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(54) 【発明の名称】 エステル交換油脂またはトリグリセリドの製造方法

(57) 【要約】

【課題】 乳幼児用の調合乳、食品、健康食品の分野で応用が期待できる、消化吸収性が高く酸化劣化しにくい特性を有する、高度不飽和脂肪酸含有油脂またはトリグリセリドを得ること。

【解決手段】 高度不飽和脂肪酸含有油脂またはトリグリセリドと植物性油脂またはトリグリセリドとを1,3位特異的リパーゼを用いてエステル交換させる。

【特許請求の範囲】

【請求項 1】

真菌類が生産し、炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を20%以上含有する油脂またはトリグリセリドを50～100質量部と植物性油脂またはトリグリセリド0～50質量部とを1,3位特異的リパーゼを用いてエステル交換してエステル交換油脂またはトリグリセリドを製造する方法。

【請求項 2】

脱酸素状態でエステル交換反応を行う請求項1に記載の製造方法。

【請求項 3】

真菌類が生産する脂肪酸が ω 6系の炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸である請求項1または2に記載の製造方法。 10

【請求項 4】

真菌類が生産する脂肪酸が ω 9系の炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸である請求項1または2に記載の製造方法。

【請求項 5】

真菌類が生産する脂肪酸がアラキドン酸である請求項1または2に記載の製造方法。

【請求項 6】

脂肪酸がモルティエラ (*Mortierella*) 属微生物が生産するアラキドン酸である請求項1または2に記載の製造方法。

【請求項 7】

真菌類が生産する脂肪酸がジホモ- γ -リノレン酸である請求項1または2に記載の製造方法。 20

【請求項 8】

真菌類が生産する脂肪酸がミード酸である請求項1または2に記載の製造方法。

【請求項 9】

リパーゼがリゾプス・デレマー (*Rhizopus delemar*)、リゾプス・ニベウス (*Rhizopus niveus*)、リゾムコール・ミーハイ (*Rhizomucor miehei*) またはリゾプス・オリザエ (*Rhizopus oryzae*) が生産するリパーゼである請求項1～8のいずれか1項に記載の製造方法。

【請求項 10】

請求項1～9のいずれか1項に記載の製造方法で得られるエステル交換油脂またはトリグリセリド。 30

【請求項 11】

請求項1～9のいずれか1項に記載の製造方法で得られる炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を20%以上含有する油脂またはトリグリセリドであり、1分子中に炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を1残基含有するトリグリセリドを40%以上含有するおよび/または炭素数20以上かつ2重結合を2個以上含む同一の高度不飽和脂肪酸を3残基含有するトリグリセリドを4.0%以下の割合で含有するエステル交換油脂またはトリグリセリド。

【請求項 12】

請求項1～9のいずれか1項に記載の製造方法で得られる真菌類生産の ω 6系の炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を20%以上含有する油脂またはトリグリセリドであり、1分子中に ω 6系の炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を1残基含有するトリグリセリドを40%以上含有するおよび/または真菌類生産の ω 6系の炭素数20以上かつ2重結合を2個以上含む同一の高度不飽和脂肪酸を3残基含有するトリグリセリドを4.0%以下の割合で含有するエステル交換油脂またはトリグリセリド。 40

【請求項 13】

請求項1～9のいずれか1項に記載の製造方法で得られる真菌類生産の ω 9系の炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を15%以上含有する油脂またはトリグ 50

リセリドであり、1分子中に ω 9系の炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を1残基含有するトリグリセリドを40%以上含有するおよび／または真菌類産生の ω 9系の炭素数20以上かつ2重結合を2個以上含む同一の高度不飽和脂肪酸を3残基含有するトリグリセリドを4.0%以下の割合いで含有するエステル交換油脂またはトリグリセリド。

【請求項14】

請求項1～9のいずれか1項に記載の製造方法で得られるアラキドン酸を20%以上含有する油脂またはトリグリセリドであり、1分子中にアラキドン酸を1残基含有するトリグリセリドを40%以上含有するおよび／またはAAA(1分子にアラキドン酸を3残基含有するトリグリセリド)を4.0%以下の割合いで含有するエステル交換油脂またはトリグリセリド。

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【請求項15】

請求項1～9のいずれか1項に記載の製造方法で得られるジホモ- γ -リノレン酸を20%以上含有する油脂またはトリグリセリドであり、1分子中にジホモ- γ -リノレン酸を1残基含有するトリグリセリドを40%以上含有するおよび／またはDDD(1分子にジホモ- γ -リノレン酸を3残基含有するトリグリセリド)を4.0%以下の割合いで含有するエステル交換油脂またはトリグリセリド。

【請求項16】

請求項1～9のいずれか1項に記載の製造方法で得られるミード酸を20%以上含有する油脂またはトリグリセリドであり、1分子中にミード酸を1残基含有するトリグリセリドを40%以上含有するおよび／またはMMM(1分子にミード酸を3残基含有するトリグリセリド)を4.0%以下の割合いで含有するエステル交換油脂またはトリグリセリド。

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【請求項17】

炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を20%以上含有する油脂またはトリグリセリドであり、1分子中に炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を1残基含有するトリグリセリドを40%以上含有するおよび／または炭素数20以上かつ2重結合を2個以上含む同一の高度不飽和脂肪酸を3残基含有するトリグリセリドを4.0%以下の割合いで含有するエステル交換油脂またはトリグリセリド。

【請求項18】

アラキドン酸を20%以上含有する油脂またはトリグリセリドであり、1分子中にアラキドン酸を1残基含有するトリグリセリドを40%以上含有するおよび／またはAAAを4.0%以下の割合いで含有する油脂またはトリグリセリド。

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【請求項19】

ジホモ- γ -リノレン酸を20%以上含有する油脂またはトリグリセリドであり、1分子中にジホモ- γ -リノレン酸を1残基含有するトリグリセリドを40%以上含有するおよび／またはDDDを4.0%以下の割合いで含有する油脂またはトリグリセリド。

【請求項20】

ミード酸を20%以上含有する油脂またはトリグリセリドであり、1分子中にミード酸を1残基含有するトリグリセリドを40%以上含有するおよび／またはMMMを4.0%以下の割合いで含有する油脂またはトリグリセリド。

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【請求項21】

炭素数20以上且つ二重結合を2個以上含む高度不飽和脂肪酸及び1個以上の中鎖脂肪酸を構成脂肪酸として含むエステル交換油脂又はトリグリセリドの製造方法であって、炭素数20以上且つ二重結合を2個以上含む高度不飽和脂肪酸を少なくとも20%含む真菌により生産された1種以上の油脂又はトリグリセリド50～100重量部と、1種以上の中鎖脂肪酸トリグリセリド(ZZZ)0～50重量部とを、1、3-位特異的リパーゼを用いてエステル交換する方法。

【請求項22】

前記炭素数20以上且つ二重結合を2個以上含む高度不飽和脂肪酸がアラキドン酸である請求項21記載の製造方法。

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【請求項 2 3】

前記中鎖脂肪酸トリグリセリドがトリオクタン酸グリセリドである請求項21又は22記載の製造方法。

【請求項 2 4】

請求項21～23のいずれか1項記載の製造方法により得られるエステル交換油脂又はトリグリセリド。

【請求項 2 5】

アラキドン酸（A）及び構成脂肪酸としての中鎖脂肪酸（Z）を含むトリグリセリド、ZA（中鎖脂肪酸の2残基及びアラキドン酸の1残基を有するトリグリセリド、ここでアラキドン酸は2位に結合している）、及びZZA（中鎖脂肪酸の2残基及びアラキドン酸の1残基を有するトリグリセリド、ここでアラキドン酸は1又は3位に結合している）の個々少なくとも1重量%を含むエステル交換油脂又はトリグリセリド。 10

【請求項 2 6】

前記中鎖脂肪酸がオクタン酸である請求項25記載のエステル交換油脂。

【請求項 2 7】

請求項10～20及び24～26のいずれか1項に記載油脂またはトリグリセリドを含有してなるヒト栄養組成物。

【請求項 2 8】

請求項10～20及び24～26のいずれか1項に記載の油脂またはトリグリセリドを含有してなる食品組成物。 20

【請求項 2 9】

前記食品組成物が、機能性食品、栄養補助食品、未熟児用調製乳、乳児用調製乳、乳児食品、妊産婦用食品または老人用食品であることを特徴とする請求項28記載の食品組成物。

【請求項 3 0】

請求項10～20及び24～26のいずれか1項に記載の油脂またはトリグリセリドを配合してなる動物用飼料。

【発明の詳細な説明】

【技術分野】

【0001】 30

微生物が生産する高度不飽和脂肪酸を構成脂肪酸としてなる油脂またはトリグリセリドをリパーゼのエステル交換反応によって改良する方法、ならびに改良された油脂またはトリグリセリド、ならびに改良された油脂を含むヒト栄養組成物に関する。

【背景技術】

【0002】

高度不飽和脂肪酸のエイコサペンタエン酸（以下「EPA」と称する）、ドコサヘキサエン酸（以下「DHA」と称する）は、特に、動脈硬化症、血栓症などの成人病の予防効果や抗ガン作用、学習能の増強作用などで多くの生理機能を有していることが知られ、医薬品、特定保健用食品への利用で様々な試みがなされている。しかし、最近ではこれらの他の高度不飽和脂肪酸の生理機能にも注目が集っている。 40

【0003】

高度不飽和脂肪酸の1種であるアラキドン酸は、血液や肝臓などの重要な器官を構成する脂肪酸の約10%程度を占めており（例えば、ヒト血液のリン脂質中の脂肪酸組成比では、アラキドン酸は11%、エイコサペンタエン酸は1%、ドコサヘキサエン酸は3%）、細胞膜の主要構成成分として膜の流動性の調節に関与し、体内の代謝で様々な機能を示す一方、プロスタグランジン類の直接の前駆体として重要な役割を果たす。特に最近では、乳幼児栄養としてのアラキドン酸の役割、神経活性作用を示す内因性カンナビノイド（2-アラキドノイルモノグリセロール、アナンダミド）の構成脂肪酸として注目されている。通常はリノール酸を富む食品を摂取すればアラキドン酸に変換されるが、成人病患者やその予備軍、乳児、老人では生合成に関与する酵素の働きが低下し、これらアラキドン酸は不足しが 50

ちとなるため、トリグリセリド型の油脂として、直接に摂取することが望まれる。

【0004】

EPAやDHAには、魚油という豊富な供給源が存在するが、シホモ- γ -リノレン酸、アラキドン酸および4,7,10,13,16-ドコサペンタエン酸(22:5 ω6)は、従来の油脂供給源から殆ど得ることができず、現在では微生物を発酵して得た高度不飽和脂肪酸を構成脂肪酸として成る油脂またはトリグリセリドが一般に使用されている。例えば、アラキドン酸を構成脂肪酸として成る油脂またはトリグリセリドを産生することのできる種々の微生物を培養して、アラキドン酸を構成脂肪酸として成る油脂またはトリグリセリドを得る方法が提案されている。この中でも、特にモルチエラ属の微生物を用いることによって、アラキドン酸含有油脂またはトリグリセリドが得られることが知られている(例えば、特許文献1、2参照)。アラキドン酸が必須の用途、例えば、乳幼児栄養の分野、具体的には調合乳に発酵で得たアラキドン酸を構成脂肪酸として成るトリグリセリドが使われ始めてきている。

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【0005】

乳幼児の栄養の分野ではアラキドン酸含有油脂を調合乳に添加して用いる方法が開示されている(特許文献3、4参照)。この添加原料に使うアラキドン酸含有油脂は真菌類によって生産され、分子的にみると、6~24%のAAA(1分子中にアラキドン酸を3残基含有するトリグリセリド)が含有されていることが特徴となっており、アラキドン酸含有率が高くなればAAAも高濃度になることが知られている(例えば、非特許文献1参照)。

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【0006】

このAAAを高濃度含む油脂は植物油脂とは異なり、生理的な条件下で人の消化酵素(膵リパーゼ)の作用を受けにくい。膵リパーゼ活性が低い幼児や老人には消化吸収されにくい油脂になっている(例えば、非特許文献1参照)。

人の母乳中に含まれるアラキドン酸の含量は全脂肪酸中に占める割合が0.5%であるため(例えば、非特許文献2参照)、上で述べたAAAのように1分子中にアラキドン酸が凝縮された形ではなく、トリグリセリド1分子に1残基のアラキドン酸が存在する可能性が高いと推定される。従って、真菌類の発酵によって得られたアラキドン酸含有油脂を脂肪酸含量の比率だけを考慮して、調整乳に配合しても良くない。

【0007】

油脂を酵素的に改変して物性(口溶性、結晶性、耐熱性)を改善する試みが多くなされてきた。その多くはカカオ代替脂の酵素的な合成に代表される植物性油脂の酵素的な改変であった(例えば、特許文献5、6参照)。ここで提示されている製造技術はリパーゼの反応性が良い植物油脂に対するものであり、反応性が悪い高度不飽和脂肪酸を多く含む油脂ではリパーゼの反応性の面から適応することが難しい。

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【0008】

高度不飽和脂肪酸高含有油脂またはトリグリセリドは酵素的にも反応性が悪いため、酵素的な改変はあまりなされていなかったが、固定化酵素を工夫することで中鎖脂肪酸と高度不飽和脂肪酸高含有油脂とを用いて高度不飽和脂肪酸の構造脂質を作る試みがなされている(特許文献7、国際特許出願PCT/JP02-06702号参照)。本方法ではトリグリセリドの1,3位に結合した脂肪酸とオクタン酸とを置き換えるため、遊離型の高度不飽和脂肪酸が放出される。このため、高度不飽和脂肪酸高含有油脂は望めない。さらには、遊離脂肪酸の除去のため、精密蒸留等の高度で複雑な精製技術を必要とする問題点がある。

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【0009】

藤本らは魚油(特にEPA,DHAを高含有の油脂)は極めて酸化されやすく、酸化防止剤の添加では十分な酸化安定性が得られていないので、油脂構造が高度不飽和脂肪酸の酸化安定性に与える影響について詳しく研究している(例えば、非特許文献3参照)。イワシ油(高度不飽和脂肪酸高含有)に特殊な油脂(中鎖脂肪酸のC8,C14のトリグリセリド)を加え、ランダム型リパーゼでエステル交換することで酸化安定性が向上することを見出し、化学的に合成した高度不飽和脂肪酸のトリグリセリドのEEE(トリ-EPA)を使って高度不飽和脂肪酸が分子間に散らばった存在形態と、同一分子内に凝縮された状態とで酸化

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されやすさを比較し、この分散型がよいことも確認している。

【0010】

魚油等に含まれる高度不飽和脂肪酸の酸化を防ぐため、エステル交換反応して油脂を安定化する方法も開示されている（特許文献8参照）。しかし、魚油等に含まれる高度不飽和脂肪酸はエステル交換反応に用いるリパーゼの反応性が低い。そこで本法ではリパーゼの反応性が高い植物性油脂を用い、魚油等から精製した高度不飽和脂肪酸含有油脂を大量希釈してリパーゼの反応性を確保している。このため、結果的には安定化された油脂中の高度不飽和脂肪酸含量を高めることができない。

【0011】

【特許文献1】特開昭63-44891号公報

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【特許文献2】特開昭63-12290号公報

【特許文献3】特開平11-151075号公報

【特許文献4】開平10-191886号公報

【非特許文献1】Jim-Wen Liu他著「試験管反応における真菌油の加水分解：アラキドン酸含有トリグリセリドの分子種 (In Vitro Hydrolysis of fungal Oils: Distribution of Arachidonic Acid-Containing Triacylglycerol molecular Species)」米国油化学会誌 (J. Am. Oil Chem. Soc.)、75、p.507-510 (1998)

【非特許文献2】Christie, W.W.著、Hamilton, R.J.およびRussell, J.B.編「トリグリセリドにおける脂肪酸の結合位置 (The Positional Distribution of Fatty Acids in Triglycerides)」、油脂の分析 (Analysis of Oil and Fats)、p. 313-339、Elsevier Applied Science (ロンドン)、(1986)

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【特許文献5】特開昭55-71797号公報

【特許文献6】特開昭58-42697号方法

【特許文献7】特開平08-214891号公報

【非特許文献3】藤本健四郎著「油脂構造が高度不飽和脂肪酸の酸化安定性に与える影響」、科学と工業、75、p.53-60、社団法人 大阪工研協会発行(2001)

【特許文献8】特開平6-287593号公報

【特許文献9】特開平5-91887号公報

【特許文献10】特開平5-91888号公報

【特許文献11】国際公開98/39468号パンフレット

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【非特許文献4】東山他著「モルティエラ・アルピナ 1S-4株によるアラキドン酸生産性の増強(Enhancement of Arachidonic Acid Production by Mortierella Alpina 1S-4)」、米国油化学会誌 (J. Am. Oil Chem. Soc.)、75、p.1501-1505 (1998)

【発明の開示】

【0012】

乳幼児用の調合乳、食品、健康食品の分野で応用が期待でき、しかも消化吸収性が高く酸化劣化しにくい特性を有する高度不飽和脂肪酸高含有油脂またはトリグリセリドが求められている。これを実現するため、リパーゼのエステル交換反応を用いて、アラキドン酸に代表される高度不飽和脂肪酸含有油脂またはトリグリセリドを改良し、高度不飽和脂肪酸を分散させた形の油脂を製造する方法およびそれを含有する組成物およびそれらを含む食品や健康食品を提供するものである。

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【0013】

高度不飽和脂肪酸含量が高く、しかも消化吸収性が高く酸化劣化しにくい特性を有する高度不飽和脂肪酸高含有油脂またはトリグリセリドは、真菌類が生産し炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を20%以上含有する油脂またはトリグリセリドを50~100質量部と植物性油脂またはトリグリセリド0~50質量部とを1,3位特異的リパーゼを用いて脱酸素状態にして、反応温度を上げてエステル交換することにより得ることができた。

【0014】

すなわち、本発明は、

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固定化酵素を用いることで熱安定性を高め、高い反応温度での酵素の使用を可能にするとともに、高温下での反応では原料・反応中油脂の酸化劣化が危惧されることから、固定化酵素自体に含まれている酸素を除去する方法を見出し、酸化劣化を防止して、実用化に適した酵素反応を完成した；

エステル交換反応は加水分解反応とエステル合成反応との可逆反応であるため、酵素の活性化のための水分を酵素の活性化後、効率的に除去して副次的に生成する遊離脂肪酸・モノグリセリド・ジグリセリドの量を抑える方法を見出し、実用化に適した酵素反応を完成した；

ことにより、エステル交換反応で変換した油脂の商業的生産に適した方法を提供するものである。

従って、本発明は、真菌類が生産する高度不飽和脂肪酸含有油脂またはトリグリセリドを原料として、リパーゼのエステル交換反応を利用した食用エステル交換油脂を製造する方法ならびにこれら油脂を含む組成物を提供する。

【発明を実施するための最良の形態】

【0015】

母乳脂質中のアラキドン酸含量は1%（質量%）に満たないため、トリグリセリド1分子中に含まれるアラキドン酸残基はせいぜい1残基と推定される。モルティエラ（*Mortierella* 11a）属真菌の醗酵法によって製造されたアラキドン酸高含有油脂（SUNTGA40S；サントリ（株）、商品名）の分子種を以下の表1に示す。

【0016】

【表1】

表1 SUNTGA40Sのアラキドン酸の存在形態

分子種	存在量（質量%）
AAA	10.57
XAA	37.56
XXA	26.52
XXX	25.35

【0017】

この場合、Aはトリグリセリドに結合したアラキドン酸を、Xはアラキドン酸以外のトリグリセリドに結合した脂肪酸を示し、具体的には「AAA」は1分子中にアラキドン酸を3残基含有するトリグリセリドを、「XAA」とはアラキドン酸残基が2残基、アラキドン酸以外の脂肪酸が1残基結合したトリグリセリドを、「XXA」とはアラキドン酸が1残基、アラキドン酸以外の脂肪酸が2残基結合したトリグリセリドを示す。アラキドン酸を含有するトリグリセリドは全トリグリセリドの74.7%であるが、母乳中に存在すると推定されるXXAは26.52%で、非存在型と考えられるAAAやXAAが48%も存在する。この48%ものAAAやXAAをXXAの形態に変換することで、母乳に近いアラキドン酸の形態になると考えられる。

【0018】

本発明者らは以上に示した醗酵生産した真菌由来のアラキドン酸高含有油脂またはトリグリセリドの改良を目的に、脱酸素状態で1,3位特異的リパーゼを用いて比較的少量の植物油脂とで、エステル交換油脂を試作した。真菌油アラキドン酸油脂に多量に含まれ、消化吸収されないAAAを原料に、1,3位に結合したアラキドン酸を分散させ、人の母乳の構造

形態 (XXA) に近づけることにも成功した。

本エステル交換法で改良された油脂は乳幼児の栄養の分野で調合乳に添加して用いること、その他、食品、健康食品等に広く利用可能である。

【0019】

酵素の活性化と酸素除去の方法について

油脂を酵素的にエステル交換して改善する方法は従来技術でも述べたように古くから行われてきた。本アラキドン酸高含有油脂にはリパーゼの生理的な反応条件では作用しにくいAAAを始め多くのアラキドン酸残基を含んでおり、エステル交換反応における酵素の反応性に問題がある。エステル交換反応の効率を高めるためにはリパーゼを固定化して、耐熱性を付与し反応温度を上げることでエステル交換率の向上が望める（例えば、特許文献7、国際特許出願PCT/JP02-06702号参照）。しかし、反応効率向上のために反応を高温にすると、原料のアラキドン酸高含有油脂は酸化劣化を引き起こされやすくなる。特に固定化酵素を用いた場合、固定化担体中に染み込んだ酸素の除去が問題となってくる。そこで発明者らはこの固定化酵素中に含まれる酸素の効率的な除去法を見出し、この低酸素条件下でエステル交換する方法を見出した。

【0020】

油脂の酸化度合いを示す1つのパラメータにPOV値（過酸化価値）が広く使われている。反応系に入る酸素の量を変えてエステル交換反応を行い、POV値を測定することで油脂の酸化の度合いを比較検討した。酸素の量は以下の4レベルで行った。すなわち、最も脱酸素レベルが高い「脱気&窒素ブロー」、常識的に窒素を通気して窒素置換するレベル「窒素ブロー」、反応容器を全く窒素置換せず行うレベル「窒素無置換」、最後に固定化酵素の担体のみを使い、窒素無置換の状態でコントロールとした「コントロール」。30、45、55℃の温度で所定期間反応した後にPOV値を測定した。表2に示すように、残存する酸素の量に比例して、POV値が上昇することがわかり、特に常識的に窒素を通気して窒素置換するレベルでの脱気状態「窒素ブロー」では、反応温度の上昇とともに、POV値が上昇することから、酸素の除去が不十分と考えられた。このことはこの条件で反応すれば油脂の劣化が防げられないことを意味し、脱酸素レベルを次の「脱気&窒素ブロー」まで上げることでPOV値の増加が抑えられ、質の良い油脂が得られることがこの結果から見出された。

【0021】

【表2】

表2 各種条件下で反応した時のPOV値

	30℃、1日	45℃、3日	55℃、1日
脱気&窒素ブロー	0.87	0.88	0.87
窒素ブロー	1.07	1.23	2.75
窒素無置換	1.28	1.86	3.15
コントロール	2.69	4.50	4.05

(POV : meq/kg油脂)

【0022】

リゾプス・デレマー (*Rhizopus delemar*, 現 *Rhizopus oryzae*) のリパーゼの場合、予め少量の水分を加え（約2%）、酵素を活性化する必要がある。従って、活性化と固定化酵素中の余分な水分を抜くための操作が必要となる。この操作を加え脱酸素する操作が必要

になるが、酸素の除去の操作は酵素の活性化や水分除去工程で同時に行うことができる。酵素の活性化時、固定化酵素に原料油脂と少量の水を加え、30～45℃で約1日反応させて酵素を活性化する。固定化酵素の活性化だけであれば高価な高度不飽和脂肪酸含有油脂の代わりに安価な植物油脂を使ってもよい。酸素の除去は固定化酵素に少量の水分を含む原料油脂を加えた段階でも、あるいは油脂を加える前でもよく、真空ポンプ等の減圧機を用いて原料油脂と固定化酵素から脱気し、常圧に戻す際には空気でリークさせるのではなく、窒素ガスをリークすることで行える。この減圧・常圧の操作を繰り返すことで固定化酵素中の酸素を取り除くことができる。活性化反応終了後、油脂を取り除き、油脂を吸った固定化酵素に対してさらに上と同様の減圧-窒素ガスリークを繰り返すことで酸素を除去し、酸素を除去した（窒素置換された）原料油脂を加えてエステル交換すると、高温の条件下でも油脂の酸化劣化は防ぐことができる。

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【0023】

酵素の活性化に用いた水分の除去や酵素に含まれる水分除去の方法について

上の操作で活性化した固定化酵素から余分な水分を除去する必要がある。余分な水分が存在するとリパーゼによる加水分解反応が進行し、エステル交換反応中に副次的にジグリセリド・モノグリセリド・遊離脂肪酸が生成する。これを防ぐ目的で、反応系から水分を除く必要がある。余分な水分を除去するには活性化した固定化酵素から活性化に用いた油脂を取り除き、反応原料の油脂（予め、脱酸素・脱水した油脂）で一度洗浄後、45℃で原料油脂と1日反応すればよい。この次の反応からはジグリセリド等の量が低く抑えられたエステル交換油脂が得られる。製造コストを低減する目的であれば、活性化と水分除去反応に高価な高度不飽和脂肪酸含有油脂の代わりに安価なパーム油等の植物油脂を用いても良い。

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【0024】

リゾプス・デレマー (*R.deleamar*) の固定化酵素の場合は水による酵素の活性化が必要であったが、市販されている固定化酵素 (*Rhizomucor miehei* のリパーゼ、ペーリンガー・マンハイム社製、キラザイム し-9, c.-f., C2, Iyo) の場合には、水による酵素の活性化は必要なく固定化酵素に含まれる微量の水分により活性化になっている。しかし、この固定化酵素にも余分な水分が含まれており、リゾプス・デレマー (*R.deleamar*) の場合と同様に水分を除去する必要がある。この水分除去の方法は以上で述べた方法を使えばよく、何ら特別な操作は必要ない。さらに、この酵素の場合には酸素の除去はこの脱水の工程で行えば良い。

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【0025】

酵素反応の反応槽について

これまでは酵素反応がバッチ式でエステル交換反応を行った場合について述べた。

固定化酵素を用いて油脂のエステル交換反応を行う方法として、バッチ式の他にカラム式の反応方法がある。すなわち、固定化酵素をカラム式のジャケット付容器に詰め、保温・加熱してカラムを温調しながら、原料油脂をカラムに導入し、出口からエステル交換油脂を取り出す方法である。場合によっては油脂を循環させながらカラムを通し、変換率を高めることも可能である。この場合には、活性化時や水分除去時に原料油脂をカラムを通し内部の固定化酵素に油をなじませて、減圧による脱気と強制的な窒素ガスのブローを組み合わせて酸素の除去が可能である。活性化して水分除去した後に、油脂のエステル交換反応を行うと良い。

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【0026】

エステル交換反応の原料油脂

高度不飽和脂肪酸を構成脂肪酸として成る油脂またはトリグリセリドを50～100質量部と植物性油脂またはトリグリセリド0～50質量部とを混合すると、均一な状態の液状の油脂になり、これまでに記載した方法で酸素を除去した固定化酵素によってエステル交換反応を行い、高度不飽和脂肪酸を含有する油脂を改良することができる。

【0027】

<植物油脂>

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反応の原料の植物性油脂は一般に食用として使用されているものを使うことができる。使用される植物油脂はまた、転化油脂であっても良い。この植物油脂はエステル交換の飽和脂肪酸の供給源の一つとして用いる。例えば、大豆油、サフラワー油、オリーブ油、米ぬか油、ごま油等のリノール酸系、オレイン-リノール酸系の油脂やパーム油、パーム核油、カカオ油、やし油、ラード油等の飽和脂肪酸系の油脂、及びトリグリセリド植物油、例えばMCT（炭素数8個の飽和中鎖脂肪酸及び炭素数10個の飽和中鎖脂肪酸を包含し、そして同じか又は異なった脂肪酸から構成されるトリグリセリド）からの転化により得られる油が挙げられる。酸化に対する抵抗性を付与することから、また、母乳成分に近づける意味から飽和脂肪酸を多く含む飽和脂肪酸系の油脂がより好ましい。

【0028】

エステル交換の飽和脂肪酸の供給源に用いる植物性油脂は飽和脂肪酸系のパーム油と比較的不飽和脂肪酸が多いリノール酸系の大豆油で比較するとエステル交換反応でのAAAの減少速度は両油脂ともほぼ同等であり、油脂の消化吸収性に問題となるAAAの含量には差が見られず、消化吸収性の良い油脂への改善効果を示すと考えられる。しかし、エステル交換反応で導入される脂肪酸の違いから、酸化劣化に対する強度には差がある。

【0029】

MCT、特に構成脂肪酸としてのオクタン酸を含むトリグリセリド、及び微生物アラキドン酸トリグリセリドは、構成脂肪酸としてのアラキドン酸、例えば“8A8”、“88A”を含むトリグリセリドを生成するために、本発明に従ってリパーゼによりエステル交換される。この方法は、廃棄アラキドン酸を伴わないで、アラキドン酸を含む油脂を経済的に製造するために有用であり、そしてそれらから得られるアラキドン酸含有脂肪は改良された消化性及び吸収性を有する新規油脂として有用である。

【0030】

さらにこれら油脂から分別したものやその他の部分水添により飽和脂肪酸含量を高めた油脂を上げることができるが、使用しうる油脂はこれに限定されるものではない。

【0031】

＜高度不飽和脂肪酸を構成脂肪酸として成る油脂＞

高度不飽和脂肪酸を構成脂肪酸として成る油脂またはトリグリセリドを産生しうる微生物を培養することが必須である。ここでいう微生物としては、炭素数が20以上で二重結合は2以上の ω 6系、 ω 9系または ω 3系の高度不飽和脂肪酸の少なくとも1種の高度不飽和脂肪酸を主にトリグリセリドの構成脂肪酸として産生する微生物が望ましい。

【0032】

そして、炭素数が20以上で二重結合は2以上の ω 6系、 ω 9系または ω 3系の高度不飽和脂肪酸としては、ジホモ- γ -リノレン酸（8,11,14-エイコサトリエン酸）、アラキドン酸（5,8,11,14-エイコサテトラエン酸）、7,10,13,16-ドコサテトラエン酸（22:4 ω 6）、DPA ω 6（4,7,10,13,16-ドコサペンタエン酸）、8,11-エイコサジエン酸、ミード酸（5,8,11-エイコサトリエン酸）、8,11,14,17-エイコサテトラエン酸（20:4 ω 3）、EPA（5,8,11,14,17-エイコサペンタエン酸）、DPA ω 3（7,10,13,16,19-ドコサペンタエン酸）およびBBA（4,7,10,13,16,19-ドコサヘキサエン酸）を挙げることができる。

【0033】

従って、本発明においては、高度不飽和脂肪酸を構成脂肪酸として成る油脂またはトリグリセリドを産生しうる微生物であればすべて使用することができる。例えば、アラキドン酸を構成脂肪酸として成る油脂またはトリグリセリドの生産能を有する微生物としては、モルティエラ (*Mortierella*) 属、コニディオボラス (*Candidiobolus*) 属、フィチウム (*Pythium*) 属、フィトフトラ (*Phytophthora*) 属、ペニシリウム (*Penicillium*) 属、クロドスポリウム (*Cladosporium*) 属、ムコール (*Mucor*) 属、フザリウム (*Fusarium*) 属、アスペルギルス (*Aspergillus*) 属、ロードトルラ (*Rhodotorula*) 属、エントモフトラ (*Entomophthora*) 属、エキノスポランジウム (*Echinosporangium*) 属、サブロレグニア (*Saprolegnia*) 属に属する微生物を挙げることができる。モルティエラ (*Mortierella*) 属モルティエラ (*Mortierella*) 亜属に属する微生物では、例えばモルティ

エレラ・エロンガタ (*Mortierella elongata*)、モルティエレラ・エキシグア (*Mortierella exigua*)、モルティエレラ・フィグロフィラ (*Mortierella hygrophila*)、モルティエレラ・アルピナ (*Mortierella alpina*) 等を挙げることができる。具体的にはモルティエレラ・エロンガタ (*Mortierella elongata*) IF08570、モルティエレラ・エキシグア (*Mortierella exigua*) IF08571、モルティエレラ・フィグロフィラ (*Mortierella hygrophila*) IF05941、モルティエレラ・アルピナ (*Mortierella alpina*) IF08588、ATCC16286、ATCC32221、ATCC42430、CBS219.35、CBS224.37、CBS250.53、CBS343.66、CBS527.72、CBS529.72、CBS608.70、CBS754.68等の菌株を挙げることができる。例えば、DHAを産生する微生物として、クリプトコデニウム (*Cryptocodinium*) 属、スラウトキトリウム (*Thraustochytrium*) 属、シゾキトリウム (*Schizochytrium*) 属、ウルケニア (*Ulkenia*) 属、ジャボノキトリウム (*Japonochytrium*) 属またはハリフォトリス (*Haliphthoros*) 属に属する微生物を挙げることができる。

【0034】

これらの菌株はいずれも、大阪市の財団法人醗酵研究所 (IFO)、および米国のアメリカン・タイプ・カルチャー・コレクション (American Type Culture Collection, ATCC) および、Centraalbureau voor Schimmelcultures (CBS) からなんら制限なく入手することができる。また本発明の研究グループが土壌から分離した菌株モルティエレラ・エロンガタ SAM0219 (微生物寄第8703号) (微生物寄第1239号) を使用することもできる。

【0035】

本発明に使用される菌株を培養する為には、その菌株の胞子、菌糸、または予め培養して得られた種培養液あるいは種培養より回収した菌体を、液体培地または固体培地に接種し本培養する。液体培地の場合に、炭素源としてはグルコース、フラクトース、キシロース、サッカロース、マルトース、可溶性デンプン、糖蜜、グリセロール、マンニトール、糖化澱粉等の一般的に使用されているものが、いずれも使用できるが、これらに限られるものではない。窒素源としてはペプトン、酵母エキス、麦芽エキス、肉エキス、カザミノ酸、コーンステイプリカー、大豆タンパク、脱脂大豆、綿実カス等の天然窒素源の他に、尿素等の有機窒素源、ならびに硝酸ナトリウム、硝酸アンモニウム、硫酸アンモニウム等の無機窒素源を用いることができるが、特に大豆から得られる窒素源、具体的には大豆、脱脂大豆、大豆フレーク、食用大豆タンパク、おから、豆乳、きな粉等が挙げられるが、特に、脱脂大豆に熱変性を施したもの、より好ましくは脱脂大豆を約70~90℃で熱処理し、さらにエタノール可溶成分を除去したものを単独または複数で、あるいは前記窒素源と組み合わせて使用することができる。その他必要に応じて、リン酸イオン、カリウムイオン、ナトリウムイオン、マグネシウムイオン、カルシウムイオン以外に、鉄、銅、亜鉛、マンガン、ニッケル、コバルト等の金属イオンやビタミン等を微量栄養源として使用できる。

【0036】

これらの培地成分は微生物の生育を害しない濃度であれば特に制限はない。実用上、一般に炭素源は総添加量は0.1~40質量%、好ましくは1~25質量%、窒素源の総添加量は2~15質量%、好ましくは2~10質量%とするのが望ましく、より好ましくは初発の炭素源添加量を1~5質量%、初発の窒素源添加量を3~8質量%として、培養途中に炭素源および窒素源を、さらにより好ましくは炭素源のみを添加して培養する。なお、不飽和脂肪酸の収率を増加せしめるために、不飽和脂肪酸の前駆体として、例えば、ヘキサデカン若しくはオクタデカンのごとき炭化水素；オレイン酸若しくはリノール酸のごとき脂肪酸またはその塩、または脂肪酸エステル、例えばエチルエステル、グリセリン脂肪酸エステル、ソルビタン脂肪酸エステル；またはオリーブ油、大豆油、なたね油、綿実油若しくはヤシ油のごとき油脂類を単独で、または組み合わせて使用できる。基質の添加量は培地に対して0.001~10質量%、好ましくは0.5~10質量%である。またこれらの基質を唯一の炭素源として培養してもよい。

【0037】

高度不飽和脂肪酸を産生する微生物の培養温度は使用する微生物によりことなるが、5

〜40℃、好ましくは20〜30℃とし、また20〜30℃にて培養して菌体を増殖せしめた後5〜20℃にて培養を続けて不飽和脂肪酸を生産せしめることもできる。このような温度管理によっても、生成脂肪酸中の高度不飽和脂肪酸の割合を上昇せしめることができる。培地のpHは4〜10、好ましくは5〜9として、通気攪拌培養、振盪培養、固體培養、または静置液体培養を行う。本培養は通常2〜30日間、好ましくは5〜20日間、より好ましくは5〜15日間行う。

【0038】

モルティエラ属モルティエラ亜属に属する微生物は、アラキドン酸を主たる構成脂肪酸として成る油脂またはトリグリセリドを産生しうる微生物として知られているが、本発明者らは、上記菌株に変異処理を施すことによって、ジホモ- γ -リノレン酸を主たる構成脂肪酸として成る油脂またはトリグリセリドを産生しうる微生物（特許文献9参照）や、 ω -9系高度不飽和脂肪酸を主たる構成脂肪酸として成る油脂またはトリグリセリドを産生しうる微生物を（特許文献10参照）得ている。さらに、高濃度の炭素源に耐性を有する微生物（特許文献11参照）も得ており、これら微生物は、モルティエラ属モルティエラ亜属の微生物である。しかし、本発明はモルティエラ属モルティエラ亜属に属する微生物に限定しているわけではなく、高度不飽和脂肪酸を構成脂肪酸として成る油脂またはトリグリセリドを産生しうる微生物を用いることができる。

【0039】

上記のように培養した微生物から、粗油を得る方法として、培養終了後、培養液をそのままかあるいは殺菌、濃縮、酸性化などの処理を施した後、自然沈降、遠心分離および／または濾過などの常用の固液分離手段により培養菌体を得る。固液分離を助けるために、凝集剤や濾過助剤を添加してもよい。凝集剤としては、例えば、塩化アルミニウム、塩化カルシウム、アルギン、キトサンなどを使用できる。濾過助剤としては、例えば、珪藻土を使用できる。培養菌体は好ましくは、水洗、破砕、乾燥する。乾燥は、凍結乾燥、風乾、流動層乾燥、凍結乾燥などによって行うことができる。乾燥菌体から粗油を得る手段としては、有機溶剤による抽出法や圧搾法を用いることができるが、好ましくは窒素気流下で有機溶剤によって抽出する。有機溶剤としてはエタノール、ヘキサン、メタノール、エタノール、クロロホルム、ジクロロメタン、石油エーテル、アセトン等を用いることができ、またメタノールと石油エーテルの交互抽出やクロロホルム-メタノール-水の一層系の溶媒も用いることができる。しかしながら、粗油の取得に用いる抽出法を上記の方法に限定しているわけではなく、菌体内の油脂を効率的に抽出する手法はすべて使用することができる。例えば、超臨界抽出法なども有効な手段として使用することができる。

【0040】

有機溶剤や超臨界流体で抽出された抽出物から減圧下などの条件下で有機溶剤や超臨界流体成分を除去することにより、目的とする粗油を得ることができる。また、上記の方法に代えて菌体を用いて抽出を行うことができる。この場合にはメタノール、エタノール、アセトン等の水に対して相溶性の溶媒、またはこれらと水および／または他の溶媒とからなる水に対して相溶性の混合溶媒を使用する。その他の手順は上記と同様である。

【0041】

また、粗油だけでなく精製油脂をエステル交換の基質として用いることもできる。油脂精製工程として、脱ガム、脱酸、脱臭、脱色、カラム処理、分子蒸留、ウィンタリングなどの常法の工程を用いることができる。

【0042】

＜エステル交換反応に用いるリパーゼ＞

本発明で用いることのできるリパーゼとして、例えば、リゾプス (*Rhizopus*) 属、リゾムコール (*Rhizomucor*) 属、アスペルギルス (*Aspergillus*) 属などの微生物が産生するもの、ブタ膵臓リパーゼなどを挙げることができる。かかるリパーゼについては、市販のものを用いることができる。例えば、リゾプス・デレマー (*Rhizopus delemar*) のリパーゼ（田辺製薬（株）製、タリパーゼ）（*Rhizopus delemar*は現在、分類学上*Rhizopus oryzae*に分類されている）、リゾプス・ニベウス (*Rhizopus niveus*) のリパーゼ（天野エンザ

イム（株）ニューラーゼ E36）（*Rhizopus niveus*も分類学上*Rhizopus delemar*と同じ菌とされ、*Rhizopus oryzae*という菌名で統一されている）、リゾムコール・ミーハイ（*Rhizomucor miehei*）のリパーゼ（ノボ・ノルディスク（株）社製、リボザイム1M、またはペーリンガー・マンハイム社製、キラザイム L-9, c.-f., 02, 1yo）、アスペルギルス・ニガー（*Aspergillus niger*）のリパーゼ（天野エンザイム（株）、リパーゼA）等が挙げられるが、これら酵素に限定しているわけではなく、1,3-位特異的リパーゼであればすべて使用することができる。

【0043】

上記リパーゼの使用形態は、高度不飽和脂肪酸に対する反応効率を高める目的であるいは繰り返し使用するために安定性を付与する目的で固定化担体に固定化したりリパーゼを使用することが望ましい。固定化担体として、セライト、イオン交換樹脂、セラミックス、たんぱく質を吸着することができる吸着樹脂などが用いられる。例えば、セライトでは粉末状珪藻土、粒状珪藻土、ポリマー系イオン交換樹脂ではDowex MARATHON WBA（ダウケミカル）、ダイヤイオンWA30（三菱化学（株））、セラミックスではSM-10（日本ガイシ）、吸着樹脂ではダイヤイオンHP20（三菱化学（株））等が挙げられる。

上記のイオン交換樹脂等は一例であり、樹脂は日々進化し、より良いものが市場に出回ってくる。これら樹脂の改良型が出回った場合でも使用することができると考えられる。

【0044】

<エステル交換反応の反応温度および時間>

エステル交換反応は酵素の反応性から考えると30～60℃が好ましい。連続的に固定化酵素を用いて反応する場合には固定化酵素の安定性を鑑み、30～50℃で行うことが好ましい。反応に要する時間は短ければ短いほどよいが、反応後のエステル交換油脂中に含まれるXXXやAAAの含量から考えて1～7日間反応が好ましい。反応時には原料油脂（高度不飽和脂肪酸含有油脂）が酸化されやすいため、先に記載した酸素の除去対策を行って、無酸素下で反応することが望ましい。

【0045】

<エステル交換反応後の精製>

このようにしてエステル交換反応で改良された油脂は酵素反応槽（カラム反応でも、バッチ式反応でも）から容易に固定化酵素と分けて分別できる。出来上がった油脂の成分の大半はトリグリセリド型の油脂であり、脱酸、脱ガム、脱色、脱臭のような通常の油脂の精製に用いられる方法で精製することができる。

【0046】

本発明の油脂は微生物が生産する高度不飽和脂肪酸を構成脂肪酸としてなる油脂またはトリグリセリドをリパーゼのエステル交換反応によって改良された油脂またはトリグリセリドであり、炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を20%以上含有する油脂またはトリグリセリドであり、1分子中に炭素数20以上かつ2重結合を2個以上含む高度不飽和脂肪酸を1残基含有するトリグリセリドを40%以上含有するおよび／または炭素数20以上かつ2重結合を2個以上含む同一の高度不飽和脂肪酸を3残基含有するトリグリセリドを4.0%以下の割合で含有するエステル交換油脂またはトリグリセリドがあげられる。

【0047】

本発明における油脂はモノグリセリド好ましくはトリグリセリドを90%以上含有する。油脂はそのいずれの形で存在するが、しかし本発明においては、それらは、エステル交換により得られる生成物としての、ジグリセリド、モノグリセリド及びたぶん、微量の遊離脂肪酸、並びに主要生成物としてのトリグリセリドを含んで成る。

【0048】

本発明の油脂、例えば、アラキドン酸を20%以上含有する油脂またはトリグリセリドであり、1分子中にアラキドン酸を1残基含有するトリグリセリドを40%以上含有するおよび／またはAAAを4.0%以下の割合で含有するエステル交換油脂またはトリグリセリド等の用途は用途に関しては無限の可能性があり、食品、飲料、化粧品、医薬品の原料並びに

添加物として使用することができる。そして、その使用目的、使用量に関して何ら制限を受けるものではない。

【0049】

例えば、食品組成物としては、一般食品の他、機能性食品、栄養補助食品、未熟児用調製乳、乳児用調製乳、乳児用食品、妊産婦食品または老人用食品等を挙げることができる。油脂を含む食品例として、肉、魚、またはナッツ等の本来油脂を含む天然食品、スープ等の調理時に油脂を加える食品、ドーナッツ等の熱媒体として油脂を用いる食品、バター等の油脂食品、クッキー等の加工時に油脂を加える加工食品、あるいはハードビスケット等の加工仕上げ時に油脂を噴霧または塗布する食品等が挙げられる。さらに、油脂を含まない、農産食品、醸造食品、畜産食品、水産食品、または飲料に添加することができる。さらに、機能性食品・医薬品の形態であってもよく、例えば、経腸栄養剤、粉末、顆粒、ドロッチ、内服液、懸濁液、乳濁液、シロップ等の加工形態であってもよい。

次に、実施例により、本発明をさらに具体的に説明する。しかし、本発明は、実施例に限定されない。

【実施例】

【0050】

実施例 1. 固定化酵素の製作（1,3-位特異的リパーゼの固定化による安定性の付加と脱酸素化）

イオン交換樹脂担体（Dowex MARATHON WBA；ダウケミカル）100gを、リゾプス・デレマ（*Rhizopus delemar*）リパーゼ水溶液（タリパーゼ現末、12.5%；田辺製薬（株））80mlに懸濁し、減圧下で乾燥させて固定化酵素を得た。次に、アラキドン酸を40%含有するトリグリセリド（SUNTGA40S、サントリー（株）、商品名）（25g）、パーム油（15g）、上記固定化リパーゼ（4g）、水（800 μ l）を密閉できるボトルに秤量した。ボトルを半開きの状態でデシケーター中に入れ、このデシケーターに真空ポンプをつなぎ中味を減圧した（デシケーター中のボトルに油脂とともに入った固定化酵素担体から油中に泡状となって酸素を含む空気が放出された）。次にこのデシケーター中を常圧に戻すため、窒素ガスをデシケーターへリークした。この減圧化、常圧化の操作を繰り返して、固定化担体のマトリックス中に存在した酸素を窒素で置き換え、ボトルを密閉した。次に固定化酵素を活性化するため、30℃で24時間、振とう（100rpm）した。活性化終了後、活性化に用いた油脂を取り除き、もう一度脱酸素操作を施し、活性化された固定化酵素を得た。他の植物油脂とのエステル交換反応を行う場合には、固定化酵素を活性化する時にパーム油の代わりにエステル交換反応に用いる植物油脂を使って、上記パーム油と同様にSUNTGA40S（25g）、植物油脂（15g）、上記固定化リパーゼ（2g）、水（800 μ l）を混ぜ、上記記載の脱酸素化の操作と、固定化酵素の活性化操作を施し、エステル交換反応に使用した。

【0051】

実施例 2. 油脂中の脂肪酸含量測定方法

油脂を約10～20mgネジ口試験管に採取し、これに塩酸メタノール2mlおよびジクロロメタン1mlを添加し、試験管の口を密封して、50℃で3時間反応させた。反応終了後、室温まで冷却した後、ヘキサンを添加して脂肪酸メチルエステルを抽出し、回収したヘキサンを減圧濃縮した。得られた脂肪酸メチルエステルを、総脂肪酸メチルエステル濃度が約1%となるようにヘキサンに溶解し、ガスクロマトグラフィーの分析に供した。ガスクロマトグラフィーの分析条件および成分同定は、「Official Methods and Recommended Practices of the AOCS 5th Edition (American Oil Chemists' Society, 1998)」の、Fatty Acid Composition by GLC (Method Ce 1b-89)に準じ、カラムはSupelcowax-10を用いた。検出されたピーク面積総和に対するアラキドン酸メチルエステルのピーク面積の割合を、油脂中のアラキドン酸含量とした。アラキドン酸以外の脂肪酸に関しても、同様の方法で各々の脂肪酸含量を求めた。

【0052】

実施例 3. トリグリセリドの分析方法

HPLCを用いて以下の条件で分析し、酵素反応で改変した油脂中の各トリグリセリド含量

を測定した。

カラム：逆相カラム (Cosmosil 4.6 x 250 mm 5C18-MS)

溶媒：アセトン/アセトニトリル (1:1) 1 ml/min

分析時間：55分

カラムオープン温度：40℃

検出器：示差屈折計検出器 (セル温度40℃)

サンプル：油脂またはトリグリセリドをクロロホルムに溶解させた10%溶液を5 μ lを注入

【0053】

以上の測定条件で各種トリグリセリドを分析した。各トリグリセリドの分子種の決定は 10
特表2000-513575で開示された方法に準じて行った。すなわち、上の条件で各トリグリセリドのピークを分取し、加水分解後、メチルエステルに変換した。ガスクロマトグラフィーを用いて、その分子種を決定した。

【0054】

この方法により、SUNTGA40Sやエステル交換反応で得られた油脂の各トリグリセリドを分析し、計算することで、SUNTGA40Sのアラキドン酸の存在形態やXXAの各々のトリグリセリドの比率や含量を示すことができた。XXAはLHA、PGA、OLA、PLA、DOA、POA、PPA、SOA、PSA、SSA、LC22Aの質量%の総和である。ここで使われている略号は、L：リノール酸、P：パルミチン酸、G： γ -リノレン酸、O：オレイン酸、S：ステアリン酸、C22：直鎖飽和の炭素数22の脂肪酸、X：アラキドン酸以外の脂肪酸、A：アラキドン酸をそれぞれ示している（それぞれの脂肪酸残基のグリセリンへの結合位置は規定されていない）。 20

【0055】

実施例4、実施例1で得た活性化型の固定化リパーゼを用いてのアラキドン酸含有油脂 (SUNTGA40S：アラキドン酸として約40%含有) の改変

以下の表3の原料組成で30℃で振とう (100rpm) して酵素反応を行い、エステル交換反応の進み具合を確認する目的でサンプリングしながら反応を続けた。サンプリングした油脂のトリグリセリド分析を行うことでAAAの変化量を測定した。

【0056】

【表3】

表3 反応の原料組成

SUNTGA40S	25g
パーム油 または 大豆油	15g
固定化リパーゼ	2g

【0057】

図1には高度不飽和脂肪酸高含有油脂またはトリグリセリドの一種であるアラキドン酸含有油脂を植物油脂のパーム油や大豆油と混合して、エステル交換した時のAAA含量の変化をしめしたものである。飽和脂肪酸含量の高いパーム油とのエステル交換でも、飽和脂肪酸含量が低く不飽和脂肪酸含量の高いリノール酸系油脂の大豆油とではAAAの減少速度は同じであった。

これは植物油脂の種類によらず、混合比率が同じであれば、本発明にかかるAAAの消失速度が同じ事を示した証拠である。

【0058】

実施例5、CDM試験

酵素的に変換したアラキドン酸高含有油脂の酸化安定化を確認する目的で、酵素変換油 50

脂を試作し、CDM試験で酸化安定性を測定した。CDM試験は試料油脂を反応容器で加熱（一定温度）しながら、清浄空気を送り込み、酸化により生成した揮発性分解物を水中に捕集し、水の導電率が急激に変化する折曲点までの時間で試料油脂の安定性を表す。この時間が短いほど酸化劣化しやすい油脂ということになる。

【0059】

実施例3に基づき、固定化酵素（活性化済）を原料油脂（40g）に対し、2倍量（4g）に加え、30℃、100rpmで反応した。反応後、油脂と固定化酵素をデカントで分離して反応油脂を得た。得られた油脂のAAA含量をHPLCで分析するとともに、CDM試験により安定性について分析した。反応時間を変えて、AAA含量の異なる修飾油脂1および修飾油脂2を得た。

【0060】

【表4】

表4 修飾油脂（エステル交換油脂）のAAA含量と安定性

試料	CDM (Hr)	AAA含量 (%)
パーム油/SUNTGA40S		
修飾油脂1	6.4	3.90
修飾油脂2	5.7	4.44
未修飾油脂	4.6	6.46
大豆油/SUNTGA40S		
修飾油脂1	4.1	3.69
修飾油脂2	3.6	4.28
未修飾油脂	3.5	7.01

【0061】

表4に示すように、反応原料の植物油脂はパーム油のような飽和脂肪酸系油脂を用いることで、問題のAAA含量も減少し、油脂の酸化に対する安定性が高くなったことが示された。

一方、リノール酸系油脂の大豆油を反応原料に用いた場合、AAAはパーム油同様に減少することが示せたが、CDMで示される安定性についてはパーム油ほど高い効果は得られなかった。

【0062】

実施例6、パーム油で希釈した高アラキドン酸含有油脂（SUNTGA40S）のエステル交換反応における各成分の時間的変化

真菌類が生産する高アラキドン酸含有油脂はAAAを多く含むため、母乳のアラキドン酸の存在形態（XXA）に近づけるため、リパーゼのエステル交換反応でAAAからXXAへ変換し、時間的な経過と各成分の比率の変化を実験的に測定した。

【0063】

【表5】

表5 エステル交換反応における各トリグリセリド成分の時間変化

トリグリセリド成分(%)	経過時間 (hr)			
	0 hr	48 hr	96 hr	176hr
AAA	6.37	5.16	4.33	3.41
XAA	23.19	19.09	17.00	14.86
XXA	16.11	29.33	35.41	40.55

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【0064】

固定化酵素は実施例1で行った方法で活性化し、活性化型固定化酵素2gに対してSUNTGA40Sを25g、パーム油を15g加え脱酸素後、30℃で反応した。各時間にサンプリングし、実施例2で記載した方法（HPLC分析）で各トリグリセリドを分析し、各成分を算出した。表5に示すように、時間とともにAAAが減少し、この変換体と考えられるXXAが増加した。AAAが油脂混合後の1/2近く、XXAが2倍以上になるためには、この条件では1週間の時間を要した。次の実施例で反応温度や、固定化酵素の添加量について検討し、最適化を図っている。

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【0065】

実施例7. エステル交換反応における反応温度の影響

実施例1で調製した固定化酵素を用いて、エステル交換反応における反応温度の影響について検討した。固定化酵素は実施例1で行った方法で活性化し、活性化型固定化酵素2gに対してSUNTGA40Sを25g、パーム油を15g加えて、脱酸素後に各温度で反応した。反応1日後に反応した油脂をサンプリングし、実施例2で記載した方法（HPLC分析）で各トリグリセリドを分析し、AAAの残存量を算出した（表6）。

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【0066】

【表6】

表6 エステル交換反応の温度の影響

反応温度	AAA残存量	AAA減少率
	(%)	(%, 24時間当たり)
反応前	6.37	
30℃	5.86	9%
45℃	4.50	29%
55℃	2.43	62%

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【0067】

エステル交換反応は60℃以下で行うことが常識とされているので、30℃、45℃、55℃で反応を行い反応性を確認した。表に示すように、エステル交換反応は反応温度が高いほど

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効率的に行えることが確認できた。このため、高温下での反応で酸化劣化を防ぐ意味で脱酸素の工程は重要になってくる。

【0068】

実施例 8. リゾムコール・ミーハイ (Rhizomucor miehei) のリパーゼを固定化した酵素剤での検討

実施例 5 と同様に、添加する酵素の量は 10% で、パーム油で希釈した SUNTGA40S (サントリ (株)、商品名) を用いて、実施例 1 で固定化し活性化したりゾプス・デレマー (*R. delemar*) のリパーゼと市販品として入手可能で水による活性化が不必要なリゾムコール・ミーハイ (*R. miehei*) の固定化リパーゼ (バーリンガー・マンハイム社製、キラザイム L-9, c.-f., G2, 1yo) のエステル交換活性を比較した。

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【0069】

【表 7】

表7 *R. delemar* リパーゼと *R. miehei* リパーゼによるエステル交換反応
の比較

分子種	<i>R. delemar</i>	<i>R. miehei</i>
AAA	2.86	2.53
XAA	14.95	14.05
XXA	43.33	44.20

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【0070】

実施例 3 で記載した方法 (HPLC 分析) で各トリグリセリドを分析し、各成分を算出した。表 7 に示すように、両酵素反応とも 48 時間、45℃ で反応したが、AAA の減少と XXA の増加速度は両酵素ともほぼ同等で、本エステル交換反応に用いることができることを示している。

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【0071】

実施例 9. アラキドン酸を高含有するエステル交換反応による改良

本発明者らはモルティエラ属に属する微生物を培養することで、アラキドン酸を主たる構成脂肪酸としてなる油脂またはトリグリセリドを産生し得る微生物を得、工業スケールで発酵生産して精製油脂を得る方法を開示している (非特許文献 4 参照)。この方法によって得られたアラキドン酸を主たる構成脂肪酸としてなる油脂またはトリグリセリドを原料油脂として、実施例 1 の方法で脱酸素化し活性化した固定化酵素 (*R. delemar* リパーゼ) を用いて植物油脂のパーム油とエステル交換した。40 質量% のアラキドン酸を主たる構成脂肪酸としてなる油脂 (250 g)、パーム油 (150 g)、固定化酵素 (40 g) を 45℃ で 48 時間反応させた。反応原料油脂の 97% はトリグリセリドの形態であり、構成脂肪酸としてのアラキドン酸が 25% 存在し、トリグリセリド中のトリアラキドン酸 (AAA) が 6.37% 存在した。このエステル交換反応で得られた油脂をろ過により、固定化酵素と分別し、トリグリセリドを 95.1%、AAA を 2.83%、XXA (アラキドン酸残基が 1 個結合したモノアラキドン酸) を 42.3% 含有するアラキドン酸高含有油脂またはトリグリセリドを 385g 調製することができた。

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【0072】

実施例 10. ジホモ- γ -リノレン酸 (DGLA) を高含有する油脂のエステル交換反応による改良

本発明者らはモルティエラ属モルティエラ亜属に属する微生物の変異処理を施すこ

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とにより、ジホモ- γ -リノレン酸 (DGLA) を主たる構成脂肪酸としてなる油脂またはトリグリセリドを産生しうる微生物を得、工業スケールで酸酵生産して精製油脂を取る方法を開示している (特許文献 9 参照)。この方法によって得られた DGLA を主たる構成脂肪酸としてなる油脂またはトリグリセリドを原料油脂として、実施例 1 の方法で脱酸素化し活性化した固定化酵素 (*R. delenae* リパーゼ) を用いて植物油のバーム油とエステル交換反応した。40 質量 % の DGLA を主たる構成脂肪酸としてなる油脂 (25g)、バーム油 (15g)、固定化酵素 (4g) を 45℃ で 48 時間反応させた。反応初期にはトリグリセリドとして 97.2%、構成脂肪酸としての DGLA が 25% 存在し、トリグリセリド中のトリ-ジホモ- γ -リノレン酸 (DDD) が 0.09% 存在したが、本反応で、トリグリセリドは 95.3% であり、DDD は 3.03% にまで低減でき、アラキドン酸含有油脂またはトリグリセリドと同様に DGLA を主たる構成脂肪酸としてなる油脂中に含まれる DDD を減少させることができた。

【0073】

実施例 11. アラキドン酸含有油脂 (粗油) の調製

アラキドン酸生産菌としてモルティエラ・アルピナ (*Mortierella alpina*) CRS754-68 を用いた。保存菌株を、酵母エキス 1%、グルコース 2%、pH6.3 の培地に接種し、往復振盪 100rpm、温度 28℃ の条件にて種培養 (第一段階) を開始し、3 日間培養した。次に、酵母エキス 1%、グルコース 2%、大豆油 0.1%、pH6.3 の培地 30L を 50L 容通気攪拌培養槽に調製し、これに種培養 (第一段階) 液を接種して、攪拌回転数 200rpm、温度 28℃、槽内圧 150kPa の条件にて、種培養 (第二段階) を開始し、2 日間培養した。

【0074】

次に、4500L の培地 (培地 A: 大豆粉 270kg、 KH_2PO_4 16.2kg、 $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ 2.7kg、 $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 2.7kg、大豆油 54kg) を、121℃、20 分の条件で滅菌した。別培地として、800L の培地 (培地 B: 含水グルコース 108kg) を 140℃、40 秒の条件で滅菌して先の培地 A に加えて培地 C を調製した。培地 C を pH6.1 に調整した後、種培養液 (第二段階) を接種して、計 5400L の初発培養液量 (培養槽容積 10kL) に合わせた。温度 26℃、通気量 49Nm³/hr、内圧 200kPa で培養を開始した。また、表 8 に示すように培地流加を行ない、210 時間の本培養を行なった。培養終了時は、培地流加による増加分と蒸発による減少分の影響で、7100L の培養液量となった。

【0075】

【表 8】

表 8: 実施例 1 の培地流加

本培養時間	流加培地
19 時間後	(含水グルコース 243kg +大豆油 54kg) / 400L
43 時間後	含水グルコース 243kg / 400L
67 時間後	含水グルコース 216kg / 380L
91 時間後	含水グルコース 162kg / 300L
120 時間後	含水グルコース 108kg / 200L

【0076】

培養終了後、120℃、20 分の条件で殺菌した後、フィルタープレスで湿菌体を回収し、

流動層乾燥機で水分含量2質量%まで乾燥し、空気輸送機を用いて充填場所に乾燥菌体を輸送した。得られた乾燥菌体を、容積約100Lのアルミパウチ製袋に窒素ガスとともに充填し、バッグ口部をヒートシールシールした後、10℃以下の冷蔵室で保管した。

【0077】

コンテナバッグより取り出した乾燥菌体に、ヘキサン抽出を施し、ヘキサン溶液を濾過して含有固形分を除去した後、減圧下で加熱することによってヘキサンを除去し、アラキドン酸を構成脂肪酸として成る粗油を得た。

粗油を分析した結果、トリグリセリド含量94%、総脂肪酸中のアラキドン酸含量29.6%であった。

【0078】

実施例12. 実施例11で調製した油脂のエステル交換反応

実施例11で調製したアラキドン酸を29.6%含有する粗油（トリグリセリド94%）に植物油脂を添加せず、リパーゼのエステル交換反応のみを使って、本粗油の改良を試みた。リゾプス・デレマー（*R. delenar*）の固定化リパーゼを用いて、実施例1で記載した方法で脱酸素、活性化し、アラキドン酸を29.6%含有する粗油（40g）に活性化した固定化酵素（4g）を加えて45℃で48時間振とうして反応させた。反応開始時にはAAAが6.08%、XXAが24.15%の組成をした油脂が反応終了時にはAAAが3.21%、XXAが40.37%の組成であった。このような粗油を使った場合、植物油脂をわざわざ加えなくとも、実施例6、8で示されたように微生物産生高度不飽和脂肪酸を主たる構成脂肪酸としてなる油脂のエステル交換反応と同様にエステル交換されて油脂が改良されることが示された。

【0079】

実施例13. ミルクへの添加

粉ミルク100gに実施例9で得られた修飾油脂1（新規エステル交換油脂）0.44gを添加することにより、ヒト母乳に近い調整乳を調製した。この調製乳の全脂肪酸に対するアラキドン酸の割合は0.5%となった。

【0080】

実施例14. バターへの添加

バター製造工程の攪拌操作（チャーニング）でバターミルクが除かれたバター脂肪100gに実施例9で得られた修飾油脂1（新規エステル交換油脂）を1.97g加えて練圧操作（ワーキング）を行い、均等な組成として、アラキドン酸を付加したバターを得た。

【0081】

実施例15. ジュースへの添加

β -デキストリン2gを20%エタノール水溶液20mlに添加し、ここにスターラーで攪拌しながら、実施例9で得られた修飾油脂1（新規エステル交換油脂）にビタミンEを0.05質量%配合し、これを100mgを加え、50℃で2時間インキュベートした。室温冷却（約1時間）後、さらに攪拌を続けながら4℃で10時間インキュベートした。生成した沈殿を、遠心分離により回収し、n-ヘキサンで洗浄後、凍結乾燥を行い、アラキドン酸含有トリグリセリドを含有するシクロデキストリン包埋化合物1.8gを得た。この粉末1gをジュース10Lに均一に混ぜ合わせ、アラキドン酸含有エステル交換油脂を含有するジュースを調製した。

【0082】

実施例16. エステル交換反応による中鎖脂肪酸とアラキドン酸を同一分子内に含有するトリグリセリドの調製とその油脂の精製

実施例1の方法で調製した固定化リパーゼを実施例1に準じて、脱酸素化と活性化操作を行った。すなわち、アラキドン酸を40%含有するトリグリセリド（SUNTGA40S、サントリー（株）、商品名）（200g）、MCT（ココナードRT、花王（株）商品名）（200g）、上記固定化リパーゼ（40g）、水（8ml）を密閉できるボトルに入れて実施例1の脱酸素化と酵素の活性化を行った。

活性化操作で用いた油脂を取り除き、新たにSUNTGA40S（200g）とMCT（200g）を固定化酵素が入ったボトルに入れ、30℃で48時間振とう（100rpm）した。

【0083】

反応終了後、油脂をボトルから取り出して実施例3に示すHPLCの分析でエステル交換された油脂のトリグリセリドの分析を行った。分析結果を表9に示す。本HPLCの方法ではエステル交換で得られた中鎖脂肪酸とアラキドン酸を含むトリグリセリド（例えば、1、2位にオクタン酸、3位にアラキドン酸が結合したトリグリセリド（88A）、1、3位にオクタン酸、2位にアラキドン酸が結合したトリグリセリド（8A8）等）が分離分析できない。そこでGC（分析条件は以下）での分析を加えることで88Aと8A8が分離分析される。88Aは17.01分、8A8は17.15分にクロマト上に出現した。

従って、本反応に於いて各種トリグリセリド含量は表10のようになった。

【0084】

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〔GC分析方法〕

カラム：Frontier Ultra ALLOY UA-17-15M-0.1F（15m×0.25mm×0.1μm）

カラム温度：260℃－（1℃/分）－290℃－（10℃/分）－390℃（5分）

分析時間：45分

注入口温度：310℃

検出器温度：370℃（水素イオン化検出器）

キャリアガス：ヘリウム

線速度：40cm/分

サンプル：油脂（トリグリセリド）をヘキサンに溶解させた1%溶液1μlを注入

さらに、分析後に残ったエステル交換油脂を分子蒸留することで、反応で残ったMCTを
ほぼ85%除去することができた。

20

【0085】

【表 9】

表 9：トリグリセリドの割合

HPLC分析の結果

トリグリセリド	反応前 (重量%)	反応後 (重量%)
8A8, など	0.00	15.87
8P8	0.00	6.96
8L8	0.00	6.58
808	0.00	15.23
AAA	4.84	1.67
8AA	0.00	6.25
GAA	0.79	0.00
LAA	3.06	2.86
PAA	5.55	4.71
SAA	3.97	1.45
C22AA	1.30	0.28
C24AA	3.72	0.52
LLA	0.55	1.45
PGA	1.88	0.91
OLA	0.67	0.28
PLA	3.04	1.01
OOA	0.60	0.00
POA	2.97	0.84
PPA	1.32	0.41
SOA	0.90	0.70
PSA	1.30	0.23
SSA	0.93	0.44
LAC22	0.57	0.27
888	50.00	23.27
その他のトリグリセリド	12.04	7.81

【0086】

8A8等：8A8 (88A, 8A8), 8G8, 8D8の混合物。

各脂肪酸を英数字で表示（但し、グリセリン骨格への結合位置は規定せず）（但し、この表では88Aと8A8以外のトリグリセリドはグリセリン骨格への結合位置を規定していない）

脂肪酸の記号と名称は以下の通り。

B：オクタン酸、A：アラキドン酸、D：DGLA、P：パルミチン酸、S：ステアリン酸、O：オレイン酸、C：γ-リノレン酸、L：リノール酸、C22：炭素数22の飽和直鎖脂肪酸、C24：炭素数24の飽和直鎖脂肪酸。

【0087】

【表 10】

表10：トリグリセリドの割合

GCとHPLCの組合せ分析結果

トリグリセリド	反応前 (重量%)	反応後 (重量%)
88A	0.00	8.36
8A8	0.00	5.37
88G + 8G8	0.00	0.35
88D + 8D8	0.00	1.79
88L + 8L8	0.00	6.58
88P + 8P8	0.00	6.96
88O + 8O8	0.00	15.23
8AA + A8A	0.00	6.25
AAA	4.84	1.67
XAA + AXA	18.39	9.82
XXA + XAX	14.73	6.54
888	50.00	23.27
その他のトリグリセリド	12.04	7.81

【0088】

上記記載の各種トリグリセリドは構成する脂肪酸の種類で表示され、この表では各脂肪酸の結合位置を1, 2, 3位または3, 2, 1位で示している。トリグリセリドの場合、グリセリンの2位は不斉炭素であり、厳密には、1位と3位は立体的に異なる。しかし、生理的にはリパーゼの認識でもわかるように1位と3位はほぼ等しいので、この表記で真中に示される脂肪酸が2位であり、両端は入れ替わっても同じトリグリセリドとして表示している。

【0089】

表中の表記説明：

各脂肪酸は英数字で表される。

脂肪酸の記号と名称は以下の通り。

8：オクタン酸、A：アラキドン酸、D：DGLA、P：パルミチン酸、S：ステアリン酸、O：オレイン酸、G：γ-リノレン酸、L：リノール酸、C22：炭素数22の飽和直鎖脂肪酸、E24：炭素数24の飽和直鎖脂肪酸。

XAA+AXA：GAA, LAA, PAA, SAA, C22AA, C24AAの総和で示す。

XXA+XAX：LLA, PGA, OLA, PLA, OOA, POA, PPA, SOA, PSA, SSA, LAC22の総和で示す。

このXAA又はXXAで示される具体的なトリグリセリド（例えば、PGA等）は脂肪酸の結合位置を特定していない。具体的な含量は、表9に示した。

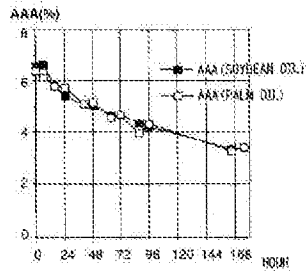
【図面の簡単な説明】

【0090】

【図1】図1はエステル交換反応におけるAAAの減少に及ぼすパーム油と大豆油の効果を示す。

【 図 1 】

Fig.1



【國際調查報告】

INTERNATIONAL SEARCH REPORT		International Application No. PCT/JP 03/11744
A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12P7/64 A23D9/007 A23D9/02 A23L1/29 A23C11/02 A23K1/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12P A23D A23L A23C A23K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 02, 26 February 1999 (1999-02-26) - & JP 10 290699 A (NIPPON SYNTHETIC CHEM IND CO LTD; THE; SHIMADA YUJI), 4 November 1998 (1998-11-04) the whole document	1-30
☒ Further documents are listed in the continuation of box C. ☐ Patent family members are listed in annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
18 March 2004		23/04/2004
Name and mailing address of the ISA European Patent Office, P.O. Box 5018 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2340, Tx. 51 651 epo nl Fax (+31-70) 340-2076		Authorized officer Douschan, K

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 03/11744

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TANE K ET AL: "PREPARATION OF POLYUNSATURATED OIL BY REPEATED TRANSESTERIFICATION WITH LIPASE" YUKAGAKU - JOURNAL OF THE JAPAN OIL CHEMISTS' SOCIETY, NIHON YUKAGAKU KYOKAI, TOKYO, JP, vol. 46, no. 7, 1997, pages 785-790, XP008012635 ISSN: 0513-398X see the abstract the whole document	1-30
X	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 04, 31 August 2000 (2000-08-31) -& JP 2000 004894 A (SUNTORY LTD, OSAKA CITY), 11 January 2000 (2000-01-11) the whole document	1-30
Y	PATENT ABSTRACTS OF JAPAN vol. 1996, no. 12, 26 December 1996 (1996-12-26) -& JP 08 214891 A (OSAKA CITY, MARUHA CORP), 27 August 1996 (1996-08-27) cited in the application the whole document	1-30
Y	PATENT ABSTRACTS OF JAPAN vol. 1995, no. 01, 28 February 1995 (1995-02-28) -& JP 06 287593 A (SNOW BRAND MILK PROD CO LTD), 11 October 1994 (1994-10-11) cited in the application the whole document	1-30

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/JP 03/11744

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 10290699 A	04-11-1998	NONE	
JP 2000004894 A	11-01-2000	NONE	
JP 08214891 4 A		NONE	
JP 06287593 4 A		NONE	

Form PCT/ISA/210 (patent family annex) (January 2004)

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C 0 7 C 69/587 (2006.01)	C 0 7 C 69/58	
A 2 3 D 9/007 (2006.01)	C 0 7 C 69/587	
C 1 2 R 1/645 (2006.01)	A 2 3 D 9/00 5 1 6	
C 1 2 R 1/845 (2006.01)	C 1 2 P 7/64	
	C 1 2 R 1:645	
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 4B026 DC05 DC20 DH01 DI09 DP10
 4B064 AD88 CA21 CB24 CC03 CD22 DA01 DA10 DA11
 4C206 AA01 AA04 DB06 DB09 DB42 DB48 MA01 MA04 MA72 NA09
 NA11 ZC01
 4B006 AA01 AA03 AB10

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Application Number:	14578075
International Application Number:	
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Title of Invention:	Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives
First Named Inventor/Applicant Name:	Jeff Addy
Customer Number:	93756
Filer:	Adam Reid Stephenson
Filer Authorized By:	
Attorney Docket Number:	FloraTech002
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Filing Date:	19-DEC-2014
Time Stamp:	00:16:10
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	SIDS002_3.pdf	1035086	no	4
			d78b863298a4ecedfc9a3886ce4db61824aeb691		

Warnings:

Vantage Exhibit 1002

Page 758 of 1215

CARGILL 00000783

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A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
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Warnings:					
Information:					
3	Foreign Reference	JP2007-528191_A_MachineTranslation.pdf	1301654 9e5c2405a2e293162ebff7d1edfef1d10d646d66	no	40
Warnings:					
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4	Foreign Reference	JPH6022690_A_MachineTranslation.pdf	361117 cdb942e437b526f058dcd2d41a423b92c21d54de	no	10
Warnings:					
Information:					
5	Foreign Reference	JPH7079786_A_MachineTranslation.pdf	114141 c76f4ef56a6f911b665772c64929e3448bea6cf1	no	8
Warnings:					
Information:					
6	Foreign Reference	FPD1.pdf	1563244 36ec8284a832af4914917add24eab658ccc1dd82	no	4
Warnings:					
Information:					
7	Foreign Reference	FPD2.pdf	1553125 fd5cbf4aa86528175a226305b1662344bb77224c	no	4
Warnings:					
Information:					

8	Foreign Reference	FPD3.pdf	3042512	no	25
			84c573bccdcf4814e1860c043ceed6d7ab9158fd		
Warnings:					
Information:					
9	Foreign Reference	FPD4.pdf	5018214	no	28
			18a4c77ea219f0b7b4d73c09c23737a3d03af79d		
Warnings:					
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Total Files Size (in bytes):				14170473	
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/578,075	12/19/2014	Jeff Addy	FloraTech002	2053
93756	7590	12/04/2019	EXAMINER	
Adam R. Stephenson, LTD. 8350 E Raintree Dr., Ste 245 Scottsdale, AZ 85260			PATURY, SRIKANTH	
			ART UNIT	PAPER NUMBER
			1657	
			NOTIFICATION DATE	DELIVERY MODE
			12/04/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

adam@iptech.law
ipdocket@iptech.law

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Status of the Claims

The amendments filed on 09/19/2019 are acknowledged and have been fully considered. Claims 1-7 are pending. Claims 3 and 4 are amended. Claims 8-20 were previously canceled. Claims 1-7 are now under consideration and the subject of this office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 11/10/2019 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Objections/Rejections Withdrawn

The previous objections to claims 3 and 4 are withdrawn in light of the claim amendments filed on 09/19/2019.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of

rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claim Rejections - 35 USC § 103 (Maintained)

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5 are rejected under 35 U.S.C. 103 as being unpatentable over **Gunawan** (Journal of Oleo Science, 2004; Of Record) **in view of Austic** (WO

2012/106701; Pub. Aug. 9, 2012; Of Record) **and as evidenced by Busson-Breysse** (JAOCS, 1994; Of Record) **and Fucosterol** (Cayman Chemical, CAS Entry, 2019; Of Record).

Gunawan teaches transesterifying palm oil using oleyl alcohol and lipase (abstract, pg. 472 col. 1, Exp. Procedures). Gunawan teaches the palm oil comprises wax esters (pg. 472 col. 1 para. 2 Exp. Procedures). Gunawan teaches adding a lipase (Lipozyme) to catalytically transesterify the oils to produce transesterified wax esters (Fig.1, Table 1). Gunawan is silent regarding the oxidative stability index (OSI) of the transesterified product being at least 2.5 times greater than the OSI of the feedstock. Gunawan teaches that wax esters can be extracted from plant materials such as jojoba oil but the process is too expensive (pg. 471 col. 2 para 1). It was also known in the art that jojoba oil can be esterified using a lipase to produce wax esters. Austic teaches that feedstocks comprising esters including jojoba oil, palm oil etc., can be esterified with an alcohol and a lipase (pg. 4 lines 25- pg. 5 lines 3, pg. 8 lines 19 – pg. 9 lines 20, Ex. 4; *Re. claim 5*). Austic teaches lipase including Lipozyme TL IM (Thermomyces lanuginosus) from Novozyme can be used in its methods (pg. 9 Enzymes). In light of these teachings, it would have been obvious to one of ordinary skill before the effective filing date of the claimed invention to use jojoba oil instead of palm oil to produce transesterified wax esters in the methods of Gunawan and the artisan would be motivated to do so because it was known in the art that jojoba oil can also be used in transesterification processes with lipases and the artisan is substituting jojoba oil instead of palm oil in the methods of Gunawan. Gunawan also teaches it is expensive to extract wax esters from jojoba oil, so therefore it would be obvious to produce wax

esters by the lipase-catalyzed synthesis method from oils as taught by Gunawan and substitute jojoba oil instead of palm oil in the methods of Gunawan.

Gunawan in view of Austic are also silent regarding the oxidative stability index (OSI) of the transesterified product being at least 2.5 times greater than the OSI of the feedstock. However, the combined teachings of Gunawan and Austic, teach a process in which jojoba oil is catalyzed by contacting with a lipase (Lipozyme TL IM), the same process taught in the instant specification (par. [0057]). Therefore it is reasonably expected that the process of Gunawan in view of Austic would also result in the OSI of the transesterified product being at 2.5 times greater than an OSI of the feedstock.

Regarding claims 3 and 4; Gunawan and Austic do not teach the feedstock to further comprise an antioxidant (claim 3), a skin conditioning agent and a volatile compound (claim 4). Jojoba oil comprises various sterols such as fucosterol (see Busson-Breyse Table 4), which is an antioxidant (see Fucosterol pg. 1 Description). The instant specification discloses that jojoba oil comprises various sterols, antioxidants (tocopherols etc.,) function as skin conditioning agents and are volatile (see par. [0050]). Gunawan in view of Austic teach using jojoba oil in their methods, and teach a process in which jojoba oil is catalyzed by contacting with a lipase (Lipozyme TL IM), the same process taught in the instant specification (par. [0057]). Therefore it is reasonably expected that the process of Gunawan in view of Austic is teaching a method in which the feedstock (jojoba oil) comprises an antioxidant, skin conditioning agent and a volatile compound and the transesterification process would occur without removing or degrading the antioxidant, skin conditioning agent and a volatile compound.

Regarding claim 2, Gunawan teaches using oleyl alcohol and does not teach using methanol in its methods to catalyze the feedstock, therefore the transesterified product would not comprise methyl esters.

The teachings of Gunawan and Austic would render claims 1-5 obvious.

Claims 1-7 are rejected under 35 U.S.C. 103 as being unpatentable over **Gunawan** (Journal of Oleo Science, 2004; Of Record) **in view of Austic** (WO 2012/106701; Pub. Aug. 9, 2012; Of Record) **and as evidenced by Busson-Breysse** (JAOCS, 1994; Of Record) **and Fucosterol** (Cayman Chemical, CAS Entry, 2019; Of Record) **and further in view of Arquette** (US 5,968,530; Iss. Oct. 19, 1999; Applicant IDS; Of Record).

Regarding claims 6 and 7, Gunawan and Austic do not teach the jojoba oil comprises hydrogenated wax esters. Arquette teaches preparing esterified products for use in cosmetic products and teaches using jojoba oil in the esterification methods (col. 4 lines 40-65). Arquette teachings jojoba oil is also called jojoba wax esters (col. 5 lines 1-15) and teaches jojoba wax esters, hydrogenated jojoba wax esters or a mixture of the two are used in the esterification reaction to produce the emollients (lubricants) for use cosmetic compositions (col. 8 lines 1-30,49-60).

In light of these teachings, it would have been obvious to one of ordinary skill before the effective filing date of the claimed invention to use jojoba oil comprising hydrogenated jojoba esters instead of jojoba oil to produce transesterified wax esters in the methods of Gunawan in view of Austic as taught by Arquette. The artisan would be motivated to do so because it was known in the art that jojoba oil, hydrogenated jojoba

oil and mixtures thereof can also be used in transesterification processes to produce emollient compositions and the artisan is substituting hydrogenated jojoba oil instead of jojoba oil in the methods of Gunawan/Austic. Gunawan, Austic and Arquette teach a method using hydrogenated jojoba oil in their methods, and teach a process in which jojoba oil is catalyzed by contacting with a lipase (Lipozyme TL IM), the same process taught in the instant specification (par. [0057]). Therefore it is reasonably expected that the process of Gunawan, Austic and Arquette would also produce a transesterified product whose dropping point is greater than the dropping point of the feedstock and the dropping point increases as a percentage of hydrogenated jojoba wax esters in the feedstock increases. Since Arquette teaches using mixtures of jojoba oil and hydrogenated jojoba oil, the percentage of hydrogenated wax esters can be varied, and the dropping point would change based on the hydrogenation since the same method steps (providing a feedstock, contacting with a lipase and catalytically transesterifying the wax esters) are taught by Gunawan, Austic and Arquette.

The teachings of Gunawan, Austic and Arquette would render claims 1-7 obvious.

Response to Arguments

Applicant's arguments filed 09/19/2019 regarding the teachings of Gunawan and Austic have been fully considered (pg. 7-10) but are not persuasive. Applicants argue that Gunawan and Austic do not disclose any evidence/data regarding the OSI data of the feedstock materials or reaction products and therefore the teachings of Gunawan/Austic do not meet the limitations that 'wherein the OSI of the transesterified

product is at least 2.5 times greater than an OSI of the feedstock' (pg. 8). However, this is not persuasive because, as discussed above, the combined teachings of Gunawan and Austic, do teach a process in which jojoba oil is catalyzed by contacting with a lipase (Lipozyme TL IM), the same process taught in the instant specification (par. [0057]) and recited in the instant claims. Therefore it is reasonably expected that the process of Gunawan in view of Austic would also result in the OSI of the transesterified product being at 2.5 times greater than an OSI of the feedstock.

Applicants argue that Gunawan teaches that jojoba oil is expensive and teaches palm oil as an alternative and therefore one would not be motivated to use jojoba oil in the methods of Gunawan. However, Austic teaches that feedstocks comprising esters including jojoba oil, palm oil etc., can be esterified with an alcohol and a lipase (pg. 4 lines 25- pg. 5 lines 3, pg. 8 lines 19 – pg. 9 lines 20, Ex. 4). Austic teaches lipase including Lipozyme TL IM (*Thermomyces lanuginosus*) from Novozyme can be used in its methods (pg. 9 Enzymes). In light of these teachings, it would have been obvious to one of ordinary skill before the effective filing date of the claimed invention to use jojoba oil instead of palm oil to produce transesterified wax esters in the methods of Gunawan and the artisan would be motivated to do so because it was known in the art that jojoba oil can also be used in transesterification processes with lipases and the artisan is substituting jojoba oil instead of palm oil in the methods of Gunawan.

Applicants argue that there are distinct differences in the methods of the instant claims and that of Gunawan/Austic. Applicants argue that Gunawan teaches using a solvent whereas the instant claims are solventless and use packed column reactors (pg. 8 last para). Applicants argue that Gunawan teaches that increasing temperature from

60°C to 70°C reduces yields and that the instant claims perform the methods at 70-72°C and still achieve 99% yields (pg. 9 para. 1,2). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., solventless reactions in packed bed reactors, higher temperatures etc.,) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Patent 10,435,726 (previously US Application No. 14/841,242)

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of US 10,435,726. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claims 1-6 of the '726 patent renders obvious that of the instant claims. The issued claims also recite process to transesterify feedstocks comprising wax esters, contacting with a lipase and catalytically transesterifying the feedstock to produce a transesterified product. The issued claims also teach feedstock to comprise jojoba wax esters (claim 4), hydrogenated jojoba wax esters (claim 5), the feedstock to comprise antioxidants and catalyzing without removing or degrading the antioxidant (claim 3). The issued claims are silent regarding the OSI and dropping point of the product, feedstock comprising skin conditioning agent and volatile compounds. However, the issued claims teach the same feedstock, jojoba oil, which comprises skin conditioning agents and volatile compounds. Regarding OSI, dropping point of the product and performing the transesterification without removing/degrading the skin conditioning agent, the issued claims teach the same process as the instant claims, catalyzing jojoba oil with lipase, therefore it is expected the product of the issued claims would also have the same functional characteristics.

Response to Arguments

Applicant's arguments filed 09/19/2019 regarding the double patenting rejections over 14/841,242 (now Patent 10,435,726) have been fully considered but are not persuasive (pg. 4-6). Applicants argue that the double patenting rejections are in error because the '242 is a continuation-in-part of the instant application and that the instant claims do not teach all of the limitations of the claims in the '242 application ('726 patent). Applicants argue that claim 8 of the '242 application (claim 1 of '726 patent) requires the addition of an alcohol with a carbon number ranging from 1-34 carbons which is a non-trivial step and is not disclosed in the instant specification/claims (pg. 5 last para) and argue that this step is not anticipated by nor obvious over the instant claims (pg. 6).

However, this is not persuasive, because a rejection under nonstatutory double patenting requires that 'at least one examined claim is not patentably distinct from the reference claim because the examined application claim is either anticipated or would have been obvious over the reference claim'. See MPEP §804 II B. Here, the reference claim is claim 1 of '726 patent (previously claim 8 of '242 application) and the examined claim is instant claim 1. Therefore, the limitations of claim 1 of '726 would need to anticipate and/or render obvious the limitations of instant claim 1, not the other way around as argued by the applicants.

As discussed above in the double patenting rejections, the issued '726 claims also recite a process to transesterify feedstocks comprising wax esters, contacting with a lipase and catalytically transesterifying the feedstock to produce a transesterified product. The issued claims also teach feedstock to comprise jojoba wax esters (claim

4), hydrogenated jojoba wax esters (claim 5), the feedstock to comprise antioxidants and catalyzing without removing or degrading the antioxidant (claim 3). The issued claims are silent regarding the OSI and dropping point of the product, feedstock comprising skin conditioning agent and volatile compounds. However, the issued claims teach the same feedstock, jojoba oil, which comprises skin conditioning agents and volatile compounds. Regarding OSI, dropping point of the product and performing the transesterification without removing/degrading the skin conditioning agent, the issued claims teach the same process as the instant claims, catalyzing jojoba oil with lipase, therefore it is expected the product of the issued claims would also have the same functional characteristics. Therefore the double patenting rejections over the '726 patent (previously '242 application) are being maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SRIKANTH PATURY whose telephone number is (571)270-1020. The examiner can normally be reached on Monday-Friday, 9:30 - 6:30 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Louise W Humphrey can be reached on 571-272-5543. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Srikanth Patury/
Examiner, Art Unit 1657

/LOUISE W HUMPHREY/
Supervisory Patent Examiner, Art Unit 1657

<i>Search Notes</i> 	Application/Control No. 14/578,075	Applicant(s)/Patent Under Reexamination Addy et al.
	Examiner SRIKANTH PATURY	Art Unit 1657

CPC - Searched*		
Symbol	Date	Examiner
Please see Partial text search in WEST appended hereto	3/20/2017	KCS
Please see Updated Partial text search in WEST appended hereto	10/19/2017	KCS
Please see Re-updated Partial text search in WEST appended hereto	06/23/2018	KCS
C12P7/6436 or C11C3/003 or C11C3/10 - text limited	05/28/2019	/sp/

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

	/SRIKANTH PATURY/ Examiner, Art Unit 1657
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Search Notes 	Application/Control No. 14/578,075	Applicant(s)/Patent Under Reexamination Addy et al.
	Examiner SRIKANTH PATURY	Art Unit 1657

US Classification - Searched*			
Class	Subclass	Date	Examiner
Partial text search in WEST	Partial text search in WEST	3/20/2017	KCS
CPC	C12P7/6436 C11C3/003	3/20/2017	KCS
IPC	C12P7/64)	3/20/2017	KCS
USPC	435/134	3/20/2017	KCS
Updated Partial text search in WEST	Updated Partial text search in WEST	10/19/2017	KCS
CPC	C12P7/6436, C11C3/003	10/19/2017	KCS
IPC	C12P7/64	10/19/2017	KCS
USPC	435/134	10/19/2017	KCS
Re-updated Partial text search in WEST	Re-updated Partial text search in WEST	06/23/2018	KCS
CPC	C12P7/6436 C11C3/003 C11C3/10	06/23/2018	KCS
IPC	C12P7/64	06/23/2018	KCS
USPC	435/134	06/23/2018	KCS

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

	/SRIKANTH PATURY/ Examiner, Art Unit 1657
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Search Notes 	Application/Control No. 14/578,075	Applicant(s)/Patent Under Reexamination Addy et al.
	Examiner SRIKANTH PATURY	Art Unit 1657

Search Notes		
Search Notes	Date	Examiner
Inventor name search in PE2E & PALMsearch in	3/1/2017	KCS
Assignee name search in PE2E & PALM	3/1/2017	KCS
Verified Application priority data in PE2E & PALM	3/1/2017	KCS
Partial Text Search in WEST:DWPI, EPAB, FPRS, JPAB, USOC, USPT according to search strtrgy and terms in WEST search history appende hereto	3/20/2017	KCS
STN Search	09/20/2016	KCS
Updated Inventor name search in PE2E, WEST & PALM	10/19/2017	KCS
Updated Assignee name search in PE2E & PALM	10/19/2017	KCS
Reverified Application priority data in PE2E & PALM	10/19/2017	KCS
Updated Partial Text Search in WEST:DWPI, EPAB, FPRS, JPAB, USOC, USPT according to search strtrgy and terms in WEST search history appende hereto	10/19/2017	KCS
14578075 Google Search Transesterification oil OI20171019	10/19/2017	KCS
Re-updated Inventor name search in PE2E, WEST & PALM	06/23/2018	KCS
Re-updated Assignee name search in WEST, PE2E & PALM	06/23/2018	KCS
Reverified Application priority data in WEST PE2E & PALM	06/23/2018	KCS
Updated Partial Text Search in WEST:DWPI, EPAB, FPRS, JPAB, USOC, USPT according to search strtrgy and terms in WEST search history appende hereto	06/23/2018	KCS
Google Search	07/31/2018	KCS
updated inventor search, see EAST search history	05/28/2019	/sp/
updated inventor search, see EAST search history	11/25/2019	/sp/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

	/SRIKANTH PATURY/ Examiner, Art Unit 1657
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Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	14578075
Filing Date	2014-12-19
First Named Inventor	Jeff Addy
Art Unit	1657
Examiner Name	PATURY, SRIKANTH
Attorney Docket Number	FLORATECH002

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	1	H06-022690	JP	A	1994-02-01	Kanegafuchi Chem Ind Co Ltd		×
	2	H07-079786	JP	A	1995-03-28	The Nisshin Oil Mills Ltd		☒
	3	2003-532705	JP	A	2003-11-05	Fan Tech Ltd.		☒

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STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

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Filing Date	2014-12-19
First Named Inventor	Jeff Addy
Art Unit	1657
Examiner Name	PATURY, SRIKANTH
Attorney Docket Number	FLORATECH002

4	2007-528191	JP	A	2007-10-11	Sun-Tory Ltd.	☒
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
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EXAMINER SIGNATURE

Examiner Signature	/SRIKANTH PATURY/	Date Considered	11/25/2019
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	14578075
Filing Date	2014-12-19
First Named Inventor	Jeff Addy
Art Unit	1657
Examiner Name	PATURY, SRIKANTH
Attorney Docket Number	FLORATECH002

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Adam Stephenson/	Date (YYYY-MM-DD)	2019-11-05
Name/Print	Adam R. Stephenson	Registration Number	58349

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Vantage Exhibit 1002
Page 780 of 1215

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Page 781 of 1215

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S19	2928	((("ADDY") near3 ("Jeff")) OR ((("DALY") near3 ("Clay")) OR ((("BROWN") near3 ("James")))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2019/11/25 08:36
S20	36	S19 and "wax ester"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2019/11/25 08:36
S21	2	"14841242"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2019/11/25 08:48

EAST Search History (Interference)

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NOTICE OF APPEAL FROM THE EXAMINER TO THE PATENT TRIAL AND APPEAL BOARD		Docket Number (Optional) FLORATECH002
I hereby certify that this correspondence is being facsimile transmitted to the USPTO, EFS-Web transmitted to the USPTO, or deposited with the United States Postal Service with sufficient postage in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, on Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on _____.	In re Application of Jeff Addy	
Signature _____ Typed or printed name _____	Application Number 14578075	Filed 12/19/2014
For Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives		
Art Unit 1657		Examiner PATURY, SRIKANTH

Applicant hereby **appeals** to the Patent Trial and Appeal Board from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) \$ 800

☒ Applicant asserts small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by 50%, and the resulting fee is: \$ 400

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Therefore, the fee shown above is reduced by 75%, and the resulting fee is: \$ _____
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 601853.

☒ Payment made via EFS-Web.

☐ A petition for an extension of time under 37 CFR 1.136(a) (PTO/AIA/22 or equivalent) is enclosed.
For extensions of time in reexamination proceedings, see 37 CFR 1.550.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant ☒ attorney or agent of record ☐ attorney or agent acting under 37 CFR 1.34

Registration number 58349 Registration number _____

Signature /Adam Stephenson/

Typed or printed name Adam R. Stephenson

Telephone Number 480.264.6075

Date 3/4/2020

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☒ * Total of 1 forms are submitted.

This collection of information is required by 37 CFR 41.20(b)(1) and 41.31. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	14578075			
Filing Date:	19-Dec-2014			
Title of Invention:	Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives			
First Named Inventor/Applicant Name:	Jeff Addy			
Filer:	Adam Reid Stephenson			
Attorney Docket Number:	FloraTech002			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
NOTICE OF APPEAL	2401	1	400	400
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				400

Electronic Acknowledgement Receipt

EFS ID:	38762046
Application Number:	14578075
International Application Number:	
Confirmation Number:	2053
Title of Invention:	Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives
First Named Inventor/Applicant Name:	Jeff Addy
Customer Number:	93756
Filer:	Adam Reid Stephenson
Filer Authorized By:	
Attorney Docket Number:	FloraTech002
Receipt Date:	04-MAR-2020
Filing Date:	19-DEC-2014
Time Stamp:	09:06:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$400
RAM confirmation Number	E202034007163229
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Vantage Exhibit 1002

Page 787 of 1215
CARGILL 00000812

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Notice of Appeal Filed	NoticeofAppeal002.pdf	240349	no	2
			67f33e501ae15e8ec8814bf6d6d885383f68140a		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30165	no	2
			55a059b4c191344d79a8249ff482bf1e135c2f02		
Warnings:					
Information:					
Total Files Size (in bytes):			270514		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **International Flora Technologies, Ltd.**

Examiner: PATURY, SRIKANTH

Docket No: FLORATECH002

Ser. No: 14578075

Group Art Unit: 1657

Filed: December 19, 2014

Technology Center: 1600

Conf. No.: 2053

Title: Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives

APPEAL BRIEF

Mail Stop Appeal Brief - Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir/Madam:

This is an appeal from the final rejection in the Office Action mailed December 4, 2019, which rejected claims 1-7 in Application Serial No. 14/578,075 ('075 application). A Notice of Appeal was filed on March 4, 2020 resulting in an Appeal Brief due date of May 4, 2020.

REAL PARTY IN INTEREST (§41.37(c)(1)(i))

The real party in interest in the present Application is the assignee International Flora Technologies, LTD., an Arizona limited liability company, as indicated by: the Assignment executed on 12/19/2014 and 12/20/2014 from the inventor(s) Jeff Addy, Clay Daly, and James H. Brown assigning the Application to the Assignee, recorded with the U.S. Patent and Trademark Office on 01/13/2015, at reel/frame number 30837/970.

RELATED APPEALS AND INTERFERENCES (§41.37(c)(1)(ii))

There are no related appeals, judicial proceedings, or declared interferences that will directly affect or will be directly affected by a decision by the Patent Trial and Appeal Board (the “Board”) in the present appeal.

SUMMARY OF CLAIMED SUBJECT MATTER (§41.37(c)(1)(iii))

This section is for the exemplary purposes of this appeal only to identify that support for the subject matter claimed exists at least in those portions of the specification and drawings cited. It is to be understood that there may be other portions of the specification and drawings beyond those cited that provide additional support.

A. Independent Claim 1

<u>Claim Language</u>	<u>Citations to specification</u>
A process for transesterifying wax esters, comprising:	FIGS. 2 – 3, [0041], [0042], [0052]
providing a feedstock comprising wax esters;	FIGS. 2 – 3, [0037], [0039], [0040], [0042], [0043], [0047], [0052], [0055]
contacting the feedstock with a lipase;	FIGS. 2 – 3, [0041], [0045], [0046], [0055], [0061], [0071]-[0073],
catalytically transesterifying the wax esters in the feedstock with the lipase to form a transesterified product;	FIGS. 2 – 3, [0036], [0041]- [0043], [0049], [0050]-[0053], [0056]-[0058], [0061], [0063]
wherein an oxidative stability index (OSI) of the transesterified product is at least 2.5 times greater than an OSI of the feedstock.	[0049]

STATUS OF CLAIMS

Claims 1-7 are pending in the application.

- Claims 1-7 stand rejected.

ARGUMENT (§41.37(c)(1)(iv))

I. Issue No. 1—Section 103 Rejection of Claims 1-7 over Gunawan (Journal of Oleo Science, 2004 “Gunawan”), in light of Austic et al. (WO Patent Publication No. WO 2012/106701A1, hereinafter “Austic”), and as evidenced by Busson-Breysse (JAOCS, 1994, hereinafter “Busson-Breysse”) and Fucosterol (Cayman Chemical, CAS Entry, 2019, hereinafter “Fucosterol”) and also in view of Arquette (U.S. Patent No. 5,968,530, hereinafter “Arquette”) is error for failure to establish a prima facie case.

In *In re Kao*, 639 F.3d 1057, 1064 (Fed. Cir. 2011), the Federal Circuit summarized the obviousness standard thusly: “[a] claimed invention is unpatentable ‘if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.’ 35 U.S.C. § 103(a). Whether an invention is obvious is a question of law based on underlying facts.” The Court then discussed what, during examination, the Examiner is required to do to establish a *prima facie* case of obviousness:

An examiner bears the initial burden of presenting a prima facie case of obviousness. See *In re Glaug*, 283 F.3d 1335 (Fed.Cir. 2002). Once the examiner establishes a prima facie case of obviousness, the burden shifts to the applicant to rebut that case. “The prima facie case is a procedural tool, and requires that the examiner initially produce evidence sufficient to support a ruling of obviousness; thereafter the burden shifts to the applicant to come forward with evidence or argument in rebuttal.” *In re Kumar*, 418 F.3d [1361] at 1366. However, once the applicant has come forward with rebuttal evidence, the examiner must consider the totality of the evidence to determine whether the obviousness rejection should stand. “When rebuttal evidence is provided, the prima facie case dissolves, and the decision is made on the entirety of the evidence.” *Id.* *In re Kao*, 639 F.3d at 1066.

Thus, in order to establish a *prima facie* case of obviousness, there must be a clear articulation of the reason(s) why the claimed invention would have been obvious.” Mere conclusory statements are insufficient.

Finally, the scope of a claimed invention is to be determined by giving the claims the “broadest reasonable interpretation consistent with the specification.” See *Phillips v. AWH Corp.* 415 F.3d 1303, 1316, 75 USPQ2d 1321, 1329 (Fed. Cir. 2005).

In making the 103 rejection of claim 1 the Examiner argues, on p. 5 of the 12/04/2019 OA, that while Gunawan and Austic are silent regarding the oxidative stability index (OSI) of the transesterified product, “it is reasonably expected that the process of Gunawan in view of Austic would also result in the OSI of the transesterified product being at 2.5 times greater than an OSI of the feedstock.” The Examiner’s argument, while not being fully stated, is that the OSI effect recited in claim 1 is inherently disclosed by the combination of the teachings of the disclosures of the methods of Gunawan and Austic. “To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.” *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985) (quoted in MPEP 706.02(j) (2014)).

As the Office well knows, MPEP. § 2112, under the heading “Examiner Must Provide Rationale or Evidence Tending to Show Inherency”, states that “[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).” M.P.E.P. § 2112 further states that “[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art.” *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

The Examiner’s rejection of claims 1-7 over Gunawan and Austic hang entirely on their alleged teaching of the same method steps as those claimed in independent claim 1. This is

because neither Gunawan nor Austic actually include any OSI data of either the feedstock materials or the reaction products—there is zero data in either reference to support the Examiner’s assertion. Unless the OSI result truly is an inherent result, there is simply no way one of ordinary skill would have, in view of the disclosures of Gunawan and Austic alone, have been able to predict this result necessarily would be present if the teachings were combined. The Examiner has to provide technical reasoning or a basis in fact that the result *necessarily* will result based on the actual teachings of the references.

An obviousness conclusion relies on the claim elements being known and a practitioner’s ability to combine those elements using known methods with no change in their respective functions. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416, 82 USPQ2d at 1395; *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson’s-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atl. & P. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). By relying on Austic and Gunawan to teach something that is not disclosed the Examiner is trying to change the function of these references.

The Examiner argues that the combination of Gunawan and Austic teach the same process as the current application. This statement is simply not accurate. The reaction in Gunawan differs from the method of the present application in a number of ways. Gunawan teaches using a solvent, hexane, in containers in small batch reactors. See pg. 472, col. 1, paragraph 2. The method in the present application is solventless and includes continuous flow through packed column reactors. It would not be obvious to take a reaction including a solvent, remove the solvent and change the reactors entirely. Because the chemical arts are *unpredictable* this significant change in the system in which the method is carried out would not clearly lead to the same results. The reactants and reaction conditions will have been changed which will most likely lead to different results.

On page 8-9 of the 12/04/2018 OA, the Examiner argues that the differences in the method of Gunawan and the present application do not need to be considered because these differences

are not in the claims. However, the fact that the processing methods in Gunawan is significantly different than the processing methods in the present application does need to be considered because the reference must be used in its entirety. Moreover, when evaluating claims for obviousness, “the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill.” *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986). Accordingly, “[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.” *Id.* (quoting *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965)). When the references are read properly, Gunawan does not teach the same method as the present application and adding Austic does not make up for this deficiency.

For a result to be predictable, the person of ordinary skill in the art must have a reasonable expectation of success in making the substitution. The law is clear that “[w]hile absolute certainty is not necessary to establish a reasonable expectation of success, *In re O'Farrell*, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir.1988), there can be little better evidence negating an expectation of success than actual reports of failure. See, e.g., *In re Rinehart*, 531 F.2d 1048, 1053-54, 189 USPQ 143, 148-49 (CCPA 1976).” *Boehringer Ingelheim Vetmedica, Inc., v. Schering-Plough Corp.* 320 F.3d 1339, 1354 (Fed. Cir. 2003).

While Guanawan fails entirely to provide any OSI data regarding its products (as does Austic), the results of the reaction of Gunawan are evidence, when compared to the results of the reactions described in the application and in view of the teachings of the Rule 1.132 Declaration of Jeff Addy filed in this record on 12/16/2018, that the process of Guanawan, as modified by Austic objectively cannot *necessarily result* in the claimed OSI ranges.

Gunawan teaches increasing the temperature of the reaction from 60 degrees Celsius to 70 degrees Celsius **reduces** the yield of the reaction. This statement in Gunawan again teaches away from the method taught in the specification and reflected in claim 1 because one skilled in the art would not increase the temperature of a reaction if they were trying to increase the yield

of the reaction in view of Gunawan's express teachings. However, the disclosed process in the present application found that increasing the reactant temperature to 70-72 C unexpectedly produces *higher* yields than disclosed in Gunawan. Gunawan reports yields of 75% using Lipozymes while the present method produced yields greater than 99%. Clearly, the present method produces result, just on the basis of yield, that are completely unexpected in view of the teachings of Gunawan—this when the temperature of the reactants in the present disclosure was raised higher than taught in Gunawan and produced better results..

Referring to FIG. 4 of Gunawan, yields are illustrated having a high of 35% with higher levels of enzymes than that disclosed in the present application. In spite of this, the disclosed reaction in the present application produced yields at greater than 99%. Not only does Gunawan not teach the method of claim 1 it does not teach the *unexpected results* observed when the claimed methods were carried out. If Gunawan cannot predict the observed yields when the process claimed in claim 1 is carried out in view of the present specification, how can the reference rationally be argued to predict the claimed OSI values?

The teachings of Austic do not make up for the deficiencies in Gunawan and therefore the combination does not make claim 1 obvious. For example, Austic teaches using large vessels for reacting gases with the feedstock. See Para. [0021]-[0024] of Austic. As previously described, the present application discloses use of packed columns and liquid reactants. Austic further teaches performing the reactions preferably under lower temperatures between 35 degrees Celsius to 65 degrees Celsius than the temperatures disclosed in the present application. Para. [0040] and [0085]-[0087] of Austic. Even if one skilled in the art tried jojoba oil in the method of Gunawan based on a teaching of Austic in large vessels the process is still not the same as that disclosed in the present application and would therefore not result in the unexpectedly high yields experienced in the present application as explained in both the originally filed application in para. [0073] and the Addy Declaration submitted with the Applicant's response on 12/6/2018. The Addy Declaration details, in a side by side test between jojoba esters and crambe oil esters that the resulting OSI values of the two feedstocks, even when processed using the process in

Steinke, produced unpredictably different results. The Addy Declaration establishes conclusively that dissimilar feedstocks produce unpredictable values of OSI *even when the same reaction process is used to process them*. Basically, the Addy Declaration establishes that a person of ordinary skill has no idea whether using the process of Gunawan with jojoba esters would result in a transesterified product where “an oxidative stability index (OSI) of the transesterified product is at least 2.5 times greater than an OSI of the feedstock.” Claim 1. The fact that the yield performance of the reaction of Gunawan fails to correlate with the observed results detailed in the specification further strengthens the conclusion that the present situation is a classic example of the unpredictability of the chemical arts. Because of the demonstrated incongruence between the yield results of Gunawan and the evidence that feedstock differences produce unpredictable changes in OSI provide all the reasoning that is needed to discredit the Examiner’s bald and unsupported reasoning that because the Gunawan process is allegedly the same as the claimed one, it *necessarily* must produce a product with the claimed range of OSI values. The 103 rejection of claim 1 in view of Gunawan and Austic alone or in combination is therefore inappropriate and the Applicant respectfully requests that the rejection be reversed.

In view of the foregoing, the Examiner has committed error by failing to establish a *prima facie* case of obviousness of claim 1.

Dependent claims 2-7 are allowable for, among other reasons, depending from allowable independent claim 1.

With respect to dependent claim 5, however, while the Examiner acknowledges that Gunawan teaches jojoba oils contain wax esters, the Examiner attempts to deny the impact of Gunawan’s teaching away from using jojoba oil on the obviousness of claim 5. Specifically, Gunawan teaches away from using jojoba oil because jojoba oils are either “too scarce or expensive for commercial use.” See Gunawan p. 1. Col. 2. The entirety of Gunawan teaches a method to make further use of palm oil because so much palm oil is produced in Malaysia and Indonesia and it is accordingly less expensive than jojoba oil. This reference would not lead

someone skilled in the art to use a reaction mixture including jojoba oil which is both more expensive and produced in different regions of the world than was focused on in Gunawan.

On page 8 of the 12/04/2019 OA, the Examiner argues that the teaching in Austic makes up for the deficiency in Gunawan for teaching away from using jojoba oil. However, Gunawan *teaching away* from using jojoba oil is not merely a deficiency in stating a starting material that can be corrected by a combination with Austic—it renders the reference legally unavailable for use in an obviousness combination.

MPEP § 2141.02(VI) states that "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Accordingly, where cited art teaches away from a claimed feature, the cited art is not available for the purposes of an obviousness rejection. In the instant case, Gunawan not only fails to teach or suggest jojoba oil in the reaction disclosed in that references, but further teaches away from the use thereof. For instance, Gunawan discusses that jojoba oil is either too scarce or expensive. Therefore, Gunawan explicitly teaches away from use of jojoba oil. Because Gunawan teaches away from using jojoba oil, one of ordinary skill in the art would not be led to modify Gunawan to incorporate certain features of Austic in an effort to arrive at the claimed process. Because of this, Guanwan cannot be combined with Austic to establish a *prima facie* case of obviousness of dependent claim 5 and the Examiner's rejection is error.

In view of the foregoing, the obviousness rejection of claims 1-7 over Guanwan in view of Austic is error and the Applicant respectfully requests that it be reversed.

II. Issue No. 2— The double patenting rejection of claims Claims 1-7 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-14 of co-pending Application No. 14/841,242 to Addy is error.

Claims 1-7 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-14 of co-pending Application No.

14/841,242 now claims 1-6 of issued Patent 10,435,726 ('726) to Addy. The Applicant notes that this rejection was made in the 11/30/2017 OA and subsequently withdrawn in the 08/06/2018 OA. The double patenting rejection was reissued in the 06/06/2019 OA and maintained in the 12/04/2019 OA.

The Examiner's analysis of why claims 1-7 of the present application are rejected based on the claims of the '726 patent is flawed and erroneous. Specifically, the Examiner states on p.10 of the 12/04/2019 OA that "Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claims 1-6 of the '726 patent renders obvious that of the instant claims. The issued claims also [a] recite process to transesterify feedstocks comprising wax esters, contacting with a lipase and catalytically transesterifying the feedstock to produce a transesterified product. The issued claims also teach feedstock to comprise jojoba wax esters (claim 4), hydrogenated jojoba wax esters (claim 5), the feedstock to comprise antioxidants and catalyzing without removing or degrading the antioxidant (claim 3). The issued claims are silent regarding the OSI and dropping point of the product, feedstock comprising skin conditioning agent and volatile compounds. However, the issued claims teach the same feedstock, jojoba oil, which comprises skin conditioning agents and volatile compounds. Regarding OSI, dropping point of the product and performing the transesterification without removing/degrading the skin conditioning agent, the co-pending claims teach the same process as the instant claims, catalyzing jojoba oil with lipase, therefore it is expected the product of the issued claims would also have the same functional characteristics." These statements are error and **wholly fail to conduct the analysis required by the MPEP in making out an obviousness type double patenting rejection**—particularly in view of the fact that the '726 patent is **a continuation-in-part** of the present application.

Specifically in MPEP § 804 (II)(B) Requirements of a Double Patenting Rejection – Nonstatutory Double Patenting, the Examiner is required to perform an Anticipation Analysis followed by an Obviousness Analysis if the previously patented claims are not found to anticipate the claims. In performing the anticipation analysis, the Examiner must determine

whether the entire scope of the reference claim falls within the scope of the examined claim so that the claim under examination is anticipated by the reference claim. MPEP § 804 (II)(B)(1).

In this case, independent claim 1 of the present application fails to recite major elements of the method of independent claim 1 of the '726 patent. Independent claim 1 of the '726 patent states that the method includes "introducing into the feedstock an alcohol with a carbon number ranging from 1 to 34 carbons, the alcohol selected from the group consisting of a straight chain alcohol, a branched chain alcohol, any combination of straight chain alcohols, any combination of branched chain alcohols, and any combination thereof..." wherein the enzymatically transesterified product is adapted to produce a finished product having a certain formula that has a viscosity that substantially matches a viscosity of a finished product having the same certain formula comprising chemically catalyzed transesterified wax esters." Clearly, the claim 1 of the present application does not anticipate the claim under examination, as the claim 1 in this application **does not include** the element of "introducing into the feedstock an alcohol with a carbon number ranging from 1 to 34 carbons, the alcohol selected from the group consisting of a straight chain alcohol, a branched chain alcohol, any combination of straight chain alcohols, any combination of branched chain alcohols, and any combination thereof..." as disclosed in Claim 1. This is not a trivial part of the claim, as **this element is not disclosed in the specification of the present application**, which is why the '726 patent is a **continuation-in-part** of the present application.

Since the independent claims are not anticipated by the claims of the '726 patent, the next step in the analysis is to determine whether the independent claims in the present application would be "an obvious variation of the invention defined in the claim of a patent..." MPEP § 804 (II)(B)(2)(a). The disclosure of the present application in this analysis cannot be used as prior art.

It would not be obvious to one skilled in the art to introduce an alcohol into the feedstock before contacting the feedstock with the lipase because it is not fundamentally obvious to conduct a reaction while adding an additional step to that reaction. No person of ordinary skill would be led to add the step of adding an alcohol to the feedstock of the present claim 1 in view of the claims of '726 patent—particularly since the disclosure to do so is found **ONLY** in the specification of the '726 patent itself, it being a continuation-in-part application of this application. There is no teaching pointed out by the examiner's analysis that would teach one of ordinary skill to add an additional step suggested in Claims 1-7. Furthermore, the addition of the alcohol in Claim 1 of the '726 patent produced unexpected results as described at least in Col. 15-16 of that patent because the addition of alcohol to the feedstock prior to transesterification unexpectedly results in a change in viscosity of finished products made using the transesterified products formed using the claimed process of the '726 patent. Because adding alcohol to the feedstock yields unexpected results, the claims of the present application, which lack the element of the claims of the '726 patent are clearly not an obvious variation of what is claimed in the present application. Furthermore, the '726 patent is a continuation-in-part application and claim 1 of the '726 patent is drawn to the newly added subject matter, making an obviousness type double patenting rejection even more unusual, given that the Applicant could not claim the subject matter of claim 1 in the present application in the first place (this alone obviates any issues of unjustifiable extension of patent term).

On p. 11 of the 12/04/2019 OA, the Examiner argues that the Applicant is doing the analysis backwards since '726 has already issued. However, the timeline of allowance does not change that '726 was a continuation in part application of the instant application and claims priority to the present application's filing date. Claim 1 of '726 has an additional step from claim 1 of the instant application. The needed disclosure to provide that step is found only in the specification of the '726 patent—not the present application.

Finally, as the ‘726 patent is a continuation-in-part application, the expiration date of its claims is not the same as the expiration date of the claims of the present application for those claims that include the additional subject matter disclosed in the ‘726 patent. As the Examiner has not shown that the claims of the ‘726 do not include that additional subject matter, then the statutory expiration date of the claims of the ‘726 patent is at least 8/31/2035; in contrast, the present application, filed on 12/19/2014 would have a statutory expiration date at least as late as 12/19/2034. Terminally disclaiming the present application to the expiration date of the ‘726 patent would have the potential effect (depending on patent term adjustment) of **extending** the term of the present application by over 8 months. **This result is what is backwards** about the Examiner’s analysis—the Examiner is attempting to create a situation where the present application is given more patent term than its statutory patent term by demanding it be terminally disclaimed over its continuation-in-part, the ‘726 patent. The Applicant is not aware of any situation where this result is legally permissible under statute, and certainly not under the judge-made doctrine of obviousness-type double patenting.

The Examiner’s rejection of claim 1 for obviousness-type nonstatutory double patenting is clearly erroneous, and the Applicant respectfully requests that it be reversed.

CONCLUSION

The Applicant/Appellant has demonstrated that the subject matter claimed is clearly patentable over the prior art cited by the Examiner. Therefore, the Appellant respectfully requests the Board reverse the final rejection of the Examiner and instruct the Examiner to issue a notice of allowance of all claims.

Respectfully submitted,

Date: 5/4/2020

By: /Adam Stephenson/
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Claims Appendix
(37 C.F.R. § 41.37(c)(1)(v))

1. (Previously presented) A process for transesterifying wax esters, the process comprising:
 - providing a feedstock comprising wax esters;
 - contacting the feedstock with a lipase;
 - catalytically transesterifying the wax esters in the feedstock with the lipase to form a transesterified product;
 - wherein an oxidative stability index (OSI) of the transesterified product is at least 2.5 times greater than an OSI of the feedstock.
2. (Original) The process of claim 1, wherein the transesterified product comprises no methyl esters.
3. (Previously presented) The process of claim 1, wherein the feedstock further comprises an antioxidant and catalytically transesterifying the wax esters in the feedstock with the lipase further comprises catalytically transesterifying without removing or degrading the antioxidant in the feedstock.
4. (Previously presented) The process of claim 3, wherein the feedstock further comprises a skin conditioning agent and a volatile compound and catalytically

transesterifying the wax esters in the feedstock with the lipase further comprises catalytically transesterifying without removing or degrading the skin conditioning agent and the volatile compound in the feedstock.

5. (Original) The process of claim 1, wherein the wax esters of the feedstock are jojoba wax esters.
6. (Original) The process of claim 5, wherein the jojoba wax esters further comprise hydrogenated jojoba wax esters.
7. (Original) The process of claim 6, wherein a dropping point of the transesterified product is greater than a dropping point of the feedstock and the dropping point of the transesterified product increases as a percentage of hydrogenated jojoba wax esters in the feedstock increases.
- 8-20. (Canceled).

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First Named Inventor/Applicant Name:	Jeff Addy
Customer Number:	93756
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Vantage Exhibit 1002

Page 808 of 1215

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Application Number: 14/578,075
Filing Date: 19 Dec 2014
Appellant(s): Addy et al.

[Adam R Stephenson]
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on 05/04/2020 in response to the
Final Rejection mailed on 12/04/2019.

(1) Grounds of Rejection to be Reviewed on Appeal

Every ground of rejection set forth in the Office action dated 12/04/2019 from which the appeal is taken is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

The following ground(s) of rejection are applicable to the appealed claims.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5 are rejected under 35 U.S.C. 103 as being unpatentable over **Gunawan** (Journal of Oleo Science, 2004; Of Record) **in view of Austic** (WO 2012/106701; Pub. Aug. 9, 2012; Of Record) **and as evidenced by Busson-Breysse** (JAOCS, 1994; Of Record) **and Fucosterol** (Cayman Chemical, CAS Entry, 2019; Of Record).

Gunawan teaches transesterifying palm oil using oleyl alcohol and lipase (abstract, pg. 472 col. 1, Exp. Procedures). Gunawan teaches the palm oil comprises wax esters (pg. 472 col. 1 para. 2 Exp. Procedures). Gunawan teaches adding a lipase (Lipozyme) to catalytically transesterify the oils to produce transesterified wax esters (Fig.1, Table 1). Gunawan is silent regarding the oxidative stability index (OSI) of the transesterified product being at least 2.5 times greater than the OSI of the feedstock. Gunawan teaches that wax esters can be extracted from plant materials such as jojoba oil but the process is too expensive (pg. 471 col. 2 para 1). It was also known in the art that jojoba oil can be esterified using a lipase to produce wax esters. Austic teaches that feedstocks comprising esters including jojoba oil, palm oil etc., can be esterified with an alcohol and a lipase (pg. 4 lines 25- pg. 5 lines 3, pg. 8 lines 19 – pg. 9 lines 20, Ex. 4; *Re. claim 5*). Austic teaches lipase including Lipozyme TL IM (Thermomyces lanuginosus) from Novozyme can be used in its methods (pg. 9 Enzymes). In light of these teachings, it would have been obvious to one of ordinary skill before the effective filing date of the claimed invention to use jojoba oil instead of palm oil to produce

transesterified wax esters in the methods of Gunawan and the artisan would be motivated to do so because it was known in the art that jojoba oil can also be used in transesterification processes with lipases and the artisan is substituting jojoba oil instead of palm oil in the methods of Gunawan. Gunawan also teaches it is expensive to extract wax esters from jojoba oil, so therefore it would be obvious to produce wax esters by the lipase-catalyzed synthesis method from oils as taught by Gunawan and substitute jojoba oil instead of palm oil in the methods of Gunawan.

Gunawan in view of Austic are also silent regarding the oxidative stability index (OSI) of the transesterified product being at least 2.5 times greater than the OSI of the feedstock. However, the combined teachings of Gunawan and Austic, teach a process in which jojoba oil is catalyzed by contacting with a lipase (Lipozyme TL IM), the same process taught in the instant specification (par. [0057]). Therefore it is reasonably expected that the process of Gunawan in view of Austic would also result in the OSI of the transesterified product being at 2.5 times greater than an OSI of the feedstock.

Regarding claims 3 and 4; Gunawan and Austic do not teach the feedstock to further comprise an antioxidant (claim 3), a skin conditioning agent and a volatile compound (claim 4). Jojoba oil comprises various sterols such as fucosterol (see Busson-Breysse Table 4), which is an antioxidant (see Fucosterol pg. 1 Description). The instant specification discloses that jojoba oil comprises various sterols, antioxidants (tocopherols etc.,) function as skin conditioning agents and are volatile (see par. [0050]). Gunawan in view of Austic teach using jojoba oil in their methods, and teach a process in which jojoba oil is catalyzed by contacting with a lipase (Lipozyme TL IM), the same process taught in the instant specification (par. [0057]). Therefore it is

reasonably expected that the process of Gunawan in view of Austic is teaching a method in which the feedstock (jojoba oil) comprises an antioxidant, skin conditioning agent and a volatile compound and the transesterification process would occur without removing or degrading the antioxidant, skin conditioning agent and a volatile compound.

Regarding claim 2, Gunawan teaches using oleyl alcohol and does not teach using methanol in its methods to catalyze the feedstock, therefore the transesterified product would not comprise methyl esters.

The teachings of Gunawan and Austic would render claims 1-5 obvious.

Claims 1-7 are rejected under 35 U.S.C. 103 as being unpatentable over **Gunawan** (Journal of Oleo Science, 2004; Of Record) **in view of Austic** (WO 2012/106701; Pub. Aug. 9, 2012; Of Record) **and as evidenced by Busson-Breyse** (JAOCS, 1994; Of Record) **and Fucosterol** (Cayman Chemical, CAS Entry, 2019; Of Record) **and further in view of Arquette** (US 5,968,530; Iss. Oct. 19, 1999; Applicant IDS; Of Record).

Regarding claims 6 and 7, Gunawan and Austic do not teach the jojoba oil comprises hydrogenated wax esters. Arquette teaches preparing esterified products for use in cosmetic products and teaches using jojoba oil in the esterification methods (col. 4 lines 40-65). Arquette teachings jojoba oil is also called jojoba wax esters (col. 5 lines 1-15) and teaches jojoba wax esters, hydrogenated jojoba wax esters or a mixture of the two are used in the esterification reaction to produce the emollients (lubricants) for use cosmetic compositions (col. 8 lines 1-30,49-60).

In light of these teachings, it would have been obvious to one of ordinary skill before the effective filing date of the claimed invention to use jojoba oil comprising hydrogenated jojoba esters instead of jojoba oil to produce transesterified wax esters in the methods of Gunawan in view of Austic as taught by Arquette. The artisan would be motivated to do so because it was known in the art that jojoba oil, hydrogenated jojoba oil and mixtures thereof can also be used in transesterification processes to produce emollient compositions and the artisan is substituting hydrogenated jojoba oil instead of jojoba oil in the methods of Gunawan/Austic. Gunawan, Austic and Arquette teach a method using hydrogenated jojoba oil in their methods, and teach a process in which jojoba oil is catalyzed by contacting with a lipase (Lipozyme TL IM), the same process taught in the instant specification (par. [0057]). Therefore it is reasonably expected that the process of Gunawan, Austic and Arquette would also produce a transesterified product whose dropping point is greater than the dropping point of the feedstock and the dropping point increases as a percentage of hydrogenated jojoba wax esters in the feedstock increases. Since Arquette teaches using mixtures of jojoba oil and hydrogenated jojoba oil, the percentage of hydrogenated wax esters can be varied, and the dropping point would change based on the hydrogenation since the same method steps (providing a feedstock, contacting with a lipase and catalytically transesterifying the wax esters) are taught by Gunawan, Austic and Arquette.

The teachings of Gunawan, Austic and Arquette would render claims 1-7 obvious.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112(a) (New Matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendments filed 12/06/2018 have introduced NEW MATTER into the claims.

Claim 1 which was amended in the claim amendments filed on 12/06/2018 currently recites limitations which were not disclosed in the original disclosure. Claim 1 in lines 7 and 8 recites “wherein an oxidative stability index (OSI) of the transesterified

product is **at least 2.5 times** greater than an OSI of the feedstock". Claim 1 contains new matter because of the term "at least 2.5 times".

The original claims and the specification do not support the claim language "at least 2.5 times". The specification and original claims disclose the 'oxidative stability index (OSI) of the transesterified product is greater than an OSI of the feedstock' (see original claim 1 filed 12/19/2014, see instant specification par. [0058,0065]). The data presented in Table 3 in the specification discloses an increase of 1.45 times (Feedstock composition OSI – 26.5, Product produced by Enzyme catalyst – 38.6, so $38.6/26.5$ is 1.45 times increase). The data presented in Table 6 in the specification discloses an increase of 1.45 times (Feedstock composition OSI – 26.5, Product produced by Enzyme catalyst – 36.2, so $36.2/26.5$ is 1.38 times increase). In the remarks filed on 12/06/2018, along with the claim amendments which introduced new matter "at least 2.5 times" into claim 1, applicants do not cite any support for the amendments in the specification. Applicants filed a declaration under 37 CFR 1.132 on 12/06/2018 disclosing data showing the OSI of the enzymatically catalyzed jojoba oil esters increased by an average of 3.84 times as compared to the feedstock OSI (jojoba pre-reaction) (see section 8 on pg. 3 of the declaration). However, the declaration states that "An additional 1.6% w/w input of oleyl alcohol was incorporated into the reaction during the transesterification reaction" (see section 7 on pg. 3 of the declaration). The original specification/claims do not disclose the use of 'oleyl alcohol' during the transesterification reaction anywhere and do not disclose any data in which "at least 2.5 times" increase in the OSI of the transesterified product as compared to the OSI of the

feedstock. Therefore, there is no implicit support for current claim 1 in the specification, either. Claim 1 is not supported by the original disclosure.

Instant claim 1 now recites limitations, which are not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in present claim 1, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in present claim 1 in the specification or claims as-filed, or remove these limitations from the claims in response to this Office Action.

Double Patenting (modified rationale)

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Patent 10,435,726 (previously US Application No. 14/841,242)

Claims 1, 3, 5 and 6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-6 of US 10,435,726 as evidenced by the Addy declaration filed on 12/06/2018. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claims 1-6 of the '726 patent renders obvious that of the instant claims.

Regarding instant claim 1, claim 1 of '726 patent recites a process to transesterify wax esters, the process comprising providing a feedstock comprising wax esters, contacting the feedstock with a lipase and catalytically transesterifying the wax esters in the feedstock with the lipase to form an enzymatically transesterified product. The '726 claim 1 recites an additional step of introducing into the feedstock an alcohol with a carbon number ranging from 1 to 34 carbons at a total concentration of 0.01% to 2.5% by weight. Claim 1 of the '726 patent is silent regarding the transesterified product having an OSI at least 2.5 times greater than the feedstocks OSI. However, it is noted, instant claim 1 recites a process using transitional phrase "comprising" which is inclusive or open-ended and does not exclude additional, unrecited method steps. See MPEP §2111.03. Claim 4 of the '726 patent recites the feedstock is jojoba wax esters and claim 6 of the '726 patent recites the alcohol is oleyl alcohol. Therefore, the claims

of the '726 teach a method in which a feedstock comprising jojoba wax esters is contacted with a lipase and oleyl alcohol at a total concentration of 0.01% to 2.5% by weight to produce transesterified jojoba wax esters. According to the Addy declaration filed by Appellants on 12/06/2018 (see pg. 3 sections 7 and 8), such a process would result in a transesterified product whose OSI is at least 2.5 times greater than the OSI of the feedstock. Therefore the method of claim 1, 4 and 6 of the '726 patent would inherently produce a transesterified product whose OSI is at least 2.5 times greater than the OSI of the feedstock and therefore instant claim 1 is rendered obvious.

Regarding instant claim 3, claim 3 of the '726 patent recites the feedstock further comprises an antioxidant and catalytically transesterifying the wax esters in the feedstock with the lipase further comprises catalytically transesterifying without removing or degrading the antioxidant in the feedstock.

Regarding instant claim 5, claim 4 of the '726 patent recites the feedstock comprises jojoba wax esters.

Regarding instant claim 6, claim 5 of the '726 patent recites the jojoba wax esters further comprise hydrogenated wax esters.

Therefore the instant claims 1, 3, 5 and 6 are rendered obvious over claims 1 and 3-6 of the '726 patent.

(2) Response to Argument

Appellants' arguments filed in the appeal brief submitted on 05/04/2020 with regards to the teachings of Gunawan and Austic (see brief pages 6-12), as these apply to the instantly rejected claims, respectfully, should not be found persuasive.

Appellants argue that rejection of claim 1 under 35 USC 103 over Gunawan and Austic is based on the argument that the method taught by Gunawan and Austic would inherently produce a transesterified product with an OSI that is at least 2.5 times greater than an OSI of the feedstock (pg. 7 para. 2). Appellants argue that the rejection over Gunawan and Austic relies entirely on their alleged teaching of the same method steps as those claimed in independent claim 1. Appellants argue that Gunawan and Austic actually do not include any OSI data of either of the feedstock or the reaction products and that no data in either of the cited references that the claimed result that a transesterified product with an OSI that is at least 2.5 times greater than an OSI of the feedstock would necessarily occur in the methods of Gunawan and Austic (see pg. 7 last para – pg. 8 first para). Appellants argue that the conditions taught by Gunawan and Austic in their methods are different from the methods *taught in the instant specification*. Appellants argue that Gunawan teaches using a solvent, hexane in containers in small batch reactors whereas the instant method is solventless and includes continuous flow through packed column reactors (pg. 8 last para). Appellants argue that Gunawan teaches increasing the temperature to 70°C reduces yields and is teaching away from the instant method. Appellants argue that Gunawan reports yields of 75% whereas the instant methods produce yields of 99% and that such a high yield is unexpected (pg. 9 last para – pg. 10 second para.). Appellants argue that Austic does not make up for the deficiencies of Gunawan and that its methods are also different from the instant method. Appellants argue that Austic uses large vessels for reacting gases with the feedstock while the instant method uses packed columns and liquid reactants. Appellants argue that Austic teaches performing reactions at lower

temperatures between 35-65°C, while the instant methods are performed at 70°C (pg. 10 para. 3). Appellants argue that the declaration filed on 12/6/2018 (Addy dec.) shows a side by side test between jojoba esters and *crambe oil* and shows that the resulting OSI value of the two feed stocks are different even processed under the same conditions and that changes in OSI values are unpredictable (pg. 10 last para – pg. 11 first para). Appellants argue that therefore a *prima facie* case of obviousness that the teachings of Gunawan in view of Austic teach the methods of claim 1 has not been established.

These arguments are not persuasive because, it is noted that instant claim 1 recites the following three method steps, 1) providing a feedstock comprising wax esters, 2) contacting the feedstock with a lipase and 3) catalytically transesterifying the wax esters in the feedstock with the lipase to form a transesterified product. The limitation that “the OSI of the transesterified product is at least 2.5 times greater than an OSI of the feedstock” is an intended outcome of the performed method. The examiner agrees with Appellants that Gunawan in view of Austic are silent regarding the oxidative stability index (OSI) of the transesterified product being at least 2.5 times greater than the OSI of the feedstock. However, as discussed above in the 103 rejection, Gunawan in view of Austic teach a method to transesterify wax esters from a feedstock, the process comprising the same three method steps as recited in instant claim 1. Gunawan and Austic, teach a process for transesterification in which jojoba oil (providing a feedstock) is catalyzed by contacting a lipase Lipozyme TL IM, (contacting and catalytically transesterifying), similar to the process taught in the instant specification (the same feedstock, the same lipase, see par. [0057]). Gunawan also

teaches transesterifying with oleyl alcohol, similar to the experimental conditions disclosed in the declaration filed on 12/06/2018, section 7. Therefore it is reasonably expected that the process of Gunawan in view of Austic would also result in the OSI of the transesterified product being at 2.5 times greater than an OSI of the feedstock, since they teach the same method steps as recited in instant claim 1.

It is also noted that instant claim 1 recites a process using transitional phrase “comprising” which is inclusive or open-ended and does not exclude additional, unrecited method steps. See MPEP §2111.03. Regarding the arguments that Gunawan and Austic teach different experimental conditions from the conditions disclosed in the instant specification (*using a solvent, large vessels, different temperatures*), it is noted that these limitations are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Appellants have not submitted any evidence that the specific experimental conditions disclosed in the instant specification which appellant argues are different from the teachings of Gunawan in view of Austic, are critical and would affect the OSI of the transesterified product. Again it is reiterated that Gunawan in view of Austic teach a method to transesterify wax esters from a feedstock the process comprising the same three method steps as recited in instant claim 1.

Appellants argue that Gunawan teaches that jojoba oil is expensive and teaches palm oil as an alternative and therefore one would not be motivated to use jojoba oil in the methods of Gunawan. Appellants argue that Gunawan is teaching away from the use of jojoba oil (see pg. 11 last para – pg. 12 para. 2). This argument is not persuasive

because Austic teaches that feedstocks comprising esters including jojoba oil, palm oil etc., can be esterified with an alcohol and a lipase (pg. 4 lines 25- pg. 5 lines 3, pg. 8 lines 19 – pg. 9 lines 20, Ex. 4). It would have been obvious to one of ordinary skill before the effective filing date of the claimed invention to use jojoba oil instead of palm oil to produce transesterified wax esters in the methods of Gunawan and the artisan would be motivated to do so because it was known in the art that jojoba oil can also be used in transesterification processes with lipases and the artisan is substituting jojoba oil instead of palm oil in the methods of Gunawan.

Regarding the argument that the Addy declaration shows that changes in OSI values are unpredictable because jojoba oil produces different OSI values as compared to crambe oil, it is noted that only instant claim 5 (and dependent claims 6 and 7) limit the oil to jojoba oil. Instant claims 1-4 are directed to any feedstock comprising wax esters. Further, the data in the Addy declaration shows that jojoba oil and crambe oil behave differently in that the OSI value is dependent on the type of oil being used (jojoba oil vs crambe oil). The fact that the OSI value of jojoba oil increases by at least 2.5 times after transesterification is an inherent property of the jojoba oil. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Appellants have not submitted any evidence that the experimental conditions that are disclosed in the instant specification are critical and are what causes the increase in the OSI by at least 2.5 times. Further, Austic teaches that feedstocks comprising esters including jojoba oil, palm oil etc., can be esterified with an alcohol and

a lipase (pg. 4 lines 25- pg. 5 lines 3, pg. 8 lines 19 – pg. 9 lines 20, Ex. 4). Therefore, the finding that when jojoba oil is used in a transesterification process, the OSI increases by 2.5 times does not rise to the level of unexpected results.

Appellants' arguments filed in the appeal brief submitted on 05/04/2020 with regards to the double patenting rejections over USP 10,435,726 (see pages 13-16), as these apply to the instantly rejected claims, respectfully, should not be found persuasive.

Appellants argue that the double patenting rejections are in error because the '726 patent (previously application US 14/841,242) is a continuation-in-part of the instant application (see pg. 16) and that the instant claim 1 fails to recite major elements of claim 1 of the '726 patent (pg. 14). Appellant argues that claim 1 of the '726 patent includes an additional step of "introducing into the feedstock an alcohol with a carbon number from 1 to 34 carbons, the alcohol selected from the group consisting of a straight chain alcohol, a branched chain alcohol, any combination of straight chain alcohols, any combination of branched chain alcohols and any combination thereof" and that instant claim 1 (or the instant specification) do not disclose this additional step (see pg. 14). Appellant argues that it would not be obvious to one skilled in the art to introduce an alcohol into the feedstock and that doing so causes unexpected results (see pg. 15). Appellant argues that the Examiner previously stated (at pg. 11 of the office action dated 12/04/2019) that the Applicant is doing the double patenting analysis backwards since '726 patent has already issued, and argue that the timeline of allowance does not change that '726 patent is a continuation in part (see pg. 15 last para).

These arguments are not persuasive because it is re-iterated that a rejection under nonstatutory double patenting requires that '*at least one examined claim is not patentably distinct from the reference claim because the examined application claim is either anticipated or would have been obvious over the reference claim*'. See MPEP §804 II B. Here, *the reference claim is claim 1 (and claims 3-6) of '726 patent and the examined claim is instant claim 1*. Therefore, the limitations of claim 1 (and claims 3-6) of '726 would need to anticipate and/or render obvious the limitations of instant claim 1, not the other way around as argued by appellants.

As discussed above in the double patenting rejections, it is noted instant claim 1 (examined claim 1) recites a process using transitional phrase "comprising" which is inclusive or open-ended and does not exclude additional, unrecited method steps. See MPEP §2111.03. Claim 1 of '726 patent recites a process to transesterify wax esters, the process comprising providing a feedstock comprising wax esters, contacting the feedstock with a lipase and catalytically transesterifying the wax esters in the feedstock with the lipase to form an enzymatically transesterified product. The '726 claim 1 recites an additional step of introducing into the feedstock an alcohol with a carbon number ranging from 1 to 34 carbons at a total concentration of 0.01% to 2.5% by weight. Claim 4 of the '726 patent recites the feedstock is jojoba wax esters and claim 6 of the '726 patent recites the alcohol is oleyl alcohol. Claim 1 of the '726 patent is silent regarding the transesterified product having an OSI at least 2.5 times greater than the feedstocks OSI. However, claims 1, 4 and 6 of the '726 (reference claims) recite a method in which a feedstock comprising jojoba wax esters is contacted with a lipase and oleyl alcohol at a total concentration of 0.01% to 2.5% by weight to produce transesterified jojoba wax

esters. According to the Addy declaration filed by Appellants on 12/06/2018 (see pg. 3 sections 7 and 8), such a process would result in a transesterified product whose OSI is at least 2.5 times greater than the OSI of the feedstock. Therefore the method of claim 1, 4 and 6 of the '726 patent (reference claims) would inherently produce a transesterified product whose OSI is at least 2.5 times greater than the OSI of the feedstock and therefore instant claim 1 (examined claim) is rendered obvious.

Regarding the Appellant argument that terminally disclaiming the present application to the expiration date of the '726 patent would have the potential effect of extending the term of the instant applicants and that this result is backwards (see pg. 16), the examiner does not take a position on when either the '726 patent will expire or when a patent issuing from this application will expire.

For the above reasons, it is believed that the rejections should be sustained.

This examiner's answer contains a new ground of rejection set forth in section (1) above. Accordingly, appellant must within TWO MONTHS from the date of this answer exercise one of the following two options to avoid *sua sponte* dismissal of the appeal as to the claims subject to the new ground of rejection:

(1) **Reopen prosecution.** Request that prosecution be reopened before the primary examiner by filing a reply under 37 CFR 1.111 with or without amendment, affidavit or other evidence. Any amendment, affidavit or other evidence must be relevant to the new grounds of rejection. A request that complies with 37 CFR 41.39(b)(1) will be entered and considered. Any request that prosecution be reopened will be treated as a request to withdraw the appeal.

(2) **Maintain appeal.** Request that the appeal be maintained by filing a reply brief as set forth in 37 CFR 41.41. Such a reply brief must address each new ground of rejection in an arguments section as set forth in 37 CFR 41.37(c)(1) and should be in compliance with the other requirements of 37 CFR 41.37(c). If a reply brief filed pursuant to 37 CFR 41.39(b)(2) is accompanied by any amendment, affidavit or other evidence, it shall be treated as a request that prosecution be reopened before the primary examiner under 37 CFR 41.39(b)(1).

Extensions of time under 37 CFR 1.136(a) are not applicable to the TWO MONTH time period set forth above. See 37 CFR 1.136(b) for extensions of time to reply for patent applications and 37 CFR 1.550(c) for extensions of time to reply for ex parte reexamination proceedings.

Respectfully submitted,

/Srikanth Patury/
Examiner, Art Unit 1657

A Technology Center Director or designee must personally approve the new ground(s) of rejection set forth in section (1) above by signing below:

/ROBERT B MONDESI/
Supervisory Patent Examiner, Art Unit 1652

Conferees:

/LOUISE W HUMPHREY/
Supervisory Patent Examiner, Art Unit 1657

/MANJUNATH N RAO/
Supervisory Patent Examiner, Art Unit 1656

Requirement to pay appeal forwarding fee. In order to avoid dismissal of the instant appeal in any application or ex parte reexamination proceeding, 37 CFR 41.45 requires payment of an appeal forwarding fee within the time permitted by 37 CFR 41.45(a),

unless appellant had timely paid the fee for filing a brief required by 37 CFR 41.20(b) in effect on March 18, 2013.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL **(Submitted Only via EFS-Web)**

Application Number	14578075	Filing Date	2014-12-19	Docket Number (if applicable)	FLORATECH002	Art Unit	1657
First Named Inventor	Jeff Addy			Examiner Name	Patury, Srikanth		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.

Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☒ Amendment/Reply

☒ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
 (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to
 Deposit Account No 601853

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

Signature of Registered U.S. Patent Practitioner			
Signature	Adam Stephenson/	Date (YYYY-MM-DD)	2021-01-19
Name	Adam R. Stephenson	Registration Number	58349

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

Application Number	14578075
Filing Date	2014-12-19
First Named Inventor	Jeff Addy
Art Unit	1657
Examiner Name	Patury, Srikanth
Attorney Docket Number	FLORATECH002

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	2	WO2011107977	WO		2011-09-09	Basheer et al.		

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	14578075
Filing Date	2014-12-19
First Named Inventor	Jeff Addy
Art Unit	1657
Examiner Name	Patury, Srikanth
Attorney Docket Number	FLORATECH002

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
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EXAMINER SIGNATURE

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	14578075
Filing Date	2014-12-19
First Named Inventor	Jeff Addy
Art Unit	1657
Examiner Name	Patury, Srikanth
Attorney Docket Number	FLORATECH002

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Adam Stephenson/	Date (YYYY-MM-DD)	2021-01-19
Name/Print	Adam R. Stephenson	Registration Number	58349

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

FLORATECH002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION

Applicant: Jeff Addy

Docket No: FLORATECH002

Examiner: Patury, Srikanth

Ser. No: 14578075

Filed: December 19, 2014

Group Art Unit: 1657

Conf. No.: 2053

Title: Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives

DECLARATION UNDER 37 C.F.R. 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

I, Jeff Addy, declare as follows:

1. I am a named inventor on this patent application. I have read and am familiar with the contents of this application. It is my understanding the rejections of the pending claims have been maintained because the Examiner believes claims 1-5 are obvious in view of the paper by Gunawan et al., "Lipase-Catalyzed Synthesis of Palm-Based Wax-esters," *J. Oleo Sci.*, Vol. 53, No. 10, 471-477 (2004)("Gunawan") in view of Austic et al., WO2012/106701 ("Austic"); the paper by Busson-Breysse et al, "Jojoba Wax: Its Esters and Some of Its Minor Components," *J. Acad. Org. Chem. Soc.* V. 71, No. 9, p. 999-1002 (1994) ("Busson-Breysse"); and Fucosterol (Cayman Chemical, CAS No. 17605-67-3, CAS Entry, 2019) ("Fucosterol").

2. It is also my understanding that the rejections of claims 1-7 have been maintained over Guanwan in view of Austic, Busson-Breyesse, Fucosterol, and further in view of Arquette (US. Pat. No. 5,968,530) ("Arquette").
3. As Gunawan provides no information regarding the oxidative stability index (OSI) values for any of the products made using the processes disclosed in the reference, I undertook to duplicate the process described in Gunawan for two different feedstocks. The original palm oil feedstock described in Gunawan 16 years ago was from a particular palm oil manufacturer and it did not seem practical to attempt to seek out that manufacturer to attempt to actually duplicate the results described in Gunawan. However, for the purposes of comparing the effect of the Gunawan process, sunflower oil and jojoba oil were utilized in this test.
4. A representative real-world quantitative measure of oxidative stability can be accomplished by Oxidative Stability Index (OSI). OSI evaluation determines the relative resistance of fats or oils to oxidation that can then infer shelf life, a higher OSI value (hours) indicates a longer shelf life.

Experimental Procedure:

5. Refined high oleic sunflower oil (Experiment 1) and refined jojoba oil (Experiment 2) were supplied in-house by Floratech (Chandler, AZ), oleyl alcohol (C18:1-OH) by Jarchem Industries Inc. (Newark, NJ), hexane by Sigma Aldrich (St. Louis, MO) and Lipozyme TL-IM by Novozyme (Bagsværd, Denmark). OSI, acid values, and peroxide values were determined by American Oil Chemist's Society (AOCS) Official Methods AOCS Cd 12b-92, Cd 3d-63, and Cd 8b-90. Reaction parameters, identification of reaction mixtures, and analysis of reaction mixtures were determined by methods used in Gunawan except for TLC procedures being adapted to a high-performance liquid chromatograph (HPLC) using a comparable solvent system and an electrospray light scattering detector (ELSD). Reaction inputs used a 3:1 molar ratio of oleyl alcohol to each respective oil tested per

Gunawan's referenced experiment. The percent yield was calculated by mmol net new ester/mmol input ester. Two percent by weight of reactants of Lipozyme TL-IP was used to catalyze each experiment.

6. Results:

Experiment 1	AV	PV
Sunflower Oil	0.22	1.04
Oleyl Alcohol (C18:1)	0.00	0.91
Combined Reactants	0.14	1.00
Product	0.08	1.04

Experiment 2	AV	PV
Jojoba Oil	0.17	12.8
Oleyl Alcohol (C18:1)	0.00	0.91
Combined Reactants	0.03	7.67
Product	0.34	7.56

Table 1. Acid Values and Peroxide Values of Reactants and Products

Experiment 1	mol ratio	% (w/w)	g
Sunflower Oil	1	49.30%	197.1
Oleyl Alcohol (C18:1)	3	45.10%	180.5
Hexane	x	5.60%	22.4
Total			400

Experiment 2	mol ratio	% (w/w)	g
Jojoba Oil	1	40.10%	160.4
Oleyl Alcohol (C18:1)	3	53.30%	213.2
Hexane	x	6.60%	26.5
Total			400

Table 2. Molar and Weight Input Ratios of Experiments

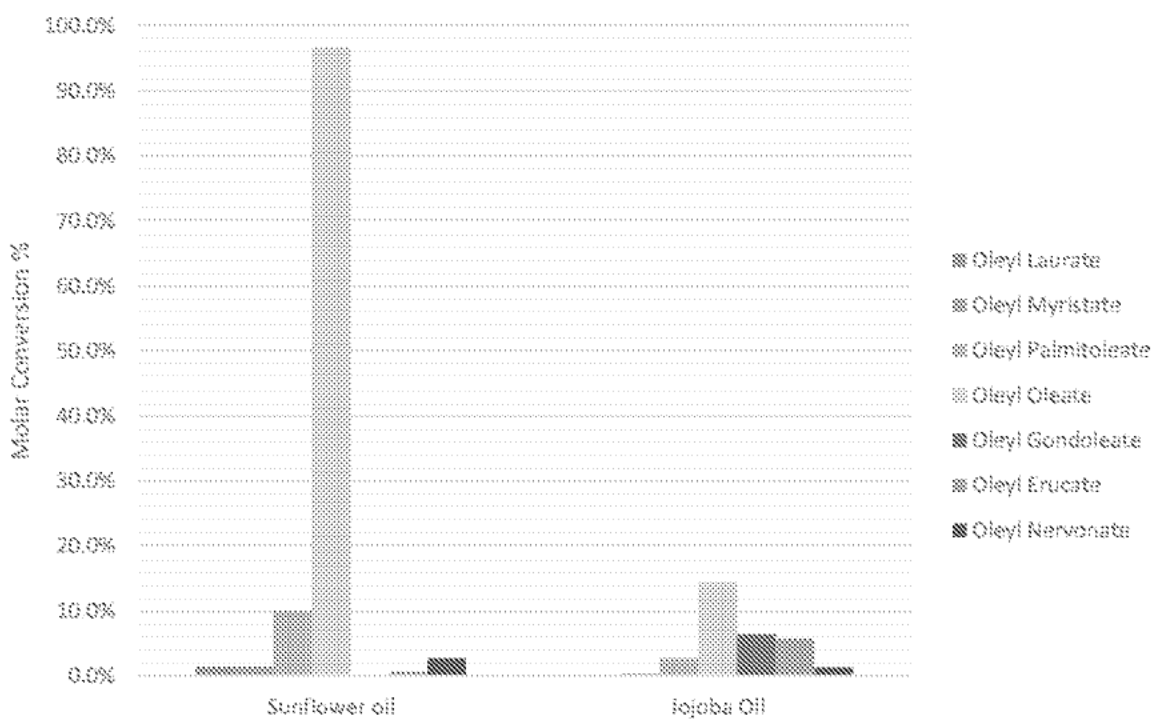


Figure 1. Sunflower Oil vs Jojoba Oil Conversion

	Experiment 1	Experiment 2
Reactants OSI (hrs)	5.8	24.0
Products OSI (hrs)	7.0	18.0
Δ %	20.7	-25.0

Table 4. Oxidative Stability Index of Experiments 1 & 2

7. The enzymatic transesterification reaction yields are shown in **Figure 1**.

Experiment 1 shows higher wax-ester yields compared to Experiment 2 because wax-esters are not present in the sunflower oil reactant prior to the reaction in contrast to the jojoba oil reactant. The transesterifications, while equally reactive in both experiments, demonstrate reaching an equilibrated wax-ester distribution for Experiment 2 with less net change in molar composition than in Experiment 1. In Experiment 2, the conversion of a jojoba oil, a wax-ester, via enzymatic transesterification to an oleyl wax-ester generated a product using the method of Guanawan that demonstrated decreased oxidative stability relative to the starting

jojoba oil reactant as shown in **Table 4**. Inversely, the conversion of sunflower oil triglycerides to oleyl wax-esters showed an increase of oxidative stability.

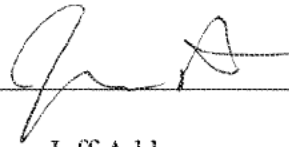
8. **Analysis.** The experimental results demonstrate that using the method of Guawan can result in products with a quantitatively significant decrease in OSI over the OSI of the feedstock. The marked quantitative and percentage increase for sunflower oil reflects that taking a product like sunflower oil, which lacks wax esters entirely, and then producing a transesterified wax ester product from that oil does predictably indicate an increase in OSI in the products versus the OSI of the reactants. However, the surprising result that the method of Gunawan fails entirely to improve the OSI of a wax ester product when a feedstock already including wax esters is utilized was not expected. Because of this, producing an increased OSI effect using the method of Gunawan appears to be feedstock specific and depend at least on whether the feedstock contains wax esters in it or not. Enzymatic transesterification adapted from Gunawan used to process a wax ester to a new wax ester does not enhance the oxidative stability of the new wax ester product.
9. Contrary to what the Examiner has asserted in the Examiner's Answer dated 11/19/2020, the observed failure of the method of Gunawan to produce a product with a higher OSI when jojoba oil was used as the feedstock demonstrates that, in my opinion, it would be impossible for a person of ordinary skill reading Gunawan to have had any ability to predict this effect. This is particularly so in view of the contrasting results on OSI when sunflower oil was used with the method of Gunawan. These unexpected results could only be determined and observed by actually carrying out the extensive and time-consuming experimentation I have detailed in this affidavit.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FURTHER AFFIANT SAYETH NOT.

19 JAN 21

Date



Jeff Addy

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 September 2011 (09.09.2011)



(10) International Publication Number
WO 2011/107977 A1

(51) International Patent Classification:
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2 February 2011 (02.02.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/309,122 1 March 2010 (01.03.2010) US

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(54) Title: A PROCESS FOR THE ENZYMATIC SYNTHESIS OF FATTY ACID ALKYL ESTERS

(57) Abstract: Disclosed are an enzymatic batchwise or continuous process for the production of fatty acid alkyl esters for use in the biofuels, food and detergent industries and a system therefor. The process utilizes enzymes immobilized on a hydrophobic resin mixed with a fatty acid source and an alcohol or alcohol donor in the presence of an alkaline or mild alkaline aqueous buffer, or in the presence of water solution. The production process for fatty acid alkyl esters is carried out by transesterification or esterification simultaneously or sequentially. The biocatalyst activity is maintained with no significant activity losses in multiple uses and also avoids the accumulation of glycerol and water by-products or other hydrophilic compounds on the biocatalyst.

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Page 844 of 1215
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A PROCESS FOR THE ENZYMATIC SYNTHESIS OF FATTY ACID ALKYL ESTERS

Field of the Invention

Disclosed is an enzymatic process for the production of fatty acid alkyl esters for use in the biofuels, food and detergent industries. In this process a fatty acid source and an alcohol or alcohol donor are reacted in the presence of enzymes immobilized on a hydrophobic resin, in the presence of an alkaline aqueous buffer or water. The disclosed process can be operated either batchwise or continuously using a continuous stirred-tank or packed-bed column reactors.

Background of the Invention

Immobilization of enzymes has been described by a vast number of techniques basically aiming at reducing the cost contribution of enzymes in the overall enzymatic process; facilitating recovery of enzymes from the products; and enabling continuous operation of the process.

Immobilization techniques are in general divided according to the following:

1. Physical adsorption of enzymes to solid supports, such as silica and insoluble polymers.
2. Adsorption on ion-exchange resins.
3. Covalent binding of enzymes to a solid support material, such as epoxidated inorganic or polymeric supports.
4. Entrapment of enzymes in a growing polymer.
5. Confinement of enzymes in a membrane reactor or in semi-permeable gels.
6. Cross-linking enzyme crystals (CLECS's) or aggregates (CLEAS's).

All the aforementioned enzyme immobilization procedures are comprised of the following steps:

1. Dissolving the enzyme in an appropriate buffer system with respect to pH, temperature, type of buffer salts and ionic strength.
2. Adding the solid support into the enzyme solution and mixing for some time till enzyme molecules are immobilized on the solid support.
3. Filtering off the solid support which contains the immobilized enzyme.
4. Washing the support with an appropriate buffer to remove loosely bound enzyme molecules and then drying the solid support.

Interfacial enzymes, mostly lipases, have been immobilized following the aforementioned techniques. These offered immobilized enzyme preparations possessing low synthetic activity and/or short operational half-life time. In an attempt to increase the synthetic activity and stability of immobilized lipases and other interfacial enzymes different activation methods have been applied. These methods include:

1. Binding the surface functional groups of enzymes with hydrophobic residues such as fatty acids or polyethylene glycol.
2. Coating the surface of enzymes with surfactants, such as polyol fatty acid esters.
3. Contacting enzymes with hydrophobic supports, typically polypropylene, which have been pretreated with hydrophilic solvents, such as ethanol or iso-propanol.

None of the above mentioned methods yielded satisfactory results with respect to stabilization and cost-effectiveness of immobilized interfacial enzymes, in order to carry out enzymatic reverse conversions at industrial quantities. Also, it has been reported that most enzymes, when immobilized according to the aforementioned procedures, either lose a significant portion of their synthetic activity or they do not exhibit their full activity

performance due to certain constraints imposed by the immobilization procedure, or because of the presence of certain enzyme inhibitors in the reaction medium.

Another major drawback of lipases and phospholipases is their low tolerance towards hydrophilic substrates, in particular short-chain alcohols and short-chain fatty acids (below C4). It has been observed in many research studies that short-chain alcohols and short-chain fatty acids, such as methanol and acetic acid, respectively, are responsible for detaching essential water molecules from the quaternary structure of those enzymes, leading to their denaturation and consequently loss of their catalytic activity. This drawback has prohibited the application of lipases for production of commercial quantities of fatty acids methyl esters "biodiesel" using oil triglycerides and methanol as substrates.

An additional drawback of using immobilized lipases for transesterification/esterification of a fatty acid source with a free alcohol is the accumulation of the formed glycerol and water by-products on the biocatalyst and therefore prohibiting the substrates from free access to the active site of the immobilized enzyme. Such biocatalysts generally lose their catalytic performance after a few cycles when the same batch of biocatalyst is used.

The present inventors have developed special immobilized enzyme preparations, exhibiting good stability over many production cycles, persisting activity. Examples of such enzyme preparations are disclosed, *inter alia*, in WO/2008/084470, WO/2008/139455 and WO2009/069116.

Conditions under which the catalytic reaction is carried out, may adversely affect the stability and efficiency of immobilized enzyme preparations. It is

important to have enzyme preparations which retain stability and activity under the reaction conditions.

These and other objects of the invention will become apparent as the description proceeds.

Summary of the Invention

In one embodiment, the invention relates to a process for the transesterification/esterification of a fatty acid source with an alcohol, to form fatty acid alkyl esters, comprising reacting a fatty acid source and an alcohol or an alcohol donor in the presence of an immobilized lipase preparation, wherein the immobilized lipase preparation comprises at least one lipase immobilized on a hydrophobic porous support and the reaction medium contains an aqueous alkaline buffer solution.

The said aqueous alkaline buffer solution may be a mild aqueous alkaline buffer solution. The said aqueous alkaline buffer solution may be contained in the reaction mixture at a quantity of up to 5% wt. of the fatty acid source. The aqueous buffer solution may have a pH from 7 to about 11, for example any one of 7-8.5, 7-9, 7-9.5, 7-10 and 7-11. The pKa of the supplemented mild alkaline reagent comprising of the buffer solution is higher or equal than the pKa of acids comprising the fatty acid source.

In another embodiment the invention relates to a process for the transesterification/esterification of a fatty acid source with an alcohol, to form fatty acid alkyl esters, comprising reacting a fatty acid source and an alcohol in the presence of an immobilized lipase preparation, wherein the immobilized lipase preparation comprises at least one lipase immobilized on a hydrophobic porous support and the reaction medium contains water. The water is in the form of a water solution with a pH of from 3 to 11. The

reaction medium may contain the water or water solution at to 5% wt. of the fatty acid source.

In all embodiments and aspects of the invention, the alcohol may be a short-chain alcohol, for example C₁-C₆ alkyl alcohol, more specifically C₁-C₄ alkyl alcohol, particularly methanol or ethanol. Where said alcohol is methanol said resulting fatty acid esters are fatty acid methyl esters (FAME – Biodiesel). The alcohol may also be a medium-chain fatty alcohol (C₆-C₁₀) or long-chain fatty alcohols (C₁₂-C₂₂). The alcohol donor may be a mono-alkyl ester or a di-alkyl carbonate, such as di-methyl carbonate or diethyl carbonate.

In all embodiments and aspects of the invention, said immobilized lipase is capable of catalyzing the esterification of free fatty acids to yield fatty acid alkyl esters and water as by-product, and the transesterification of triglycerides and partial glycerides to yield fatty acid alkyl esters and glycerol as by-product.

In all embodiments and aspects of the invention related to the use of an alkaline buffer or alkaline solution, the amount of said alkaline buffer or solution in the reaction medium is from 0.001 to 5% wt. of the fatty acid source.

In all embodiments and aspects of the invention, said at least one lipase may be a lipase derived from any one *Rhizomucor miehei*, *Pseudomonas sp.*, *Rhizopus niveus*, *Mucor javanicus*, *Rhizopus oryzae*, *Aspergillus niger*, *Penicillium camembertii*, *Alcaligenes sp.*, *Acromobacter sp.*, *Burkholderia sp.*, *Thermomyces lanuginosa*, *Chromobacterium viscosum*, *Candida antarctica B*, *Candida rugosa*, *Candida antarctica A*, papaya seeds and pancreatin. The lipase preparation may comprise at least two lipases which may be each

separately immobilized on a hydrophobic support or co-immobilized on the same hydrophobic support. The said lipases may possess identical or different regio-specificity. The said lipases are capable of simultaneously or consecutively catalyzing the esterification of free fatty acids to yield fatty acid alkyl esters and water as by-product, and the transesterification of triglycerides and partial glycerides to yield fatty acid alkyl esters and glycerol as by-product.

In all embodiments and aspects of the invention, said support may be any one of hydrophobic aliphatic polymer-based support and hydrophobic aromatic polymer-based support. The said hydrophobic polymer support may be comprised of linear or branched organic chains. The said support may comprise macroreticular organic polymer or co-polymer chains. The said support may be porous or non-porous inorganic support, which may be hydrophobic or is coated with hydrophobic organic material. The said organic material may be a linear, branched, or functionalized hydrophobic organic chain.

In all embodiments and aspects of the invention where an alkaline buffer solution is used, said aqueous alkaline buffer solution may be a solution of an inorganic alkaline salt or an organic base. The said alkaline buffer solution may be a solution of any one of an alkaline metal hydroxide, carbonate, bicarbonate, phosphate, sulfate, acetate and citrate, a primary, secondary and tertiary amine, and any mixture thereof. In specific embodiments, the said alkaline buffer solution may be a solution of a weak base selected from sodium or potassium bicarbonates and carbonates. In some specific embodiments of the process of the invention, the said alkaline buffer solution may be added to said fatty acid source in a pre-mixing stage or directly to the reaction medium.

In all embodiments and aspects of the invention where an alkaline buffer solution is used, the content of said alkaline buffer solution in the transesterification/esterification reaction medium may be in the range of 0.001-5% wt. of the oil feedstock., for example 1-2% wt. of the oil feedstock.

In some embodiments of the invention, the fatty acid source may be first mixed with the alkaline buffer solution or with the water or water solution, and the mixture may be then treated with said immobilized lipase preparation, followed by adding said alcohol and allowing the reaction to proceed under suitable conditions until said fatty acid source is converted to fatty acid esters.

In all embodiments and aspects of the invention said fatty acid source may be any one of plant oil, animal fat, algal oil, fish oil, waste oil and any mixtures thereof. The said fatty acid source may comprise free fatty acids, mono-, di- or tri-glycerides, their mixtures at any ratio, in the absence or presence of other minor fatty acid derivatives such as phospholipids and sterol esters. The fatty acid source may be unrefined, refined, bleached, deodorized or any of their combinations.

In all embodiments and aspects of the invention, the reaction may be carried out at a temperature between 10°C and 100°C, specifically between 25-30°C.

In all embodiments and aspects of the invention, the said fatty acid source may be pre-mixed with said alcohol or alcohol donor and with said water or buffer solution in a pre-reaction preparation vessel to form an emulsion which may then be fed together with said immobilized lipase preparation into a transesterification/esterification reaction vessel.

In all embodiments and aspects of the invention, said immobilized lipase may be used in packed-bed column reactors operating in batch or continuous modes.

According to another aspect of the invention there is provided a system for the transesterification/esterification of a fatty acid with an alcohol, to form fatty acid alkyl esters, comprising:

a reaction vessel configured for reacting a reaction medium including a fatty acid and at least one of an alcohol and an alcohol donor in the presence of an immobilized lipase preparation, wherein the immobilized lipase preparation comprises at least one lipase immobilized on a hydrophobic porous support and the reaction medium contains at least one of an aqueous alkaline buffer solution and water.

The system may comprise one or more of the following features, in any desired combination or permutation:

- A. The reaction vessel can comprise the immobilized lipase preparation, at least during operation of said system for the production of said fatty acid alkyl esters.
- B. Additionally or alternatively to feature A, the reaction vessel can comprise the fatty acid and the at least one of an alcohol and an alcohol donor, at least during operation of said system for the production of said fatty acid alkyl esters.
- C. Additionally or alternatively to features A or B, said reaction medium comprises a mixture, said system further comprising a pre-reaction vessel in selective fluid communication with said reaction vessel, said pre-reaction vessel being configured for premixing at least the fatty acid and the at least one of an alcohol and an alcohol donor to form said mixture, and for selectively delivering said mixture to said reaction vessel at least during operation of said system for the production of said fatty acid alkyl esters. The

system can optionally further comprise a fatty acid source in selective fluid communication with said pre-reaction vessel and configured for selectively delivering the fatty acid to said pre-reaction vessel at least during said operation of said system, and an alcohol source in selective fluid communication with said pre-reaction vessel and configured for selectively delivering the at least one of an alcohol and an alcohol donor to said pre-reaction vessel at least during said operation of said system. The system can optionally further comprise a buffer source in selective fluid communication with said pre-reaction vessel and configured for selectively delivering the at least one of an aqueous alkaline buffer solution and water to said pre-reaction vessel to be included in said mixture at least during said operation of said system.

D. Additionally or alternatively to features A to C, the system can be configured for selectively delivering one or more of the fatty acid and/or the at least one of an alcohol and an alcohol donor and/or the at least one of an aqueous alkaline buffer solution and water to said pre-reaction vessel each in either a continuous manner or in discrete batches, at least during said operation of said system.

E. Additionally or alternatively to features A to D, the pre-reaction vessel can be configured for selectively delivering said mixture to said reaction vessel in a continuous manner and/or in discrete batches at least during said operation of said system.

F. Additionally or alternatively to features A to E, the system can be configured for selectively and directly delivering to said reaction vessel at least one of the fatty acid; the at least one of an alcohol and an alcohol donor; and the at least one of an aqueous alkaline buffer solution and water.

G. Additionally or alternatively to features A to F, the reaction vessel can comprise a thermal regulation system configured for maintain the reaction medium in said reaction vessel within a selected temperature range.

H. Additionally or alternatively to features A to G, the system can optionally further comprise a retaining arrangement configured for retaining the immobilized lipase preparation within said reaction vessel at least during operation of said system.

I. Additionally or alternatively to features A to H, the system further comprises a product separation vessel in selective fluid communication with said reaction vessel, said system being configured for selectively delivering a reaction mixture including reaction products from said reaction vessel to said product separation vessel, and wherein said product separation vessel is configured for selectively separating a yield of the fatty acid alkyl esters from the reaction mixture delivered thereto. For example, the product separation vessel can be one of a centrifuge and gravity separation system.

J. Additionally or alternatively to features A to I, the reaction vessel is configured for selectively delivering said reaction mixture to said product separation vessel in a continuous manner and/or in discrete batches at least during said operation of said system.

K. Additionally or alternatively to features I to J, the system is configured for selectively delivering said yield of fatty acid alkyl esters from said product separation vessel. For example, the system is configured for selectively delivering said yield of fatty acid alkyl esters from said product separation vessel in a continuous manner and/or in discrete batches.

L. Additionally or alternatively to features A to K, the system is configured for increasing said yield of the fatty acid alkyl esters from the reaction mixture delivered to said product separation vessel. In one configuration of the system having this feature, the system is configured for selectively rerouting said yield of the fatty acid alkyl esters to said reaction vessel to further increase said yield of the fatty acid alkyl esters from the reaction mixture subsequently delivered to said product separation vessel. In another configuration of the system having this feature, the system is configured for selectively rerouting said yield of the fatty acid alkyl esters to

an auxiliary reactor module, wherein said auxiliary reactor module comprises an auxiliary reactor vessel and an auxiliary product separation vessel, wherein said further increased yield of the fatty acid alkyl esters is selectively subsequently delivered via said auxiliary product separation vessel.

Brief Description of the Figures

In order to understand the invention and to see how it may be carried out in practice, embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Figure 1: The transesterification activity of lipase *Thermomyces lanuginosa* (TL) immobilized on Amberlite XAD 1600 (Amb. XAD 1600) as a hydrophobic resin and on Duolite D568 (Duo D568) as a hydrophilic resin, and lipase *Pseudomonas sp.* (PS) immobilized on Sepabeads SP70 (SB SP70) as a hydrophobic resin and on porous silica (Sil.) as a hydrophilic resin.

Abbreviations: Conv. – conversion; Cyc. - Cycle

Figure 2: The conversion of soybean oil to biodiesel and glycerol after 6 hours of reaction at different levels of sodium bicarbonate solution of 0.1M using the same batch of biocatalyst in multiple batch experiments. Biocatalyst was lipase derived from *Thermomyces lanuginosa* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin.

Abbreviations: Conv. – conversion; Cyc. - cycle

Figure 3: The conversion of soybean oil to biodiesel and glycerol after 6 hours of reaction at different levels of sodium bicarbonate solution of 0.1M using the same batch of biocatalyst in multiple batch experiments.

Biocatalyst was lipase derived from *Pseudomonas sp.* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin.

Abbreviations: Conv. – conversion; Cyc. - cycle

Figure 4: The conversion of soybean oil to biodiesel and glycerol after 6 hours of reaction without water and at different levels of water using the same batch of biocatalyst in multiple batch experiments. Biocatalist was lipase derived from *Thermomyces lanuginosa* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin.

Abbreviations: Conv. – conversion; Cyc. – cycle; DW – distilled water

Figure 5: The conversion of soybean oil to biodiesel and glycerol after 6 hours of reaction at different levels of water using the same batch of biocatalyst in multiple batch experiments. Biocatalyst was lipase derived from *Pseudomonas sp.* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin.

Abbreviations: Conv. – conversion; Cyc. – cycle; DW – distilled water

Figure 6: The conversion of a mixture of FFA's and soybean oil to biodiesel, and glycerol and water by-products after 4 hours of esterification/transesterification at different levels of sodium bicarbonate solution of 0.1M using the same batch of biocatalyst in multiple batch experiments. Biocatalyst was lipase derived from *Pseudomonas sp.* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin.

Abbreviations: Conv. – conversion; Cyc. – cycle; DW – distilled water

Figure 7: The esterification of soybean oil hydrolysate to biodiesel and water after 4 hours of reaction in the presence of 2% sodium bicarbonate solution of 0.1M using the same batch of biocatalyst in multiple batch experiments. Biocatalyst was lipase derived from *Pseudomonas sp.* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin.

Abbreviations: Ac. Val. – acid value; Cyc. – cycle

Figure 8: The transesterification of fish oil with ethanol after 6 hours of reaction in the presence of 1% wt. of sodium bicarbonate solution of 0.1M using the same batch of biocatalyst in multiple batch experiments. The biocatalysts were lipases derived from *Thermomyces lanuginosa* (TL Lip.) and *Pseudomonas sp.* (PS Lip.) immobilized on Amberlite XAD 1600.

Abbreviations: Conv. – conversion; Cyc. – cycle

Figure 9: The transesterification of Tallow fat with ethanol after 6 hours of reaction in the presence of 2% wt. of sodium bicarbonate solution of 0.1M using the same batch of biocatalyst in multiple batch experiments. The biocatalysts were *Thermomyces lanuginosa*, *Pseudomonas sp.* lipases (PS Lip.; TL Lip.) immobilized on Amberlite XAD 1600.

Abbreviations: Conv. – conversion; Cyc. – cycle

Figure 10: The treatment of the transesterification/esterification reaction medium obtained after 4 hours containing FFA value of 7 mg KOH/1g using *Pseudomonas sp.* or *Thermomyces lanuginosa* immobilized on hydrophobic porous resins with *Candida Antarctica* immobilized on a hydrophobic porous resin.

Abbreviations: Ac. Val. – acid value; Cyc. – cycle

Fig. 11: illustrates schematically a first embodiment of a system for the production of fatty acid alkyl esters according to an aspect of the invention.

Fig. 12 illustrates schematically a second embodiment of a system for the production of fatty acid alkyl esters according to an aspect of the invention.

Detailed Description of the Invention

In search for improvement of enzymatically catalyzed industrial processes, particularly processes for transesterification/esterification of a fatty acid source with an alcohol in the presence of immobilized lipase/s, the present

inventors has developed specific conditions under which the stability of the immobilized lipase/s is preserved over scores of production cycles.

In an embodiment of the invention, the invention relates to a process for the preparation of alkyl esters of fatty acids, specifically short-chain alkyl esters of fatty acids, such as fatty acid methyl and ethyl esters (biodiesel) in a solvent-free alkaline microaqueous system. In specific embodiments, the alkaline microaqueous system is a mild alkaline microaqueous system. The process comprises providing a fatty acid source and reacting it with a free alcohol or an alcohol donor, in the presence of an immobilized lipase preparation, under said alkaline or mild alkaline conditions. Without being bound by theory, pretreatment of the fatty acid source with an alkaline buffer solution would result in neutralizing acids that might have an inhibitory effect on the enzyme. The quantity of alcohol required to complete the reaction up to 100% conversion may be added stepwise or in a one batch. Further, the alcohol may be short-chain alcohol, for example methanol or ethanol. Other alcohol donors may be used in the reaction with the fatty acid source in the presence of a hydrolase and allowing the reaction to proceed under suitable conditions, until said fatty acid source is converted to fatty acid alkyl esters, specifically, fatty acid methyl esters (FAME) or fatty acid ethyl esters, wherein said hydrolase preparation comprises one or more lipases, separately or jointly immobilized on a suitable macroreticular porous hydrophobic polymer-based support.

In an additional embodiment, the transesterification/esterification reaction between the fatty acid source and the alcohol or alcohol donor is carried out in an aqueous microenvironment, with the addition of water to the reaction mixture. In specific embodiments, water may be added at 0.0001 to 5% wt. of the fatty acid source. By water as used here is meant pure or distilled water, and also "water solutions", which may be, but are not limited to, tap water,

sea water or water from any other natural water resource or reservoir, desalinated water, chemically or enzymatically purified or treated water, and any other aqueous solutions. The pH of the reaction system or of the water solution may vary, and may be, for example, about 3-11, for example 4-10, 5-10, 5-9, 6-10, 6-9, or 7-9.

The process of the invention may be carried out while continuously removing the formed glycerol and any excess water from the reaction mixture. The conversion of the fatty acid acyl groups or free fatty acids comprised in said fatty acid source to fatty acid alkyl, specifically methyl esters may be monitored at various time points during the reaction. The reaction medium may be removed by suitable means at any desired time point during the reaction, thereby stopping the reaction, and the formed fatty acid methyl esters and optionally the formed glycerol are isolated from the reaction medium. The reaction may be specifically stopped when the conversion of the fatty acid acyl groups or free fatty acids comprised in said fatty acid source to fatty acid methyl esters has reached at least 70%, for example at least 85%, or at least 90%.

The reaction system may be similar to that described in co-pending WO2009/069116. For example, the production system may use a stirred tank reactor with a bottom sintered glass or stainless steel filter which retains the biocatalyst in the reactor, however allows the reaction medium to permeate through out of the reactor. Such reactor configuration allows by-products, specifically glycerol and water, which are self-desorbed from the immobilized enzyme, to sink to the bottom of the reactor, and permeate out through the filter. The result is continuous removal of the desorbed formed glycerol and also of excess water, out of the reaction medium, leading to shift of the reaction towards synthesis, thereby reaching conversions above 98%. The biocatalyst used in this reactor may be comprised of a single or multi-types of

lipases, in consideration of their positional specificity as well as their origin, as described herein. Alternative, two consecutive stirred tank reactors with a bottom filter may be used. A settling tank or centrifuge may be used between the two reactors. The first reactor may contain an immobilized biocatalyst comprised of a single or multi-types of lipases. The role of the settling tank or centrifuge between both reactors is to remove the formed glycerol and excess water from the reaction medium, leading to an increase in the conversion of the raw materials to their corresponding fatty acid alkyl esters to above 98% in the second reactor at reasonable reaction time. Some specific reaction systems and methods are described below.

The terms "reaction mixture", "reaction system" and "reaction medium" may be used herein synonymously.

The use of lipases immobilized on hydrophobic resins in the presence of alkaline buffer solution or water, as in embodiments of the process of the invention, ensures high stability of the enzyme and also avoidance of the accumulation of hydrophilic substances, such as water and the formed glycerol by-product, on the biocatalyst. In specific embodiments of the process of the invention uses 0.001-5% alkaline or mild alkaline buffer solution, for example 0.01-5%, 0.05-5%, 0.1-5%, 0.5-5%, such as 0.001%, 0.01%, 0.05%, 0.1%, 0.5%, 0.75%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5% or 5%. In specific embodiments of the process of the invention where water is used, the water is used at levels of 0.0001-5% water, for example 0.001-5%, 0.01-5%, 0.05-5%, 0.1-5%, 0.5-5%, such as 0.0001%, 0.001%, 0.01%, 0.05%, 0.1%, 0.5%, 0.75%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5% or 5%. As mentioned, when alkaline solution is used, it may neutralize acids typically present in the fatty acid source or produce due to side reactions. Continuous active removal of these by-products may even increase the efficiency of the process. The isolated glycerol may be industrially used.

The fatty acid source used in the process of the invention may comprise at least one of soybean oil, canola oil, algae oil, rapeseed oil, olive oil, castor oil, palm oil, sunflower oil, peanut oil, cotton seed oil, *Jatropha* oil, crude corn oil, fish oil, animal-derived fat, waste cooking oil, brown grease, oil triglycerides derived from inedible plant sources, partial glycerides and free fatty acids derived from those oils or any mixture of at least two thereof, at any desired ratio.

In all processes of the invention, the fatty acid short-chain alkyl esters formed by the reaction are specifically fatty acid methyl, ethyl, *iso*-propyl or butyl esters (biodiesel). Other medium-chain fatty alcohols (C_6 - C_{10}) and long-chain fatty alcohols (C_{12} - C_{22}) might also be used in the process of production of this invention. These longer alcohols may be specifically suitable in the production of waxes, for example for cosmetic products.

The lipases may be lipases derived from *Thermomyces lanuginose*, *Rhizomucor miehei*, *Mucor miehei*, *Pseudomonas sp.*, *Rhizopus sp.*, *Mucor javanicus*, *Penicillium roqueforti*, *Aspergillus niger*, *Chromobacterium viscosum*, *Acromobacter sp.*, *Burkholderia sp.*, *Candida antarctica A*, *Candida antarctica B*, *Candida rugosa*, *Alcaligenes sp.*, *Penicillium camembertii*, papaya seeds and pancreatin, but are not limited thereto.

The lipases may be jointly immobilized on a suitable support, specifically a hydrophobic aliphatic polymer-based support or a hydrophobic aromatic polymeric support. Each of said lipases may be immobilized on a suitable support, wherein the supports on which the said lipases are immobilized are identical or different. Lipases employed may be *regio*-specific to their substrate, or random. When more than one lipase is used, the lipases may be immobilized on the same or on different hydrophobic supports. Lipases co-

immobilized on the same support can exhibit identical or different substrate selectivities or *regio*-specificities to their substrates.

Lipases may be regio-specific (or site-specific), each used alone or in combination with lipases of same or different site specificity. When referring to positions sn-1, sn-2 or sn-3, these are positions on the glycerol backbone of the various glycerides. Thus, the lipases used in the process of the invention may possess selectivity towards sn-2 position higher than that of random lipases, i.e. their favour catalyzing the reaction between the alcohol or alcohol donor with the fatty acyl group of the sn-2 position, while random lipases exhibit the same transesterification activity for fatty acyl groups at all three positions on the glycerol backbone. Some lipases uniquely exhibit positional activity on sn-2 position, especially under specific conditions determined by the substrates, products, etc. Other lipases used in the process of the invention are sn-1,3 positional specific. They may be used alone or together with a random lipase, specifically lipase that has affinity to partial glycerides, and optionally a third lipase with a high affinity to the sn-2 position.

The support is specifically a porous and macroreticular hydrophobic support, which may be organic or inorganic. Examples of supports are porous inorganic supports, such as, but not limited hydrophobized silica- or and alumina-based supports, and hydrophobic organic supports such as, but not limited to polymeric or polymer-based support. The supports may optionally contain active functional groups selected from epoxy or and aldehyde groups, or ionic groups.

The insoluble support used in the processes of the invention is specifically a porous and reticular hydrophobic aliphatic or aromatic polymer-based support, such as Amberlite[®] XAD 1600 and Sepabeads[®] SP70 both comprised

of porous microreticular resin prepared from divinylbenzene or from a mixture of divinylbenzene and polystyrene, Amberlite^R XAD 7HP comprised of microreticular aliphatic acrylic polymer, and porous aliphatic polymer such as porous polypropylene (Accurel^R).

The support may be a reticular hydrophobic polymer comprised of divinylbenzene, or a mixture of divinylbenzene and styrene, and reticular hydrophobic aliphatic polymer comprised of aliphatic acrylic polymers or polyalkene, such as polypropylene. Specific supports are porous matrices, of pore size in the range of 25-1000 Å, and more specifically in the range of 80-200 Å. The support also may be powderous or granular porous hydrophobic silica or other inorganic oxides. The support also may be powderous or granular porous hydrophobicized silica or other inorganic oxides. In specific embodiments, the surface area of the support resins is higher than 100m²/g.

The amount of the alkaline or mild alkaline aqueous solution to be supplemented into the lipase catalyzed transesterification/ esterification reaction between the fatty acid source and the alcohol is generally below 5%wt. of the reaction medium. This alkaline solution is prepared, for example, from an inorganic alkaline base or salt or from an organic base. Inorganic bases and salts are, for example, alkaline metal hydroxides, carbonates, bicarbonates, phosphates, sulfates, acetates and citrates. Organic bases can be, for example, primary, secondary or tertiary amines. Mixtures of these alkaline agents are also contemplated. In the process according to the invention, the pH of the microenvironment of the immobilized enzyme is maintained at alkaline or mild alkaline values. While the addition of distilled water to the reaction system improves the performance of lipases immobilized on hydrophobic support (resins), as illustrated in Figures 4 and 5, the addition of various alkaline buffer, with different pH values depending on the type of base used, resulted in further stabilization of lipases

immobilized on hydrophobic supports (resins), as shown, for example, in Figures 2 and 3. Carbonate and bicarbonate buffers are examples of mild bases that are efficient in increasing the stability of lipases immobilized on hydrophobic supports. Other suitable bases are described herein. Generally the pKa of the supplemented alkaline or mild alkaline reagent comprising of the buffer solution is equal or higher than the pKa of acids comprising the fatty acid source. Mild alkaline solution as used herein is generally a solution with a pH of from 7 to about 11, for example, 7-8.5, 7-9, 7-9.5, 7-10 or 7-11. Generally, the amount of alkaline or mild alkaline aqueous solution used is expressed by weight percents (wt.%) on basis of the amount of oil used in the reaction.

The use of lipases immobilized on porous hydrophobic polymer-based supports (resins) in the presence of an alkaline or mild alkaline solution, for example in an amount of 0.01-5% wt., 0.05-5% wt., 0.05-4% wt., 1-5% wt., or 1-4% wt., results in stabilizing the activity of the biocatalysts in the transesterification/ esterification reactions between the fatty acid source and the alcohol. This is shown in the following Examples.

The fatty acid source is at least one of triglycerides, partial glycerides, free fatty acids, phospholipids, esters and amides of fatty acids or a mixture comprised of at least two said sources.

The production of fatty acid alkyl esters is carried out by transesterification or esterification, simultaneously or sequentially. Under such reaction system the biocatalyst activity is maintained with no significant activity losses in multiple uses and also avoids the accumulation of glycerol and water by-products or other hydrophilic compounds on the biocatalyst.

This invention provides processes employing specific immobilized interfacial enzymes that retain high activity and stability over many production cycles. Specifically, lipases and phospholipases preparation are used, in transesterification/esterification reactions. These reactions may be employed in the production of food articles, cosmetics and biofuels ("biodiesel"). Of particular interest, these enzymes may be used for the synthesis of fatty acids short-chain alkyl esters for use as "biodiesel".

The present invention employed stable immobilized interfacial enzymes, of high tolerance towards short-chain alcohols, such as methanol, ethanol and glycerol, as well as short-chain fatty acids, such as acetic acid. The use of these enzyme preparations also prevents accumulation on the immobilized biocatalyst of hydrophilic substances, in particularly glycerol and water.

In an embodiment of the invention there is provided a process for simultaneous or sequential transesterification/esterification reactions of a fatty acid source with an alcohol using one or more types of lipases, immobilized on a hydrophobic support (resin), in the presence of an alkaline or mild alkaline aqueous solution, for obtaining the desired product, namely, fatty acid alkyl esters, at near to complete conversions during reasonable reaction time, typically below 5 hours. A mild alkaline solution, for example a 0.001M, 0.1M, 0.5M or 1M solution of sodium bicarbonate, may be present in the reaction system in an amount of below about 5% wt. or about 4% wt. of the amount of oil used in the reaction.

As shown in the following Examples, the operational life time of lipases can also be extended by using hydrophobic resin support for lipase immobilization in combination with the use of an alkaline or mild alkaline buffer solution, for example in the range of 0.001-5% wt. in the transesterification/esterification reaction medium. As further shown in the

following Examples, the water content of the reaction mixture may be increased regardless of pH value. Thus, in another embodiment, the stability of the biocatalyst increases with increasing the water content of the reaction system by adding water, for example at 0.0001-5% wt. of the fatty acid source, or any of the specific sub-ranges defined above. The results show that the addition of an alkaline solution in the range of 0.0001-5% wt. of the fatty acid source (Figures 2 and 3) or water at 0.001-4% of the fatty acid source (Figures 4 and 5) results in maintaining the enzyme activity and stability over many cycles of the reaction.

The alcohol or alcohol donor employed in the processes of the invention may be a short-chain alkyl alcohol, specifically C₁-C₆ alkyl alcohol, more specifically C₁-C₄ alkyl alcohol, and particularly methanol or ethanol or the alcohol donor may be mono-alkyl ester or dialkyl carbonate, such as dimethyl carbonate. An alcohol donor such as for example dialkyl carbonate can also serve as a source for alkalinity or mild alkalinity of the reaction system.

According to another aspect of the invention there is provided a system for the production of fatty acid alkyl esters. Referring to Fig. 11, a first embodiment of such a system, generally designated with the reference numeral 100, comprises a reactor vessel 120, a pre-reaction preparation vessel 140, and a product separation vessel 160.

Pre-reaction preparation vessel 140 is configured for receiving feedstock materials and buffer (and/or water), for forming a suitable emulsion therefrom, and for feeding the prepared emulsion PE (also referred to herein as emulsified feedstock) to the reactor vessel 120. In particular, such feedstock materials may include fatty acid FA (for example waste cooking oil) from a fatty acid source 182, and alcohol AL (for example methanol) from alcohol source 184, and buffer (and/or water) BU from buffer/water source

186, provided via suitable supply lines 152, 154, 156, respectively, in fluid communication with said pre-reaction preparation vessel 140 via vessel inlets 172, 174, 176, respectively and suitable valves (not shown).

The pre-reaction preparation vessel 140 defines an internal volume V1 in which the reaction mixture, including feedstock materials and buffer/water, provided therein via vessel inlets 172, 174, 176, are mixed together by means of a suitable stirring system 142, driven by a powered source (not shown), to form emulsion PE. The pre-reaction preparation vessel 140 comprises an outer jacket 149 through which a suitable work fluid may be circulated to maintain the volume V1 at a desired steady state temperature. For example, the work fluid may be oil or water, heated or cooled in a different vessel (not shown) and pumped through the jacket 149 via suitable inlet and exit ports (not shown). In alternative variations of this embodiment, pre-reaction preparation vessel 140 may comprise a system of heating and/or cooling elements, for example electrically powered heating and/or cooling elements, instead of or in addition to the jacket 149.

Reactor vessel 120 is configured for receiving prepared emulsion PE from pre-reaction preparation vessel 140, for reacting the feedstock materials therein in the presence of a suitable biocatalyst BC to produce reaction products RP, and for feeding the reaction products RP from the reaction mixture to the product separation vessel 160. Outlet line 148 provides selective fluid communication between pre-reaction preparation vessel 140 and reactor vessel 120 via suitable valves (not shown) and allows the prepared emulsion PE prepared by the pre-reaction preparation vessel 140 to be fed to the reactor vessel 120 as desired.

The reaction vessel 120 defines an internal volume V2 in which the prepared emulsion PE in the reaction mixture, provided therein via vessel inlet 122, is reacted, and the reaction mixture may be stirred by means of a suitable stirring system 124, driven by a powered source (not shown) to form the

reaction products RP. The biocatalyst BC may comprise a suitable enzyme and is provided in the form of immobilized enzyme beads which remain in the reactor vessel 120 until they become ineffective or are not sufficiently effective, whereupon they may be removed and replaced with new biocatalyst BC. For example, the biocatalyst BC may comprise lipase derived from *Thermomyces lanuginosa* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin.

The reactor vessel 120 comprises a thermal regulation system in the form of an outer jacket 129 through which a suitable work fluid may be circulated to maintain the volume V2 at a desired steady state temperature. For example, the work fluid may be oil or water, heated or cooled in a different vessel (not shown) and pumped through the jacket 129 via suitable inlet and exit ports 123. In alternative variations of this embodiment, the thermal regulation system comprises a system of heating and/or cooling elements, for example electrically powered heating and/or cooling elements, instead of or in addition to the jacket 129.

The lower part of the reactor vessel 120 comprises an outlet 127, and a suitable retaining arrangement in the form of filter 125 is provided upstream of the outlet 127 configured for, filtering the reaction mixture, in particular the reaction products RP prior to being removed from reactor vessel 120, and for preventing the biocatalyst BC from being removed with the reaction products RP.

The product separation vessel 160 is configured for separating out, from the reaction products RP, the desired product P (fatty acid alkyl ester), from by products including excess water and glycerol G. Outlet line 147 provides selective fluid communication between product separation vessel 160 and reactor vessel 120 via suitable valves (not shown) and allows the reaction products RP to be fed to the product separation vessel 160 from the reactor

vessel 120 as desired. In this embodiment, the product separation vessel 160 comprises a centrifuge or gravity separation system for carrying out the aforesaid separation, and includes a first outlet 162 for outputting the product P, and a second outlet 164 for collecting the excess water and glycerol G. Product P may be collected via tap 163.

The system can thus be operated in a continuous production mode, in which prepared emulsion PE is fed into the reactor vessel 120, and the desired product P collected in a continuous manner via tap 163. The emulsion PE can be prepared and delivered in a continuous manner to the reactor vessel 120 to top up the volume of reactant therein at the same rate as the reaction products RP are being removed from outlet 127. Alternatively, emulsion PE can be prepared and delivered in batches to the reactor vessel 120 to top up the volume of reactant in the reaction mixture at discrete intervals whenever the level of reactants in the reactor vessel 120 drops to a particular minimum level following the continuous removal of reaction products RP via outlet 127. Of course, it is also possible to operate the system 100 to provide the desired product P in batches rather than continuously.

Alternatively, the system 100 may be operated in enhanced yield mode, wherein product P is, instead of being immediately collected via tap 163, rerouted to the reactor vessel 120 via an optional rerouting system, including line 165, vessel inlet 121 and valve 166, wherein valve 166 may be selectively operated to divert the product P from tap 163. When rerouted to reactor vessel 120, the product P may be further reacted therein with alcohol AL, provided via a separate line (not shown) from source 184, from a different alcohol source (not shown), or from source 184 via pre-reaction preparation vessel 140, to produce a higher yield of product P, which again may be separated out from byproducts using product separation vessel 160. When the alcohol is provided via preparation vessel 140, the latter is first emptied

of the prepared emulsion PE, and suitable valves prevent fatty acids FA and optionally buffer/water being provided by respective sources 182 and 186. Suitable pumps or gravity feeds and controllable valves may be provided for selectively transporting the respective materials through the respective lines 152, 154, 156, 148, 147, 165, and a suitable controller (not shown) monitors and controls operation of the system.

In at least some alternative variations of the first embodiment, the pre-reaction preparation vessel 140 may be integral with the reactor vessel 120. For example, the respective internal volumes V1 and V2 may be separated by a wall having an opening arrangement corresponding to the line 148. Alternatively, the respective internal volumes V1 and V2 may be contiguous, but internal volume V1 is sufficiently spaced from the biocatalyst BC to provide sufficient time for the emulsion PE to form before reaching the biocatalyst BC.

In alternative variations of the first embodiment, one, two or all of the fatty acid FA, alcohol AL, and buffer/water BU may be provided directly to the reactor vessel 120, bypassing the pre-reaction preparation vessel 140. For example, one or more of the fatty acid source 182, alcohol source 184, and buffer/water source 186, may be in selective fluid communication directly with reactor vessel 120 via suitable supply lines (not shown) bypassing the pre-reaction preparation vessel 140.

It is appreciated that all components of the system 100 according to the first embodiment, or alternative variations thereof, are of a suitable form and made from suitable materials as known in the art, such as to enable each component to carrying out the respective functions at the respective conditions, including temperature, pressure, pH and so on.

Referring to Fig. 12, a second embodiment of the system, designated with the reference number 200, comprises all the elements and features of the first

embodiment, including alternative variations thereof, including all like-numbered components as in Fig. 11, *mutatis mutandis*, with some differences. For example system 200 also comprises: a reactor vessel 120, a pre-reaction preparation vessel 140, a product separation vessel 160, fatty acid source 182, alcohol source 184, buffer/water source 186, supply lines 152, 154, 156, vessel inlets 172, 174, 176, stirring system 142, outer jacket 149, outlet line 148 vessel inlet 122, stirring system 124, biocatalyst BC outer jacket 129, inlet and exit ports 123, outlet 127, filter 125, outlet line 147 first outlet 162 second outlet 164; as disclosed for the first embodiment, *mutatis mutandis*.

However, in the second embodiment, the line 165, tap 163 and valve 166 of the first embodiment are omitted, and instead an auxiliary reactor module 300 is operatively connected to the first outlet 162 of the product separation vessel 160.

Auxiliary reactor module 300 comprises an auxiliary reactor vessel 220 and an auxiliary product separation vessel 260, which in this embodiment are respectively substantially similar to reactor vessel 120 and product separation vessel 160, *mutatis mutandis*. In operation, the desired product P from product separation vessel 160 is routed to the auxiliary reactor vessel 220 via line 266, valve 267 and vessel inlet 221. When routed to auxiliary reactor vessel 220, the product P may be further reacted therein with alcohol AL, provided via a separate line (not shown) from source 184 or from a different alcohol source (not shown), to produce further reacted products FRP. Line 249 enables the further reacted products FRP to be transported to the auxiliary product separation vessel 260, which then operates to separate a higher yield of product P' from byproducts.

System 200 may be operated in a similar manner to system 100, *mutatis mutandis*.

Disclosed and described, it is to be understood that this invention is not limited to the particular examples, process steps, and materials disclosed herein as such process steps and materials may vary somewhat. It is also to be understood that the terminology used herein is used for the purpose of describing particular embodiments only and not intended to be limiting since the scope of the present invention, will be limited only by the appended claims and equivalents thereof.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The following Examples are representative of techniques employed by the inventors in carrying out aspects of the present invention. It should be appreciated that while these techniques are exemplary of preferred embodiments for the practice of the invention, those of skill in the art, in light of the present disclosure, will recognize that numerous modifications can be made without departing from the intended scope of the invention.

Examples

General

All experiments were carried out either in glass tubes of 30ml in volume bottomed with a centered glass filter or in mechanically stirred reactors of 500 ml in volume bottomed with a sintered glass filter of porosity of 150-250 μm . Typical reaction medium contained fatty acid source, alcohol, normally, methanol or ethanol in molar basis 1:1 in relation to the fatty acid regardless free or bound on a glycerol backbone (for free fatty acids and monoglycerides 1:1, for diglycerides 1:2, and for triglycerides 1:3 in favor of the alcohol). The fatty acid source was premixed with different amounts of alkaline buffer, in specific embodiments sodium bicarbonate. The reactions were initiated by the addition of lipase immobilized on a hydrophobic resin (10-15%wt.) and the reaction medium was either shaken mechanically or stirred at 30°C. The alcohol amount was added equally in three steps each one hour apart, unless indicated differently. Reaction conversions were followed by taking samples from the reaction medium at different time intervals and analyzing fatty acid components. The conversion to biodiesel was calculated as: $100 \times \text{peak area of fatty acid alkyl ester} / \text{sum of all peaks areas}$.

Lipase immobilization: Lipases were immobilized following standard procedures where lipase derived from a certain microorganism is solubilized in buffer solution of 0.1M at a certain pH value, for example 7.5. An organic or inorganic polymer resin was introduced into the lipase solution. The mixture was shaken at room temperature for 8 hour. Cold acetone was optionally added into the mixture in order to increase the protein enzyme precipitation on the resin. The mixture was filtered and the enzyme beads were dried to reduce the water content to less than 5%.

Different resins were used including hydrophobic polymer resins based on polystyrene/divinylbenzen, paraffin or any of their combinations, to obtain resins of hydrophobic characteristics. Typical hydrophobic resins used

included Amberlite[®] XAD 1600 (Rohm & Haas, USA) and Sepabeads[®] SP70 (Resindion, Italy). Typical hydrophilic resins used included Duolite[®] D568 (Rohm & Haas) and porous silica gel. Lipases may be immobilized separately on a resin or different lipases are co-immobilized on the same resin.

Example 1

The transesterification activity of lipase derived from *Thermomyces lanuginosa* immobilized on Amberlite[®] XAD 1600 as a hydrophobic resin and on Duolite[®] D568 as a hydrophilic resin, and lipase derived from *Pseudomonas sp.* immobilized on Sepabeads[®] SP70 as a hydrophobic resin and on porous silica as a hydrophilic resin.

Reaction conditions: Refined and bleached soybean oil (20g) containing 1% wt. of sodium bicarbonate solution of 0.1M. Methanol (2.5ml) was added stepwise in three equivalent batches each one hour apart. The reaction medium containing 10% wt. lipase preparation was shaken at 300rpm and 30°C. Results are shown in Figure 1.

The results presented in Figure 1 show that both the *Thermomyces lanuginosa* and *Pseudomonas sp.* lipases immobilized on different resins in the presence of 1% wt. of sodium bicarbonate solution showed high transesterification activity during the first 5 cycles using the same batch of enzyme. It was observed that after the 5th batch, when the same batch of enzyme was used, the filtration of the reaction medium from the system became difficult due to the formation of gel-like deposit around the beads of both lipases immobilized on hydrophilic resins, namely Duolite[®] D568 and porous silica. The interesterification activity of both lipases immobilized on hydrophilic resins decreased sharply in further consecutive batches, and they became inactive after the 10th cycle. In contrast, *Pseudomonas sp.* lipase immobilized on the hydrophobic resin, Sepabeads[®] SP70, retained more than 80% of its initial activity after 70 cycles, while *Thermomyces lanuginosa*

lipase immobilized on the hydrophobic resin, Amberlite[®] XAD1600, retained more than 20% of its initial activity after more than 70 cycles.

Example 2

A. The conversion of soybean oil to biodiesel and glycerol after 6 hours of reaction using the same batch of biocatalyst in multiple batch experiments.

Reaction conditions: Refined and bleached soybean oil (20g) containing different concentrations of sodium bicarbonate solution of 0.1M. Methanol (2.5ml) was added stepwise in three equivalent batches each one hour apart. Lipase derived from *Thermomyces lanuginosa* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin, was used (10%wt.). The reaction medium was shaken at 300 rpm and 30°C. Results are shown in Figure 2.

B. The conversion of soybean oil to biodiesel and glycerol after 6 hours of reaction using the same batch of biocatalyst in multiple batch experiments.

Reaction conditions: Refined and bleached soybean oil (20g) containing different concentrations of sodium bicarbonate solution of 0.1M. Methanol (2.5ml) was added stepwise in three equivalent batches each one hour apart. Lipase derived from *Pseudomonas sp.* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin, was used (10%wt.). The reaction medium was shaken at 300rpm and 30°C. Results are shown in Figure 3.

Figures 2 and 3 show that the amount of sodium carbonate in the reaction medium has a major role on the operational life of *Thermomyces lanuginosa* and *Pseudomonas sp.* lipases immobilized on hydrophobic resins. It can be seen in Figures 2 and 3 that in the absence of an alkaline solution both immobilized lipases drastically lose their activity after a few cycles, while the same immobilized lipases maintain their transesterification activity over

multiple uses in the presence of sodium bicarbonate solution as a base in the reaction system. The results for both immobilized enzymes show that increasing the amount of sodium bicarbonate solution in the reaction medium in the range of 0 – 4% wt. results in decreasing the loss of enzyme activity in multiple uses of the same batch of immobilized enzyme.

Example 3

A. The conversion of soybean oil to biodiesel and glycerol after 6 hours of reaction using the same batch of biocatalyst in multiple batch experiments.

Reaction conditions: Refined and bleached soybean oil (20g) containing different concentrations of distilled water. Methanol (2.5ml) was added stepwise in three equivalent batches each one hour apart. Lipase derived from *Thermomyces lanuginosa* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin, was used (10%wt.). The reaction medium was shaken at 300rpm and 30°C. Results are shown in Figure 4.

B. The conversion of soybean oil to biodiesel and glycerol after 6 hours of reaction using the same batch of biocatalyst in multiple batch experiments.

Reaction conditions: Refined and bleached soybean oil (20g) containing different concentrations of distilled water. Methanol (2.5ml) was added stepwise in three equivalent batches each one hour apart. Lipase derived from *Pseudomonas sp.* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin, was used (10%wt.). The reaction medium was shaken at 300rpm and 30°C. Results are shown in Figure 5.

Figures 4 and 5 show that the transesterification activity using the same batch of lipases *Thermomyces lanuginosa* and *Pseudomonas sp.* immobilized on hydrophobic resins in multiple experiments is also affected by the amount of water in the reaction system. It can be seen that increasing the water amount from none (zero) to 4% wt. resulted in maintaining higher residual

transesterification activity of biocatalyst when used in consecutive cycles. The results presented in Figures 2 to 5 evidently show that using mild base, such as sodium bicarbonate solution in the transesterification reactions is favored for maintaining the activity of lipases immobilized on hydrophobic resins when used in consecutive cycles.

Example 4

The conversion of a mixture of free fatty acids (FFA's) and soybean oil to biodiesel, and glycerol and water by-products after 4 hours of esterification/transesterification using the same batch of biocatalyst in multiple batch experiments.

Reaction conditions: A mixture of free fatty acids soybean hydrolysate (50%wt.) and soybean oil (50%wt.) of initial FFA value 72 mg KOH/1g containing different amount of sodium bicarbonate solution of 0.1M. Methanol (4.5ml) was added stepwise in three equivalent batches each one hour apart. Lipase derived from *Pseudomonas sp.* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin, was used (20%wt.). The reaction medium was shaken at 300rpm and 30°C. Results are shown in Figure 6.

Figure 6 shows that different amount of base solution has a major effect on the simultaneous esterification reaction of FFA present in the reaction mixture comprised of equivalent proportions of soybean oil hydrolysate and soybean oil triglycerides. It can be seen that *Pseudomonas sp.* lipase immobilized on a hydrophobic resin lost its esterification activity when no alkaline solution was added into the esterification/transesterification reaction system, while the same biocatalyst has maintained its activity in consecutive cycles when 1 and 2% wt. of sodium bicarbonate solutions of 0.1 M were added separately into the reaction systems. The results presented in Figure 6 show that the use of *Pseudomonas sp.* lipase immobilized on a hydrophobic

resin reduced the FFA content in the presence of 1% and 2%wt. of sodium bicarbonate solution of 0.1M from initial value of 72 mg KOH/1g down to 8 and 6 mg KOH/1g in average, respectively, and maintained this activity in 22 subsequent cycles.

Example 5

The esterification of soybean oil hydrolysate to biodiesel and water after 4 hours of reaction using the same batch of biocatalyst in multiple batch experiments.

Reaction conditions: Free fatty acids soybean hydrolysate (20g) of FFA value of 150 mg KOH/1g containing 1% wt. sodium bicarbonate solution of 0.1M. Methanol (2ml) was added into the reaction medium in one batch. Lipase derived from *Pseudomonas sp.* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin, was used (10%wt.). The reaction medium was shaken at 300rpm and 30°C. Results are shown in Figure 7.

Figure 7 shows that *Pseudomonas sp.* lipase immobilized on a hydrophobic resin is also capable of catalyzing the esterification of free fatty acids to form fatty acid methyl esters and water by-product. The results show that the lipase preparation maintained its esterification/transesterification activity in a medium containing 1% sodium bicarbonate solution of 0.1M over more than 25 cycles using the same batch of biocatalyst without the observation of any significant loss of activity.

Example 6

The transesterification of fish oil with ethanol after 6 hours of reaction using the same batch of biocatalyst in multiple batch experiments.

Reaction conditions: Refined fish oil (20g) containing 1% sodium bicarbonate solution of 0.1M. Ethanol (2.5ml) was added stepwise in three

equivalent batches each one hour apart. Lipases derived from *Thermomyces lanuginosa* and *Pseudomonas sp.* immobilized on Amberlite^R XAD 1600, were used separately (10%wt.). The reaction medium was shaken at 300rpm and 30°C. Results are shown in Figure 8.

Figure 8 shows that both lipases derived from *Thermomyces lanuginosa* and *Pseudomonas sp.* immobilized on hydrophobic resins are also capable of catalyzing the transesterification of fish oil triglycerides with ethanol to form fatty acid ethyl esters and glycerol by-product. The results also show that both biocatalyst preparations maintained their transesterification activity in the presence of 1% sodium bicarbonate solution without significant activity losses over more than 20 cycles using the same batch of biocatalyst.

Example 7

The transesterification of Tallow fat with ethanol after 6 hours of reaction using the same batch of biocatalyst in multiple batch experiments.

Reaction conditions: Tallow fat (16g) containing fatty acid ethyl ester of tallow fat (4g) and 1% potassium carbonate solution of 1M. Ethanol (2.5ml) was added stepwise in three equivalent batches each one hour apart. Lipases derived from *Thermomyces lanuginosa*, *Pseudomonas sp.* immobilized on Amberlite^R XAD 1600 (10%wt.) were used separately or in combination at an equivalent ratio. The reaction medium was shaken at 300rpm and 37°C. Results are shown in Figure 9.

Figure 9 shows that both lipases derived from *Thermomyces lanuginosa* and *Pseudomonas sp.* separately or in combination immobilized on hydrophobic resins are also capable of catalyzing the transesterification of tallow fat triglycerides with ethanol to form fatty acid ethyl esters and glycerol by-product. The feedstock of the reaction medium was comprised of tallow fat (80%) and fatty acid ethyl esters derived from tallow fat in order to lower the

melting point of the reaction medium. The results presented in Figure 9 show that all biocatalysts retained more than 80% of their initial activity in the presence of mild alkaline solution, such as potassium carbonate of 1M, when the same batch of biocatalysts were used in 100 consecutive cycles.

Example 8

The treatment of the transesterification/esterification reaction medium obtained after 4 hours containing FFA value of 7 mg KOH/1g using *Pseudomonas sp.* lipase or *Thermomyces lanuginosa* lipase immobilized on hydrophobic porous resins with *Candida Antarctica B* lipase immobilized on a hydrophobic porous resin and methanol (ratio of 1:10 on molar basic between FFA and methanol, respectively) using the same batch of biocatalyst (10%wt.) in multiple batch experiments. The reaction medium was shaken at 300rpm and 30°C. Results are shown in Figure 10.

Figure 10 shows that the transesterification reaction medium obtained after treatment either with *Thermomyces lanuginosa* lipase or *Pseudomonas sp.* lipase as described above, which typically contain FFAs values of 3-7 mg KOH/1g, can be treated with *Candida antarctica B* lipase immobilized on either hydrophilic or hydrophobic support, results in reducing the FFA value down to less than 2 mg KOH/1g. The immobilized lipase can maintain its activity in more than 100 cycles.

Example 9

Example 8

Transesterification/esterification of waste-cooking oil containing 10% FFA with methanol to form biodiesel, water and glycerol using the first embodiment of the system illustrated in Figure 11.

Reaction conditions: Waste-cooking oil (1100g) containing 2% of sodium bicarbonate solution of 0.1M and methanol (140g) were first premixed in pre-reaction preparation vessel 140 to form an emulsion, which was then introduced to the reactor vessel 120 having an internal volume V2 of about 2 liters. The reaction mixture was mixed in the reactor vessel 120 with a lipase derived from *Thermomyces lanuginosa* immobilized on a hydrophobic and porous polystyrene-divinylbenzene-based resin (30% wt of the oil) for 6 hours at 30°C. The reaction mixture was filtered off through the filter 125 and fed to product separation vessel 160. Glycerol and excess of water were removed from the reaction mixture in the product separation vessel 160. The upper phase containing of the fatty acid methyl esters and the unreacted glycerides were re-introduced to the reactor vessel 120 via rerouting line 165, and stirring in the reactor vessel 120 was resumed after the addition of methanol (110g) in to the reaction medium in the reactor vessel 120. The conversion to methyl ester after 2 hours was 98%. An emulsified reaction medium (prepared emulsion) containing waste-cooking oil (83% wt), methanol (15%) and sodium bicarbonate solution of 0.1M (2%) was continuously fed into the reactor vessel 120 at a flow rate of about 30ml/min. The conversion to fatty acid methyl esters was maintained to more than 3 months without significant activity losses when using the same batch of biocatalyst derived from *Thermomyces lanuginosa* lipase immobilized on a macroporous hydrophobic resin.

Claims:

1. A process for the transesterification/esterification of a fatty acid source with an alcohol, to form fatty acid alkyl esters, comprising reacting a fatty acid source and an alcohol or an alcohol donor in the presence of an immobilized lipase preparation, wherein the immobilized lipase preparation comprises at least one lipase immobilized on a hydrophobic porous support and the reaction medium contains an aqueous alkaline buffer solution.
2. The process of claim 1, wherein said aqueous alkaline buffer solution is a mild aqueous alkaline buffer solution.
3. The process of claim 1 or claim 2, wherein said aqueous alkaline buffer solution is contained at a quantity of up to 5% wt. of the fatty acid source.
4. The process of any one of claims 1 to 3, wherein the aqueous buffer solution has a pH from 7 to about 11.
5. The process of claim 4, wherein the pH is any one of 7-8.5, 7-9, 7-9.5, 7-10 and 7-11.
6. The process of claim 1, wherein the pKa of the supplemented mild alkaline reagent comprising of the buffer solution is higher or equal than the pKa of acids comprising the fatty acid source.
7. A process for the transesterification/esterification of a fatty acid source with an alcohol, to form fatty acid alkyl esters, comprising reacting a fatty acid source and an alcohol in the presence of an immobilized lipase preparation, wherein the immobilized lipase preparation comprises at least one lipase immobilized on a hydrophobic porous support and the reaction medium contains water.

8. The process of claim 7, wherein the water is in the form of a water solution with a pH of from 3 to 11.
9. The process of claim 7 or claim 8, wherein the reaction medium contains the water or water solution up to 5% wt. of the fatty acid source.
10. The process of any one of the preceding claims, wherein said alcohol is a short-chain alcohol.
11. The process of any one of claims 1 to 9, wherein said alcohol donor is a mono-alkyl ester, such as methyl acetate or a di-alkyl carbonate, such as dimethyl carbonate, serving also as a source for mild alkaline reagent in the reaction medium.
12. The process of any one of the preceding claims, wherein said at least one lipase is a lipase derived from any one *Rhizomucor miehei*, *Pseudomonas sp.*, *Rhizopus niveus*, *Mucor javanicus*, *Rhizopus oryzae*, *Aspergillus niger*, *Penicillium camembertii*, *Alcaligenes sp.*, *Acromobacter sp.*, *Burkholderia sp.*, *Thermomyces lanuginosa*, *Chromobacterium viscosum*, *Candida antarctica B*, *Candida rugosa*, *Candida antarctica A*, papaya seeds and pancreatin.
13. The process of any one of the preceding claims, wherein said immobilized lipase is capable of catalyzing the esterification of free fatty acids to yield fatty acid alkyl esters and water as by-product, and the transesterification of triglycerides and partial glycerides to yield fatty acid alkyl esters and glycerol as by-product.
14. The process of any one of claims 1 to 6 and 10 to 13, wherein the amount of said alkaline solution in the reaction medium is from 0.001 to 5% wt. of the fatty acid source.

15. The process of any one of the preceding claims, wherein said lipase preparation comprises at least two lipases which may be each separately immobilized on a hydrophobic support or co-immobilized on the same hydrophobic support.

16. The process of claim 15, wherein said lipases possess identical or different regio-specificity.

17. The process of claim 15 or claim 16, wherein said lipases are capable of simultaneously or consecutively catalyzing the esterification of free fatty acids to yield fatty acid alkyl esters and water as by-product, and the transesterification of triglycerides and partial glycerides to yield fatty acid alkyl esters and glycerol as by-product.

18. The process of any one of the preceding claims, wherein said support is any one of hydrophobic aliphatic polymer-based support and hydrophobic aromatic polymer-based support.

19. The process of claim 18, wherein said hydrophobic polymer support is comprised of linear or branched organic chains.

20. The process of claim 19, wherein said support comprises macroreticular organic polymer or co-polymer chains.

21. The process of any one of claims 1 to 17, wherein said support is porous or non-porous inorganic support, which may be hydrophobic or is coated with hydrophobic organic material.

22. The process of claim 21, wherein said organic material is a linear, branched, or functionalized hydrophobic organic chain.

23. The process of any one of claims 1 to 6 and 10 to 22, wherein said aqueous alkaline buffer solution is a solution of an inorganic alkaline salt or an organic base.

24. The process of claim 23, wherein said alkaline buffer solution is a solution of any one of an alkaline metal hydroxide, carbonate, bicarbonate, phosphate, sulfate, acetate and citrate, a primary, secondary and tertiary amine, and any mixture thereof.

25. The process of claim 24, wherein said alkaline buffer solution is a solution of a weak base selected from sodium or potassium bicarbonates and carbonates.

26. The process of any one of claims 1 to 6 and 10 to 25, wherein said alkaline buffer solution is added to said fatty acid source in a premixing stage or directly to the reaction medium.

27. The process of any one of claims 1 to 6 and 10 to 26, wherein the content of said alkaline buffer solution in the transesterification/esterification reaction medium is in the range of 0.001-5% wt. of the oil feedstock.

28. The process of claim 27, wherein the content of said alkaline buffer solution is 1-2% wt. of the oil feedstock.

29. The process of any one of claims 1 to 6 and 10 to 28, wherein the fatty acid source is first mixed with said alkaline buffer solution, the mixture is

then treated with said immobilized lipase preparation, followed by adding said alcohol and allowing the reaction to proceed under suitable conditions until said fatty acid source is converted to fatty acid esters.

30. The process of any one of the preceding claims wherein said fatty acid source is any one of plant oil, animal fat, algal oil, fish oil, waste oil and any mixtures thereof.

31. The process of any one of the preceding claims wherein said fatty acid source comprises free fatty acids, mono-, di- or tri-glycerides, their mixtures at any ratio, in the absence or presence of other minor fatty acid derivatives such as phospholipids and sterol esters, more specifically said fatty acid source is unrefined, refined, bleached, deodorized or any of their combinations.

32. The process of any one of claims 1 to 10 and 12 to 31, wherein said alcohol is a short-chain alkyl alcohol, specifically C₁-C₆ alkyl alcohol, more specifically C₁-C₄ alkyl alcohol, particularly methanol or ethanol.

33. The process of any one of claims 1 to 10 and 12 to 31, wherein said alcohol is methanol and said resulting fatty acid esters are fatty acid methyl esters (FAME – Biodiesel).

34. The process of any one of claims 1 to 10 and 12 to 31, wherein said alcohol is a medium-chain fatty alcohol (C₆-C₁₀) or long-chain fatty alcohols (C₁₂-C₂₂).

35. The process of any one of the preceding claims, wherein the reaction is carried out at a temperature between 10°C and 100°C, specifically between 25-30°C.

36. The process of any one of the preceding claims wherein said fatty acid source is pre-mixed with said alcohol or alcohol donor and with said water or buffer solution in a pre-reaction preparation vessel to form an emulsion which is then fed together with said immobilized lipase preparation into a transesterification/esterification reaction vessel.

37. The process of any one of the preceding claims, wherein said immobilized lipase is used in continuous stirred-tank reactors or in packed-bed column reactors operating in batch or continuous modes.

38. A system for the transesterification/esterification of a fatty acid with an alcohol, to form fatty acid alkyl esters, comprising:
a reaction vessel configured for reacting a reaction medium including a fatty acid and at least one of an alcohol and an alcohol donor in the presence of an immobilized lipase preparation, wherein the immobilized lipase preparation comprises at least one lipase immobilized on a hydrophobic porous support and the reaction medium contains at least one of an aqueous alkaline buffer solution and water.

39. The system according to claim 38, wherein said reaction vessel comprises the immobilized lipase preparation, at least during operation of said system for the production of said fatty acid alkyl esters.

40. The system according to claim 38 or claim 39, wherein said reaction vessel comprises the fatty acid and the at least one of an alcohol and an alcohol donor, at least during operation of said system for the production of said fatty acid alkyl esters.

41. The system according to any one of claims 38 to 40, wherein said reaction medium comprises a mixture, said system further comprising a pre-reaction vessel in selective fluid communication with said reaction vessel, said pre-reaction vessel being configured for premixing at least the fatty acid and the at least one of an alcohol and an alcohol donor to form said mixture, and for selectively delivering said mixture to said reaction vessel at least during operation of said system for the production of said fatty acid alkyl esters.

42. The system according to claim 41, further comprising a fatty acid source in selective fluid communication with said pre-reaction vessel and configured for selectively delivering the fatty acid to said pre-reaction vessel at least during said operation of said system, and an alcohol source in selective fluid communication with said pre-reaction vessel and configured for selectively delivering the at least one of an alcohol and an alcohol donor to said pre-reaction vessel at least during said operation of said system.

43. The system according to claim 42, further comprising a buffer source in selective fluid communication with said pre-reaction vessel and configured for selectively delivering the at least one of an aqueous alkaline buffer solution and water to said pre-reaction vessel to be included in said mixture at least during said operation of said system.

44. The system according to claim 42 or claim 45, configured for selectively delivering one or more of the fatty acid and the at least one of an alcohol and an alcohol donor to said pre-reaction vessel in a continuous manner at least during said operation of said system.

45. The system according to claim 43 or claim 44, configured for selectively delivering the at least one of an aqueous alkaline buffer solution and water to

said pre-reaction vessel in a continuous manner at least during said operation of said system.

46. The system according to any one of claims 42 to 45, configured for selectively delivering one or more of the fatty acid and the at least one of an alcohol and an alcohol donor to said pre-reaction vessel in discrete batches at least during said operation of said system.

47. The system according to any one of claims 43 to 46, configured for selectively delivering the at least one of an aqueous alkaline buffer solution and water to said pre-reaction vessel in discrete batches at least during said operation of said system.

48. The system according to any one of claims 41 to 47, wherein said pre-reaction vessel is configured for selectively delivering said mixture to said reaction vessel in a continuous manner at least during said operation of said system.

49. The system according to any one of claims 41 to 48, wherein said pre-reaction vessel is configured for selectively delivering said mixture to said reaction vessel in discrete batches at least during said operation of said system.

50. The system according to any one of claims 38 to 49, the system being configured for selectively and directly delivering to said reaction vessel at least one of the fatty acid; the at least one of an alcohol and an alcohol donor; and the at least one of an aqueous alkaline buffer solution and water.

51. The system according to any one of claims 38 to 50, wherein said reaction vessel comprises a thermal regulation system configured for

maintain the reaction medium in said reaction vessel within a selected temperature range.

52. The system according to any one of claims 38 to 51, further comprising a retaining arrangement configured for retaining the immobilized lipase preparation within said reaction vessel at least during operation of said system.

53. The system according to any one of claims 38 to 52, further comprising a product separation vessel in selective fluid communication with said reaction vessel, said system being configured for selectively delivering a reaction mixture including reaction products from said reaction vessel to said product separation vessel, and wherein said product separation vessel is configured for selectively separating a yield of the fatty acid alkyl esters from the reaction mixture delivered thereto.

54. The system according to claim 53, wherein said product separation vessel comprises one of a centrifuge and gravity separation system.

55. The system according to any one of claims 53 and 54, wherein said reaction vessel is configured for selectively delivering said reaction mixture to said product separation vessel in a continuous manner at least during said operation of said system.

56. The system according to any one of claims 53 to 55, wherein said reaction vessel is configured for selectively delivering said reaction mixture to said product separation vessel in discrete batches at least during said operation of said system.

57. The system according to any one of claims 53 to 56, configured for selectively delivering said yield of fatty acid alkyl esters from said product separation vessel.

58. The system according to claim 57, configured for selectively delivering said yield of fatty acid alkyl esters from said product separation vessel in a continuous manner.

59. The system according to claim 57, configured for selectively delivering said yield of fatty acid alkyl esters from said product separation vessel in discrete batches.

60. The system according to any one of claims 53 to 59, wherein said system is configured for increasing said yield of the fatty acid alkyl esters from the reaction mixture delivered to said product separation vessel.

61. The system according to claim 60, wherein said system is configured for selectively rerouting said yield of the fatty acid alkyl esters to said reaction vessel to further increase said yield of the fatty acid alkyl esters from the reaction mixture subsequently delivered to said product separation vessel.

62. The system according to claim 60, wherein said system is configured for selectively rerouting said yield of the fatty acid alkyl esters to an auxiliary reactor module, wherein said auxiliary reactor module comprises an auxiliary reactor vessel and an auxiliary product separation vessel, wherein said further increased yield of the fatty acid alkyl esters is selectively subsequently delivered via said auxiliary product separation vessel.

63. The process of any one of claims 1 to 37, conducted in the system of any one of claims 38 to 62.

1/7

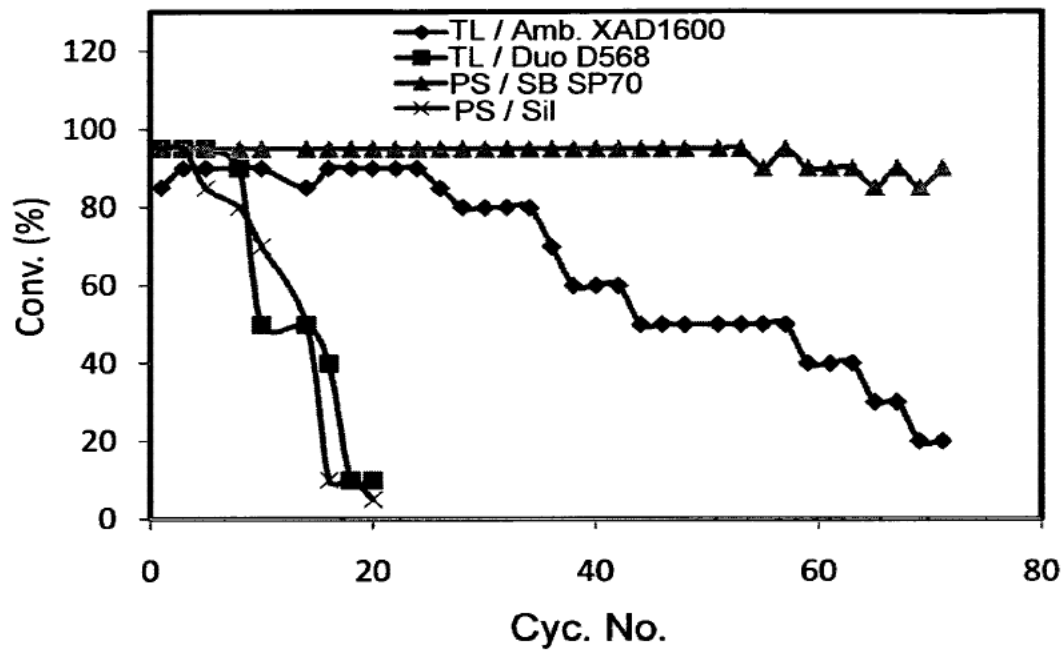


Figure 1

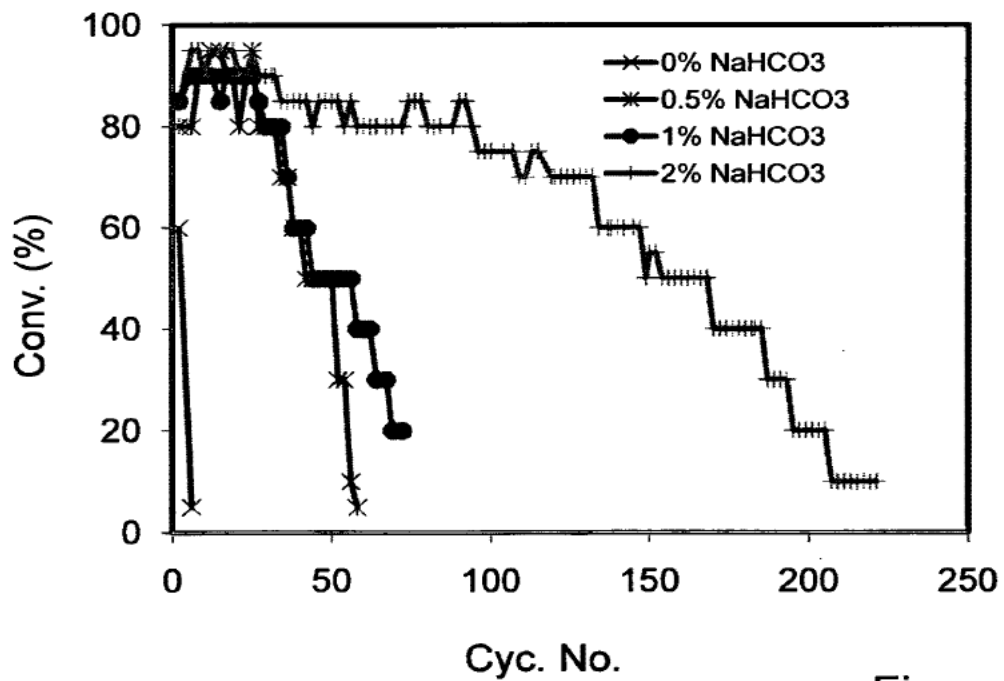


Figure 2

2/7

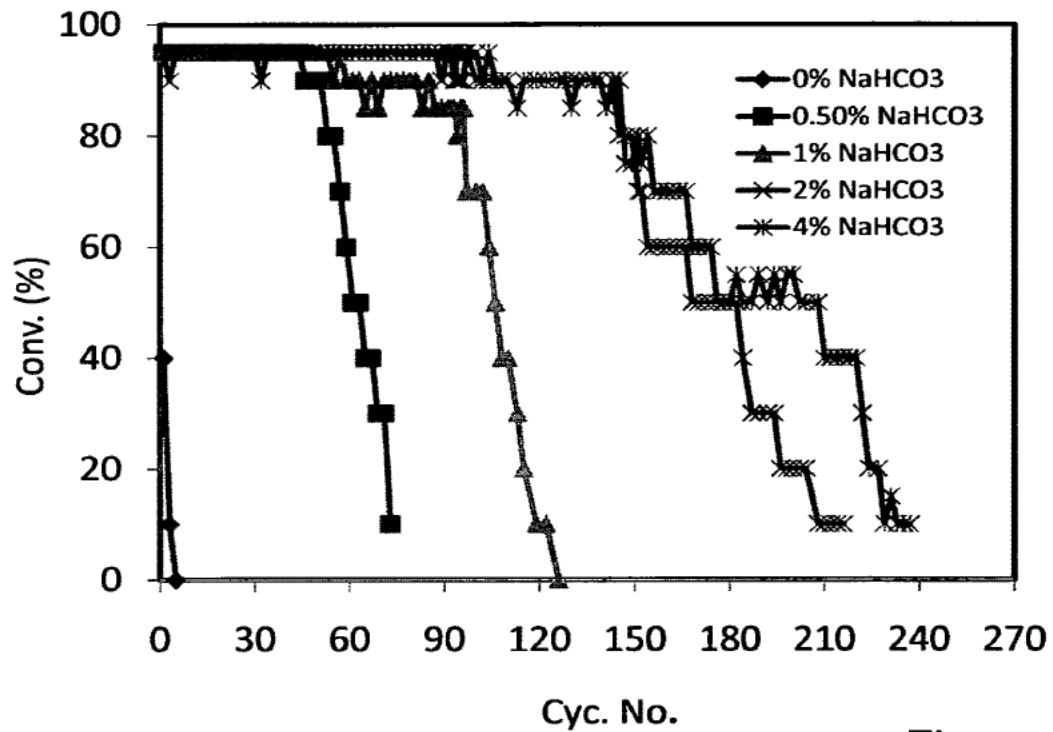


Figure 3

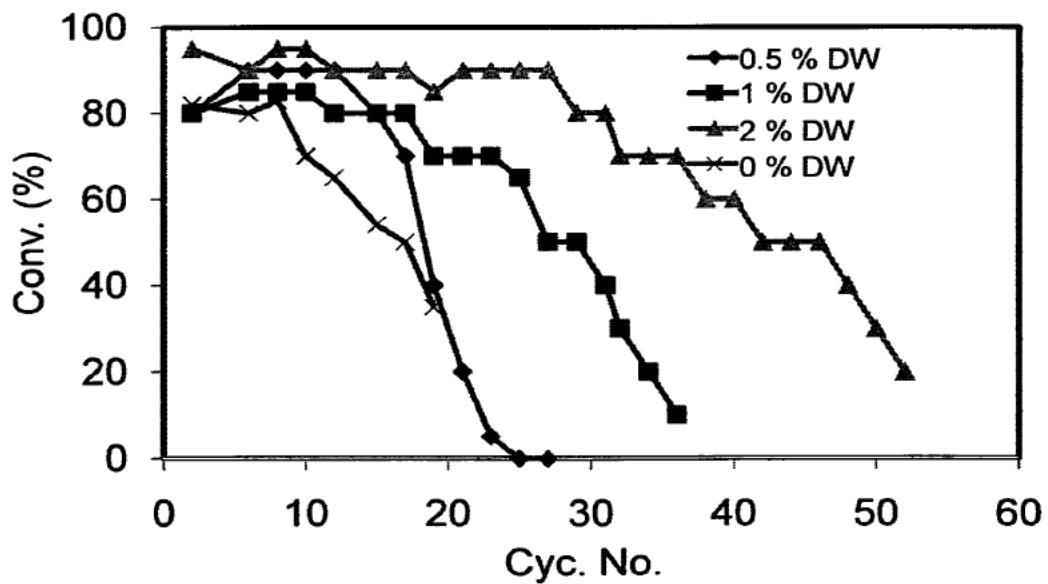


Figure 4

3/7

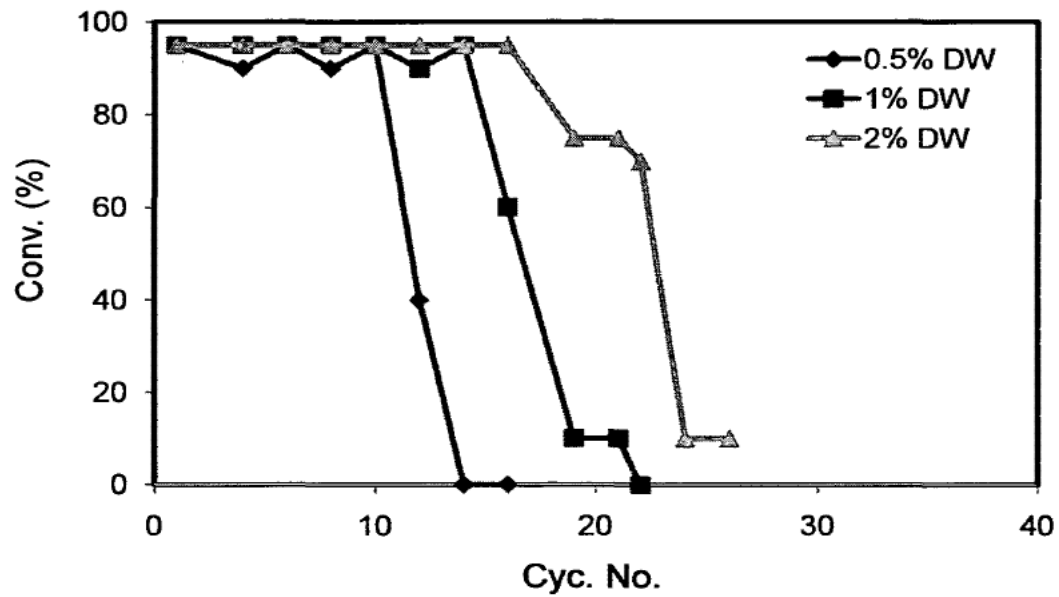


Figure 5

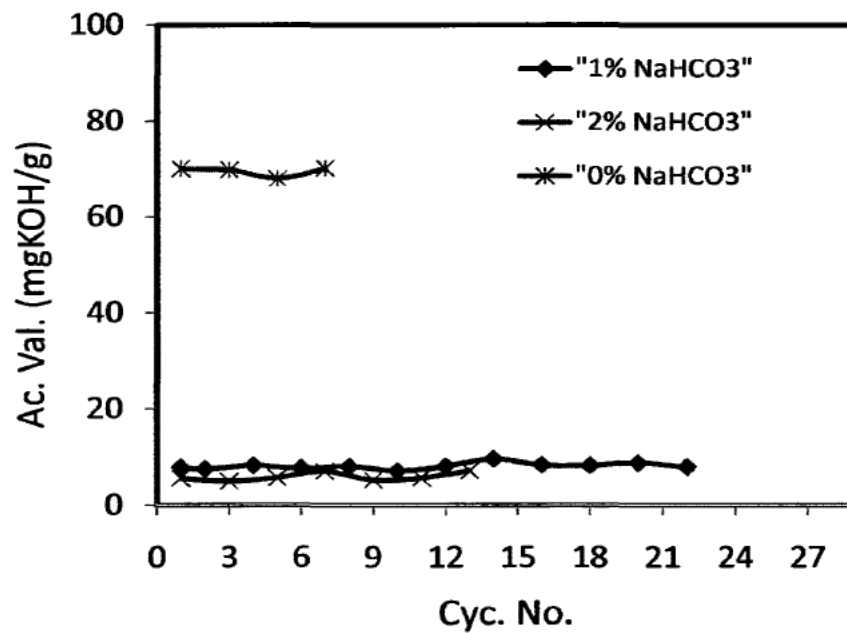


Figure 6

4/7

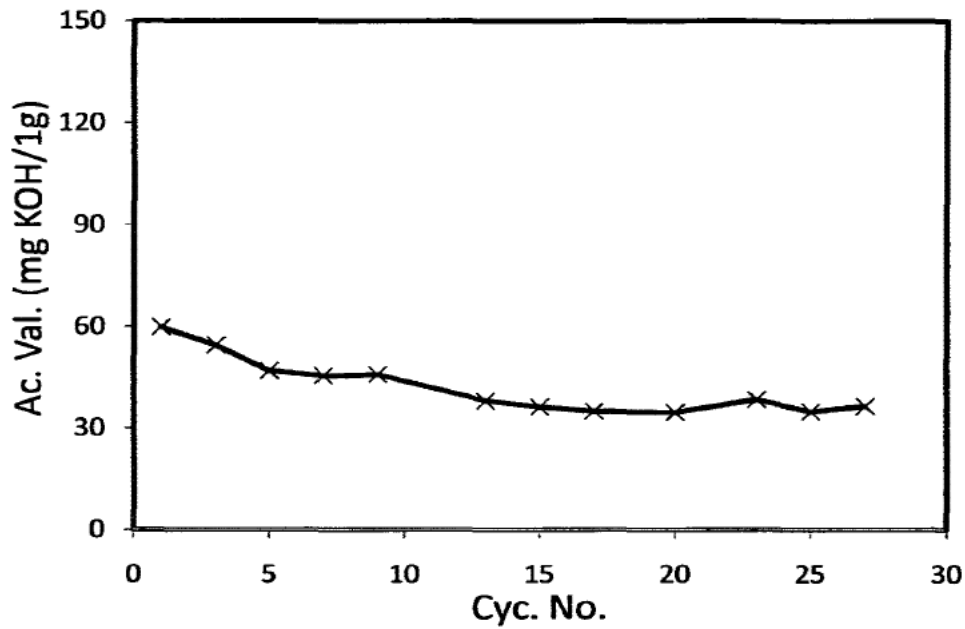


Figure 7

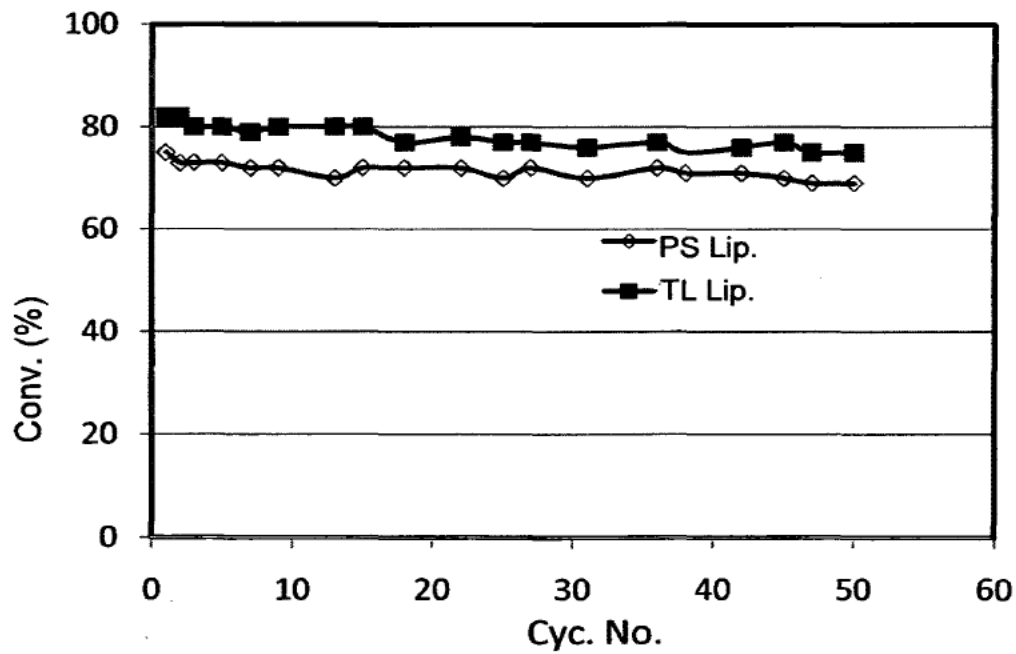


Figure 8

5/7

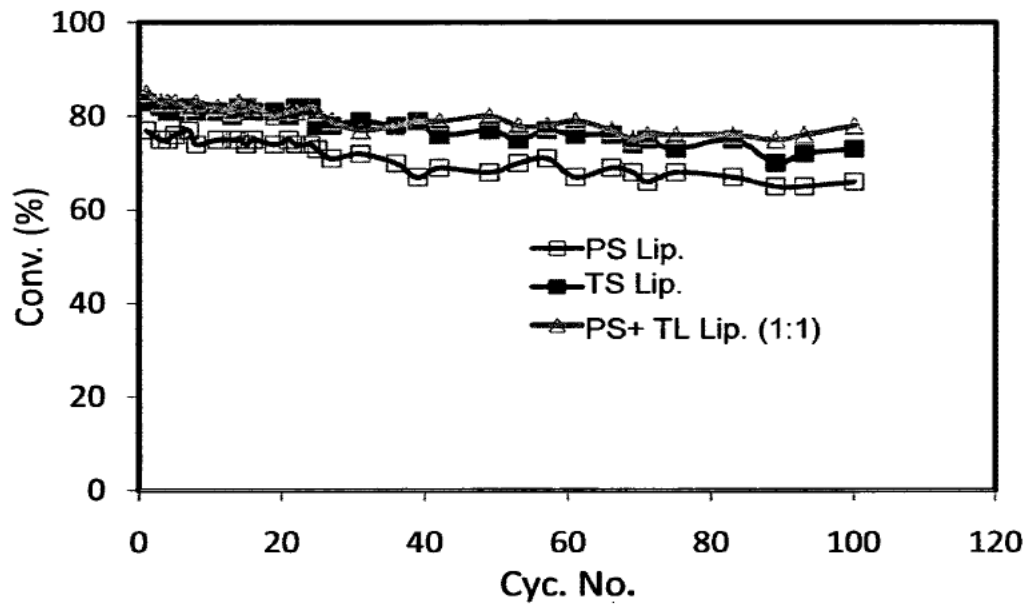


Figure 9

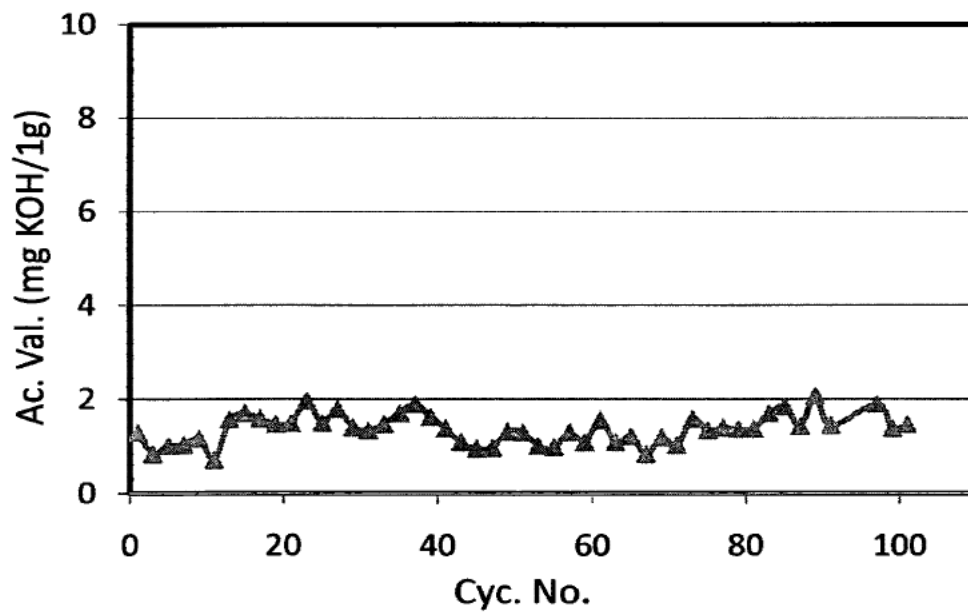


Figure 10

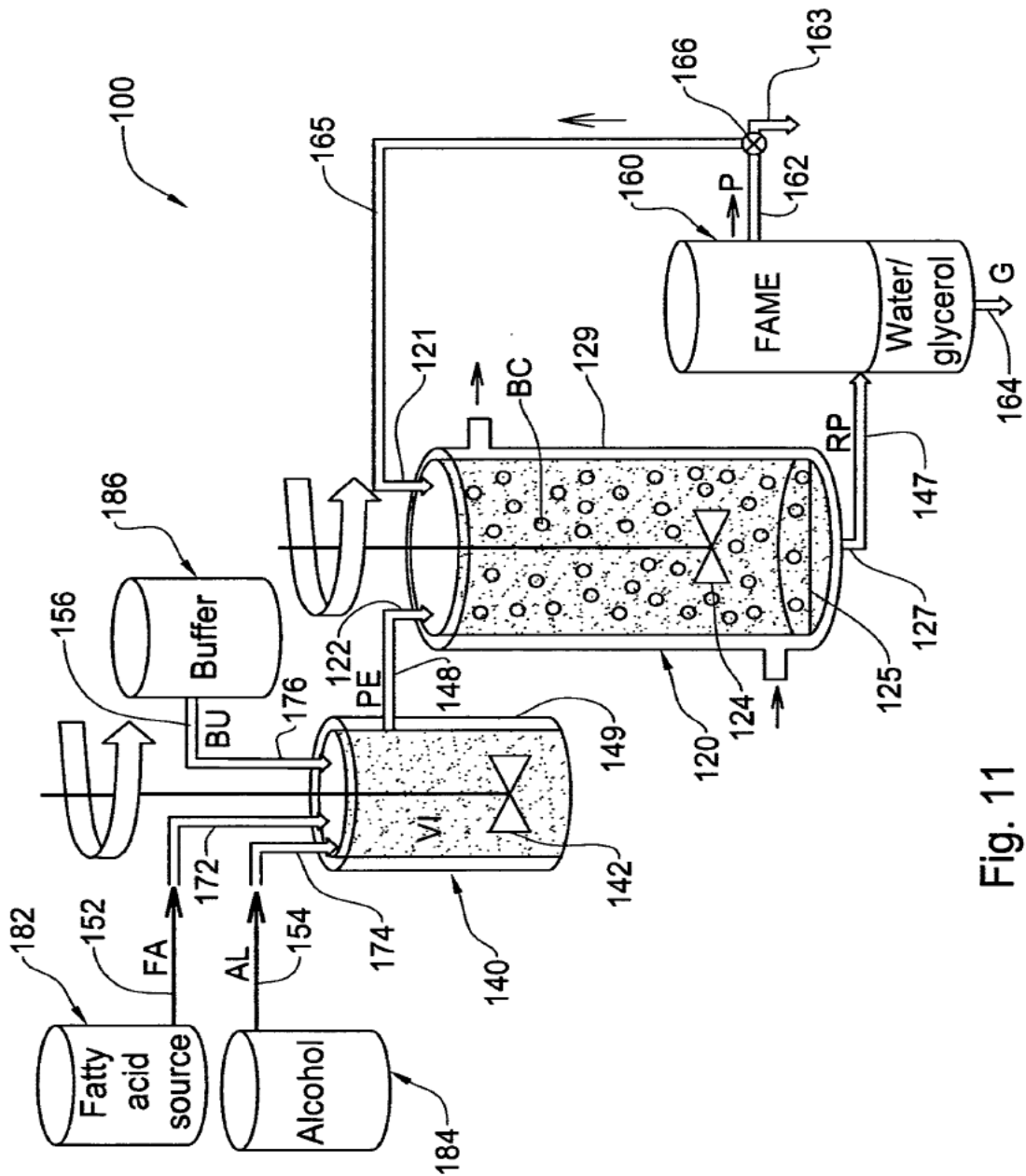


Fig. 11

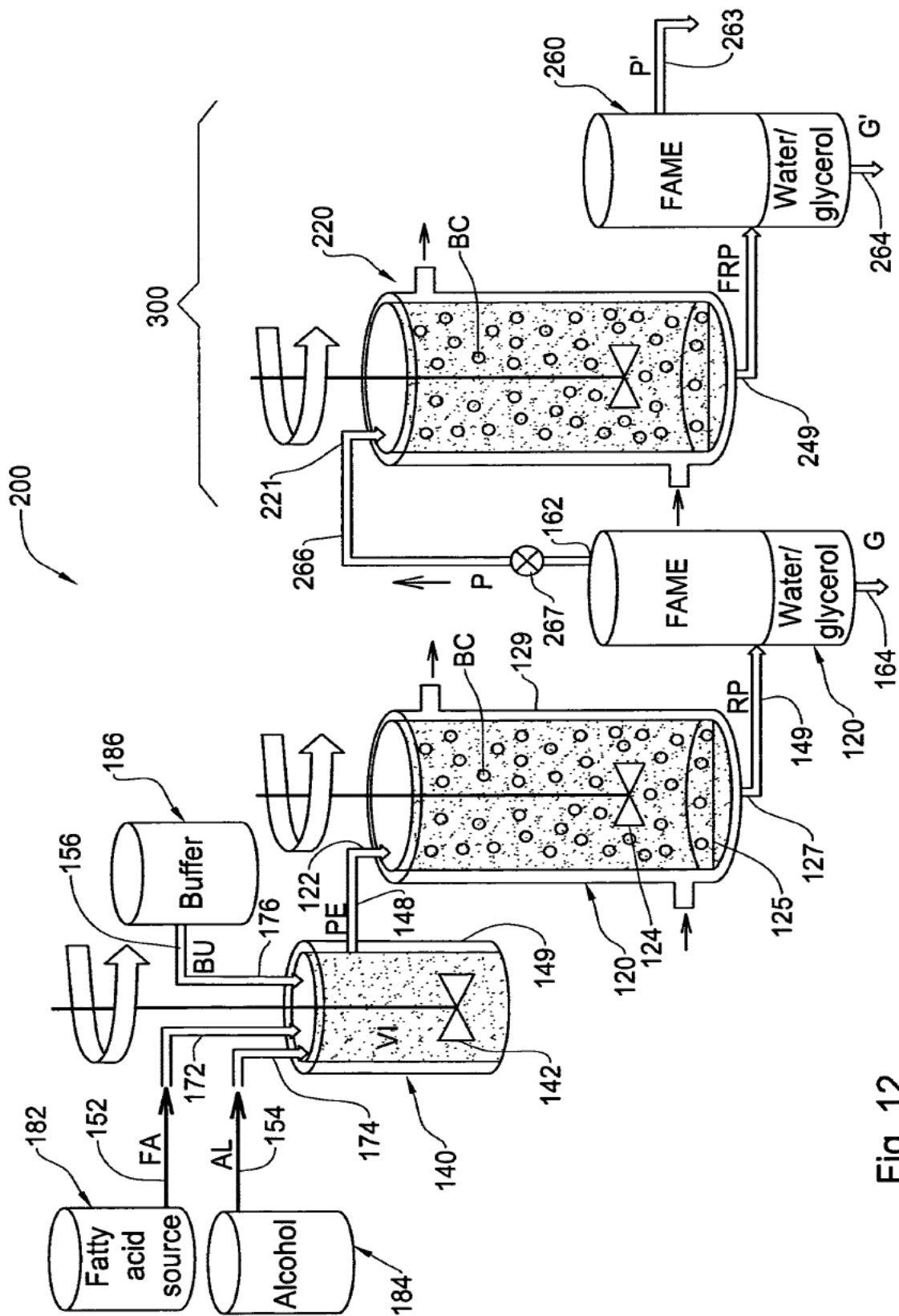


Fig. 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2011/000121

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12P7/64
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 582 594 A2 (COGNIS IP MAN GMBH [DE]) 5 October 2005 (2005-10-05) claims 1-10 examples 2-3 -----	1-14,17, 23-35, 37-40, 50-52,63
X	WO 2009/069116 A2 (TRANS BIODIESEL LTD [IL]; BASHEER SOBHI [IL]; HAJ MAISA [IL]; KAIYAL M) 4 June 2009 (2009-06-04) cited in the application example 3 claims 1-44 ----- -/--	7-63



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

26 July 2011

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2011/000121

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANDREW D. MACKENZIE ET AL: "Production of high-oleic acid tallow fractions using lipase-catalyzed direct interesterification, using both batch and continuous processing", ENZYME AND MICROBIAL TECHNOLOGY, vol. 27, 2000, pages 302-311, XP002653352, abstract page 304, paragraph 2.8 page 308, paragraph 3.6 page 311, left-hand column, last paragraph - right-hand column	7-37
X	----- FORESTI ET AL: "Multiple effects of water on solvent-free enzymatic esterifications", ENZYME AND MICROBIAL TECHNOLOGY, STONEHAM, MA, US, vol. 41, no. 1-2, 10 May 2007 (2007-05-10) , pages 62-70, XP022069882, ISSN: 0141-0229, DOI: DOI:10.1016/J.ENZMICTEC.2006.11.023 abstract	7-37
A	----- WO 2008/084470 A2 (TRANS BIODIESEL LTD [IL]; BASHEER SOBHI [IL]) 17 July 2008 (2008-07-17) cited in the application claims 1-20	1-63
A	----- XIN CHEN ET AL: "Effect of several factors on soluble lipase-mediated biodiesel preparation in the biphasic aqueous-oil systems", WORLD JOURNAL OF MICROBIOLOGY AND BIOTECHNOLOGY, KLUWER ACADEMIC PUBLISHERS, DO, vol. 24, no. 10, 13 March 2008 (2008-03-13), pages 2097-2102, XP019617136, ISSN: 1573-0972 abstract	1-63
A	----- SOK-JOONG KIM ET AL: "Lipase Catalyzed Transesterification of Soybean Oil using Ethyl Acetate, an Alternative Acyl Acceptor", BIOTECHNOLOGY AND BIOPROCESS ENGINEERING, vol. 12, 2007, pages 441-445, XP002653353, abstract page 442, left-hand column, last paragraph - right-hand column, paragraph f page 444, right-hand column, last paragraph	1-63

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IL2011/000121

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		KR 20090117725 A	12-11-2009
		US 2010035312 A1	11-02-2010



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶ : A61K	A2	(11) International Publication Number: WO 99/20224 (43) International Publication Date: 29 April 1999 (29.04.99)
(21) International Application Number: PCT/US98/21744 (22) International Filing Date: 15 October 1998 (15.10.98) (30) Priority Data: 08/953,132 17 October 1997 (17.10.97) US (71) Applicant: INTERNATIONAL FLORA TECHNOLOGIES, LTD. [US/US]; 1151 North Fiesta Boulevard, Gilbert, AZ 85233-2238 (US). (72) Inventor: ARQUETTE, Demetrios, James, G.; 434 E. Larkspur Drive, Tempe, AZ 85281 (US). (74) Agent: SLIFER, Russell, D.; Schwegman, Lundberg, Woessner & Kluth, P.O. Box 2938, Minneapolis, MN 55402 (US).		(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: EMOLLIENT COMPOSITIONS (57) Abstract An emollient composition is described which comprises: partially saturated wax esters comprising: IV. $R^1\text{-COO-CH}_2$ and/or V. $R^2\text{-COO-CH}_2\text{-R}^1$, at least 10 % by weight of alkyl esters comprising: VI. $R^1\text{-COO-R}^4$ and/or VII. $R^2\text{-COO-R}^4$ and at least 10 % by weight of fatty alcohols comprising: VIII. $R^1\text{CH}_2\text{-OH}$ and/or IX. $R^2\text{CH}_2\text{-OH}$ wherein R^4 comprises an alkyl or other aliphatic group, such as $\text{C}_n\text{H}_{2n+1}$, wherein $n=1$ to 12, R^1 comprises $\text{CH}_3\text{-(CH}_2)_7\text{-CH=CH-CH}_2\text{-(CH}_2)_x\text{-}$, and R^2 comprises $\text{CH}_3\text{-(CH}_2)_y$ wherein x is 6, 8, 10 and/or 12 and y is 16, 18, 20 and/or 22. A process for producing the emollient comprises the steps of: a) providing a composition comprising jojoba oil and/or hydrogenated jojoba oil, b) adding an alcohol, e.g., having from 1 to 12 carbon atoms, to said composition, c) effecting alcoholysis on said jojoba oil mixed with said alcohol to produce an emollient, and d) effecting an interesterification of residual wax esters.		

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EMOLLIENT COMPOSITIONS

This invention relates to emollient compositions for use in cosmetic,
5 personal care and pharmaceutical preparations and more particularly to such
emollient compositions and processes for their preparation.

BACKGROUND OF THE INVENTION:

In the field of cosmetic, personal care, and pharmaceutical products
emollients are usually defined as an agent that softens or smooths the skin and
10 which tend to reduce the roughness, cracking and irritation of the skin. The
ancient Greek physician, Galen, is thought to have made one of the first
emollients consisting of beeswax, spermaceti, almond oil, borax and rosewater.

At the present, there are numerous ingredients which function as
emollients in a wide variety of products, and which ingredients may act in subtly
15 different ways. For example, certain emollients sit on the surface of the skin and
serve to impede water loss from the skin. Such ingredients generally comprise
large molecules that form a hydrophobic barrier to help prevent water from
leaving the surface of the skin. Examples of such emollients are silicone
derivatives and petroleum jelly.

20 Other ingredients that have been used as emollients include a number of
fatty acids derived from either plant or animal sources. Fatty acids generally
comprise aliphatic hydrocarbon or other organic chains with carboxylic
substituents on them, typically having between 8 and 24 carbon atoms in the
chain backbone. Fatty acids are often used in creams, lotions, shaving creams,
25 lipsticks and as pressing agents in pressed powders and blushes. Fatty acids
which are used in cosmetics formulations generally include at least stearic acid,
oleic acid, myristic acid and palmitic acid. Other typical fatty acids include
linoleic acid, behenic acid, and other common fatty acids of the general formula
 $C_nH_{2n+1}COOH$.

30 Fatty alcohols are also used as emollients. They are said to be less sticky
and less heavy than many other fatty materials, such as the fatty acids, and are
frequently used to improve the viscosity and stability of lotions and creams.

They also have utility in reactive hair dying and perming products. Examples of fatty alcohols which find use in the field of cosmetics and personal care products are cetyl alcohol, lauryl alcohol, stearyl alcohol and oleyl alcohol, and others of the general formula $C_nH_{2n+1}OH$.

- 5 Additional examples of emollients are fatty esters. One of the best qualities of fatty esters is that they do not feel as oily to the touch as some other types of emollient fatty ingredients. Examples include isopropyl palmitate, isopropyl myristate and glyceryl stearate.

- An important emollient is jojoba oil which is derived from the seed of the species *Simmondsia chinensis*. It is a plant derived oil with excellent skin feel which is composed almost exclusively of wax esters, with little or no triglycerides present. A major portion of the production of jojoba oil is used by the cosmetic industry as an emollient in a variety of products. Although jojoba oil has long been used as an emollient, some difficulty has been found in forming stable emulsions using the oil.

- The synthesis of esters and waxy esters of natural oils is known, as disclosed in U.S. Patent Nos. 4,031,019 and 4,152,278 (the "Bell" patents), and this technology may be traced back to earlier seminal work done in U.S. Patent No. 1,944,887. In the Bell patents, wax esters are prepared from acids obtained from hydrogenated vegetable oils. Fatty alcohols are esterified with the fatty acids to yield the wax esters which are described as useful for lubricants in replacement of sperm oil. U.S. Patent No. 1,944,887 describes the manufacture of esters from monobasic saturated fatty acids containing 6 to 13 carbon atoms with aliphatic monohydric alcohols containing from 12 to eighteen carbon atoms.

SUMMARY OF THE INVENTION:

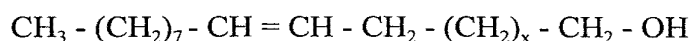
- The present invention describes a very effective emollient composition for use in personal care, cosmetic and pharmaceutical products and a novel method of producing that composition. The composition can be produced from

combinations of fatty alcohols, isopropyl esters and wax esters obtained from the oil contained in the seed of the jojoba plant (*Simmondsia chinensis*), jojoba oil.

These new emollient compositions preserve the excellent skin feel attributed to jojoba oil, which has long been used as an emollient, and also
5 increase the range of applications for cosmetic compositions by providing an emollient that can provide a more polar and hydrophilic quality than is found in jojoba oils, (which may also be referred to in the art as jojoba wax esters). The composition forms stable emulsions much more readily than does jojoba oil. The composition may also further provide excellent emolliency to normally dry
10 cosmetic systems involving high levels of pigments, with the emollient acting as a pigment wetting agent. It also functions as an excipient in pressed powder.

The compositions comprising fatty alcohols, isopropyl esters and jojoba wax esters (jojoba oil) may be obtained by the base catalyzed alcoholysis reaction between jojoba oil and isopropyl alcohol.

15 The fatty alcohol components of jojoba oil include a mixture of ingredients, but the largest segment of the oil comprises the fatty alcohols of the following general formula:



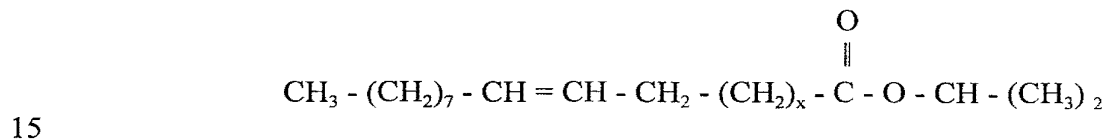
wherein X= 6, 8 , 10 or 12. The preferred fatty alcohols comprise those
20 where X= 8, 10 and/or 12.

Such fatty alcohols useful in the invention can be described as monounsaturated, straight chain, primary fatty alcohols (e.g., of 18 to 24 carbon atoms). A single double bond is located towards the middle of the respective fatty alcohol chain, specifically in the n-9 position (i.e., counted from the
25 terminal (-CH₃) group). The preferred fatty alcohols are composed of even numbers of carbon atoms, specifically, 20 and 22 carbon atoms. The typical composition of the fatty alcohols used in this invention as determined by gas chromatography (GC) is:

FATTY ALCOHOLS

X	(No. of carbon: No. of double bonds)	Typical % (area by GC)
6	18:1	1
8	20:1	52
5 10	22:1	38
12	24:1	6
	other fatty alcohols	3
	Total	100

- 10 The isopropyl esters derived from jojoba oils according to a practice of this invention may have the following general formula:



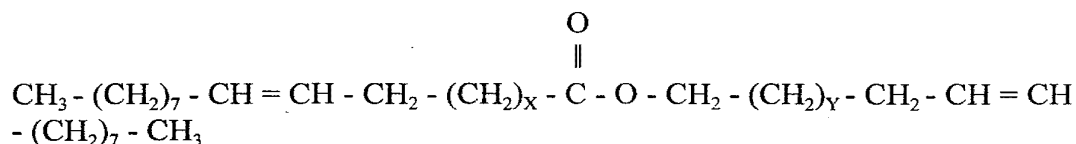
wherein X= 6, 8, 10 and/or 12, preferably 8, 10 and/or 12.

- Thus, the isopropyl esters useful in this invention are composed of monounsaturated, straight-chain fatty acids combined with isopropyl alcohol. The double bond is located in the middle of the respective fatty acid, specifically
- 20 in the n-9 position. The fatty acids are all of even number of carbon atoms, primarily 20 and 22 carbons. The typical composition of the isopropyl esters found in this invention as determined by gas chromatography is:

Fatty Acid Component of Isopropyl Ester (No. of carbon atoms: No. of double bonds)		
X	No. of double bonds)	Typical % (area by GC)
6	18:1	11
25 8	20:1	71
10	22:1	14
12	24:1	1
	trace isopropyl esters	3

- 30 The jojoba wax esters which have been described in the present invention for use in the emollient composition can also be called randomized or interesterified jojoba esters. Such wax esters have the following general formula:

5



5

wherein X and Y are 6, 8, 10 or 12.

The foregoing wax esters are composed of straight chain monounsaturated fatty alcohols and monounsaturated fatty acids. The single double bond is located in the middle (n-9 position), counting from the terminal methyl group, (-CH₃) of the respective fatty acid or alcohol chain. Such wax esters are composed of fatty alcohols and fatty acids of even number of carbon atoms, primarily 20 and 22 carbons. The resulting esters have chain lengths of 38, 40, 42 and 44 with a small amount of esters of 36- and 46-carbon atoms being present. The typical composition of the wax esters is set out below.

WAX ESTERS

(X, Y)	Wax Ester Chain Length	Typical % (area by GC)
(6,6)	36	1
(6,8) (8,6)	38	8
(6,10) (8,8) (10,6)	40	39
(10,8) (8,10)	42	38
(10,10)	44	13
(12,10) (10,12)	46	1

The emollient compositions of the present invention comprise fatty alcohols, alkyl esters (including the isopropyl esters), and interesterified esters as described herein. The emollient composition should have a minimum of at least about 10% by weight of the foregoing fatty alcohols, at least 10% by weight of the foregoing isopropyl esters, with the balance preferably comprising interesterified jojoba esters, that is, the wax esters. Preferably the amount of each of the fatty alcohols and isopropyl esters will be from about 30-35% by weight of the composition, with the balance being the wax esters (with other

emollient materials completing the balance). An especially preferred emollient composition will be as follows:

	<u>Ingredient</u>	<u>% by weight</u>
	Fatty alcohols	33
5	Isopropyl esters	33
	Wax esters	33

Other emollients may be blended, mixed or dissolved with the basic emollient compositions described above.

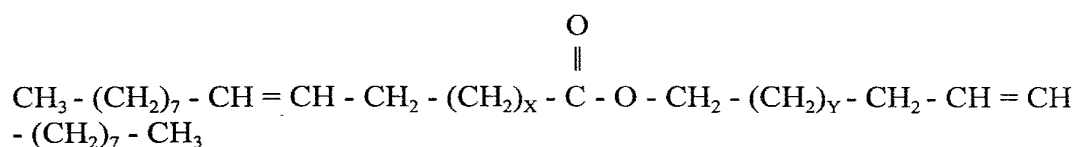
10 **DETAILED DESCRIPTION OF THE INVENTION:**

The present invention describes a very effective emollient composition for use in personal care, cosmetic and pharmaceutical products (especially topically applied pharmaceuticals) which can be produced from a combination of certain fatty alcohols, isopropyl esters and wax esters. More particularly, such
15 components of the emollient composition can be obtained from the oil contained in the seed of the jojoba plant (*Simmondsia chinensis*), jojoba oil.

The new emollient composition may preserve the excellent skin feel attributed to jojoba oil, which has long been used as an emollient, but increases the range of application and types of ingredients which may be combined into a
20 stable system with the emollient by providing an emollient that has a more polar and hydrophilic quality than is found in natural jojoba oils, also called jojoba wax esters. The composition forms stable emulsions much more readily than does jojoba oil and may further provide excellent emolliency to normally dry cosmetic systems involving high levels of pigments. It may also function as an
25 excipient in pressed powders.

The seed of the jojoba plant contains about 50% by weight of an oil composed mainly of the straight chain monoesters of the C₂₀ and C₂₂ monoenoic alcohols and C₂₀ and C₂₂ monoenoic acids. The almost complete absence of glycerin in jojoba oil indicates that it is unique from all known seed oils in that it
30 is not a triglyceride oil but a liquid wax. Jojoba oil, also known as jojoba wax esters, comprises materials which have the following general formula:

7



5

wherein X and Y are 6, 8, 10 or 12.

The foregoing wax esters are composed of straight chain monounsaturated fatty alcohols and monounsaturated fatty acids. The single double bond is located towards the middle (n-9 position), counting from the terminal methyl group, (-CH₃) of the respective fatty acid or alcohol chain. Such wax esters are composed of fatty alcohols and fatty acids of even number of carbon atoms, primarily 20 and 22 carbons. The resulting esters have chain lengths of 38, 40, 42 and 44 with a small amount of esters of 36-carbon and 46-carbon atoms being present. The typical composition of the wax esters is set out below.

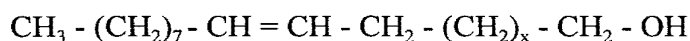
15

WAX ESTERS

(X, Y)	Wax Ester Chain Length	Typical % (area by GC)
(6,6)	36	1
(6,8) (8,6)	38	8
20 (6,10) (8,8) (10,6)	40	31
(8,10) (10,8)	42	49
(10,10)	44	10
(12,10) (10,12)	46	1

The fatty alcohols and alkyl (e.g., C1 to C12, especially isopropyl) esters useful in this invention may be obtained by the base catalyzed alcoholysis reaction between the jojoba esters (jojoba oil) and an appropriate aliphatic, e.g., appropriate alkyl alcohol, such as isopropyl alcohol. Thus the fatty alcohols useful in this invention have the following general formula:

30



wherein X= 6, 8, 10 and/or 12, preferably 8, 10 and 12.

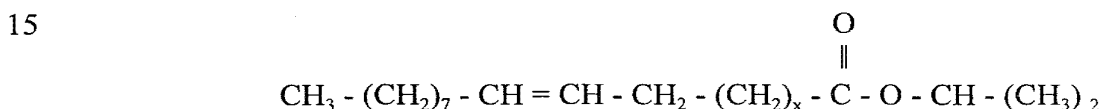
The fatty alcohols useful in the invention are monounsaturated, straight chain, primary fatty alcohols. The single double bond is located approximately in the middle of the respective fatty alcohol chain, specifically in the n-9

position. The fatty alcohols are composed of even numbers of carbon atoms, specifically, 20 and 22. The typical composition of the fatty alcohols found in this invention is:

FATTY ALCOHOLS

5	X	(No. of carbon: No. of double bonds)	Typical % (area by GC)
	6	18:1	1
	8	20:1	52
	10	22:1	38
	12	24:1	6
10		other fatty alcohols	3
		Total	100

The isopropyl esters typically found in this invention have the following general formula:



wherein X= 6, 8, 10 and/or 12, preferably 6, 8 or 10.

20 Thus, the isopropyl esters useful in this invention are composed of monounsaturated, straight chain fatty acids combined with isopropyl alcohol. The double bond is located in the middle of the respective fatty acid, specifically in the n-9 position. The fatty acids are all of even number of carbon atoms, primarily 20 and 22 carbons. The typical composition of the isopropyl esters

25 found in this invention is:

Fatty Acid Component of Isopropyl Ester (No. of carbon atoms:

	X	No. of double bonds)	Typical % (area by GC)
	6	18:1	11
	8	20:1	71
	10	22:1	14
30	12	24:1	1
		trace isopropyl esters	3

The emollient composition should have a minimum of at least about 10% by weight of the foregoing fatty alcohols, at least about 10% by weight of the foregoing isopropyl esters, preferably with the balance of the composition being jojoba esters, that is, the wax esters (although other emollient or inert or filler materials may be present in the emollient composition, not considering active or other functional materials). Preferably the amount of each of the fatty alcohols and isopropyl esters will be from about 30-35% by weight of the composition, with the balance being the wax esters. An especially preferred emollient composition is as follows:

<u>Ingredient</u>	<u>% by weight</u>
Fatty alcohols	33
Isopropyl esters	33
Wax esters	33

As the proportion of isopropyl esters and/or the fatty alcohols is increased, the emollient becomes more polar and of a lower viscosity, properties which should be very useful to the formulator. See the table immediately below.

Emollient Viscosity as a Function of Ester Content

	<u>Wax Ester %</u>	<u>Fatty Alcohol & Isopropyl Ester</u>	<u>Viscosity, centipoise @ 25°C</u>
20	100	0	41
	75	25	28
	50	50	22
	25	75	20
	10	90	17
25	0	100	17

One aspect of the present invention comprises an emollient carrier composition comprising:

partially saturated wax esters comprising:

(IV) $R^1\text{-COOO-CH}_2\text{-R}^2$ and/or (V) $R^2\text{-COOO-CH}_2\text{-R}^1$

at least 10% by weight of alkyl esters comprising:

(VI) $R^1\text{-COOO-R}^4$ and/or (VII) $R^2\text{-COOO-R}^4$, and

at least 10% by weight of fatty alcohols comprising:

(VIII) R^1CH_2-OH and/or (IX) R^2CH_2-OH

wherein R^4 comprises an alkyl or other aliphatic group (particularly $C_nH_{2n+1}OH$, where $n = 1$ to 12), R^1 comprises



5 R^2 comprises $CH_3 - (CH_2)_y -$

wherein x is 6, 8, 10 and/or 12, and y is 16, 18, 20 and/or 22. The term emollient carrier reflects the fact that the at least three materials described above (the partially saturated wax esters, the alkyl esters and the fatty alcohols) form a component which may be mixed, blended, dispersed, emulsified or dissolved with other materials, is itself an emollient, and may be a carrier for these other materials. Typical additional materials which may be combined with the emollient carrier of the invention may include, but are not limited to, additional emollients, oils, fragrances, pigments (e.g., inorganic pigments, organic pigments, dyes, medicaments (e.g., antimicrobial agents, antibacterial materials, antifungal materials, anti-inflammatory agents, transcutaneously administered drugs, etc.), emulsifying agents, stabilizing agents, binders, fillers, antiagglomerants (especially where powders are present in the emollient carrier, as with certain cosmetics), ultraviolet radiation absorbers (as in the formulation of sunblocks and sunscreens), insect repellants (e.g., DEET), pheromones, enzymes, barrier materials (e.g., resins to prevent contact with toxins such as plant irritants), and the like. These materials may be present in essentially any desired amount, but usually within the range of from 0.1% by weight of total composition up to 99% by weight of total composition, with 0.1 to 50% by weight preferred, and 0.5% to 25% by weight being more preferred.

25 The fundamental reactions used in the practice of the present invention may be generally considered in the following manner. Starting materials could include:

I. The alcohol,

R^4-OH (with isopropyl alcohol (IPA, $HO-CH_2-(CH_2)_2$) being primarily emphasized),

II. Jojoba Wax Esters
$$R^1 - \text{COO-CH}_2 - R^1, \text{ and}$$
III. Fully hydrogenated Jojoba Wax Esters
$$R^2 - \text{COO-CH}_2 - R^2$$

- 5 wherein R^4 is an alkyl or other aliphatic group, preferably of 1 to 12 carbon atoms, more preferably an *iso*-alkyl group, and most preferably an isopropyl group,

$$R^1 \text{ comprises } \text{CH}_3 - (\text{CH}_2)_7 - \text{CH} = \text{CH} - \text{CH}_2 - (\text{CH}_2)_x -, \text{ and}$$

$$R^2 \text{ comprises } \text{CH}_3 - (\text{CH}_2)_y -$$

- 10 wherein x is 6, 8, 10 and/or 12, and y is 16, 18, 20 or 22.

$$R^4 \text{ comprises } \text{C}_n\text{H}_{2n+1} -, \text{ wherein } n = 1 \text{ to } 12.$$

Typical product components from the preferred synthetic reactions used in the practice of the present invention with jojoba oil may include:

Partially saturated wax esters:

- 15 **IV.** $R^1 - \text{COO} - \text{CH}_2 - R^2$ and/or **V.** $R^2 - \text{COO-CH}_2 - R^1$,
(Where isopropyl alcohol was used) *Iso*-propyl esters
- VI.** $R^1 - \text{COO-CH} - (\text{CH}_3)_2$ [generically $R^1 - \text{COO-R}^4$] and/or **VII.** $R^2 - \text{COO-CH} - (\text{CH}_3)_2$ and
wax esters comprising
- 20 **VIII.** $R^1 \text{CH}_2 - \text{OH}$ and/or **IX.** $R^2 \text{CH}_2 - \text{OH}$.

The basic reactions which may be used in the preparation of the emollient compositions of the invention derived from jojoba oil may include at least the following procedures.

- Reaction A** **I** and **II**_n (catalyst) → **VI**, **VIII** and **II**_r. This product is
25 referred to herein as "IPJ" and is a liquid.

Reaction B **I** and **III**_n (catalyst) → **VII**, **IX** and **III**_r. This product is referred to herein as "fully hydrogenated IPJ" or "HIPJ" and is a solid.

- Reaction C** **I**, and **II**_n and **III**_n (catalyst) → **IV**, **V**, **VI**, **VII**, **VIII**, **IX**, **II**_r and **III**_r. This product is referred to herein as "the broad melting range
30 emollient" and the properties of the emollient depend upon the relative amounts of **II**_n and **III**_n.

The subscripts n and r respectively represent n= the naturally occurring distribution of wax esters and r= the randomized distribution of wax esters resulting from rearrangements which occur during the reactions. It is to be noted that mixing of the reaction products from A and B will give emollients with a wide range of melting points, but will not be identical to the reaction product of C because of the absence of IV and V.

A process for producing an emollient may comprise the steps of:

- a) providing a composition comprising jojoba oil,
- b) adding an alcohol, e.g., having from 1 to 12 carbon atoms, to said composition,
- c) effecting alcoholysis on said jojoba oil mixed with said alcohol to produce an emollient, and
- d) effecting interesterification of remaining wax esters.

In preparing the emollient composition, refined jojoba oil (or hydrogenated jojoba oil or a mixture of the oil and hydrogenated oil) is introduced into an appropriate vessel (capable of excluding air) equipped with stirring and means of heating and cooling. The jojoba oil is first dried under vacuum and at a temperature of 90°C to remove most or all moisture. The anhydrous isopropyl alcohol (or other alcohol) is then added with the amount of isopropyl used being from about 20% to about 50% by weight of jojoba oil. The reactor is sealed and heat is applied to bring the temperature of the reaction mixture to about 70-75°C. It is important that air be excluded and that the reactor be vented through a condenser to recover any unreacted alcohol. When the temperature has reached 70-75°C, a first addition of catalyst (e.g., a catalyst for alcoholysis and interesterification such as sodium methoxide) is made. The amount added ranges from about 0.5% to about 0.6% by weight of the jojoba oil with about 0.3% being preferred. After about 2 hours, a sample is taken and analyzed for the presence of the wax esters. If the wax ester content is greater than about 25% by weight, and it is desired to have a lower level of wax esters present in the reaction mixture, a second addition of catalyst is made, about 0.1% by weight of the original amount of jojoba oil. The reaction is then continued for

an additional one hour. The reaction mixture is then sampled and analyzed again. If the residual wax ester content is less than about 25-35%, the reaction may be considered to be complete. Heating is discontinued but no cooling is applied. If the reaction is considered incomplete, a third catalyst addition may be made and the reaction continued as previously described. Any remaining catalyst can be neutralized and deactivated by the addition of citric acid. After about 15 minutes of agitation the neutralized catalyst (sodium citrate) is removed by filtration. Once the catalyst has been removed, any remaining isopropyl alcohol can be distilled from the product and the recovered isopropyl alcohol should be kept absolutely dry in order to be able to be used again.

Following the previously described procedure, Examples I, II and III detail the preparation of three batches of emollient compositions.

Example I

15	<u>Input Material</u>	<u>Weight kg</u>
	Refined jojoba oil	99.90
	Isopropyl Alcohol	24.80
	Catalyst (Na methoxide)	0.43
20	Filter Aid	2.00
	<u>Output Materials</u>	<u>Weight kg</u>
	Emollient composition	99.4
25	comprising jojoba esters, fatty alcohols and isopropyl esters	
	Recovered isopropyl alcohol	13.0

30 The emollient composition was then bleached using 1% by weight of Clarion™ 470 bleaching clay supplied by American Colloid Company. The amount of bleached emollient composition obtained was 89.8 kg, a yield of about 90.8% based on the weight of the starting jojoba oil. After bleaching, the composition was deodorized followed by the addition of 0.5 kg. (500 ppm) of the antioxidant, Tenox GT-2, supplied by Eastman Chemical Company.

Analysis of the emollient composition by gas chromatograph gave the following results:

	Fatty Alcohols (Chain Length)	%
5	20	14.6
	22	15.0
	24	<u>3.3</u>
	Total	32.9
10	Isopropyl Esters (Chain length)	
	18	3.0
	20	21.0
	22	4.5
	24	<u>0.6</u>
15	Total	29.1
	Wax Esters (Chain length)	
	38	3.2
	40	15.6
20	42	12.9
	44	4.8
	46	<u>0.6</u>
		37.4

25 **Observations:**

The reaction was run at 70-75°C. Starting with an amount of isopropyl alcohol equal to 25% of jojoba oil added, the reduction of wax esters became very slow after reaching 47%. Addition of more catalyst (0.1%), four hours after the initial addition, had only a slight effect of further reduction of wax esters.

30 This product is liquid at room temperature.

	Time, hours	Comments
	0	Addition of 0.3% catalyst, beginning of reaction, 100% wax esters
	2	46.9% residual wax esters
35	3.5	42% residual wax esters
	4	add 0.1% catalyst
	4.5	38% residual wax esters
	6	add citric acid and end reaction

15

Example II

	<u>Input Material</u>	<u>Weight kg</u>
	Refined jojoba oil	101.00
	Isopropyl Alcohol	46.50
5	Catalyst (Na methoxide)	0.30
	Filter Aid	2.00
	Citric Acid	0.25
	<u>Output Materials</u>	<u>Weight kg</u>
10	Emollient composition comprising jojoba oil, fatty alcohols and isopropyl esters	100.00
15	Recovered isopropyl alcohol	29.25

The foregoing composition was then bleached using 2.03% by weight of Clarion™ 470 bleaching clay supplied by American Colloid Company. The amount of bleached emollient composition obtained was 91.9 kg, a yield of about 91.4% based on the weight of the starting jojoba oil. After bleaching, the composition was deodorized followed by addition of 0.55 kg. of Tenox GT-2, supplied by Eastman Chemical Company.

Analysis of the composition by gas chromatograph gave the following results:

	Fatty Alcohols (Chain Length)	%
	20	17.2
	22	15.7
	24	<u>3.1</u>
30	Total	36.0
	Isopropyl Esters (Chain length)	
	18	4.2
	20	25.8
35	22	4.9
	24	<u>0.5</u>
	Total	35.4

16

Wax Esters (Chain length)		
5	38	2.2
	40	10.6
	42	10.9
	44	3.1
	46	<u>0.8</u>
		27.6

Observations:

- 10 This reaction was run at 80-85°C. Starting with an amount of isopropyl alcohol equal to 46% of jojoba oil added, the reduction of wax esters was accelerated. The residual wax ester content was approximately 28% after two hours with no additional catalyst being added. There was no change in the ester composition after an additional hour. The reaction was terminated by the
- 15 addition of citric acid. The filtration of the sodium citrate proved difficult. There was a darker yellow color in this run as compared with example I. This was attributed to running the reaction at the higher temperature.

Example III

20	<u>Input Material</u>	<u>Weight, kg</u>
	Hydrogenated jojoba oil	144
	Isopropyl alcohol	72
	Catalyst (Na methoxide)	0.576
	Citric acid	0.36
25	<u>Output Materials</u>	
	Emollient composition comprising saturated jojoba ester; Saturated fatty alcohols and saturated isopropyl esters	117.3
30	Recovered isopropyl alcohol	42

The foregoing composition was then bleached using 2% by weight Clarion 470 bleaching clay supplied by American Colloid Co. Following bleaching, the composition was deodorized. To the final product 0.08 kg of

Tenox GT-2 supplied by Eastman Chemical Co. were added as an antioxidant.

The yield was 81%.

Analysis of the emollient composition by gas chromatography gave the following results:

5	Saturated Fatty Alcohols (Chain length)	Percent (%)
	20	17.2
	22	17.2
	24	3.4
	<i>Total</i>	37.8
10	Saturated Isopropyl Esters (Chain length)	Percent (%)
	18	4.0
	20	24.5
	22	4.8
15	24	3.4
	<i>Total</i>	36.7
	Saturated Jojoba Esters (Chain length)	Percent (%)
	38	1.8
20	40	9.7
	42	9.7
	44	3.1
	46	0.4
	<i>Total</i>	24.7

25

Observations:

This reaction was run at 70-74°C for two hours. Starting with an amount of isopropyl alcohol equal to 50% of the hydrogenated jojoba oil added, the reduction of wax esters was essentially complete when the residual wax esters reached 25%. The melting point of the product was 50-60°C.

To demonstrate the usefulness of the emollient compositions of this invention, the following examples show the preparation of a sun screen, eye cream, lipstick and foundation product. In each example, the product was prepared using an emollient composition of this invention and compared to the same product using a commercially available emollient.

35

Example IV

Two (2) different lipsticks were prepared, one using an emollient composition of this invention; the other a conventional emollient, jojoba oil.

5	Phase	Ingredient	Product	
			III-A	III-B
10	A	Castor Oil	41.0	41.0
		Jojoba Oil	15.0	-----
		Special Emollient *	-----	15.0
		Jojoba Esters	1.0	1.0
		Carnauba Wax	4.0	4.0
		Candelilla Wax	5.0	5.0
		Beeswax	3.5	3.5
		Microcrystalline Wax	4.0	4.0
		Propylparaben	0.1	0.1
		Silica	0.2	0.2
20	B	Castor Oil	13.0	13.0
		Polyhydroxystearic Acid	0.5	0.5
		Titanium Dioxide	5.5	5.5
		Iron Oxides - Red 3511	4.0	4.0
		D & C Red 30, Talc Lake	2.5	2.5
		FD & C Blue No. 1, Aluminum Lake	0.1	0.1
		Iron Oxides - Black 3070	0.5	0.5
25	C	Tocopherol	<u>0.1</u>	<u>0.1</u>
		TOTAL	100.0	100.0

* Emollient consisted of IPJ: 30% jojoba wax esters; 32% isopropyl esters; and 36% jojoba alcohols.

30

- I. Combine ingredients of Phase A and heat to 85°C with moderate agitation.
- II. Combine Phase B and pass 2 times through a 3-roll mill. Add Phase B to Phase A with propeller agitation.
- 35 III. Cool batch to 75°C, add Phase C and mix with propeller agitation. Fill as soon as possible.

Observations:

In comparing products III-A and III-B, it was observed that product III-B, which contained an emollient composition of this invention, had a smoother
40 application, better slip and more gloss than product III-A.

Example V

Three different foundation creams were prepared, one using the emollient composition of this invention.

5	Phase	Ingredient	IV-A	IV-B	IV-C
	A	Water	53.63	53.63	53.63
		Cellulose Gum	0.30	0.30	0.30
		Magnesium Aluminum Silicate	0.80	0.80	0.80
10		Propylene Glycol	10.00	10.00	10.00
	B	Talc	3.00	3.00	3.00
		Titanium Dioxide	11.00	11.00	11.00
		Iron Oxides - Red 3080	0.20	0.20	0.20
		Iron Oxides - Yellow 3170	1.14	1.14	1.14
15		Iron Oxides - Red 3551	0.22	0.22	0.22
		Iron Oxides - Black 3070	0.28	0.28	0.28
	C	Disodium Oleamide PEG-2 Sulfosuccinate	0.13	0.13	0.13
	D	Special Emollient *	11.00	-----	-----
		Jjoba Esters	-----	11.00	-----
20		Isopropyl Palmitate	-----	-----	11.00
		Tocopheryl Acetate	0.20	0.20	0.20
		Cetyl Alcohol	0.50	0.50	0.50
		Stearic Acid	2.40	2.40	2.40
		Glyceryl Stearate & PEG-100 Stearate	0.60	0.60	0.60
25		Dimethicone	0.20	0.20	0.20
		Cyclomethicone	3.00	3.00	3.00
	E	Propylene Glycol & Diazolidinyl Urea	1.00	1.00	1.00
		(and) Methylparaben (and) Propylparaben			
		Triethanolamine	0.40	0.40	0.40
30		TOTAL	100.00	100.00	100.00

* Emollient consisted of: IPJ 30% jojoba wax esters; 32% isopropyl esters; and 36% jojoba alcohols.

- I. Heat water of Phase A to 75°C, Premix CMC and Veegum. Add CMC and Veegum to water with rapid propeller agitation. Mix for 30 minutes. Add propylene glycol to water with moderate agitation; mix for 10 minutes at 75°C.
- II. Add pigments/talc of Phase B to Phase A at 75°C with high speed homomixer agitation. Agitate for 30 minutes.
- III. Add Phase C to Phase AB with moderate homomixer agitation. Mix 10 minutes and hold at 80°C.

- IV. Combine Phase D and heat to 80°C with agitation. With Phase ABC and Phase D at 80°C, add Phase D slowly to Phase ABC with moderate propeller agitation. Mix 20 minutes and then force cool with agitation to 75°C.
- 5 V. Add Phase E to batch at 75°C and cool to room temperature with moderate propeller agitation.

Observations:

The foregoing products are oil in water emulsions. It was observed that product IV-A, which contained an emollient composition of this invention,

10 exhibited longer playtime, smoother application, and a richer, more moist feel than products IV-B and IV-C.

Example VI

Two eye creams were prepared; one using the emollient composition of

15 this invention.

Phase	Ingredient	V-A	V-B
A	Water	73.35	73.35
	Disodium EDTA	0.05	0.05
	Carbomer	0.30	0.30
	20 Methylparaben	0.20	0.20
	Imidiazolidinyl Urea	0.15	0.15
B	Special Emollient *	18.0	-----
	Isopropyl Palmitate	-----	18.00
	25 Glyceryl Stearate & PEG-100 Stearate	1.50	1.50
	Propylparaben	0.10	0.10
	Polysorbate 60	2.20	2.20
	Sorbitan Stearate	0.50	0.50
	Cetyl Alcohol	1.10	1.10
	30 Stearic Acid	0.50	0.50
	Tocopheryl Acetate	0.20	0.20
C	Triethanolamine	0.35	0.35
35 D	Acetamide MEA	<u>1.50</u>	<u>1.50</u>
	TOTAL	100.0	100.0

* Emollient consisted of: IPJ 30% jojoba wax esters; 32% isopropyl esters; and 36% jojoba alcohols.

- I. Slowly sprinkle Carbopol of Phase A into cold water with rapid propeller agitation. Add remaining ingredients and heat Phase A to 80° with agitation.
- II. Heat Phase B to 80°C with agitation.
- III. Add Phase B slowly to Phase A with moderate propeller agitation. Mix 10-15 minutes until mixture is uniform.
- IV. Add Phase C and Phase D to batch with moderate propeller agitation. Mix 10-15 minutes until mixture is uniform. Cool to room temperature.

Observations:

These eye creams are oil in water emulsions. It was observed that product V-A exhibited less drying, was of a smoother consistency, longer playtime and easier to emulsify than product V-B.

Example VII

Two sun screen preparations were made; one using isopropyl palmitate (IPP) and the other using the emollient of this invention in place of the IPP.

Phase	Ingredient	VI-A	VI-B
A	Special Emollient *	4.60	-----
	Isopropyl Palmitate	-----	4.60
	Cetyl Dimethicone Copolyol	2.00	2.00
	PPG-3 Myristyl Ester	0.50	0.50
25	Hydrogenated Caster Oil	0.75	0.75
	Microcrystalline Wax	1.25	1.25
	Cyclomethicone	4.00	4.00
	Cetyl Dimethicone	1.00	1.00
	Titanium Dioxide & Hybrid Sunflower	3.00	3.00
30	(Helianthus Annuus) Oil		
B	Octyl Methoxycinnamate	4.50	4.50
	Benzophenone-3	2.50	2.50
	Octyl Palmitate	5.50	5.50
35	C		
	Water	68.20	68.20
	Propylene Glycol	0.40	0.40
	Sodium Chloride	0.80	0.80

D	Propylene Glycol & Diazolidinyl Urea (and) Methylparaben (and) Propylparaben Triethanolamine	1.00	1.00
5	TOTAL	100.0	100.0

* Emollient consisted of: IPJ 30% jojoba wax esters; 32% isopropyl esters; and 36% jojoba alcohols.

- 10 I. Combine Phase A and heat to 75°C, making sure all waxes melt and mixture is homogeneous. Then cool to 55°C.
- II. Premix and heat Phase B to 45°C with moderate agitation until all the Benzophenone-3 has dissolved.
- III. Add Phase B to Phase A with moderate agitation.
- 15 IV. Heat water of Phase C to 65°C. Premix propylene glycol, methylparaben and propylparaben and add to heated water with agitation. Add sodium chloride. Mix 5-10 minutes, allowing sodium chloride to dissolve and mixture to cool to 55°C.
- V. Add Phase C slowly and continuously to Phase AB with moderate
- 20 agitation. Maintain a creamy appearance by increasing agitation as mixture increases viscosity.
- VI. Once combined allow to mix for 10-15 minutes and cool to 45°C.
- VII. Add Phase D with agitation and force cool to 30°C.
- VIII. Once batch has cooled to 30°C, homogenize for approximately 10
- 25 minutes.

Observations:

The foregoing sunscreen products are water in oil emulsions. It was observed that product VI-A exhibited better spreadability and a smoother feel than product VI-B.

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Example VIII: Lipstick

A lipstick was prepared using the two special emollients of this invention.

	Phase	Ingredient	% wt./wt.
	A.	Castor Oil	Q.S.
		Special emollient **	5.0
		Special emollient *	7.5
5		Jojoba Esters-15	5.0
		Jojoba Esters-70	1.0
		Jojoba Oil	2.5
		Ceresin	3.5
		Ozokerite	4.0
10		Microcrystalline Wax	4.0
		Polyparaben	0.1
		Silica	0.2
	B.	Castor Oil	13.0
		Polyhydroxystearic Acid	0.5
15		Titanium Dioxide	5.5
		Iron Oxides	3.5
		D&C Red No. 30 Talc Lake	2.5
		FD&C Blue No. 1 Aluminum Lake	0.1
		Iron Oxides	0.8
20		Carmine	0.2
	C.	Tocopherol	0.1
		TOTAL	100.0

* Emollient consisted of: IPJ: 30% by weight jojoba wax esters; 32% isopropyl
 25 esters; and 36% jojoba alcohols.

** Emollient consisted of: HIPJ: 25% saturated jojoba wax esters; 37%
 saturated isopropyl esters; and 38% saturated jojoba alcohols.

- I. Combine ingredients of Phase A and heat to 85°C with moderate
 30 agitation.
- II. Combine Phase B and pass 2 times through a 3-roll mill. Add Phase B to
 Phase A with propeller agitation.
- III. Cool batch to 75°C, add Phase C and mix with propeller agitation. Fill as
 soon as possible.

Observations: The IBJ helps to wet and disperse the pigments in this lipstick, yielding a smoother, more even coverage to the lipstick. IPJ provides slip and gloss, and has no objectionable taste. HIPJ contributes to the wax matrix and strengthens the stick.

5

Example IX: Mascara

A mascara was prepared using the Special Emollient ** of this invention.

	Phase	Ingredient	% wt./wt.
10	A.	Water	Q.S.
		Propylene Glycol	3.0
		Triethanolamine	2.6
	B.	Acrylates/Octylacrylamide Copolymer	4.0
15	C.	Jojoba Esters 20	5.0
		Carnauba Wax	1.0
		Candelilla Wax	4.0
		Synthetic Beeswax	5.0
		Special Emollient **	3.0
		Cetyl Alcohol	3.0
20		Stearic Acid	5.0
		Tocopheryl Acetate	0.2
	D.	Iron Oxides (and) Isopropyl Titanium Triisostearate	11.0
25	E.	Keratin Amino Acids	0.1
		Panthenol	0.5
		Preservative	Q.S.
		TOTAL	100.0

** Emollient consists of: HIPJ: 25% saturated jojoba wax esters; 37% saturated isopropyl esters; and 38% saturated jojoba alcohols.

- I. Heat water of Phase A to 90-95°C and hold for 30 minutes. Begin cooling to 85-90°C and add remaining ingredients in order listed with moderate propeller agitation.
- II. Slowly sprinkle Phase B into Phase A at 85-90°C with moderate propeller agitation. Mix for 30 minutes with propeller agitation at 85-90°C (cover beaker to avoid water loss).
- III. Combine Phase C and heat to 90°C with moderate propeller agitation. When Phase C reaches 90°C, add Phase D (iron oxides) to Phase C with high shear homomixer agitation for 30 minutes.
- IV. Add Phase CD slowly to AB at 85-90°C with moderate propeller agitation. Mix 10 minutes. Force cool with propeller and sweep agitation to 50°C.
- V. At 50°C, add Phase E in given order to Phase ABCD (batch) with sweep agitation for 20 minutes. Cool batch to 28-30°C with sweep agitation.
- Observations:** This luxurious water-resistant mascara will add thickness and length to the eyelashes. The HIPJ helps to condition and thicken the lash, and contribute to the smooth, even application of this mascara to the lash.

Example X: Lipbalm

A lipbalm wax prepared using the Special Emollient** of this invention.

Phase	INCI Name	% wt./wt.
A.	Castor Oil	Q.S.
	Jjoba Esters	13.000
	Jjoba Esters	6.500
	Jjoba Esters (or) Hydrogenated	1.000
	Jjoba Oil	
	Carnauba Wax	4.100
	Candelilla (Euphorbia Cerifera) Wax	5.100
	Beeswax	2.000
	Special Emollient**	3.000
	Cetyl Ricinoleate	2.000
	Isopropylparaben (and)	Q.S.
	Isobutylparaben (and) Butylparaben	

	Phase	INCI Name	% wt./wt.
	B.	Titanium Dioxide (and) Hybrid Sunflower (Helianthus Annuus) Oil	3.000
	C.	Beta-Carotene	0.003
		Octyl Methoxycinnamate	5.000
		Tocopherol	0.500
5		Flavor	2.000
		TOTAL	100.000

** Emollient consisted of: HIPJ: 25% saturated jojoba wax esters; 37% saturated isopropyl esters; and 38% saturated jojoba alcohols.

10

- I. Combine ingredients of Phase A and heat to 85°C with moderate agitation.
- II. Add Phase B to Phase A and mix with propeller agitation.
- III. Cool batch to 75°C, add Phase C and mix with propeller agitation. Fill as soon as possible.

15

Observations: HIPJ forms an occlusive, emollient moisture barrier on the lips that helps keep them soft and supple when exposed to the elements (wind, sun, cold and dry heat). Each of the natural botanical emollients exhibits excellent oxidative stability. HIPJ contributes to the strength of the wax matrix.

20

The following list of cosmetic category codes identifies fields of use for the cosmetic emollient compositions and carriers of the present invention.

Table 1-2. FDA cosmetic category codes

- 25 01. Baby products.
 - A. Baby shampoos
 - B. Lotions, oils, powders and creams
 - C. Other baby products
- 30 02. Bath preparations
 - A. Bath oils, tablets and salts
 - B. Bubble Baths
 - C. Bath capsules
 - D. Other bath preparations

- 03. Eye makeup preparations
 - A. Eyebrow pencil
 - B. Eyeliner
 - C. Eye shadow
 - 5 D. Eye lotion
 - E. Eye makeup remover
 - F. Mascara
 - G. Other eye makeup preparations
- 10 04. Fragrance preparations
 - A. Cologne and toilet waters
 - B. Perfumes
 - C. Powders (dusting and talcum, excluding aftershave talc)
 - D. Sachets
 - 15 E. Other fragrance preparations
- 05. Hair preparations (non-coloring)
 - A. Hair conditioner
 - B. Hair spray (aerosol fixatives)
 - 20 C. Hair straighteners
 - D. Permanent waves
 - E. Rinses (non-coloring)
 - F. Shampoos (non-coloring)
 - G. Tonics, dressings, and other hair grooming aids
 - 25 H. Wave sets
 - I. Other hair preparations
- 06. Hair coloring preparations
 - A. Hair dyes and colors (all types requiring caution statements and patch tests)
 - 30 B. Hair tints
 - C. Hair rinses (coloring)
 - D. Hair shampoos (coloring)
 - E. Hair color sprays (aerosol)
 - 35 F. Hair lighteners with color
 - G. Hair bleaches
 - H. Other hair coloring preparations
- 07. Makeup preparations (not eye)
 - 40 A. Blushers (all types)
 - B. Face powders
 - C. Foundations
 - D. Leg and body paints
 - E. Lipstick
 - 45 F. Makeup bases
 - G. Rouges
 - H. Makeup fixatives

- I. Other makeup preparations
 - 08. Manicuring preparations
 - A. Basecoats and undercoats
 - 5 B. Cuticle softeners
 - C. Hair creams and lotions
 - D. Nail extenders
 - E. Nail polish and enamel
 - F. Nail polish and enamel removers
 - 10 G. Other manicuring preparations
 - 09. Oral hygiene products
 - A. Dentifrices (aerosol, liquid, pastes and powders)
 - B. Mouthwashes and breath fresheners (liquids and sprays)
 - 15 C. Other oral hygiene products
 - 10. Personal cleanliness
 - A. Bar soaps and detergents
 - B. Deodorants (underarm)
 - 20 C. Douches
 - D. Feminine hygiene deodorants
 - F. Other personal Cleanliness products
 - 11. Shaving preparations
 - 25 A. Aftershave lotion
 - B. Beard softeners
 - C. Men's talcum
 - D. Preshave lotions (all types)
 - E. Shaving cream (aerosol, brushless and lather)
 - 30 F. Shaving soap (cakes, sticks, etc.)
 - G. Other shaving preparations products
 - 12. Skin care preparations (creams, lotions, powder and sprays)
 - A. Cleansing (cold creams, cleansing lotions, liquids and pads)
 - 35 B. Depilatories
 - C. Face and neck (excluding shaving preparations)
 - D. Body and hand (excluding shaving preparations)
 - E. Foot powders and sprays
 - F. Moisturizing
 - 40 G. Night
 - H. Paste masks (mud pacts)
 - I. Skin fresheners
 - J. Other skin products
 - 45 13. Suntan preparations
 - A. Suntan gels, creams and liquids
 - B. Indoor tanning preparations

C. Other suntan preparations

WHAT IS CLAIMED:

1. An emollient composition comprising:
 at least 10% by weight fatty alcohols comprising:
VIII. R^1CH_2-OH and/or **IX.** R^2CH_2-OH
 5 at least 10% by weight of alkyl esters comprising:
VI. $R^1-COO-R^4$ and/or **VII.** $R^2-COO-R^4$ and
 wax esters comprising:
IV. $R^1-COO-CH_2-R^2$ and/or **V.** $R^2-COO-CH_2-R^1$,
 wherein R^4 comprises an alkyl, a $(C_nH_{2n+1})-$, or other aliphatic group,
 10 R^1 comprises $CH_3-(CH_2)_7-CH=CH-CH_2-(CH_2)_x-$, and
 R^2 comprises $CH_3-(CH_2)_y$ wherein
 n is 1 to 12, x is 6, 8, 10 and/or 12, and y is 16, 18, 20 and/or 22.
2. The emollient composition of claim 1, wherein R^4 is $(CH_3)_2-CH-$.
- 15 3. The emollient composition of claim 1 wherein at least one R^4 comprises
 an isopropyl group.
4. An emollient carrier composition comprising:
 20 partially saturated wax esters comprising:
IV. $R^1-COO-CH_2-R^2$ and/or **V.** $R^2-COO-CH_2-R^1$,
 at least 10% by weight of alkyl esters comprising:
VI. $R^1-COO-R^4$ and/or **VII.** $R^2-COO-R^4$ and
 at least 10% by weight of fatty alcohols comprising:
 25 **VIII.** R^1CH_2-OH and/or **IX.** R^2CH_2-OH
 wherein R^4 comprises an alkyl, a $(C_nH_{2n+1})-$, or other aliphatic group,
 R^1 comprises $CH_3-(CH_2)_7-CH=CH-CH_2-(CH_2)_x-$, and
 R^2 comprises $CH_3-(CH_2)_y$ wherein x is 6, 8, 10 and/or 12 and y is 16, 18,
 20 and 22, and
 30 at least one additional ingredient selected from the group consisting of
 oils, fragrances, pigments, inorganic pigments, organic pigments, dyes,

medicaments, antimicrobial agents, antibacterial materials, antifungal materials, anti-inflammatory agents, transcutaneously administered drugs, emulsifying agents, stabilizing agents, binders, fillers, antiagglomerants, ultraviolet radiation absorbers, insect repellants, pheromones, enzymes, and barrier materials.

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5. The emollient carrier of claim 4 wherein R^4 comprises an alkyl, C_nH_{2n+1} wherein n is a positive integer.

6. The emollient carrier of claim 5 wherein at least one R^4 comprises an
10 isopropyl group.

7. The emollient of claim 1 wherein said fatty alcohol (R^1CH_2-OH and/or R^2CH_2-OH) comprises at least 33% by weight of said emollient carrier.

15 8. The emollient of claim 1 wherein said wax ester ($R^1-COO-CH_2-R^2$ and/or $R^2-COO-CH_2-R^1$) comprises at least 33% by weight of said emollient carrier.

9. The emollient of claim 1 wherein said alkyl esters ($R^1-COO-CH_2-(CH_3)_2$ and/or $R^2-COO-CH_2-(CH_3)_2$) comprises at least 33% by weight of said
20 emollient carrier.

10. A cosmetic composition comprising the emollient carrier of claim 4 and at least 5% by total weight of said cosmetic composition of pigment.

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11. A cosmetic composition comprising the emollient carrier of claim 5 and at least 5% by total weight of said cosmetic composition pigment.

12. A cosmetic composition comprising the emollient carrier of claim 6 and
30 at least 5% by total weight of said cosmetic composition of pigment.

13. A process for producing an emollient, the process comprising the steps of:
- a) providing a composition comprising jojoba oil,
 - b) adding an alcohol having from 1 to 12 carbon atoms to said composition,
 - c) effecting alcoholysis on said jojoba oil mixed with said alcohol to produce an emollient, and
 - d) effecting an esterification of residual wax esters.
14. The process of claim 13 wherein said alcoholysis is performed in the presence of a catalyst for alcoholysis.
15. The process of claim 14 wherein said catalyst for alcoholysis comprises an alkali metal alkoxide.
16. The process of claim 14 wherein said catalyst for alcoholysis comprises sodium methoxide.
17. The process of claim 13 wherein the jojoba oil is first dried under vacuum to remove moisture, the alcohol is then added within a reactor, heat is applied to elevate the temperature of the reaction mixture, with air excluded from the reaction mixture, and after elevation of the temperature of the reaction mixture at least a first addition of catalyst for the reaction of the jojoba oil and the alcohol is made.
18. The process of claim 15 wherein the amount of catalyst ranges from about 0.1% to about 2.0% by weight of the jojoba oil.
19. The process of claim 17 wherein the amount of catalyst ranges from about 0.1% to about 2.0% by weight of the jojoba oil.

20. A process for producing an emollient, the process comprising the steps of:
- a) providing a composition comprising hydrogenated jojoba oil,
 - b) adding an alcohol having from 1 to 12 carbon atoms to said composition,
 - c) effecting alcoholysis on said jojoba oil mixed with said alcohol to produce an emollient, and
 - d) effecting an esterification of residual wax esters.
21. The process of claim 20 wherein said hydrogenated jojoba oil also comprises jojoba oil in admixture with said hydrogenated jojoba oil.
22. A cosmetic product containing the emollient of claim 1.
23. A topically applied pharmaceutical product containing the emollient of claim 1.

Electronic Patent Application Fee Transmittal

Application Number:	14578075			
Filing Date:	19-Dec-2014			
Title of Invention:	Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives			
First Named Inventor/Applicant Name:	Jeff Addy			
Filer:	Adam Reid Stephenson			
Attorney Docket Number:	FloraTech002			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
RCE- 1ST REQUEST	2801	1	680	680
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	130	130
Total in USD (\$)				810

Electronic Acknowledgement Receipt

EFS ID:	41687543
Application Number:	14578075
International Application Number:	
Confirmation Number:	2053
Title of Invention:	Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives
First Named Inventor/Applicant Name:	Jeff Addy
Customer Number:	93756
Filer:	Adam Reid Stephenson
Filer Authorized By:	
Attorney Docket Number:	FloraTech002
Receipt Date:	19-JAN-2021
Filing Date:	19-DEC-2014
Time Stamp:	20:41:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$810
RAM confirmation Number	E20211K41383763
Deposit Account	
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Vantage Exhibit 1002

Page 940 of 1215
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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	RCEForm002.pdf	697663	no	3
			6d30559ff4081924658447f0aca2684455e16a34		
Warnings:					
Information:					
2	Amendment Submitted/Entered with Filing of CPA/RCE	RCE1.pdf	155779	no	10
			cb13aa49557b5f4c8ab56379d33486e7700f9a98		
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	SIDS002_4.pdf	1034225	no	4
			4920e20b9bec26560cc5d4591edbbb3cbc49ff20		
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A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
4	Affidavit-traversing rejectns or objectns rule 132	2ndAddy132Declaration.pdf	589420	no	6
			b234b26663953c4294e18cf47e9b93d0a51ea9a		
Warnings:					
Information:					
5	Foreign Reference	WO2011107977.pdf	2357821	no	59
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Warnings:					
Information:					

6	Foreign Reference	WO1999020224.pdf	1153358 632dc7bb88d0a3189a293b9d27d8377bfc5418ea	no	35
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	32180 16026b54f581bd5b0a4a8a25c98aa32b094e5348	no	2
Warnings:					
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

FLORATECH002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

AMENDMENT/REPLY

Applicant: Jeff Addy

Docket No: FLORATECH002

Examiner: Patury, Srikanth

Ser. No: 14578075

Filed: December 19, 2014

Group Art Unit: 1657

Conf. No.: 2053

Title: Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives

**AMENDMENT ACCOMPANYING REQUEST FOR
CONTINUED EXAMINATION UNDER 37 C.F.R. 1.114**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

The following is responsive to the Examiner's Answer mailed Nov 19, 2019. Applicant respectfully requests reconsideration of the application in view of the following:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

Please amend claims 1, 3, 4, and 6 and cancel claim 5 as indicated among the following complete set of pending claims:

1. (Currently amended) A process for transesterifying wax esters, the process comprising:
 - providing a feedstock comprising jojoba wax esters;
 - contacting the feedstock with a lipase;
 - catalytically transesterifying the jojoba wax esters in the feedstock with the lipase to form a transesterified product;
 - wherein an oxidative stability index (OSI) of the transesterified product is ~~at least 2.5 times greater tghan~~ an OSI of the feedstock.
2. (Original) The process of claim 1, wherein the transesterified product comprises no methyl esters.
3. (Currently amended) The process of claim 1, wherein the feedstock further comprises an antioxidant and catalytically transesterifying the jojoba wax esters in the feedstock with the lipase further comprises catalytically transesterifying without removing or degrading the antioxidant in the feedstock.
4. (Currently amended) The process of claim 3, wherein the feedstock further comprises a skin conditioning agent and a volatile compound and catalytically transesterifying the

jojoba wax esters in the feedstock with the lipase further comprises catalytically transesterifying without removing or degrading the skin conditioning agent and the volatile compound in the feedstock.

5. (Canceled).
6. (Currently amended) The process of claim [[5]]1, wherein the jojoba wax esters further comprise hydrogenated jojoba wax esters.
7. (Original) The process of claim 6, wherein a dropping point of the transesterified product is greater than a dropping point of the feedstock and the dropping point of the transesterified product increases as a percentage of hydrogenated jojoba wax esters in the feedstock increases.
- 8-20. (Canceled).

REMARKS

Claims 1-8 are currently pending in the application. Applicant has amended claims 1, 3, 4, and 6 and canceled claim 5. Applicant requests reconsideration of the application in light of the following remarks.

New ground of rejection under 35 U.S.C. 112(a) - New Matter

In the 11/19/20 Examiner's Answer, Claims 1-7 were rejected as allegedly reciting limitations which are not disclosed in the original disclosure. Specifically the recitation "wherein an oxidative stability index (OSI) of the transesterified product is **at least 2.5 times** greater than an OSI of the feedstock." Emphasis in original. Although Applicant disagrees with the Examiner's assessment that new matter has been entered, Applicant has removed this language via amendment of independent claim 1 and thus the new ground of rejection is moot. As dependent claim 5 has been canceled, the rejection of it is also moot. Dependent claims 2-4 and 6-7 are allowable, among other reasons, for depending from otherwise allowable independent claim 1. In view of the foregoing, Applicant respectfully requests that the Examiner withdraw the rejection of claims 1-7 as allegedly reciting new matter.

New ground of rejection: Obviousness Type Double Patenting Rejection

Claims 1, 3, 5, and 6 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-6 of U.S. Patent No. 10,435,726 to Addy. In order to avoid further expenses and time delay, Applicant elects to expedite the prosecution of the present application by filing a terminal disclaimer to obviate the double patenting rejections in compliance with 37 CFR 1.321 (c). Applicant's filing of the terminal disclaimer should not be construed as acquiescence of the Examiner's double patenting or obviousness-type double patenting rejections which the Applicant still avers are improper in the present circumstance. Filed herewith is the terminal disclaimer and accompanying fee.

Rejections under 35 U.S.C. 103

In the Answer, the rejection of claims 1-5 under 35 U.S.C. 103 as being unpatentable was maintained in view of the paper by Gunawan et al., “Lipase-Catalyzed Synthesis of Palm-Based Wax-esters,” *J. Oleo Sci.*, Vol. 53, No. 10, 471-477 (2004)(“Gunawan”) in view of Austic et al., WO2012/106701 (“Austic”); the paper by Busson-Breyse et al., “Jjoba Wax: Its Esters and Some of Its Minor Components,” *J. Acad. Org. Chem. Soc.* V. 71, No. 9, p. 999-1002 (1994) (“Busson-Breyse”); and Fucosterol (Cayman Chemical, CAS No. 17605-67-3, CAS Entry, 2019) (“Fucosterol”). The obviousness rejection of claims 1-7 was also maintained over Gunawan in view of Austic, Busson-Breyse, Fucosterol, and further in view of Arquette (US. Pat. No. 5,968,530) (“Arquette”). Applicant respectfully traverses these rejections and requests reconsideration of the claims.

Referring to the legal standards set forth in Appendix A, Applicant observes that, in the Answer, the Examiner has not explicitly stated which of the obviousness rationales endorsed in *KSR International Co. v. Teleflex Inc.* 550 U.S. 398, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007) are being used. The Applicant believes the rationale being used is B/C:

“(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;” MPEP § 2141(II), (III) and 72 Federal Register 57527 (October 10, 2007).

On p. 14 of 11/19/20 Answer, the Examiner stated that the arguments presented in the appeal brief were not persuasive because “the limitation that the ‘The OSI of the transesterified product is at least 2.5 times greater than an OSI the feedstock’ 8 and is intended outcome of the reformed method”” and on p. 15 “... It is reasonably expected of the process of Gunawan in view of Austic would also result in the OSI of the transesterified product being at least 2.5 times greater than an OSI of the feedstock, since they teach the same method steps as recited in instant claim 1.” While may appear that the Examiner is trying to make an intended use argument here, the actual reasoning is an inherency argument since a reciting a physical property in a claim for the product of a claimed chemical reaction does not recite a use of that

product but rather recites a result of the reaction. Since the Examiner admits on p. 14 of the 11/19/20 that neither of these references discloses anything about an OSI of the feedstock or products of these reactions, the Examiner's argument rests entirely on the proposition that the method of Gunawan carried out on a different feedstock material must necessarily result in the same physical property with the new feedstock material (supplied by Austic). Such an argument is inherency plain and simple regardless of how it is dressed up in different language. Because of this, the Examiner bears a high burden to prove inherency which does not permit a statement that a probable result is sufficient. The Examiner is required to show that the observed physical property must necessarily result from the method of Gunawan performed with wax esters in a feedstock in order to show inherency. The Examiner's new arguments fail entirely to do this as they rest only in Examiner argument and speculation and not in the teachings and information provided by the references themselves.

As a matter of demonstrating the fallacy of the Examiner's argument, the Applicant submits the Second Declaration of Jeff Addy filed herewith which details experiments performed with both sunflower oil and jojoba oil using the method taught in Gunawan. If the Examiner's speculations were correct, processing jojoba wax esters with the method of Gunawan should produce a product that demonstrates a higher OSI than the OSI of the feedstock materials. The experimental results directly contradict these speculative arguments. The jojoba wax ester product actually had a 25% reduction in observed OSI compared to the feedstock materials when the method of Gunawan was employed. In contrast, the sunflower oil product demonstrated a higher OSI than the OSI of the product. Clearly, these experiments demonstrate the unpredictable nature of the chemical arts, a fact which is often been observed by the courts. In view of the Second Addy Declaration, the Examiner has entirely failed to establish a sufficient basis in fact and provide technical reasoning to support that the claimed increase in OSI is merely an inherent result of utilizing the process of Gunawan with jojoba wax esters from Austin.

Also, contrary to the Examiner's assertion on p. 16 of the 11/19/20 Answer, the Second Addy Declaration provides specific evidence that the claimed in effect of increasing OSI is a

feedstock dependent effect and thus the use of the proper feedstock is what is involved in causing the observed increase in the OSI. While as an effort to draw prosecution of this case to rapid conclusion independent claim 1 has been amended to recite jojoba wax esters in the feedstock, the Applicant believes that claim 1, as originally filed reciting just wax esters in the feedstock (and not jojoba wax esters) is still fully supported and enabled by the specification as filed and reserves the right to file a claim with similar scope in a continuing application.

As Busson-Breysse, Fucosterol, and Arquette fail individually and collectively to remedy the defects of the combination of Gunawan and Austic, their combination fail to teach or disclose, or, in the alternative, render obvious, each and every element of independent claim 1, as amended in view of the Second Addy Declaration.

As dependent claim 5 has been canceled, the rejection of it is therefore rendered moot. Dependent claims 2-4 and 6-7 are allowable, among other reasons, for depending from otherwise allowable independent claim 1.

Accordingly, the Applicant respectfully requests that the 103 rejections of claims 1-7 over Gunawan, Austic, Busson-Breysse, Fucosterol, and Arquette be withdrawn.

Regarding Doctrine of Equivalents

Applicant hereby declares that any amendments herein that are not specifically made for the purpose of patentability are made for other purposes, such as clarification, and that no such changes shall be construed as limiting the scope of the claims or the application of the Doctrine of Equivalents.

CONCLUSION

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

If any fees, including extension of time fees or additional claims fees, are due as a result of this response, please charge Deposit Account No. 60-1853. This authorization is intended to act as a constructive petition for an extension of time, should an extension of time be needed as a result of this response. The Examiner is invited to telephone the undersigned if this would in any way advance the prosecution of this case.

Respectfully submitted,

Date: 1/19/21

By: /Adam Stephenson/
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Reg. No. 58,349

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Appendix A:
Legal Standard for Finding Obviousness under 35 U.S.C. 103

The most recent guidelines published by the USPTO regarding the implementation of the Supreme Court's decision in *KSR International Co. v. Teleflex Inc.* 550 U.S. 398, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007) state that:

An invention that would have been obvious to a person of ordinary skill at the time of the invention is not patentable. See 35 U.S.C. 103(a). As reiterated by the Supreme Court in *KSR*, the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

- (A) Determining the scope and content of the prior art;
- (B) Ascertaining the differences between the claimed invention and the prior art; and
- (C) Resolving the level of ordinary skill in the pertinent art...

Office personnel fulfill the critical role of fact-finder when resolving the *Graham* inquiries... When making an obviousness rejection, Office personnel must therefore ensure that the written record includes findings of fact concerning the state of the art and the teachings of the references applied. In certain circumstances, it may also be important to include explicit findings as to how a person of ordinary skill would have understood prior art teachings, or what a person of ordinary skill would have known or could have done. Factual findings made by Office personnel are the necessary underpinnings to establish obviousness...

In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person should reasonably have been able to do in view of that knowledge. This is so regardless of whether the source of that knowledge and ability was documentary prior art, general knowledge in the art, or common sense...

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) stated

that “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”
KSR. . . Exemplary rationales that may support a conclusion of obviousness include:

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) “Obvious to try”-choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. MPEP § 2141(II), (III) and 72 Federal Register 57527 (October 10, 2007).

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 14/578,075		Filing Date 12/19/2014		☐ To be Mailed		
ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO										
APPLICATION AS FILED - PART I										
		(Column 1)	(Column 2)							
FOR		NUMBER FILED	NUMBER EXTRA	RATE (\$)		FEE (\$)				
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A	N/A	N/A						
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A	N/A	N/A						
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A	N/A	N/A						
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 =	*	x \$80 =						
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =	*	x \$420 =						
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).								
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))										
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL						
APPLICATION AS AMENDED - PART II										
		(Column 1)	(Column 2)	(Column 3)						
AMENDMENT	01/19/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	* 6	Minus	** 20	= 0	x \$100 =		0		
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0	x \$480 =		0		
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE		0		
		(Column 1)	(Column 2)	(Column 3)						
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	*	Minus	**	=	x \$0 =				
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x \$0 =				
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE				
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.						LIE				
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".						/TERRY BRYANT/				
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".										
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.										

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed		PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce	
Electronic Petition Request	TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT		
Application Number	14578075		
Filing Date	19-Dec-2014		
First Named Inventor	Jeff Addy		
Attorney Docket Number	FloraTech002		
Title of Invention	Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives		
☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action ☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.			
Owner		Percent Interest	
International Flora Technologies, Ltd.		100%	
The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s) 10435726 as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns. In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later: - expires for failure to pay a maintenance fee; - is held unenforceable; - is found invalid by a court of competent jurisdiction; - is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321; - has all claims canceled by a reexamination certificate; - is reissued; or - is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer. ☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer.			

☐ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.	
Applicant claims the following fee status: ☒ Small Entity ☐ Micro Entity ☐ Regular Undiscounted	
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ☒ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number <u>58349</u> ☐ A sole inventor ☐ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ☐ A joint inventor; all of whom are signing this request	
Signature	/Adam Stephenson/
Name	Adam R. Stephenson

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
 Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	14578075			
Filing Date:	19-Dec-2014			
Title of Invention:	Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives			
First Named Inventor/Applicant Name:	Jeff Addy			
Filer:	Adam Reid Stephenson			
Attorney Docket Number:	FloraTech002			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	2814	1	170	170
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				170

Doc Code: DISQ.E.FILE

Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 14578075

Filing Date: 19-Dec-2014

Applicant/Patent under Reexamination: Addy

Electronic Terminal Disclaimer filed on January 20, 2021

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	41691959
Application Number:	14578075
International Application Number:	
Confirmation Number:	2053
Title of Invention:	Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives
First Named Inventor/Applicant Name:	Jeff Addy
Customer Number:	93756
Filer:	Adam Reid Stephenson
Filer Authorized By:	
Attorney Docket Number:	FloraTech002
Receipt Date:	20-JAN-2021
Filing Date:	19-DEC-2014
Time Stamp:	14:34:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 170
RAM confirmation Number	E20211JE34291759
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Vantage Exhibit 1002

Page 959 of 1215

CARGILL 00000984

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	33495	no	2
			efb3249f9b7b74acb1a3c0e6bc611fb18f90bb12		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30251	no	2
			da93977c6c86d2b6a99bfff24cb995e5142dce134		
Warnings:					
Information:					
Total Files Size (in bytes):			63746		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

**PETITION TO MAKE SPECIAL BASED ON AGE FOR ADVANCEMENT OF EXAMINATION
UNDER 37 CFR 1.102(c)(1)**

Application Information

Application Number	14578075	Confirmation Number	9375	Filing Date	19-Dec-2014
Attorney Docket Number (optional)	FloraTech002	Art Unit	1657	Examiner	SRIKANTH PATURY
First Named Inventor	Jeff Addy				
Title of Invention	Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives				

Attention: Office of Petitions

An application may be made special for advancement of examination upon filing of a petition showing that the applicant is 65 years of age, or more. No fee is required with such a petition. See 37 CFR 1.102(c)(1) and MPEP 708.02 (II).

APPLICANT HEREBY PETITIONS TO MAKE SPECIAL FOR ADVANCEMENT OF EXAMINATION IN THIS APPLICATION UNDER 37 CFR 1.102(c)(1) and MPEP 708.02 (II) ON THE BASIS OF THE APPLICANT'S AGE.

A grantable petition requires one of the following items:

- (1) Statement by one named inventor in the application that he/she is 65 years of age, or more; or
- (2) Certification by a registered attorney/agent having evidence such as a birth certificate, passport, driver's license, etc. showing one named inventor in the application is 65 years of age, or more.

Name of Inventor who is 65 years of age, or older

Given Name	Middle Name	Family Name	Suffix
James	H.	Brown	

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18.
Please see 37 CFR 1.4(d) for the format of the signature.

Select (1) or (2) :

- ☐ (1) I am an inventor in this application and I am 65 years of age, or more.
- ☒ (2) I am an attorney or agent registered to practice before the Patent and Trademark Office, and I certify that I am in possession of evidence, and will retain such in the application file record, showing that the inventor listed above is 65 years of age, or more.

Signature	/Adam Stephenson/		
Name	Adam R. Stephenson	Registration Number	58349

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.



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P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

In re Application of
Jeff Addy

Application No. 14578075

Filed: December 19, 2014

Attorney Docket No. FloraTech002

:

:

:DECISION ON PETITION TO MAKE SPECIAL
:UNDER 37 CFR 1.102(c)(1)

:

This is a decision on the electronic petition under 37 CFR 1.102 (c)(1), filed 22-JAN-2021 to make the above-identified application special based on applicant's age as set forth in MPEP § 708.02, Section II.

The petition is **GRANTED**.

A grantable petition to make an application special under 37 CFR 1.102(c)(1), MPEP § 708.02, Section II : Applicant's Age must include a statement by applicant or a registered practitioner having evidence that applicant is at least 65 years of age. No fee is required.

Accordingly, the above-identified application has been accorded "special" status and will be taken up for action by the examiner upon the completion of all pre-examination processing.

Telephone inquiries concerning this electronic decision should be directed to the Electronic Business Center at 866-217-9197.

All other inquiries concerning either the examination or status of the application should be directed to the Technology Center.

Electronic Acknowledgement Receipt

EFS ID:	41709926
Application Number:	14578075
International Application Number:	
Confirmation Number:	2053
Title of Invention:	Processes and Systems for Catalytic Manufacture of Wax Ester Derivatives
First Named Inventor/Applicant Name:	Jeff Addy
Customer Number:	93756
Filer:	Adam Reid Stephenson
Filer Authorized By:	
Attorney Docket Number:	FloraTech002
Receipt Date:	22-JAN-2021
Filing Date:	19-DEC-2014
Time Stamp:	18:11:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition automatically granted by EFS	petition-request.pdf	38195	no	2
			a33b90b97da71b716a931b3fb8246186d3 293137		

Warnings:

Vantage Exhibit 1002

Page 964 of 1215

CARGILL 00000989

Information:	
Total Files Size (in bytes):	38195
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.	



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/578,075	12/19/2014	Jeff Addy	FloraTech002	2053
93756	7590	02/11/2021	EXAMINER	
Adam R. Stephenson, LTD. 8350 E Raintree Dr., Ste 245 Scottsdale, AZ 85260			PATURY, SRIKANTH	
			ART UNIT	PAPER NUMBER
			1657	
			NOTIFICATION DATE	DELIVERY MODE
			02/11/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

adam@iptech.law
ipdocket@iptech.law

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Patent Trial and Appeal Board, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 01/19/2021 has been entered.

The amendments and remarks filed on 01/19/2021 are acknowledged and have been fully considered. Claims 1-4, 6 and 7 are pending. Claims 1, 3, 4 and 6 have been amended. Claim 5 is canceled. Claims 8-20 were previously canceled. Claims 1-4, 6 and 7 are now under consideration and the subject of this office action.

Information Disclosure Statement

The information disclosure statement(s) (IDS) submitted on 01/19/2021 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement(s) is being considered by the examiner.

Terminal Disclaimer

The terminal disclaimer filed on 01/20/2021 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **USP 10,435,726** has been reviewed and is accepted.

The previous rejections of claims 1, 3 and 6 under obviousness-type double patenting over USP 10,435,726 are withdrawn in light of the terminal disclaimer filed on 01/20/2021.

Declaration Under 37 C.F.R §1.132

The declaration under 37 C.F.R §1.132 filed on 01/19/2021 is sufficient to overcome the rejections of claims 1-4 under 35 USC §103 as being obvious over Gunawan in view of Austic and the rejections of claims 6 and 7 under 35 USC §103 as being obvious over Gunawan in view of Austic and Arquette. Applicants presented evidence showing that when feedstock comprising jojoba wax esters is transesterified under the conditions disclosed in Gunawan, the OSI of the transesterified product is not greater than the OSI of the feedstock as recited in claim 1 (see Table 4, section 8 on page 5).

The previous rejections of claims 1-4 under 35 USC 103 over Gunawan in view of Austic and of claim 6 and 7 under 35 USC 103 over Gunawan in view of Austic and Arquette are withdrawn in light of the declaration under 37 C.F.R 1.132 by inventor Jeff Addy filed on 01/19/2021.

Response to Amendment

The previous rejections of claim 5 are moot in light of the cancellation of the claim in the amendments filed on 01/19/2021.

The previous rejections of claims 1-4, 6 and 7 under 35 USC 112(a) for New Matter are withdrawn in light of the amendments to claim 1 filed on 01/19/2021. The phrase “at least 2.5 times” has been deleted.

Specification - Objection

The instant application uses multiple tradenames/trademarks (LIPOZYME, LIPEX, NOVOZYM, NOVOCOR, LIPOLASE, CALB, AMANO, VERSENE, etc.). See paragraph [0045] on page 11, see Table 4, paragraph [0059] on pages 18 and 19 of the instant specification for the different tradenames/marks used in the application. The terms should be accompanied by the generic terminology; furthermore the term should be capitalized wherever it appears or, where appropriate, include a proper symbol indicating use in commerce such as TM, SM, or [®] following the term.

Although the use of trade names and marks used in commerce (i.e., trademarks, service marks, certification marks, and collective marks) are permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as commercial marks. See MPEP §608.01 (v).

Claim Objections

Claim 1 is objected to because of the following informalities: The term “tghan” in line 8 of claim 1 is a typographical error. It is suggested to amend to “than”. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

(a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

Claims 1 and 2 are rejected under 35 U.S.C. 102(a)(1) and under 35 U.S.C. 102(a)(2) as being anticipated by **Austic** (WO 2012/106701; Pub. Aug. 9, 2012; Of Record).

Regarding claim 1, Austic teaches methods for the production of fatty acid alkyl esters from a fatty acid feedstock (transesterification) comprising the steps of providing a reaction mixture comprising the fatty acid feedstock and a lipolytic enzyme and allowing the reaction mixture to react to form fatty acid alkyl esters (pg. 3 lines 26-30). Austic teaches avoiding the use of solvents (pg. 2 line 32) and teaches performing the reaction under an inert gas (pg. 3 line 12). Austic teaches the feedstock comprises fatty acid esters (pg. 4 lines 25-34) and the feedstock can be jojoba oil in one embodiment: “The fatty acid feedstock may be oil selected from the group consisting of: algae oil, canola oil, coconut oil, castor oil, coconut oil (copra oil), corn oil, cottonseed oil, flax oil, fish oil, grape seed oil, hemp oil, jatropha oil, jojoba oil, mustard oil, canola oil, palm oil, palm stearin, palm olein, palm kernel oil, peanut oil, rapeseed oil, rice bran oil, safflower oil, soybean oil, sunflower oil, tall oil, and oil from halophytes, pennycress oil, camelina

oil, jojoba oil, coriander seed oil, meadowfoam oil, seashore mallow oil, microbial oils or any combination thereof.” (pg. 4 line 37). Austic teaches the enzyme catalyst (pg. 8 line 7) can be a lipase selected from *Candida antarctica* lipase A (CALA), *C. antarctica* lipase B (CALB) (see pg. 9 lines 19-21), commercial lipolytic enzymes such as LIPOZYME TL 100L (see pg. 10 lines 7-10), NOVOZYM 435, LIPOZYME TL IM (see pg. 10 lines 11-15). Austic teaches examples wherein the feedstock (yellow grease) is transesterified with lipase NOVOZYM 435 at a dosage of 4% w/w of oil (see Example 1, 6). The instant specification teaches wax esters are found in jojoba plant (par. [0002] on pg. 1) and teaches using jojoba oil in its methods (see instant specification par. [0055] on pg. 16, par. [0062] on pg. 20). Since Austic discloses jojoba oil as a specific oil that can be used as a feedstock for transesterification (among a list of other oils), Austic anticipates the limitation ‘feedstock comprising jojoba wax esters’. A reference that clearly names the claimed species anticipates the claim no matter how many other species are named. See MPEP §2131.02 II.

Austic is silent regarding the oxidative stability index (OSI) of the transesterified product being greater than the OSI of the feedstock. The limitations “wherein an oxidative stability index (OSI) of the transesterified product is greater than an OSI of the feedstock” is the intended result of the method of claim 1 and would inherently be met if the prior art process teaches the same active method steps as recited in claim 1. Austic teaches performing the transesterification reaction on feedstock comprising jojoba esters (same feedstock as instant claims), using the same enzymes at the same dosage (LIPOZYME TL IM at 4% w/w oil) under solventless conditions. The instant specification teaches the same conditions (see instant specification par. [0055] on pg.