skin imperfections (pores and follicles), so the actives from nanostructured lipid carriers might more closely interact with the skin, providing better drug penetration through the stratum corneum or the skin (Guo et al., 2012).

The data for freshly prepared samples ($T = 0$) and after 14 days were of close value, which confirms the stability of the systems.

3.1.1. Assessment of rheological properties

Rheological measurements are important for the characterization of lipid-based nanostructure strength. The viscosity of each sample as a function of shear rate is presented in Figure 2. Shear thinning phenomenon was observed in all samples. This thixotropic property illustrated that the obtained formulations exhibited a non-Newtonian, pseudoplastic flow character. Due to the thixotropic property, satisfactory consistency and spreadability might be obtained, which is a key factor for the formulations applied on the skin. Therefore, rheological properties, particularly viscosity, are critical parameters in characterizing lipid-based dispersions intended for topical applications (Yang et al., 2015; Zheng et al., 2013).

Analysing the viscosity curves of the investigated, incorporated and non-incorporated lipid-based systems, (Fig. 3a, 3c, 3d) a significant decrease can be noticed in the viscosity of the quercetin-loaded carriers. Comparing this combination of viscosity curves with the viscosity curves presented in Fig. 3b, quite opposite result is observed indicating a clear influence of the HA modification.

3.2. In vitro quercetin release study

The study of quercetin release from three lipid nanoparticle formulations – NLCQ1, NLCQ5 and SLNQ1 was successfully performed based on diffusion through a dialysis membrane. The ethanol addition to acceptor solution was dictated by the poor solubility of the active substance in the buffer (Talarico et al., 2021). The amount of released quercetin, expressed as weight percent ratio between concentration of the released active and the total amount of incorporated active, was reported as a function of incubation time. Each sample was analysed in triplicate.

The release profiles of quercetin are shown in Fig. 4. Drug release profiles were identical. All three formulations demonstrated limited burst release of quercetin in the initial hours, which is an exceptionally important characteristic for controlled drug delivery (Ulker Turan and Guvenilir, 2022). NLCQ1 exhibited the highest drug release rate, achieving approx. 25% cumulative release within the first 5 hours. The cumulative release values for NLCQ5 and SLNQ1 were approx. 17% and 14%, respectively, in the same time frame. The release of quercetin was retarded noticeably in later hours. A biphasic release profile was observed for all formulations. Due to the semisolid core, NLC possesses crystalline structure. A part of quercetin might be dissolved in the liquid shell composed of surfactants, while the other part might be located in the semisolid core. The high amount of quercetin dissolved in the liquid shell with a large surface area may give rise to the fast release at the initial stage and the incorporated quercetin in the semisolid core of NLC may lead to the sustained release in the later phase (Sun et al., 2014). The profile of released quercetin from the lipid-based systems is quite similar to that described in the literature (Aditya et al., 2014; Bose and Michniak-Kohn, 2013; de Barros et al., 2022).

Total drug release percentages increased by several percent and reached approx. 27%, 21.5% and 20% for NLCQ1, NLCQ5 and SLNQ1, respectively. Release trends for NLCQ1 and NLCQ5 appeared quite similar but NLCQ1 with a smaller particle size and consequently high surface area showed rapid and higher release rates. Additionally, the observed difference between release profiles could be related to the viscosity of the formulations. The NLCQ1 system is less viscous than the HA modified NLCQ5.

The NLCQ1 formulation provides a more sustained release of quercetin throughout the study, suggesting that it may be more effective in sustained delivery of the active ingredient. The slow release of QC potentially minimizes the active's negative side effects and protects the chemical stability of the bioactive compound.

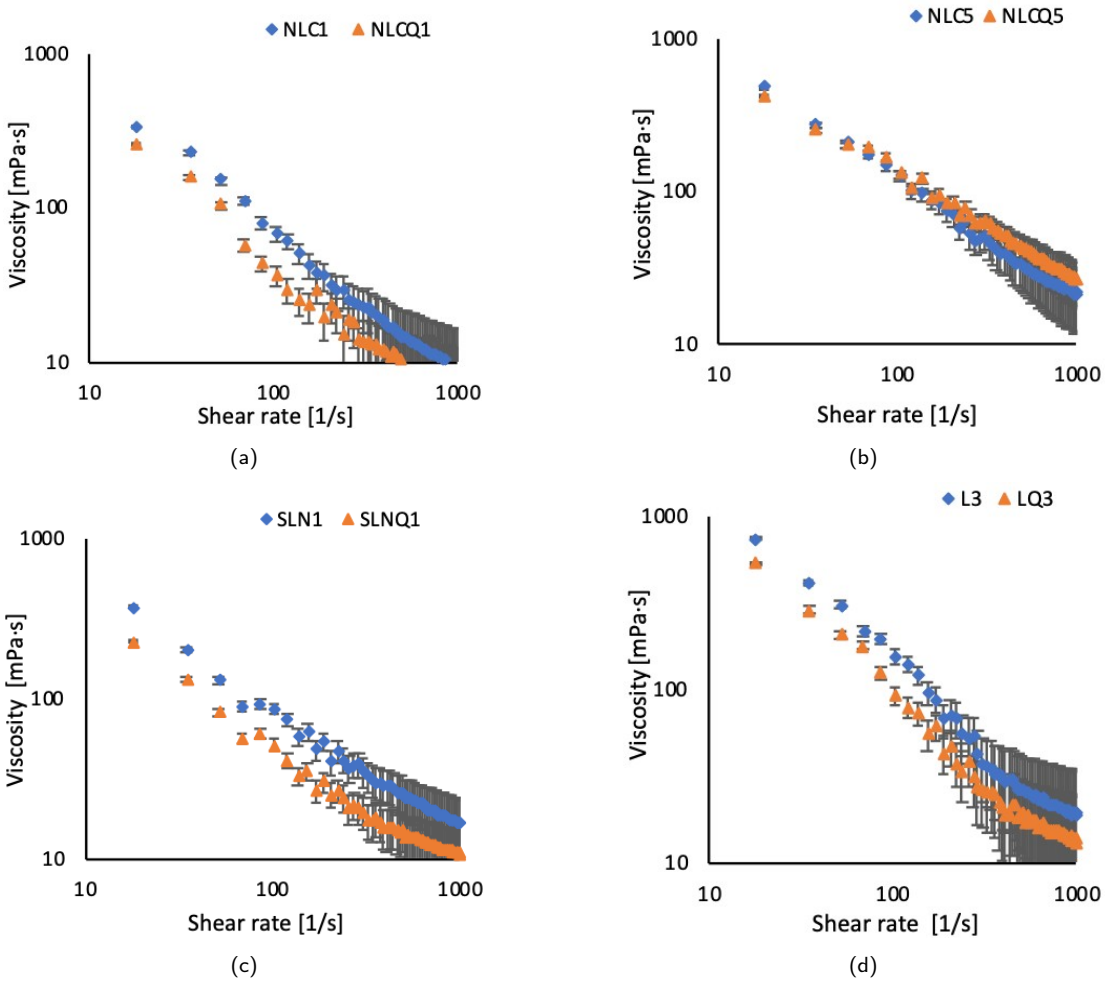


Figure 3. Viscosity curves of unloaded and QC-loaded lipid-based nanosystems for (a) – NLC1, NLCQ1, (b) – NLC5, NLCQ5, (c) – SLN1, SLNQ1, (d) – L3, LQ3.

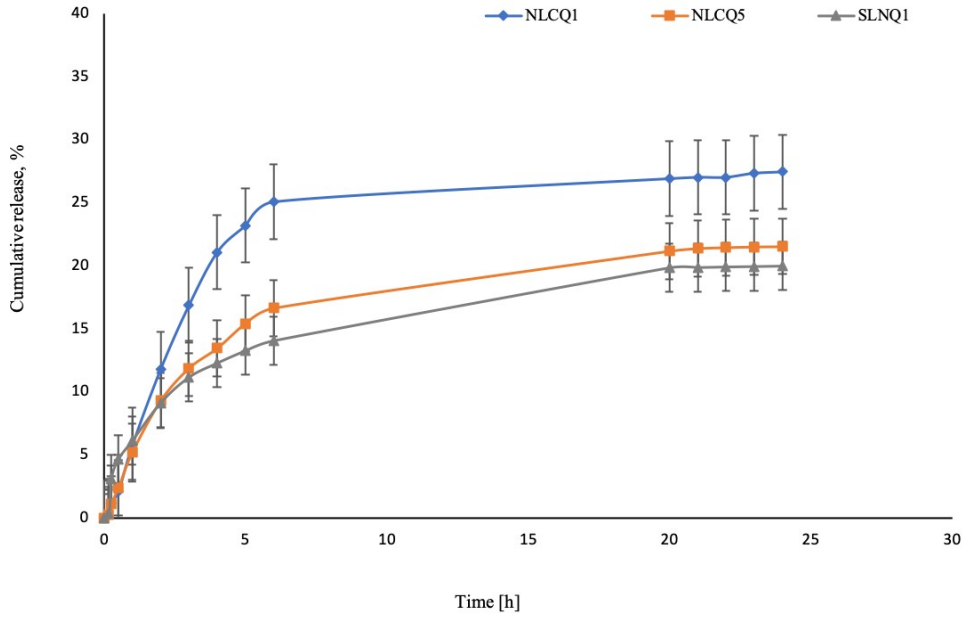


Figure 4. Release profiles of quercetin from NLCs and SLN dispersions expressed as percentage % wt. of released active ($n = 3$).

3.3. Kinetics of quercetin release

The kinetics of a drug release from the encapsulating matrices is a very complex process that may depend on the chemical composition of the carrier material, structure, medium conditions (such as pH), as well as external factors like temperature. Controlled release carriers, such as those obtained in our studies, must regulate the active ingredient release rate and duration in an expected medium. Therefore, an initial faster release is needed in order to rapidly accomplish the effective therapeutic concentration of the active. Subsequently, well-defined drug release kinetics must be followed in order to deliver and maintain drug levels over a desired period of time (Bayer, 2023). For better understanding of the mechanism of quercetin release from the prepared lipid carriers, a mathematical analysis was performed by fitting the most appropriate kinetic model. Among many mathematical models, the zero order Eq. (1), first order Eq. (2), Higuchi Eq. (3) and Korsmeyer–Peppas Eq. (4) models were selected to describe the release process. The selection of the best fitting kinetic model was based on the comparison of the determination coefficient (R^2). The calculated parameters of kinetic models used for description of the quercetin release from different carriers are presented in Table 4.

$$C_t = C_0 + K_0 \cdot t \tag{1}$$

$$\ln C_t = \ln C_0 + K_1 \cdot t \tag{2}$$

$$C_t = C_0 + K_H \cdot t^{\frac{1}{2}} \tag{3}$$

$$C_t = C_0 + K_{KP} \cdot t^n$$
$$\ln C_t = \ln C_0 + \ln K_{KP} + n \ln t \tag{4}$$

According to the results, the best fit of QC release from NLCQ1, NLCQ5 and SLNQ1 was obtained for the Higuchi model as the plots showed high linearity, ($R^2 = 0.8327$, $R^2 = 0.9195$, and $R^2 = 0.9437$, respectively). This model suggests that the active was released by pure diffusion and the release medium did not penetrate into the nanoparticles. However, the values of the characteristic exponent n were much higher than the literature values of 0.43 (0.8069; 0.7168; 0.5659, respectively for NLCQ1, NLCQ5 and SLNQ1) suggesting that more than one mechanism may be involved in release process, like erosion or swelling of the matrix (Ritger and Peppas, 1987; Dash et al., 2010).

Generally, the release of the active substance from nanostructured lipid carriers is based on the Korsmeyer–Pepas model. Nevertheless, in this case a slightly better fit was achieved by Higuchi. It can therefore be assumed that the release occurs by anomalous diffusion, which is characteristic for nanoparticles and suspensions. The results are consistent with the data provided by literature reports confirming that the release of actives from nanostructured lipid carriers occurs mainly according to the Higuchi and Korsmeyer–Peppas models (Gönüllü et al., 2015; Nagaich and Gulati, 2016; Üner et al., 2014).

4. CONCLUSIONS

In this research, the potential of NLC, hyaluronic acid-modified NLC, SLN, and liposomes were investigated for quercetin delivery. Stable QC-loaded nanocarriers were successfully prepared using the ultrasonification method. The optimal formulations are nano-sized with good physicochemical stability and satisfying rheological properties. The release of QC from the systems was found to be biphasic, with the burst effect at the beginning followed by gradual release of the active during the time. The obtained results indicate the potential use of nanocarriers for both rapid and prolonged release of the active. Lipid phase composition, when comparing SLN with only solid lipid and NLC, with both solid and liquid lipid, influenced the release rate of QC from the formulations. A similar situation was observed when comparing NLC and HA-modified NLC. The results also showed that the process of QC release from the carriers was diffusion controlled and the best fit of experimental data was achieved for the Higuchi model.

Table 4. The kinetic model parameters for the release results.

Model	Parameter	Formulation		
		NLCQ1	NLCQ5	SLNQ1
Zero-order	R^2	0.6631	0.7771	0.8119
	K_0 [mg/h]	0.9416	0.7635	0.6776
First order	R^2	0.3795	0.4340	0.4189
	K_1 [h^{-1}]	–0.0418	–0.0388	–0.0315
Higuchi	R^2	0.8327	0.9195	0.9437
	K_H [$mg/h^{1/2}$]	5.7364	4.5151	3.9715
Korsmeyer–Peppas	R^2	0.8171	0.8565	0.7838
	K_{KP} [h^{-n}]	2.2410	2.0479	1.7610
	n	0.8069	0.7168	0.5659

To sum up, the obtained results confirm that the fabricated carriers are suitable for controlled release of quercetin for skin delivery. Moreover, they may enhance its therapeutic potential by improving stability and bioavailability, which is consistent with literature reports (Cai et al., 2013).

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SYMBOLS

QC, Q	quercetin
HA	hyaluronic acid
T	time
C_1	concentration of the released quercetin at time t, mg/cm^3
C_0	initial quercetin concentration, mg/cm^3
K_0	constant for the zero-order kinetics model, mg/h
K_1	constant for the first order kinetics model, h^{-1}
K_H	constant for the Higuchi model, mg/h$^{1/2}$
K_{KP}	constant for the Korsmeyer–Peppas model, h^{-n}
n	exponent characteristic for specific diffusion mechanisms

Greek symbols

λ	wavelength, nm

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