BJPS

Brazilian Journal of
Pharmaceutical Sciences
vol. 47, n. 2, apr./jun., 2011

Article

The evaluation of coated granules to mask the bitter taste of dihydroartemisinin

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The purpose of this study was to mask the bitter taste imparted by dihydroartemisinin (DHA) by the use of different coating materials. Trial-1 and trial-2 were conducted to prepare the DHA granules. The granules produced from trial-1 were irregular in shape and smaller in size while the trial-2 granules were more regular and larger in size. The granules obtained from both trials were then coated with two different coating methods, namely A and B, depending upon coating material. The trial-2 granules showed better flow properties than trial-1 granules. *In vitro* dissolution studies in phosphate buffer at pH 6.8 revealed that granules of trial-2B released only 34% ± 3 DHA in two minutes compared with trial-1A (57% ± 2), trial-1B (48% ± 2) and trial-2A (53% ± 7). The pleasant taste perception (PTP) test also confirmed the taste masking efficacy of trial-2B ($P < 0.05$). Scanning electron microscopy (SEM) revealed the more regular and smooth surface of trial-2B granules. In addition, the differential thermal and thermogravimetric analysis (TG-DTA) confirmed no interaction between the materials and pure DHA. DHA has shown its characteristic peaks in the x-ray diffraction (XRD) patterns which were also prominent in all the granules. In conclusion, the granules obtained from trial-2B displayed considerable decrease in the bitter taste of DHA thereby fulfilling the purpose of this study.

Uniterms: Medicines/coating. Granules/coating. Dihydroartemisinin (DHA)/taste masking. Thermogravimetric analysis/medicines analysis. X-ray diffraction/medicines analysis.

O objetivo deste estudo foi o de mascarar o gosto amargo característico da diidroartemisinina (DHA) pelo uso de diferentes materiais de revestimento. Experimento-1 e experimento-2 foram realizados para preparar grânulos de DHA. Os grânulos produzidos pelo experimento-1 mostraram-se irregulares e menores se comparados aos obtidos pelo experimento-2, que foram mais regulares e maiores. Os grânulos obtidos em ambos os experimentos foram, então, revestidos por dois métodos distintos de revestimento, designados como A e B, dependendo do material de revestimento empregado. Os grânulos do experimento-2 mostraram melhor propriedade de fluxo que os obtidos no experimento-1. Estudos de dissolução *in vitro* em tampão fosfato pH 6,8 revelaram que grânulos do experimento-2B liberaram apenas 34% ± 3 da DHA em dois minutos se comparado com experimento-1A (57% ± 2), experimento-1B (48% ± 2) e experimento-2A (53% ± 7). A Análise Sensorial quanto ao sabor (Pleasant Taste Perception - PTP) também confirmou a eficácia do experimento-2B ($P < 0,05$) em mascarar o gosto amargo da DHA. Microscopia Eletrônica de Varredura (SEM) revelou a superfície mais regular e lisa dos grânulos obtidos pelo experimento-2B. Além disso, Análise Termogravimétrica e Análise Térmica Diferencial (TG-DTA) confirmaram que não há nenhuma interação entre os materiais e a DHA pura. DHA mostrou seus picos característicos na Difração de Raios X (XRD) em padrões que também foram proeminentes em todas as amostras. Em conclusão, os grânulos obtidos pelo experimento-2B exibiram diminuição considerável no gosto amargo da DHA, o que era o propósito deste estudo.

Unitermos: Medicamentos/revestimento. Granulados/revestimento. Diidroartemisinina. Granulados. Análise termogravimétrica/análise de medicamentos. Difração de raio X/análise de medicamentos.

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INTRODUCTION

Bitter, astringent, metallic or unpleasant tastes are highly unacceptable if using the oral route of delivery, especially in the case of pediatric drugs (Roy, 1994; Szejtli, Szente, 2005). The majority of the orally administered drugs including alkaloids such as quinine, and antibiotics such as sparfloxacin or clarithromycin, are bitter in taste (Shirai *et al.*, 1993, 1994; Katsuragi *et al.*, 1995, 1997; Yajima *et al.*, 1999). However, for patients, such drugs are not necessarily easy to swallow, resulting in non-compliance and a subsequent decrease in efficacy. To overcome this problem various techniques have been developed to mask the unpleasant and bitter taste of drugs including capsules, coated tablets, microencapsulation, complexation and chemical modification (Cuña *et al.*, 1997; Barra *et al.*, 1999). But in most cases, solid preparations like tablets and capsules are not recommended for pediatric patients, instead liquid preparations are used. It is known that only dissolved substances elicit taste sensation and substances which are completely insoluble in water are tasteless. In many cases, however, the drugs are so intensely bitter, that they are barely tolerable even at ppm levels (Szejtli, Szente, 2005).

The most effective method of achieving maximum taste masking is to coat the drug particles, thereby creating a physical barrier around the drug. This may be achieved using microencapsulation techniques such as spray-drying (Yajima *et al.*, 1999; Wilson *et al.*, 1994), spray-congealing (Shimano *et al.*, 1995; Robson *et al.*, 1999), coacervation (Chukuwu *et al.* 1991; Al-Omranm *et al.*, 2002) or the solvent evaporation method (Hashimoto *et al.*, 2002).

Dihydroartemisinin (DHA), a more water-soluble metabolite of artemisinin derivatives, is a safe and highly effective antimalarial analog of artemisinin (Chen *et al.*, 2004). It is isolated from the traditional Chinese herb *Artemisia annua*, and recommended as a first-line anti-malarial drug with low toxicity (Dhingra *et al.*, 2000). This drug has a very bitter taste and therefore serves as a model drug to evaluate taste-masking efficiency for several kinds of oral formulations.

In the present investigation, our goal was to prepare DHA granules using the wet granulation technique (Ameye *et al.*, 2002) and to apply enteric coating by using different coating materials to mask the bitter taste of DHA. The influence of these coatings on the surface morphology of granules were then examined using scanning electron microscopy (SEM) as well as the influence on their dissolution behavior at pH 6.8 of the oral cavity. In addition, the palatability of the granules was evaluated in a pleasant taste perception (PTP) test. Finally, differential thermal analysis (DTA), thermogravimetric analysis (TGA), and x-ray diffraction (XRD), was used to investigate possible interactions between the components of the formulation.

EXPERIMENTAL

Materials

Dihydroartemisinin (DHA) was a gift sample from AMSON Vaccines & Pharma (Pvt.) Ltd. Islamabad, Pakistan. Methocel® E5 was obtained from Dow Chemical Co., Midland. Opadry® was purchased from Colorcon, West Point, PA. Carbopol 934P was obtained from B.F Goodrich, Cleveland, OH, USA. Polyvinylpyrrolidone (PVP-K30) and isopropyl alcohol (IPA) were obtained from Fluka (Buchs, Switzerland). Acetonitrile was 99% HPLC grade (Merck, Germany). All the chemicals and reagents were of analytical grade.

Chromatographic conditions and analysis

The DHA analysis was performed on a HPLC Gradient SPD 10 A (Schimadzu**)** with UV detector at 209 nm. The HPLC was equipped with a 20 µL loop Rheodyne injector. A symmetry C-18 column (Waters corporation, 5 µm, 4.6 x 150 mm i.d.) was used as the stationary phase. The mobile phase was prepared by mixing HPLC grade acetonitrile and water (milli-Q) in a 35:65 v/v ratio and vacuum filtering it through a 0.45 µm nylon filter. Filtered solvents were degassed before use. The flow rate was set at 1.2 mL/min (Ansari *et al.*, 2009).

Solubility studies

The test samples were prepared in water with an excess amount of pure DHA and placed on an orbital shaker at 100 rpm for five days in a temperature controlled room at 37 ^{o}C. Samples were centrifuged and withdrawn with a syringe equipped with a 0.40 µm syringe filter. All samples were diluted and immediately analyzed with HPLC for drug content. Samples were prepared in duplicate (Ansari *et al.*, 2009).

Preparation of granules

The wet granules of DHA were prepared using two trials in a laboratory-scale low-shear mixer. The formulation of each trial is given in Table I. The batch size was 500 g for each trial (trial-1: granulation with starch, PVP-K30, and IPA in 100 mL of distilled water, and trial-2: granulation with Carbopol 934P, sodium metabisulphite,

and methyl paraben sodium in 150 mL of distilled water). The impeller speed was set at 100 rpm for 10 min in all the trials to mix the powders, then, during addition of the granulation liquid, the impeller speed was raised to 400 rpm for 10 minutes to wet the whole powder mixture.

Finally, the granules were dried at a reduced pressure at 60 °C with an impeller speed of 100 rpm for 10 s every 100 s, while tilting the bowl to move the granules increasing the surface exposed to the evaporation process. The drying time, as a function of the amount of water used, was 25 minutes for trial-1, and 30 min for trial-2. Therefore, the total granulation time was 45 min for trial-1, and 50 min for trial-2. The granules were spread out in thin layers in a tray allowing them to cool at room temperature, then collected and sieved as described in the following section.

TABLE I - Formulation of DHA granules

Trial 1		Trial 2	
Ingredients	Quantity	Ingredients	Quantity
DHA	350 g	DHA	350 g
Starch	30 g	Carbapol	25g
PVP-K30	40 g	Sodium Metabisulphite	50 g
IPA	80 ml	Methyl Paraben Sodium	75 g
DI water	QS	DI water	QS

Coating of granules

Coating was undertaken to mask the bitter taste and to improve the aesthetic appeal of the formulated granules of DHA. For this purpose, two coating methods namely A and B were used to coat the granules of each trial-1 and 2 in conventional coating pans. In coating method A, Methocil™ E5 (60 g) was mixed in 250 g of IPA with fast stirring. Titanium dioxide (6 g) and talcum (10 g) were then dissolved in 50 mL of methylene chloride. Both the solutions were then mixed together for 10 minutes for uniformity and then filtered. In coating method B, Opadry® enteric (30 g) was mixed in methylene chloride (50 mL) and IPA (300 g) with fast stirring for 40 minutes. A small quantity of methylene chloride was added and mixed for another 10 minutes for uniformity and then filtered. The trials were designated as trial-1A & trial-1B, and trial-2A & trial-2B based on the method of coating applied to each formulation respectively. A laboratory scale coating pan (SH-506, Taiwan) was used to coat the granules. The operating speed of pan was 20 rpm with high atomization and slow air speed. The distance of the coating gun was 25 inches from the granules bed for efficient coating. The granules were dried after coating by blowing hot air.

Characterization of Granules

Granule size distribution

The granule size distribution was evaluated by sieve analysis, using a vibrating shaker (Octagon Digital, Endecotts, London, UK) at a medium vibration level for 15 min and three standard sieves (Scientific Instruments s.r.l., Milan, Italy) in the range 250–2000 um. The fractions were then collected and stored in desiccators at 30±2 °C. The granulation tests were performed at least in duplicate and the mean of each particle size ± standard deviation (S.D.) was then calculated.

Rheological study of formulated granules

The rheological properties of formulated granules were determined by Carr's index (Leon, *et al.*, 1986):

$$C = \frac{\rho_t - \rho_p}{\rho_t} \times 100$$

Where ρ_p is the poured density described by mass of sample granules divided by the undistributed volume in a 10 mL cylinder after filling, and ρ_t is the tapped density described by mass of sample granules per unit volume after tapping a bed of granules, after no change of volume was observed.

Drug content estimation

The analysis of the DHA content in each fraction was carried out by dissolving 50 mg of granules in 100 mL of phosphate buffer at pH 6.8 (within the pH range of saliva); the amount of the drug was then determined by HPLC Gradient SPD 10 A (Schimadzu**)** at 209 nm. Each fraction was analyzed in triplicate.

In vitro dissolution studies

In vitro dissolution tests were performed using the USP 24 paddle method (Pharmatest, Steinhein, Germany) rotating at 60 rpm. A volume of 900 mL of pH 6.8 phosphate buffer was used at a temperature of 37 ± 1 °C to evaluate the taste-masking efficiency of the granules. Each sample contained 35 mg of DHA. The samples were taken at a pre-determined time and analyzed by HPLC Gradiant SPD 10 A (Schimadzu). The amount of drug dissolved was analyzed at 209 nm. The dissolution tests were performed

in triplicate and the three absorption values were averaged and their S.D. was then calculated.

Pleasant taste perception (PTP) test

The PTP test was performed by six volunteers at the Gustatory Evaluation Laboratory of the Institute of Biotechnology, Bahauddin Zakariya University Multan (Pakistan). The involvement of human volunteers in this study was ethically approved by the Gustatory Evaluation Laboratory of the Institute of Biotechnology, Bahauddin Zakariya University. To find a suitable concentration for the evaluation of the bitterness taste intensity during the comparative test, the perception and bitterness recognition threshold of pure DHA was evaluated as described previously (Beatrice *et al.*, 2004).

To determine the threshold of bitterness, seven standard solutions of pure DHA in distilled water at different concentrations were prepared as follows:

I. 0.00% (w/v); **II.** 0.01% (w/v); **III.** 0.025% (w/v); **IV.** 0.05% (w/v); **V.** 0.1% (w/v); **VI.** 0.2% (w/v) and **VII.** 0.4% (w/v).

The volunteers were then asked to taste 5ml of solution IV by keeping it in their mouth for 5 Seconds. Then, they were required to give one of these following perceptions:

1. "I feel a bitter taste".
2. "I do not feel any difference between solutions IV and I",
3. "I feel something but I can not identify the taste",

The volunteers whose answer perception was 2 or 3 were then asked to taste solution V (having a higher drug concentration than IV), while volunteers whose answer perception was 1 were then asked to taste solution III. The results yielded the perception threshold at 0.05% (w/v) (range 0.025–0.08%, w/v) and bitterness recognition threshold at 0.08% (w/v) (range 0.06–0.2%, w/v). Subsequently, in order to have homogeneity in the sensation of the bitterness intensity among the volunteers, a trained panel evaluation was performed testing some solutions at different concentrations of DHA and the volunteers were told the bitterness scores (from 0 to 100) of these solutions.

The evaluation of the granules taste was then carried out by dispersing 250 mg of each sample in 100 mL of water to obtain a 0.21% (w/v) DHA granules suspension, which is higher than the bitterness recognition threshold. The granule particle size was the same as that used for the dissolution tests. The PTP test was performed on the granule suspension instead of the solid sample to evaluate if the *in vitro* drug release of the four samples could reflect upon the bitterness sensation after the same time (2 min) and also to reduce the wide variability of drug concentration in the mouth, because of the different salivation conditions between volunteers, occurring when a solid sample is used.

The volunteers were then asked to taste 5 mL of each sample as previously described and to give a bitterness score (based on a 0.21% (w/v) granule suspension bitterness score of 100). Significant differences among granules were analyzed using the unpaired student's t-test and a value of $P<0.05$ was considered significantly different.

Scanning electron microscopy (SEM)

The surface morphology of the developed formulations was examined using a scanning electron microscope (Hitachi S-6000).

Differential thermal & thermogravimetric Analysis (TG-DTA)

The thermal stability of DHA granules was studied. For this, simultaneous TG-DTA experiments were performed using a Linesis STA PT 1600 instrument under an air flow of 100 mL/min at heating rate of 5 °C/min with an initial sample mass of 5 mg. Alumina crucibles were used for analysis.

X-ray diffraction (XRD)

X-ray powder diffraction (XRD) for DHA and granules was performed using a Bruker D8 Discover (Germany) apparatus. Measurement conditions included target (CuKα), voltage (35 KV), and current (35 mA). A system of diverging, receiving, and anti-scattering slits of 1^o, 1^o, 0.15^o, respectively, were used. Eva software was used for the data processing (Evaluation Package Bruker, Germany). Patterns were obtained using a scan speed of 4 degree/minute with 2θ between 6^o, and 35^o (Ansari *et al.*, 2009).

RESULTS AND DISCUSSION

DHA granules were prepared by the conventional wet granulation method and characterized to confirm the suitability of granulation and coating method for reducing the unpleasant taste of the drug. DHA being a lipophilic drug showed low solubility in water as expected i.e. 0.12±0.01 mg/mL. The result obtained is very similar to a previously reported result (Ansari *et al.*, 2009). The Carr's index for trial-1 granules was 17.4 and 12.6 for trial-2 granules which indicates the better flowability of trial-2 granules as compared to trial-1 granules. Both the trials were designed to produce granules of better quality and to test the coating technique which favors more regular shaped granules. The

granules produced from trial-1 were of smaller size mainly due to the addition of PVP (Beatrice *et al.*, 2004). The granules produced from trial-2 were bigger in size than granules of trial-1. For trial-1, the cumulative frequency percent was 42 for granules having a size of 250 µm, 35 for 500 µm and 22 were greater than 1000 µm, respectively (Figure 1). For trial-2, the cumulative frequency percent was only 19 for the 250 µm size range, 43 for 500 µm and 35 were greater than 1500 µm. Overall trial-2 yielded larger granules compared with trial-1. The yield of granules from granulation trial-1 and trial-2 was 94% (w/w) and 95% (w/w) respectively, which represents a very small loss of material during the granulation process.

Secondly, coating method A & B were considered using SEM. Trial-1A produced granules which were not sufficiently regular in shape to be considered ideal. This was also the case with the granules of trial-1B and trial-2A. However, coating method B when employed in trial-2 produced granules which were more regular in shape than any of the other trials (Figure 2). These granules were considered ideal for masking the bitter taste of DHA. The content of DHA in each fraction of trial-1 and trial-2 was also measured as described in the Methods section of this paper. Table 2 represents the actual amount of DHA in the formulated granules which was uniformly distributed in the range of 84 -88 % (w/w) of the theoretical mass for both trials.

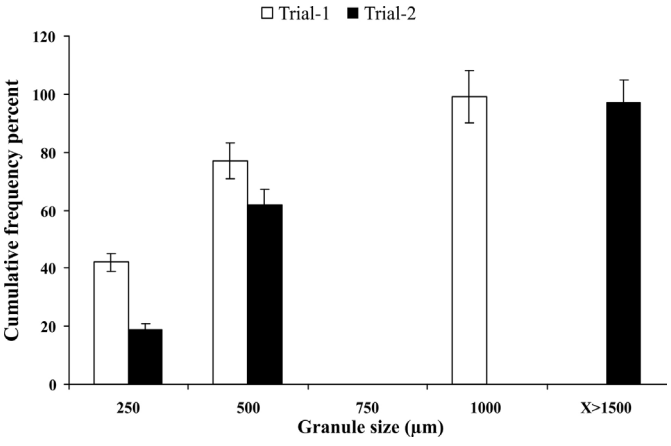

FIGURE 1 - Granule size distribution.

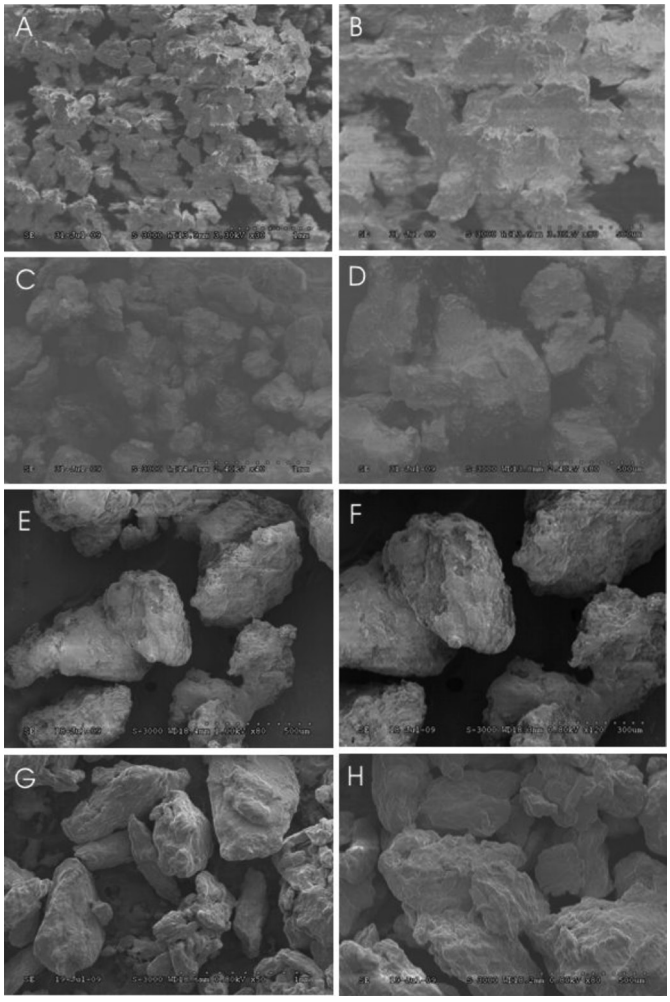

FIGURE 2 - SEM pictures of trial-1A (A) 30x and (B) 100x; trial-1B (C) 40x and (D) 80x; trial-2A (E) 80x and (F) 120x; trial-2B (G) 50x and (H) 80x.

The results of the pleasant taste perception test, performed by six volunteers, indicated that the taste-masking strategy is related not only to the granulation method but also the choice of coating material and formulation method. The trial-1A, trial-2A, trial-1B, and trial-2B granule solutions had bitter taste intensity scores of 87.5 (S.D. = 4.63; $P > 0.05$), 80.5 (S.D. = 4.8; $P > 0.05$), 74.16 (S.D. = 3.14; $P > 0.05$), and 47.33 (S.D. = 5.81; $P < 0.05$), res-

TABLE II - Content of DHA granules as a function of particle size

Size of Particles (µm)	Theoretical amount of DHA per 50 mg of Granules (mg)	Actual amount of DHA calculated in mg* (% drug Loading)	
		Trial-1	Trial-2
250<x<500	35	29.97 ± 0.97 (84.48)	30.44 ± 0.78 (86.97)
500<x<1000	35	29.51 ± 1.01 (84.31)	30.93 ± 0.45 (88.37)
1000<x<2000	35	30.13 ± 1.12 (86.08)	30.99 ± 0.91 (88.54)

*Values are given as mean ± S.D

pectively. These data confirm that the trial-2B granules successfully masked the bitter taste of DHA compared to the other formulations. The *in vitro* dissolution profiles of the granules were performed in phosphate buffer at 6.8 pH, which lies in range of saliva pH (6.2-7.4), and compared to those of pure DHA (Figure 3). The results comply with the findings of the PTP test. The dissolution of drug in 2 minutes is of particular interest as it suggests the dissolved amount is below the threshold of taste as observed in the PTP test. The dissolution profile of pure DHA was relatively high (64% ± 4 at 2 min) followed by trial-1A (57% ± 2), trial-2A (53% ± 7), and trial-1B (48% ± 2). However the trial-2B formulation showed the lowest *in vitro* drug release and only 34% ± 3 was dissolved after 2 minutes. From the result, it is clear that trial-2B granules could represent the suitable pharmaceutical form to mask the bitter taste of DHA without modifying its release which was found to be almost 98% in all trial samples.

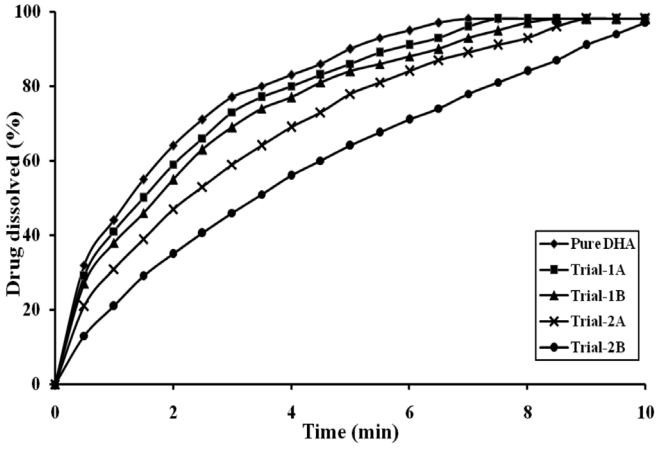

FIGURE 3 - In vitro dissolution profile of DHA granules.

To study the effect of formulation on the solid state of DHA, differential thermal analysis (DTA), thermogravimetric analysis (TGA) and x-ray diffraction (XRD) studies were conducted. Thermal and gravimetric analyses were performed at a typical storage temperature of 30 °C to reflect the climate where this research was conducted. The DTA curves (Figure 4) revealed the thermal stability of granules at the studied temperature confirming that from 30-125 °C, the granules are completely stable. The TG curves (Figure 5) for all granule trials were similar and with minimal decrease in weight from 30-125 °C. These results suggest that the granules have shown significant thermal stability in relation to the pure DHA.

XRD patterns display the characteristic peaks of DHA as described in earlier studies (Ansari *et al.*, 2009). This confirms the presence of the crystalline form of DHA

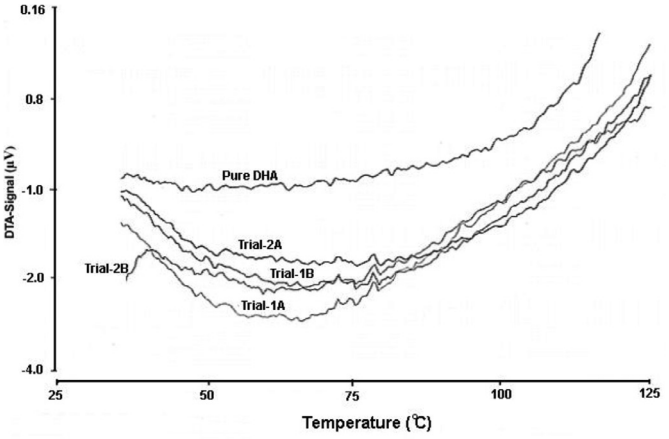

FIGURE 4 - DTA comparison of pure DHA and DHA granules.

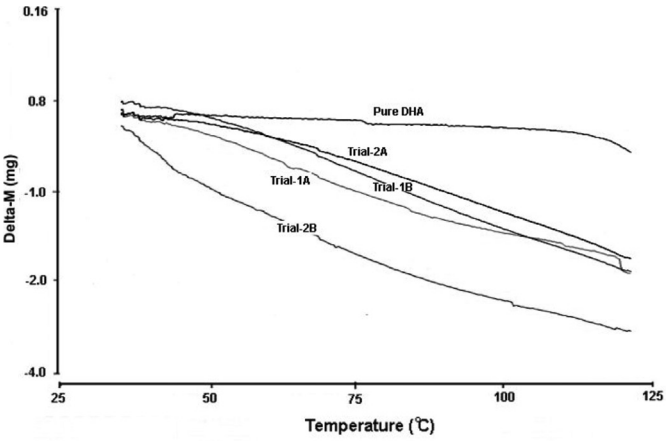

FIGURE 5 - TGA comparison of pure DHA and DHA granules.

and no phase transformations were seen in any of the formulations (Figure 6).

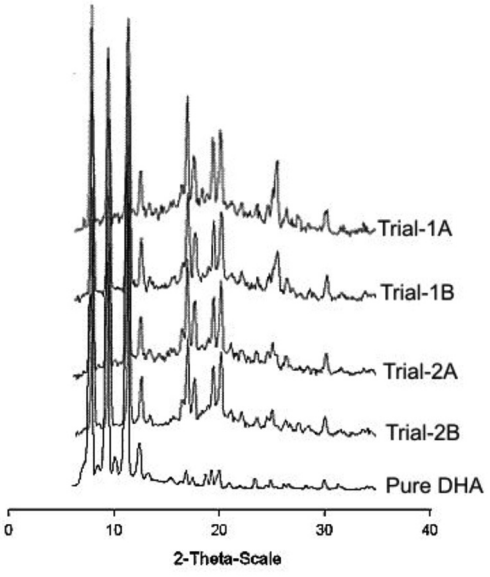

FIGURE 6 - XRD comparison of pure DHA and DHA granules.

CONCLUSION

In conclusion, it was possible to reduce the bitterness of DHA using coating method B (coating material: Opadry enteric, methylene chloride and IPA) with granules of trial-2, confirmed by taste perception tests and *in vitro* dissolution testing. Trial-2 granules showed excellent flowability. The SEM showed a more regular coating on the surface of trial-2B granules which means an efficient coating on the surface of granules can inhibit the early escape of drug from granules resulting in less impart of bitter taste. The granules showed acceptable thermal stability and no phase transformations were revealed, therefore, no interaction was evident between the excipients and DHA itself. The present study has described a novel taste masking strategy which can possibly be used for other drugs in future studies.

ACKNOWLEDGMENTS

The authors would like to thank Prof. Dr Muhammad Ali Shah, Director of the *Institute of Biotechnology,* Bahauddin Zakariya University, Multan, for the pleasant taste perception test (ethically approved) and are also thankful to Mr. Waheed Ahmed for the helpful contribution to this research. Furthermore, authors extend their thanks to Bahauddin Zakariya University, Multan for providing funds to conduct this research.

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Received for publication on 26th May 2010.
Accepted for publication on 01st July 2010.