UNIVERSITI PUTRA MALAYSIA

FORMULATION, OPTIMIZATION AND CHARACTERIZATION OF PALM KERNEL OIL ESTERS NANOEMULSION SYSTEM CONTAINING SODIUM DICLOFENAC

MALAHAT REZAEE

IBS 2014 11

FORMULATION, OPTIMIZATION AND CHARACTERIZATION OF PALM KERNEL OIL ESTERS NANOEMULSION SYSTEM CONTAINING SODIUM DICLOFENAC

By

MALAHAT REZAEE

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

November 2014

This thesis is dedicated to:

The first and best leaders of my life

my beloved father and mother, Naser and Mina with love and gratitude,

and my best friends

my beloved brother and sister, Mehran and Mahshid.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

FORMULATION, OPTIMIZATION AND CHARACTERIZATION OF PALM KERNEL OIL ESTERS NANOEMULSION SYSTEM CONTAINING SODIUM DICLOFENAC

By

MALAHAT REZAEE

November 2014

Chairman: Professor Mahiran bt. Basri, PhD
Faculty: Institute of Bioscience

Nanoemulsions are nano-size emulsions which are used in many applications such as cosmetics and pharmaceuticals as delivery systems for parenteral, oral, ocular or transdermal administration. Transdermal administration is a suitable route for sodium diclofenac to prevent its adverse side effects which exhibited in other routes. Palm kernel oil esters (PKOEs) were selected as the oil phase for the preparation of nanoemulsion formulations containing sodium diclofenac. Special characteristic of PKOEs which has been reported is excellent wetting behavior without the oily feeling which makes it suitable for delivery of actives. Ternary phase diagrams of palm kernel oil esters with three surfactants (lecithin, Tween 20, Cremophor EL) as single and binary surfactants were constructed in three systems. The binary systems consisted of lecithin/Tween 20 and lecithin/Cremophor EL in two ratios of 80:20 and 60:40 for both systems. The increase of hydrophilic lipophilic balance (HLB) value and synergism effect between the surfactants in the binary surfactants systems gave larger homogenous and isotropic phases.

The isotropic region in the PKOEs/Lecithin:Cremophore EL (60:40)/water system was selected as nano-size emulsions composition range to be optimized and evaluated for their independent variables on responses of particle size and viscosity using Response Surface Methodology. The independent variables were water content, oil and surfactant ratio, stirring rate and stirring time. The study showed that third-order polynomial model was sufficient to describe and predict the responses. The smallest P-value and largest F-value belonged to O/S ratio for both responses. The optimized formulation (Opt.F) was formulated based on the achieved optimum conditions for preparation of sodium diclofenac nanoemulsions with the lowest values of particle size and viscosity to provide better drug penetration. As the O/S ratio was found to be the most efficient factor on the particle size and viscosity, in addition of Opt.F, five other formulations with different O/S ratio were selected for characterization.

The stability of the all formulations was evaluated by centrifugation, freeze-thaw cycle test and storage stability test. The Opt.F depicted good stability through the stability tests with no phase separation. The F-3 and F-4 formulations exhibited better stability than the other formulations. Rheology study showed that all nanoemulsion formulations exhibited non-Newtonian flow behaviour by displaying a pseudoplastic behaviour. Aerobic plate count, and yeast and mould count tests showed that there were no bacteria and fungus growth in the samples. The nanoemulsion formulations were found to be non-irritating by Irritancy Test. Permeation study was carried out by using cellulose acetate membrane and Wistar male rat skin. Opt.F and F-2 had the higher percentage of drug release. Five different terpenes based on the different chemical structure in five different concentrations were chosen as enhancer in Opt.F. All terpenes showed promoting effect on sodium diclofenac penetration. In addition, increase in terpenes concentration exhibited enhancement effect on drug permeation. Menthol had the highest permeation coefficient with the highest enhancement ratio for penetration of sodium diclofenac. Menthol and menthone in all concentrations of terpenes were shown to have significant effect on sodium diclofenc permeation. Different ratio of O/S is an effective factor on drug permeation. In conclusion, nanoemulsion formulations with good stability and suitable properties for transdermal delivery of sodium diclofenac were designed and developed.

Abstrak tesis yang dikemukan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

FORMULASI, PENGOPTIMUMAN DAN PENCIRIAN SISTEM NANO-EMULSI ESTER MINYAK ISIRUNG KELAPA SAWIT YANG MENGANDUNGI NATRIUM DIKLOROFENAK

Oleh

MALAHAT REZAEE

November 2014

Pengerusi: Professor Mahiran bt. Basri, PhD
Fakulti: Institut Biosains

Nano-emulsi adalah emulsi bersaiz nano yang digunakan dalam banyak aplikasi seperti kosmetik dan farmasi sebagai sistem penyampaian parenteral, lisan, okulus atau transdermal. Pemberian transdermal merupakan laluan sesuai bagi diclofenac sodium bagi mengelakkan kesan sampingan buruk seperti yang didapati pada laluan lain. Ester minyak isirung kelapa sawit (PKOEs) telah dipilih sebagai fasa minyak bagi persediaan formulasi nano emulsi yang mengandungi diclofenac sodium. Ciri-ciri khusus PKOEs yang telah dilaporkan ialah ciri pembasahan yang cemerlang tanpa rasa berminyak yang menjadikannya sesuai bagi penghantaran aktif. Gambar rajah fasa ternar (pseudo) ester minyak isirung kelapa sawit dengan tiga surfaktan (lesitin, Tween 20, Cremophor EL) sebagai surfaktan individu dan dedua telah dibina dalam tiga sistem. Sistem perduaan terdiri daripada lesitin/ Tween 20 dan lesitin/ Cremophor EL dalam nisbah 80:20 dan 60:40 bagi kedua-dua sistem. Peningkatan nilai baki hidrofilik lipofilik (HLB) dan kesan sinergisme antara surfaktan dalam sistem surfaktan dedua memberikan fasa homogen isotropik yang lebih besar.

Kawasan isotrop dalam PKOEs/Lesitin: Cremophor EL (60:40)/sistem air telah dipilih sebagai kawasan emulsi bersaiz nano bagi mengoptimum dan menilai pembolehubah bebas terhadap tindak balas saiz zarah dan kelikatan dengan menggunakan Metodologi Permukaan Gerak Balas. Pembolehubah bebas adalah kandungan air, minyak dan nisbah surfaktan, kadar adukan dan masa adukan. Kajian ini menunjukkan bahawa model polinomial tertib ketiga mencukupi bagi memperihal dan meramal tindak balas tersebut. Nilai P terkecil dan nilai F terbesar tergolong dalam nisbah O/S bagi kedua-dua tindak balas. Formulasi optimum (Opt.F) telah diformulasi berdasarkan syarat optimum tercapai bagi penyediaan nano emulsi diclofenac sodium dengan nilai terendah bagi saiz partikel dan kelikatan agar dapat memberi penembusan dadah yang lebih baik. Memandangkan nisbah O/S didapati sebagai faktor paling berkesan terhadap saiz zarah dan kelikatan, ditambah dengan Opt.F, lima formulasi lain dengan nisbah O/S yang berbeza telah dipilih untuk pencirian.

Kestabilan kesemua formulasi telah dinilai oleh pengemparan, ujian kitaran beku-cair dan ujian kestabilan simpanan. Opt.F menggambarkan kestabilan yang baik menerusi ujian kestabilan tanpa tahap pemisahan. Formulasi F-3 dan F-4 menunjukkan kestabilan yang lebih baik berbanding yang lain. Kajian reologi menunjukkan bahawa semua formulasi nano emulsi menunjukkan perilaku aliran bukan Newtonan dengan memaparkan perilaku pseudoplastik. Setelah pelaksanaan kiraan plat aerob, ujian kiraan ragi dan acuan, didapati bahawa tiada pertumbuhan bakteria atau kulat di dalam sampel. Formulasi emulsi nano didapati tidak merengsa oleh Ujian Kerengsaan. Kajian penelapan telah dijalankan oleh membran asetat selulosa dan kulit tikus Wistar jantan. Lima terpenes berbeza pada struktur bahan kimia yang berbeza dalam lima kepekatan yang berbeza telah dipilih sebagai peningkat dalam Opt.F. Semua terpenes menunjukkan mempunyai kesan penggalak terhadap penembusan diclofenac sodium. Selain itu, peningkatan kepekatan terpenes menyebabkan kesan peningkatan terhadap penelapan dadah. Mentol mempunyai korelasi penelapan tertinggi dengan nisbah peningkatan tertinggi bagi penembusan diclofenac sodium. Mentol dan mentona dalam semua kepekatan terpenes menunjukkan kesan signifikan terhadap penelapan diclofenac sodium. Akhir sekali, ianya didapati bahawa nisbah O/S yang berbeza merupakan faktor berkesan terhadap penelapan drug. Kesimpulannya, formulasi nano emulsi dengan kestabilan yang tinggi dan sifat-sifat yang sesuai bagi penyampaian transdermal diclofenac sodium telah direka dan dibangunkan.

AKNOWLEDGEMENTS

All praises is devoted to Allah, with whose gracious help it was possible to accomplish this work.

My deepest gratitude and sincere appreciation is owed to my supervisor Professor Dr. Mahiran Basri for her invaluable guidance, patience and encouragement from the beginning till end of this study. I would like to express my appreciation to my committee members, Professor Dr. Raja Noor Zaliha Raja Abd. Rahman and Professor Dr. Abu Bakar Salleh for their great concern and valuable advice during the course of this study.

Special thanks are due to Department of Chemistry, Faculty of Science and Institute of Bioscience for their help and cooperation during my experimental work. Thanks are extended to my friends Casey, Syila, Salwa, Liza, Naz, Atena, Emmy, Lim, Maha, Zahra, Brian, Sook Han, and also Dr Rosa and Dr hamid, and all my lab-mate in lab 401. Thank you for their support and sharing their knowledge, and making my stay during this research as sweet memories.

Finally, love and sincere thanks to my beloved family for their unconditional care, support and encouragement that has helped me achieve my educational accomplishment.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Mahiran Basri, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Dato' Abu Bakar Salleh, PhD
Prefossor
Faculty of Biotechnology and Biomolecular Science
University Putra Malaysia
(Member)

Raja Noor Zaliha Raja Abdul Rahman, PhD
Prefossor
Faculty of Biotechnology and Biomolecular Science
University Putra Malaysia
(Member)

BUJANG BIN KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURE

LIST OF ABBREVIATION

2P	Two phase
3P	Three phase
ANOVA	Analysis of variance
CCRD	Central composite rotatable design
COX	Cyclooxygenase
Cr EL	Cremophor El
ER	Enhancement ratios
FFA	Free fatty acids
H	Homogeneous
BA	Hydrogen bond acceptor
HBD	Hydrogen bond dodnor
HIE	Human irritancy equivalent
HLB	Hydrophilic-lipophilic balance
I	Isotropic
Kp	Permeability coefficients
L	Lecithin
LB	LB broth
LBA	LB agar
min	Minute
mL	Milliliter
mV	Millivolt
NA	Nutrient agar
NB	Nutrient broth
NSAIDs	Nonsteroidal anti-inflammatory drugs
O/S	Oil and surfactant
O/W	Oil-in-water
PDA	Potato dextrose agar
PGG2	Prostaglandin G2
PGH2	Prostaglandin H2
PGs	Glycerophospholipids
PIC	Phase inversion composition

PIT	Phase inversion temperature
PRESS	Prediction error sum of squares
R^2	Coefficient of determination
RMSE	Root mean squared error
rpm	Rotation per minute
RSM	Response surface methodology
SC	Stratum corneum
T20	Tween 20
TEM	Transmission electron microscopy
TSA	Tryptic soy agar
TSB	Tryptic soy broth
UPLC	Ultra-performance liquid chromatography
W/O	Water-in-oil

CHAPTER 1

INTRODUCTION

1.1 Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) belong to a group of drugs that are most commonly used in the world for their anti-inflammatory, antipyretic and analgesic properties (Pereira-Leite et al., 2013). Oral administration of NSAIDs is a very efficient route. However, potential of NSAIDs in creating adverse effects such as irritation and ulceration of the gastrointestinal (GI) mucosa often limits its usage in clinical application. NSAIDs must be prescribed frequently in daily doses in order for the therapeutic blood levels to remain constant. Therefore, patient noncompliance is also other usual problem in the administration of the drugs in oral or parenteral routes (Vonkeman et al., 2010; Sintov and Botner, 2006).

Sodium diclofenac is one of the most commonly used drugs of this group and is especially effective in the controlling the severe conditions of inflammation and pain, musculoskeletal disorders, arthritis, and dysmenorrhea. It is often prescribed for a period of time. Formulation as nanoemulsions is one of the nanoscience approaches that has been progressively considered in pharmaceutical science for transdermal delivery of drug. These nano-delivery systems in comparison to micron-size emulsions have been shown to have higher bioavailability and increase the effect of a number of compounds such as nonsteroidal anti-inflammatory drugs (NSAIDs) (Kotyla et al., 2008).

Nanoemulsions are a type of emulsion with particle sizes ranging from 20 nm to 200 nm, which are only kinetically stable (Solans et al., 2005). They may appear transparent or translucent mixtures of the oil phase, aqueous phase, surfactant(s), and co-surfactant(s) that create oil-in-water (O/W) or water-in-oil (W/O) emulsion (Solans and Sole, 2012). An emulsion is formed by the dispersion of one liquid, usually the oil phase in another immiscible liquid, water phase that is stabilized using surfactant. Palm kernel oil esters (PKOEs), in comparison to other oils, contain higher amounts of shorter chain esters, which suitable to be applied in micro and nanoemulsion systems as a carrier for actives. Furthermore, the higher iodine and saponification values, as well as lower slip melting point and the lower acidity values of PKOEs compared to other esters, provide some favorable properties for micro and nanoemulsions in many applications (Keng et al., 2009; Salim et al., 2012).

Nanoemulsions as non-equilibrium systems cannot be formed spontaneously and for their formation, extrinsic energy is necessary. There are two main methods for preparation of nanoemulsions: condensation or low-energy methods, and dispersion or high-energy methods. High-energy emulsification methods result in emulsions having the most homogeneous flow and adjustable control of droplet size and thus are suitable for industrial utilizations (Solans et al., 2005). The prepared nanoemulsions properties in addition of formation preparation mechanisms, are influenced by formulation compositions. Evaluation of nanoemulsion formulations and optimization according to the best formulation composition and preparation conditions can be carried out through an experimental design.

The experimental design allows the study of the effect of variables alone, as well as their interactions. Response Surface Methodology (RSM) which is used for experimental design is an efficient statistical and mathematical tool used for the modeling and analysis of processes that exist between the independent factors and their responses, and for optimization of the processes or products (Yuan et al., 2008). When the independent variables have complex interactions, RSM is also beneficial in simultaneously analyse their process (Hao et al., 2011). The first aim of RSM is to detect the optimum response, and the second is to understand how is the changes of response against the adjusting the variables.

1.2 Problem Statements

Although sodium diclofenac is one of the best-tolerated classical NSAIDs, like other drugs in this category, it can cause gastrointestinal adverse effects such as gastrointestinal bleeding, ulceration, nausea and vomiting by oral route, and cutaneous lesions by intramuscular injection (Suwalsky, et al., 2009; Zhai et al., 2013). It is a challenge to overcome the drug's adverse effects, high hepatic first-pass metabolism, and the short biological half-life. Therefore, development of a transdermal nanodelivery system like nanoemulsions could be beneficial.

The selection of suitable type and concentration of surfactant, and applying a proper input energy are the main challenges for preparation a nanoemulsion. Therefore, it is necessary to develop a model that in addition of formulation compositions, study and optimize the processing conditions, so as to avoid spending time and energy to save cost, particularly in industrial applications. Since particle size and viscosity are important factors for an efficient drug release (Cross et al., 2001; Tsai et al., 2011), these parameters were selected as responses in the study. In spite of importance of viscosity in stability and drug permeation, there are few reports on the effect of various factors on nanoemulsion viscosity, or its optimization especially in pharmaceutical research. Since nanoemulsions are thermodynamically unstable, they have tendency to coalescence and Ostwald ripening processes which result in phase separation. Therefore, stability of nanoemulsions is a critical factor to be analysed, especially when the achievement of formulations with long time stability (three years shelf life) was favorable.

In addition, sodium diclofenac is solved in aqueous solutions as ionized salt and has low logP value, thus it is not absorbed easily by transdermal application (Nokhodchi et al., 2007). One challenge to overcome this problem and the skin's strong barrier function is to design a functional transdermal drug delivery system by using enhancers.

1.3 Objectives

The main objective of the research was to develop an efficient palm kernel oil esters-based nanodelivery system for the transdermal delivery of sodium diclofenac. To achieve this aim the following objectives was carried out:

1. To determine the phase behaviour of palm kernel oil esters (PKOEs) system by constructing the ternary phase diagrams.
2. To optimize and evaluate the condition for preparation of nanoemulsions with the smallest values of particle size and viscosity using Response Surface Methodology (RSM).
3. To characterize the physicochemical properties of the nanoemulsion systems, such as stability, rheology, and safety evaluation.
4. To determine the delivery potential of the nanoemulsion systems containing sodium diclofenac in *in-vitro* tests through cellulose membrane and Wistar rat skin, and improve the drug permeation using enhancers.

REFERENCES

Abd Gani, S. S., Basri, M., Rahman, M. B. A., Kassim, A., Rahman, R. N. Z. R. A. Salleh, A. B. and Ismail, Z. (2010). Characterization and effect on skin hydration of Engkabang-based emulsions. *Bioscience, Biotechnology, and Biochemistry*, 74(6): 1188–1193.

Abd Gani, S. S. A., Basri, M., Rahman, M. B. A., Kassim, A., Salleh, A. B., Abdul Rahman, R. N. Z. R. and Ismail, Z. (2009). Phase behavior of engkabang fat with nonionic surfactants. *Tenside Surfactant Detergents*, 46: 195–198.

Abdulkarim, M. F., Abdullah, G. Z., Sakeena, M. H. F., Chitneni, M., Yam, M. F. Mahdi, E. S., Salman, I. M., Ameer, O. Z., Sattar, M. A., Basri, M. and Noor. A. M. (2011). Study of pseudoternary phase diagram behaviour and the effect of several tweens and spans on palm oil esters characteristics. *International Journal of Drug Delivery*, 3: 95–100.

Abdurahman, N. H., Rosli, Y. M., Azhari, N. H. and Hayder, B. A. (2012). Pipeline transportation of viscous crudes as concentrated oil-in-water emulsions. *Journal of Petroleum Science and Engineering*, (90–91): 139–144.

Alexander, A., Dwivedi, S., Ajazuddin, Giri, T. K., Saraf, S., Saraf, S. and Tripathi, D. K. (2012). Approaches for breaking the barriers of drug permeation through transdermal drug delivery. *Journal of Controlled Release*, 164: 26–40.

Anton, N., Benoit, J. P. and Saulnier, P. (2008). Design and production of nanoparticles formulated from nano-emulsion templates — A review. *Journal of Controlled Release*, 128: 185–199.

Aqil, M., Ahad, A., Sultana, Y. and Ali, A. (2007). Status of terpenes as skin penetration enhancers. *Drug Discovery Today*, 12(23/24): 1061–1067.

Arellano, A., Santoyo, S., Martín, C., Ygartua, P. (1996). Enhancing effect of terpenes on the in vitro percutaneous absorption of diclofenac sodium. *Intenational Journal of Pharmaceutic*, 130: 141-145.

Bas¸er, K. H. C. and Buchbauer, G. (2010). *Handbook of essential oils, science, technology,and applications*, Boca Raton: CRC Press.

Beetge, E., Plessis, J., Muller, D. G., Goosen, C. and Rensburg, F. V. (2000). The influence of the physicochemical characteristics and pharmacokinetic properties of selected NSAID's on their transdermal absorption. *Intenational Journal of Pharmaceutic*, 193: 261 – 264.

Birdi, K. S. (2010). *Surface and colloid chemistry, principles and applications*. Boca Raton: CRC Press.

Boinpally, R. R., Zhou, S. L., Poondru, S., Devraj, G. and Jasti, B. R. (2003). Lecithin vesicles for topical delivery of diclofenac. *European Journal of Pharmaceutics and Biopharmaceutics*, 56: 389–392.

Bradley, N. (2007). *The response surface methodology* University of South Bend, U.S.A.

Brocklehurst, T. F. and Wilson, P. D. G. (2000). The role of lipids in controlling microbial growth. *Grasasy Aceites*, 51: 66–73.

Chaibakhsh, N., Rahman, M. B. A., Abd-Aziz, S., Basri, M., Salleh, A. B. and Rahman, R. N. Z. R. A. (2009). Optimized lipase-catalyzed synthesis of adipate ester in a solvent-free system. *Journal of Industrial Microbiology and Biotechnology*, 36: 1149–1155.

Chanana, G. D. and Sheth, .B. B. (1995). Particle size reduction of emulsions by formulation design-II: effect of oil and surfactant concentration. *PDA Journal Of Pharmaceutical Science And Technology*, 49: 71–6.

Chen, Y., Quan, P., Liu, X., Wang, M. and Fang, L. (2014). Novel chemical permeation enhancers for transdermal drug delivery. *Asian Journal of Pharmaceutical Sciences*, 9: 51–64.

Cross, S. E., Jiang, R., Benson, H. A. and Roberts, M. S. (2001). Can increasing the viscosity of formulations be used to reduce the human skin penetration of the sunscreen oxybenzone? *Journal of Investigative Dermatology*, 117(1): 147–150.

Das, S. C., Hatta, M., Wilker, P. R., Myc, A., Hamouda, T., Neumann, G., Baker Jr., J. R. and Kawaoka, Y. (2012). Nanoemulsion W805EC improves immune responses upon intranasal delivery of an inactivated pandemic H1N1 influenza vaccine. *Vaccine*, 30: 6871–6877.

Denyer, S. P. and Baird, R. M. (2007). *Guide to microbiological control in pharmaceuticals and medical devices.* Boca Raton: CRC Press.

Desai, N. (2012). Challenges in development of nanoparticle-based therapeutics**.** *The AAPS Journal*, 14(2): 282–295.

Dinarvand, M., Rezaee, M., Masomian, M., Jazayeri, S. D., Zareian, M., Abbasi, S. and Ariff, A. B. (2013). Effect of C/N ratio and media optimization through response surface methodology on simultaneous productions of intra-and extracellular inulinase and invertase from *Aspergillus niger* ATCC 20611. *BioMed Research International*, (2013): 1–13.

Djordjevic, L., Primorac, M. and Stupar, M. (2005). In vitro release of diclofenac diethylamine from caprylocaproyl macrogolglycerides based microemulsions. *International Journal of Pharmaceutics*, 296: 73–79.

Drakulic, B. J., Juranic, I. O., Eric, S. and Zloh, M. (2008). Role of complexes formation between drugs and penetration enhancers in transdermal delivery. *International Journal of Pharmaceutics,* 363: 40–49.

Ebrahimpour, A., Rahman, R. N. Z. R. A., Ch'ng,D.H.E., Basri, M. and Salleh, A.B. (2008). A modeling study by response surface methodology and artificial neural network on culture parameters optimization for thermostable lipase production from a newly isolated thermophilic *Geobacillus* sp. strain ARM. *BMC Biotechnology,* 8: 96–111.

El-Kattan, A.F., Asbilla, C. S., Kima, N. and Michniak, B. B. (2001) The effects of terpene enhancers on the percutaneous permeation of drugs with different lipophilicities. *International Journal of Pharmaceutics,* 215: 229–240.

Fang, J. Y., Hwang, T. L. and Leu, Y. L. (2003). Effect of enhancers and retarders on percutaneous absorption of flurbiprofen from hydrogels. *International Journal of Pharmaceutics,* 250: 313–325.

Fanun, M. (2008). Phase behavior, transport, diffusion and structural parameters of nonionic surfactants microemulsions. *Journal of Molecular Liquids* 139: 14– 22.

Fini, A., Bassini, G., Monastero, A. and Cavallari, C. (2012). Diclofenac salts, VIII. effect of the counterions on the permeation through porcine membrane from aqueous saturated solutions, *Pharmaceutics,* 4: 413–429.

Fini, A., Fazio, G., Gonzalez-Rodriguez, M., Cavallari, C. and Passerini, N. (1999). Formation of ion-pairs in aqueous solutions of diclofenac salts. *Intenational Journal of Pharmaceutics,* 187: 163–173.

Forgiarini, A., Esquena, J., González, C. and Solans, C. (2001). Formation and stability of nano-emulsions in mixed nonionic surfactant systems, *Prog Colloid Polymer Science,* 118: 184–189.

Fox, L. T., Gerber, M., Jeanetta Du Plessis, J. D. and Hamman, J. H. (2011). Transdermal drug delivery enhancement by compounds of natural origin. *Molecules,* 16: 10507–10540.

Fredrick, E., Walstra, P. and Dewettinck, K. (2010). Factors governing partial coalescence in oil-in-water emulsions. *Advances in Colloid and Interface Science,* 153: 30–42.

Fu, Z., Liu, M., Xu, J., Wang, Q. and Fan, Z. (2010). Part I: Stabilized by mixed surfactant systems. *Fuel,* 89: 2838–2843.

Ghosh, S. and Coupland, J. N. (2008). Factors affecting the freeze–thaw stability of emulsions. *Food Hydrocolloids,* 22: 105–111.

Godwin, D.A. and Michniak, B.B. (1999). Influence of drug lipophilicity on terpenes as penetration enhancers. *Drug Development and Industrial Pharmacy,* 25: 905–915.

Graf, A., Ablinger, E., Peters, S., Zimmer, A., Hook, S. and Rade, T. (2008). Microemulsions containing lecithin and sugar-based surfactants: Nanoparticle templates for delivery of proteins and peptides. *International Journal of Pharmaceutics,* 350: 351–360.

Gunawan, E. R., Basri, M., Abdul Rahman, M. B., Salleh, A. B. and Rahman, R. N. Z. R. A (2005). Study on response surface methodology (RSM) of lipase-catalyzed synthesis of palm-based wax ester. *Enzyme and Microbial Technology,* 37: 739–744.

Gutiérrez, J. M., González, C., Maestro, A., Solè, I., Pey, C. M. and Nolla, J. (2008). Nano-emulsions: New applications and optimization of their preparation. *Current Opinion in Colloid & Interface Science,* 13: 245–251.

Hadgraft, J. (2001). Skin, the final frontier. *International Journal of Pharmaceutics* 224: 1-18.

Hanning, S. M., Yu, T., Jones, D. S., Andrews, G. P., Kieser, J. A. and Medlicott, N. J. (2013). Lecithin-based emulsions for potential use as saliva substitutes in patients with xerostomia – viscoelastic properties. *International Journal of Pharmaceutics,* 456: 560–568.

Hao, J., Fang, X., Zhou, Y., Wang, J., Guo, F., Li, F. and Peng, X. (2011). Development and optimization of solid lipid nanoparticle formulation for ophthalmic delivery of chloramphenicol using a Box-Behnken design. *International Journal of Nanomedicine,* 6: 683–692.

Hayati, I. N. (2007). Stability and rheology of concentrated O/W emulsions based on soybean oil/palm kernel olein blend. *Food Research International* ,40: 1051–1061.

Hu, L., Silva, S. M. C., Damaj, B. B., Martin, R. and Michniak-Kohn, B. B. (2011). Transdermal and transbuccal drug delivery systems: Enhancement using iontophoretic and chemical approaches. *International Journal of Pharmaceutics,* 421: 53–62.

Isar, J., Agarwal, L., Saran, S. and Saxena, R. K. (2006), A statistical method for enhancing the production of succinic acid from *Escherichia coli* under anaerobic conditions, *Bioresource Technology,* 97:1443–1448.

Jafari, S. M., Assadpoor, E., Yinghe He, Y. and Bhandari, B. (2008). Re-coalescence of emulsion droplets during high-energy emulsification, *Food Hydrocolloids*, 22: 1191–1202.

Jafari, S. M., He, Y. and Bhandari. B. (2007). Production of sub-micron emulsions by ultrasound and microfluidization techniques. *Journal of Food Engineering*, 82: 478–488.

Jain, A. K., Thomas, N. S. and Panchagnula, R. (2002). Transdermal drug delivery of imipramine hydrochloride. I. Effect of terpenes. *Journal of Controlled Release*, 79: 93–101.

Jain, R., Aqil, M., Ahad, A., Ali, A. and Khar, R. K. (2008). Basil oil is a promising skin penetration enhancer for transdermal delivery of labetolol hydrochloride. *Drug Development and Industrial Pharmacy*, 34: 384-389.

Jiao, J. (2008). Polyoxyethylated nonionic surfactants and their applications in topical ocular drug delivery. *Advanced Drug Delivery Reviews*, 60: 1663–1673.

Kelmann, R. G., Kuminek, G., Teixeira, H. F. and Koester, L. S. (2007). Carbamazepine parenteral nanoemulsions prepared by spontaneous emulsification process. *International Journal of Pharmaceutics*, 342: 231–239.

Keng, P. S., Basri, M., Zakaria, M. R. S., Abdul Rahman, M. B., Ariff, A. B., Abdul Rahman, R.N.Z. and Salleh, A.B. (2009). Newly synthesized palm esters for cosmetics industry. *Industrial Crops and Products*, 29: 37–44.

Kentish, S., Wooster, T. J. M. Ashokkumar, M., Balachandran, S., Mawson, R. and Simons, L. (2008). The use of ultrasonics for nanoemulsion preparation. *Innovative Food Science and Emerging*, (2):170–175.

Khan, A. and Marques, E. F. (2000). Synergism and polymorphism in mixed surfactant systems. *Current Opinion in Colloid & Interface Science*, 4: 402–410.

Kirjavainen, M., Monkkonen, J., Saukkosaari, M., Koskela, R.V., Kiesvaara, J. and Urtti, A. (1999). Phospholipids affect stratum corneum lipid bilayer fluidity and drug partitioning into the bilayers. *Journal of Controlled Release*, 58: 207–214.

Kogan, A. and Garti, N. (2006). Microemulsions as transdermal drug delivery vehicles. *Advances in Colloid and Interface Science*, 123–126: 369–385.

Kong, M., Chen, X. G., Kweon, D. K. and Park, H. J. (2011). Investigations on skin permeation of hyaluronic acid based nanoemulsionmas transdermal carrier. *Carbohydrate Polymers*, 86: 837–843.

Kotyla, T., Kuo, F., Moolchandani, V., Wilson, T. and Nicolosi, R. (2008). Increased bioavailability of a transdermal application of a nano-sized emulsion preparation. *International Journal of Pharmaceutics*, 347: 144–148.

Kunieda, H., Nakano, A. and Akimaru, M. (1995). The effect of mixing of surfactants on solubilization in a microemulsion system. *Journal of colloid and interface science,* 170: 78-84.

Langer, R. (2004). Transdermal drug delivery: past progress, current status,and future prospects. *Advanced Drug Delivery Reviews,* 56: 557–558.

Lawrence, M. J. and Rees, G. D. (2012). Microemulsion-based media as novel drug delivery systems. *Advanced Drug Delivery Reviews,* 64: 175–193.

Lee, A., Chaibakhsh, N., Rahman, M. B. A., Basri, M. and Tejo, B. A. (2010). Optimized enzymatic synthesis of levulinate ester in solvent-free system. *Industrial Crops and Produscts,* 32:246–251.

Lee, H. V., Yunus, R., Juan, J. C. and Taufiq-Yap, Y. H. (2011). Process optimization design for jatropha-based biodiesel production using response surface methodology. *Fuel Proc essing Technology,* 92: 2420–2428.

Li, P., Ghosh, A., Wagner, R. F., Krill, S., Joshi, Y. M. and Serajuddin, A. T. M. (2005). Effect of combined use of nonionic surfactant on formation of oil-in-water microemulsions. *International Journal of Pharmaceutics,* 288: 27–34.

Li, P. H. and Chiang, B. H. (2012). Process optimization and stability of D-limonene-in-water nanoemulsions prepared by ultrasonic emulsification using response surface methodology. *Ultrasonics Sonochemistry,* 19(1): 192–197.

Li, T., Ren, Ch., Wang, M., Zhao, L., Wang, X. and Fang, L. (2007). Optimized preparation and evaluation of indomethacin transdermal patch. *Asian Journal of Pharmaceutical Sciences,* 6: 249–259.

Lim, C. J., Basri, M., Omar, D., Rahman, M. B. A., Salleh, A. B. and Rahman, R. N. Z. R. A. (2012). Physicochemical characterization and formation of glyphosate-laden nano-emulsion for herbicide formulation, *Industrial Crops and Products,* 36: 607– 613.

Lim, P. F. C., Liu, X. Y., Kang, L., Ho, P. C. L., Chan, Y. W. and Chan, S. Y. (2006). Limonene GP1/PG organogel as a vehicle in transdermal delivery of haloperidol. *International Journal of Pharmaceutics,* 311: 157–164.

Lin, C. Y. and Chen, L. W. (2006). Emulsification characteristics of three- and two-phase emulsions prepared by the ultrasonic emulsification method, *Fuel Processing Technology,* 87(4): 309–317.

Liu, J. Z.; Weng, L. P. and Zhang, Q. L. (2003), Optimization of glucose oxidase production by *Aspergillus niger* in a benchtop bioreactor using response surface methodology. *World Journal of Microbiology and Biotechnology,* 19:317–323.

Liu, W., Sun, D., Li, C., Liu, Q. and Xu, J. (2006). Formation and stability of paraffin oil-in-water nano-emulsions prepared by the emulsion inversion point method. *Journal of Colloid and Interface Science,* 303: 557–563.

Lovelyn, C. and Attama, A. A. (2011). Current state of nanoemulsions in drug delivery. *Journal of Biomaterials and Nanobiotechnology*, 2: 626–639.

Lundstedt, T., Seifert, E., Abramo, L., Thelin, B., Nystrom, A., Pettersen, J. and Bergman, R. (1998). Experimental design and optimization. *Chemometrics and Intelligent Laboratory Systems*, 42: 3–40.

Maa, Y. F. and Hsu, C. (1996). Liquid–liquid emulsification by rotor/stator homogenization. *Journal of Controlled Release,* 38:219–228.

Mahdi, E. S., Noor, A. M. and Abdul Sattar, M. Z. (2012). Formulation and characterization of extract from *phyllanthus niruri* loaded nanocreams as skin antiaging. *Journal of Pharmacy Research,* 5(6): 3172–3180.

Malzert-Fréon, A., Saint-Lorant, G., Hennequin, D., Gauduchon, P., Poulain, L. and Rault, S. (2010). Influence of the introduction of a solubility enhancer on the formulation of lipidic nanoparticles with improved drug loading rates. *European Journal of Pharmaceutics and Biopharmaceutics,* 75: 117–127.

Manconi, M., Mura, S., Sinico, C., Fadda, A. M., Vila, A. O. and Molina, F. (2009). Development and characterization of liposomes containing glycols as carriers for diclofenac. *colloids and Surfaces A: Physicochemical and Engineering Aspects*, 342: 53–58.

Martinez-Pla, J. J., Martin-Biosca, Y., Sagrado, S., Villanueva-Camanas, R. M. and Medina-Hernandez, M. J. (2004). Evaluation of the pH effect of formulations on the skin permeability of drugs by biopartitioning micellar chromatography. *Journal of Chromatography A*, 1047: 255–262.

Mason, T. (2000). Large scale sonochemical Processing: Aspiration and actuality, *Ultrasonics Sonochemistry,* 7: 145–149.

Mason, T. G., Wilking, J. N., Meleson, K., Chang, C. B. and Graves, S. M. (2006). Nanoemulsions: formation, structure, and physical properties. *Journal of Physics: Condensed Matter*, 18 : 635–666.

Masoumi, H. R., Kassim, A., Basri, M. and Abdullah, D. K.(2011). Determining optimum conditions for lipase-catalyzed synthesis of triethanolamine (tea)-based esterquat cationic surfactant by a taguchi robust design method. *Molecules,* 16: 4872–4680.

McClements D. J. and Rao, J. (2011). Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity. *Critical Reviews in Food Science and Nutrition,* 51: 285–330.

McClements D. J. (2005). *Food emulsions, principles, practices, and technique*. Boca Raton: CRC Press.

McClements D. J. (1999). *Food emulsions, principles, practices, and technique*. Boca Raton: CRC Press.

Mehrgan, H., Elmi, F,. Fazeli, M. R., Shahverdi A. R and Samadi, N. (2006). Evaluation of neutralizing efficacy and possible microbial cell toxicity of a universal neutralizer proposed by the CTPA. *Iranian Journal of Pharmaceutical Research,* 3: 173–178.

Monti, D., Chetoni, P., Burgalassi, S., Najarro, M., Fabrizio Saettone, M. and Boldrini, E. (2002). Effect of different terpene-containing essential oils on permeation of estradiol through hairless mouse skin. *International Journal of Pharmaceutics*, 237: 209–214.

Moore, D. J. and Rerek, M. E. (2000). Insights into the molecular organisation of lipids in the skin barrier from infrared spectroscopy studies of stratum corneum lipid models. *Acta Dermato-Venereologica,* 298:16-22.

Narishetty, S. T. K. and Panchagnula, R. (2005). Effect of l -menthol and 1,8-cineole on phase behavior and molecular organization of SC lipids and skin permeation of zidovudine. *Journal of Controlled Release*, 102: 59–70.

Nijkamp, F. P. and Parnham, M. J. (2011). *Principles of Immunopharmacology* Switzerland: Springer.

Niraula, B., King, T. C. and Misran, M. (2004). Evaluation of rheology property of dodecyl maltoside, sucrose dodecanoate, Brij 35p and SDS stabilized O/W emulsion: effect of head group structure on rheology property and emulsion stability. *Colloids and Surfaces A: Physicochemical and Engineering Aspects,* 25: 59–74.

Nokhodchi, A., Sharabiani, K., Rashidi, M. R. and Ghafourian, T. (2007). The effect of terpene concentrations on the skin penetration of diclofenac sodium. *International Journal of Pharmaceutics,* 335: 97–105.

Noordin, M. Y., Venkatesh, V. C., Sharif, S., Elting, S. and Abdullah, A. (2004). Application of response surface methodology in describing the performance of coated carbide tools when turning AISI 1045 steel. *Journal of Materials Processing Technology,* 145: 46–58.

Nostro, A. Cannatelli, M. A. I. Morelli, I. Musolino,A. D. Scuderi, F. Pizzimenti, F. and Alonzo, V. (2004). Efficiency of *Calamintha officinalis* essential oil as of nonionic surfactants microemulsions. *Journal of Molecular Liquids,* 139: 14–22.

Ogawa, S., Decker, E. A. and McClements, D. J. (2003). Influence of environmental conditions on the stability of oil in water emulsions containing droplets stabilized by lecithin−chitosan membranes. *Journal of Agricultural and Food Chemistry,* 51: 5522–5527.

Onuki, Y., Morishita, M. and Takayama, K. (2004). Formulation optimization of water-in-oil-water multiple emulsion for intestinal insulin delivery. *Journal of Controlled Release,* 97: 91–99.

Pal, R. (2000). Shear viscosity behavior of emulsions of two immiscible liquids. *Journal of Colloid and Interface Science,* 22:359–366.

Palazolo, G. G., Sobral, P. A. and Wagner. J. R. (2011). Freeze-thaw stability of oil-in -water emulsions prepared with native and thermally-denatured soybean isolates. *Food Hydrocolloids,* 25: 398–409.

Pathan, I. B. and Setty, M. (2009). Chemical penetration enhancers for transdermal drug delivery systems. *Tropical Journal of Pharmaceutical Research,* 8(2): 173–179.

Pereira-Leite, C., Nunes, C. and Reis, S. (2013). Interaction of nonsteroidal anti-inflammatory drugs with membranes: In vitro assessment and relevance for their biological actions. *Progress in Lipid Research*, 52: 571–584.

Pey, C. M., Maestro, A., Sol´e, I., Gonz´alez, C., Solans, C. and Guti´errez, J. M. (2006). Optimization of nano-emulsions prepared by low-energy emulsification methods at constant temperature using a factorial design study *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 288: 144–150.

Pogorzelski, S., Watrobska-Swietlikowska, D. and Sznitowska, M. (2012). Surface tensometry studies on formulations of surfactants with preservatives as a tool for antimicrobial drug protection characterization. *Journal of Biophysical Chemistry*, 3(4): 324–333.

Price, D. T., McKenney, D.W., Nalder, I. A., Hutchinson, M. F. and Kesteven, J. L. (2000). A comparison of two statistical methods for spatial interpolation of Canadian monthly mean climate data. *Agricultural and Forest Meteorology,* 101: 81–94.

Rabinovich-Guilatt, L., Couvreur, P., Lambert, G., Goldstein, D., Benita, S. and Dubernet, C. (2004). Extensive surface studies help to analyse zeta potential data: the case of cationic emulsions. *Chemistry and Physics of Lipids,* 131: 1–13.

Rapoport, N. Y., Kennedy, A. M., Shea, J. E., Scaife, C. L. and Nam, K. H. (2009). Controlled and targeted tumor chemotherapy by ultrasound-activated nanoemulsions/microbubbles. *Journal of Cont rolled Release,* 138(26): 8–276.

Rastogi, N. K. and Rashmi, K. R. (1999). Optimisation of enzymatic liquefaction of mango pulp by response surface methodology. *European Food Research and Technology*, 20: 57–62.

Roland, I., Piel, G., Delattre, L., and Evrard, B. (2003). Systematic characterization of oil-in-water emulsions for formulation design. *International Journal of Pharmaceutics*, 263: 85–94.

Rozaini, M. Z. H. (2012). Phase behavior of pseudo-ternary gemini surfactant + 1-hexanol/oil/water systems. *Journal of Atomic, Molecular, and Optical Physics*, 2012: 1–6.

Saikaew, C., Wisitsoraat, A. and Sootticoon, R. (2010). Optimization of carbon doped molybdenum oxide thin film coating process using designed experiments. *Surface & Coatings Technology*, 204: 1493–1502.

Salim, N., Basri, M., Rahman, M. B., Abdullah, D. K. and Basri, H. (2012). Modification of palm kernel oil esters nanoemulsions with hydrocolloid gum for enhanced topical delivery of ibuprofen. *International Journal Nanomedicine*,7: 4739–4747.

Shakeel, F. and Ramadan, W. (2010). Transdermal delivery of anticancer drug caffeine from water-in-oil nanoemulsions. *Colloids and Surfaces B: Biointerfaces*, 75: 356–362.

Shokri, J., Nokhodchi, A., Dashbolaghi, A., Hassan-Zadeh, D., Ghafourian, T. and Barzegar Jalali, M. (2001). The effect of surfactants on the skin penetration of diazepam. *International Journal of Pharmaceutics*, 228: 99–107.

Saija, A., Tomaino, A., Trombetta, D., Giacchi, M., Pasquale, A. P. and Bonina, F. (1998). Influence of different penetration enhancers on in vitro skin permeation and in vivo photoprotective effect of flavonoids. *International Journal of Pharmaceutics*, 175: 85–94.

Sintov, A. C. and Botner, Sh. (2006). Transdermal drug delivery using microemulsion and aqueous systems: Influence of skin storage conditions on the in vitro permeability of diclofenac from aqueous vehicle systems. *International Journal of Pharmaceutics*, 311:55–62.

Small, R. E. (1989). Diclofenac sodium. *Clinical Pharmacy* 8(8): 545–58.

Solans, C. and Solé, I. (2012). Nano-emulsions: Formation by low-energy methods. *Current Opinion in Colloid & Interface* Science, 17: 246–254.

Solans, C., Izquierdo, P., Nolla, J., Azemar, N. and Garcia-Celma, M. J. (2005). Nano-emulsions. *Current Opinion in Colloid & Interface Science*, 10: 102–110.

Songkro, S. (2009). An overview of skin penetration enhancers: penetration enhancing activity, skin irritation potential and mechanism of action. *Songklanakarin Journal of Science and Technology*, 31(3): 299–321.

Souza, V. B., Netoa, J. S. G., Spinellia, L. S. and Mansura, C. R. E. (2013). Application of oil/water nanoemulsions as a new alternative to demulsify crude oil. *Separation Science and Technology*, 48(8): 1159–1166.

Spernath, A., Aserin, A., Sintov, A.C. and Garti, N. (2008). Phosphatidylcholine embedded micellar systems: Enhanced permeability through rat skin. *Journal of Colloid and Interface Science,* 318: 421–429.

Spernath, A., Aserin, A., Ziserman, L., Danino, D. and Garti, N. (2007) Phosphatidylcholine embedded microemulsions: Physical properties and improved Caco-2 cell permeability. *Journal of Controlled Release,* 119: 279–290.

Sutradhar, K. B. and Amin, M. L. (2013). Nanoemulsions: increasing possibilities in drug delivery. *European Journal of Nanomedicine,* 5(2): 97–110.

Suwalsky, M., Manrique, M., Villena, F. and Sotomayor, C. P. (2009). Structural effects in vitro of the anti-inflammatory drug diclofenac on human erythrocytes and molecular models of cell membranes. *Biophysical Chemistry,* 141: 34–40.

Tadros, T., Izquierdo, P., Esquena, J. and Solans, C. (2004). Formation and stability of nano-emulsions, *Advances in Colloid and Interface Science,* 108–109: 303–318.

Tang, S. Y., Manickam, S., Wei, T. K. and Nashiru, B. (2012). Formulation development and optimization of a novel Cremophore EL-based nanoemulsion using ultrasound cavitation. *Ultrasonics Sonochemistry,* 19: 330–345.

Taylor, P. (1998). Ostwald ripening in emulsions. *Advances in Colloid and Interface Science,* 75: 107–163.

Taylor, P. (2003). Ostwald ripening in emulsions: estimation of solution thermodynamics of the disperse phase. *Advances in Colloid and Interface Science,* 106: 261–285.

Teo, B. S. X., Basri, M., Zakaria, M. R. S., Salleh, A. B., Rahman, R. N. Z. R. A. and Rahman, M. B. A. (2010). A potential tocopherol acetate loaded palm oil esters-in-water nanoemulsions for nanocosmeceuticals. *Journal of Nanobiotechnology,* 8(4): 2–11.

Thakur, C., Srivastava, V. C. and Mall, I. D. (2009), Electrochemical treatment of a distillery wastewater. Parametric and residue disposal study, *Chemical Engineering Journal*,148: 496–505.

Torres, L.,G., Iturbe, R., Snowden, M.,J., Chowdhry, B.,Z. and Leharne, S. A. (2007). Preparation of o/w emulsions stabilized by solid particles and their characterization by oscillatory rheology. *Colloids and Surfaces A: Physicochemical and Engineering Aspects,* 302: 439–448.

Trotta, M., Cavalli, R., Ugazio, E. and Gasco, M. R. (1996). Phase behaviour of microemulsion systems containing lecithin and lysolecithin as surfactants. *International Journal of Pharmaceutics,* 143: 67–73.

Trotta, M., Pattarino, F. and Grosa, G. (1998). Formation of lecithin-based microemulsions containing n-alkanol phosphocholines. *International Journal of Pharmaceutics*, 174: 253–259.

Tsai, Y. H., Chang, J. T., Chang, J. S., Huang, C. T., Huang, Y. B. and Wu, P. C. (2011). The effect of component of microemulsions on transdermal delivery of buspirone hydrochloride. *Journal of Pharmaceutical Sciences*, 100(6): 2358–2365.

Vianna-Filho, R. P., Petkowicz, C. L. O. and Silveira, J. L. M. (2013). Rheological characterization of O/W emulsions incorporated with neutral and charged polysaccharides. *Carbohydrate Polymers*, 93: 266– 272.

Villar, A. M. S., Naveros, B. C., Campmany, A. C. C., Trenchs, M. A., Rocabert, C.B. and Bellowa, L.H. (2012). Design and optimization of self-nanoemulsifying drug delivery systems (SNEDDS) for enhanced dissolution of gemfibrozil. *International Journal of Pharmaceutics*, 431: 161–175.

Villarino, N. and Landoni, M. F. (2006). Transdermal drug delivery: A new frontier in the administration of therapeutic drugs to veterinary species. *Veterinary Journal*, 172: 200–201.

Vonkeman, H., and Van de Laar, M. A. F. J. (2010). Nonsteroidal anti-inflammatory drugs: adverse effects and their prevention. *Seminars in Arthritis and Rheumatism*, 39(4): 294–312.

Watanabe, H., Obata, Y., Ishida, K. and Takayama, K. (2009). Effect of l-menthol on the thermotropic behavior of ceramide 2/cholesterol mixtures as a model for the intercellular lipids in stratum corneum. *Colloids and Surfaces B: Biointerfaces*, 73: 116–121.

Williams, A.C., Barry, B.W. (1991). Terpenes and the lipid-protein-partitioning theory of skin penetration enhancement. *Pharmaceutical Research*, 8: 17-24.

Williams, A. C. and Barry, B. W. (2012). Penetration enhancers. *Advanced Drug Delivery Reviews*, 64: 128–137.

Winn, D. (2009). *Preservative for cosmetic, toiletry and pharmaceutical compositions*. Patent Application, Patentdoc, US20090143489A1.

Woitiski C. M., Veiga, F., Ribeiro, A. and Neufeld, R. (2009). Design for optimization of nanoparticles integrating biomaterials for orally dosed insulin, *European Journal of Pharmaceutics and Biopharmaceutics*, 73:25–33.

Yuan, Y., Gao, Y., Mao, L. and Zhao, J. (2008). Optimisation of conditions for the preparation of β-carotene nanoemulsions using response surface methodology. *Food Chemistry*, 107(3): 1300–1306.

Yuan, J. S. (2009). *Linker-based lecithin microemulsions as transdermal drug delivery systems*. University of Toronto, Canada.

Zainol, S., Basri, M., Basri, H. B., Shamsuddin, A. F., Abdul-Gani S. S., Abedi Karjiban, R. and Abdul-Malek, E. (2012). Formulation optimization of a palm-based nanoemulsion system containing levodopa. *International Journal of Molecular Sciences*, 13: 13049–13064.

Zhao, K., Singh, S. and Singh. J. (2001). Effect of menthone on the in vitro percutaneous absorption of tamoxifen and skin reversibility. *International Journal of Pharmaceutics*, 219: 177 – 181.

Zhai, X. J., Yu, Y., Chen, F. and Lu, Y. N. (2013). Comparative bioavailability and tolerability of single and multiple doses of 2 diclofenac sodium sustained-release tablet formulations in fasting, healthy chinese male volunteers. *Current Therapeutic Research*, 75: 53–58.

Zhang, A. and Proctor, A. (1997). Rheology and stability of phospholipid-stabilized emulsions. *Journal of the American Oil Chemists' Society*, 74: 869–874.

Zu, Y., Zhang, Y., Zhao, X., Zhang, Q., Liu, Y. and Jiang. R. (2009). Optimization of the preparation process of vinblastine sulfate (VBLS)-loaded folate-conjugated bovine serum albumin (BSA) nanoparticles for tumor-targeted drug delivery using response surface methodology (RSM). *International Journal of Nanomedicine*, 4: 321–333.