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Original Article

Preparation and Development of Self Nano Emulsifying Drug Delivery System of Curcumin

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Abstract: Curcumin, the main pharmacologic agent in turmeric, is known to have a wide spectrum of biological and pharmacological activities which could be utilized in various medical applications; however, it is unable to be used in a formulation due to its poor water solubility. In order to overcome solubility issue, curcumin can be formulated into a self-nanoemulsifying drug delivery system (SNEDDS). Therefore, solubility of curcumin was first tested in various oils including castor oil (with highest solubility around 72%), soyabean oil (solubility of 56%), black seed oil (with least solubility around 3.8%), and olive oil (solubility of 18%) to formulate an O/W nanoemulsion. The ability of emulsification of selected oils by various surfactants (Tween 20, Tween 80) and co-surfactants (PEG 600, PEG 400) were screened. A systematic procedure was used to develop a formulation using curcumin (10 mg), Tween 20/Tween 80 (2 ml) and PEG 400/PEG 600 (10 mg). Formulation prepared using Tween 20 showed highest transmittance of 68% and PEG 600 gave a fine cloudy emulsion. This formulation has the ability to self-emulsify upon mild agitation (peristaltic movement of GIT) followed by dilution in gastric fluid (aqueous medium). SNEDDS of curcumin was further characterized in terms of percentage transmittance, stability testing (stable for 30days in room temperature), emulsification time (2min), dispersibility test, drug content, phase separation, droplet size (mean size 100 nm), polydispersity index (PDI) and zeta potential. The study is mainly focused on the factors necessary for successful development of lipid formulation classification system (LFCS) Type IIIB SNEDDS formulation, which can improve solubility leading to better bioavailability and therapeutic response.

Keywords: SNEDDS; nano-emulsion; drug loading; solubility; novel drug delivery system; amphipathic.

1. Introduction

Curcumin (diferuloylmethane), a phenolic compound with antioxidant property, is considered as the main pharmacological agent in turmeric and is known as the wonder drug of life [1]. It possesses effects such as anti-inflammatory, antibacterial, antifungal, antiyeast, antihypocholesterolemic,anticancer, antimutagen, antiparasitic,

antitumor promoting, antiproliferative, multidrug resistance (MDR) modulator effects, and so on. It is also effective in the prevention and alleviation of gastric lesions. The chemical structure of curcumin is shown in **Figure 1**. Powdered dry rhizome of *Curcuma longa Linn* is used to isolate first grade curcumin which contains approximately 77% curcumin, 17% desmethoxycurcumin, and 3% bisdemethoxycurcumin (**Figure 1**). The maximum absorption wavelength for the detection of curcumin is ~425 nm [2,3].

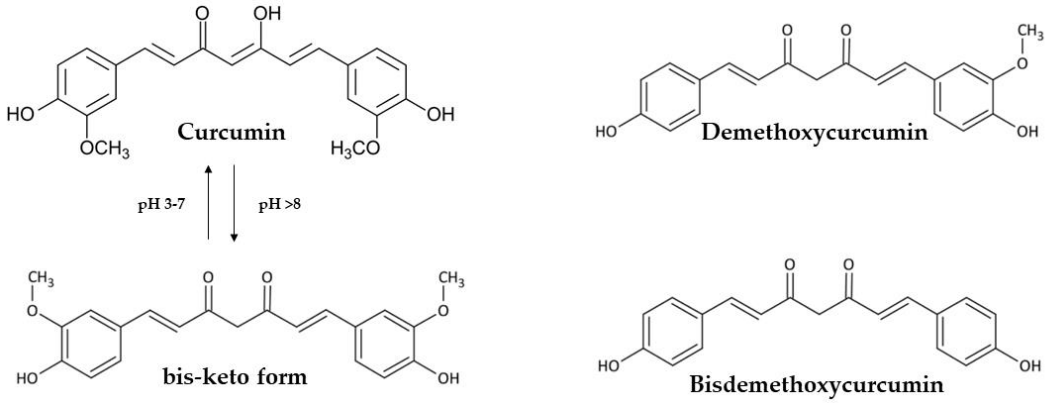


Figure 1: Structure of curcumin and curcuminoids

Curcumin is categorized under the biopharmaceutical classification system (BCS) class II and IV. For which, curcumin has some significant drawbacks such as, poor water solubility, low absorption, and rapid metabolic elimination, hence results in low bioavailability limiting its medicinal applications. Due to low solubility, it becomes a challenge to achieve suitable levels in plasma. As a result, the desired pharmacological effect is not observed [4-7]. To address such issues, the key approaches to maximize oral drug absorption include four major ways. Firstly, P-glycoprotein (P-gp) inhibitors can be used to improve the efficiency of drug transport. The overexpression of P-gp causes the exclusion of the drug from the diseased site and causes reduced accumulation at the targeted site of action. So, inhibiting P-gp can help absorb the drugs and in turn increase its bioavailability. Secondly, permeation enhancers can be used to inhibit drug degradation and improve permeability. In such cases, surfactants (commonly Tween 80) play a vital role. Thirdly, metabolism of curcumin can be reduced by complexing it with piperine so that it is available in the circulation for longer time. Finally, nanoparticles, microparticles and liposomes can be formulated to improve the solubility and absorption of the drug and protect it from harsh environment of the gastrointestinal tract [8-9]. Curcumin can be encapsulated into polymeric nanoparticles that allow an easy dispersion in aqueous media; self-emulsification in a lipid-based dosage form that controls the release of the compound and at the same time protects and improves the delivery efficiency of it [10-11]. The structural characteristics give an emulsion to incorporate hydrophobic and amphipathic drugs. Since curcumin has a hydrophobic nature, a lipid nano-emulsion (SNEDDS, for its self-emulsifying ability) can be a promising vehicle for the delivery of curcumin. Lipid based drug delivery system can be used to overcome problems related to solubility and bioavailability along with other issues

related to cost, stability, toxicity, route of administration, disease identification and efficiency. SNEDDS fall under lipid-based formulation classification system Type IIIB (**Table 1**) [12-14].

Table 1: Lipid based formulation classification system.

Content of Formulation (%w/w)					
Excipients in Formulation	**Type 1 OIL**	**Type 2 SEDDS**	**Type 3A SEDDS**	**Type 3B SNEDDS**	**Type 4 OIL-FREE**
Oils, tri, di, and mono glycerides	100	40-80	40-80	<20	-
Water insoluble surfactants	-	20-60	_	_	0-20
Water soluble surfactants	-	-	20-40	20-50	30-80
Hydrophilic co-colvents	-	-	0-40	20-50	0-50
Types of dispersion	Limited or no dispersion	Rapidly dispersing	Rapidly dispersing	Transparent dispersion	Micellar solution
Digestion requirement	Requires digestion	Likely to be digested	Digestion may not be necessary	Digestion may not be necessary	Limited digestion

There are five grades of nano-emulsions. Amongst which, grade A nano-emulsions have a clear and bluish appearance, grade B nano-emulsions form rapidly and has a slightly less clear appearance which is bluish white, grade C nano-emulsions have a fine milky appearance that is formed in two minutes, grade D nano-emulsions have a dull and greyish white oily appearance that takes longer than 2minutes to emulsify, and grade E nano-emulsions exhibit a poor or minimal emulsification with large oil globules present on the surface. Grade A & Grade B formulation will remain as nano-emulsion when dispersed in GIT. Formulation falling in Grade C could be recommend for SNEDDS formulation [15-16].

SNEDDS (Self Nano Emulsifying Drug Delivery System) is thermodynamically and kinetically stable isotropic mixture of oil, surfactant, co-surfactant, and drug that helps form fine oil-in-water nano-emulsion (Lipids Based Formulation Class IIIB) of 20-200 nm size range. It is a novel drug delivery system that can be used in delivery of drugs via parenteral, intranasal, and ophthalmic routes as well. SNEDDS offer an improvement in bioavailability, and reproducibility in plasma profiles of drugs. The ability of the SNEDDS in enhancing C_{max}, oral bioavailability and therapeutic effect has been established for various hydrophobic drugs. Apart from these, SNEDDS also provide protection for the sensitive drugs in the hostile environment of the gut and also reduces plasma concentration variability due to food effects. Moreover, it provides a high drug payload and quick onset

of action. On the contrary, SNEDDS is not a suitable delivery system for the administration of drugs that require very high dose for showing therapeutic effect. At the same time, there is a lack of good predicative in vitro models for assessment of formulations as it requires digestion before the release of the drug alongside the presence of gastric fluid where the nano-emulsion is formed via peristatic movement. In order to overcome this issue, lipid-based formulations need to be developed and tested in vivo in an animal model. SNEDDS have the ability of forming fine oil-in-water (o/w) nano-emulsions after mild agitation followed by dilution in gastric fluids that is an aqueous media. SNEDDS easily spread in the gastrointestinal tract and provides a large interfacial area, and the peristaltic movement of the stomach and the intestine provides the agitation necessary for self-emulsification (**Figure 2**). A larger interfacial area helps increase the activity of pancreatic lipase to hydrolyze triglycerides and, thus, results in a faster release of the drug. In most cases, the surfactant used for such emulsions increases the bioavailability of the drug by activating various mechanisms and helps maintain the drug to remain in solution. In addition, this helps avoid the dissolution step from crystalline state. At the same time, this enhances intestinal epithelial permeability. The oil droplets induce a faster and more consistent distribution of the drug in the gastrointestinal tract, which minimizes the irritation caused by the drug on the gut wall. Moreover, lipids affect the oral bioavailability of drugs by protecting the drug from enzymatic or chemical degradation in the oil droplets. Upon mixing with water, they form fine colloidal droplets with a very high surface area [17-24].

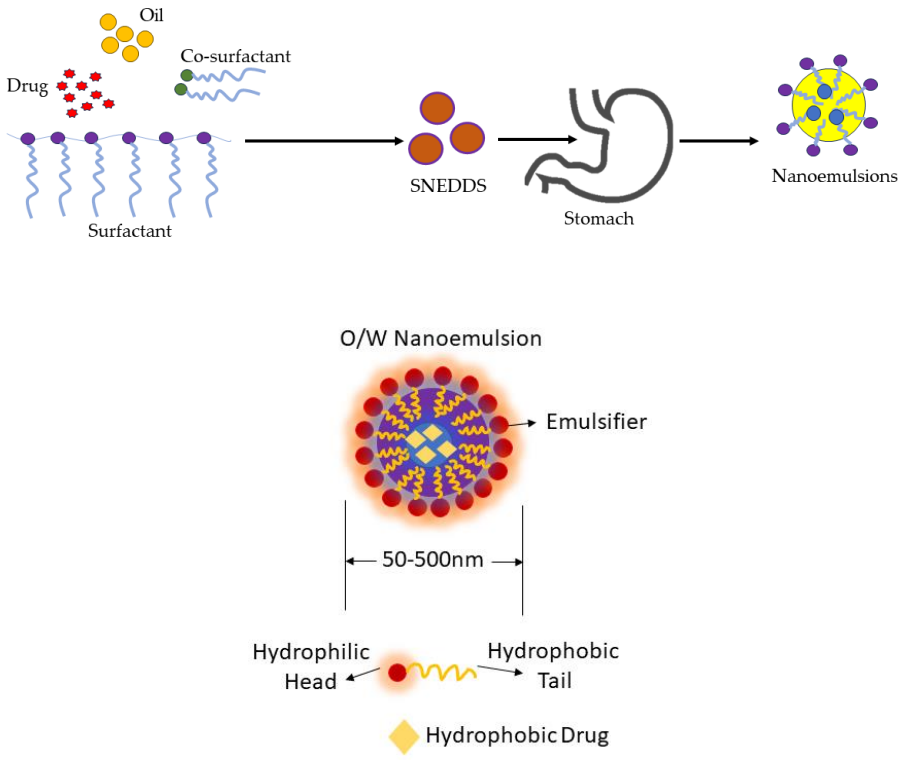


Figure 2: Formation of nano-emulsion in GIT.

2. Materials and methods

2.1 Materials

The sample of curcumin used in this study was extracted using fresh turmeric. Castor oil, soya bean oil, black seed oil and olive oil were extracted for solubility analysis. Tween20, Tween80, PEG600 and Acetone (HPLC grade) were purchased from Merck. Lechithin, PEG400, distilled water, concentrated HCL, potassium dihydrogen phosphate, NaOH pellets etc. were obtained from the laboratory.

2.2 Methods

2.2.1 Extraction Process

At first the raw turmeric was chopped and dried with care to make it free from contaminants. The dried turmeric (**Figure 3a**) was grinded in a new blender and sieved with a strainer to remove all lumps and 120g of turmeric powder (**Figure 3b**) was obtained. 26g of powder was taken in each 2000ml clean dry conical flask (4 conical flasks). The conical flask was rinsed with acetone. 1500ml acetone was added in each conical flask. Then the conical flasks were mounted on a digital shaker (**Figure 3c**) and were shaken for 7 days. Acetone is used as solvent as it can yield the maximum amount of curcumin. After 7 days, the solution was filtered to obtain the liquid portion only. Then the filtered liquid solution was taken in a round bottom flask and placed on the rotary evaporator. Then the flask was rotated at 100rpm with vacuum turned on and then the flask was lowered into the water bath at a temperature 44˚C. After 30-40 minutes, once all the solvent has been removed, the vacuum line was closed, and rotation was stopped. Following this, the flask was raised from the water bath and removed from the adapter. The compound was scraped out of the flask for downstream use (**Figure 3d**). After rotary evaporation, the sample obtained were in two phases, solid (**Figure 3e**) and semi-solid (**Figure 3f**) in consistency.

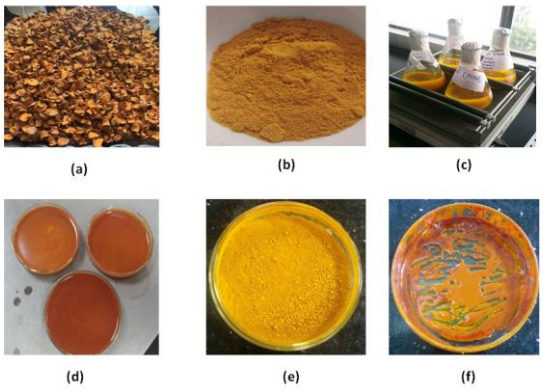


Figure 3: (a) Dried turmeric, (b) Powdered turmeric, (c) Curcumin and acetone loaded on digital shaker, (d) Curcumin obtained after evaporation in rotary evaporator, (e) Solid phase of extracted sample, (f) Semi-solid phase of extracted sample.

Ultraviolet Spectrophotometer was then done to determine the concentration of curcumin in each of the samples. In order to do so, at first, 1 mg of each sample was measured in a beaker and with the help of a syringe; 9 ml of acetone was transferred into the beaker. Then it was observed under the UV-Spectrophotometer at λ_{max}=421nm.

2.3 Oil screening

To check the solubility of the sample oil screening is done as an assessment. The assessment compares the solubility of the sample in different kinds of oil. After obtaining two kinds of sample we took the semisolid sample and ran it with four different oils namely, olive oil, castor oil, black seed oil and soya bean oil. Four 25 ml beakers were taken and in it we measured 5 micro grams of sample and added 10 ml of each solvent to every beaker. With the help of a magnetic stirrer the beaker was put on a hot plate and ran for 48 hours. After 48 hours it was seen that only castor oil dissolved all the sample, and the other oils did not dissolve the sample completely. A new 25 ml beaker was taken and 20mg of sample was added in 10ml of castor oil. After 5 hours it was seen that 20 mg was dissolved completely and so we added more samples until no more sample was dissolved. We added the sample in milligram in 10 hours interval mentioned in **Table 2**.

Table 2: Solubility analysis of curcumin at different time intervals.

Hours	Sample in mg
5	20
5-10	40
10-20	80
30-40	100
40-50	200

We found that a total of 720 mg was added after which sediment was seen.

2.4 Centrifugation

Centrifugation, a separation technique, helps separate particles from a solution and produces supernatant and precipitate. The precipitate is formed according to their size, shape, density, viscosity of the medium and rotor speed. The tube containing particles suspended in a liquid medium is placed in a rotor and spun at a defined speed. Our sample (**Figure 4**) was filled in 6 eppendorf and the other 6 eppendorf contained water. Then it was centrifuged for 15 min at 12000 rpm and 10 Degree Celsius.

Figure 4: Eppendorf tubes containing Castor oil after centrifugation.

Filtration was done to obtain the supernatant by using a syringe filter of 0.2 macro size, which is then run though UV-vis spectroscopy. Ultraviolet–visible spectroscopy (UV-Vis or UV/Vis) is an absorption spectroscopy in the ultraviolet-visible spectral region. Under the observation of UV Spectrophotometer, we obtained the following results at a wavelength of 421 nm (**Table 3**).

Table 3: UV analysis.

Sample Number	WL 421nm
1	2.834
2	2.683
3	2.591
4	0.500
5	0.502
6	0.504

2.5 Calibration curve

In analytical chemistry, a calibration curve, also known as a standard curve, is a method that compares a sample with unknown concentration with that of a set of standard samples with known concentrations to determine the sample with unknown concentration. 1 mg of reference standard sample was taken and diluted with 9 ml of acetone to obtain a calibration curve (**Figure 5**).

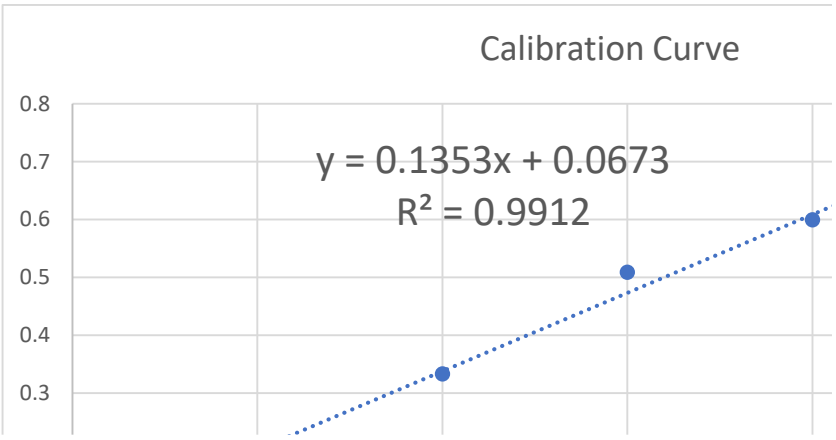


Figure 5: Calibration Curve

2.6 Pre-formulation studies

Screening of surfactants and co-surfactants for SNEDDS formulation of curcumin nanoemulsion:

Different surfactants Tween® 20, Tween® 80 and Lecithin were screened for emulsification ability of the selected oil phase. Surfactant selection was performed based on percent (%) transparency and ease of emulsification. Briefly, 1ml of the surfactant was added to 3ml of water, 1ml oil and 5mg Curcumin. It has been reported that well-formulated SNEDDS is dispersed within seconds under gentle stirring conditions, which ultimately depends on the emulsification ability of the surfactant. The mixture was gently stirred in a vortex mixture for 10-15 minutes. Results refer to the highest emulsification efficiency with castor oil and Tween 20 together. On the contrary, castor oil showed reduced emulsification properties with other surfactants. For this reason, the use of castor oil as oil phase and Tween 20 as surfactant was selected for further study. The resulting emulsions were observed visually for the relative turbidity in dissolution vessel. Co-surfactants were screened for SNEDDS formulation, which included PEG 400, PEG 600. The screening of the co-surfactants was conducted based on percent (%) transparency and ease of emulsification [25-27].

Assessment of emulsification improvement through addition of co-surfactant:

1:2 (oil: surfactant) has a proportion of surfactant too high to develop a cost effective optimum SNEDDS formulation. 15mg of the chosen co-surfactant is added to the oil/surfactant ratio to enhance their emulsifying capacity. The resulting emulsions were observed visually for the relative turbidity. Then the emulsions were allowed to stand overnight to see if there is any phase separation.

2.7 Optimization of formulation attributes

Based on the pre formulation studies that offered an understanding of the efficacy of SNEDDS formulation designed by the manipulation of the types and relative quantity of the excipients and solubility of curcumin in the excipient selected for the formulation process (959mg in castor oil), the following ratio (**Figure 6**) of excipients was fixed to formulate SNEDDS containing 25mg of curcumin.

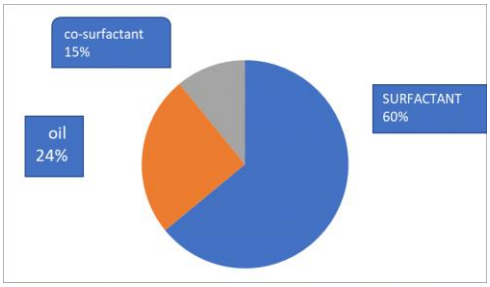


Figure 6: Ratio of Excipients for proposed SNEDDS formulation

Process A: The formulation process can be conducted by the conventional approach where the drug is mixed with surfactant, and co-surfactant and sonicated in a water bath type sonicator for 30mins. Then a specific amount of oil is mixed with the sonicated concoction. Finally, it is stirred for 15minutes with a magnetic stirrer (**Figure 7**).

Process B: It is an alternative process that resulted in a much preferable outcome, both in terms of stability of our SNEDDS formulation as well as the facilities offered by our laboratory setup. In this process, 25mg of curcumin is dissolved in 1ml castor oil. Concurrently, a specific ratio of surfactant and oil is mixed. Then the mixture is vortexed at high speed (3000rpm) for 30 minutes that produced a homogenous mixture (**Figure 7**).

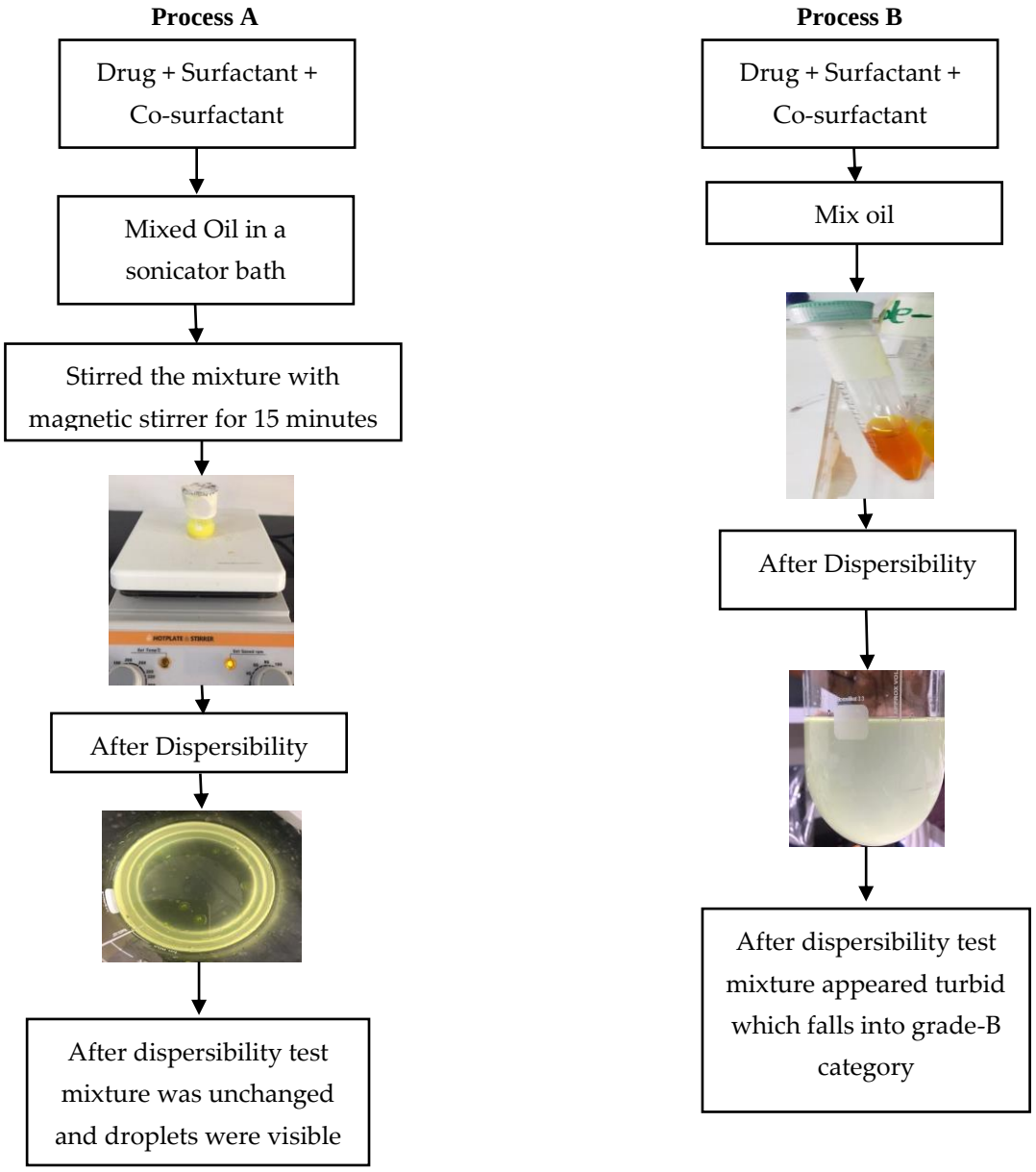


Figure 7: SNEDDS emulsification steps of process A and B.

2.8 Optimization of process prameters using design of experiment (DoE)

Process parameters are the measured values of a particular part of a process which is being monitored or controlled. It enables us to exert control over specific steps of the formulation process and identify the parameters that yield considerable influence on the outcome of the process, and the quality attributes of its output. The production parameters are affected by critical process parameters (CPPs). CPPs are specific attributes that are monitored to detect any sort of deviations related to production operation, changes in Critical Quality Attributes (CQAs) and changes in product output quality. The attributes that have a higher impact on CQAs should be prioritized. Acceptable range limits of the CPPs need to be set by the manufacturer to define acceptable process variables. The process variables of Process B were optimized by design of experiment (DoE) and studied as mentioned in **Table 4**.

Table 4: Process parameters by design of experiment (DoE).

Formulation Number	**Process parameters**		
	Speed	**Time**	**Surfactant**
1	High - 3000	High – 30mins	High – 1mL
2	High - 3000	High – 30mins	Low – 0.5mL
3	High - 3000	Low – 15mins	High – 1mL
4	Low - 1500	High – 30mins	High – 1mL
5	Low - 1500	High – 30mins	Low – 0.5mL
6	Low - 1500	Low – 15mins	Low – 0.5mL
7	High - 3000	Low – 15mins	Low – 0.5mL
8	Low - 1500	Low – 15mins	High – 1mL

2.9 Dispersibility test

A standard USP XXII dissolution apparatus 2 is used to determine the efficiency of self-emulsification of oral nano or micro emulsion. One milliliter of each formulation was added to 500ml of water at 37±0.5˚C where a standard stainless-steel dissolution paddle rotating at 50rpm provided gentle agitation.

Grading system visual observation of self-emulsifying formulations:

Grade A: Rapidly forming (within 1 minute) nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 minutes.

Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2min).

Grade E: Formulation exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A & Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SNEDDS formulation [15-16].

2.10 Determination of emulsification time

The primary means of self-micro emulsification assessment is visual evaluation. The efficiency of SNEDDS could be estimated by using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500ml of water at 37±0.5˚C. A standard stainless steel dissolution paddle rotating at 100rpm provided gentle agitation or a glass beaker containing water at 37˚C and the contents being mixed gently with a magnetic stirring bar at 100 rpm & determining the time required to form micro emulsion upon dilution of SNEDDS with water.

2.11 Droplet size analysis

Droplet size of (SNEDDS) was determined by photon correlation spectroscopy that uses a Zeta sizer 100HS (Malvern Instruments, UK) to analyze the fluctuations in light scattering. This light scattering occurs due to Brownian motion of the particle. The parameters to monitor light scattering was 25˚C temperature at 90˚ angle. The optimized nanoemulsion sample was diluted by distilled water placed in quartz cuvette and subjected to droplet size analysis.

2.12 Stability study

In order to determine the quality and purity of a nanoemulsion system, stability study plays a vital role. Stability studies conducted in a nanoemulsion include the determination of stability under mechanical stress condition, and at different room temperatures for specific time intervals. The stability under mechanical stress condition was determined by observing the percent phase separation, physical changes and breaking of nanoemulsions.

3. Results and Discussion

3.1 Curcumin quantification after extraction

The curcumin extracted from turmeric powder was in two phases, solid and semi-solid. The quantification of curcumin in both phases performed using UV spectroscopy shows that high percentage of curcumin is present in the semi-solid phase (**Table 5**).

Table 5: Amount of Curcumin (mg/g, % w/w) present after extraction from semi-solid and solid sample [Data are presented as ±SD (N=3)].

Sample number/Name	Mass (mg/g)	%	SD
Curcumin Semi-solid	156.00	15%	1.01
Curcumin Solid	45.56	4.5%	0.54

3.2 Preformulation studies

3.2.1 Solubility analysis of Curcumin in various natural oils

The ultraviolet spectrophotometry results suggested that the highest amount of curcumin was dissolved in castor oil and was least dissolved in black seed oil. The percentage solubility of curcumin in different oils obtained is as follows, Castor oil = 72%, Soybean oil =56%, Olive oil = 18%, and Black seed oil = 3.8%. These oils were selected to develop SNEDDS formulation due to their easy accessibility, cost efficiency, lower toxicity in comparison to synthetic oils and synergistic health benefit potential (**Figure 8**).

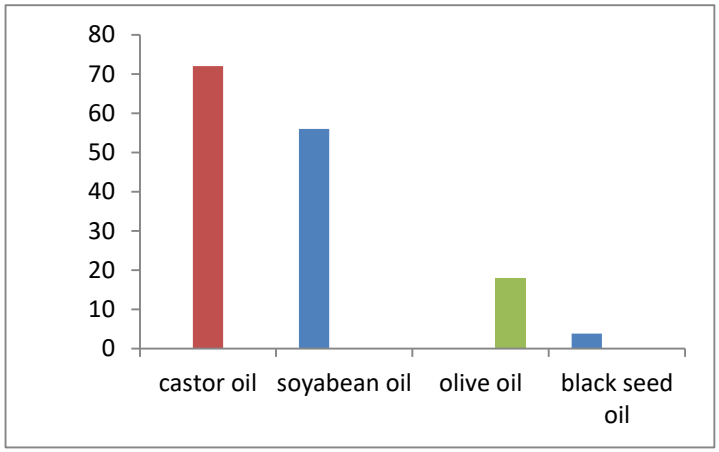


Figure 8: Solubility of curcumin in various oils.

3.2.2 Screening of surfactants for SNEEDS formulation of Curcumin

The average percentage transmittance values obtained from surfactant screening studies between Tween 20 and Tween 80 portray higher emulsifying capacity of Tween 20 in castor oil. The percentage transmittance of emulsion formed with Tween 20 in 68%, in contrast with 43% as depicted by Tween 80. A higher percentage transmittance indicates lower turbidity of emulsion, alternately, a finer emulsion for this reason, Tween 20 is more suitable for SNEDDS preparation (**Figure 9**).

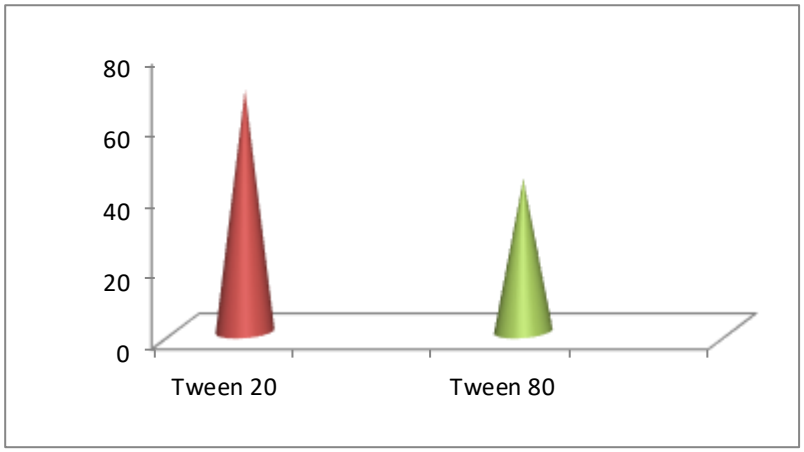


Figure 9: Comparative transmittance of surfactants.

3.2.3 Screening for co surfactant

Emulsification capacity was greatly enhanced by PEG 600 than the latter PEG 400. PEG 400 was unable to form turbidity and showed visualization of tiny droplets of oil on the surface of the mixture whereas PEG 600 was observed to give a fine cloudy emulsion forming no droplets of oil.

3.2.4 Assessment of emulsification improvement through addition of co-surfactant

The percentage transmittance value of emulsion formed by adding 15 mg PEG 600 to the formulation comprised of oil:surfactant in a ratio of 1:2, showed remarkable emulsifying capability. It consists of 959 mg of castor oil, 2937 mg of Tween 20, 15 mg of PEG 600 showed in **Table 6**.

Table 6: Excipients in percentage (%).

Excipients	**Amount**	**Percentage**
Oil	959mg	24%
Surfactant (Tween20)	2937mg	75%
Co-surfactant (PEG600)	15mg	0.38%

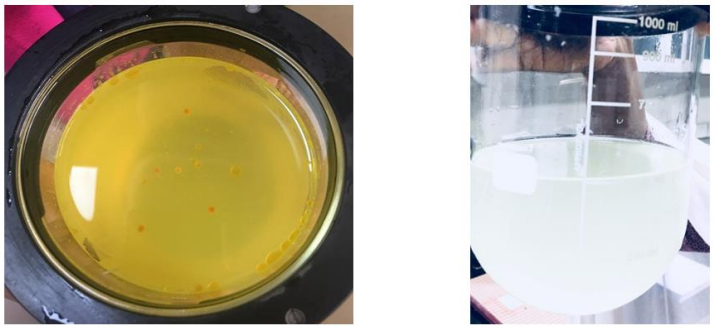
3.3 Optimization of formulation attributes

Process B was adopted to carry out liquid SNEDDS formulation for curcumin. Process B resulted in a stable homogenous formulation. On the other hand, Process A caused phase separation in a formulation with identical ratio to that in Process B.

3.4 Dispersibility test

According to grading system for visual observation of self-emulsifying formulations, the formulation prepared by following Process A had poor emulsification with large oil globules present on the surface

(Grade E emulsion) showed in **Figure 10(a)**. The formulation(prepared by following Process A), hence, is unsuitable as SNEDDS. On the other hand, the formulation prepared by following Process B, formed less clear emulsion with a cloudy white appearance (Grade B emulsion) and the emulsion formed rapidly showed in **Figure 10(b)**. The formulation (prepared by following Process B), hence, is suitable for preparation of SNEDDS.



(a) (b)

Figure 10: (a) Poor emulsification of SNEDDS formulation, (b) Fine, and rapid emulsification of improved formulation.

3.5 Determination of emulsification time

The formulation made by the conventional method (Process A) did not show satisfactory emulsion. While the improved formulation (Process B) dispersed into fine emulsification in 2 mins.

3.6 Droplet size analysis

In this study, Process B formed desired SNEDDS of curcumin within 2mins (Grade B) of emulsification time, hence, we prepared four different batches of SNEDDS to find out the droplet size and polydispersity index value (PDI). The lowest Mean droplet size was found to be 100 nm (**Table 7**), which is well within the permissible range of SNEDDS droplet size (20-200nm).

Table 7: Result of particle size analysis

Sl. No.	Z Average Value	PDI
1	100	0.232
2	116.8	0.265
3	140.7	0.167
4	181.2	0.062

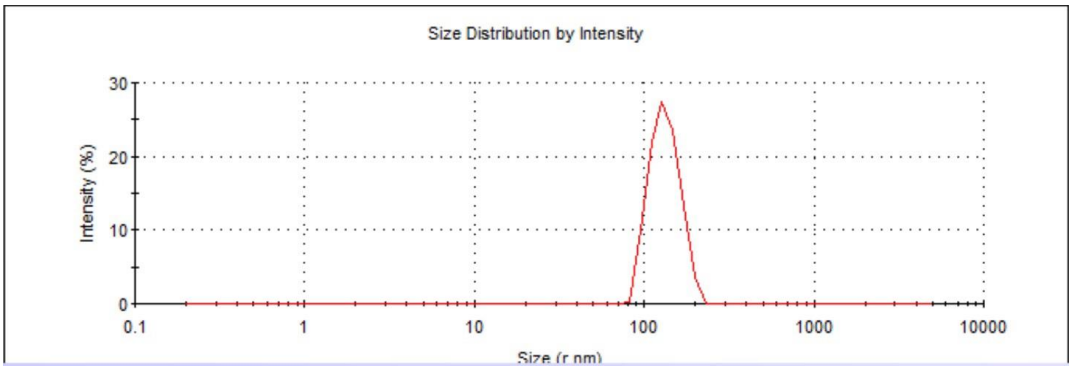


Figure 11: Particle size distribution of SNEDDS formulation

Figure 11 shows the SNEDDS particle size distribution of curcumin having a monodisperse distribution of the particles around 100 nm size.

3.7 Stability study

There was no noteworthy changes in the average prticle size (Initial : 100 nm ± 4.5, 1 month: 105.2 ± 2.3) of SNEDDS formulation. At the same time there was no phase separation, coalescence, creaming and drug precipitation. It was found to be physically stable after 30 days at room temperature (RT=25˚C).

4. Conclusion

The extracted curcumin was found in two phases (solid and semi solid) and semi-solid phase showed the highest amount of curcumin (156 mg/g of turmeric powder). The solubility of curcumin was highest (72%) in castor oils and Tween 20 used as a surfactant resulted in higher emulsification capacity. SNEDDS of curcumin prepared using Process B forms cloudy white emulsion (Grade B emulsion) with rapid emulsification time (2mins) with a mean droplet size of 100nm. SNEDDS of curcumin was physically stable for 30 days at room temperature (25˚C). These results suggest that SNEDDS can be used for the formulation of poorly water-soluble drugs like curcumin.

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