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Characterization of omega-3 tablets

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ABSTRACT

Omega-3 nutraceuticals are extensively used as health supplements worldwide. Various administration forms for delivery of omega-3 are available. However, the niche omega-3 tablets have so far remained unexplored. In this work tablets containing 25–40% (w/w) omega-3 oil as triglycerides or ethyl esters were prepared utilizing a direct compaction grade powder with β-cyclodextrin as encapsulating agent. It was found that powders with up to 35% (w/w) triglyceride oil and 30% (w/w) ethyl ester oil, respectively, can be directly compressed into tablets of excellent quality. Physical properties of omega-3 containing powders and tablets are described. The powder X-ray diffractograms of the powders and crushed tablets show evidence of the formation of new crystalline phases not present in β-cyclodextrin. In addition, ^{1}H NMR data suggest that the ethyl esters form inclusion complexes with β-cyclodextrin. Compaction of other, commercially available, omega-3 powders was performed as a comparison and deemed unsuccessful.

1. Introduction

Omega-3 fatty acids are considered essential fatty acids, and humans have to ingest certain amounts regularly for a full nutritional diet. Long chained polyunsaturated fatty acids from marine sources have been documented to have positive effects on human health. Of these, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the most prominent (Riediger, Othman, Suh, & Moghadasian, 2009).

Omega-3 fish oils are available in triglyceride (TG) form or ethyl ester (EE) form. The TG form of omega-3 fatty acids differs from the EE form by having a different molecular structure. In TG oil the fatty acids are connected to a glycerol backbone via three ester linkages, whereas the EE oil consists of simple esters with ethanol (Saghir, Werner, & Laposata, 1997).

The recommended daily intake of omega-3 is debated and as of today, each country tends to issue their own individual recommendations. The European Food Safety Authority (EFSA) has approached the EPA and DHA requirements scientifically and has stated that healthy adults should ingest a minimum of 250 mg EPA + DHA every day (European Food Safety Authority, 2010). Individuals on a seafood rich diet can get their recommended daily intake of EPA and DHA via their diet, but the majority is dependent on supplement products for a satisfactory supply. Omega-3 supplements for human consumption are available in various formulations including pure bulk oil and soft-gel capsules.

It is of great interest to develop products combining omega-3 and other active substances like vitamins, minerals or drug substances in single unit administration forms. For this purpose there are some disadvantages with the soft-gel capsule form. Firstly, the capsules containing only omega-3 oil are quite large; the capsules cannot be divided and can be difficult to swallow. Secondly, possible physical or chemical compatibility issues between the liquid oil and the other active ingredients require specialized production techniques. In addition, soft-gel capsules are usually made with bovine gelatin, a material which a large part of the global population will not ingest for religious reasons.

Tablets are solids comprising dry powders and hence exhibit fewer compatibility issues when more than one active are included in one unit. Tablets can be mass-produced at low cost using conventional tableting machines and there is a large selection of excipients available, thereby avoiding the need for gelatin.

To be able to prepare tablets containing omega-3 the oil has to be converted to a compactible powder, which is challenging to achieve as omega-3 oil is liquid at room temperature. To achieve

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sufficient omega-3 per tablet, the oil load in the powder has to be quite high, typically above 20% (w/w) if the oil is an omega-3 concentrate (>60% omega-3).

Ideally, the powder should be direct compaction grade powder. Direct compaction (DC) is the tableting technique of choice when manufacturing thermo-labile and moisture-sensitive compounds (Jivraj, Martini, & Thomson, 2000).

If a powder is to be designated as DC grade it must possess good flow properties since conventional tableting machines rely only on gravity when powder is fed to the die table. Furthermore, good compactibility is needed. Compactibility is a measure of the ability of a powder to be compressed into a tablet with specified strength (Leuenberger & Rohera, 1986).

β-Cyclodextrin (β-CD) is a cyclic oligosaccharide comprising seven glucose units. Cyclodextrins (CDs) and chemical derivatives of CDs form complexes with hydrophobic compounds through non-covalent interactions between the hydrophobic cavity of the cyclodextrins and the hydrophobic part of the guest molecule (Magnusdottir, Masson, & Loftsson, 2002).

According to literature, pure β-CD may function as a DC grade powder (ElShaboury, 1990; Ghorab, Abdel-Salam, El-Sayad, & Mekhel, 2004). Hence, utilizing CDs as complexing agents might improve compactibility of hydrophobic substances otherwise challenging to compress; including hydrophobic substances with low melting points.

However, compaction of hard tablets containing hydrophobic actives have typically been limited to substances with a relatively high melting point (typically >100 °C) and the rationale for use of CDs has mainly been to improve bioavailability of the actives, not to solidify liquids (Brewster & Loftsson, 2007; Loftsson, Jarho, Másson, & Järvinen, 2005; Szejtli & Szente, 2005).

Nicotine and nitroglycerine, which have melting points of −79 and 14 °C, respectively, are among the few substances with low melting points that have been complexed with CDs and included in hard tablets. Szejtli and Szente (2005) reported that a nicotine: β-CD complex was prepared by simply mixing nicotine with finely powdered crystalline β-CD and storing the mixture in a closed container at ambient temperature (Szejtli & Szente, 2005). However, less than 2 mg of the active substances were included in each tablet.

Previously reported observations showed that it was possible to prepare compactible powders based on β-CD and a fish oil concentrate containing 60% (w/w) omega-3 in the form of EEs or TGs (Vestland, Jacobsen, Sande, Myrset, & Klaveness, 2015). The powders were dried by freeze drying or spray granulation. The results showed that spray granulation was superior to freeze drying with respect to obtaining compactible powders. The spray granulated powders met the requirements for a DC grade powder with regards to flow and compactibility. The reported method may, hence, represent a potentially important advance, as it makes it possible to prepare DC grade powders with high loadings (up to 30% (w/w)) of actives (EE or TG oils) that are liquids at room temperature. The study demonstrated differences in the quality of the finished powders depending on whether the omega-3 oil was a triglyceride oil (TGO) or an ethyl ester oil (EEO). In particular, the results indicated that TGO powders had superior compactibility compared to EEO powders.

The purpose of the experiments presented in the present paper was to further explore the new space created by the possibility to prepare DC grade powder containing omega-3 oil. The focus has been on investigating the differences previously observed between EEO and TGO powders with the aim of determining the maximum load of omega-3 oil in DC grade powder prepared by spray granulation. It has been a goal to prepare tablets with a combined total of 250 mg EPA + DHA in two tablets. Powders and tablets have been characterized by their compactibilities, by X-ray diffraction and by NMR.

For the purpose of comparison the compactibility of three other, commercially available, omega-3 powders have been tested.

2. Materials and methods

2.1. Materials

The following materials were used: β-cyclodextrin (Roquette, France), Avicel HFE-102 (IMCD, Sweden), talc (Fluka, Germany), magnesium stearate (Ligamed MF-2-V, IMCD, Sweden), triglyceride concentrate Vivomega 3322 TG (EPA as TG 300 mg/g, DHA as TG 200 mg/g, total omega-3 as TG 600 mg/g, ethyl esters maximum 10% (w/w)) (GC Rieber, Norway), ethyl ester concentrate EE6000 (EPA as EE 300 mg/g, DHA as EE 200 mg/g, total omega-3 as EE 600 mg/g) (EPAX AS, Norway), and ethyl ester concentrate Omega-3 H Ethyl Ester 90 (EPA + DHA as EE minimum 800 mg/g, total omega-3 minimum 90%) (Huatai Biopharm Inc., China).

2.2. Methods

2.2.1. Preparation of omega-3: β-cyclodextrin powders

An aqueous suspension of β-cyclodextrin was mechanically paddle-stirred at room temperature in an open stainless steel tank (5 l) for 10 min. The mass of water was typically 2–5 times the mass of the β-cyclodextrin. Omega-3 oil (EE or TG) was added and the mixture was further stirred for 30–60 min at 50 rpm at room temperature under air until a homogeneous mixture was obtained.

2.2.2. Spray granulation

Spray granulation was performed in a ProCell LabSystem (Glatt GmbH, Germany). Typical process parameters included an air flow of 100 m^3/h, an inlet air temperature of 88 °C and spray pressure of 1.2 bar. The spray rate was typically 50–60 g/min.

2.2.3. NMR spectroscopy

A sample of pure β-CD and samples of two spray granulated powders containing 30% (w/w) ethyl ester oil and 30% (w/w) triglyceride oil, respectively, were stirred with D_2O until the three solutions appeared to be saturated. The excess solid was removed by centrifugation at 14,500 rpm. For each sample ^{1}H NMR data (1000 scans) were recorded at 300.13 MHz and 298.2 K with a relaxation delay of 2000 s on a Bruker DPX300 spectrometer equipped with a BACS-60 autosampler. The data were processed using the program MestReNova 8.0.1-10878 from Mestrelab Research S.L., Santiago de Compostela, Spain. All spectra were calibrated against residual HDO (δ_H = 4.79 ppm).

2.2.4. Determination of residual moisture

Water activity in the powders was measured using a digital water activity analyzer, Hygrolab Digital Water Activity Analyzer (Rotronic, Bassersdorf, Germany). Water activity (A_W) is the relative humidity reached at equilibrium in a sealed container, expressed on a scale from 0 to 1. Relative moisture content or relative humidity (RH) is the water activity expressed on a scale from 0% to 100%.

2.2.5. Bulk density testing

The bulk volume/bulk density of the powders was measured using a jolting volumeter type Stav II (J. Engelsmann AG, Germany). Exactly 70 g powder was weighed out in a 250 ml measuring cylinder. The volume was recorded. This volume was taken to be the