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Self-microemulsifying, Reconstituted Granules for Oral Administration of Curcumin: Development and *In Vitro* Characterization

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***SUMMARY*. Self-microemulsifying, reconstituted granules for oral administration of curcumin were prepared using a wet granulation technique. Mannitol and lactose were used as solid carriers, and SCMC, acacia and PVP K-30 as binders. Granule flow properties were evaluated by bulk and tapped densities, angle of repose, Carr's index, and Hausner ratio and deemed to be passable to good. Scanning electron microscopy revealed that increased binder concentrations results in condensed granules with smoother surfaces. The optimal granule formulation exhibited complete solubility and presented as a spherical microemulsion with a droplet size of 36.13 ± 0.08 nm. The antioxidant activity of the optimized formulation was equivalent to ascorbic acid and higher than that of butylated hydroxytoluene. Reconstituted granules containing self-microemulsifying curcumin could provide a potential approach to deliver poorly water soluble compounds for oral administration.**

RESUMEN. Se prepararon gránulos reconstituidos automicromulsionantes para la administración oral de curcumina usando una técnica de granulación húmeda. El manitol y la lactosa se usaron como portadores sólidos, y SCMC, acacia y PVP K-30 como aglutinantes. Las propiedades de flujo de los gránulos se evaluaron mediante densidades aparejadas y medidas, ángulo de reposo, índice de Carr y relación de Hausner, y se consideró que eran aceptables a buenas. La microscopía electrónica de barrido reveló que el aumento de las concentraciones de aglutinante da como resultado gránulos condensados con superficies más lisas. La formulación óptima de los gránulos exhibió solubilidad completa y se presentó como una microemulsión esférica con un tamaño de gotita de 36,13 ± 0,08 nm. La actividad antioxidante de la formulación optimizada fue equivalente a la del ácido ascórbico y más alta que la del hidroxitolueno butilado. Los gránulos reconstituidos que contienen curcumina automicroemulsionante podrían proporcionar un enfoque potencial para administrar compuestos poco solubles en agua para administración oral.

INTRODUCTION

Curcumin is a polyphenolic compound derived from the rhizome of turmeric (*Curcuma longa* Linn.). Turmeric powder has been used as a spice and a therapeutically active compound for centuries. It has been demonstrated to exhibit anti-oxidative [1], anti-inflammatory [2,3], antimicrobial [4], antiproliferative [5] and anti-cancer activities [6]. Curcumin's therapeutic application via oral administration however, is restricted due to poor solubility (30 pmol/ml) [7], and poor bioavailability resulting from its rapid metabolism [8].

Recent researches [9-12] indicate that lipid-based formulations, in the term of self-microemulsifying drug delivery systems (SMEDDS), can enhance the solubility of poorly water-soluble compounds. However, these delivery systems have limitations, including diminishment of the active ingredient due to precipitation, when the products are kept at lower temperatures [13]. Solid SMEDDS (S-SMEDDS) are expected to circumvent drawbacks associated with liquid SMEDDS, by combining the advantages of liquid forms such as enhanced solubility and bioavailability, with the high stability, reproducibility, convenience and better patient compliance associated with solid dosage [14,15].

KEY WORDS: curcumin, reconstituted granules, self-microemulsifying formulation.

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S-SMEDDS have been manufactured in various forms including powders [16-18], tablets [11], pellets [9], beads [10] and sponges [12] with the oral route being preferred for administration. Recent trends in dietary supplementation have focused on reconstituted granules as an alternative strategy for oral administration since these are more acceptable to patients with swallowing disorders, including the elderly. In addition, complicated additional excipients are unnecessary for granule formulation, facilitating higher drug loading.

Mannitol, a sugar alcohol derived from reduction of mannose, and lactose, a simple sugar found in mammalian milk are both water-soluble and display good physical- and chemical stability, which are desirable characteristics for pharmaceutical applications. Research has demonstrated advantages associated with both types of sugar in the preparation of drug delivery systems [19-21]. The aims of the current study were to evaluate the effect of type and amount of solid carrier on the physicochemical properties of curcumin SMEDDS granules. In addition, antioxidant activity was evaluated in parallel with liquid SMEDDS and unformulated curcumin powder.

MATERIALS AND METHODS

Materials

Curcumin, SCMC (Sodium carboxymethylcellulose; low viscosity) and BHT (butylated hydroxytoluene) were obtained from Sigma Aldrich (Buchs, Switzerland). Capryol 90™ (propylene glycol monocaprylate), Labrafac PG™ (propylene glycol caprylate/caprate) and Labrasol™ (caprylocaproyl macrogol-8 glycerides) were obtained from Gattefossè (Saint-Priest, France). Cremophor EL™ (polyoxyethylene castor oil derivative) was obtained from BASF (Ludwigshafen, Germany). Tablettose™ 80 (lactose) was obtained from Meggle GmbH (Wasserburg, Germany). Mannitol and acacia were obtained from the PC Drug Center Co., Ltd. (Bangkok, Thailand). PVP K-30 was obtained from BASF (Bangkok, Thailand). Ascorbic acid was obtained from Chem supply (Adelaide, Australia). Methanol (AR grade) was obtained from RCI Labscan (Bangkok, Thailand).

Preparation of Curcumin Liquid SMEDDS

Curcumin liquid SMEDDS were prepared using previously published methodology [9]. Briefly, powdered curcumin (40 mg) was dispersed into a liquid mixture of surfactants and oils (Cremophor EL 315 mg, Labrasol 315 mg, Capryol 90 135 mg, and Labrafac PG 135 mg) and mixed until homogeneous. Curcumin liquid SMEDDS were stored in tightly sealed glass bottles, protected from light at room temperature.

Preparation of curcumin SMEDDS reconstituted granules

Reconstituted granules were prepared using wet granulation. Five hundred milligrams of liquid SMEDDS were mixed with 4 g of sugar (lactose or mannitol) until homogeneous. A binder solution consisting of either SCMC, acacia or PVP K-30 (1 or 5 %w/w) was then added and blended together with liquid SMEDDS-sugar mixture. The damp mass was passed through a sieve (size no. 14) to obtain granules and these were then dried in an oven at 45 °C for 4 h. Dried granules were again passed through a sieve (size no. 14) and retained on a second sieve (size no. 16) to obtain uniform sized granules. The compositions of curcumin SMEDDS reconstituted granules is given in Table 1.

Characterization of the flow properties of curcumin SMEDDS reconstituted granules

The flow properties of the granules were assessed using three methods: 1) Angle of repose, 2) Hausner ratio, and 3) compressibility index according to the criteria of United States Pharmacopeia (USP) <1174> powder flow.

Angle of repose

Angle of repose was measured using the fixed funnel method in which, granules are allowed to flow through a funnel and fall freely onto a circular plate. The height of the pile formed on the circular plate beneath the funnel was measured and the angle of repose was calculated using Eq. [**1**]:

$$tan\phi = \frac{h}{r} \qquad [1]$$

where h is the height of the cone, r is the radius of the circular plate and Ø is the angle of repose. Table 2 gives values of granule flowability as determined by angle of repose.

Bulk density and tapped density

To measure granule density, a 100 mL capacity measuring cylinder was filled with granules to > 75 % of the cylinders height to ascertain the volume they occupied. Bulk density was calculated as the quotient of weight to the volume of the sample (weight / volume). Tapped density

Formulation code	Curcumin SMEDDS (g)	Sugar	Binder	Binder concentration (%w/w)
MP1	0.5	Lactose (4 g)	SCMC	1
MP5				5
MA1			Acacia	1
MA5				5
MS1			PVP	1
MS5				5
LP1		Mannitol (4 g)	SCMC	1
LP5				5
LA1			Acacia	1
LA5				5
LS1			PVP	1
LS5				5

Table 1. Compositions of curcumin SMEDDS reconstituted granules.

Flow property	Angle of repose
excellent	25-30
good	31-35
fair	36-40
passable	41-45
poor	46-55
very poor	56-65
extremely poor	> 66

Table 2. Granule flowability as determined by angle of repose.

Compressibility index (%)	Flow character	Hausner ratio
<10	excellent	1.00-1.11
11-15	good	1.12-1.18
16-20	fair	1.19-1.25
21-25	passable	1.26-1.34
26-31	poor	1.35-1.45
31-37	very poor	1.46-1.59
>38	extremely poor	>1.60

Table 3. Scale of granule flowability as determined by compressibility index and Hausner ratio.

is the quotient of weight of the sample to the volume after tapping a measuring cylinder 500 times from a height of about 4 cm.

Hausner ratio and Carr's index

Hausner's ratio was calculated as the ratio of tapped density to bulk density. The compressibility of the granules was determined using Carr's index, which was calculated using the Eq. [**2**]:

$$Carr's\ index = \frac{(Tapped\ density - Bulk\ density)}{Tapped\ density} \times 100 \quad [2]$$

The scale of granule flowability as determined by compressibility index and Hausner ratio is consigned in Table 3.

Morphological analysis of curcumin SMEDDS reconstituted granules and microemulsions droplets

The outer macroscopic structure of the reconstituted granules was investigated by scanning electron microscope (SEM). In addition, the microstructure of the microemulsion of the reconstituted curcumin SMEDDS granules were investigated and compared with those of liquid SMEDDS using transmission electron microscopy (TEM) (JEOL Ltd., Japan). Granules (equivalent to 1 g of curcumin liquid SMEDDS) were introduced into 100 mL of water (100-fold dilution) at room temperature and stirred for 10 min. The content was filtered using a 0.45-µm membrane filter and the filtrate was then directly deposited on to copper grids. Filter paper was used to remove excess fluid and the copper grids were stained with a 2% aqueous solution of phosphotungstic acid for 10 min, and imaged following drying.

Determination of drug content

Curcumin SMEDDS granules were accurately weighed, transferred to a 50 mL volumetric flask, and reconstituted with distilled water added to 50 mL total volume. The cylinders

contents were then throughly mixed by shaking for 15 min, then further diluted with methanol. The solution was filtered through a 0.45 µm membrane filter and the filtrate subsequently analyzed for curcumin using a ultraviolet–visible spectrophotometer (Spectronicgenesys 5, USA) at 425 nm, with methanol used as a blank. The concentration of curcumin used in the calibration curve ranged from 5 to 25 µg/ml with a correlation coefficient of 0.9998. The drug content of the sample was calculated from a calibration curve [22,23]. Then, the percentage drug content was calculated using the Eq. [**3**]. The data were presented as the mean ± SD (n = 3).

$$\%Drug\ content = \frac{The\ actual\ amount\ of\ curcumin\ in\ granules}{The\ initial\ amount\ of\ curcumin} \times 100 \quad [3]$$

Reconstitution properties of curcumin SMEDDS reconstituted granules

Curcumin SMEDDS reconstituted granules (2 g) were dispersed in 20 mL of distilled water with constant stirring at 70 rpm followed by incubation with continuous stirring for 30 min at 37 ± 0.5 °C. The qualitative estimation of the tendency to form a microemulsion was assessed as good when the granules dissolved and formed a fine transparent emulsion of droplets. It was judged as bad when a milky emulsion formed [24]. The average time required to completely dissolve the granules was also recorded.

Droplet size of reconstituted microemulsions

Granules containing curcumin SMEDDS (equivalent to 100 mg of curcumin SMEDDS) were introduced into 20 mL of water at room temperature, gently stirred, filtered through a 0.45-µm filter. The Zetasizer Nano ZS, a zeta potential and particle size analyzer (Malvern, UK), was used to measure the droplet size distribution and polydispersity index (PDI) of the resultant microemulsion [11]. Light scattering analysis was performed using a single detector at 90 degrees and at a temperature of 25 °C. The detection time was 1 min and each run had 10 subruns. Each sample was analyzed in triplicate and the data presented as the mean ± SD.

Selection and comparison of the best batch of curcumin SMEDDS reconstituted granules

Selection of the optimal granule batch was accomplished on the basis of flowability, drug content, reconstitution properties and reconstituted droplet size. The optimized granule formulation was compared with curcumin liquid SMEDDS and unformulated curcumin powder.

Stability testing

The stability of the optimized granules was studied according to ICH guidelines with regards to Q 1 A (R2): stability testing of new drug substances and products under intermediate conditions (30 ± 2 °C/65 ± 5% RH) and comprised accelerated conditions (45 ± 2 °C/75 ± 5% RH). Samples were preserved with controlled humidity and temperature in a HPP constant climate chamber (Memmert HPP 260, Germany) for 6 months. Following stability testing, microemulsion droplet size and granule drug content were assessed.

Determination of antioxidant activity of curcumin SMEDDS reconstituted granules by DPPH assay

Briefly, 0.1 mM methanolic solution of DPPH (2,2-diphenyl-1-picrylhydrazyl) was prepared, and 1 mL of this solution was added to 3 mL of various concentrations of curcumin formulations and the reference compounds which were ascorbic acid and BHT (5, 10, 15, 30 and 60 µg/mL). Absorbance was measured at 517 nm. The experiment was carried out in triplicate and free radical scavenging capability was expressed as Eq. [**4**]

$$Radical\ scavenging\ activity(\%) = \frac{A-B}{A} \times 100 \quad [4]$$

where *A* represents the absorbance of methanol without sample as control and *B* represents the absorbance of the sample. Ascorbic acid and BHT were used as positive controls.

RESULTS AND DISCUSSION

The physical properties and flowability of curcumin SMEDDS reconstituted granules

Curcumin SMEDDS reconstituted granules were chosen as a method of curcumin delivery as they provide a formulation which can be simply administered as an oral solution to patients of all age groups. The curcumin SMEDDS granules were yellow, brittle and of a uniform size distribution (Fig. 1).

Figure 1. Physical appearance of curcumin SMEDDS reconstituted granules (MS1) for oral solution.

The flow properties of the dried granules were determined by measurement of angle of repose, bulk- and tapped density, Hausner ratio, and % compressibility (Table 4). Granule flowability was scored as being passable to good. The type or concentration of sugar used in the formulation as a binder did not affect the granule flow properties, potentially due to the small quantity of binder (1 and 5% w/w) used.

Determination of drug content

The quantity of curcumin in the 12 different reconstituted formulations ranged from 92.64 ± 1.21% to 99.38 ± 0.95% (Table 5). The drug content in reconstituted mannitol-based granules was higher than that in the corresponding re-

Formulation code	Angle of repose (degree ± SD)	Bulk density (mg/mL ± SD)	Tapped density (mg/mL ± SD)	Hausner's ratio (± SD)	%Compressibility (± SD)	Flowability
MP1	22.38 ± 0.58	0.48 ± 0.01	0.59 ± 0.03	1.23 ± 0.07	18.81 ± 4.44	fair
MP5	22.95 ± 0.99	0.49 ± 0.01	0.59 ± 0.01	1.22 ± 0.03	18.15 ± 2.26	fair
MA1	22.57 ± 0.67	0.48 ± 0.01	0.57 ± 0.02	1.20 ± 0.03	16.84 ± 1.87	fair
MA5	23.14 ± 1.19	0.47 ± 0.01	0.59 ± 0.04	1.26 ± 0.05	20.63 ± 3.23	passable
MS1	22.57 ± 0.67	0.48 ± 0.02	0.56 ± 0.01	1.17 ± 0.03	14.56 ± 1.99	good
MS5	23.33 ± 0.65	0.48 ± 0.01	0.58 ± 0.02	1.20 ± 0.03	16.59 ± 2.31	fair
LP1	23.33 ± 0.65	0.53 ± 0.01	0.67 ± 0.03	1.27 ± 0.08	20.82 ± 4.63	passable
LP5	21.40 ± 1.34	0.53 ± 0.01	0.62 ± 0.02	1.17 ± 0.07	14.23 ± 4.74	good
LA1	22.57 ± 0.67	0.52 ± 0.02	0.66 ± 0.04	1.28 ± 0.07	21.49 ± 4.71	passable
LA5	23.70 ± 1.73	0.52 ± 0.02	0.62 ± 0.01	1.21 ± 0.06	17.11 ± 4.35	fair
LS1	22.57 ± 0.67	0.55 ± 0.01	0.68 ± 0.02	1.24 ± 0.03	19.31 ± 1.82	fair
LS5	23.33 ± 0.65	0.52 ± 0.01	0.61 ± 0.01	1.16 ± 0.02	14.12 ± 1.75	good

Table 4. Characteristics of curcumin SMEDDS reconstituted granules.

Formulation code	Droplet size (nm ± SD)	PDI (± SD)	% Drug content (% ± SD)	Time to dissolve (s ± SD)
MP1	31.21 ± 0.09	0.198 ± 0.002	98.48 ± 0.38	1.31 ± 0.10
MP5	34.47 ± 0.19	0.128 ± 0.015	98.68 ± 1.10	2.23 ± 0.18
MA1	33.53 ± 0.06	0.216 ± 0.010	98.19 ± 0.82	1.24 ± 0.02
MA5	32.96 ± 0.11	0.202 ± 0.002	99.38 ± 0.95	2.06 ± 0.04
MS1	36.13 ± 0.08	0.162 ± 0.011	97.10 ± 1.49	1.44 ± 0.17
MS5	42.34 ± 0.14	0.154 ± 0.007	98.08 ± 1.22	3.12 ± 0.32
LP1	45.88 ± 0.24	0.318 ± 0.003	92.64 ± 1.21	3.50 ± 0.20
LP5	40.40 ± 0.32	0.218 ± 0.003	93.90 ± 0.55	4.22 ± 0.26
LA1	34.08 ± 0.05	0.120 ± 0.021	95.24 ± 1.14	3.02 ± 0.13
LA5	47.98 ± 0.66	0.308 ± 0.028	96.88 ± 1.67	3.53 ± 0.20
LS1	35.13 ± 0.08	0.138 ± 0.002	94.01 ± 0.44	2.56 ± 0.14
LS5	38.74 ± 0.23	0.218 ± 0.003	96.51 ± 1.26	3.17 ± 0.24

Table 5. The droplet size, percent drug content and time required to dissolve the reconstituted granules.

constituted lactose-based formulations. Minor differences in drug content were not statistically significant. These data indicate that the amount of binder does not influence drug content to a significant extent.

Microemulsion droplet size after reconstitution of granules

The microemulsion droplet size and polydispersity index (PDI) value of the reconstituted individual formulations ranged from 31.21 ± 0.09 to 45.8 8 ± 0.24 nm and 0.120 ± 0.021 to 0.318 ± 0.003, respectively (Table 5). Granules containing curcumin SMEDDS resulted in a microemulsion droplet size of less than 50 nm and a uniform droplet size distribution was observed. From these data, it is clear that the choice of sugar (mannitol or lactose) used in the solidifying procedure of the liquid SMEDDS did not affect droplet size.

TEM imaging of the microemulsion (Fig. 2) revealed globules of an almost spherical shape, with sizes correlating with those observed using a particle size analyzer. The nanosize range of the droplets was maintained even after dilution with water proving that it did not change during the solidifying process. Similarly, use of other solidification techniques [9-12] has also revealed that microemulsion droplet size that released from solid dosage forms is comparable to its liquid SMEDDS form.

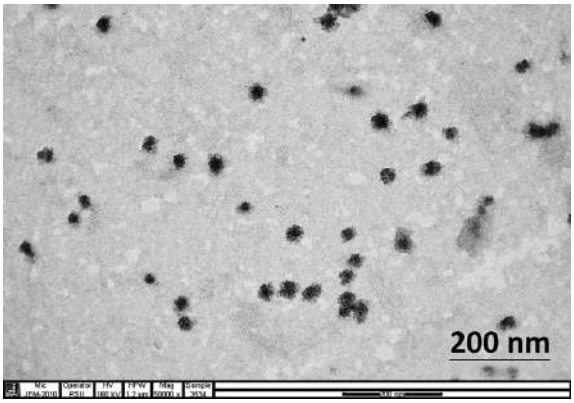

Figure 2. TEM micrograph of the microemulsion after reconstitution of granules.

After reconstitution of the curcumin SMEDDS granules, the spontaneous formation of a microemulsion presents the drug in a dissolved form with a small droplet size. When given orally, curcumin can be directly absorbed as the microemulsion droplet in the gastrointestinal tract, without the dissolution step. The large surface area of the small droplet size are expected to enhance the rate and extent of absorption of curcumin.

Reconstitution time of curcumin SMEDDS reconstituted granules

In almost all of the granule formulations those with higher binder contents took longer to dissolve in water. The amount of binder in the LP and LS formulations did not significantly affect granule dissolving time. The lactose-based granules produced a white, cloudy liquid after dissolving and were thus deemed unacceptable for further analysis. In all of the preparations, the reconstituted liquid was transparent yellow and neither phase separation nor phase inversion was observed after incubation for 30 min. Clarity of the reconstituted solution indicated that the granules were dissolved completely, with an absence of visible undissolved matter.

Surface morphology

SEM analysis of granule morphology indicated that the granules had a spherical shape and that their surfaces were nearly smooth (Fig. 3). From the photomicrographs, it appeared that binder particles covered the granule surface. Smoother surfaces were observed from those granules with greater binder content. The uniform size distribution of granules with smooth surfaces generally signified faster flow. In the

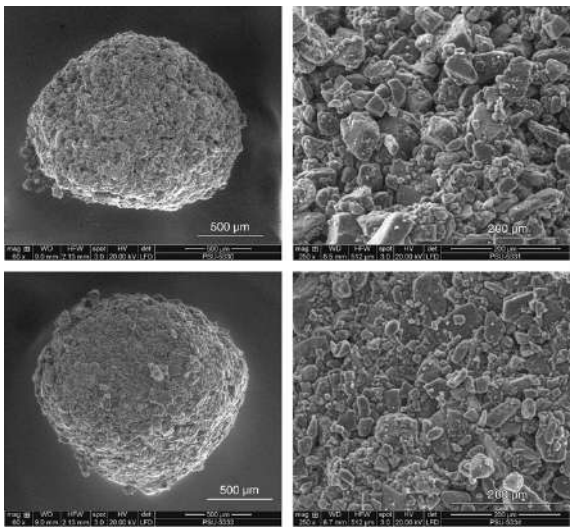

Figure 3. SEM micrographs of curcumin SMEDDS reconstituted granules. Upper row: MS1 formulation (1% binder concentration) and lower row: MS5 formulation (5% binder concentration), Left and right columns: 60x and 250x magnification of granule surfaces, respectively.

Time (months)	Droplet size (nm ± SD)	PDI (± SD)	% Drug content (± SD)
	(A) 30 °C /65% RH		
0	36.13 ± 0.08	0.162 ± 0.011	97.10 ± 1.49
3	36.90 ± 0.49	0.175 ± 0.067	96.32 ± 2.75
6	36.94 ± 0.08	0.261 ± 0.059	97.74 ± 2.28
	(B) 45 °C /75% RH		
0	36.13 ± 0.08	0.162 ± 0.011	97.10 ± 1.49
3	35.69 ± 0.99	0.280 ± 0.048	96.28 ± 2.13
6	36.86 ± 0.42	0.263 ± 0.043	95.70 ± 2.83

Table 6. Stability data for the optimum formulation of curcumin SMEDDS reconstituted granules (Formulation MS1) under intermediate (A) and accelerated (B) conditions.

current study, the binder content may not impact those flow properties.

The optimized formulation of curcumin SMEDDS reconstituted granules

The optimal formulation was selected based on granule flowability, reconstitution properties, microemulsion globule size, and drug content. The MS1, LP5 and LS5 formulations resulted in good flowability, while other properties seemed unaltered. The lactose-based formulations resulted in formation of a white cloudy mixture during attempts to dissolve them which was considered undesirable. Hence, the best formulation for further studies was deemed to be MS1 formulation which possessed good flowability, uniform spherical droplet size, and the ability to form a clear liquid spontaneously when dissolved in water. In addition, the mannitol used in this formulation is incompletely absorbed by the small intestine. In contrast, lactose is absorbed and provides some calories. Mannitol based formulations are therefore advantageous for individuals who are dieting, and also for those patients suffering from diabetes, since blood sugar levels would not be increased.

Stability studies

Stability data for the optimum formulation of curcumin SMEDDS reconstituted granules under intermediate (A) and accelerated (B) conditions are given in Table 6. Granule properties were assessed after 6 months to determine long term stability. The color of the granules did not change, nor did the microemulsion droplet size or drug content significantly change after storage under both intermediate and accelerated conditions. The PDI values after storage at 30 °C were slightly increased. It was indicated that nanoparticles were of broad polydispersity (0.25-0.50); however, the microemulsion droplet size was not significantly changed. Thus, it was acceptable. This may be a consequence of the low hygroscopicity and strong inertness of mannitol.

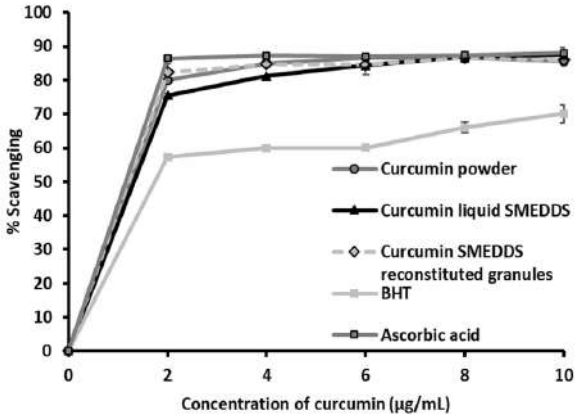

Figure 4. Antioxidant activity of the optimal granule formulation (MS1) compared with that of unformulated curcumin powder, curcumin liquid SMEDDS, and BHT and ascorbic acid standards.

Antioxidant activity

Curcumin's antioxidant activity is a result of its free radical scavenging ability. Various dosage forms of curcumin (2-10 µg/mL) and ascorbic acid exhibited nearly 90% scavenging compared to BHT which only displayed 60 to 70%. These results imply that curcumin is able to reduce DPPH radicals into the neutral DPPH-H form. Unformulated curcumin powder, or curcumin in liquid or solid formulations were all found to be excellent scavengers for DPPH radicals comparable with ascorbic acid and being

superior in that regard to BHT. In similar studies [25,26], curcumin's antioxidant activity was demonstrated to be comparable to ascorbic acid and better than BHT under the same reaction conditions. Therefore, the antioxidant activity of curcumin was not altered by the solidification process presented in the current study (Fig. 4)

CONCLUSION

The optimal formulation of curcumin SMEDDS reconstituted granules were prepared using mannitol and 1% SCMC with the wet granulation technique. It presented good flow properties and following reconstitution resulted in spherical microemulsion droplets with a size of less than 50 nm (the same as observed for liquid SMEDDS). The antioxidant properties of the optimal granules were comparable to those of unformulated curcumin powder, liquid SMEDDS or ascorbic acid, and were greater than those of BHT. These data indicate reconstituted granules are a feasible means by which to deliver lipid-based formulation via oral administration. In addition, they could provide a suitable dosage form for children, the elderly and for unconscious patients.

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