INVESTIGATION ON SOLUBILITY AND STABILITY OF CURCUMIN IN AQUEOUS POLYSORBATE MICELLE

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Abstract- Solubility and stability are two key aspects of any successful formulation for curcumin beverage development. In the present study, the effect of polysorbate on the solubility of curcumin in aqueous solution with or without the autoclave treatment was studied. The remarkable effect of the autoclave treatment on enhancing the solubility was confirmed. Among polysorbate 20, 60 and 80, polysorbate 20 exhibited the highest solubility of approximately 6 mg/ml in 20% aqueous solution by the autoclave treatment, while the solubility was approximately 4 mg/ml in polysorbate 60 and 80, prepared under the same condition. Without the autoclave treatment, the solubility in 20% aqueous solutions of polysorbate 20, 60 and 80 was 2.7, 3.4 and 3.4 mg/ml, respectively. The stability of curcumin was obviously improved a lot by applying the micelle formation with polysorbate. However, the remarkable decomposition of curcumin at 30 and 40°C was observed over a few weeks. Dynamic light scattering study found that the curcumin and polysorbate formed the micelle (meandiameter, approximately 10nm). Through the present study, the feasibility of the development of curcumin beverage by micellar formation technique with polysorbate is confirmed though the further study for improving the stability remained untouched.

Keywords- curcumin, polysorbate, autoclave, solubility

I. INTRODUCTION

Curcumin, the major biologically active substance found in Curcuma longa, exhibits many biological activities such as antioxidant[1], anti-inflammatory[2], antidiabetic [3], antifungals [4], anti-carcinogenic effects [5], and hepatoprotectives [6,7].However, the potential of curcumin in treating the various diseases is limited mainly owing to their poor bioavailability. One of the main reasons for the poor availability has been considered to be their low solubility in aqueous solutions. In fact, the solubility of curcumin has been reported to be very low (0.0004 mg/mL in water at pH 7.3) [8].

The present study aimed to improve the solubility and to investigate the stability of curcumin in aqueous polysorbatemicelle prepared by applying polysorbate as a surfactant under various conditions including autoclave treatment. Polysorbate was chosen in the present study, considering the facts that they can improve the solubility of various drugs and the membrane permeability to eventually enhance the bioavailability of various drugs by inhibiting the activity of P-glycoprotein, which is one of the responsible factors for the efflux of the various drugs[9-13].

II. DETAILS EXPERIMENTAL

2.1 Materials and Procedures

Curcuminoid mixture(content of curcumin approximately was 81.0%)was purchased from China (C&V International Co., Ltd, Hong Kong). Polysorbate 20, polysorbate 60, and polysorbate 80 were purchased from Ajax Finechem, New Zealand, Merck, Germany, and QRec, New Zealand. Other chemicals were analytical grade.

TLC silica gel 60 F254 plate (Merck, Germany) was used. Developing solvent was chloroform-methanol (95:5). The spots on TLC plate were detected under the UV light at 254 nm.

HPLC analysis was performed using hp1100 system (Hewlett Packard, USA) consisting of degasser, quaternary pump, auto-sampler with 100 µl injector loop, Eurospher-100 column (4x250 mm; i.d., 5 µm) (Knauer, Germany), diode array detector, and Chem Station software. All samples dissolved in methanol were filtratedthough the 0.45µm pore sizenylon filter (Filtrex, USA), then diluted appropriately with methanol, and 10 µl of each sample was injected into HPLC.The column was elutedby a solvent consisting of acetronitrile-0.2% acetic acid in water (50:50) at a flow rate (1 ml/min), and a detection wavelength was 425 nm.

Spectra of ^{1}H-NMR of curcumin was determined in DMSO-d_6, operating at 400 MHz, using a Bruker Avance III 400 MHz NMR spectrometer (Bruker, Switzerland).

DSC analysis was performed using differential scanning calorimeter Model DSC7 (Perkin Elmer, USA). Curcumin was placed in sealed aluminum pans and heated from 100˚C to 200˚C at a heat increase rate (5˚C/min) under nitrogen purge.

Particle size of curcumin-polysorbate micelle was analyzed by Zetasizer Nano ZS (Malvern, UK) without dilution at room temperature.

2.2 Purification of Standard Curcumin

Curcuminoid mixture (500mg) was dissolved in acetone and mixed with silica gel (500 mg). The mixture was placed on the top of the silica gel column packed with 30g of silica gel 60 (0.063–0.200 mesh, Merck, Germany), which was impregnated with 1.5g of sodium dihydrogenphosphate (NaH_2PO_4). The

column was eluted with dichloromethane. All the fractions which showed one spot of curcumin by TLCwere collected. The solvent was evaporated under vacuum at 40°Cand dried in an oven at 60°C. The resultant curcumin was analyzed by HPLC,^{1}H-NMR, and DSC.

2.3 Preparation of Curcumin by Recrystallization

Curcumin used in the present study was prepared by repeating the recrystallization. Curcuminoid mixture (5g) was dissolved inmethanol (500ml), and the mixture was warmed at 60 °C for 10-15 min to dissolvedcurcuminoidcompletely. Then 100 ml of water was added, and the mixture was kept at 5-7℃ overnight. The resultant curcumin crystals were collected by suction filtration. The obtained wet crystals were used for the further recrystallization without drying in the similar manner. The overall number of recrystallization was 5 times. The obtained curcumin crystals were analyzed by DSC and HPLC.

2.4 Solubility Enhancement of Curcumin by Curcumin-Polysorbate Micelle

1) Solubility of curcumin prepared at room temperature

Polysorbate 20, 60 and 80 were used.Excessive curcumin was added to 20 ml of 1, 5, 10, 20, 30, and 50% (w/w) aqueous polysorbate solutions. The mixtures were stirred vigorously with the magnetic stirrer for 30 min and kept for 24 hratroom temperature. The mixtures were filtrated through 0.45 µm nylon filters. The concentration of curcumin in the filtrate was determined by HPLC.

2) Solubility of curcumin prepared by applying autoclave treatment

Polysorbate 20, 60 and 80 were used. Excessive curcumin was added to 20 ml of 1, 5, 10, 20, 30 and 50 (w/w) of aqueous polysorbates solutions. The mixtures were stirred vigorously with the magnetic stirrer for 30 min. Then, the mixtures were autoclaved at 121 ℃ for 30 min and placed at room temperature for 24 hr. The mixtures were filtrated though 0.45 µm nylon filters. The concentration of curcumin in the filtrate was determined by HPLC.

2.5 Stability of Curcumin in Polysorbate-Micelle

The same samples prepared for solubility enhancement of curcumin by curcumin-polysorbate micelle were kept at 4, 30 and 40℃ for 8 weeks.At 1, 2, 3, 4 and 8 weeks of storage, the remaining curcumin in the samples was determined by HPLC.

III. RESULTS AND DISCUSSION

3.1 Physico-chemical Characterization and Identification of the Purified Curcumin TLC showed one spot (Rf values was 5.8). HPLC chromatogram showed one peak at retention time of 11.1 min. DSC chart also showed only one peak at 183.7℃, which was in good agreement with 184 °C (mp) reported by Péret-Almeida et al., (2005).The structure of the purified curcumin was confirmed by comparing the ^{1}H-NMR with that reported by Péret-Almeida et al., (2005)[14]. ^{1}H-NMR (in DMSO-d6) δ 3.84 (-CH3, s, 6H), 6.06 (H-1, s, 1H), 6.76 (H-3, H-3', d, J=15.8 Hz, 2H), 6.82 (H-9, H-9', d, J=8.2 Hz, 2H), 7.15 (H-10, H-10', dd, J=8.2 Hz, J=1.6 Hz, 2H), 7.32 (H-6, H-6', d, J=1.6 Hz, 2H), 7.55 (H-4, H-4', d, J=15.8 Hz, 2H), 9.68 (H-8, H-8', s, 2H).

3.2 Purity of curcumin prepared by repeated recrystallization

The purity was determined by HPLC and confirmed to be 95.2 ± 0.6 %, with reference to the curcumin purified by the silica gel chromatography.

3.3Solubility Enhancement of Curcumin by Curcumin-Polysorbate Micelle

As shown in Table 1, the solubility of curcumin increased with increasing concentration of polysorbate. The autoclave treatment increased the solubility up to 2 – 3 times in 10 - 20% polysorbate 20 solution, compared with solubility without the autoclave treatment. In the case of polysorbate 60 and 80, the maximal increase in solubility was approximately 1.5 – 2 times. Polysorbate 20 exhibited the highest solubility of curcumin and the most potent effect of the autoclave treatment on enhancing the solubility of curcumin (approximately 6 mg/ml).Polysorbate 60 and 80 exhibited the similar results. At the concentration of 20%, both polysorbate 60 and 80 exhibited the solubility of approximately 4 mg/ml.Zhang et al., (2011) reported the application of the autoclave treatment for enhancing the solubility of curcumin by curcumin-rubusoside complex formation of nanoparticles. They speculated that

Table 1: Solubility of curcumin in aqueous polysorbate solution prepared at room temperature and by autoclave treatment

PS	PS (%) (w/w)	Solubility of curcumin (mg/ml) at room temerature			
		At room temperature[a]	Curcumin: PS[b]	By autoclave treatment[c]	Curcumin: PS[d]
PS 20	1	0.10 ± 0.02[e]	1 : 100	0.20 ± 0.01[e]	1 : 50
	5	0.69 ± 0.01	1 : 72	1.55 ± 0.13	1 : 32
	10	1.29 ± 0.02	1 : 78	3.58 ± 0.22	1 : 28
	20	2.67 ± 0.12	1 : 75	6.02 ± 0.66	1 : 33
	30	3.47 ± 0.21	1 : 87	6.68 ± 0.47	1 : 45
	50	5.01 ± 0.32	1 : 100	6.19 ± 0.16	1 : 81

PS 60	1	0.17 ± 0.02	1 : 59	0.33 ± 0.01	1 : 30
	5	0.83 ± 0.03	1 : 60	1.09 ± 0.06	1 : 46
	10	1.59 ± 0.13	1 : 63	3.20 ± 0.19	1 : 31
	20	3.42 ± 0.17	1 : 59	4.17 ± 0.20	1 : 48
	30	4.68 ± 0.07	1 : 64	5.02 ± 0.42	1 : 60
	50	NA[f]		NA[f]	
PS 80	1	0.18 ± 0.00	1 : 56	0.27 ± 0.01	1 : 37
	5	0.82 ± 0.05	1 : 61	1.19 ± 0.01	1 : 42
	10	1.62 ± 0.21	1 : 62	2.80 ± 0.01	1 : 36
	20	3.35 ± 0.21	1 : 60	4.01 ± 0.17	1 : 50
	30	4.90 ± 0.40	1 : 61	4.54 ± 0.19	1 : 66
	50	NA		NA	

Table 1: Solubility of curcumin in aqueous polysorbate solution prepared at room temperature and by autoclave treatment[a]Curcumin-polysorbate micelle was prepared at room temperature;

[b]Curcumin : PS of curcumin-polysorbate micelle prepared at room temperature; [c]Curcumin-polysorbate micelle prepared by autoclave treatment; [d]Curcumin : PS of curcumin-polysorbate micelle prepared by autoclave treatment; [e]mean ± SD (n = 3); [f]NA, Not available due to the formation of solid phase like liquid crystal of polysorbate.

Formulation	Solubilizing agent	Ratio[a]	Solubility (mg/ml)	Reference
Liposomeencapsulated	DMPC, DMPG		NA	[15]
Polymeric nanoparticle -encapsulated	NIPAAM, VP, PEG-A		NA	[16]
Biocurcumax	NA		NA	[17]
Micelle	PEO-b-PCL	5:1	0.628	[18]
PLGA nanospheres	PLGA		NA	[19]
Cyclodextrin	HP-β-CD		0.61	[20]
Cyclodextrin	M-β-cyclodextrin	8.4:1	0.59	[20]
Micelle	SDS	31:1	0.75	[21]
Nanocrystal solid dispersion	HPC-SL, SDS		NA	[22]
Nanocrystal solid dispersion	HPMC-AS		NA	[22]
Nanoemulsion	PEG400, ethanol, PG, Tween-80		NA	[22]
Solid lipid particle	Lecithin, phospholi-pids, DHA		NA	[23]
Phospholipid	Phosphati-dylcholine		NA	[24]
Rubusoside-encapsulated	Rubusoside	43:1	≥2.32	[25]
Micelle	M-EPL	5:1	0.053	[26]
Solid dispersion	Solutol® HS15	10:1	0.56	[27]
Niosome and micelle	Tween 20, 80		NA	[28]
Micelle	Tween 20	31:1	6.0	This study

Table 2: Solubility enhancement of curcumin by various formations

NA, not available; [a]Ratio: Solubilizing agent : curcumin (w/w), DMPC, 1,2-dimyristoyl-sn-glycero-3-phosphocholine; DMPG,1,2-dimyristoyl-sn-glycero- 3-[phospho-rac- (1-glycerol)] [sodium salt]); NIPAAM, nisopropylacrylamide; VP, N-vinyl-2-pyrrolidone; PEG-A, poly(ethyleneglycol)monoacrylate; PEO-b-PCL, poly(ethylene oxide)-block-poly(ε-caprolactone); PLGA, Poly(D, L-lactide-co-glycolide); HP-β-CD, 2-hydroxypropyl-β-cyclodextrin; M-β-CD, methyl-β-cyclodextrin; SDS, sodium dodecyl sulphate; HPC-SL, hydroxypropyl cellulose-SL; HPMC-AS, hydroxypropyl methylcellulose acetate succinate; PG, propylene glycol, DHA, docosahexaenoic acid; M-EPL, octenyl succinic anhydride modified ε-polylysine.

the heat and pressure of autoclave method may have stabilized the already formed curcumin-rubusoside nanoparticles and created new curcumin-rubusoside nanoparticles by facilitating their interactions, thus resulting in the increased number of curcumin-polysorbate nanostructures [25].

There have been reported many studies on enhancing the solubility of curcumin as shown in Table 2. Among these attempts to improve solubility of cucumin, polysorbate 20 with applying the autoclave treatment exhibited the highest solubility of approximately 6 mg/ml, which was the highest solubility among all the reported values in the past until today.

PS[a]	Con[b] (%)	Week			
		1	2	4	8
20	10	99.7±2.4	87.5±2.0	79.2±2.7	70.3±1.5
	20	97.1±2.9	89.3±1.7	82.8±1.0	75.0±3.8
60	10	99.0±2.0	98.2±3.5	93.2±1.2	90.5±1.4
	20	96.1±2.5	95.1±3.2	93.6±2.0	89.3±1.8
80	10	99.2±2.1	95.4±2.5	90.5±1.8	84.4±3.9
	20	98.5±3.8	96.8±3.0	92.6±2.5	90.4±3.2

Table 3: Comparison of eight week stability test at 30° C among polysorbate 20, 60 and 80, prepared at room temperature [a]Polysorbate;[b]Concentration

3.4 Stability of Curcumin in Polysorbate-Micelle

As shown in Table 3 and 4, the eight weeks stability of the samples in 10 and 20% of polysorbate 20, 60 and 80 at 30 °C, prepared at room temperature and by the autoclave treatment, the significant differences among polysorbate 20, 60 and 80 were not observed. Interestingly, the stability of polysorbate 60 in spite of the conditions prepared at room temperature and 121°C was nearly the same.

In the case of the formulation prepared by the autoclave treatment with polysorbate 20, the stability in 1% polysorbate 20 was remarkably low and the stability in 5% polysorbate 20 was low, compared with those in more than 10%. The stability in 10, 20 and 30% polysorbate 20 was nearly same as shown in Table 5.

Table 4: Comparison of eight week stability test at 30° C among polysorbate 20, 60 and 80, prepared by the autoclave treatment

PS[a]	Con[b] (%)	Week 1	2	4	8
20	10	99.7±2.4	87.5±2.0	79.2±2.7	70.3±1.5
	20	97.1±2.9	89.3±1.7	82.8±1.0	75.0±3.8
60	10	99.0±2.0	98.2±3.5	93.2±1.2	90.5±1.4
	20	96.1±2.5	95.1±3.2	93.6±2.0	89.3±1.8
80	10	99.2+2.1	95.4+2.5	90.5+1.8	84.4+3.9
	20	98.5±3.8	96.8±3.0	92.6±2.5	90.4±3.2

[a]Polysorbate;[b]Concentration

Table 5: Comparison of eight week stability test of the formulations by the autoclave treatment with various concentrations of polysorbate 20

PS[a]	Con[b] (%)	Week 1	2	4	8
20	1	73.4±1.0	66.5±0.9	64.4±1.6	62.9±2.4
	5	88.6±0.4	80.9±1.5	72.7±0.9	64.8±1.9
	10	91.0±3.4	82.3±0.3	76.6±1.2	70.9±2.9
	20	93.0±2.1	86.2±0.9	72.6±1.7	69.0±6.5
	30	93.4±1.2	89.2±2.3	86.2±2.1	81.3±1.4
	100	99.8±1.7	99.4±2.6	94.7±0.4	90.3±1.9

[a]Polysorbate;[b]Concentration

The decomposition of curcumin in 1% polysorbate 20, 60 and 80, the results at 40°C were shown in Table 6. Approximately 50 – 60% decomposition was observed after 8 weeks at 40°C.A little fading of yellow was observed as shown in Fig. 1.

Table 6: Decomposition of the formulations in 1% polysorbates at 40 °C

PS[a]	Week 1	2	4	8
20	77.5±1.0	75.7±2.5	59.6±2.8	49.5±1.7
60	93.4±0.8	88.8±1.4	51.0±0.9	43.6±1.5
80	88.2±2.5	82.8±1.3	65.3±2.6	53.3±0.5

[a]Polysorbate



Fig. 1: Photograph of the formulation, freshly prepared (left) and after 8 weeks at 40 °C (right)

The stability of curcumin was obviously improved a lot by applying the micelle formation with polysorbate. Actually, it was reported that curcumin was unstable at neutral and basic pH values and degraded by 90% within 30 min in 0.1 M phosphate buffer at pH 7.2 and 37°C and that the stability of curcumin under acidic conditions improved a lot[24]. The pH value of the formulations studied in the present study was neutral. Then the further studies on developing the formulations with the satisfactory shelf life, focusing on the formulations of an acidic condition, are awaited. The application of curcumin-polysorbate micelle with neutral pH value in the present study to the solid form of products is of great interesting as well.

CONCLUSIONS

Among polysorbate 20, 60 and 80, polysorbate 20 exhibited the highest solubility of approximately 6 mg/ml, which was the highest solubility among all the reported values in the past, when the autoclave treatment was applied. The autoclave treatment increased the solubility up to 1.5 – 3 times, compared with solubility without the autoclave treatment. Curucumin in polysorbate micelle remarkably increased the stability of curcumin. However, it was estimated that the stability was not sufficient for the real commercial productof curcumin beverage with neutral pH because the remarkable decomposition of curcumin at 30 and 40°C was observed over a few weeks. Polysorbate 20, 60 and 80 brought the similar results to stability. The autoclave treatment did not show the increase or decrease in the stability.

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