PARTICLE SIZE ANALYSIS ON GINGER ESSENTIAL OIL NANOEMULSIONS

SITI AISHAH BINTI MOHD ALI

A thesis submitted in fulfilment of the
requirements for the award of the degree of
Master of Philosophy

School of Chemical and Energy Engineering
Faculty of Engineering
Universiti Teknologi Malaysia

MARCH 2019

DEDICATION

"My dearest mother, father, husband and son"

This is for all of you

ACKNOWLEDGEMENT

This work was originally submitted in fulfilment of the requirements for the award of the degree of Master of Philosophy at the School of Chemical and Energy Engineering, Faculty of Engineering, Universiti Teknologi Malaysia. The supervisor of my thesis is Associate Professor Dr. Siti Hamidah binti Mohd Setapar, who gives advice, guidance and help in financial for this journey.

Special thanks to my colleagues at the School of Chemical and Energy Engineering, UTM that have given a great support and help along the way to finish this thesis. I am grateful for the scholarship that I get from Jabatan Perkhidmatan Awam (JPA) that helped to cover my cost of study.

A special appreciation is dedicated to my husband and family that provided great support and encouragement in this journey to complete the thesis. May Allah give a greatest blessing to all of them.

ABSTRACT

Ginger essential oil has various biological properties such as antioxidant and anti-inflammatory. However, ginger essential oils has its own weaknesses, such as high volatility, low absorption, and poor water-solubility. Transdermal drug delivery is one of the alternatives to transport ginger essential oil into the body. The transdermal drug delivery system which is a nanoemulsion was introduced to overcome the weakness of essential oil. The droplet size of a nanoemulsion is an important property which determines the stability and ease of penetration. In this research, the nanoemulsions were prepared using a spontaneous emulsification method. The effect of preparation conditions and system composition on particle size of ginger essential oil nanoemulsions were examined. In organic phase, ginger essential oil and surfactants which are Tween 40, 60 and 80 were used. In aqueous phase, distilled water and co-solvent (glycerol) were used. For nanoemulsion formation, the organic phase was slowly added into the aqueous phase while being stirred at 500 rpm. The surfactant type had a major effect on particle size, where the smallest droplets particle size were formed by using Tween 80 (15.40 nm). The surfactant concentration also shows a great impact on particle size, where at surfactant-to-emulsion ratio (SER) 25 %, the smallest droplets were formed (11.3 nm). By increasing the temperature of organic phase and stirring speed, the particle size was reduced with the smallest droplets being formed at 90 °C (11.16 nm) and at 800 rpm (11.23 nm). Co-solvent addition also had shown an impact on particle size where at 10 % of co-solvent concentration, the smallest droplets were formed (11.22 nm). For thermodynamic stability, nanoemulsions with SER 15 %, 20 %, 25 % and 30% had shown a great stability with no phase and size separation. For storage stability, the droplets particle size were increased by 23 % throughout the two months of storage. In conclusion, a smaller droplet particle (< 15 nm) can be formed by optimizing the system composition and homogenization conditions of nanoemulsions.

ABSTRAK

Minyak pati halia mempunyai pelbagai sifat-sifat biologi seperti antioksidan dan anti-radang. Walau bagaimanapun, minyak pati halia mempunyai kelemahan tersendiri seperti pemeruwapan yang tinggi, penyerapan yang rendah, dan kelarutan air yang lemah. Penghantaran dadah secara transdermal adalah salah satu alternatif untuk menghantar minyak pati halia ke dalam badan. Sistem penghantaran dadah transdermal iaitu nanoemulsi diperkenalkan untuk mengatasi kelemahan minyak pati. Saiz titisan nanoemulsi adalah sifat penting iaitu yang menentukan kestabilan dan penembusan yang lebih mudah. Dalam kajian ini, nanoemulsi telah disediakan menggunakan kaedah pengemulsian spontan. Kesan syarat penyediaan dan komposisi sistem pada saiz zarah nanoemulsi minyak halia telah disiasat. Dalam fasa organik, minyak halia dan surfaktan iaitu Tween 40, 60 dan 80 digunakan. Dalam fasa akueus, air suling dan pelarut bersama (gliserol) digunakan. Untuk pembentukan nanoemulsi, fasa organik ditambah perlahan-lahan ke dalam fasa akueus sambil dikacau pada 500 rpm. Jenis surfaktan memberi pengaruh pada saiz zarah, di mana saiz titisan terkecil saiz zarah dibentuk dengan menggunakan Tween 80 (15.40 nm) . Kepekatan surfaktan juga menunjukkan kesan besar pada saiz zarah, di mana pada nisbah surfaktan-ke-emulsi (SER) 25%, titisan terkecil terbentuk (11.3 nm). Dengan meningkatkan suhu fasa organik dan kelajuan pengacau, saiz zarah dikurangkan dengan titisan terkecil dibentuk pada 90 °C(11.16 nm) dan pada 800 rpm (11.23 nm). Penambahan pelarut bersama juga menunjukkan kesan pada saiz zarah di mana pada 10% kepekatan pelarut bersama, titisan terkecil dibentuk (11.22 nm). Untuk kestabilan termodinamik, nanoemulsi dengan SER 15%, 20%, 25% dan 30% telah menunjukkan kestabilan yang baik tanpa pemisahan fasa dan saiz. Untuk kestabilan penyimpanan, saiz zarah titisan meningkat 23% sepanjang dua bulan penyimpanan. Kesimpulannya, zarah titisan yang lebih kecil (< 15 nm) dapat dibentuk dengan mengoptimumkan komposisi sistem dan keadaan homogenisasi nanoemulsi.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATION

AFM	-	Atomic force microscope
API	-	Active pharmaceutical ingredient
BAC	-	Benzalkonium chloride
BHA	-	Butylated hydroxyanisole
BZT	-	Benzethonium chloride
CMC	-	Critical micelle concentration
CTAB	-	Cetyl trimethylammonium bromide
CO_2	-	Carbon dioxide
DPPH	-	2, diphenyl – pricyhygrazyl
EPI	-	Emulsion phase inversion
FTC	-	Ferric thiocynate
GC-MS	-	Gas chromatography mass spectrometry
HLB	-	Hydrophile – lipophile balance
NF-κB	-	Nuclear factor kappa light chain enhancer of activated B cells
NLC	-	Nanostructured lipid carriers
NSAIDs	-	Nonsteroidal anti-inflammatory drugs
O/W	-	Oil-in-water
O/W/O	-	Oil-in-water-in-oil
PAMAM	-	Polyamidoamine
PDI	-	Polydispersity Index
PIC	-	Phase inversion composition
PIT	-	Phase inversion temperature
PFOA	-	Perfluorooctanoate
PFOS	-	Perfluorooctanesulfonate
ROS	-	Reactive oxygen species
SDS	-	Sodium dodecyl sulphate
SE	-	Spontaneous emulsification
SER	-	Surfactant-to-emulsion ratio
SLES	-	Sodium lauryl ether sulphate
SLN	-	Solid lipid nanoparticles

STM	-	Scanning tunneling microscope
TBA	-	Thiobarturic acid
W/O	-	Water-in-oil
W/O/W	-	Water-in-oil-in-water

LIST OF SYMBOLS

atm	-	Standard atmosphere
°C	-	Temperature
D	-	Diameter
Φ	-	Phase volume ratio
%	-	Percentage
eV	-	Electron volt
Hz	-	Hertz
min	-	minute
nm	-	Nanometre
rpm	-	Revolutions per minute
U	-	Unified atomic mass unit

CHAPTER 1

INTRODUCTION

1.1 Background of Study

From the past century, it is proven that nanotehnology has the great potential to bring benefits to pharmaceutical industry for its ability in formulation development and drug delivery system (Amiji, 2007). Nanopharmaceuticals have become huge industry because of its ability to overcome solubility and stability issues in drug delivery. With rising interest in nanopharmaceutical, researchers have produce great number of improvement and widening the range of drug delivery systems. These systems can improve the stability, absorption, and therapeutic concentration of the drug within the target tissue and allow the long-term release of the drug at the target site (Chaudhari, 2012; Kaiser *et al.*, 2005). These advancement in drug delivery have facilitated the targeting of specific tissues. The most common drug delivery routes are oral and parenteral routes. The oral route has the advantage of pre-determined doses, portability and patient self-administration. Therefore, the oral route has become the most convenient in delivering the medications (Brambilla *et al.*, 2014). However, there is some limitations to oral route which are large amount of drug is lost in the vicinity of the target organ, drugs are exposed to the first-past effect and highly dependent on patient compliance (Prausnitz and Langer, 2008; Rastoga and Yadav, 2012). That limitations can possibly be overcome by advanced drug delivery methodologies such as transdermal drug delivery.

Transdermal drug delivery is one of the systems lying under the category of controlled drug delivery, with the objective to deliver the drug through the skin in a predetermined and controlled rate. It has various advantages such as prolonged therapeutic effect, improved bioavailability, reduced side-effects, better patient compliance and easy termination of drug therapy (Rastoga and Yadav, 2012). There

are two main route of drug penetration which are intercellular and transcellular routes. There are some factors that need to be considered while using this delivery system such as biological, physicochemical and environmental factors.

Nowadays, the type of nanostructures that is being used have shown a significant increased. There are wide range of drug delivery systems that are available for various type of drug. Liposomes, polymeric micelles, dendrimers and nanoemulsions are some of potential nanostructures used for drug delivery. Liposomes are lipid bilayer system that can accommodate hydrophilic drug inside the core and lipophilic drug between the bilayer (Escobar-Chavez, 2012). Its nontoxic characteristic and it remain in the bloodstream for a long period of time make it to be one of the best alternatives for drug delivery system (Bakowsky *et al.*, 2008). Polymeric micelles are macromolecular assembly that form from synthetic block copolymer and has a spherical inner core and outer core (Yokoyama, 2011). It has a large solubilisation power, higher stability in bloodstream, more loading capacity and longevity (Ahmad, *et al.*, 2014). Dendrimers are nanostructures that are made up of a series of branches around an inner core. They were chosen to be drug delivery system because of their functionalization, ease of preparation, and the ability to exhibit multiple versions of surface groups for biological identification process.

Nanoemulsions are one of the nanostructures and part of the drug delivery system. Nanoemulsion are isotropic dispersed systems of two immiscible liquids, usually containing of an oily system dispersed in an aqueous system (oil-in-water), or an aqueous system dispersed in an oily system (water-in-oil) which forming droplet (Escobar-Chávez, 2012). There are three types of nanoemulsions. The types are oil-in-water (O/W) nanoemulsions, water-in-oil (W/O) nanoemulsions and also bicontinuous nanoemulsions (W/O/W) (Mishra *et al.*, 2014; Singh *et al.*, 2017). The types of nanoemulsions formed can be predicted by the type of surfactants used weather it is water soluble or oil soluble (Singh *et al.*, 2017). There are three main components in nanoemulsions which are oils, surfactants and aqueous phase. The oil is used to form internal phase of the emulsion. The oil phase can carry the drugs compound in soluble form. Usually, the oils used are mineral oil, vegetable oil, medium-chain triglycerides, and squalene (Lee *et al.*, 2010). Surfactants are used as

the stabilizer in nanoemulsions by reducing interfacial tension and prevent droplet aggregation (Singh *et al.*, 2017). Tweens 20, 40, 60, and 80 (Polyoxyethlene sorbitan monolaurate), Spans 20, 40, 60, 80 (Sorbitan monolaurate), and cremophor EL (Polyoxyl-35 castor oil) are example of surfactants that have been used to produce nanoemulsions (Singh *et al.*, 2017). For the aqueous phase, a purified water are usually used (Lee *et al.*, 2010).

Nanoemulsions can be fabricate by using various methods. The methods are divided into two categories which are high energy methods and low energy methods. In high energy methods, it involve the use of mechanical devices to produce intense disruptive forces which lead to smaller droplets size (Solan and Solé, 2012). Most commonly used high energy methods for producing nanoemulsions are high pressure homogenization, ultrasonification and microfluidization (Mishra *et al.*, 2014; Singh *et al.*, 2017; Saberi *et al.*, 2013). In low energy methods, the formation of droplets particle are depends on the surfactant-oil-water mixture in specific condition and environment. Some of low energy methods that have been introduced for fabrication of nanoemulsions are spontaneous emulsification, phase inversion temperature and emulsion phase inversion (Mcclements and Rao, 2011; Solan and Solé, 2012).

There are more than 3000 types of essential oils that have been produced but only 300 types of essential oils that is important for a commercial purpose (Bakkali *et al.*, 2008). Essential oils have been used for many application such as pharmaceutical, perfumes, sanitary products, agriculture, dentistry, as food preservative and flavour additives, cosmetics and natural remedies (Burt, 2004; Bakkali *et al.*, 2008). Essential oils are a volatile, natural, have a pungent odour and produce from a different parts of the plant (flowers, barks, buds, seeds, leaves, wood, fruits and roots) (Perricone *et al.*, 2015; Burt, 2004). They are normally stored in different anatomical parts of the plant such as oil ducts, resin ducts, and grandular trichomes (Baser and Demirci, 2007; El Asbahani *et al.*, 2015). An individual essential oils contain 20-100 components with different concentrations and some of it are the main compound with higher concentration (Perricone *et al.*, 2015; Bakkali *et al.*, 2008). The components are separated into several groups which are terpenes and terpenoid, aromatic and aliphatic

constituents, and phenylpropanoids (Bakkali *et al.*, 2008). The biological properties are determined by the main compound in the essential oils.

Ginger has been used worldwide as a cooking spice and home remedy for thousands of years. In traditional usage, ginger has been used to treat nausea, digestive aids, rheumatism, reduce cholesterol, and to fight arthritis. Ginger or also known as *Zingiber officinale* is belong to the Zingiberaceae family. The ginger family is cultivated in a tropical climate especially in Southeast Asia like Malaysia and Indonesia (Banerjee *et al.*, 2011). Ginger essential oils are extracted from its rhizomes. The ginger rhizome contains 60–70% carbohydrates, 9% protein, 8% ash, 3–8% crude fiber, 3–6% fatty oil and 2–3% volatile oil. The volatile oils that contain in ginger are only one to three percentage of its weight (Srinivasan, 2017). The main organic compound in ginger essential oil is α-zingiberene which represent the special aroma of ginger. The ginger essential oil can be extracted using various techniques such as steam distillation, microwave application methods and hydrodistillation (Kamaliroosta *et al.*, 2013). Studies has shown that ginger essential oils has broad range of pharmacological activities including anti-inflammatory, antioxidant, antibacterial, and insecticidal (Ficker *et al.*, 2003).

1.2 Problem Statement

Essential oils such as ginger essential oil contain a several of biological properties which include antioxidant, antimicrobial and anti-inflammatory. With these functional properties of ginger essential oil, it is attracted the pharmaceutical and health industries to use the essential oils to replace the used of synthetic drugs as their active pharmaceutical ingredient (API). However, it has some weakness which are highly volatile, low absorption, and it has poor water-solubility which the ability of essential oil constituents to move through water-based blood stream and cellular target is weak. A suitable colloidal delivery system need to be introduced to overcome the weaknesses. Transdermal drug delivery is one of the alternative to transport drug into the body. The drug is delivered through the skin at controlled rate. The use of transdermal drug delivery can prolonged therapeutic effect, improved bioavailability,

and reduced side-effects. Therefore, transdermal nanocarrier such as nanoemulsion can be used to transport the ginger essential oil because it can reduce volatility, improve the absorption mechanism and improve the bioefficacy of ginger essential oil towards the targeting tissue. Nanoemulsions is a suitable drug delivery system because of their unique properties such as small droplet size, high physical stability, high bioavailability and optical transparency compared to other conventional emulsions. The droplet size of is very important property because it determine the stability, bioavailability, and transparency of the nanoemulsions. In transdermal drug delivery, the molecular size is important because the smaller the size, the easier the drug to penetrate into the skin. Therefore, a study about the factors affecting particle size of ginger essential oil nanoemulsions are proposed.

1.3 Objectives

The main objectives of this research are:

1. To identify the factors for particle size optimization of ginger essential oil nanoemulsions.
2. To evaluate the thermodynamic and storage stability of ginger essential oil nanoemulsions.

1.4 Scopes of Study

1.4.1 The Emulsion Preparation Using Spontaneous Emulsification Method

The formulation of nanoemulsions will be prepared by using spontaneous emulsification method. In this method, an organic phase (containing ginger essential oil and surfactant) are poured into an aqueous phase (distilled water) while

magnetically stirred. The nanoemulsions will be stirred at 500 rpm and the temperature for the organic phase and aqueous phase is at room temperature of 25 °C.

1.4.2 The Factors for Particle Size Optimization of Nanoemulsions

The nanoemulsions will be formulate by manipulating the surfactant type's usage, the concentration of surfactant, temperature of organic phase, stirring speed, and addition of co-solvent. For manipulating the surfactant type, the surfactants that will be used are Tween 40, Tween 60 and Tween 80. Concentration of surfactant will be manipulated by varying the surfactant-to-emulsion (SER) percentage from 10 % to 30 % while maintaining the oil content. The temperature of organic phase will be manipulated by varying the temperature from 0 to 90 °C and maintaining the temperature of aqueous phase. For stirring speed, it will be manipulated by changing the speed at three different speed which are 200 rpm, 500 rpm and 800 rpm. Lastly, for addition of co-solvent, the co-solvent that will be used is glycerol. The co-solvent will be added to the aqueous phase. The addition of co-solvent will be manipulated by varying the concentration of co-solvent from 0 % to 50 %.

1.4.3 The Stability of Ginger Essential Oil Nanoemulsions

The stability of ginger essential oil nanoemulsions will be examine using two parameters which are thermodynamic stability and storage stability. Thermodynamic stability will be analysed using heating-cooling cycle method and Freeze-Thaw stress method. For Heating-Cooling cycle, the nanoemulsions will be keep at 40 °C and 4 °C alternatively each temperature for 48 hours. For Freeze-Thaw stress, the nanoemulsions were kept at -21 °C and 25 °C for 48 hours for each temperature. For storage stability, the ginger essential oil nanoemulsions will be analysed by storing the nanoemulsions for two month and the droplet size of the nanoemulsions will be taken at day one, first month and second month to see any changes occur during the storage time. The changes in droplet size of the nanoemulsions will determine the stability of the nanoemulsions.

1.5 Significance of Study

Ginger essential oil has a broad biological properties such as anti-inflammatory, antioxidant and antiviral but it is highly volatile, poor water-solubility, and low absorption. The ginger essential oil can be transport into the body using transdermal drug delivery because it prolonged therapeutic effect, improved bioavailability, and reduced side-effects. To overcome this disadvantages, a colloidal transdermal drug delivery system which is nanoemulsions is introduce. Nanoemulsions can reduce the volatility, improve absorption and improve the efficacy of ginger essential oil. Droplet particle size is one of the functional properties of nanoemulsions which is very important because it decide the stability, efficacy, bioavailability, and appearance of emulsions. In transdermal drug delivery, the molecular size determine the penetration rate into the skin. The smaller the molecular size, the easier the drug to penetrate. Therefore, determining the factors that effecting particle size of nanoemulsions is perform.

1.6 Thesis Outline

There are five chapters in this thesis that covered a detailed explanation of the research study. The first chapter in this thesis are covering the introduction of study, problem statement, objectives, scopes, significance of study and also the outline of the thesis. The problem background discussed a problem facing by the essential oil and the importance of particle size nanoemulsions. In Chapter 2, more detailed in literature review on nanotechnology in drug delivery, essential oil industry and current researches that are being studied to search solutions for the problem facing. Chapter 2 also reviewed the details about properties, structures and characteristics of nanoemulsions.

Chapter 3 reported the chemicals used in this study and also the experimental methods that were applied in this study. Chapter 4 was discussed the experimental results and findings which were achieved according to the objectives and scopes that were designed for this research. Finally Chapter 5 presented the appropriate

conclusion for the findings of this research. A few recommendations were suggested to improve the stability of essential oil nanoemulsions. Lastly, the future studies for the next researchers were also discussed.

REFERENCES

Ahmad, Z., Shah, A., Siddiq, M. and Kraatz, H.B., 2014. Polymeric micelles as drug delivery vehicles. *Rsc Advances*, *4*(33), pp.17028-17038.

Aggarwal, B.B., Kumar, A., Aggarwal, M.S. and Shishodia, S., 2005. Curcumin derived from turmeric (Curcuma longa): a spice for all seasons. *Phytopharmaceuticals in cancer chemoprevention*, *23*, pp.351-387.

Aksu, K., Topal, F., Gulcin, I., Tümer, F. and Göksu, S., 2015. Acetylcholinesterase inhibitory and antioxidant activities of novel symmetric sulfamides derived from phenethylamines. *Archiv der Pharmazie*, *348*(6), pp.446-455.

Alkilani, A., McCrudden, M.T. and Donnelly, R., 2015. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. *Pharmaceutics*, *7*(4), pp.438-470.

Allen, T.M. and Cullis, P.R., 2004. Drug delivery systems: entering the mainstream. *Science*, *303*(5665), pp.1818-1822.

Alwadani, N. and Fatehi, P., 2018. Synthetic and lignin based surfactants: challenges and opportunities. *Carbon Resources Conversion*.

Angioni, A., Barra, A., Coroneo, V., Dessi, S. and Cabras, P., 2006. Chemical composition, seasonal variability, and antifungal activity of Lavandula stoechas L. ssp. stoechas essential oils from stem/leaves and flowers. *Journal of agricultural and food chemistry*, *54*(12), pp.4364-4370.

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*(3), pp.185-199.

Anton, N. and Vandamme, T.F., 2009. The universality of low-energy nano-emulsification. *International Journal of Pharmaceutics*, *377*(1-2), pp.142-147.

Amiji, M.M., 2007. Nanotechnology—improving targeted delivery. *Drug Delivery*, *17*, pp.53-56.

Asyikin binti Abdul Aziz, Z., Ahmad, A., Hamidah Mohd-Setapar, S., Hassan, H., Lokhat, D. and Amjad Kamal, M., 2017. Recent advances in drug delivery of polymeric nano-micelles. *Current drug metabolism*, *18*(1), pp.16-29.

Azeem, A., Rizwan, M., Ahmad, F.J., Iqbal, Z., Khar, R.K., Aqil, M. and Talegaonkar, S., 2009. Nanoemulsion components screening and selection: a technical note. *Aaps Pharmscitech*, *10*(1), pp.69-76.

Bakkali, F., Averbeck, S., Averbeck, D. and Idaomar, M., 2008. Biological effects of essential oils–a review. *Food and chemical toxicology*, *46*(2), pp.446-475.

Bakowsky, H., Richter, T., Kneuer, C., Hoekstra, D., Rothe, U., Bendas, G., Ehrhardt, C. and Bakowsky, U., 2008. Adhesion characteristics and stability assessment of lectin-modified liposomes for site-specific drug delivery. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, *1778*(1), pp.242-249.

Baser, K.H.C., Demirci, F., and Berger, R.G. ed., 2007. *Flavours and fragrances: chemistry, bioprocessing and sustainability*. Springer Science & Business Media. pp. 43-86

Banerjee, R., 2001. Liposomes: applications in medicine. *Journal of Biomaterials applications*, *16*(1), pp.3-21.

Banerjee, S., Mullick, H.I., Banerjee, J. and Ghosh, A., 2011. Zingiber officinale:'a natural gold'. *Int J Pharmaceutical Bio-Sci*, *2*, pp.283-94.

Benson, H.A. and Watkinson, A.C. eds., 2012. *Topical and transdermal drug delivery: principles and practice*. John Wiley & Sons.

Bilbao-Sáinz, C., Avena-Bustillos, R.J., Wood, D.F., Williams, T.G. and McHugh, T.H., 2010. Nanoemulsions prepared by a low-energy emulsification method applied to edible films. *Journal of agricultural and food chemistry*, *58*(22), pp.11932-11938.

Borgia, S.L., Regehly, M., Sivaramakrishnan, R., Mehnert, W., Korting, H.C., Danker, K., Röder, B., Kramer, K.D. and Schäfer-Korting, M., 2005. Lipid nanoparticles for skin penetration enhancement—correlation to drug localization within the particle matrix as determined by fluorescence and parelectric spectroscopy. *Journal of Controlled Release*, *110*(1), pp.151-163.

Burt, S., 2004. Essential oils: their antibacterial properties and potential applications in foods—a review. *International journal of food microbiology*, *94*(3), pp.223-253.

Brambilla, D., Luciani, P. and Leroux, J.C., 2014. Breakthrough discoveries in drug delivery technologies: the next 30 years. *Journal of Controlled Release*, *190*, pp.9-14.

Chaudhari, Y.S., 2012. Nanoparticles-A paradigm for topical drug delivery. *Chronicles of Young Scientists*, *3*(1), p.82.

Chanasattru, W., Decker, E.A. and McClements, D.J., 2007. Physicochemical basis for cosolvent modulation of β-lactoglobulin functionality: Interfacial tension study. *Food research international*, *40*(8), pp.1098-1105.

Chang, W.S., Chang, Y.H., Lu, F.J. and Chiang, H.C., 1994. Inhibitory effects of phenolics on xanthine oxidase. *Anticancer research*, *14*(2A), pp.501-506.

Couvreur, P. and Vauthier, C., 2006. Nanotechnology: intelligent design to treat complex disease. *Pharmaceutical research*, *23*(7), pp.1417-1450.

Date, A.A. and Nagarsenker, M.S., 2008. Parenteral microemulsions: an overview. *International journal of pharmaceutics*, *355*(1-2), pp.19-30.

Dima, C. and Dima, S., 2015. Essential oils in foods: extraction, stabilization, and toxicity. *Current Opinion in Food Science*, *5*, pp.29-35.

Donnelly, R.F., Singh, T.R.R., Morrow, D.I. and Woolfson, A.D., 2012. *Microneedle-mediated transdermal and intradermal drug delivery*. John Wiley & Sons.

El Asbahani, A., Miladi, K., Badri, W., Sala, M., Addi, E.A., Casabianca, H., El Mousadik, A., Hartmann, D., Jilale, A., Renaud, F.N.R. and Elaissari, A., 2015. Essential oils: from extraction to encapsulation. *International journal of pharmaceutics*, *483*(1-2), pp.220-243.

Emerich, D.F. and Thanos, C.G., 2003. Nanotechnology and medicine. *Expert Opinion on Biological Therapy*, *3*(4), pp.655-663.

Escobar-Chávez, J.J., 2012. Nanocarriers for transdermal drug delivery. *Research and reports in transdermal drug delivery*, *1*, pp.3-17.

Farokhzad, O.C. and Langer, R., 2009. Impact of nanotechnology on drug delivery. *ACS nano*, *3*(1), pp.16-20.

Fernandez, P., André, V., Rieger, J. and Kühnle, A., 2004. Nano-emulsion formation by emulsion phase inversion. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, *251*(1-3), pp.53-58.

Ficker, C., Smith, M.L., Akpagana, K., Gbeassor, M., Zhang, J., Durst, T., Assabgui, R. and Arnason, J.T., 2003. Bioassay-guided isolation and identification of antifungal compounds from ginger. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *17*(8), pp.897-902.

Gadhave, A.D., 2014. Nanoemulsions: formation, stability and applications. *International Journal of Reserch in Science & Advanced Technologies*, *2*(3).

Gaucher, G., Dufresne, M.H., Sant, V.P., Kang, N., Maysinger, D. and Leroux, J.C., 2005. Block copolymer micelles: preparation, characterization and application in drug delivery. *Journal of controlled release*, *109*(1-3), pp.169-188.

Ghosh, V., Saranya, S., Mukherjee, A. and Chandrasekaran, N., 2013. Cinnamon oil nanoemulsion formulation by ultrasonic emulsification: investigation of its bactericidal activity. *Journal of nanoscience and nanotechnology*, *13*(1), pp.114-122.

Gupta, U., Agashe, H.B., Asthana, A. and Jain, N.K., 2006. A review of in vitro–in vivo investigations on dendrimers: the novel nanoscopic drug carriers. *Nanomedicine: Nanotechnology, Biology and Medicine*, *2*(2), pp.66-73.

Gupta, A., Eral, H.B., Hatton, T.A. and Doyle, P.S., 2016. Nanoemulsions: formation, properties and applications. *Soft matter*, *12*(11), pp.2826-2841.

Han, T. and Das, D.B., 2015. Potential of combined ultrasound and microneedles for enhanced transdermal drug permeation: a review. *European Journal of Pharmaceutics and Biopharmaceutics*, *89*, pp.312-328.

Hasani, F., Pezeshki, A. and Hamishehkar, H., 2015. Effect of surfactant and oil type on size droplets of betacarotene-bearing nanoemulsions. *Int J Curr Microbiol App Sci*, *4*, p.146.

He, X., Wu, X., Gao, C., Wang, K., Lin, S., Huang, W., Xie, M. and Yan, D., 2011. Synthesis and self-assembly of a hydrophilic, thermo-responsive poly (ethylene oxide) monomethyl ether-block-poly (acrylic acid)-block-poly (N-isopropylacrylamide) copolymer to form micelles for drug delivery. *Reactive and Functional Polymers*, *71*(5), pp.544-552.

He, W., Lu, Y., Qi, J., Chen, L., Hu, F. and Wu, W., 2013. Food proteins as novel nanosuspension stabilizers for poorly water-soluble drugs. *International journal of pharmaceutics*, *441*(1-2), pp.269-278.

Israelachvili, J.N., 2011. Intermolecular and surface forces. Third Edition. Academic press, Santa Barbara, California.

Jadhav, C., Kate, V. and Payghan, S.A., 2015. Investigation of effect of non-ionic surfactant on preparation of griseofulvin non-aqueous nanoemulsion. *Journal of Nanostructure in Chemistry*, *5*(1), pp.107-113.

Jafari, S.M., He, Y. and Bhandari, B., 2006. Nano-emulsion production by sonication and microfluidization—a comparison. *International Journal of Food Properties*, *9*(3), pp.475-485.

Jafari, S.M., He, Y. and Bhandari, B., 2007. Production of sub-micron emulsions by ultrasound and microfluidization techniques. *Journal of Food Engineering*, *82*(4), pp.478-488.

Jaiswal, M., Dudhe, R. and Sharma, P.K., 2015. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech, 5(2), pp.123-127.

Jiang, H., Xie, Z., Koo, H.J., McLaughlin, S.P., Timmermann, B.N. and Gang, D.R., 2006. Metabolic profiling and phylogenetic analysis of medicinal Zingiber species: Tools for authentication of ginger (Zingiber officinale Rosc.). *Phytochemistry*, *67*(15), pp.1673-1685.

Jeena, K., Liju, V.B., Kuttan, R., 2013. Antioxidant, anti-inflammatory and antinociceptive activities of essential oil from ginger. *Indian J. physiolol. physiol*. 57, 51-62.

Jones, M.C. and Leroux, J.C., 1999. Polymeric micelles–a new generation of colloidal drug carriers. *European journal of pharmaceutics and biopharmaceutics*, *48*(2), pp.101-111.

Kargozar, S. and Mozafari, M., 2018. Nanotechnology and Nanomedicine: Start small, think big. *Materials Today: Proceedings*, *5*(7), pp.15492-15500.

Kayser, O., Lemke, A. and Hernandez-Trejo, N., 2005. The impact of nanobiotechnology on the development of new drug delivery systems. *Current pharmaceutical biotechnology*, *6*(1), pp.3-5.

Kumar, J.A., Pullakandam, N., Prabu, S.L. and Gopal, V., 2010. Transdermal drug delivery system: an overview. *International Journal of Pharmaceutical Sciences Review and Research*, *3*(2), pp.49-54.

Kumar, D., Sharma, N., Rana, A.C., Agarwal, G. and Bhat, Z.A., 2011. A review: transdermal drug delivery system: a tools for novel drug delivery sestem. *Int. J Drug Dev. Res*, *3*(3), pp.70-84.

Kumar, S., Saxena, K., Singh, U.N. and Saxena, R., 2013. Anti-inflammatory action of ginger: A critical review in anemia of inflammation and its future aspects. *Int J Herb Med*, *1*, pp.16-20.

Kumar, G.P. and Divya, A., 2015. Nanoemulsion based targeting in cancer therapeutics. *Medicinal Chemistry*, *5*(5), pp.272-284.

Kusuma, H.S. and Mahfud, M., 2016, April. Preliminary study: Kinetics of oil extraction from sandalwood by microwave-assisted hydrodistillation. In *IOP Conference Series: Materials Science and Engineering* (Vol. 128, No. 1, p. 012009). IOP Publishing.

Komaiko, J.S. and McClements, D.J., 2016. Formation of food-grade nanoemulsions using low-energy preparation methods: A review of available methods. *Comprehensive Reviews in Food Science and Food Safety*, *15*(2), pp.331-352.

Kretsos, K. and Kasting, G.B., 2007. A geometrical model of dermal capillary clearance. *Mathematical biosciences*, *208*(2), pp.430-453.

Lee, R.W., Shenoy, D.B. and Sheel, R., 2010. Micellar nanoparticles: applications for topical and passive transdermal drug delivery. In *Handbook of non-invasive drug delivery systems* (pp. 37-58).

Leong, T.S.H., Wooster, T.J., Kentish, S.E. and Ashokkumar, M., 2009. Minimising oil droplet size using ultrasonic emulsification. *Ultrasonics Sonochemistry*, *16*(6), pp.721-727.

Li, Y., Zheng, J., Xiao, H. and McClements, D.J., 2012. Nanoemulsion-based delivery systems for poorly water-soluble bioactive compounds: Influence of formulation parameters on polymethoxyflavone crystallization. *Food hydrocolloids*, *27*(2), pp.517-528.

Lim, H.J., Cho, E.C., Shim, J., Kim, D.H., An, E.J. and Kim, J., 2008. Polymer-associated liposomes as a novel delivery system for cyclodextrin-bound drugs. *Journal of colloid and interface science*, *320*(2), pp.460-468.

Lin, R.J., Chen, C.Y., Lu, C.M., Ma, Y.H., Chung, L.Y., Wang, J.J., Lee, J.D. and Yen, C.M., 2014. Anthelmintic constituents from ginger (Zingiber officinale) against Hymenolepis nana. *Acta tropica*, *140*, pp.50-60.

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*(2), pp.557-563.

Liu, X., Kruger, P., Maibach, H., Colditz, P.B. and Roberts, M.S., 2014. Using skin for drug delivery and diagnosis in the critically ill. *Advanced drug delivery reviews*, *77*, pp.40-49.

Logothetidis, S., 2012. Nanotechnology: Principles and applications. In *Nanostructured materials and their applications* (pp. 1-22). Springer, Berlin, Heidelberg.

López, E.I.C., Balcázar, M.F.H., Mendoza, J.M.R., Ortiz, A.D.R., Melo, M.T.O., Parrales, R.S. and Delgado, T.H., 2017. Antimicrobial activity of essential oil of Zingiber officinale Roscoe (Zingiberaceae). *American Journal of Plant Sciences*, *8*(07), p.1511.

Majeed, H., Liu, F., Hategekimana, J., Sharif, H.R., Qi, J., Ali, B., Bian, Y.Y., Ma, J., Yokoyama, W. and Zhong, F., 2016. Bactericidal action mechanism of negatively charged food grade clove oil nanoemulsions. *Food chemistry*, *197*, pp.75-83.

Malam, Y., Loizidou, M. and Seifalian, A.M., 2009. Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer. *Trends in pharmacological sciences*, *30*(11), pp.592-599.

Malhotra, S. and Singh, A.P., 2003. Medicinal properties of ginger (Zingiber officinale Rosc.).

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*(41), p.R635.

McClements, D.J., 2011. Edible nanoemulsions: fabrication, properties, and functional performance. *Soft Matter*, *7*(6), pp.2297-2316.

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*(4), pp.285-330.

Mehnert, W., Mäder, K., 2001. Solid lipid nanoparticles: production, characterization and applications. *Adv. Drug Deliver Rev. 47* (2-3), pp 165-196.

Mesomo, M.C., de Paula Scheer, A., Perez, E., Ndiaye, P.M. and Corazza, M.L., 2012. Ginger (Zingiber officinale R.) extracts obtained using supercritical CO2 and compressed propane: kinetics and antioxidant activity evaluation. *The Journal of Supercritical Fluids*, *71*, pp.102-109.

Miguel, M.G., 2010. Antioxidant and anti-inflammatory activities of essential oils: a short review. *Molecules*, *15*(12), pp.9252-9287.

Mishra, R.K., Soni, G.C. and Mishra, R.P., 2014. A review article: on nanoemulsion. *World journal of pharmacy and pharmaceutical sciences*, *3*(9), pp.258-274.

Mudshinge, S.R., Deore, A.B., Patil, S. and Bhalgat, C.M., 2011. Nanoparticles: emerging carriers for drug delivery. *Saudi pharmaceutical journal*, *19*(3), pp.129-141.

Müller, R.H., Radtke, M., Wissing, S.A., 2002. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv. Drug Deliver. Rev. 54,* S131-S155.

Mulvaney, J., 2012. Essential oils and steam distillation. *Australian Journal of Herbal Medicine*, *24*(4), p.140.

Moghaddasi, M.S. and Kashani, H.H., 2012. Ginger (Zingiber officinale): A review. *Journal of Medicinal Plants Research*, *6*(26), pp.4255-4258.

Mohammed, N., Munassar, A. & Govardhan, A., 2010. A Comparison Between Five Models Of Software Engineering. *IJCSI International Journal of Computer Science Issues ISSN*, 7(5), pp.1694–814.

Morsy, S.M., 2014. Role of surfactants in nanotechnology and their applications. *Int. J. Curr. Microbiol. App. Sci*, *3*(5), pp.237-260.

Moussaoui, N., Cansell, M. and Denizot, A., 2002. Marinosomes®, marine lipid-based liposomes: physical characterization and potential application in cosmetics. *International journal of pharmaceutics*, *242*(1-2), pp.361-365.

Nagy, Z.K., Balogh, A., Vajna, B., Farkas, A., Patyi, G., Kramarics, Á. and Marosi, G., 2012. Comparison of electrospun and extruded Soluplus®-based solid dosage forms of improved dissolution. *Journal of pharmaceutical sciences*, *101*(1), pp.322-332.

Nikalje, A.P., 2015. Nanotechnology and its applications in medicine. *Med chem*, *5*(2), pp.081-089.

Noori, S., Zeynali, F. and Almasi, H., 2018. Antimicrobial and antioxidant efficiency of nanoemulsion-based edible coating containing ginger (Zingiber officinale) essential oil and its effect on safety and quality attributes of chicken breast fillets. *Food Control*, *84*, pp.312-320.

Nychas, G.J., Skandamis, P.N. and Tassou, C.C., 2003. Antimicrobials from herbs and spices. In *Natural antimicrobials for the minimal processing of foods* (pp. 176-200).

Ochekpe, N.A., Olorunfemi, P.O. and Ngwuluka, N.C., 2009. Nanotechnology and drug delivery part 2: nanostructures for drug delivery. *Tropical Journal of Pharmaceutical Research*, *8*(3).

Ostertag, F., Weiss, J. and McClements, D.J., 2012. Low-energy formation of edible nanoemulsions: factors influencing droplet size produced by emulsion phase inversion. *Journal of colloid and interface science*, *388*(1), pp.95-102.

Patel, H., Raval, G., Nazari, M. and Heerklotz, H., 2010. Effects of glycerol and urea on micellization, membrane partitioning and solubilization by a non-ionic surfactant. *Biophysical chemistry*, *150*(1-3), pp.119-128

Perricone, M., Arace, E., Corbo, M.R., Sinigaglia, M. and Bevilacqua, A., 2015. Bioactivity of essential oils: a review on their interaction with food components. *Frontiers in microbiology*, *6*, p.76.

Pichersky, E., Noel, J.P. and Dudareva, N., 2006. Biosynthesis of plant volatiles: nature's diversity and ingenuity. *Science*, *311*(5762), pp.808-811.

Prasad, M.M. and Seenayya, G., 2000. Effect of spices on the growth of red halophilic cocci isolated from salt cured fish and solar salt. *Food Research International*, *33*(9), pp.793-798.

Prausnitz, M.R. and Langer, R., 2008. Transdermal drug delivery. *Nature biotechnology*, *26*(11), p.1261.

Qiu, Y., Gao, Y., Hu, K. and Li, F., 2008. Enhancement of skin permeation of docetaxel: a novel approach combining microneedle and elastic liposomes. *Journal of Controlled Release*, *129*(2), pp.144-150.

Rajalakshmi, R., Mahesh, K. and Kumar, C.K., 2011. A critical review on nanoemulsions. *Int J Innov Drug Discov*, *1*, pp.1-8.

Raji, Y., Udoh, U.S., Oluwadara, O.O., Akinsomisoye, O.S., Awobajo, O. and Adeshoga, K., 2002. Anti-flammatory and analgesic properties of the rhizome extract of zingiber officinale. *African Journal of Biomedical Research*, *5*(3).

Rashidian, A., Mehrzadi, S., Ghannadi, A.R., Mahzooni, P., Sadr, S., Minaiyan, M., 2014. Protective effect of ginger volatileoil against acetic acid-induced colitis in rats: a light microscopic evaluation. *Journal Integr. Med.* 12, 115-120.

Rastogi, V. and Yadav, P., 2014. Transdermal drug delivery system: An overview. *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm*, *6*(3).

Raut, J.S. and Karuppayil, S.M., 2014. A status review on the medicinal properties of essential oils. *Industrial Crops and Products*, *62*, pp.250-264.

Raut, J.S. and Karuppayil, S.M., 2014. A status review on the medicinal properties of essential oils. *Industrial Crops and Products*, *62*, pp.250-264.

Saberi, A.H., Fang, Y. and McClements, D.J., 2013. Fabrication of vitamin E-enriched nanoemulsions: factors affecting particle size using spontaneous emulsification. *Journal of Colloid and Interface Science*, *391*, pp.95-102.

Saberi, A.H., Fang, Y. and McClements, D.J., 2013b. Effect of glycerol on formation, stability, and properties of vitamin-E enriched nanoemulsions produced using spontaneous emulsification. *Journal of colloid and interface science*, *411*, pp.105-113.

Safari, J. and Zarnegar, Z., 2014. Advanced drug delivery systems: Nanotechnology of health design A review. *Journal of Saudi Chemical Society*, *18*(2), pp.85-99.

Sahoo, S.K. and Labhasetwar, V., 2003. Nanotech approaches to drug delivery and imaging. *Drug discovery today*, *8*(24), pp.1112-1120.

Sahoo, S.K., Dilnawaz, F. and Krishnakumar, S., 2008. Nanotechnology in ocular drug delivery. *Drug discovery today*, *13*(3-4), pp.144-151.

Sa-Nguanpuag, K., Kanlayanarat, S., Srilaong, V., Tanprasert, K. and Techavuthiporn, C., 2011. Ginger (Zingiber officinale) oil as an antimicrobial agent for minimally processed produce: a case study in shredded green papaya. *International Journal of Agriculture & Biology*, *13*(6).

Schoellhammer, C.M., Blankschtein, D. and Langer, R., 2014. Skin permeabilization for transdermal drug delivery: recent advances and future prospects. *Expert opinion on drug delivery*, *11*(3), pp.393-407.

Schuh, R.S., Bruxel, F. and Teixeira, H.F., 2014. Physicochemical properties of lecithin-based nanoemulsions obtained by spontaneous emulsification or high-pressure homogenization. *Química Nova*, *37*(7), pp.1193-1198.

Setya, S., Talegaonkar, S. and Razdan, B.K., 2014. Nanoemulsions: formulation methods and stability aspects. *World J. Pharm. Pharm. Sci*, *3*(2), pp.2214-2228.

Shams, N. and Sahari, M.A., 2016. Nanoemulsions: preparation, structure, functional properties and their antimicrobial effects. *Applied Food Biotechnology*, *3*(3), pp.138-149.

Sharif, H.R., Sharif, M.K. and Zhong, F., 2017. Preparation, characterization and rheological properties of vitamin E enriched nanoemulsion. *Pakistan Journal of Food Sciences*, *27*(1), pp.7-14.

Sharifi-Rad, M., Varoni, E.M., Salehi, B., Sharifi-Rad, J., Matthews, K.R., Ayatollahi, S.A., Kobarfard, F., Ibrahim, S.A., Mnayer, D., Zakaria, Z.A. and Sharifi-Rad, M., 2017. Plants of the genus Zingiber as a source of bioactive phytochemicals: From tradition to pharmacy. *Molecules*, *22*(12), p.2145.

Sharma, P.K., Singh, V. and Ali, M., 2016. Chemical composition and antimicrobial activity of fresh rhizome essential oil of Zingiber officinale Roscoe. *Pharmacognosy Journal,*, *8*(3).

Sherwood, A., Bower, J.K., McFetridge-Durdle, J., Blumenthal, J.A., Newby, L.K. and Hinderliter, A.L., 2007. Age moderates the short-term effects of transdermal 17β-estradiol on endothelium-dependent vascular function in postmenopausal women. *Arteriosclerosis, thrombosis, and vascular biology*, *27*(8), pp.1782-1787.

Siewiera, K. and Labieniec-Watala, M., 2012. Ambiguous effect of dendrimer PAMAM G3 on rat heart respiration in a model of an experimental diabetes–Objective causes of laboratory misfortune or unpredictable G3 activity?. *International journal of pharmaceutics*, *430*(1-2), pp.258-265.

Silva, C.D.B.D., Guterres, S.S., Weisheimer, V. and Schapoval, E.E., 2008. Antifungal activity of the lemongrass oil and citral against Candida spp. *Brazilian Journal of Infectious Diseases*, *12*(1), pp.63-66.

Singh, G., Kapoor, I.P.S., Singh, P., de Heluani, C.S., de Lampasona, M.P. and Catalan, C.A., 2008. Chemistry, antioxidant and antimicrobial investigations on essential oil and oleoresins of Zingiber officinale. *Food and Chemical Toxicology*, *46*(10), pp.3295-3302.

Singh, M.C., Naik, A.S. and Sawant, S.D., 2010. Transdermal drug delivery systems with major emphasis on transdermal patches: A review. *J Pharm Res*, *3*(10), pp.2537-43.

Singh, S.P., 2013. Herbal plant used in anti-inflammatory and analgesic activity. *Journal of Drug Discovery And Therapeutics*, *1*(07).

Singh, Y., Meher, J.G., Raval, K., Khan, F.A., Chaurasia, M., Jain, N.K. and Chourasia, M.K., 2017. Nanoemulsion: Concepts, development and applications in drug delivery. *Journal of Controlled Release*, *252*, pp.28-49.

Solans, C. and Solé, I., 2012. Nano-emulsions: formation by low-energy methods. *Current opinion in colloid & interface science*, *17*(5), pp.246-254.

Soppimath, K.S., Aminabhavi, T.M., Kulkarni, A.R. and Rudzinski, W.E., 2001. Biodegradable polymeric nanoparticles as drug delivery devices. *Journal of controlled release*, *70*(1-2), pp.1-20.

Srinivasan, K., 2017. Ginger rhizomes (Zingiber officinale): A spice with multiple health beneficial potentials. *PharmaNutrition*, *5*(1), pp.18-28.

Sultan, M., Bhatti, H.N. and Iqbal, Z., 2005. Chemical analysis of essential oil. of ginger (Zingiber officinale).

Suri, S.S., Fenniri, H. and Singh, B., 2007. Nanotechnology-based drug delivery systems. *Journal of occupational medicine and toxicology*, *2*(1), p.16.

Suyal, J. and Bhatt, G., 2017. An introductory review article on nanoemulsion. *International Journal of Research in Pharmacy and Pharmaceutical Sciences,* *2*(4), pp. 35-40.

Tan, B.K. and Vanitha, J., 2004. Immunomodulatory and antimicrobial effects of some traditional Chinese medicinal herbs: a review. *Current medicinal chemistry*, *11*(11), pp.1423-1430.

Tanwar, H. and Sachdeva, R., 2016. Transdermal drug delivery system: A review. *Int. J. Pharm. Sci. Res*, *7*, pp.2274-2290

Tohma, H., Gülçin, İ., Bursal, E., Gören, A.C., Alwasel, S.H. and Köksal, E., 2017. Antioxidant activity and phenolic compounds of ginger (Zingiber officinale Rosc.) determined by HPLC-MS/MS. *Journal of Food Measurement and Characterization*, *11*(2), pp.556-566.

Touitou, E., 2002. Drug delivery across the skin. *Expert opinion on biological therapy*, *2*(7), pp.723-733.

van der Maaden, K., Jiskoot, W. and Bouwstra, J., 2012. Microneedle technologies for (trans) dermal drug and vaccine delivery. *Journal of controlled release*, *161*(2), pp.645-655.

Vane, J.O.H.N. and Botting, R., 1987. Inflammation and the mechanism of action of anti-inflammatory drugs. *The FASEB journal*, *1*(2), pp.89-96.

Wanigasekara, J. and Witharana, C., 2016. Applications of Nanotechnology in Drug Delivery and Design-An Insight. *Current Trends in Biotechnology & Pharmacy*, *10*(1), pp.78-91

Wang, Z., Wang, L., Li, T., Zhou, X., Ding, L., Yu, Y., Yu, A. and Zhang, H., 2006. Rapid analysis of the essential oils from dried Illicium verum Hook. f. and Zingiber officinale Rosc. by improved solvent-free microwave extraction with three types of microwave-absorption medium. *Analytical and bioanalytical chemistry*, *386*(6), pp.1863-1868.

Wang, L., Dong, J., Chen, J., Eastoe, J. and Li, X., 2009. Design and optimization of a new self-nanoemulsifying drug delivery system. *Journal of colloid and interface science*, *330*(2), pp.443-448.

Williams, A.C. and Barry, B.W., 2012. Penetration enhancers. *Advanced drug delivery reviews*, *64*, pp.128-137.

Wong, H.L., Bendayan, R., Rauth, A.M., Li, Y. and Wu, X.Y., 2007. Chemotherapy with anticancer drugs encapsulated in solid lipid nanoparticles. *Advanced drug delivery reviews*, *59*(6), pp.491-504.

Xu, J., Mukherjee, D. and Chang, S.K., 2018. Physicochemical properties and storage stability of soybean protein nanoemulsions prepared by ultra-high pressure homogenization. *Food chemistry*, *240*, pp.1005-1013.

Yeh, H.Y., Chuang, C.H., Chen, H.C., Wan, C.J., Chen, T.L. and Lin, L.Y., 2014. Bioactive components analysis of two various gingers (Zingiber officinale Roscoe) and antioxidant effect of ginger extracts. *LWT-Food Science and Technology*, *55*(1), pp.329-334.

Yokoyama, M., 2011. Clinical applications of polymeric micelle carrier systems in chemotherapy and image diagnosis of solid tumors. *Journal of Experimental & Clinical Medicine*, *3*(4), pp.151-158.

Zhang, L., Pornpattananangkul, D., Hu, C.M.J., Huang, C.M., 2010. Development of nanoparticles for antimicrobial drug delivery. *Curr. Med. Chem. 17* (6),pp 585-594.

Ziani, K., Fang, Y. and McClements, D.J., 2012. Fabrication and stability of colloidal delivery systems for flavor oils: Effect of composition and storage conditions. *Food Research International*, *46*(1), pp.209-216.