JURNAL KARTIKA KIMIA

J. Kartika Kimia, May 2022, 5, (1), 79-89
Journal homepage: http://jkk.unjani.ac.id/index.php/jkk
P-ISSN: 2655-1322 E-ISSN: 2655-0938

Review of Surfactant Use in Curcumin Drug Delivery System

Titin Rostinawati[1,*], Sriwododo[2], Yasmiwar Susilawati[1], Anis Yohana Ch.[1]
[1]Department of Pharmaceuticals and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran
[2]Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Padjadjaran

*E-mail: titin19001@mail.unpad.ac.id

DOI: https://doi.org/10.26874/jkk.v5i1.96

Received: 12 March 2022, *Revised*: 16 April 2022, *Accepted*: 23 April 2022, O*nline*: 25 May 2022

Abstract

Curcuminoids are the active components of the dried rhizome of *Curcuma longa* Linn. Curcuminoids consist of the three most basic constituents: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Traditionally, turmeric is widely used to treat flatulence, liver, menstrual disorders, hematuria, bleeding, and colic. With more research, turmeric's benefits are increasing, ranging from anti-inflammatory, cancer, autoimmune, neurological, cardiovascular disease, and diabetes. However, this is limited by the Physicochemical properties of curcumin which is not soluble in water; its metabolism is fast, and it is unstable in physiological pH and alkaline, causing low bioavailability and resulting in less optimal therapeutic effect. Currently, several drug delivery systems have been developed to improve the bioavailability of curcumin, such as adjuvants, liposomes, nanoparticles, curcumin-phospholipid complexes, curcumin structural analogs, micronization, and nanonization, Self Micro Emulsifying Drug Delivery Systems (SMEDDS), cyclodextrin inclusions, solid dispersions, nanoemulsions, nano balls, nanobeads, and nanofibers. Many of these preparations use the help of surfactants. Surfactants are used as emulsifiers, wetting agents, and solvents. In principle, surfactants help reduce surface tension and interfacial tension in gases, liquids, and solids, allowing these substances to diffuse and spread. Factors that must be considered when selecting a surfactant are the critical micelle concentration and the HLB value. Selection of the right surfactant will help increase bioavailability.

Keywords: *curcuminoids, curcumin, bioavailability, drug delivery systems, surfactants.*

1 Introduction

Curcuminoids are active components of the dried rhizome of *Curcuma longa* L., widely cultivated in tropical and subtropical regions (Asia and Central America). The dried rhizome of *C. longa* L. is also known as turmeric and belongs to the Zingiberaceae family. Curcuminoids consist of the three most basic constituents, namely curcumin (75%), demethoxycurcumin (10–25%), and bisdemethoxycurcumin (5%), which belong to the diferuloylmethane group of phenolic compounds [1, 2]. The chemical structure of polyphenolic substances shows antioxidant [3], antimicrobial, anti-inflammatory, antiangiogenic, antimutagenic, and antiplatelet properties. Curcumin is known to have antioxidant, anti-inflammatory, hepatoprotective, and anticancer [4, 5]. Due to these effects, it has an important role in preventing and treating various diseases ranging from cancer to autoimmune, neurological, cardiovascular disease, and diabetes [2].

Behind the many benefits in its use, there are several limitations related to the low bioavailability of curcumin caused by high hydrophobicity, low absorption, low solubility in air, unstable in alkaline pH, and rapidly metabolized [6–8]. Curcumin is sensitive to light, so samples containing curcumin must be stored away from light. Its low bioavailability significantly limits its therapeutic effect. Recently, a method has been developed to increase the bioavailability of curcumin [9]. Researchers have tried various strategies to increase bioavailability, such as: (i) adjuvants such as piperine which interfere with glucuronidation, (ii) liposomal curcumin, (iii) nanoparticles, (iv) curcumin-

phospholipid complexes, (v) curcumin analog structure. (vi) micronization and nanonization (vii) Self Micro Emulsifying Drug Delivery Systems (SMEDDS), (vii) cyclodextrin inclusions, (ix) solid dispersions, (x) nanoemulsions, nano balls, nanobeads, and nanofibers. Nanoparticle-based drug delivery strategies can potentially convert hydrophobic agents such as curcumin dispersed in aqueous media, thereby eliminating poor solubility [10, 11].

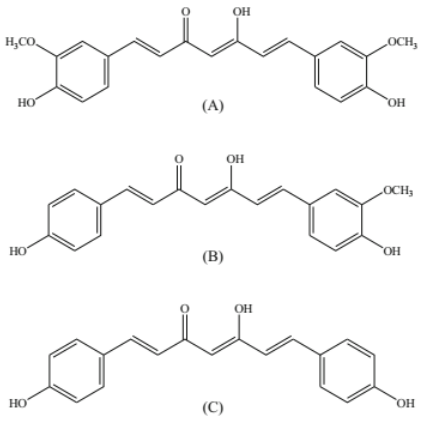

Figure 1. The chemical structure of curcuminoids (A) curcumin, (B) demethoxycurcumin, (C) bisdemethoxycurcumin [12, 13]

2 Methods

This article review took sources from international journals from 2015 – 2021, obtained 91 articles with the keywords "surfactant for curcumin drug delivery system" and "surfactant for curcumin encapsulation". After screening, only 40 articles were used with details: 1 article in 2015, 4 articles in 2016, 4 articles in 2017, 5 articles in 2018, 16 articles in 2019, 6 articles in 2020, and 4 articles in 2021.

3 Result and Discussion

In the development of pharmaceutical preparations, we often deal with interfacial phenomena. In order to avoid this, surfactants are usually added. Surfactants are surface-active substances that are amphiphilic, having polar (Hydrophilic) and non-polar (Lipophilic) groups in the same molecule [14]. When the lipophilic group is weaker than the hydrophilic, the surfactant is water soluble, and the surfactant is oil soluble when the lipophilic group is stronger than the hydrophilic group [15]. Surfactants can reduce surface tension and interfacial tension at gas, liquid and solid interfaces, allowing these substances to diffuse and spread [16]. The role of surfactants is very important in the development of pharmaceutical formulations. Its use is very diverse in drug delivery systems, both conventional and modern delivery systems. The relevance of critical micelle concentrations and Hydrophilic Lipophilic Balance (HLB) values becomes important when selecting surfactants for different drug delivery systems [15].

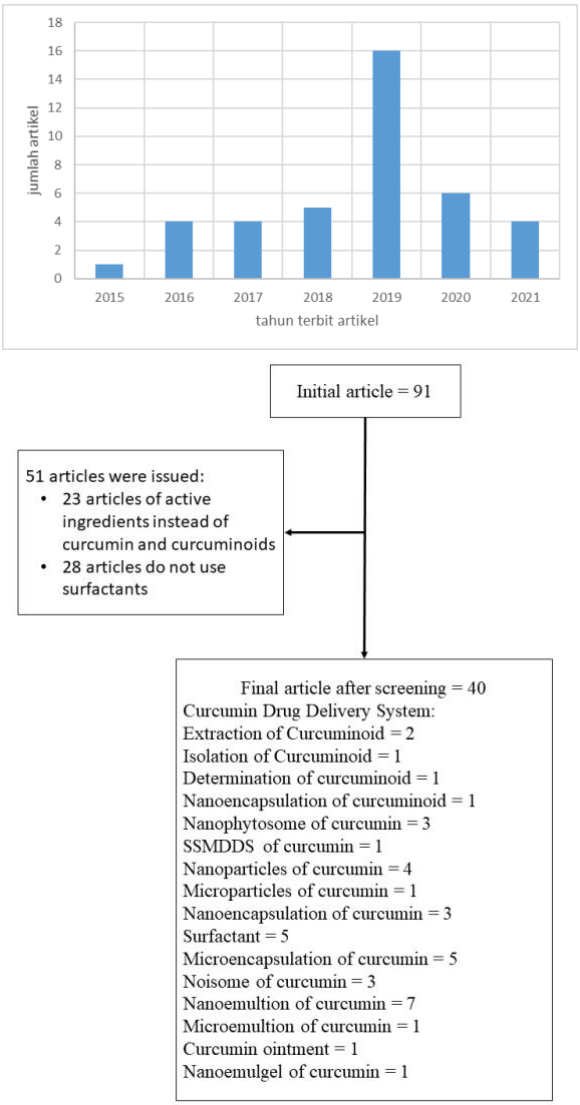

Figure 2. Article collection scheme and article screening

3.1 Critical Micelle Concentrations

The active substance forms micelles or aggregates on the solution surface due to the hydrophobic effect. Surfactants reduce the free

energy in the system by reducing the hydrophobic surface area. The ability of surfactant molecules to lower surface tension depending on the free monomer concentration at which micelle formation begins is called the critical micelle concentration. Ionic surfactants have a higher critical micelle concentration than non-ionic surfactants because the electrostatic repulsion of the head groups makes micelle formation more difficult [15].

3.2 HLB value (Hydrophilic Lipophilic Balance)

The HLB value indicates the polarity of the surfactant, which is used to describe the functional properties of the surfactant. Surfactants with high polarity are given a higher score, while those with low polarity are given a lower score [16].

3.3 Surfactant Classification

Surfactants are classified according to the charge group of the head group.

3.3.1 Anionic Surfactant

These surfactants have a negative charge on their head groups, whereas the straight tail chains consist of aliphatic groups containing saturated/unsaturated carbon chains 12 to 18 (C12-C18). The water solubility potential of these surfactants depends on the double bonds present in the molecule [15]. The most commonly used anionic surfactants are alkyl sulfates, alkyl ethoxylate sulfates, and soaps. Most of the anionic surfactants are carboxylate ions, sulfates, and sulfonates. The presence of double bonds determines the solubility potential in the water.

Anionic surfactant group [16]:

a. Alkaline soap and ammonium: ($C_{18}H_{34}O_2$) oleic acid, ($C_{18}H_{36}O_2$) stearic acid, and ($C_{18}H_{34}O_3$) ricinoleic acid.
b. Divalent dan Trivalent metal soap
c. Amine soap: triethanolamine
d. Alkyl sulfate: fatty acid esters, sodium lauryl sulfate
e. Alkyl fosfate

3.3.2 Cationic Surfactant

This surfactant has a positive charge on its head. Cationic surfactants having a single long alkyl group show good water solubility, whereas surfactants with several long alkyl groups (hydrophobic) are dispensable in water and show solubility in organic solvents. Cationic surfactants are quaternary ammonium compounds and are mostly used for their disinfectant and preservative properties due to their good bactericidal properties. Examples of cationic surfactants: are benzalkonium chloride and cetylpyridinium chloride [15, 17].

3.3.3 Non ionic surfactant

This surfactant has no charge. Can be classified as:

a. Polyol esters: glycol, glycerol ester, sorbitan derivates.
b. Ester polioksietilen: PEG 40, PEG 50, PEG 55
c. Poloxamers

The most commonly used are fatty alcohol ethers [16].

3.3.4 Amfoter Surfactant

These surfactant heads consist of groups of positive and negative charges, known as zwitterionic surfactants. This group is soluble in water but has minimal solubility at the isoelectric point. Surfactants are stable in acidic and basic solvents. The surface activity of amphoteric surfactants depends on the distance between the charged groups so that the maximum surface activity occurs at the isoelectric point. The positive charge is almost always ammonium, while the negative charge can vary, such as carboxylates, sulfates, or sulfonates [15].

3.4 Surfactant Proteins

A total of 10% by weight of protein has been isolated from surfactants. The main part of this protein is serum protein, which is about 80%, and the remaining 20% is specific for surfactants [15].

3.5 Macromolecular Surfactant

Generally, a polymer with a molecular mass higher than 10,000. It can be used as a gelling agent, thickener, emulsifier, fluidity-enhancing agent, and dispersing agent [15].

Surfactants have an important role in drug delivery systems. Surfactants can help increase solubility in manufacturing preparations with hydrophobic active ingredients. Encapsulating hydrophobic drugs into polymer micelles containing surfactants is an excellent alternative

[16]. Surfactants used as emulsifiers generally play a role in surface activity. These surfactants are used to form o/a and w/o emulsions depending on their individual properties. Non-ionic surfactants are effective in the range of pH 3-10; cationic surfactants are effective in the range of pH 3-7; anionic surfactants are effective in the range of more than pH 8 [15]. Surfactants can also affect drug absorption in the gastrointestinal tract by increasing gastrointestinal drug penetration [16].

Polymer or surfactant mixtures have various applications in industry and technology, one of which is used in microencapsulation and emulsion stabilization processes. This mixture can form an adsorption layer on the oil droplets' surface, affecting the emulsion's stability, which depends on the polyelectrolyte or surfactant properties, concentration ratio, emulsification method, and others. Polyelectrolytes exhibit low surface activity in contrast to surfactants, which adsorb at the water or oil interface, forming charged droplets but not sufficient to stabilize the emulsion. When oppositely charged polymers are added to a surfactant solution, a steric barrier is formed, which prevents coalescence and increases stability [18–20].

3.6 Examples of Surfactant Use in Various Drug Delivery Systems

Microencapsulation of curcuminoids using complex coacervation technique using a mixture of gelatin polymer and chitosan (30:1) with a concentration of 2.55%. During manufacture, Tween 80 is added as a surfactant. Curcuminoids were suspended in Tween 80 to reduce surface tension so that when mixed with chitosan and gelatin, each of which had been dissolved in acetic acid, they could be dispersed homogeneously and formed micelles. Then 1M NaOH was added to pH 5.5 and 2.5% formaldehyde from the total colloid volume to produce cross-linked covalent microcapsules. The microcapsules formed were in the form of free-flowing balls with lower color intensity. Microcapsules generally improve heat, light, and oxidative resistance. The increase is shown by the cross-links formed in the capsule. This cross-linking increases the density of the polymer capsule wall, increasing the level of resistance to drug degradation and drug solubility. Overall, it was shown that these curcuminoid microcapsules could be used for topical sustained-release delivery systems [21].

Curcumin niosomes were prepared by solvent evaporation technique, using a mixture of surfactants (0.05 g Span 80, 0.05 g Poloxamer 188, and 0.15 g Tween 80, with a weight ratio of 1: 1: 3), to produce spherical curcumin niosomes which homogeneous and smooth surface without aggregation. Curcumin is thought to bind to lipophilic surfactant molecules, resulting in a more compact particle size and niosome structure of curcumin. The resulting curcumin niosomes are also more stable in storage and produce a constant continuous release pattern and high encapsulation efficiency, which is around 92.3 ± 0.4% [22].

Microencapsulation of curcumin used a polymer mixture of Eudragit RS 100 and RL 100 (70:30) with the addition of 0.02% Tween 80 surfactant. The Comparison of curcumin and polymer 1:5 and 1:10 showed the optimal particle size distribution. The particle size distribution test found that a low polymer concentration resulted in a large particle size which caused several aggregates. Solubility testing showed that microencapsulation increased the amount of soluble curcumin up to 5 times. Meanwhile, encapsulation efficiency yields 70.42% for a 1:5 ratio and 83.40% for a 1:10 ratio. The results of bioavailability testing microencapsulation increase Cmax almost 5 times; this shows that microencapsulation can slow metabolism, increase absorption, and slow release [23].

Preparation of curcumin nanoparticles by evaporation miniemulsification technique, using PLLA and Eudragit S100 encapsulants and lecithin surfactant. High encapsulation efficiency was obtained in formulas containing low levels of curcumin (1% and 3%) and decreased drastically in formulas containing higher curcumin (6% and 12%). The encapsulation efficiency of nanoparticles with Eudragit encapsulant is lower than that of PLLA encapsulant [24].

Turmeric oleoresin microencapsulation using maltodextrin as Tween 80 encapsulant as surfactant. Encapsulation has an important role in the stability of the emulsion. The high emulsion stability is shown by the low creaming index. The higher the viscosity, the lower the possibility of creaming. The Creaming Index decreased due to Tween 80 interacting with oil. Formulas containing Tween 80 provide an average decrease

in the diameter of 52.2% and are more stable than formulas without surfactants [25].

The Niosom Curcumin Formula developed by microfluidic admixture allows the formation of small and monodispersed particles within a few seconds. The preparation of niosomes using a microfluidic mixture of two types of surfactants (Span 80 and Tween 85) with cholesterol aims to observe the effect of changing the type of surfactant on the encapsulation of curcumin. At a ratio of 1:1 parts of oil and water, the change in the type of surfactant from Span 80 to Tween 85 resulted in a significant increase in particle size ($p < 0.05$). However, this is different for the 3:1 ratio, where the particle size and particle size distribution are the same for both surfactants. The use of Tween 85 resulted in significantly higher ($p < 0.05$) encapsulation of curcumin than that prepared using Span 80 at the same ratio. At the same ratio, the only factor that changed was the type of non-ionic surfactant, which significantly impacted the final curcumin encapsulation. In niosomes with Span 80, a ratio of 3:1 resulted in an encapsulation efficiency of 11% curcumin, while in niosomes prepared using Tween 85, a ratio of 3:1 resulted in an encapsulation efficiency of around 60%. The niosomes obtained had an average particle size of 70-230 nm, depending on the type of non-ionic surfactant used and the mixing parameters. In addition, all the niosomes prepared were monodispersity with an average polydispersity index ranging from 0.07 to 0.3. All prepared niosomes were spherical, as shown by transmission electron microscopy. Curcumin was encapsulated with a maximum efficiency of about 60% using Tween 85 as a non-ionic surfactant. Niosomes prepared with microfluidic admixture provide a controlled release of curcumin, as shown by the curcumin release profile can improve its therapeutic ability [26].

In the preparation of curcumin nanoparticles with PLGA encapsulant and Pluronic F68 surfactant, there was a decrease in particle size in the formula using Pluronic F68. This observation is consistent with previously presented results concerning the addition of stabilizers. The cause of the small size effect is thought to be the increase in the viscosity of the aqueous phase resulting in a long mixing time. The small particle size at low concentrations of Pluronic F68 may be due to the predominant effect of surface tension on the change in viscosity. The viscosity of Pluronic F68 solutions at low concentrations is not strong enough to affect particle size. However, it may help to stabilize the surface and to prevent nucleation. These results are consistent with the results of conventional methods, which show a more stable system using stabilizers. Overall, the size differences are very small, and higher stabilizer concentrations can increase the stability of the colloid system. Therefore, 1% Pluronic F68 is the most suitable system. PLGA NP stabilized with Pluronic F68 or Pluronic 10500 did not show strong interaction with mucin from 0 to 180 minutes [27].

Curcumin nanoparticles made with alginate polymers with the addition of Tween 80 as a surfactant, showed a higher encapsulation efficiency of close to 95%, and the resulting nanoparticles were in the range of 105-383 nm. The formulation exhibited very low dissolution in simulated gastric fluids and simulated intestinal fluids. Nanoparticles can be converted into easily re-dispersible powder preparations by either freeze drying or spray drying for applications in nutraceuticals and controlled drug delivery systems. In healthy human volunteers, the oral bioavailability (AUC) of curcumin was increased 5-fold after ingestion of curcumin nanosuspension compared to curcumin suspension [11].

Turmeric nanoemulsion using spray drying technique prepared four formulations, varying the ratio of surfactant: control (lecithin: Tween 20, 1:1). Particle diameter tends to decrease as the moisture content increases, with the smallest droplets (<170 nm) corresponding to a 90% water formulation. In contrast, the formulation containing 75% water exhibited larger droplets (>1000 nm) which were outside the “nano” range and had a high PDI (0.5). Formulations containing 85% water exhibited small droplet sizes (<300 nm) with low PDI (0.23–0.33) and high zeta potential (mean -35 mV). A low PDI value indicates homogeneity in the size distribution, while a high zeta potential measures the droplet surface charge and stability. To determine the effect of replacing Tween 20 with whey protein isolate and the feasibility of the formulation, the surfactant ratios of 1:1:1, 0:1:2, and 1:0:2 of lecithin: Tween 20: whey protein isolate were evaluated and identified as Form-A, B, and C. As a result, Form-B produced droplets with the

smallest diameter (104.2 nm) and PDI (0.15), whereas the other two formulations, which contained lecithin, produced substantially larger diameters. These results are in agreement with previous studies, which reported that using protein emulsifiers resulted in smaller droplets than achieved with other stabilizers [28].

Preparation of curcuminoid microemulsions from soybean oil, Tween 80, ethanol, and water resulted in an average particle size of 10.9 nm, a zeta-potential of 65.2 mV, and encapsulation efficiency of 85.7% with a very homogeneous particle size distribution. TEM images of curcuminoid microemulsions are oval, and the average particle size is 10.2 nm. These results are similar to those obtained by the Particle Size Analyzer. The stability test of the curcuminoid microemulsions was carried out by storing the samples at 4°C and 25°C for 90 days, during which the particle size, size distribution, and zeta potential were determined every 15 days. The results are small differences in the particle size distribution and zeta potential. It shows that the stability of the microemulsion is very high. [29].

A turmeric extract ointment made with the addition of various lecithin surfactants showed a significant decrease in the arthritis index with a 15% lecithin formulation compared to the control group, which was not added lecithin [30].

Turmeric extract nanoemulsion was prepared by adding Tween 80 surfactant and 90% ethanol cosurfactant. Cosurfactants help surfactants reduce surface tension to stabilize the resulting nanoemulsion. Tween 80, as a non-ionic surfactant, is generally safe and biocompatible compared to ionic surfactants. The resulting particle size is 16.2 nm with a polydispersity index of 0.243 (the particle size distribution is quite homogeneous) [31]

The development of curcumin nanoemulsion formulations to be made into coated tablets begins with the solubility orientation of curcumin in oil. In solubility orientation, several oil types were used: Capmul, oleic acid, castor oil, sesame oil, corn oil, and peanut oil. In addition, surfactants (Labrasol and Kolliphor) and cosurfactants (Transkutol) are used. The results of the solubility test using a spectrophotometer at a wavelength of 428 nm, the result is that the greatest solubility of curcumin in a mixture of oil and surfactants, namely Capmul: Labrafac (1:1) is 45.33 mg/mL [32].

Ang et al. researched the production of curcuminoid microcapsules using the coacervation complex method, using a combination of carrier gelatin B and chitosan (at an optimal ratio of 30: 1% w/w). Gelatin B and chitosan were each dissolved in 1% w/w acetic acid. Curcuminoids (0.2 g) were suspended in Tween 80, then dispersed in 20 mL of chitosan solution using a stirrer at 1000 rpm and 50°C for 30 minutes. After that, 20 mL of gelatin solution was added at the addition of 1 mL/minute using a syringe pump (Green Streamfi SY-P Argus 600, ARGUS Medical AG, Heimberg, Switzerland) at a speed of 500 rpm and a temperature of 50°C, both of which were kept constant. (IKAfi Werke Staufen, Breisgau, Germany). The colloidal pH was adjusted to pH 5.50 by adding 1 M NaOH solution. Stirring at 500 rpm was continued for 4 hours at 50°C to induce coacervation. The liquid coacervate was cooled to room temperature gradually, then cooled rapidly to <10°C by incubating the system in an ice bath with constant stirring for 1 hour. 1 mL of formaldehyde was added dropwise to the system and stirred for 30 min to produce covalently crosslinked microcapsules. The coacervate containing the drug was washed with ethanol 3 times, then with cold distilled water for the final wash. Then centrifuged at 1000 rpm for 5 minutes at a constant temperature of 10°C. Then, the coacervate formed was frozen overnight at -70°C followed by freeze-drying. Freeze-dried microcapsules were stored in airtight glass vials, protected from light, and stored in a desiccator [33].

Another study regarding the formulation of curcumin SNDDS was conducted to determine the effect of surfactants and cosurfactants on the efficiency and stability of SNDDS. The research was started by determining the solubility of curcumin in various oils until 4 types of oil were selected which showed maximum solubility, namely eucalyptus oil, coconut oil, almond oil, and olive oil. Next, determining the type of surfactant and cosurfactant, which resulted in maximum solubility, was carried out, and Tween 80 and Transcutol HP were obtained. Tween 80 has an HLB value of 15, which shows a synergistic effect in reducing interfacial tension and helping to form stable nanoemulsions. Meanwhile,

Transcutol HP can improve the stability and efficiency of emulsification well. The curcumin SNDDS formula using Tween 80 and Transcutol HP showed the smallest particle size and low polydispersity index (59.56 ± 0.94 and 0.207). The combination of Tween 80 and Transcutol HP (1:1) produces a thermodynamically stable curcumin nanoemulsion product with good emulsification efficiency, minimum droplet size, higher in vitro release, and optimal drug diffusion [34].

Research on the effect of emulsifiers on the stability of curcumin nanoemulsions was carried out with five different types of emulsifiers, namely Tween 80, Span 80, sodium dodecyl sulfate, soy protein isolate, and lecithin. The results concluded that Tween 80 and Lecithin produced good stability, high adsorption effect, and good bactericidal properties in nanoemulsions after stability tests were carried out both at room temperature and by heating [35].

In-situ preparation of ophthalmic nanoemulgel using Pluronic F127 polymer, Tween 80 surfactant, and Transcutol P cosurfactant. The comparison of surfactant and cosurfactant was used (1:0.5), while the ratio of curcumin and polymer made several concentration variations. This study aimed to develop an in-situ curcumin ophthalmic nanoemulgel using Pluronic F127 as a thermosensitive polymer to extend the period of the drug in the ocular area, thereby reducing the frequency and increasing patient compliance. Pluronic F127 was added slowly in 20 ml of distilled water with continuous stirring, then stored in the refrigerator until clear. In a separate container, curcumin is dissolved in a mixture of oils, surfactants, and cosurfactants. Then vortexed until a clear solution was obtained and stored at room temperature. Then 1 ml of the drug solution was added to the polymer solution and homogenized at high speed until a homogeneous gel was formed. An optimal formula is obtained with the composition of curcumin:oil:Tween 80:Transcutol P:Pluronic F127 (1:15:10:5:3) [36].

Developing a curcumin nanoemulsion formula for transdermal use begins with screening for oils, surfactants, and cosurfactants to be used during formulation. The oils used were oleic acid, olive oil, almond oil, castor oil, clove oil, coconut oil, ethyl oleate, isostearyl isostearate, and Arachis oil. Surfactants and cosurfactants are selected based on biodegradability and ease of obtaining. The materials used are Tween-20, Labrasol®, Tween-80, Labrasol, PEG-400, PEG-200, propylene glycol, carbitol, and ethanol. Oils, surfactants, and cosurfactants were used as excipients, and their selection was based on the solubility of curcumin, leading to a stable nanoemulsion. Screening results for curcumin solubility and nanoemulsion stability were obtained from clove oil (oil), Tween-80 (surfactant), and PEG-400 (co-surfactant). Nanoemulsion preparation was carried out by microtitration and ultrasonication methods. The optimal formulation is obtained with a composition of 5% oil, 10% surfactant, and cosurfactant, ultrasonication time of 10 minutes, ultrasonication intensity of 40%, and temperature of 50°C [37].

Formulation of curcumin solid lipid nanoparticles using Cutina® HR as solid lipid, Carbopol 934, and soy lecithin as hydrophilic and lipophilic surfactants. Parameters for evaluation of formulations were drug content, entrapment efficiency, in vitro drug release, particle size, zeta potential, SEM (Scanning Electron Microscope) analysis, and stability studies. Formula C (1:1:1) obtained good results with an evaluation of drug content of 83.1%, entrapment efficiency of 67.2%, drug release of 66.1%, the particle size of 796 nm, and zeta potential of -29.4 mV. This study demonstrated that drug solubility was enhanced by trapping the drug into the solid lipid carrier, leading to prolonged drug release time [38].

Curcumin nanoemulgel was prepared by high energy ultrasonic emulsification technique at the minimum concentration of surfactant required for the nanoemulsion system. Labrafac was chosen as the oil phase, Tween 80 and PEG 400 were chosen as the Smix phase (a combination of surfactant and co-surfactant) based on the curcumin solubility. Smix phase concentration variations were made (1:1, 2:1, 3:1, 4:1, 5:1). Initially, a homogeneous dispersion system was prepared by mixing 1% w/w (10 mg/g) curcumin in a mixture of the oil phase and Smix phase (with a ratio of 1:1 and 2:1) by vortexing. After that, the aqueous phase was added by continuous vortexing for 1 minute. Then it was ultrasonicated for various durations (3 and 5 minutes) at a constant ultrasonic amplitude of 40%. A Smix ratio of 2:1 indicates a droplet size of <100 nm. The droplet sizes varied from 84.23 ±

1.33 to 49.61 ± 0.53 nm, and the PDI varied from 0.23 ± 0.05 to 0.10 ± 0.01. Nanoemulsified curcumin prepared via high energy ultrasonic emulsification technique could achieve droplet size <100 nm at significantly lower Smix concentration ($p < 0.05$) compared to curcumin nanoemulsion prepared via low energy spontaneous emulsification technique. It is widely seen that nanoemulsions prepared by low-energy spontaneous emulsification techniques generally require two or more times the Smix concentration relative to the oil concentration in the NE composition to achieve a droplet size of <100 nm. While NE prepared via high energy ultrasonic emulsification technique can achieve the same droplet size even at Smix concentration less than 1.5 times relative to oil concentration. The droplet size of the nanoemulsion can be affected by the emulsification technique, the type of oil, surfactant, and the cosurfactant used [39].

A study of a self-nano emulsifying drug delivery system (SNEDDS) to improve the oral bioavailability of curcumin was initiated by selecting the oil, surfactant, and cosurfactant phases. The selection of the oil, surfactant, and cosurfactant phases was based on the emulsification ability and the ability to dissolve curcumin. Tween 80, PEG 200, and cinnamon oil were selected as surfactant, cosurfactant, and oil phase, respectively. The emulsification potential of surfactants is determined by analyzing the amount required to emulsify the lipid phase in water. The oil (300 mg) was mixed with equal amounts of various surfactants, followed by heating at 45-50 °C, then added to 30 mL of water. The percent transmittance of the mixture was observed at 638 nm with a UV-vis spectrophotometer using distilled water as a blank. The selection of co-surfactants is based on their efficiency in increasing the emulsifying ability of surfactants. The turbidimetric method was used to select the appropriate co-surfactant from various co-surfactants. For this purpose, the selected surfactant is mixed with various cosurfactants in a ratio of 2:1 to produce a mixture referred to as an "S-mixture". The mixture was heated at 45-50°C to homogenize the constituents, followed by adding oil to the S-mixture at a ratio of 1:1. Each resulting mixture (300mg) can be emulsified with 30 mL of distilled water to give a nano-emulsion. The transparent nano-emulsion was observed for relative turbidity and allowed to stand for 2 hours, and then the transmittance percentage was recorded as was done when selecting surfactants. Drug solubility studies assessed suitable surfactants, oils, and cosurfactants for developing curcumin's SNEDDS. Cinnamon oil has the highest curcumin dissolving capacity (11.33 mg/mL). Likewise, among surfactants and cosurfactants, Tween 80 and PEG 400 showed the highest dissolving ability of 98.23 mg/mL and 94.87 mg/mL, respectively. The highest solubility in cinnamon oil is a result of the polar nature of this oil. Curcumin has two hydrogen bond donors, which can easily interact with polar mediums through hydrogen bonds and pi-pi interactions. The ability of cinnamon oil to dissolve curcumin could be due to cinnamaldehyde's presence, which makes the oil more polar. Based on the percent transmittance and drug solubility, Tween 80 was selected for the preparation of SNEDDS.

The addition of cosurfactants in lipid-based formulations aims to improve drug dispersibility and absorption. Based on the good surfactant solubility and emulsification, PEG 200 was chosen as a cosurfactant to design and develop the desired SNEDDS formulation. The optimal formulation contains 30% of selected surfactants, co-surfactants, and 40% oil. Distributed nano-size droplets (106.44 ± 22.27 nm) with a surface negative of -26.2 ± 2.43 mV after drug loading were obtained. The developed SNEDDS is very stable and increases bioavailability. Droplet size is considered an important parameter for assessing SNEDDS because it affects the storage and stability of the emulsion in-vivo upon oral administration. In addition, droplet size significantly affects drug release and absorption. Smaller droplet sizes (106.44 ± 22.27 nm) were obtained, with the formulation having an oil content of 40% followed by 46.7% and 50% oil, respectively. It shows a direct relationship between droplet size and oil concentration (size decreases as oil concentration decreases). Second, the droplet size is also affected by surfactant concentration. Increasing surfactant concentration results in smaller droplet sizes. The formulation showing the smaller droplet size had a 30% larger surfactant concentration than the formula containing a relatively lower surfactant concentration (23.3% and 26.7%, respectively). In the case of the cosurfactant, the droplet size

increases with increasing cosurfactant concentration. This phenomenon can be attributed to interfacial disturbance due to increased water permeation into oily droplets due to increased concentration of cosurfactant. The zeta potential provides information regarding the stability potential of the dispersing colloids. Particles with greater positive or negative zeta potential provide dispersion stability and resist aggregate formation because like-charged particles repel each other. On the other hand, a lower zeta potential value indicates that the particles do not have enough ability to remain suspended because no force can protect the particles, causing aggregation and causing dispersion instability [40].

4 Conclusion

According to the author, surfactants play an important role in the curcumin delivery system. Surfactants can help reduce particle size, increasing absorption, penetration, and stability to improve bioavailability and the therapeutic effect is more optimal. The selection of the right surfactant will affect the results of the preparation.

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