CHARACTERIZATION OF PALM OLEIN-IN-WATER EMULSION AS A VEHICLE FOR TOPICAL DRUG DELIVERY OF BETAMETHASONE 17-VALERATE

BY

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ABSTRACT

Palm olein, the major commodity of Malaysia, is inexhaustible and contains natural surfactants with the potential to be used widely in pharmaceutical formulations. However, there is little data available on the use of palm olein as an alternative in the production of topical products. The current study aims to produce pharmaceutical formulation using palm olein as the oil phase with betamethasone 17-valerate as the active ingredient and to compare the characteristics with those of commercial products. The emulsions were prepared using Span® 20 and Tween® 20 as surfactants, Carbopol® 940 as thickener, methyl paraben sodium, propyl paraben sodium and chlorocresol as preservatives, propylene glycol as solubilizer and distilled water as the aqueous phase. The formulations were characterised for particle size distribution, microscopic examination, viscosity, rheology, phase separation, pH and zeta potential. Evaluation on drug release with three different viscosities was further performed with Hanson Verticle Diffusion Cell System using cellulose acetate as well as rat skin as membranes and the samples were quantified with HPLC. The results were compared with that of three commmercially available products which were Betnovate, Betasone and Axcel Betamethasone creams. The creams stabilized with 0.3% (w/w) of Carbopol® 940 were further tested for microbial limit studies according to the monographs stated in the British Pharmacopoeia (2009). The creams were further subjected to stability studies for 3 months at three different temperatures (4˚C, 25˚C and 40˚C) and degradation of betamethasone 17-valerate in the formulations was analysed using HPLC. The formulations showed mean particle size between 2 to 4 µm, viscosity 50 to 250 mPa.s, pH 5 to 5.9 and zeta potential -45 to -68 mV. The emulsions exhibited pseudoplastic behaviour with yield stress and found to be thixotrophic. The drug release rates from palm-olein-in-water emulsions were up to 4.5 times higher than that of commercial products. Less than 5 % of drug was degraded in the formulations during the 3-month period when they were subjected to three different temperatures. In conclusion, these findings proved that the creams produced from palm-olein-in-water emulsion could be a superior alternative vehicle for topical drug delivery system.

خلاصة البحث

يعد زيت النخيل البضاعة الرئيسية في ماليزيا وهو يوجد بوفرة عالية ويحتوي على عوامل طبيعية فعالة على السطح والتي من الممكن استخدامها في المستحضرات الصيدلانية. على كل حال هناك القليل من المعلومات حول استخدام زيت النخيل كبديل في المستحضرات الموضعية. تهدف الدراسة الحالية الى انتاج مستحضرات صيدلانية باستخدام زيت النخيل كطور زيتي ومادة البيتاميتازون فاليروات كمادة فعالة وتهدف أيضا الى مقارنة هذا الشكل الجديد بالأشكال المتوفرة في الاسواق. تم انتاج المستحضر باستخدام التوين 20 والسبان 20 كعوامل فعالة على السطح و الكاربوبول 940 كرافع قوام والصوديوم ميتيل بارابين والصوديوم بروبيل بارابين والكلوروكريزول كمواد حافظة وكذلك تم استخدام البروبيلين غليكول كمثبت والماء للطور المائي. تم فحص وتوصيف التحضيرات من جهة توزع حجم الجزيئات والفحص المجهري واللزوجة و الجريان و فصل الاطوار ودرجة الحموضة و كمون بيتا. تم تقييم تحرر الدواء عند ثلاث مستويات لزوجة مختلفة باستخدام نظام خلية الحلول Hanson Verticle وأغشية السللوز اسيتات و بشرة الجرذان وتم معايرة التراكيز باستخدام الكروماتوغرافيا السائلة عالية الانجاز. لقد تمت مقارنة النتائج مع ثلاث أشكال صيدلانية متوفرة في الأسواق وهي Betnovate, Betasoneو Axcel . وقد تمت دراسة حدود النمو الميكروبي للتحضيرات المستحضرة مع 0.3% من الكاربوبول طبقا لدستور الادوية البريطاني. درست ثباتية الكريم لمدة ثلاثة اشهر في ثلاث درجات حرارة مختلفة (4˚C, 25˚C and 40˚C) وتم مراقبة تخرب البيتاميتازون باستخدام ال HPLC . أظهرت النتائج أن متوسط الحجم الجزيئي تراوح بين 2-4 ميكروميتر واللزوجة بين 50-250 ميلي ثانية باسكال أما درجة الحموضة فقد تراوحت بين 5-5.9 وكمون زيتا بين -45 و -68 ميلي فولط. أبدت المستحلبات سلوكا بلاستيكيا كاذبا كنتيجة للشد ووجد أنها متميعة بالهز. كانت مستويات تحرر الدواء من مستحلبات زيت النخيل في الماء أعلى ب 4.5 مرة من مثيلاتها المتوفرة في الأسواق. أبدت دراسة الثباتية أن أقل من 5% من الدواء تخربت بعد تعريضها لدرجات حرارة مختلفة لمدة 3 اشهر. في الخاتمة فقد برهنت النتائج أن الكريمات المنتجة من مستحلبات زيت النخيل في الماء يمكن أن تكون بديلا عظيما كحامل في أنظمة الاعطاء الدوائي الموضعي.

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 of 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.

Thazin Win

Signature……. Date ….....

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Signature Date

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LIST OF EQUATIONS

LIST OF SYMBOLS

τ	Shear stress
η	Viscosity
δ	Phase angle
ε	Membrane porosity
G^*	Complex modulus
G'	Storage modulus
G"	Loss modulus
$-E_a$	Activation energy
τ	Membrane tortuosity
mV	Millivolt
uS	MicroSiemens
Q	Cumulative amount of the compound released per surface area of the membrane
J_{ss}	Permeation rate at steady state
f	Frequency
$\dot{\gamma}$	Shear rate
τ°	Yield stress

LIST OF ABBREVIATIONS

API	Active pharmaceutical ingredient
B	Betamethasone
BP	British Pharmacopoeia
BSA	Bovine serum albumin
BV17	Betamethasone 17-valerate
BV21	Betamethasone 21-valerate
cGMP	Current good manufacturing practice
D(v, 10)	Diameter below which 10% of the particle size of the sample exists
D(v, 50)	Diameter below which 50% of the particle size of the sample exists or median volume
D(v, 90)	Diameter below which 90% of the particle size of the sample exists
DLVO theory	Deryaguin, Landau, Verwey and Overbeek theory
EP	European Pharmacopoeia
FDA	Food and Drug Adminitsration
HLB	Hydrophile-lipophile balance
HPLC	High performance liquid chromatography
ICH guidelines	International Conference on Harmonisation Guidelines
ISO	International Organization for Standardization
JP	Japan Pharmacopoeia
LSE	Living skin equivalent
LVR	Linear visoelastic region
OECD guidelines	Organisation for Economic Co-Operation and Development Guidelines
PBS	Phosphate buffer solution