Original Article

FORMULATION OF TABLET CONTAINING CURCUMIN NANOEMULSION

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ABSTRACT

Objective: The formula of curcumin nanoemulsion had been established in our previous research. Encapsulation of curcumin in this nanocarrier system is expected to increase the bioavailability of the curcumin after oral administration, hence giving better effects. The objective of this study is to formulate tablet containing curcumin nanoemulsion for oral delivery.

Methods: The formulation of curcumin nanoemulsion was done by using oil phase: glycerylmonooleate, cremophor RH 40 as surfactant and polyethylene glycol 400 as co-surfactant in the ratio of 1:8:1, and was dispersed in water with mild stirring. Tablet was produced by wet granulation method, using 9% PEG 6000 as lubricant, polyvinylpyrrolidone 5% as binder, mannitol as filler, 1% sodium chloride as glidant and 2% sodium lauryl sulphate as lubricant. Tablet evaluation was performed according to standard quality of tablet.

Results: Curcumin nanoemulsion with particle size of 125.7± 1.029 nm and percentage of drug encapsulated of 99.52% was formed. Tablet containing this nanoemulsion has good physical characteristics with hardness of 5.95 kg/cm^2 and 99.79% of curcumin dissolved in 60 minutes. Curcumin nanoemulsion formulated into tablet dosage form still maintained the particle size of 134±1.45 nm when the tablet was dispersed in water.

Conclusion: Taken together, curcumin nanoemulsion was able to be formulated into solid dosage form, resulting good physical characteristic of the tablet while maintaining the nanoemulsion form when the tablet was dispersed in water. The comparison of the dissolution profile between tablet curcumin and tablet containing curcumin nanoemulsion should be done to ensure that the tablet formulation using curcumin nanoemulsion is better.

Keywords: Curcumin, SNEDDs, Tablet, Transformation, Wet granulation.

INTRODUCTION

Curcumin is lipophilic in nature which shows low solubility and stability in aqueous solution, therefore exhibits very poor oral bioavailability [1,2,3,4]. As curcumin exhibits broad range of beneficial biological and pharmacological activities, efforts are done to overcome these limitations. One of the methods developed to improve solubility and oral absorption of curcumin is nanoemulsifcation technique. Generally, an oil-in-water (o/w) emulsion is formed using nanoemulsification technique which gives great advantages for curcumin such as improved anti-inflammatory properties of curcumin [5,6].

In this case, a self-nanoemulsification technique was developed using oil:glycerylmonooleate (GMO), surfactant-cremophor RH40 and co-surfactant-PEG 400 in the ratio of 1:8:1, and finally addition of aqueous phase that enables spontaneously formation of nanoemulsion, aids by gentle agitation using magnetic stirrer. Based on research and studies, nanoemulsion has reported to show significant increase in oral absorption of curcumin in mice, which makes nanoemulsification as a possible alternative formulation results in better oral bioavailability [7-9].

Various dosage forms can be prepared from nanoemulsion for different route of administrations. Transforming nanoemulsion, a liquid form, into tablet, a solid form, of course will be complicated. This is because of the compression force which can damage the structure of the nanoemulsion.

Therefore, careful selection on the tablet composition and process is the important step in this formulation. On top of that, the filler will contribute mainly on the successful tableting. To evaluate the potential of the filler in the tableting of curcumin nanoemulsion, several parameters were performed. The observation of nanoemulsion morphology and particle size after tableting were important parameter which will tell the successful transformation from nanoemulsion to tablet.

MATERIALS AND METHODS

Materials and Reagents

Curcumin, glycerylmonooleate (GMO), cremophor RH40, PEG400, were obtained from PT Combiphar, Bandung-Indonesia, DMSO, curcumin (PT Phytochemindo Lestari, Indonesia), PVP K-30, PEG 6000, and mannitol were obtained from PT Meprofarm-Indonesia, sodium lauryl sulphate (SLS, Merck), sodium chloride (NaCl, Merck), acetonitrile pro analysis (JB Baker).

Methods

Preparation of Curcumin Nanoemulsion using Self-Nanoemulsification (SNE) Technique

During the preparation of curcumin nanoemulsion, oil-glycerylmonooleate (GMO), surfactant- cremophor RH40, co-surfactant-PEG400 in the ratio of (1:8:1) were mixed to form the oil phase. The optimization of the loading capacity of curcumin into the oil phase was done using 100 mg, 200 mg and 500 mg of curcumin. Curcumin was added into the oil phase and stirred using magnetic stirrer at 100rpm for 2 hours. Stirring for 2 hours was optimal that enabled curcumin to be dispersed homogenously in the oil phase. Then, the mixture was placed in sonicator bath (Branson, Model 5510) for 1 hour, at temperature 25oC. Subsequently, the SNE formed was added with water by which the ratio of SNE: deionized water was 1 g:5 mL and proceed with stirring at 100rpm for 15 minutes. A clear, homogenous nanoemulsion was obtained.

Evaluation and Characterization of Curcumin Nanoemulsion

Particle Size Distribution Analysis

DelsaNano C Particle Analyzer (Beckman Coulter) was used to determine the particle size of the globules in the nanoemulsion and its distribution, based on the photon correlation spectroscopy (PCS). DelsaNano C can be used for both particle size and zeta potential measurements and it gives the highest degree of sensitivity, resolution and accuracy, despite the sample concentration compare to other DelsaNano Series.
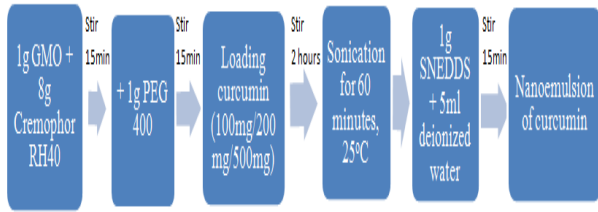
Fig. 1: Schematic diagram on preparation of curcuin nanoemulsion

Percentage of Curcumin Encapsulated in Nanoemulsion

The percentage of curcumin in nanoemulsion was determined by direct method, by measuring the difference between the initial amount of curcumin used in nanoemulsion preparation and the amount of curcumin encapsulated. One mL of the nanoemulsion was centrifuged at 14000 rpm for 20 minutes. Then, the supernatant was diluted in DMSO. The percentage of curcumin encapsulated was then measured using UV/Vis spectrophotometer (Beckman DU 7500i) at the wavelength of 430nm.

A standard calibration curve of 2 to 5 µg/mL of curcumin in DMSO was provided. The percentage of curcumin encapsulated in nanoemulsion was calculated using the equation below

$$\text{Percentage of curcumin encapsulated} = \frac{\text{Amount of curcumin entrapped}}{\text{Initial amount of curcumin in nanoemulsion}} \times 100\%$$

[1]

Preparation of Tablet (Wet Granulation)

Optimization of Excipient

Optimization of the excipient and its concentration used in tablet formulation was performed as shown in table 1:

Formulation of Curcumin Nanoemulsion into Tablet

Upon optimization of the formulation, curcumin was loaded into nanoemulsion and formulated into tablet by using wet granulation method (figure 2).

Table 1: Optimization of excipients and its concentration

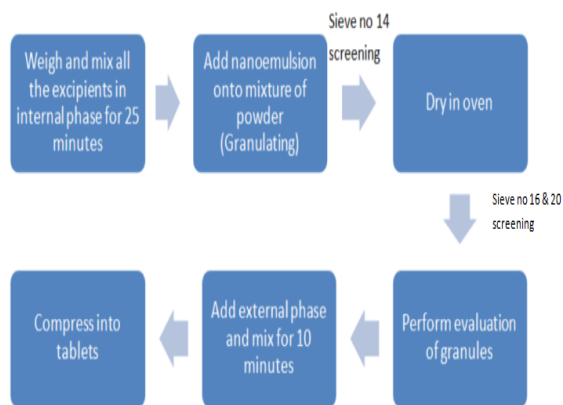| Excipients		F1	F2	F3	F4	F5	F6
Internal Phase							
Binder	PVP K-30 (%)	3	5	5	5	5	5
Lubricant	PEG 6000 (%)	-	-	7	9	9	9
Filler	Mannitol	qs	qs	qs	qs	qs	qs
External Phase							
Glidant	NaCl (%)	-	-	-	-	3	1
Lubricant	SLS (%)	-	-	-	-	-	2

Fig. 2: Schematic flow chart on wet granulation process.

Characterization of Curcumin Granules

Moisture Content

Two g of granules was weighed on aluminum plate and the moisture content was determined using moisture analyzer. The result was noted after number that represents percentage of moisture remained constant.

Bulk Density

The granules were weighed and slowly poured through the upper funnel until they over flows the receiving cup. The top of the receiving tube was leveled with a spatula such that it was completely full. The bulk density was calculated using the equation:

$$\text{Bulk Density} = \frac{\text{Weigh of the granules}}{\text{Intial volume occupied by granules}}$$

[2]

Tapped Density

After the bulk density test, 500 times of tapping was run. The resulting tap volume was noted and tapped density was calculated.

$$\text{Tapped Density} = \frac{\text{Weigh of the granules}}{\text{Volume occupied by granules after 500 taps}}$$

[3]

Carr Index

Carr Index was determined using the data of bulk and tapped density, by which it gave prediction on the compressibility of granules. If Carr Index was less than 15%, the granules predicted to have good compressibility and vice versa. Carr index was calculated using the formula below:

$$\text{Carr Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

[4]

Flowability

An empty glass beaker (W_0) was weighed and put under the apparatus. The funnel was filled with some granules. The flow tester was run, and the granules were loaded in the empty glass beaker. Measurement was stopped before all the granules were emptied from the funnel. The time required for the granules to flow was noted. The loaded beaker glass (W_t) was weighed and the flow rate of granules was calculated.

$$\text{Flowability} = \frac{W_t - W_0}{\text{Time}}$$

[5]

Characterization of Curcumin Tablets

Organoleptic Properties

The organoleptic properties of the tablet such as the appearance, tablet's size, shape, color, odour, taste and surface textures were observed.

Particle Size Distribution

One tablet of curcumin nanoemulsion was dissolved in 10 mL of deionized water. Then, it was loaded into sample cell in DelsaNano C Particle Analyzer (Beckman Coulter) for measurement of the particle size and distribution of the globules in the tablet.

Friability and Abrasion

Twenty tablets was chosen randomly and placed into the friability tester and abrasion tester respectively. One hundred rotations were run. All the twenty tablets were cleaned and weighed again. The percentage of weigh loss during friability and abrasion test was calculated.

$$\text{Percentage of weigh lost (\%)} = \frac{\text{Weight loss}}{\text{Initial weight of 20 tablets}} \times 100\%$$

[6]

Disintegration Time

Six tablets were placed in the basket, lifted the basket up and down consistency for an hour. The disintegration apparatus was operated using SLS (sdoium lauryl sulphate) as the immersion fluid, maintained at 37 ± 2°C. The time required for disintegration of each tablet was noted.

Content Uniformity

Content uniformity test was performed by weighed 10 tablets individually, crushed them separately and dilution is made. Then, the content of curcumin in each tablet was determined using HPLC with same condition and operation procedure as in dissolution test.

Drug Content

In drug content evaluation, twenty tablets were weighed individually and the average weigh was noted. Then, all twenty tablets were being crushed together. After that, the average weigh of the sample was took and diluted, then further analyzed using HPLC as in dissolution test.

Hardness

Twenty tablets were picked randomly. The hardness of individual tablet was measured using hardness tester and noted. The average tablet hardness and its hardness variety based on its standard deviation (SD) were calculated.

Diameter and Thickness

Twenty tablets were taken randomly and then the diameter and the thickness of the tablet were measured using vernier calliper.

Weigh Variation

Twenty tablets were picked randomly, weighed and average weigh was calculated. Then, each tablet was weighed individually and the percentage of deviation from the average weight was determined.

Dissolution Rate

The dissolution test was carried out using 900 mL of water containing 1% SLS as medium, operated using apparatus 2 paddle type for 60 minutes. HPLC Hewlett Packard Agilent Series 1100 connected with 425 nm detector, using mobile phase, acetonitrile:phosphate buffer (55:45) with flow rate 1mL/min was used and retention time of curcumin was found at 8.3 minutes. For the tolerance of the determination, there should be not less than 75% of curcumin that dissolved in 60 minutes.

Transmission Electron Spectroscopy (TEM)

TEM was used to analyze the morphology of the tablet of curcumin. One tablet of curcumin was dissolved in 10 mL of deionized water and mixed homogenously. Then 10 μL of the solution was dropped on the specimen with a grid 400 mesh being placed on top of specimen and let for 1 minute. Then, the leftover of the solution of tablet on the grid was cleaned using filter paper, followed by addition of 10 μl uranyl acetate and cleaned the leftover. The grid was left to dry and placed into TEM apparatus for capturing the photo of the morphology of tablet of curcumin.

RESULTS AND DISCUSSION

Evaluation and Characterization of Curcumin Nanoemulsion

Particle Size Distribution Analysis

Nanoemulsion of curcumin was formed spontaneously by addition of 1g of oil phase to 5mL of deionized water, with mild agitation using magnetic stirrer. Optimization was done by determined the loading capacity of curcumin in 10g of oil phase which gave a targeted particle size of less than 200nm. The result of the evaluation was shown in the table 2 below:

Table 2: Physical Evaluationof curcumin nanoemulsion

Formula	Curcumin (mg) per 10g of oil phase	Visual Observation	Particle Size of Globules (nm)	Polydispersity Index
F1	100	Clear Yellow	48.8± 0.142	0.117±0.028
F2	200	Clear Yellow	125.7± 1.029	0.137±0.009
F3	500	Clear Yellowish-orange	559.9±1.334	0.264±0.237

Based on the evaluation result on table 2 and figure 3, it was clearly shown that the particle size of the globules increased when the amount of curcumin was higher.

As a result, there is limitation of the amount of curcumin that can be incorporate into nanoemulsion. Loading capacity of 100 mg and 200 mg of curcumin into the oil phase gave the particle size of globules of less than 200 nm, meanwhile when the amount of curcumin increased up to 500 mg in 10 g of nanoemulsion, the particle size of globules showed a significant increased up to 560 nm.

In addition, based on table 2, it was noticed that for all three formulas using 100 mg, 200 mg and 500 mg of curcumin in 10 g of oil phase resulted in the polydispersity index of less than 0.5. As

polydispersity index represents the particle size distribution of globules in nanoemulsion, the preferable range of polydispersity index lies in 0 to 0.5, indicates the particle size of globules are distributed evenly in the nanoemulsion.

Upon the optimization, only 200 mg of curcumin loaded in nanoemulsion was used for further experiment.

Percentage of Curcumin Encapsulated in Nanoemulsion

Percentage of curcumin encapsulated in nanoemulsion was performed using direct method, by determining the amount of curcumin that was encapsulated in the nanoemulsion. As a result, the nanoemulsion of curcumin was centrifuged at 14000 rpm for 20 minutes which caused the free curcumin to be

sedimented. Then, 5 µL of supernatant layer was taken and dissolved in DMSO to 1 mL, and the percentage of curcumin encapsulated in nanoemulsion (the supernatant layer) was analysed using UV-Visible spectrophotometer at wavelength 430 nm.

$$\text{Percentage of curcumin encapsulated (\%)} = \frac{3317.4ppm}{3333.3ppm} \times 100\% = 99.52\%$$

Preparation of Tablet (Wet Granulation)

Optimization of Excipient

Optimization on the excipients and its concentration was performed and the results were shown below (table 3).

Fig. 3: Relationship between loading capacity of curcumin with the particle size of globules and polydispersity index.

Table 3: Visual observation on tablet of Formula F1- F6

Formula	F1	F2	F3	F4	F5	F6
Binder	PVP K-30 3%	PVP K-30 5%	PVP K-30 5%	PVP K-30 5%	PVP K-30 5%	PVP K-30 5%
Lubricant	-	-	PEG 6000 7%	PEG 6000 9%	PEG 6000 7%	PEG 6000 7%
Glidant (External phase)	-	-	-	-	NaCl 3%	NaCl 1%
Lubricant (External phase)	-	-	-	-	-	SLS 2%
Interference	• brittle • punch Very Stick on	• Brittle • punch Stick on	• Can be compressed • Stick on punch • Tablet surface not smooth	• Good tablet, but surface of tablet not smooth enough	• Tablet changes color • Stick on punch • Tablet surface not smooth	• Good tablet • Smooth surface • Perfect hardness
Visual Characteristic						

In formula 1, by using only the PVP K-30 3% as binder and filler mannitol, it was shown that the tablet formed was very fragile and brittle, which gave an irregular shape, defect tablet. This may due to insufficient concentration of binder used as binder helps to improve the cohesiveness of powder. As a result, in formula 2, a higher concentration of PVP K-30 (5%) was used. However, based on the result, there were still some tablets which were brittle and in irregular form, in addition some granules were observed to stick on upper punch.

Therefore, the addition of lubricant, PEG 6000 7% (formula 3) was done. Initially, nanoemulsion without any loading curcumin gave a perfect tablet, but when curcumin was loaded the tablet turns to be a little sticky to upper punch and the surface was not perfectly smooth. By tracking down the compatibility of curcumin with all the excipients used, it was found that no incompatibility was shown. Thus, it was believed that the unit processes involving in granulating and tablet compression, such as amount of nanoemulsion added as granulating liquid, mixing time, drying period, and size screening caused the matter. Thus, in further formulation, optimizations on the processes were done with nanoemulsion loaded with curcumin. This was because the curcumin gives a yellow color which acts as a good
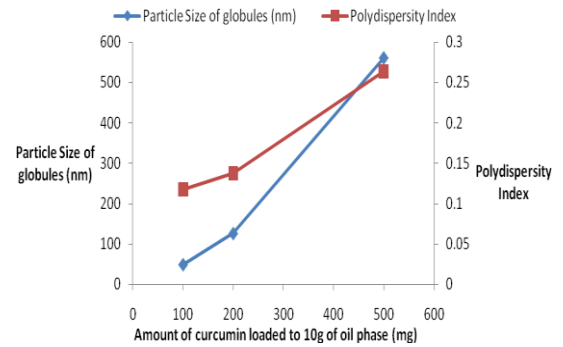
indicator to determine if the granulation process was homogenous enough.

A higher lubricant level of PEG 6000 9% was used to reduce the friction between the granules and punch, which may results in smooth and good tablet (formula 4). The outcome was good instead, although there was still very little not perfect smoothness observed on the surface of tablet. To avoid that problem, NaCl 3% as glidant was incorporated (formula 5). However, the color changes as observed and highly stickiness to punch, which gave a rough tablet surface were obtained. Therefore, extra excipient, SLS 2% as lubricant, was included (formula 6). In this formulation, the tablet was formed with perfect hardness, smooth surface and texture with no any stickiness to punch.

Formulation of Curcumin Nanoemulsion into Tablet

Curcumin nanoemulsion was then formulated into tablet dosage form by wet granulation method. The amount of granulating liquid added was optimized as it affects the granules and tablet characteristic. In this experiment, the amount of granulating liquid (nanoemulsion of curcumin) was optimized at which for 60 g of powder, 3.2 mL of granulating liquid was required.

Evaluation and Characterization of Curcumin Granules

Table 4: Characteristic of granule containing curcumin nanoemulsion

Parameter	Results
Moisture Content (%)	1.1
Bulk Density (g/mL)	0.492
Tapped Density (g/mL)	0.574
Carr Index (%)	14.28
Flowability (g/s)	6.44

For our information, the moisture content evaluation is a very critical parameter which it should lies in the range of 1-3% in order to produce a qualified tablet. This is because too low moisture content will leads to a phenomena known as 'capping' and excess moisture content of granules will cause 'chipping' of the tablet formed.

Evaluation and Characterization of Curcumin Tablets

Table 5: Characteristic of tablet containing curcumin nanoemulsion

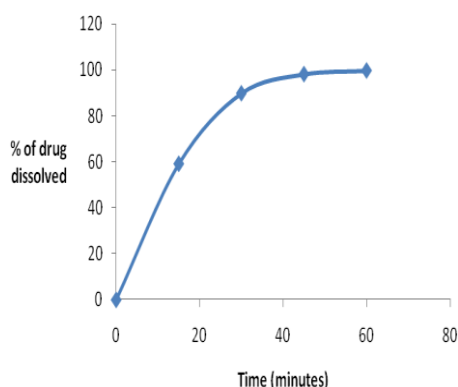| Parameter	Results
Organoleptic properties	Round, yellow, smooth surface, very mild spice aroma
Particle size (nm)	134±1.45
Polydispersity index	0.277±0.006
Friability and abrasion (Percentage of weigh loss)	Friability test: 0.15,Abrasion test: 0.09.
Disintegration time (min)	6.23±0.146
Content uniformity (%)	98 - 103
Drug content (µg)	99.76 ±0.44
Hardness	5.95 ±0.81
Diameter and thickness (cm)	Diameter:0.7096±0.008, Thickness:0.3974±0.007
Tablet weight (mg)	202±0.004

Fig. 4: Dissolution profile of tablet containing curcumin nanoemulsion.

Fig. 5:Transmission Electron Micrograph of globules of curcumin nanoemulsion after tablet was dispersed in water. Magnification 15000x.

The physical properties of tablet containing curcumin nanoemulsion are presented in table 5, indicating that the formula developed resulted in good physical appearance of the product. Incorporation of nanoemulsion into solid dosage form takes high risk as nanoemulsion is liquid dosage form containing oil, which obviously difficult for solid dosage form. However, by careful selection of excipients, the good tablet in term of physical appearance was formed. The main excipient such as filler, adsorbent, and lubricant are suggested to contribute. The purpose of incorporation of curcumin in the nanoemulsion was to improve the lack of physicochemical characteristic of curcumin: solubility. In addition, due to sensitivity of curcumin on light exposure, the encapsulation into oil globule was expected to protect its light-triggered degradation.

As seen in figure 4, the dissolution profile of curcumin from nanoemulsion formulated into tablet indicated the successful of our work. Curcumin was maintained in the nanoglobule after compressed into tablet while was able to release the curcumin when dissolved in dissolution medium.
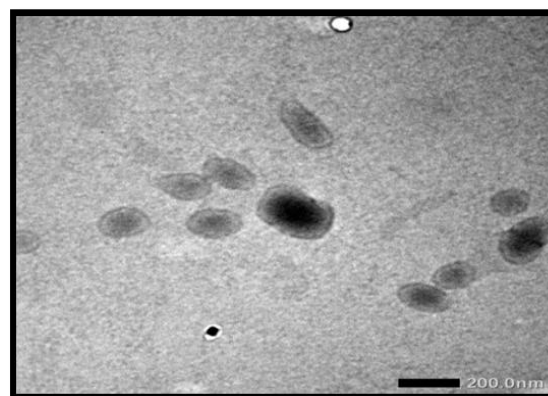
To confirm our hypothesis, TEM study was performed and shown in figure 5. As indicated in that figure, the globules of nanoemulsion of curcumin tablet give a spherical shape with the particle size of approximate 200 nm, indicates the curcumin tablet still able to maintain the structure of nanoemulsion when it was re-dispersed in water. This explains that the compression force used in tablet formulation did not rupture the structure of nanoemulsion. The use of selective excipient, in particular the filler, preserving this structure and is very important in the formulation development. The mechanical strength of the filler contributed dominantly to this result.

ABBREVIATIONS

CI	=	carr index
DMSO	=	dimethylsulfoxide
GMO	=	glycerylmonooleate
HLB	=	hydrophilic-lipophillic balance
HPLC	=	high performance liquid chromatography
LTR	=	long term repeat
Nm	=	nanometer
o/w	=	oil-in-water

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PCS	=	photon correlation spectroscopy
SD	=	standard deviation
SNE	=	self nanoemulsification
SNEDDS	=	self-nanoemulsifying drug delivery system
TEM	=	transmission electron microscopy
UV/Vis	=	ultraviolet-visible

CONCLUSION

A good quality of tablet containing curcumin nanoemulsion, which fulfils all the evaluation test requirements was successfully formed with the formula using nanoemulsion of curcumin as active ingredient, 9% PEG 6000 as lubricant, PVP 5% as binding agent, 1% sodium chloride NaCl as glidant, 2% sodium lauryl sulphate as lubricant and mannitol as filler. The comparison of the dissolution profile between tablet curcumin and tablet containing curcumin nanoemulsion should be done to ensure that the tablet formulation using curcumin nanoemulsion is better.

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