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INVESTIGATION OF THE IMPACT OF DIFFERENT FORMULATION AND PROCESSING PARAMETERS ON THE PHYSICOCHEMICAL PROPERTIES OF CURCUMIN-LOADED NANOSTRUCTURED LIPID CARRIERS

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Nanostructured lipid carriers (NLCs) are drug delivery systems with remarkable physicochemical stability, biocompatibility, biodegradability and can offer controlled drug release. This study aimed to develop and characterize nanostructured lipid carriers (NLCs) containing curcumin (CUR-NLCs) as a primary step in improving curcumin delivery. The effect of certain formulation and processing parameters on the developed CUR-NLCs properties were investigated. In this work, different concentrations and types of surfactants (Pluronic F-127, Pluronic F-68, and Tween 80) were used to stabilize NLC dispersions. Moreover, two different solid lipids (Compritol 888 ATO and Precirol ATO 5) and several liquid lipids (Labrafac lipophile WL 1349, refined olive oil, oleic acid and glyceryl caprylate/caprate) were used. The emulsification/ultrasonication technique was employed to prepare the CUR-NLCs, either using a magnetic stirrer/probe sonicator method or rotor-stator homogenizer/ultrasonic water bath method. The physical and chemical properties of the formulations were evaluated, including particle size, polydispersity index, and zeta potential. The obtained results showed that increasing surfactant concentration from 0.5 to 2% w/v and reducing the total lipid percentage by weight from 5 to 2% w/v had significant impact on the nanoparticle properties. Finally, the formulation with the lowest mean particle size diameter (59.49 ± 0.71 nm) with a zeta potential of –14.13 ± 1.06 mV and PDI of 0.27 was selected and it showed relatively high entrapment efficiency (75.33 ± 5.06%) and prolonged drug release (≈ 60% within 72 hours).

Keywords: NLCs, Particle size, PDI, Zeta potential, Drug Delivery.

INTRODUCTION

Curcumin (1,7-bis-(4-hydroxy-3-methoxy-phenyl)-hepta-1,6-diene-3,5-dione) is a polyphenolic natural compound, extracted from the rhizomes of Curcuma longa (C. longa)[1&2]. Since it is a multitarget molecule, curcumin is currently the focus of many researchers for the prevention and treatment of multiple diseases including ocular diseases[3], various types of cancer[4-7], central nervous system diseases[8], gastrointestinal diseases[9], lung diseases[10] and skin diseases[11], among others. Unfortunately, its clinical efficiency is diminished by its poor aqueous solubility, short circulation half-life, and low stability in physiological pH[12&13]. In order to overcome these drawbacks, numerous attempts of curcumin encapsulation in different nanocarriers were successfully reported by many researchers[12].

Nanocarriers are nanometer-scale materials intended for therapeutic or diagnostic

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use. Lipid-based nanocarriers, such as solid lipid nanoparticles (SLNs), liposomes, and nanostructured lipid carriers, have been used to improve the dispersibility of lipophilic molecules[14].

Compared to liposomal nanoparticles, SLNs and NLCs showed several advantages such as ease of formulation and cost-effective scale up, the ability to protect lipophilic drugs from aqueous environments, and the ability to effectively control drug release. Moreover, it can be formulated with organic solvent-free techniques and with biodegradable and biocompatible lipids. Nevertheless, the use of SLNs as drug carriers is restricted by their low drug payloads and drug expulsion from the perfectly crystallized lipids upon storage due to polymorphic transitions. Further, NLCs are described as a second generation of SLNs which consist of a blend of spatially different lipid molecules, usually of liquid and solid lipids, which results in an imperfectly crystallized lipid particles with increased entrapment efficiency and less drug expulsion[15]. NLCs may be produced by various methods including, high pressure homogenization, microemulsion, solvent emulsification-evaporation, high shear homogenization and/or ultrasonication, solvent emulsification-diffusion, melting dispersion, solvent injection, and double emulsion[16&17].

NLC preparation should be optimized to get the best characteristics for its intended use. Several characteristics of formulations including particle size, polydispersity index, zeta potential, drug release pattern and entrapment efficiency were investigated in this study. Particle size and polydispersity index influence nanoparticle *in-vivo* distribution, targeting ability and drug release[18-20].

Moreover, Zeta potential influences the stability of the formulation during storage, preventing particle aggregation through electrostatic repulsion between particles of the same charge.

This study aimed to develop and analyze curcumin-loaded nanostructured lipid carriers (CUR-NLCs) utilizing the melt emulsification/ultrasonication method. Various formulation and processing factors, including surfactant concentration, surfactant type, solid and liquid lipid types, emulsification method, and total lipid percentage, were investigated to determine their impact on the important physicochemical properties of CUR-NLCs. These investigations may provide insights that would help guide further optimization studies on NLCs produced by Emulsification/ Ultrasonication to prepare formulations with average size under 100 nm and low PDI and high ZP intended for ocular drug delivery.

EXPERIMENTAL

Materials

Curcumin (Assay ≥ 65%), Pluronic F-127 and Pluronic F-68 were obtained from Sigma Aldrich, USA. Precirol ATO 5, Compritol ATO 888 and Labrafac Lipophile WL 1349 were received as a gift from Gattefosse, France. Refined olive oil, oleic acid and glyceryl caprylatae/caprate was obtained as a kind gift from Alesraa Optima, Egypt. Tween 80 was purchased from Alpha Chemicals. L-Ascorbic acid was obtained from Alpha Chemika. All other chemicals, solvents and reagents used during the studies were of analytical reagent grade and were used as obtained. Regenerated cellulose dialysis tubing, 20.4 mm × 32 mm, with a molecular weight cut off (MWCO) 12-14 kDa was obtained from Frey scientific, Nashua, NH, USA.

Methodology

Preparation of CUR-NLCs

Two different approaches of the hot melt emulsification/ultrasonication technique were used to prepare CUR-NLCs. In the first approach, we used a high shear mechanical homogenizer (rotor and stator type) and an ultrasonic water bath, wherein the solid lipid was melted in an ultrasound water bath adjusted 5°C above its melting point. Then, the liquid lipid was added to reach the same temperature. Curcumin (0.03% w/v) was dispersed in the lipid mixture by ultrasonication (frequency, 37 hz; amplitude, 100%) for two minutes. A primary emulsion was formed by adding 4 ml of the aqueous surfactant solution at the same temperature, and the mixture was further sonicated for two minutes. The mechanical homogenizer (CAT X 120, M. Zipperer GmbH, Germany) was operated for 10 minutes at 20000 rpm, and the nano-emulsion was formed by gradually adding surfactant solution to reach a final volume of

50 ml followed by ultrasonication (Elmasonic P300H, Elma Schmidbauer GmbH, Singen, Germany) for 10 minutes. The second approach entailed dispersing CUR in the molten lipids, adding 4 ml of surfactant solution while stirring, then diluting the formed emulsion using a magnetic stirrer operated at 1500 rpm for 10 minutes. Further, the hot emulsion was sonicated for 15 minutes using a Probe Sonicator (VCX 750 Processor, Sonics and Material Inc., Connecticut, USA) adjusted to 75% amplitude; pulse, 5 sec. on and 5 sec. off. The final step in both approaches was cooling the nanodispersions to room temperature on a magnetic stirrer for one hour. The prepared nanodispersion was then packed in Eppendorf tubes and kept at 4 ˚C until analysis.

Particle size and zeta potential analysis

Particle size in terms of average hydrodynamic diameter was measured by dynamic light scattering (DLS), using the Zetasizer Nano ZS Malvern Instrument at an angle 173°, in 10 mm diameter disposable polystyrene cells[21]. Before measurement, samples were sonicated for 3 minutes and diluted 40X using double distilled water to generate suitable scattering intensity. The same equipment was used to determine polydispersity index (PDI) and zeta potential (ZP) as measures of particle size distribution and particle surface charge, respectively. All experiments were conducted at a temperature of 25°C, and the results were determined by averaging three measurements.

Entrapment efficiency

Samples of the selected formula (F12) were mixed with ethyl acetate to induce CUR-NLCs aggregation at a ratio of (1:9) in 2 ml Eppendorf tubes. They were vortexed for 20 seconds and then centrifuged (Centurion scientific centrifuge, Pro-research. K2015, UK) at 10,000 rpm for 10 minutes. One milliliter of the clear supernatants containing the unentrapped drug was withdrawn and diluted to 3 ml with ethanol 96%. The absorbance of samples was measured spectrophotometrically at 425 nm, and the concentration of the free drug was determined using a calibration curve. The final result was obtained by averaging at least three independent experiments.

The entrapment efficiency of the drug was calculated as follows:

Entrapment efficiency % =
CUR-total – CUR-supernatant / CUR-total *100

where “CUR-total” is the weight of total incorporated drug and the “CUR-supernatant” is the weight of free drug analyzed in supernatant layer[22].

***In-vitro* release kinetics**

In-vitro release experiments of CUR-NLCs were performed through a modified dialysis diffusion method. Phosphate buffer saline (PBS) 0.01 M at pH 7.4 and ethanol (70:30 v/v) were selected for the release medium. Tween 80 (2% w/v) was added to ensure sink conditions, and ascorbic acid (0.5% w/v) was used as antioxidant to protect released curcumin.

Aliquots of the CUR-NLCs formulation, equivalent to 300 mcg CUR, were pipetted over a cellulose membrane fitted at the lower end of a polypropylene tube to act as a donor compartment. The cellulose membrane was soaked overnight before the experiment. The tube was then dipped in a receiver compartment containing 50 ml of the dissolution medium, then covered to stop evaporation of the release medium. This experiment was conducted in the dark at a temperature of 37±0.5°C with constant agitation at 60 rpm using a temperature-controlled water bath[23].

At predetermined intervals, one milliliter of dissolution medium was withdrawn, assayed spectrophotometrically at 425 nm, and replaced with an equal volume of pre-warmed freshly prepared medium. Experiment was performed in triplicate. The percentage cumulative drug release was calculated using a previously established calibration curve. A graph was then created to visualize the relationship between percentage cumulative drug release and time.

The drug release data from the selected formula (F12) were then fitted to the following kinetic models.

Zero order kinetics: $X = K * t$

First order kinetics: $X = 1 - e^{-K*t}$

Higuchi model: $X = K* t^{1/2}$

Korsmeyer–Peppas: $X = K*t^{n}$

where X is the fraction of drug released at time t; K is a release rate constant; and n is the diffusional release exponent that could be used to characterize the different release mechanisms (n= 0.43, Fickian diffusion; 0.43 < n <0.85, non-Fickian drug release which includes a combination of diffusional, swelling, and matrix erosion mechanisms [anomalous transport]; n= 0.85 [case II transport; i.e. zero-order release]; and n> 0.89, super case II[24&25].

RESULTS AND DISCUSSION

Table 1 lists the composition and the measured physicochemical parameters of the prepared CUR-NLCs. Particle size of the developed nanoparticles ranged from 59.49 ± 0.71 to 387.87 ± 1.76 nm, and the PDI ranged from 0.15 to 0.48. The ZP of CUR-NLCs ranged from -11.73 ± 0.67 to -34.07 ± 2.02 mV.

Effect of various parameters on particle size, PDI and ZP

Effect of surfactant concentration (F1-F3)

As shown in table 1, elevation of the surfactant concentration from 0.5 to 2% w/v significantly (p< 0.0001) decreased the particle size of the CUR-NLCs from 387.87 ± 1.76 to 174.27 ± 1.99 nm. This can be attributed to the ample number of nonionic surfactant molecules present at the interface between lipid and aqueous phases during homogenization, which were adsorbed rapidly on the surfaces of small droplets before coalescence offering steric stabilization of the nanodispersion[26&27]. Figure 1a and figure 1b depicts the DLS data of F1 and F3, respectively. DLS measurements of formula F1 showed two populations of particles with the major peak in the submicron level and a second peak located around 3-6 µm range of size (Fig. 1a), probably due to particles aggregation. In F3 a sharper peak shifted more closely to the nanoscale indicates smaller particle size and PDI (Fig. 1b). Formulae with low surfactant concentration showed high PDI values. This amount of surfactant was probably insufficient to stabilize the nanoparticles[28]. On the contrary, homogeneous particle size distributions were achieved at a higher surfactant concentration (2% w/v).

At low surfactant concentration (0.5% w/v), a decline in the value of the ZP and an increase in the average size of nanoparticle may be attributed to the overlapping and compression of nearby double layers[29].

At higher surfactant concentration (1% w/v), surfactants levels were sufficient to saturate a monolayer at the nanoparticle surface that yields higher ZP for that surfactant–NLC system. As the surfactant amount increases (2% w/v), the ZP also had lower negative values. Expansion of the diffuse layer as a result of accumulation of surfactant on NLCs' surfaces resulted in steric effects on ZP[30&31].

Effect of surfactant type (F3-F5)

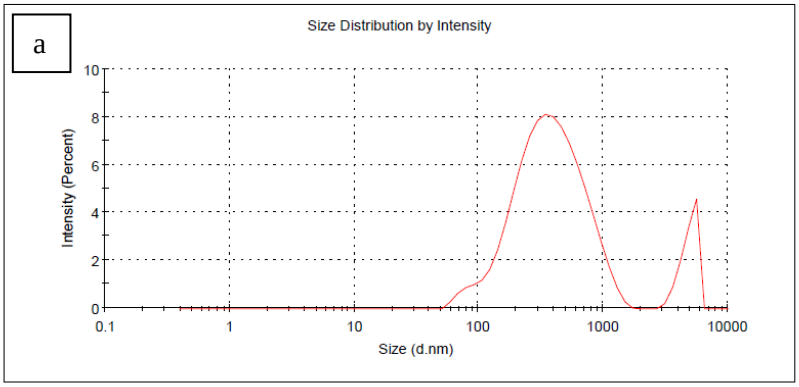
Three nonionic surfactants, with a different hydrophilic character depending on their Hydrophilic-Lipophilic Balance (HLB) values, namely, Tween 80 (HLB = 15.0), Pluronic F-127 (HLB = 22.0) and Pluronic F-68 (HLB = 29.0) were evaluated for their impact on particle size, PDI, and NLC surface charge. Obviously, for the same concentration, surfactant type markedly affected the particle size. By comparing formulae F3 through F5, we found that using Tween 80 in F3 produced NLCs with the smallest mean particle size. Among all, Pluronic F-68 yielded particles that were largest in size (mean PS = 235.73 ± 1.19 nm), heterogeneous (mean PDI = 0.31), and had the highest zeta potential (- 34.07 ± 2.02 mV). These findings suggested a different method of interaction of the three surfactants with lipids at the particles' outer shells[32]. Different molecular weights of the surfactants (MW of tween 80 ≈ 1310 < pluronic F-68 ≈ 8400 < pluronic F-127 ≈ 12600) suggested that for the same concentration of surfactant (2% w/v) in the formulation, a lower number of pluronic molecules were present in the nano-dispersion than in tween 80, leading to lower stabilization the NLCs. Furthermore, the presence of the larger molecules of Pluronics on the NLC surfaces should contribute to a greater NLC size because of a larger hydrodynamic radius[32]. Since Pluronic F-68 is more hydrophilic and has a short hydrophobic segment, it may not interact adequately with the lipids of the nanoparticles leading to less stabilization of the NLCs[33&34].

Table 1: Composition of the CUR-NLCs dispersions, F1-F9 produced by mechanical homogenizer/ultrasonic water bath method. F10-F12 produced by magnetic stirrer/probe sonicator method. All formulae contained CUR (0.03% w/v) and adjusted to 50 ml final volume with distilled water.

	Solid Lipid (%w/v)			Liquid Lipid (%w/v)			Surfactant (%w/v)			Responses		
Formula Code	Compritol ATO 888	Precirol ATO 5	Labrafac Lipophile WL 1349	Oleic acid	Refined Olive Oil	Glyceryl Caprylate /Caprate	Tween 80	Pluronic F68	Pluronic F127	Size (nm)	PDI	Zeta Potential (mV)
F1	3%	-	2%	-	-	-	0.5%	-	-	387.87 ± 1.76	0.48 ± 0.06	- 20.5 ± 0.46
F2	3%	-	2%	-	-	-	1%	-	-	305.97 ± 6.64	0.30 ± 0.05	-26.43 ± 1.72
F3	3%	-	2%	-	-	-	2%	-	-	174.27 ± 1.99	0.21 ± 0.01	-22.97 ± 0.47
F4	3%	-	2%	-	-	-	-	2%	-	235.73 ± 1.19	0.31 ± 0.02	-34.07 ± 2.02
F5	3%	-	2%	-	-	-	-	-	2%	198.23 ± 1.10	0.21 ± 0.01	-20.4 ± 0.70
F6	3%	-	-	2%	-	-	-	-	2%	265.83 ± 4.60	0.44 ± 0.01	-33.33 ± 3.52
F7	3%	-	-	-	2%	-	-	-	2%	195.6 ± 0.75	0.21 ± 0.01	-26.27 ± 0.5
F8	3%	-	-	-	-	2%	-	-	2%	314.17 ± 3.30	0.23 ± 0.01	-11.73 ± 0.67
F9	-	3%	2%	-	-	-	2%	-	-	132.43 ± 1.42	0.15 ± 0.01	-20.53 ± 0.50
F10	3%	-	2%	-	-	-	2%	-	-	159.67 ± 1.77	0.19 ± 0.02	-15.7 ± 0.17
F11	-	2%	1%	-	-	-	2%	-	-	90.37 ± 8.27	0.26 ± 0.03	-20.73 ± 1.54
F12	-	1%	1%	-	-	-	2%	-	-	59.49 ± 0.71	0.27 ±0.002	-14.13 ± 1.06

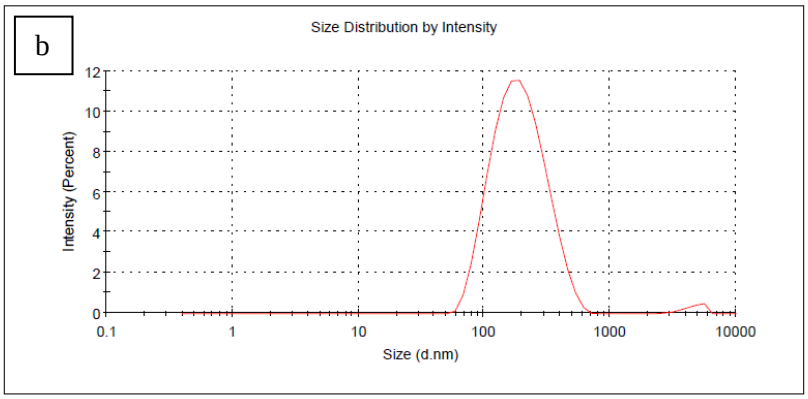
Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 386.8	Peak 1:	423.5	88.9	257.8
PdI: 0.531	Peak 2:	4860	11.1	700.3
Intercept: 0.948	Peak 3:	0.000	0.0	0.000
Result quality : Good				



Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 172.0	Peak 1:	206.0	98.5	98.18
PdI: 0.203	Peak 2:	4656	1.5	802.6
Intercept: 0.959	Peak 3:	0.000	0.0	0.000
Result quality : Good				



Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 59.40	Peak 1:	91.32	98.5	82.36
PdI: 0.267	Peak 2:	3982	1.5	1099
Intercept: 0.930	Peak 3:	0.000	0.0	0.000
Result quality : Good				

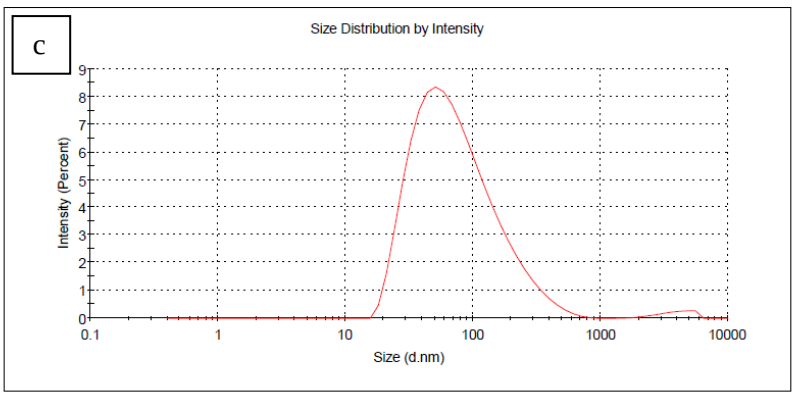


Fig. 1: Particle size measurements by DLS for a) F1 (low surfactant concentration 0.5% w/v), b) F3 (high surfactant concentration 2.0% w/v) and c) F12 (high surfactant concentration 2.0% w/v and low total lipids percentage by weight 2.0% w/v).

Effect of liquid lipid type (F5-F8)

Formulae containing Labarfac lipophile (F5) and refined olive oil (F7) as liquid lipids showed approximately the same mean particle size (198.23 ± 1.10 and 195.60 ± 0.75 nm, respectively) and a PDI of 0.21. In contrast, F6 and F8 containing oleic acid and glyceryl caprylate/caprate revealed higher values of these parameters. The higher viscosity of the latter two lipids may have decreased the shearing force required for size reduction during processing. Moreover, higher HLB values (5-6) of glyceryl caprylate/caprate compared to the other liquid lipids (HLB ≈ 1) could cause inadequate interaction with the solid lipid Compritol (HLB = 2) leading to its separation in the form of coalesced larger oil droplets. Liquid lipids with less negative ZP values ranked as follows: glyceryl caprylate/caprate < Labrafac lipophile WL 1349 < olive oil < oleic acid**.** No definite association between liquid lipid type and charge was observed.

Effect of solid lipid type (F3 and F9)

Two different solid lipids, Compritol ATO 888 (F3) and Precirol ATO 5 (F9) were investigated. Compritol 888 ATO is composed of a mixture of various esters of behenic acid and glycerol and with a high melting point of 69-74°C, on the other hand, the major constituents of Precirol ATO 5 are glyceryl palmitate/stearate, which have low melting points (50-60°C). The longer hydrocarbon chain resulted in a larger particle size and a higher melting point[35]. CUR-NLCs prepared with Precirol (F9) were found to have smaller PS (132.43 ± 1.42 nm), were monodisperse with PDI (0.15), but had lower negative ZP (-20.53 ± 0.50 mV) than those fabricated with Compritol (F3). The incorporation of low melting point lipids reduced the viscosity ratio between the lipid dispersed phase and the aqueous phase, leading to NLCs with smaller PS and lower PDI values[36] . Additionally, increasing the hydrophobicity of the solid lipid molecules resulted in increasing the ZP for less negative values[37].

Effect of preparation method (F3 and F10)

Two emulsifying devices, a high energy probe sonicator and a lower energy mechanical homogenizer (rotor-stator), were exploited for the emulsification and size reduction of two formulae with identical compositions (F10 and F3, respectively). The high energy device was able to produce small particles with large interfacial area, which was then stabilized by the surfactant molecules. In other words, for the same composition of dispersed phase and stabilizing agent, the smallest particles (159.67 ± 1.77 nm) were produced by the probe sonicator (F10)[38]. Additionally, these particles (F10) showed low PDI value (0.19) and lower negative ZP (-15.67 ± 0.17 mV), presumably due to better coverage by the surfactant molecules, which would mask the charge at the nanoparticle surface.

Effect of total lipid concentration (F9, F11 and F12)

Three different levels of total lipid percentages by weight were tested (5%, 3% and 2% w/v). The use of 3% total lipids yielded CUR-NLCs (F11) with a mean particle diameter of 90.37 ± 8.27 nm. Further decrease in the total lipids to 2% as represented by CUR-NLCs (F12) resulted in even smaller particles (59.49 ± 0.71 nm) as illustrated in figure 1c. Therefore, particle size analysis revealed that decreasing the lipid content of CUR-NLCs led to smaller particles. This is likely due to the lower viscosity and surface tension of the less concentrated lipid dispersion, which facilitated more efficient homogenization. Moreover, at low lipid concentrations, the surfactant is capable of covering the particles adequately, which leads to particle stabilization[37&39]. The low ZP (-14.13 ± 1.06) of F12 may be attributed to increased surfactant concentration relative to total lipid concentration.

Entrapment efficiency of selected formula

According to the previous results, formula (F12) with the smallest particle size and acceptable PDI and ZP was selected for further investigations. It was found to have an entrapment efficiency of 75.33 ± 5.06%, which is a promising result and represents a starting point for further optimization. Since curcumin is known to exhibit high solubility in Precirol® ATO 5 and in Labrafac lipophile WL 1349[40&41], it would be expected to show high entrapment efficiency in nanoparticles formulated using these lipids.

In-vitro release kinetics of selected formula

In-vitro release kinetics of selected CUR-NLC formula (F12) were assessed by UV-visible spectrophotometry at 425 nm. Figure 2 shows the release patterns of the CUR-loaded NLCs containing 0.3 $mg.ml^{-1}$ of CUR. In the first hours, no burst release of the unentrapped drug was observed. It may have been masked by slow drug permeation across the dialysis membrane. However, the amount of CUR released after 72 hours was close to 60%. As anticipated for NLCs, a gradual and sustained release of the lipophilic CUR was observed due to its strong affinity for the solid and liquid lipids forming the NLC matrix[24]. Furthermore, to determine the mechanism of CUR release from NLCs, *in-vitro* release data was fitted to various kinetic equations. The coefficient of determination (R^2) was used to identify the best-fitting model (Table 2)[42].

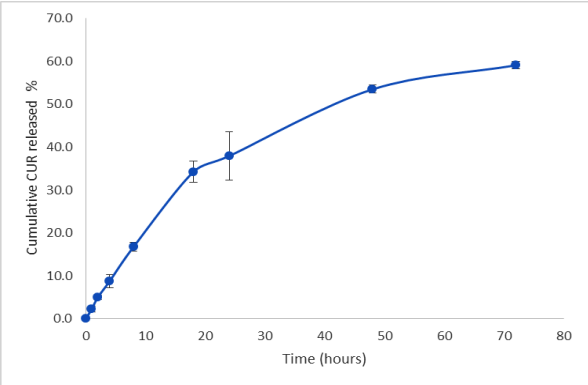


Fig. 2: *In-vitro* release of CUR from CUR-NLCs (F12) through dialysis membrane (12-14 KD MWCO), within 72 hours (mean ± SD, *n*= 3).

Table 2: Mean parameters obtained after fitting the release data from CUR-NLCs different release models (R^2, determination coefficient, K release constant, and n release exponent).

Parame-ter	Kinetic Model			
	Zero order	First order	Higuchi diffusion	Korsmeyer -Peppas
R^2	0.8823	0.9411	0.9792	0.9757
K	0.8162	0.0127	8.1593	2.8428
n	-	-	-	0.7767

The drug release mechanism from lipid matrices is primarily influenced by matrix diffusion and erosion[43]. Additionally, incorporating a liquid lipid into NLCs formulation creates a less ordered structure , which reduces drug expulsion[44&45].

Model fitting showed that the selected CUR–NLCs followed the Higuchi model, which had the highest R^2 (0.9792) value (Table 2). Based on the diffusional exponent (*n*= 0.7767) calculated using the Korsmeyer-Peppas equation, a non-Fickian mechanism (anomalous transport) appears to be involved in the release of CUR from the NLCs. The non-Fickian drug release indicates that water penetration into the matrix was not the major factor involved in the release process, which is distinctive of lipid-based systems[46].

Conclusions

Based on the literature and past experience, authors have used one factor at a time approach to investigate the effects of various factors on the characteristics of developed CUR-NLCs. Among all the factors studied, surfactant concentration and total lipid percentage by weight had the most significant effects on the physicochemical characteristics of the prepared CUR-NLCs. Given the findings of the current study, a more sophisticated experimental design is recommended to explore the interactions between the significant factors which cannot be interpreted by the one factor at a time approach. Nonetheless, this study represents a cornerstone for future optimization studies toward the development of stable NLCs for prolonged curcumin delivery.

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دراسة تأثير عوامل الصياغة والتحضير المختلفة على الخواص الفيزيائية والكيميائية للحوامل الدهنية ذات البنية النانوية المحملة بالكركمين

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الحوامل الدهنية متناهية الصغر ذات البنية النانوية هي أنظمة لتوصيل الأدوية تتمتع بثبات فيزيائي وكيميائي ملحوظ، وتوافق حيوي، وقابلية للتحلل الحيوي، وتتيح التحكم في معدل إنطلاق الدواء. تهدف هذه الدراسة إلى تطوير وتوصيف الحوامل الدهنية متناهية الصغر تحتوي على الكركمين كخطوة أساسية في تحسين توصيل عقار الكركمين. تم دراسة تأثير بعض عوامل الصياغة والتحضير على خصائص الحوامل الدهنية متناهية الصغر المطورة المحملة بعقار الكركمين . في هذا العمل، تم استخدام تركيزات وأنواع مختلفة من المواد الخافضة للتوتر السطحي مثل التوين ٨٠ والبلورونيك ٦٨ والبلورونيك ١٢٧ لتأكيد تشتت الحوامل الدهنية متناهية الصغر وتباعدهاعن بعضها. علاوة على ذلك، تم استخدام نوعين مختلفين من الدهون الصلبة (الكمبريتول ٨٨٨ والبريسيرول ٥) والعديد من الدهون السائلة (اللابرافاك ليبوفيل ١٣٤٩، وزيت الزيتون المكرر، وحمض الأوليك، وجليسريد الكابريلات/الكابرات). تم استخدام تقنية الاستحلاب مع الموجات فوق الصوتية لإعداد الحوامل الدهنية متناهية الصغر المحملة بعقار الكركمين ، إما باستخدام طريقة الخلط بإستخدام التحريك المغناطيسي مع مسبار الموجات فوق الصوتية أو طريقة حمام الماء بالموجات فوق الصوتية مع الخلط بإستخدام المجانس الدوار/الثابت. تم تقييم الخواص الفيزيائية والكيميائية للتركيبات، بما في ذلك حجم الجسيمات، ومؤشر توزيع الحجم، وشحنة السطح. أظهرت النتائج التي تم الحصول عليها أن زيادة تركيز المواد الخافضة للتوتر السطحي من ٠.٥ إلى ٢% وزن/حجم وتقليل النسبة الكلية للدهون من ٥ إلى ٢% وزن/حجم كان له تأثير كبير على خصائص الجسيمات النانوية. أخيرًا، تم اختيار التركيبة ذات أقل متوسط لحجم الجسيمات (٥٩.٤٩ ± ٠.٧١ نانومتر) مع شحنة سطح تبلغ -١٤.١٣ ± ١.٠٦ مللي فولت بقيمة ٠.٢٧ وأظهرت كفاءة تغليف للعقارعالية نسبيًا (٧٥.٣٣ ± ٥.٠٦٪) وإطلاق للدواء طويل الأمد (≈ ٦٠% خلال ٧٢ ساعة).