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A novel process for preparation of fatty acid oil mixture in solid form

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ABSTRACT

The present study describes a novel and scalable process for preparation of omega-3 and omega-6 fatty acids in solid form. The process involves multiple steps consisting of combining the oil with a metal base in alcohol to form a solution, followed by addition of reaction mixture to acetonitrile (anti-solvent) to form a slurry and further separating the solid through filtration. This process results in formation of a flowable solid with yield of 44–76% depending on the procedure employed. The fatty acid profile of the calcium and magnesium salts was stable after one year of storage in ambient conditions. The type of solvent and anti-solvent employed in such process has tremendous effect on the resulting solid texture, which could range from complete gum to a workable, filterable solid. It was also demonstrated that increasing the concentration of base in alcohol reduces the amount of residual acetonitrile in the solid.

1. Introduction

Polyunsaturated fatty acid oils (PUFAs), including omega-3 and omega-6 fatty acids, which are primarily found in natural sources such as fish oil, flaxseed oil and krill oil, have been shown to have a range of health benefits including reducing the risk of cardiovascular disease, inflammatory disease, blood pressure and cancer (Balk et al., 2004; Simopoulos, 1991, 2002; Sahena et al. 2009; Simopoulos & Bazan 2009). Eicosapentaenoic acid (EPA, 20:5ω3) and docosahexaenoic acid (DHA, 22:6ω3), which belong to the class of omega-3 fatty acids, have been particularly recognized for a variety of positive health effects. For example, DHA has been recommended by several health agencies to be incorporated into infant's formula due to its positive effect on brain and eye development (Simopoulos & Bazan, 2009, Ward & Singh, 2005).

Currently, PUFAs are primarily obtained from oceanic fish oil (Sahena et al., 2009) and given the increasing body of evidence on the health benefits of PUFAs and subsequent market demand, significant research is focused on the recovery and concentrating PUFAs from fish oil (Lembke, 2013). Conventional methods of PUFAs extraction from fish oil rely on hydraulic pressing of moderately cooked fish and solvent extraction. The common concentrating methods include winterization, urea complexation, and molecular distillation. Enzymatic extraction and supercritical carbon dioxide extraction of PUFAs are among the more recently developed methods for concentrating PUFAs (Sahena et al., 2009, Lembke, 2013).

Fish oil is typically sold in the form of liquid in gelatine capsules to avoid the fishy smell and odour (Kralovec et al., 2009). Decomposition of the gelatine in the gastrointestinal tract causes release of macroscopic drops of fish oil, which interfere with the absorption of the fish oil, resulting in discomfort hours after the gelatine capsules are taken (Kabaradjian, 2015). Additionally, the gelatin used in capsules normally originates from animals, which might eliminate a portion of potential consumers due to religious or dietary reasons. Production of omega-3 and omega-6 fatty acids in solid form is desirable given the increased stability of solid form compared to liquid form, ease of swallowing, and potentially lower manufacturing cost (Kralovec et al., 2009).

There have been prior attempts to produce fatty acid oils in solid form. Barrow and Kralovec (Barrow & Kralovec, 2007) developed a process to make salts of fatty acids in an aqueous system through reaction of the fatty acid with a metal base. The resulting product of this process is not isolatable through filtration and therefore, lyophilisation was performed to isolate the solid, followed by pulverization of the solid to obtain powder. Several methods have been developed in which oils were physically mixed with fillers (e.g., cyclodextrin, microcrystalline cellulose) to make a powder (Torgersen, Kaveness, & Myrset, 2012; Kabaradjian, 2015).

The objective of this study was to produce solid form of fatty acids via a scalable and economically sound process. In the novel process described here, fatty acid oil reacts with metal base in the presence of alcohol as solvent. The reaction mixture is then

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combined with acetonitrile to form a filterable, flowable off-white powder. The major novel aspect of the process is the use of anhydrous acetonitrile as anti-solvent. A large number of solvents (e.g., methanol, ethanol, *tert*-butyl methyl ether, isopropanol, acetone, ethyl acetate, tetrahydrofuran, acetonitrile) were used for screening experiments in an attempt to precipitate the solid. Of the solvents tested, only acetonitrile resulted in flowable solid powder, highlighting the significance of the role of acetonitrile in precipitating the flowable solid.

2. Materials and methods

2.1. Materials

Various oils were used for synthesis of fatty acid salts. Flax/fish/borage oil comprising 30.4 wt.% omega-3 and 26.6 wt.% omega-6 with respect to total fatty acids (Webber Naturals), salmon oil comprising 27.1 wt.% omega-3 and 3.08 wt.% omega-6 with respect to total fatty acids (Webber Naturals), omega-3 concentrate oil comprising 75.6 wt.% omega-3 and 6.6 wt.% omega-6 with respect to total fatty acids (Life Brand) were used. The following solvents were used during the solvent screening; acetonitrile (HPLC, Sigma Aldrich), ethanol (denatured, Anachemia), toluene (ACS, Anachemia), *n*-butanol (ACS, Fisher), methanol (ACS, Fisher), methyl *tert*-butyl ether (99%, Alfa Aesar), isopropanol (ACS, Anachemia), acetone (99.5%, Anachemia), ethyl acetate (ACS, Anachemia), and tetrahydrofuran (inhibitor free, >99.9%, Sigma Aldrich). Bases used included potassium hydroxide (Anachemia), calcium oxide (reagent grade, Sigma Aldrich), and magnesium chloride hexahydrate (ACS, Amresco).

2.2. Methods

2.2.1. Synthesis of potassium salt of fatty acids from mixture of fish/flax/borage oil

2 mL of a mixture of fish/flax/borage oil comprising 30.4 wt.% omega-3 and 26.6 wt.% omega-6 with respect to total fatty acids (Fig. 2) was heated to about 45 °C. 1.3 mL of a base solution comprising 27 wt.% potassium hydroxide dissolved in denatured ethanol was added to the oil and the solution was stirred for about 15 min. A molecular weight of 281 was considered for fish/flax/borage oil, which was calculated from the fatty acid profile. The resulting homogeneous solution was added slowly to 10 mL of acetonitrile that was already warmed up to about 45 °C, while stirring. A slurry was formed as soon as the solution was added to acetonitrile. The slurry was then cooled to room temperature and filtered. The resulting cake was washed with acetonitrile and dried under vacuum at room temperature.

a b

Fig. 1. Comparison of the sticky solid (left) with the flowable solid (right) produced in the novel process reported in this study.

2.2.2. Synthesis of potassium salt of fatty acids from salmon oil

2 mL of salmon oil comprising 27.1 wt.% omega-3 and 3.08 wt.% omega-6 with respect to total fatty acids (Fig. 2) was heated to about 45 °C. 1.3 mL of a base solution compromising 29 wt.% potassium hydroxide dissolved in denatured ethanol was added to the oil. A molecular weight of 292 was considered for salmon oil, which was calculated from the fatty acid profile. The solution was stirred for about 15 min. The resulting homogeneous solution was added slowly to 10 mL of acetonitrile that was already warmed up to about 45 °C, while stirring. A slurry was formed as the solution was added to acetonitrile. The slurry was then cooled to room temperature and filtered. The resulting filter cake was washed with 4 mL acetonitrile and dried at room temperature under vacuum.

2.2.3. Synthesis of potassium salt of fatty acids from omega-3 concentrate oil

2 mL of omega-3 concentrate oil comprising 75.6 wt.% omega-3 and 6.6 wt.% omega-6 with respect to total fatty acids (Fig. 2) was heated to about 45 °C. 1.3 mL of a base solution comprising 27 wt.% potassium hydroxide in denatured ethanol was added to the oil and the solution was stirred for about 15 min. A molecular weight of 309 was considered for concentrate oil, which was calculated from the fatty acid profile. The resulting homogeneous solution was added slowly to 10 mL of acetonitrile that was already warmed up to about 45 °C, while stirring. Solids were formed as the solution was added to acetonitrile to result in a slurry. The slurry was then cooled to room temperature and filtered. The resulting filter cake was washed with acetonitrile and dried at room temperature under vacuum.

2.2.4. Synthesis of calcium salt of fatty acids from fish/flax/borage oil

8 mL of a mixture of fish/flax/borage oil comprising 30.08 wt.% omega-3 and 26.9 wt.% omega-6 with respect to total fatty acids (Fig. 3) and 709 mg of CaO was stirred and heated to about 100 °C. 2.9 mL distilled water was added to the mixture and the mixture was stirred for about one hour. The reaction between calcium oxide and water results in in-situ calcium hydroxide, which subsequently react with the fatty acid and forms the salt. This is more effective than directly using calcium hydroxide due to poor solubility of calcium hydroxide. 8 mL toluene was added to the mixture and was distilled down to 12 mL total volume. Then, 8 mL *n*-butanol was added to the mixture and again distilled down to 12 mL total volume. Furthermore, 8 mL *n*-butanol was added and the resulting mixture was cooled to about 45 °C. Water content was 0 wt.% as determined by Karl Fisher titration. 70 mL acetonitrile was warmed up to 45 °C in an EasyMax 402 Basic Synthesis Workstation (Mettler Toledo, Mississauga, ON) equipped with overhead stirrer. The reaction mixture was added slowly to acetonitrile while maintaining a temperature of 45 °C. Solids were formed as the solution was added to the acetonitrile. The slurry was stirred for about 40 min and then filtered under nitrogen atmosphere. The resulting solid was washed with 4 mL acetonitrile, dried at room temperature under vacuum for about one day and at 50 °C under vacuum for about one day.