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PALM OLEIN-IN-WATER EMULSIONS STABILISED BY SPAN® AND TWEEN® SURFACTANTS AS POTENTIAL VEHICLES FOR DRUG DELIVERY

BY

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ABSTRACT

Palm olein emulsions were produced using the combinations of Span® and Tween® surfactants by mechanical homogenisation. Effects of the types of surfactants, concentrations, effective HLB and the types of viscosity modifiers and concentrations on the characteristics of the emulsions were investigated. With palm olein content of 20% (w/w), stable oil droplets were produced at HLB values ranging from 8.5 to 11.0. Optimal concentrations of surfactants ranged from 25 to 30% (w/w to oil) depending on the types of the Span®/Tween® mixtures. Among the viscosity modifiers used, Carbopol®940 was the most effective. Suitable concentrations of Carbopol®940 for the emulsions prepared with Span®20/Tween®20 ranged from 0.1 to 0.3% (w/w). Beyond this concentration, destabilisation of emulsion due to at least depletion of water molecules could have occurred as a result of competitive hydration between Carbopol®940 and the surfactants. The emulsions produced exhibited viscoelastic and pseudoplastic behaviour, with yield value ranging from 0.1 to 35.2 Pa. Depending on the concentration of Carbopol®940 and within the linear viscoelastic region, the emulsions were elastic in nature as shown by domination of storage modulus (G') over the loss modulus (G") and with tan $\delta < 1$ in the frequency range of 0.01 to 10 Hz. These favourable rheological properties were induced by the formation of three-dimensional network of Carbopol®940 molecules in the continuous aqueous phase, which also entrapped the oil droplets and thus increased the stability of the emulsion. To the optimised o/w emulsion formulation, active pharmaceutical ingredients and extracts of *Cassia alata* were incorporated. Betamethasone dipropionate and tolnaftate at concentrations of 0.5 mg/g and 1 mg/g respectively, did not affect the size of droplets and stability of the palm olein emulsions. Nonetheless, betamethasone dipropionate increased the viscosity and elasticity of the emulsion; while tolnaftate slightly reduced the viscosity, thixotropy and elasticity of the emulsion. *Cassia alata* extracts affected the emulsion stability. With up to 0.5 mg/g of ethanol extract and 0.25 mg/g of ethanol/water extract of *Cassia alata,* emulsions were stable. Further, *Cassia alata* extracts did not alter the pseudoplasticity of the emulsion despite decreasing viscosity with increasing concentration of the extracts. Desired rheological properties for the development of topical cream and lotion can be attained by changing the concentration of Carbopol®940 in palm olein-in-water emulsion, which is a potential vehicle for drug delivery.

ملخّص البحث

تم انتاج مستحلبات زيت النخيل باستخدام الخليط من سبان (Span®) وتوين (Tween®) سرفقتنات (surfactants) بطريقة التجانس الميكانيكي (mechanical homogenisation). كما تم التحقق من آثار أنواع سرفقتنات, والتركيزات، وفعّال HLB وأنواع من معدلات اللزوجة، بإضافة إلى التركيزات على خصائص المستحلبات. أنتجت قطرات النفط المستقرة بنسبة 20 ٪ (وزن / وزن) من محتوى زيت النخيل فيما يتراوح بين 8,5 إلى 11,0من قيم معدلات HLB. والتركيزات المثلى لشرفقتنات ما يتراوح من 25 إلى 30 ٪ على حسب نوعية المخاليط من سبَنْ (Span®) وتُوين (Tween®). كانCarbopol®940 هو الأكثر فعالة من بين معدلات اللزوجة المستخدمة. كما تم إعداد التركيزات المناسبة من Carbopol®940 للمستحلبات ب Span20® و Tween20® الذي يتراوح بين 0,1 إلى 0,3 (وزن / وزن). وفوق هذه التركيزات، يمكن أن يحدث عدم استقرار المستحلب على الأقل، وهذا بسبب نضوب جزئيات المياه، نتيجة تنافس الهيدراسن (hydration) بين Carbopol®940 وسرفقنات. وتتصف المستحلبات المنتجة لزجا مطاطيا (viscoelastic) و pseudoplastic و yield value فيما تتراوح من 1,0 إلى 35,2 على حسب تركيزات Carbopol®940، وداخل طول منطقة لزج مطاطي (linear viscoelastic region) وكانت المستحلبات مرونة بطبيعة كما اتضحت من سيطرة معامل التخزين (storage modulus) على معامل الفقد (loss modulus) و بطريقة (tan δ < 1) في نطاق التردد من0,01 إلى 10Hz. وهذه الخصائص الطبيعية المواتية كانت ناجمة عن تشكيل شبكة ثلاثية الأبعاد من جزئيات Carbopol®940 في استمرار المرحلة المائية، التي تحاصر قطرات النفط وبالتالي تزيد في استقرار المستحلب. بصياغة المستحلب بالأداء الأمثل، وخلطه بالمكونات الصيدلية الناشطة والمقتطفات من *Cassia alata*. ولم يؤثر كل من بيتاميثاسون دبروبيونات (betamethasone dipropionate) وتُلنَفتات (tolnaftate) في تركيزات 0،5 g/mg في حجم قطرات واستقرار مستحلب زيت النخيل. ومع ذلك, بيتاميثاسون دبروبيونات تزيد في لزوجة ومرونة المستحلب بينما تُلنَفتات تخفّض قليلا من لزوجة وthixotropy ومرونة المستحلب. ولا تؤثر مقتطفات Cassia alata في استقرار المستحلب الا أن يصل إلى ما بعد 0,5 g/mg من الإيثانول وما فوق 0,25 g/mg لإيثانول بالماء المستخرج من *Cassia alata*. علاوة على ذلك، وإن مقتطفات *Cassia alata* لم تغير pseudoplasticity المستحلب على الرغم من تناقص اللزوجة مع التركيز المتزايد للمقتطفات. ويمكن أن تتحقق الخصائص الطبيعية المرجوة لتطوير وتنمية كريم ومستحضر عن طريق تغيير تركيز Carbopol®940 في مياه مستحلب زيت النخيل التي هي الوسيلة الممكنة لإيصال الأدوية.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion; it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master in Pharmaceutical Sciences (Pharmaceutical Technology).

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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LIST OF ABBREVIATIONS

A_{cmc}	area per molecule just below the cmc
API	active pharmaceutical ingredients
BET	betamethasone dipropionate
BNF	British National Formulary
BP	British Pharmacopoeia
CAE	ethanol extract of *C. alata*
CAEW	ethanol/water extract of *C. alata*
CAW	water extract of *C. alata*
CMC	sodium carboxymethyl cellulose
cmc	critical micelle concentration
CR	controlled rate
D(v,0.1)	diameter at which 10% of the volume falls below it
D(v,0.5)	diameter at which 50% of volume of particles falls below it or median diameter
D(v,0.9)	diameter at which 90% of volume of particles falls below it
D[4,3]	volume average diameter
EO	oxyethylene
HLB	hydrophile-lipophile balance
LVR	linear viscoelastic region
MIMS	Malaysian Index of Medical Specialities
PPG	polypropylene glycol
RO	reverse osmosis
SD	standard deviation
tan δ	tangent of the phase angle
TL	tolnaftate
USP/NF	United State Pharmacopoeia/National Formulary

LIST OF SYMBOLS

τ	shear stress
$\dot{\gamma}$	shear rate
τ°	yield stress
v	terminal velocity
f	frequency
G*	complex modulus
G’	storage modulus
G”	loss modulus
r	radius of the particle
δ	phase angle
η	viscosity

CHAPTER 1

INTRODUCTION

An emulsion is a dispersed system containing at least two immiscible liquid phases. Emulsions can be divided into either oil-in-water (o/w) or water-in-oil (w/o) emulsions. In the o/w emulsion oil droplets are dispersed throughout the aqueous phase, while in w/o emulsion aqueous is dispersed throughout the oil phase. In addition to these simple emulsions, multiple emulsions can also be prepared. These can be either o/w/o or w/o/w emulsions.

Generally, emulsion is one of the most widely used dosage form in pharmaceutical delivery system and is an attractive vehicle for the administration of poorly soluble drugs. Pharmaceutical and cosmetic form of emulsions can be prepared in the form of liquids or semisolids, based on intended application. Pharmaceutically, the roots of administration of emulsion are oral, topical, mucosal, parenteral and ophthalmic.

There are many advantages and interest in lipid-emulsions formulations. The advantage of oral emulsion preparation is its ability to prepare formulation for easy compliance especially for paediatric and geriatric patients (Marti-Mestres and Nielloud, 2000). For total parenteral nutrition, fat emulsion prepared from vegetable oil emulsified by phospholipids (eg. Intralipid®) is not recognised as a foreign substance by the body (Buszello and Muller, 2000). Topical emulsion is less greasy and more aesthetically appealing to patients (Thomson, 2004). For skin irritant medicinal agents, incorporation into the emulsion reduces irritation (Howard, Loyd and Nicholas, 1999). In ophthalmic emulsion formulation, it gives an advantage in

providing a vehicle for slow release of drug in a nonviscous medium, thus reducing the frequency of application (Fialho and Silva-Cunha, 2004).

There is a possibility of dissolving lipophilic components such as propofol in a safe and tolerable matrix of emulsion with the advantage of having less pain upon injection compared with solvent based. Lipid emulsions also minimise losses of more lipophilic drugs during infusion into plastic tubing and infusion sets (Collins-Gold, Feichtinger and Warnhein, 2000).

1.1 USE OF MINERAL OIL

Mineral oil is a mixture of aliphatic hydrocarbons obtained from petroleum. They are available as liquid hydrocarbon (light liquid paraffin), solid hydrocarbon (hard paraffin) and semisolid hydrocarbon (white soft paraffin) (Reilly, 2000) and are widely used as excipients in cosmetics and pharmaceuticals. Most of the topical cosmetic and pharmaceutical and oral emulsion preparations are mineral oil based such as betamethasone cream (Betnovate® cream) using white soft paraffin and phenolphthalein (Agarol®) using liquid paraffin and others (Walker, 1991-92).

Unfortunately, the source of fossil oil is diminishing and the price of petroleum products thus has been escalating. The average of 2001-2006 gas price rised by 75% compared to the average of 1996-2001 (Ruhl, 2007). Therefore, it is indeed imminent in finding new source of oil, which is renewable and inexhaustible.

1.2 USE OF VEGETABLE OILS IN PHARMACEUTICALS

Vegetable oil has many advantages over mineral oil. Vegetable oils and fats and their derivatives, are renewable, biodegradable and harmless to the environment. They have been widely used as excipients and active ingredients in pharmaceutical and

cosmeceutical preparations.

The major components of vegetable oils are triglycerides. Triglycerides are esters of glycerol with three fatty acid molecules. The minor components include fatty alcohol, phytosterols, vitamins and phospholipids.

The oil uses depend mainly on the type and proportion of fatty acids which vary according to the species of plants. The oils with high content of unsaturated fatty acids (oleic, linoleic and linolenic acid) such as almond oil, apricot oil, avocado oil, soybean oil, cocoa oil and palm oil have emollient properties and are used in bar soaps, shampoos and hair conditioners, creams and lotions, lip balms and suntan products. However, the oils with high content of polyunsaturated fatty acid such as walnut oil and safflower oil are less stable and therefore less suitable to be used in its original state into the formulation. Safflower oil which contains 75-80% of linoleic acid need treatment to convert linoleic acid to oleic acid, to produce stable formulations.

Highly saturated vegetable oils are also gaining interest in the cosmetic and pharmaceutical fields due to their fewer tendencies to produce free radical from the oxidation process (Alias and Julianto, 2005). For instance, coconut oil is suitable for the preparation of cosmetic due to its high content of saturated fatty acids (lauric, 50% and myristic, 20%) and minor content of caprylic acid that exhibited antifungal activity (Alvarez and Rodriguez, 2000).

Vegetable oils are used as excipients in the formulation of cosmetics and pharmaceuticals in the form of its oil or its derivatives. For example, soybean oil has been used as oil phase in the preparation of intravenous fat emulsion for total parenteral nutrition (Intralipid®). Derivatives of castor oil, polyethoxylated castor oil (Cremofor®), is used as emulsifier and solubiliser in pharmaceutical preparations

containing volatile oils and fat-soluble vitamins and hydrogenated castor oil is used in some oral dosage forms and topical creams (Alvarez and Rodriguez, 2000).

Soybean oil is the major oil exploited in the parenteral preparation. Diprivan® (propofol), a general anaesthesia; Intralipid®, a parenteral nutrition; Limethasone® (dexamethasone palmitate), for chronic rheumatoid arthritis and Lipo-NSAID® (flubiprofen axetil), for post-operative and cancer pain. These are commercially available emulsion formulations using soybean oil as the oil base.

1.2.1 Palm oil as an alternative

Palm oil is a form of edible vegetable oil obtained from the fruit of Elaeis Guineensis. Palm oil is the major commodity of Malaysia. Malaysia supplied 47% of world palm oil making it the largest world supplier in year 2005. It is now the first widely produced edible oil contributing to about 33% of world vegetable oil demand in 2005. Soybean oil only contributed 31% for the same year (Sumathi, Chai and Mohamed, 2007).

90% of the palm oil production is used as food and only 10% in non-food industry. The major uses in the foods are as cooking oil, shortening, margarine and spread and substitutes of dairy product. Non-food application of palm oil is mainly as a feedstock for manufacturing of soaps and oleochemicals. Palm oil based soaps produce high quality soap with better perfume retention and well accepted by all religions. The derivatives of oleochemicals are fatty acids, fatty acid methyl esters, fatty amines, fatty alcohols and glycerine. These compounds are widely used as essential ingredients in food emulsifiers, cosmetics, pharmaceuticals and fabric softeners. Palm oil has also been used in vulcanisation of natural rubber, natural rubber dipped-processing, lubricants, fertiliser industries and antistatic agent for