
**UNIVERSITI PUTRA MALAYSIA**

***DESIGN AND DEVELOPMENT OF GALANTAMINE HYDROBROMIDE TRANSDERMAL PATCH FOR TREATMENT OF ALZHEIMER'S DISEASE***

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# DESIGN AND DEVELOPMENT OF GALANTAMINE HYDROBROMIDE TRANSDERMAL PATCH FOR TREATMENT OF ALZHEIMER'S DISEASE

By

**WOO FONG YEN**

**Thesis Submitted to the School of Graduated Studies, Universiti Putra Malaysia, in the Fulfilment of the Requirements for the Degree of Doctor of Philosophy**

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**November 2015**

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Alzheimer's disease (AD) is a neurodegenerative disease, which is caused by abnormal accumulation of beta amyloid (Aβ) peptide in brain and degeneration of cholinergic neurons. Galantamine hydrobromide (GH) is an effective drug for the treatment of AD with its function as the acetylcholinesterase enzyme (AChE) inhibitor. It is currently prescribed through oral and parenteral delivery in the form of tablets, capsules and solutions. These administration methods of GH can cause unwanted effects such as disturbed sleep, vomiting and nausea. These effects can be reduced by using transdermal delivery of GH, which are more patient compliance, more controlled drug release, less frequent drug dosing and longer treatment time.

GH was first formulated in gel drug reservoir and then fabricated in the three-layered patch system. HPLC analysis confirmed the loading of GH in the prepared gel. Preliminary studies showed that amount of carbopol, triethanolamine (TEA), GH and propylene glycol (PG) can affect the drug release from gel. Higher drug release was observed when gel consisted of lower amount of carbopol and TEA, with higher amount of GH and PG. Response surface methodology (RSM) based on central composite design (CCD) proposed that optimized gel consisted of 0.89% w/w carbopol, 1.16% w/w TEA and 4.19% w/w GH gave predicted cumulative drug release amount at 8 h (Q8) of 17.80 $mg.cm^{-2}$ and permeation flux (J) of 2.27 $mg.cm^{-2}/h$. These values were closely fitted to the actual values of Q8 (16.93 ± 0.08 $mg.cm^{-2}$) and J (2.32 ± 0.02 $mg.cm^{-2}/h$).

The results from artificial neural network (ANN) gave insignificant standard deviations between actual with predicted Q8 (16.23 $mg.cm^{-2}$) and J (2.17 $mg.cm^{-2}/h$). The importance chart obtained from ANN revealed that the carbopol and TEA amount were the main factors affecting Q8 and J. FTIR study showed the interactions between GH with other compositions in gel. The physicochemical evaluations showed the moderate pH, successful drug loading and high moisture content in gel. Rheological studies proved the elastic network structure of GH-loaded gel, with the presence of non-Newtonian behaviour, shear thinning properties and temperature-dependent viscosities.

The porous network structure of gel formulation was confirmed with TEM analysis. Toxicity test on fibroblast cells found that the gel was skin compatible.

The GH-loaded gel was then fabricated into the patch system. This system consisted of backing layer, gel drug reservoir in pad layer and release liner. The size of patch is 6 cm × 7 cm, while the size of gel drug reservoir layer is 2 cm × 3 cm. Thickness of this patch is 0.2 cm and loaded with 13.97 mg/cm$^2$ of GH. This patch had neutral pH, successful drug loading and high moisture content. Histological examinations showed there was no irritation on rat skins after application of the patch. GH release from gel and patch system provided more controlled and sustained drug release compared to the control, with the involvement of super case-II transportation. Both GH-loaded systems exhibited good inhibition of AChE activities.

Stability evaluation on GH-loaded gel and patch systems revealed the high stability of both systems under centrifugation. Both systems were unstable at 4 ℃ and 45 ℃, but stable at 25 ℃. The systems were physically stable, with no crystals formation and no phase separation for at least 6 months at 25 ℃. The systems also showed insignificant changes in pH, drug content and moisture content through 6 months of storage. pH studies showed gel and patch formulations had pH ranged from 6.84 to 7.12, which would not cause skin irritation. Drug loading and moisture content analysis proved the successful drug loading and high moisture content in gel and patch system, with less than 10% drug and moisture loss. Therefore, it can be concluded that both GH-loaded systems were stable and potent to be used for the treatment of AD.

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

**REKA BENTUK DAN PEMBANGUNAN BAGI GALANTAMINA HIDROBROMIDA BERASASKAN PENAMPALAN MELALUI KULIT UNTUK RAWATAN PENYAKIT ALZHEIMER**

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Penyakit Alzheimer (AD) merupakan penyakit degeneratif yang dapat mengancam otak. AD disebabkan oleh pengumpulan peptida amiloid beta (Aβ) dalam otak dan degenarasi neuron kolinergik dalam otak. Galantamina hidrobromida (GH) adalah ubat yang berkesan untuk rawatan AD dengan fungsinya sebagai perencat enzim asetilkolinesterase (AChE). Pada masa kini, ubat ini diambil secara pemakanan dan suntikan dalam bentuk tablet, kapsul dan larutan. Pengambilan GH dengan kaedah ini boleh menyebabkan kesan yang tidak diingini seperti gangguan tidur, mual dan muntah. Ini dapat dikurangkan dengan pengambilan GH melalui kulit kerana cara ini dapat meningkatkan keselesaan pesakit, mengawalkan kadar pelepasan ubat, mengurangkan kadar pengambilan ubat dan memanjangkan masa rawatan.

GH diformulakan dalam takungan ubat jenis gel dan seterusnya difabrikasikan dalam sistem penampalan tiga lapisan. Analisis HPLC mengesahkan kandungan GH dalam gel yang disediakan. Kajian awal menunjukkan kuantiti karbopol, triethanolamina (TEA), GH dan propilena glikol (PG) dapat mempengaruhi pelepasan ubat dari gel. Pelepasan ubat yang lebih tinggi berlaku apabila gel mengandungi kuantiti karbopol dan TEA yang lebih rendah, berserta dengan kuantiti GH dan PG yang lebih tinggi. Kaedah gerak balas permukaan (RSM) berasaskan reka bentuk komposit pusat (CCD) mencadangkan gel dengan komposisi 0.89% w/w karbopol, 1.16% w/w TEA dan 4.19% w/w GH boleh menghasilkan nilai jangkaan 17.80 $mg.cm^{-2}$ bagi kuantiti kumulatif pelepasan ubat pada jam ke-8 (Q8) dan 2.27 $mg.cm^{-2}/h$ bagi fluks kemeresapan ubat (J). Nilai ini hampir bersamaan dengan nilai sebenar $16.93 \pm 0.08$ $mg.cm^{-2}$ bagi Q8 dan $2.32 \pm 0.02$ $mg.cm^{-2}/h$ bagi J.

Keputusan dari jaringan neural tiruan (ANN) juga memberikan sisihan yang tidak ketara antara nilai sebenar dengan nilai jangkaan Q8 (16.23 $mg.cm^{-2}$) dan J (2.17 $mg.cm^{-2}/h$). Carta kepentingan yang diperolehi daripada ANN mendedahkan kuantiti karbopol dan TEA adalah faktor utama mempengaruhi Q8 dan J. Kajian FTIR menunjukkan interaksi antara GH dengan komposisi lain dalam gel. Kajian fisikokimia

menunjukkan pH sederhana, pemuatan ubat yang berjaya dan kandungan lembapan yang tinggi dalam gel. Kajian reologi membuktikan gel mengandungi GH mempunyai struktur jaringan elastik, berserta dengan sifat non-Newtonian, penipisan ricih dan kelikatannya bergantung pada suhu. Struktur jaringan berliang bagi formulasi gel disahkan dengan analisis TEM. Ujian keracunan pada sel fibroblas mendapati bahawa gel adalah bersesuaian dengan kulit.

Gel takungan ubat GH kemudiannya difabrikasikan dalam sistem penampalan. Sistem ini mempunyai lapisan belakang, lapisan gel takungan ubat dalam pad dan lapisan lapik pelepasan. Saiz bagi sistem penampalan ialah 6 cm × 7 cm manakala saiz bagi lapisan gel takungan ubat ialah 2 cm × 3 cm. Ketebalan bagi sistem ini ialah 0.2 cm dan mengandungi GH sebanyak 13.97 mg/cm$^2$. Sistem penampalan ini mempunyai pH neutral, pemuatan ubat yang berjaya dan kandungan lembapan yang tinggi. Pemeriksaan histologi menunjukkan mengaplikasikan sistem penampalan tidak merengsakan kulit tikus. Pelepasan GH dari gel dan sistem penampalan memberi pengawalan dan pengekalan yang lebih baik berbanding dengan kontrol, berserta dengan penghantaran secara super kes-II. Sistem mengandugi GH menunjukkan kemampuannya dalam merencat aktiviti AChE.

Kajian kestabilan bagi sistem gel dan penampalan mengandungi GH membuktikan kestabilan yang tinggi selepas pengemparan. Sistem ini tidak stabil pada 4 ℃ dan 45 ℃, tetapi stabil pada 25 ℃. Sistem ini menunjukkan kestabilan fizikal, tiada pembentukan hablur dan tiada pemisahan fasa selepas simpanan selama 6 bulan pada 25 ℃. Sistem ini juga tidak menunjukkan perubahan ketara terhadap pH, kandungan ubat dan kandungan lembapan. Kajian pH menunjukkan formulasi gel dan penampalan mempunyai pH antara 6.84 – 7.12 yang tidak akan menyebabkan kerengsaan kulit. Analisis kandungan ubat dan lembapan membuktikan pemuatan ubat yang berjaya dan kandungan lembapan yang tinggi dalam gel dan sistem penampalan, berserta dengan kehilangan kurang daripada 10%. Kesimpulannya, sistem mengandungi GH adalah stabil dan berpotensi untuk rawatan AD.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirements for the Degree of Doctor of Philosophy. The members of the Supervisory Committee are as follows:

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| | |
|---|---|
| ACN | Acetonitrile |
| ACh | Acetylcholine |
| AChE | Acetylcholinesterase enzyme |
| AD | Alzheimer's disease |
| AR | Amplex red |
| Aβ | Amyloid beta |
| APP | Amyloid precursor proteins |
| ANOVA | Analysis of variance |
| ANN | Artificial neural network |
| BP | Back-propagation algorithms |
| BBB | Blood brain barrier |
| CA | Cellulose acetate |
| CCD | Central composite design |
| CNS | Central nervous system |
| CPE | Chemical penetration enhancers |
| CO | Choline oxidase |
| ChEI | Cholinesterase inhibitors |
| CCM | Complete culture media |
| DI | De-ionized water |
| DF | Dilution factor |
| DMSO | Dimethyl sulfoxide |
| DG | Drug-loaded gel |
| ER | Enhancement ratio |
| FBS | Fetal bovine serum |
| FGS | Fibroblast growth supplement |
| FDA | Food and Drug Administration |
| FT-IR | Fourier Transform-Infrared spectrophotometer |
| GH | Galantamine hydrobromide |
| GA | Generic algorithm |
| XG | Gel without drug |
| HPLC | High Performance Liquid Chromatography |
| HP | Horseradish peroxidase |
| HDF-a | Human dermal fibroblast-adult |
| IBP | Incremental back propagation algorithm |
| ISF | Interstitial fluid |
| LM | Levernberg-Marquadt |
| LVR | Linear viscoelastic region |
| MTT | 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide |
| NO | Nitric oxide |
| NMDA | N-methyl-D-aspartate |
| OVAT | One variable at a time |
| ODDS | Oral drug delivery system |
| PDDS | Parenteral drug delivery system |
| PE | Penetration enhancer |
| P/S | Penicillin/streptomycin solution |
| PG | Propylene glycol |

| | |
|---|---|
| QP | Quick-propagation algorithm |
| ROS | Reactive oxygen species |
| RSM | Response surface methodology |
| RMSE | Root-mean-square-error |
| S.D. | Standard deviation |
| SC | Stratum corneum |
| 3D | Three-dimensional |
| TDDS | Transdermal drug delivery system |
| TEM | Transmission Electron Microscope |
| TEA | Triethanolamine |
| TFA | Trifluoroacetic acid |
| 2FI | Two-factorial interaction |
| UV/VIS | Ultraviolet/Visible |

## LIST OF SYMBOLS

| | |
|---|---|
| $E_a$ | Activation energy |
| U | Bingham plastic viscosity |
| C | Concentration |
| K | Consistency value |
| $R^2$ | Correlation coefficient |
| Q | Cumulative drug release amount |
| Q8 | Cumulative drug release amount at 8 h |
| A | Effective diffusion area |
| E | Elastic modulus |
| F-value | Fisher distribution value |
| J | Flux rate |
| $t_{1/2}$ | Half-life |
| R | Ideal gas constant |
| G'' | Loss modulus |
| P | Partition coefficient |
| δ | Phase angle |
| n | Flow behaviour index |
| P-value | Probability value |
| $n_k$ | Korsmeyer-Peppas diffusion exponent |
| $A_e$ | Pre-exponential factor |
| $k_r$ | Rate of reaction |
| k | Release constant |
| G | Shear modulus |
| ý | Shear rate |
| γ | Shear strain |
| σ | Shear stress |
| G' | Storage modulus |
| T | Temperature |
| $\sigma_E$ | Tensile stress |
| t | Time |
| η | Viscosity |
| V | Volume |
| $\sigma_Y$ | Yield stress |

## LIST OF UNITS

| | |
|---|---|
| AU | Absorbance Unit |
| cm | Centimetre |
| ° | Degree |
| ℃ | Degree Celsius |
| g | Gram |
| Hz | Hertz |
| h | Hour |
| J | Joule |
| K | Kelvin |
| kPa | Kilopascal |
| Pa | Pascal |
| % | Percentage |
| µg | Microgram |
| µL | Microlitre |
| mg | Milligram |
| mL | Millilitre |
| nm | Nanometre |
| kg | Kilogram |
| µm | Micrometer |
| mm | Millimetre |
| min | Minute |
| mol | Mole |
| ppm | Part per million |
| rpm | Revolutions per minute |
| s | Second |
| v/v | Volume-to-volume |
| wt % | Weight percentage |
| w/w | Weight-to-weight |

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of Research

Pharmaceuticals are defined as the drug actives-consisting products or medicines, which are used for the treatment and prevention of the diseases. The pharmacotherapy is thus described as the drug therapy, with the involvement of pharmacology and pharmacy sciences. One branch of pharmaceuticals is plant-based or plant-derived pharmaceuticals. They are used traditionally as herbs for Chinese and Indian society, while they still remain as the important source for drugs discovery and development in modern world (Xu *et al.*, 2015). The patients and scientists put their focuses on the plant-based drugs because of the high accessibility and affordability of these drugs (Saklani and Kutty, 2008). These drugs can be obtained from many parts of a plant, for examples, leaves, flowers, seeds and fruits (Edwards *et al.*, 2015).

Nevertheless, pharmaceutical industry is encountered with the problems such as high cost, low effectiveness and time consuming in drug discovery and drug development (Hughes *et al.*, 2001; Raoof and Aerssens, 2015). These processes involved pre-discovery, drug discovery from 5000 – 10000 compounds, preclinical studies, clinical trials on volunteers and approval from related organizations. This could take an average of 10 – 15 years and $ 800 million – $ 1 billion from the emerging idea to the global market (PhRMA, 2007). Furthermore, the processes will be even more complicated for the new drugs of central nervous system (CNS) diseases (Alavijeh and Palmer, 2010). Therefore, an alternative way is to find new and better technologies for the improvement of the performance of existing drugs.

Galantamine hydrobromide (GH) is one of the plant-based neuroactive drug that were approved by Food and Drug Administration (FDA) for Alzheimer's disease (AD). It is neuroactive, which is able to modify the chemical signals in brain, penetrate through the blood brain barrier (BBB) and then enter the brain interstitial fluid (ISF) (Pohanka, 2014; Samochocki *et al.*, 2000). This enabled GH to interact with its targets and achieved therapeutic effects (Alavijeh and Palmer, 2010). The main function of GH is to inhibit the activities of degradative acetylcholinesterase enzyme (AChE) and maintain the number of neurotransmitter acetylcholine (ACh) in brain ISF. The beneficial effects of GH in cognitive function and behavioural symptoms were proven (Coyle and Kershaw, 2001; Suh *et al.*, 2004).

Conventional delivery of GH such as injection solutions, oral solutions, tablets and capsules are non patient friendly and will cause undesired effects such as nausea, vomiting, gastrointestinal disturbance and drug toxicity (Kavirajan and Schneider, 2007; Tariot *et al.*, 2000). These adverse events are expected to be reduced if transdermal patch drug delivery system is applied. Transdermal patch drug delivery system can be defined as a multi-layered system which is used to deliver drugs to the targeted sites by penetrating through the skin. This patch system is proved to have fewer side effects compared to conventional drug delivery system, besides being more

patient compliance, with less frequent dosing and longer duration of treatment process (Lefèvre *et al.*, 2007; Patil *et al.*, 2015).

## 1.2 Problems Statement

AD can cause many difficulties in the daily life of an individual. However, the situation is worsened with the application of current drug delivery systems for GH. This is because the conventional drug delivery methods are often associated with the problems such as low effectiveness, non patient compliance, burst drug release and frequent dosing, which then cause the inconvenience and adverse symptoms to the patients. Moreover, the previous transdermal patch for GH showed behaviours such as instability at room temperature, drugs precipitation after storage, low drug loading, high drug flux, high usage of organic solvents and low skin biocompatibility.

Transdermal patch application on skin is also encountered with side effects from its polymeric compositions. For instances, stiff polymers and high polymer concentrations can cause adverse events such as restrict the drug release, decrease the skin absorption and trigger irritation symptoms. Suitable polymer should able to give prolonged therapeutic effect, high drug retention capacity, high degree of softness and high compatibility to skin. Therefore, there is a need to design and develop a novel patch with carbopol polymeric system, in which enables the effective loading and releasing of GH for the treatment of AD.

## 1.3 Objectives

The main objective of this research is to fabricate a transdermal patch system loaded with GH for AD treatment. Hence, the following objectives were targeted to aid the achievement of main objective:

1. To design and formulate GH-loaded gel drug reservoir and transdermal patch.
2. To optimize the *in vitro* drug release properties from GH-loaded gel drug reservoir using appropriate mathematical models.
3. To characterize the physicochemical properties of formulated gel drug reservoir and patch.
4. To evaluate the *in vitro* release ability, efficacy, toxicity and stability of gel drug reservoir and patch.

## REFERENCES


Abbastabar, B., Azizi, M. H., Adnani, A., and Abbasi, S. (2015). Determining and Modeling Rheological Characteristics of Quince Seed Gum. *Food Hydrocolloids, 43*(0), 259-264.

Abdollahi, Y., Zakaria, A., Abbasiyannejad, M., Masoumi, H. R. F., Moghaddam, M. G., Matori, K. A., Jahangirian, H., and Keshavarzi, A. (2013). Artificial Neural Network Modeling of P-Cresol Photodegradation. *Chemistry Central Journal, 7*, 96.

Adhyapak, A. and Desai, B. (2011). Preparation and in Vitro Characterization of the Transdermal Drug Delivery System Containing Tamoxifen Citrate for Breast Cancer. *Asian Journal of Pharmaceutics, 5*(1), 41-45.

Ahad, A., Aqil, M., and Ali, A. (2014). Investigation of Antihypertensive Activity of Carbopol Valsartan Transdermal Gel Containing 1, 8-Cineole. *International Journal of Biological Macromolecules, 64*, 144-149.

Ajayan, P. M. (2004). Bulk Metal and Ceramics Nanocomposites. In P. M. Ajayan, L. S. Schadler and P. V. Braun (Eds.), *Nanocomposite Science and Technology*. KGaA, Weinheim, FRG: Wiley-VCH Verlag GmbH & Co.

Akbari, J., Saeedi, M., Farzin, D., Morteza-Semnani, K., and Esmaili, Z. (2015). Transdermal Absorption Enhancing Effect of the Essential Oil of Rosmarinus Officinalis on Percutaneous Absorption of Na Diclofenac from Topical Gel. *Pharmaceutical Biology*, 1-6.

Akhtar, N., Rehman, M. U., Khan, H. M. S., Rasool, F., Saeed, T., and Murtaza, G. (2011). Penetration Enhancing Effect of Polysorbate 20 and 80 on the in Vitro Percutaneous Absorption of L-Ascorbic Acid. *Tropical Journal of Pharmaceutical Research, 10*(3), 281-288.

Alavijeh, M. S. and Palmer, A. M. (2010). Measurement of the Pharmacokinetics and Pharmacodynamics of Neuroactive Compounds. *Neurobiology of Disease, 37*(1), 38-47.

Albuquerque, E. X., Pereira, E. F. R., Aracava, Y., Fawcett, W. P., Oliveira, M., Randall, W. R., Hamilton, T. A., Kan, R. K., Romano, J. A., and Adler, M. (2006). Effective Countermeasure against Poisoning by Organophosphorus Insecticides and Nerve Agents. *Proceedings of the National Academy of Sciences, 103*(35), 13220-13225.

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*(1), 26-40.

Ali, H. and Nazzal, S. (2009). Development and Validation of a Reversed-Phase HPLC Method for the Simultaneous Analysis of Simvastatin and Tocotrienols in Combined Dosage Forms. *Journal of Pharmaceutical and Biomedical Analysis, 49*(4), 950-956.

Alves, M. P., Raffin, R. P., and Fagan, S. B. (2011). Rheological Behavior of Semisolid Formulations Containing Nanostructured Systems. In R. Beck, S. Guterres and A. Pohlmann (Eds.), *Nanocosmetics and Nanomedicines* (pp. 37-48). Berlin Heidelberg: Springer-Verlag.

Amin, R. M., Abdelmonem, A., Verwanger, T., Elsherbini, E., and Krammer, B. (2014). Cytotoxicity of Magnetic Nanoparticles on Normal and Malignant Human Skin Cells. *Nano LIFE, 04*(01), 1440002.

Arani, A., Murphy, M. C., Glaser, K. J., Manduca, A., Lake, D. S., Kruse, S. A., Jack Jr, C. R., Ehman, R. L., and Huston 3rd, J. (2015). Measuring the Effects of Aging and Sex on Regional Brain Stiffness with Mr Elastography in Healthy Older Adults. *NeuroImage, 111*(0), 59-64.

Aronson, S., Van Baelen, B., Kavanagh, S., and Schwalen, S. (2009). Optimal Dosing of Galantamine in Patients with Mild or Moderate Alzheimer's Disease. *Drugs and Aging, 26*(3), 231-239.

Atkins, P. and de Paula, J. (2007). The Rates of Chemical Reactions *Physical Chemistry* (pp. 791-829). United States: W. H. Freeman.

Atobe, T., Mori, M., Yamashita, F., Hashida, M., and Kouzuki, H. (2015). Artificial Neural Network Analysis for Predicting Human Percutaneous Absorption Taking Account of Vehicle Properties. *The Journal of Toxicological Sciences, 40*(2), 277-294.

Baba, H., Takahara, J.-i., and Mamitsuka, H. (2015). In Silico Predictions of Human Skin Permeability Using Nonlinear Quantitative Structure–Property Relationship Models. *Pharmaceutical Research*, 1-12.

Badhan, A. C., Mashru, R. C., Shah, P. P., Thakkar, A. R., and Dobaria, N. B. (2009). Development and Evaluation of Sustained Release Gastroretentive Minimatrices for Effective Treatment of H. Pylori Infection. *AAPS PharmSciTech, 10*(2), 459-467.

Baek, G. and Kim, C. (2011). Rheological Properties of Carbopol Containing Nanoparticles. *Journal of Rheology, 55*(2), 313-330.

Balakrishnan, P., Shanmugam, S., Lee, W. S., Lee, W. M., Kim, J. O., Oh, D. H., Kim, D.-D., Kim, J. S., Yoo, B. K., Choi, H.-G., Woo, J. S., and Yong, C. S. (2009). Formulation and in Vitro Assessment of Minoxidil Niosomes for Enhanced Skin Delivery. *International Journal of Pharmaceutics, 377*(1–2), 1-8.

Banerjee, P., Singh, V. S., Chatttopadhyay, K., Chandra, P. C., and Singh, B. (2011). Artificial Neural Network Model as a Potential Alternative for Groundwater Salinity Forecasting. *Journal of Hydrology, 398*(3–4), 212-220.

Barry, B. W. (2001). Novel Mechanisms and Devices to Enable Successful Transdermal Drug Delivery. *European Journal of Pharmaceutical Sciences, 14*(2), 101-114.

Batheja, P., Sheihet, L., Kohn, J., Singer, A. J., and Michniak-Kohn, B. (2011). Topical Drug Delivery by a Polymeric Nanosphere Gel: Formulation Optimization and in Vitro and in Vivo Skin Distribution Studies. *Journal of Controlled Release, 149*(2), 159-167.

Bažant, Z. P. and Donmez, A. (2015). Extrapolation of Short-Time Drying Shrinkage Tests Based on Measured Diffusion Size Effect: Concept and Reality. *Materials and Structures*, 1-10.

Bera, R., Dey, A., and Chakrabarty, D. (2015). Synthesis, Characterization, and Drug Release Study of Acrylamide-co-Itaconic Acid Based Smart Hydrogel. *Polymer Engineering and Science, 55*(1), 113-122.

Betancourt, F., Concha, F., and Uribe, L. (2015). Settling Velocities of Particulate Systems Part 17. Settling Velocities of Individual Spherical Particles in Power-Law Non-Newtonian Fluids. *International Journal of Mineral Processing, 143*, 125-130.

Bezerra, M. A., Santelli, R. E., Oliveira, E. P., Villar, L. S., and Escaleira, L. A. (2008). Response Surface Methodology (RSM) as a Tool for Optimization in Analytical Chemistry. *Talanta, 76*(5), 965-977.

Bhattacharya, S., Maelicke, A., and Montag, D. (2015). Nasal Application of the Galantamine Pro-Drug Memogain Slows Down Plaque Deposition and Ameliorates Behavior in 5x Familial Alzheimer's Disease Mice. *Journal of Alzheimer's Disease,46*(1), 1-9.

Biswal, B. and Sharma, D. (2013). Design, Development and Evaluation of Galantamine Hydrobromide Bilayer Sustained Release Tablet. *Der Pharmacia Lettre, 5*(6), 12-19.

Blessy, M., Patel, R. D., Prajapati, P. N., and Agrawal, Y. K. (2014). Development of Forced Degradation and Stability Indicating Studies of Drugs—a Review. *Journal of Pharmaceutical Analysis, 4*(3), 159-165.

Boddu, S. H. S., Gupta, H., and Bonam, S. P. (2014). Preclinical Evaluation of a Ricinoleic Acid Poloxamer Gel System for Transdermal Eyelid Delivery. *International Journal of Pharmaceutics, 470*(1–2), 158-161.

Bonacucina, G., Martelli, S., and Palmieri, G. F. (2004). Rheological, Mucoadhesive and Release Properties of Carbopol Gels in Hydrophilic Cosolvents. *International Journal of Pharmaceutics, 282*(1–2), 115-130.

Bono, G. F., Simão-Silva, D. P., Batistela, M. S., Josviak, N. D., Dias, P. F. R., Nascimento, G. A., Souza, R. L. R., Piovezan, M. R., Souza, R. K. M., and Furtado-Alle, L. (2015). Butyrylcholinesterase: K Variant, Plasma Activity, Molecular Forms and Rivastigmine Treatment in Alzheimer's Disease in a Southern Brazilian Population. *Neurochemistry International, 81*(0), 57-62.

Bourne, D. W. A. (2002). Pharmacokinetics. In G. S. Banker and C. T. Rhodes (Eds.), *Modern Pharmaceutics* (4th ed., pp. 67-92). New York: Marcel Dekker Inc.

Bowen, J. L. and Heard, C. M. (2006). Film Drying and Complexation Effects in the Simultaneous Skin Permeation of Ketoprofen and Propylene Glycol from Simple Gel Formulations. *International Journal of Pharmaceutics, 307*(2), 251-257.

Brereton, R. (2003). *Chemometrics: Data Analysis for the Laboratory and Chemical Plant*. New York: John Wiley & Sons.

Bruno, G. and Enrico, M. (2009). US8013151.

Budai, L., Szabadi, E., Hajdú, M., Budai, M., Klebovich, I., and Antal, I. (2015). The Influence of Selected Excipients on the Rheological Behaviour of Chitosan Based Ocular Pharmaceutical Systems. *Journal of Physics: Conference Series, 602*(1).

Chan, H. (2001). Effects of Injection Duration on Site-Pain Intensity and Bruising Associated with Subcutaneous Heparin. *Journal of Advanced Nursing, 35*(6), 882-892.

Chaterji, S., Kwon, I. K., and Park, K. (2007). Smart Polymeric Gels: Redefining the Limits of Biomedical Devices. *Progress in Polymer Science, 32*(8–9), 1083-1122.

Chen, G., Cui, S., You, L., Li, Y., Mei, Y.-H., and Chen, X. (2015). Experimental Study on Multi-Step Creep Properties of Rat Skins. *Journal of the Mechanical Behavior of Biomedical Materials, 46*, 49-58.

Chhabra, R. P. and Richardson, J. F. (2008). *Non-Newtonian Flow and Applied Rheology: Engineering Applications*. Oxford, UK: Elselvier Ltd.

Christensen, J. M., Chuong, M. C., Le, H., Pham, L., and Bendas, E. (2011). Hydrocortisone Diffusion through Synthetic Membrane, Mouse Skin, and Epiderm™ Cultured Skin. *Archives of Drug Information, 4*(1), 10-21.

Christodoulou, C., Melville, P., Scherl, W. F., MacAllister, W. S., Elkins, L. E., and Krupp, L. B. (2006). Effects of Donepezil on Memory and Cognition in Multiple Sclerosis. *Journal of the Neurological Sciences, 245*(1–2), 127-136.

Cohen, M., Wolfe, R., Mai, T., and Lewis, D. (2003). A Randomized, Double Blind, Placebo Controlled Trial of a Topical Cream Containing Glucosamine Sulfate, Chondroitin Sulfate, and Camphor for Osteoarthritis of the Knee. *The Journal of Rheumatology, 30*(3), 523-528.

Contreras, M. J. F., Diéguez, A. R., and Soriano, M. M. J. (2001). Rheological Characterization of Hydroalcoholic Gels — 15% Ethanol — of Carbopol® Ultrez™ 10. *Il Farmaco, 56*(5–7), 437-441.

Coyle, J. and Kershaw, P. (2001). Galantamine, a Cholinesterase Inhibitor That Allosterically Modulates Nicotinic Receptors: Effects on the Course of Alzheimer's Disease. *Biological Psychiatry, 49*(3), 289-299.

Craig, D. Q. M. (2002). The Mechanisms of Drug Release from Solid Dispersions in Water-Soluble Polymers. *International Journal of Pharmaceutics, 231*(2), 131-144.

Danysz, W. and Parsons, C. G. (2003). The NMDA Receptor Antagonist Memantine as a Symptomatological and Neuroprotective Treatment for Alzheimer's Disease: Preclinical Evidence. *International Journal of Geriatric Psychiatry, 18*(S1), S23-S32.

Danyuo, Y., Dozie-Nwachukwu, S., Obayemi, J. D., Ani, C. J., Odusanya, O. S., Oni, Y., Anuku, N., Malatesta, K., and Soboyejo, W. O. (2016). Swelling of Poly(N-isopropylacrylamide) P(NIPA)-Based Hydrogels with Bacterial-Synthesized Prodigiosin for Localized Cancer Drug Delivery. *Materials Science and Engineering: C, 59*, 19-29.

Das, B., Nayak, A. K., and Nanda, U. (2013). Topical Gels of Lidocaine HCl Using Cashew Gum and Carbopol 940: Preparation and in Vitro Skin Permeation. *International Journal of Biological Macromolecules, 62*(0), 514-517.

Dash, S., Murthy, P. N., Nath, L., and Chowdhury, P. (2010). Kinetic Modeling on Drug Release from Controlled Drug Delivery Systems. *Acta Poloniae Pharmaceutica, 67*(3), 217-223.

De Caro, V., Giandalia, G., Siragusa, M., Campisi, G., and Giannola, L. (2009). Galantamine Delivery on Buccal Mucosa: Permeation Enhancement and Design of Matrix Tablets. *Journal of Bioequivalence and Bioavailability, 1*, 127-134.

De Felice, F. G., Velasco, P. T., Lambert, M. P., Viola, K., Fernandez, S. J., Ferreira, S. T., and Klein, W. L. (2007). Aβ Oligomers Induce Neuronal Oxidative Stress through an N-Methyl-D-Aspartate Receptor-Dependent Mechanism That Is Blocked by the Alzheimer Drug Memantine. *Journal of Biological Chemistry, 282*(15), 11590-11601.

Dey, A., Bera, R., Ahmed, S., and Chakrabarty, D. (2015). Smart Superabsorbent UV Resistant Etherified PVA Gel: Synthesis and Characterization. *Journal of Industrial and Engineering Chemistry, 21*(0), 1219-1230.

Di Giuseppe, E., Corbi, F., Funiciello, F., Massmeyer, A., Santimano, T. N., Rosenau, M., and Davaille, A. (2015). Characterization of Carbopol® Hydrogel Rheology for Experimental Tectonics and Geodynamics. *Tectonophysics, 642*(0), 29-45.

Driscoll, D. F., Bistrian, B. R., Demmelmair, H., and Koletzko, B. (2008). Pharmaceutical and Clinical Aspects of Parenteral Lipid Emulsions in Neonatology. *Clinical Nutrition, 27*(4), 497-503.

Edwards, S. E., da Costa Rocha, I., Heinrich, M., and Williamson, E. M. (2015). *Phytopharmacy: An Evidence-Based Guide to Herbal Medicinal Products*. United States: John Wiley & Sons.

Elewa, R. M., Abdallah, M. A., and Zouboulis, C. C. (2015). Age-Associated Skin Changes in Innate Immunity Markers Reflect a Complex Interaction between Aging Mechanisms in the Sebaceous Gland. *The Journal of Dermatology, 42*(5), 467-476.

Elias, P. M., Tsai, J., Menon, G. K., Holleran, W. M., and Feingold, K. R. (2002). The Potential of Metabolic Interventions to Enhance Transdermal Drug Delivery. *Journal of Investigative Dermatology Symposium Proceedings, 7*(1), 79-85.

Emard, J.-F., Thouez, J.-P., and Gauvreau, D. (1995). Neurodegenerative Diseases and Risk Factors: A Literature Review. *Social Science and Medicine, 40*(6), 847-858.

Erkinjuntti, T., Kurz, A., Small, G. W., Bullock, R., Lilienfeld, S., and Damaraju, C. V. (2003). An Open-Label Extension Trial of Galantamine in Patients with Probable Vascular Dementia and Mixed Dementia. *Clinical Therapeutics, 25*(6), 1765-1782.

Esparza, F., Cobián, C., Jiménez, J. F., García-Cota, J. J., Sánchez, C. and Setrade, A. M. (2007). Topical Ketoprofen TDS Patch Versus Diclofenac Gel: Efficacy and Tolerability in Benign Sport Related Soft-Tissue Injuries. *British Journal of Sports Medicine, 41*(3), 134-139.

Fagerberg, J. H., Sjögren, E., and Bergström, C. A. S. (2015). Concomitant Intake of Alcohol May Increase the Absorption of Poorly Soluble Drugs. *European Journal of Pharmaceutical Sciences, 67*(0), 12-20.

Fasano, W. J., ten Berge, W. F., Banton, M. I., Heneweer, M., and Moore, N. P. (2011). Dermal Penetration of Propylene Glycols: Measured Absorption across Human Abdominal Skin in Vitro and Comparison with a QSAR Model. *Toxicology in Vitro, 25*(8), 1664-1670.

Faujan, N. H., Abedi Karjiban, R., Kashaban, I., Basri, M., and Basri, H. (2015). Computational Simulation of Palm Kernel Oil-Based Esters Nano-Emulsions Aggregation as a Potential Parenteral Drug Delivery System. *Arabian Journal of Chemistry*, In Press, Corrected Proof.

Gabathuler, R. (2010). Approaches to Transport Therapeutic Drugs across the Blood–Brain Barrier to Treat Brain Diseases. *Neurobiology of Disease, 37*(1), 48-57.

Gao, Y., Liang, J., Liu, J., and Xiao, Y. (2009). Double-Layer Weekly Sustained Release Transdermal Patch Containing Gestodene and Ethinylestradiol. *International Journal of Pharmaceutics, 377*(1–2), 128-134.

Garala, K., Joshi, P., Shah, M., Ramkishan, A., and Patel, J. (2013). Formulation and Evaluation of Periodontal in Situ Gel. *International Journal of Pharmaceutical Investigation, 3*(1), 29-41.

Garrod, D. and Chidgey, M. (2008). Desmosome Structure, Composition and Function. *Biochimica et Biophysica Acta (BBA) - Biomembranes, 1778*(3), 572-587.

George, K. E. (2009). 2 - Non-Newtonian Fluid Mechanics and Polymer Rheology. In S. Thomas and Y. Weimin (Eds.), *Advances in Polymer Processing* (pp. 13-46). Cambridge: Woodhead Publishing.

Ghanbarzadeh, S., Valizadeh, H., and Zakeri-Milani, P. (2013). Application of Response Surface Methodology in Development of Sirolimus Liposomes Prepared by Thin Film Hydration Technique. *BioImpacts, 3*(2), 75.

Gore, S., Rajlakshmy, A. K., Ravinder, K., Sreedharala, V., Bhushan, I., and Mohan, M. (2007). US20070092568 A1.

Gracia-Garc á, P., de-la-C ámara, C., Santab árbara, J., Lopez-Anton, R., Quintanilla, M. A., Ventura, T., Marcos, G., Campayo, A., Saz, P., Lyketsos, C., and Lobo, A. (2015). Depression and Incident Alzheimer Disease: The Impact of Disease Severity. *The American Journal of Geriatric Psychiatry, 23*(2), 119-129.

Greenhalgh, K. R. (2007). Development of Biocompatible Multi-Drug Conjugated Nanoparticles/Smart Polymer Films For Biomedicinal Applications. United States: ProQuest.

Grossberg, G. T., Farlow, M. R., Meng, X., and Velting, D. M. (2015). Evaluating High-Dose Rivastigmine Patch in Severe Alzheimer's Disease: Analyses with Concomitant Memantine Usage as a Factor. *Current Alzheimer Research, 12*(1), 53-60.

Growdon, M. E., Schultz, A. P., Dagley, A. S., Amariglio, R. E., Hedden, T., Rentz, D. M., Johnson, K. A., Sperling, R. A., Albers, M. W., and Marshall, G. A. (2015). Odor Identification and Alzheimer Disease Biomarkers in Clinically Normal Elderly. *Neurology, 84*(21), 2153-60.

Guo, R., Du, X., Zhang, R., Deng, L., Dong, A., and Zhang, J. (2011). Bioadhesive Film Formed from a Novel Organic–Inorganic Hybrid Gel for Transdermal Drug Delivery System. *European Journal of Pharmaceutics and Biopharmaceutics, 79*(3), 574-583.

Habbu, P., Madagundi, S., Kulkarni, R., Jadav, S., Vanakudri, R., and Kulkarni, V. (2013). Preparation and Evaluation of Bacopa–Phospholipid Complex for Antiamnesic Activity in Rodents. *Drug Invention Today, 5*(1), 13-21.

Hai, N. T., Kim, J., Park, E.-S., and Chi, S.-C. (2008). Formulation and Biopharmaceutical Evaluation of Transdermal Patch Containing Benztropine. *International Journal of Pharmaceutics, 357*(1–2), 55-60.

Han, F., Yin, R., Wei, M., Sun, X. J., Zhao, S., and Li, S. M. (2012). Application of Central Composite Design-Response Surface Methodology to the Formulation of Flurbiprofen-Loaded Nanostructured Lipid Carriers Gel. *Journal of Shenyang Pharmaceutical University, 3*, 001.

Hassan, M. A., Pathak, M., and Khan, M. K. (2015). Rayleigh–Benard Convection in Herschel–Bulkley Fluid. *Journal of Non-Newtonian Fluid Mechanics, 226*, 32-45.

Hayashi, A., Saito, T., Mukai, Y., Kurita, S., and Hori, T.-a. (2005). Genetic Variations in *Lycoris Radiata* Var. *Radiata* in Japan. *Genes and Genetic Systems, 80*(3), 199-212.

Hector, A. L. (2007). Materials Synthesis Using Oxide Free Sol-Gel Systems. *Chemical Society Reviews, 36*(11), 1745-1753.

Hertzman, M. (2003). Galantamine in the Treatment of Adult Autism: A Report of Three Clinical Cases. *The International Journal of Psychiatry in Medicine, 33*(4), 395-398.

Hilmas, C. J., Poole, M. J., Finneran, K., Clark, M. G., and Williams, P. T. (2009). Galantamine Is a Novel Post-Exposure Therapeutic against Lethal VX Challenge. *Toxicology and Applied Pharmacology, 240*(2), 166-173.

Hiruta, Y., Funatsu, T., Matsuura, M., Wang, J., Ayano, E., and Kanazawa, H. (2015). pH/Temperature-Responsive Fluorescence Polymer Probe with pH-Controlled Cellular Uptake. *Sensors and Actuators B: Chemical, 207*(A), 724-731.

Ho, K. Y. and Dodou, K. (2007). Rheological Studies on Pressure-Sensitive Silicone Adhesives and Drug-in-Adhesive Layers as a Means to Characterise Adhesive Performance. *International Journal of Pharmaceutics, 333*(1–2), 24-33.

Hoffman, R. M. (2000). The Hair Follicle as a Gene Therapy Target. *Nature Biotechnology, 18*(1), 20-21.

Hossain, M. K., Subedi, R. K., Chun, M.-K., Kim, E.-J., Moon, H.-S., and Choi, H.-K. (2011). Formulation and in Vitro Evaluation of Transdermal Drug Delivery System for Galantamine. *Journal of Pharmaceutical Investigation, 41*(1), 1-7.

Huang, L., Bai, J., Yang, H., Liu, J., and Cui, H. (2015). Combined Use of Borneol or Menthol with Labrasol Promotes Penetration of Baicalin through Rabbit Cornea in Vitro. *Pakistan Journal of Pharmaceutical Sciences, 28*(1), 1-7.

Hughes, D. A., Bagust, A., Haycox, A., and Walley, T. (2001). The Impact of Non-Compliance on the Cost-Effectiveness of Pharmaceuticals: A Review of the Literature. *Health Economics, 10*(7), 601-615.

Huynh, J. and Aebi, C. (2008). Transdermal Patches: To Cut or Not Cut. *Orgeon Dur Board Newsletter, 10*(8), 1-2.

Imani, R., Emami, S. H., Moshtagh, P. R., Baheiraei, N., and Sharifi, A. M. (2012). Preparation and Characterization of Agarose-Gelatin Blend Hydrogels as a Cell Encapsulation Matrix: An in-Vitro Study. *Journal of Macromolecular Science, Part B, 51*(8), 1606-1616.

Islam, M. T., Rodriguez-Hornedo, N., Ciotti, S., and Ackermann, C. (2004). Rheological Characterization of Topical Carbomer Gels Neutralized to Different pH. *Pharmaceutical Research, 21*(7), 1192-1199.

Jain, J. B., Bariya, S. D., Kapadia, J. R., Jani, G. K., and Prajapati, V. D. (2015). Rapid Mouth Dissolving Film: An Innovative Drug Delivery System. *World Journal of Pharmacy and Pharmaceutical Sciences, 4*(05), 484-495.

Jana, S., Manna, S., Nayak, A. K., Sen, K. K., and Basu, S. K. (2014). Carbopol Gel Containing Chitosan-Egg Albumin Nanoparticles for Transdermal Aceclofenac Delivery. *Colloids and Surfaces B: Biointerfaces, 114*(0), 36-44.

Jenkins, A. D. (2013). *Polymer Science: A Materials Science Handbook*. (Vol. 2). UK: Elsevier.

Jia, P., Sheng, R., Zhang, J., Fang, L., He, Q., Yang, B., and Hu, Y. (2009). Design, Synthesis and Evaluation of Galanthamine Derivatives as Acetylcholinesterase Inhibitors. *European Journal of Medicinal Chemistry, 44*(2), 772-784.

Johannsson, M., Snaedal, J., Johannesson, G. H., Gudmundsson, T. E., and Johnsen, K. (2015). The Acetylcholine Index: An Electroencephalographic Marker of Cholinergic Activity in the Living Human Brain Applied to Alzheimer's Disease and Other Dementias. *Dementia and Geriatric Cognitive Disorders, 39*(3-4), 132-142.

Kadirgama, K., Amirruddin, A. K., and Bakar, R. A. (2014). Estimation of Solar Radiation by Artificial Networks: East Coast Malaysia. *Energy Procedia, 52*(0), 383-388.

Karavas, E., Georgarakis, M., Docoslis, A., and Bikiaris, D. (2007). Combining SEM, TEM, and Micro-Raman Techniques to Differentiate between the Amorphous Molecular Level Dispersions and Nanodispersions of a Poorly Water-Soluble Drug within a Polymer Matrix. *International Journal of Pharmaceutics, 340*(1–2), 76-83.

Kaur, D., Raina, A., and Singh, N. (2014). Formulation and Evaluation of Carbopol 940 Based Glibenclamide Transdermal Gel. *International Journal of Pharmacy and Pharmaceutical Sciences, 6*(8), 434-440.

Kaur, N., Sarkar, B., Mittal, S., Dhiman, M., Taglialatela, G., Perez-Polo, R., and Mantha, A. (2015). Oxidative Stress Events and Neuronal Dysfunction in Alzheimer's Disease: Focus on APE1/Ref-1-Mediated Survival Strategies. In V. Rani and U. C. S. Yadav (Eds.), *Free Radicals in Human Health and Disease* (pp. 175-207). India: Springer India.

Kavirajan, H. and Schneider, L. S. (2007). Efficacy and Adverse Effects of Cholinesterase Inhibitors and Memantine in Vascular Dementia: A Meta-Analysis of Randomised Controlled Trials. *The Lancet Neurology, 6*(9), 782-792.

Keleb, E., Sharma, R. K., Mosa, E. B., and Aljahwi, A.-a. Z. (2011). Transdermal Drug Delivery System- Design and Evaluation. *International Jornal of Advances in Pharmaceutical Sciences, 1*(3), 201-211.

Kelessidis, V. C., Maglione, R., Tsamantaki, C., and Aspirtakis, Y. (2006). Optimal Determination of Rheological Parameters for Herschel-Bulkley Drilling Fluids and Impact on Pressure Drop, Velocity Profiles and Penetration Rates During Drilling. *Journal of Petroleum Science and Engineering, 53*(3-4), 203-224.

Kemppainen, B. W. and Reifenrath, W. G. (1990). *Methods for Skin Absorption*. United States: CRC Press.

Keshavarz, M. and Kaffashi, B. (2014). The Ability of Retention, Drug Release and Rheological Properties of Nanogel Bioadhesives Based on Cellulose Derivatives. *Pharmaceutical Development and Technology, 19*(8), 952-959.

Keshri, L. and Pathak, K. (2013). Development of Thermodynamically Stable Nanostructured Lipid Carrier System Using Central Composite Design for Zero Order Permeation of Econazole Nitrate through Epidermis. *Pharmaceutical Development and Technology, 18*(3), 634-644.

Khurana, S., Jain, N., and Bedi, P. (2013). Nanoemulsion Based Gel for Transdermal Delivery of Meloxicam: Physico-Chemical, Mechanistic Investigation. *Life Sciences, 92*(6), 383-392.

Kim, J. Y., Song, J. Y., Lee, E. J., and Park, S. K. (2003). Rheological Properties and Microstructures of Carbopol Gel Network System. *Colloid and Polymer Science, 281*(7), 614-623.

Kim, Y. H., Choi, H. Y., Lim, H.-S., Lee, S. H., Jeon, H. S., Hong, D., Kim, S. S., Choi, Y. K., and Bae, K.-S. (2015). Single Dose Pharmacokinetics of the Novel Transdermal Donepezil Patch in Healthy Volunteers. *Drug Design, Development and Therapy, 9*, 1419.

Kishi, T. and Iwata, N. (2013). NMDA Receptor Antagonists Interventions in Schizophrenia: Meta-Analysis of Randomized, Placebo-Controlled Trials. *Journal of Psychiatric Research, 47*(9), 1143-1149.

Kotiyan, P. N. and Vavia, P. R. (2001). Eudragits: Role as Crystallization Inhibitors in Drug-in-Adhesive Transdermal Systems of Estradiol. *European Journal of Pharmaceutics and Biopharmaceutics, 52*(2), 173-180.

Kotzki, S., Roustit, M., Arnaud, C., Godin-Ribuot, D., and Cracowski, J.-L. (2015). Effect of Continuous vs Pulsed Iontophoresis of Treprostinil on Skin Blood Flow. *European Journal of Pharmaceutical Sciences, 72*(0), 21-26.

Krishnaiah, Y. S. R., Xu, X., Rahman, Z., Yang, Y., Katragadda, U., Lionberger, R., Peters, J. R., Uhl, K., and Khan, M. A. (2014). Development of Performance Matrix for Generic Product Equivalence of Acyclovir Topical Creams. *International Journal of Pharmaceutics, 475*(1–2), 110-122.

Labouta, H. I. and Schneider, M. (2013). Interaction of Inorganic Nanoparticles with the Skin Barrier: Current Status and Critical Review. *Nanomedicine: Nanotechnology, Biology and Medicine, 9*(1), 39-54.

Lambers, H., Piessens, S., Bloem, A., Pronk, H., and Finkel, P. (2006). Natural Skin Surface pH Is on Average Below 5, Which Is Beneficial for Its Resident Flora. *International Journal of Cosmetic Science*, *28*(5), 359-370.

Lamoke, F., Mazzone, V., Persichini, T., Maraschi, A., Harris, M., Venema, R., Colasanti, M., Gliozzi, M., Muscoli, C., Bartoli, M., and Mollace, V. (2015). Amyloid Beta Peptide-Induced Inhibition of Endothelial Nitric Oxide Production Involves Oxidative Stress-Mediated Constitutive eNOS/HSP90 Interaction and Disruption of Agonist-Mediated Akt Activation. *Journal of Neuroinflammation*, *12*(1), 84.

Latif, M. A., Zaki, M. Z. M., Leng, T. M., Rahman, N. H. A., Arshad, S. A., and Hamid, A. (2015). Alocasia Denudata Engler Treatment Enhance Open Wound Healing Activities in Wistar Rat's Skin. *Journal of Ethnopharmacology*, *176*, 258-267.

Law, V., Knox, C., Djoumbou, Y., Jewison, T., Guo, A. C., Liu, Y., Maciejewski, A., Arndt, D., Wilson, M., Neveu, V., Tang, A., Gabriel, G., Ly, C., Adamjee, S., Dame, Z. T., Han, B., Zhou, Y., and Wishart, D. S. (2014). Drugbank 4.0: Shedding New Light on Drug Metabolism. *Nucleic Acids Research*, *42*(Database issue), D1091-D1097.

Leardi, R. (2009). Experimental Design in Chemistry: A Tutorial. *Analytica Chimica Acta*, *652*(1–2), 161-172.

Lecanu, L., Tillement, L., McCourty, A., Rammouz, G., Yao, W., Greeson, J., and Papadopoulos, V. (2010). Dimethyl-Carbamic Acid 2, 3-Bis-Dimethylcarbamoyloxy-6-(4-Ethyl-Piperazine-1-Carbonyl)-Phenyl Ester: A Novel Multi-Target Therapeutic Approach to Neuroprotection. *Medicinal Chemistry*, *6*(3), 123-140.

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 Products*, *32*(3), 246-251.

Lee, J.-S. and Song, K.-W. (2011). Rheological Characterization of Carbopol 940 in Steady Shear and Start-up Flow Fields. *Annual Transactions of The Nordic Rheology Society*, *19*.

Lee, M., McGeer, E., and McGeer, P. L. (2015). Activated Human Microglia Stimulate Neuroblastoma Cells to Upregulate Production of Beta Amyloid Protein and Tau: Implications for Alzheimer's Disease Pathogenesis. *Neurobiology of Aging*, *36*(1), 42-52.

Lee, N.-Y., Choi, H.-O., and Kang, Y.-S. (2012). The Acetylcholinesterase Inhibitors Competitively Inhibited an Acetyl L-Carnitine Transport through the Blood–Brain Barrier. *Neurochemical Research*, *37*(7), 1499-1507.

Lee, P. F., Misran, M., and Abdullah, W. A. T. W. (2011). Effects of Joule Heating on Electrophoretic Mobility of Titanium Dioxide ($TiO_2$), Escherichia Coli and Staphylococcus Aureus (Live and Dead). In N. Osman, W. Abas, A. Wahab and H.-N. Ting (Eds.), *5th Kuala Lumpur International Conference on Biomedical Engineering 2011* (Vol. 35, pp. 60-68). Berlin Heidelberg: Springer.

Lefèvre, G., Sędek, G., Huang, H.-L. A., Saltzman, M., Rosenberg, M., Kiese, B., and Fordham, P. (2007). Pharmacokinetics of a Rivastigmine Transdermal Patch Formulation in Healthy Volunteers: Relative Effects of Body Site Application. *The Journal of Clinical Pharmacology, 47*(4), 471-478.

Lémery, E., Briançon, S., Chevalier, Y., Bordes, C., Oddos, T., Gohier, A., and Bolzinger, M.-A. (2015). Skin Toxicity of Surfactants: Structure/Toxicity Relationships. *Colloids and Surfaces A: Physicochemical and Engineering Aspects, 469*(0), 166-179.

Leonard, A. K., Sileno, A. P., Brandt, G. C., Foerder, C. A., Quay, S. C., and Costantino, H. R. (2007). In Vitro Formulation Optimization of Intranasal Galantamine Leading to Enhanced Bioavailability and Reduced Emetic Response in Vivo. *International Journal of Pharmaceutics, 335*(1–2), 138-146.

Leonard, A. K., Sileno, A. P., MacEvilly, C., Foerder, C. A., Quay, S. C., and Costantino, H. R. (2005). Development of a Novel High-Concentration Galantamine Formulation Suitable for Intranasal Delivery. *Journal of Pharmaceutical Sciences, 94*(8), 1736-1746.

Lerche, D. (2002). Dispersion Stability and Particle Characterization by Sedimentation Kinetics in a Centrifugal Field. *Journal of Dispersion Science and Technology, 23*(5), 699-709.

Liu, G.-J., Liu, Y., Wang, Z.-Y., Lei, Y.-H., Chen, Z.-A., and Deng, L.-W. (2015). The Effects of Temperature, Organic Matter and Time-Dependency on Rheological Properties of Dry Anaerobic Digested Swine Manure. *Waste Management, 38*, 449-454.

Liu, X., Fu, L., Dai, W., Liu, W., Zhao, J., Wu, Y., Teng, L., Sun, F., and Li, Y. (2014). Design of Transparent Film-Forming Hydrogels of Tolterodine and Their Effects on Stratum Corneum. *International Journal of Pharmaceutics, 471*(1–2), 322-331.

Liu, Y., Wang, L., Liu, J., and Di, Y. (2013). A Study of Human Skin and Surface Temperatures in Stable and Unstable Thermal Environments. *Journal of Thermal Biology, 38*(7), 440-448.

Liu, Z.-M., Huang, X.-Y., Cui, M.-R., Zhang, X.-D., Chen, Z., Yang, B.-S., and Zhao, X.-K. (2015). Amaryllidaceae Alkaloids from the Bulbs of Lycoris Radiata with Cytotoxic and Anti-Inflammatory Activities. *Fitoterapia, 101*(0), 188-193.

Loo, C. H., Basri, M., Ismail, R., Lau, H. L. N., Tejo, B. A., Kanthimathi, M. S., Hassan, H. A., and Choo, Y. M. (2013). Effect of Compositions in Nanostructured Lipid Carriers (NLC) on Skin Hydration and Occlusion. *International Journal of Nanomedicine, 8*, 13-22.

Lubbe, A., Pomahačová, B., Choi, Y. H., and Verpoorte, R. (2010). Analysis of Metabolic Variation and Galanthamine Content in Narcissus Bulbs by 1h NMR. *Phytochemical Analysis, 21*(1), 66-72.

Luo, Y., Yue, W., Quan, X., Wang, Y., Zhao, B., and Lu, Z. (2015). Asymmetric Dimethylarginine Exacerbates Aβ-Induced Toxicity and Oxidative Stress in Human Cell and Caenorhabditis Elegans Models of Alzheimer Disease. *Free Radical Biology and Medicine, 79*(0), 117-126.

Mahapatra, D. M. and Ramachandra, T. V. (2013). Algal Biofuel: Bountiful Lipid from Chlorococcum Sp. Proliferatingin Municipal Wastewater. *Current Science, 105*(1), 47-55.

Malkin, A. Y. and Isayev, A. I. (2006). *Rheology. Concepts, Methods, and Applications*. ChemTec Publishing.

Mallot, H. (2013). Artificial Neural Networks *Computational Neuroscience* (Vol. 2, pp. 83-112): Springer International Publishing.

Maran, J. P., Sivakumar, V., Thirugnanasambandham, K., and Sridhar, R. (2013). Artificial Neural Network and Response Surface Methodology Modeling in Mass Transfer Parameters Predictions During Osmotic Dehydration of Carica Papaya L. *Alexandria Engineering Journal, 52*(3), 507-516.

Margetts, L. and Sawyer, R. (2007). Transdermal Drug Delivery: Principles and Opioid Therapy. *Continuing Education in Anaesthesia, Critical Care & Pain, 7*(5), 171-176.

Martanto, W., Davis, S., Holiday, N., Wang, J., Gill, H., and Prausnitz, M. (2004). Transdermal Delivery of Insulin Using Microneedles in Vivo. *Pharmaceutical Research, 21*(6), 947-952.

Martinez, A. (2010). *Emerging Drugs and Targets for Alzheimer's Disease*. London: RSC publishing.

Masoumi, H. R. F., Basri, M., Kassim, A., Abdullah, D. K., Abdollahi, Y., Gani, S. S. A., and Rezaee, M. (2013). Statistical Optimization of Process Parameters for Lipase-Catalyzed Synthesis of Triethanolamine-Based Esterquats Using Response Surface Methodology in 2-Liter Bioreactor. *The Scientific World Journal, 2013*, 9.

Masoumi, H. R. F., Kassim, A., Basri, M., Abdullah, D. K., and Haron, M. J. (2011). Multivariate Optimization in the Biosynthesis of a Triethanolamine (TEA)-Based Esterquat Cationic Surfactant Using an Artificial Neural Network. *Molecules, 16*(7), 5538-5549.

Matsunaga, S., Kishi, T., and Iwata, N. (2015). Memantine Monotherapy for Alzheimer's Disease: A Systematic Review and Meta-Analysis. *PLoS ONE, 10*(4), e0123289.

Matthews, J. D., Blais, M., Park, L., Welch, C., Baity, M., Murakami, J., Sklarsky, K., Homberger, C., and Fava, M. (2008). The Impact of Galantamine on Cognition and Mood During Electroconvulsive Therapy: A Pilot Study. *Journal of Psychiatric Research, 42*(7), 526-531.

Menon, G. K. (2002). New Insights into Skin Structure: Scratching the Surface. *Advanced Drug Delivery Reviews, 54, Supplement*(0), S3-S17.

Meyer, R. J. and Hussain, A. S. Awareness Topic: Mitigating the Risks of Ethanol Induced Dose Dumping from Oral Sustained/Controlled Release Dosage Forms. FDA's ACPS Meeting, October 2005.

Mezger, T. G. (2006). *The Rheology Handbook: For Users of Rotational and Oscillatory Rheometers*. Germany: Vincentz Network GmbH & Co KG.

Miles, A., Berthet, A., Hopf, N. B., Gilliet, M., Raffoul, W., Vernez, D., and Spring, P. (2014). A New Alternative Method for Testing Skin Irritation Using a Human Skin Model: A Pilot Study. *Toxicology in Vitro, 28*(2), 240-247.

Mills, A., Wang, J., and McGrady, M. (2006). Method of Rapid Assessment of Photocatalytic Activities of Self-Cleaning Films. *The Journal of Physical Chemistry B, 110*(37), 18324-18331.

Misra, S., Chopra, K., Sinha, V. R., and Medhi, B. (2015). Galantamine-Loaded Solid–Lipid Nanoparticles for Enhanced Brain Delivery: Preparation, Characterization, in Vitro and in Vivo Evaluations. *Drug Delivery*, 1-10.

Musa, S. H., Basri, M., Masoumi, H. R. F., Karjiban, R. A., Malek, E. A., Basri, H., and Shamsuddin, A. F. (2013). Formulation Optimization of Palm Kernel Oil Esters Nanoemulsion-Loaded with Chloramphenicol Suitable for Meningitis Treatment. *Colloids and Surfaces B: Biointerfaces, 112*(0), 113-119.

Muzzalupo, R., Tavano, L., Lai, F., and Picci, N. (2014). Niosomes Containing Hydroxyl Additives as Percutaneous Penetration Enhancers: Effect on the Transdermal Delivery of Sulfadiazine Sodium Salt. *Colloids and Surfaces B: Biointerfaces, 123*, 207-212.

Na, H. R., Park, M. H., Kim, S., Yang, D. W., Choi, S.-H., Yang, H. D., Yang, Y., Han, H. J., Lee, J. S., Yoon, Y.-C., Koh, S.-H., Kim, J. E., Ku, B. D., Kim, H.-J., Park, K. W., Kim, E.-J., Yoon, B., and Park, K. J. (2015). Factors Influencing Skin Tolerability to the Rivastigmine Patch in Patients with Alzheimer's Disease. *Dementia and Neurocognitive Disorders, 14*(1), 31-38.

Nafee, N. A., Ismail, F. A., Boraie, N. A., and Mortada, L. M. (2003). Mucoadhesive Buccal Patches of Miconazole Nitrate: In Vitro/in Vivo Performance and Effect of Ageing. *International Journal of Pharmaceutics, 264*(1–2), 1-14.

Naharci, M., Ozturk, A., Yasar, H., Cintosun, U., Kocak, N., Bozoglu, E., Tasci, I., and Doruk, H. (2015). Galantamine Improves Sleep Quality in Patients with Dementia. *Acta Neurologica Belgica*, 1-6.

Naik, A., Kalia, Y. N., and Guy, R. H. (2000). Transdermal Drug Delivery: Overcoming the Skin's Barrier Function. *Pharmaceutical Science and Technology Today, 3*(9), 318-326.

Narendra, C., Srinath, M. S., and Prakash Rao, B. (2005). Development of Three Layered Buccal Compact Containing Metoprolol Tartrate by Statistical Optimization Technique. *International Journal of Pharmaceutics, 304*(1–2), 102-114.

Ng, S.-F., Rouse, J., Sanderson, D., and Eccleston, G. (2010). A Comparative Study of Transmembrane Diffusion and Permeation of Ibuprofen across Synthetic Membranes Using Franz Diffusion Cells. *Pharmaceutics, 2*(2), 209-223.

Ng, S. H., Basri, M., Abd Rahman, M. B., Abd Rahman, R. N., Salleh, A. B., and Ismail, Z. (2012). Preparation of Emulsions by Rotor-Stator Homogenizer and Ultrasonic Cavitation for the Cosmeceutical Industry. *Journal of Cosmetic Science, 63*(5), 333-344.

Ng, S. H., Woi, P. M., Basri, M., and Ismail, Z. (2013). Characterization of Structural Stability of Palm Oil Esters-Based Nanocosmeceuticals Loaded with Tocotrienol. *Journal of Nanobiotechnology, 11*(1), 27.

Nishida, N., Taniyama, K., Sawabe, T., and Manome, Y. (2010). Development and Evaluation of a Monolithic Drug-in-Adhesive Patch for Valsartan. *International Journal of Pharmaceutics, 402*(1–2), 103-109.

Niyaz, B. B., Prakasam, K., and Goli, D. (2011). Formulation and Evaluation of Gel Containing Fluconazole-Antifungal Agent. *International Journal of Drug Development and Research, 3*(4), 109-128.

Oboh, G., Ademiluyi, A. O., and Akinyemi, A. J. (2012). Inhibition of Acetylcholinesterase Activities and Some Pro-Oxidant Induced Lipid Peroxidation in Rat Brain by Two Varieties of Ginger (Zingiber Officinale). *Experimental and Toxicologic Pathology, 64*(4), 315-319.

Olivares-Morales, A., Kamiyama, Y., Darwich, A. S., Aarons, L., and Rostami-Hodjegan, A. (2015). Analysis of the Impact of Controlled Release Formulations on Oral Drug Absorption, Gut Wall Metabolism and Relative Bioavailability of CYP3A Substrates Using a Physiologically-Based Pharmacokinetic Model. *European Journal of Pharmaceutical Sciences, 67*(0), 32-44.

Ortan, A., Parvu, C. D., Ghica, M. V., Popescu, L. M., and Ionita, L. (2011). Rheological Study of a Liposomal Hydrogel Based on Carbopol. *Romanian Biotechnological Letters, 16*(1), 47-54.

Oyama, R., Yamamoto, H., and Titani, K. (2000). Glutamine Synthetase, Hemoglobin A-Chain, and Macrophage Migration Inhibitory Factor Binding to Amyloid B-Protein: Their Identification in Rat Brain by a Novel Affinity Chromatography and in Alzheimer's Disease Brain by Immunoprecipitation. *Biochimica et Biophysica Acta (BBA) - Protein Structure and Molecular Enzymology, 1479*(1–2), 91-102.

Paganini-Hill, A., Kawas, C. H., and Corrada, M. M. (2015). Lifestyle Factors and Dementia in the Oldest-Old: The 90+ Study. *Alzheimer Disease and Associated Disorders*.

Paquet, C., Amin, J., Mouton-Liger, F., Nasser, M., Love, S., Gray, F., Pickering, R. M., Nicoll, J. A. R., Holmes, C., Hugon, J., and Boche, D. (2015). Effect of Active Aβ Immunotherapy on Neurons in Human Alzheimer's Disease. *The Journal of Pathology, 235*(5), 721-730.

Parashar, B., Kabra, A., and Chandel, A. (2013). Formulation and Evaluation of Gel Containing Miconazole Nitrate an Antifungal Agent. *International Journal of Pharma Research and Review, 2*, 8-28.

Park, C.-W., Son, D.-D., Kim, J.-Y., Oh, T.-O., Ha, J.-M., Rhee, Y.-S., and Park, E.-S. (2012). Investigation of Formulation Factors Affecting in Vitro and in Vivo Characteristics of a Galantamine Transdermal System. *International Journal of Pharmaceutics, 436*(1–2), 32-40.

Park, E.-S., Chang, S.-Y., Hahn, M., and Chi, S.-C. (2000). Enhancing Effect of Polyoxyethylene Alkyl Ethers on the Skin Permeation of Ibuprofen. *International Journal of Pharmaceutics, 209*(1–2), 109-119.

Patel, M., Bharadia, P., and Patel, M. (2015). Effect of Gelling Agents & Rate Controlling Membranes on Permeability of Propranolol Hydrochloride through Reservoir-Type Transdermal Delivery System. *The Pharma Innovation Journal, 3*(12), 44-49.

Patel, R. P., Patel, H. H., and Baria, A. H. (2009). Formulation and Evaluation of Carbopol Gel Containing Liposomes of Ketoconazole. *International Journal of Drug Delivery Technology, 1*(2), 42-45.

Patil, B., Puranik, P., Pol, S., Khobragade, P., Ramteke, P., Palasakar, R., and Ransing-Patil, N. (2015). Formulation and Development of Industry Feasible Proniosomal Transdermal Drug Delivery System of Granisetron Hydrochloride. *Asian Journal of Pharmaceutics*, 113-119.

Pavlov, V. A., Parrish, W. R., Rosas-Ballina, M., Ochani, M., Puerta, M., Ochani, K., Chavan, S., Al-Abed, Y., and Tracey, K. J. (2009). Brain Acetylcholinesterase Activity Controls Systemic Cytokine Levels through the Cholinergic Anti-Inflammatory Pathway. *Brain, Behavior, and Immunity, 23*(1), 41-45.

PhRMA. (2007). Drug Discovery and Development. Retrieved 10 June 2015, from http://www.phrma.org.

Pichayakorn, W., Suksaeree, J., Boonme, P., Taweepreda, W., Amnuaikit, T., and Ritthidej, G. C. (2013). Deproteinised Natural Rubber Used as a Controlling Layer Membrane in Reservoir-Type Nicotine Transdermal Patches. *Chemical Engineering Research and Design, 91*(3), 520-529.

Pohanka, M. (2014). Inhibitors of Acetylcholinesterase and Butyrylcholinesterase Meet Immunity. *International Journal of Molecular Sciences, 15*(6), 9809-9825.

Porcellotti, S., Fanelli, F., Fracassi, A., Sepe, S., Cecconi, F., Bernardi, C., Cimini, A., Ceru, M. P., and Moreno, S. (2015). Oxidative Stress During the Progression of B-Amyloid Pathology in the Neocortex of the Tg2576 Mouse Model of Alzheimer's Disease. *Oxidative Medicine and Cellular Longevity, 2015*, 18.

Pradhan, R., Budhathoki, U., and Thapa, P. (2008). Formulation of Once a Day Controlled Release Tablet of Indomethacin Based on HPMC-Mannitol. *Kathmandu University Journal of Science, Engineering and Technology, I*(V), 55-67.

Prince, M., Prina, M., and Guerchet, M. (2013). *World Alzheimer Report 2013, Journal of Caring: An Analysis of Long-Term Care for Dementia*. London: Alzheimer's Disease International.

Quan, M. H., She, C. W., Ou, L. J., and Chen, D. M. (2012). Effect of Shading on Contents of Lycorine and Galantamine in the Bulb of Lycoris Aurea. *Journal of China Agricultural University, 4*, 011.

Rai, V. K., Yadav, N. P., Sinha, P., Mishra, N., Luqman, S., Dwivedi, H., Kymonil, K. M., and Saraf, S. A. (2014). Development of Cellulosic Polymer Based Gel of Novel Ternary Mixture of Miconazole Nitrate for Buccal Delivery. *Carbohydrate Polymers, 103*(0), 126-133.

Rao, N. G. R. and Suryakar, V. B. (2011). Design and Development of Mucoadhesive Drug Delivery System of Montelukast Sodium. *International Journal of Reasearch in Ayurveda & Pharmacy, 2*(2), 491-497.

Raoof, A. A. and Aerssens, J. (2015). Patient-Centered Drug Discovery as the Means to Improved R&D Productivity. *Drug Discovery Today*.

Raskind, M. A., Peskind, E. R., Truyen, L., Kershaw, P., and Damaraju, C. (2004). The Cognitive Benefits of Galantamine Are Sustained for at Least 36 Months: A Long-Term Extension Trial. *Archives of Neurology, 61*(2), 252-256.

Rattan, S. and Kassem, M. (2006). *Prevention and Treatment of Age-Related Diseases*. (7th ed.). Berlin: Springer.

Rhee, Y.-S., Choi, J.-G., Park, E.-S., and Chi, S.-C. (2001). Transdermal Delivery of Ketoprofen Using Microemulsions. *International Journal of Pharmaceutics, 228*(1–2), 161-170.

Ringman, J. M., Liang, L.-J., Zhou, Y., Vangala, S., Teng, E., Kremen, S., Wharton, D., Goate, A., Marcus, D. S., Farlow, M., Ghetti, B., McDade, E., Masters, C. L., Mayeux, R. P., Rossor, M., Salloway, S., Schofield, P. R., Cummings, J. L., Buckles, V., Bateman, R., and Morris, J. C. (2015). Early Behavioural Changes in Familial Alzheimer's Disease in the Dominantly Inherited Alzheimer Network. *Brain, 138*(4), 1036-1045.

Roberts, G. P. and Barnes, H. A. (2001). New Measurements of the Flow-Curves for Carbopol Dispersions without Slip Artefacts. *Rheologica Acta, 40*(5), 499-503.

Rösler, A., Pfeil, S., Lessmann, H., Höder, J., Befahr, A., and Renteln-Kruse, W. V. (2015). Dysphagia in Dementia: Influence of Dementia Severity and Food Texture on the Prevalence of Aspiration and Latency to Swallow in Hospitalized Geriatric Patients. *Journal of the American Medical Directors Association, 16*(8), 697-701.

Roussel, M. R. (2012). *A Life Scientist's Guide to Physical Chemistry*. United States: Cambridge University Press.

Rudraraju, V. S. and Wyandt, C. M. (2005). Rheological Characterization of Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose Hydrogels Using a Controlled Stress Rheometer: Part I. *International Journal of Pharmaceutics, 292*(1–2), 53-61.

Saadat, E., Abdollahi, A., and Dorkoosh, F. (2015). Fabrication and Characterization of Risperidone Implants as an Extended Antipsychotic Delivery System, Exploring the Role of Excipients. *Journal of Pharmaceutical Innovation, 10*(2), 118-129.

Saklani, A. and Kutty, S. K. (2008). Plant-Derived Compounds in Clinical Trials. *Drug Discovery Today, 13*(3–4), 161-171.

Salim, N., Basri, M., Rahman, M. B. A., Abdullah, D., and Basri, H. (2012). Modification of Palm Kernel Oil Esters Nanoemulsions with Hydrocolloid Gum for Enhanced Topical Delivery of Ibuprofen. *International Journal of Nanomedicine, 7*, 4739-4747.

Samochocki, M., Zerlin, M., Jostock, R., Groot Kormelink, P. J., Luyten, W. H. M. L., Albuquerque, E. X., and Maelicke, A. (2000). Galantamine Is an Allosterically Potentiating Ligand of the Human A4/B2 nAChR. *Acta Neurologica Scandinavica, 102*, 68-73.

Santhanam, A. V. R., d'Uscio, L. V., and Katusic, Z. S. (2015). Abstract W P230: Tetrahydrobiopterin Attenuates Cerebrovascular Oxidative Stress in Tg2576 Mouse Model of Alzheimer's Disease. *Stroke, 46*(1), AWP230.

Santos, P., Watkinson, A. C., Hadgraft, J., and Lane, M. E. (2012). Influence of Penetration Enhancer on Drug Permeation from Volatile Formulations. *International Journal of Pharmaceutics, 439*(1–2), 260-268.

Sarkar, A. and Pandey, P. (2015). River Water Quality Modelling Using Artificial Neural Network Technique. *Aquatic Procedia, 4*(0), 1070-1077.

Sarve, A., Sonawane, S. S., and Varma, M. N. (2015). Ultrasound Assisted Biodiesel Production from Sesame (Sesamum Indicum L.) Oil Using Barium Hydroxide as a Heterogeneous Catalyst: Comparative Assessment of Prediction Abilities between Response Surface Methodology (RSM) and Artificial Neural Network (ANN). *Ultrasonics Sonochemistry, 26*(0), 218-228.

Schneider, L. S., Kennedy, R. E., Wang, G., and Cutter, G. R. (2015). Differences in Alzheimer Disease Clinical Trial Outcomes Based on Age of the Participants. *Neurology, 84*(11), 1121-1127.

Scott, L. and Goa, K. (2000). Galantamine. *Drugs, 60*(5), 1095-1122.

Selkoe, D. J. (2001). Presenilins, B-Amyloid Precursor Protein and the Molecular Basis of Alzheimer's Disease. *Clinical Neuroscience Research, 1*(1–2), 91-103.

Seyfried, N., Dammer, E., Ren, R., Gearing, M., Duong, D., Lah, J., and Levey, A. (2015). Tau Phosphosignatures Discriminate Alzheimer Disease from Other Tauopathies. *The FASEB Journal, 29*(1), LB208.

Shakeel, F., Ramadan, W., Gargum, H. M., and Singh, R. (2010). Preparation and in Vivo Evaluation of Indomethacin Loaded True Nanoemulsions. *Scientia Pharmaceutica, 78*(1), 47-56.

Shakeel, F., Salem-Bekhit, M. M., Iqbal, M., and Haq, N. (2015). Solubility and Thermodynamic Function of a New Anticancer Drug Ibrutinib in 2-(2-Ethoxyethoxy) Ethanol + Water Mixtures at Different Temperatures. *The Journal of Chemical Thermodynamics, 89*, 159-163.

Shao, Z.-Q. (2015). Comparison of the Efficacy of Four Cholinesterase Inhibitors in Combination with Memantine for the Treatment of Alzheimer's Disease. *International Journal of Clinical and Experimental Medicine, 8*(2), 2944-2948.

Sharma, B., Nanda, S., and Saroha, K. (2014). In Vitro Sonicated Transdermal Transport across Hairless Rat Skin Using Optimized Batch of Ketorolac Tromethamine Gel. *International Journal of Pharmaceutical Sciences Review and Research, 26*(1), 179-185.

Shoaib, M. H., Tazeen, J., Merchant, H. A., and Yousuf, R. I. (2006). Evaluation of Drug Release Kinetics from Ibuprofen Matrix Tablets Using HPMC. *Pakistan Journal of Pharmaceutical Sciences, 19*(2), 119-124.

Sistla, R., Tata, V. S. S. K., Kashyap, Y. V., Chandrasekar, D., and Diwan, P. V. (2005). Development and Validation of a Reversed-Phase HPLC Method for the Determination of Ezetimibe in Pharmaceutical Dosage Forms. *Journal of Pharmaceutical and Biomedical Analysis, 39*(3–4), 517-522.

Sobrado, M., Roda, J. M., López, M. G., Egea, J., and García, A. G. (2004). Galantamine and Memantine Produce Different Degrees of Neuroprotection in Rat Hippocampal Slices Subjected to Oxygen–Glucose Deprivation. *Neuroscience Letters, 365*(2), 132-136.

Song, E. J., Lee, J. A., Park, J. J., Kim, H. J., Kim, N. S., Byun, K. S., Choi, G. S., and Moon, T. K. (2015). A Study on Seasonal Variation of Skin Parameters in Korean Males. *International Journal of Cosmetic Science, 37*(1), 92-97.

Soni, M. (2015). Formulation and Evaluation of Poly Herbal Cream. *International Journal of Pharmaceutical and Biological Archive, 5*(4).

Suh, G.-H., Yeon Jung, H., Uk Lee, C., Hoon Oh, B., Nam Bae, J., Jung, H.-Y., Ju, Y.-S., Kil Yeon, B., Park, J., Hong, I., Choi, S., and Ho Lee, J. (2004). A Prospective, Double-Blind, Community-Controlled Comparison of Three Doses of Galantamine in the Treatment of Mild to Moderate Alzheimer's Disease in a Korean Population. *Clinical Therapeutics, 26*(10), 1608-1618.

Svoboda, Z., Kvetina, J., Josef, H., Jiri, B., Bartosova, L., Palicka, V., and Zivny, P. (2005). Galantamine Antiacetylcholinesterase Activity in Rat Brain Influenced by L-Carnitine. *Biomedical Papers, 149*(2), 335.

Swamy, N. G. N., Pasha, M., and Abbas, Z. (2010). Formulation and Evaluation of Diclofenac Sodium Gels Using Sodium Carboxymethyl Hydroxypropyl Guar and Hydroxypropyl Methylcellulose. Indian Journal of Pharmaceutical Education and Research. *Indian Journal of Pharmaceutical Education and Research, 44*(4), 310-314.

Takata, K., Kitamura, Y., Saeki, M., Terada, M., Kagitani, S., Kitamura, R., Fujikawa, Y., Maelicke, A., Tomimoto, H., Taniguchi, T., and Shimohama, S. (2010). Galantamine-Induced Amyloid-B Clearance Mediated Via Stimulation of Microglial Nicotinic Acetylcholine Receptors. *The Journal of Biological Chemistry, 285*(51), 40180-40191.

Tang, W. K., Zhang, C. F., and Zhao, S. J. (2010). Galantamine Hydrobromide Transdermal Patch in Vitro Release and Percutaneous Permeation Of. Retrieved 10 June 2015, from http://eng.hi138.com/medicine-papers/pharmacy-papers.

Tanwar, Y. S. and Jain, A. K. (2012). Formulation and Evaluation of Topical Diclofenac Sodium Gel Using Different Gelling Agent *Asian Journal of Pharmaceutical Research and Health Care, 4*(1), 1-6.

Tariot, P. N., Solomon, P., Morris, J., Kershaw, P., Lilienfeld, S., and Ding, C. (2000). A 5-Month, Randomized, Placebo-Controlled Trial of Galantamine in Ad. *Neurology, 54*(12), 2269-2276.

Tateno, A., Sakayori, T., Takizawa, Y., Yamamoto, K., Minagawa, K., and Okubo, Y. (2015). A Case of Alzheimer's Disease Following Mild Traumatic Brain Injury. *General Hospital Psychiatry, 37*(1), 97.e97-97.e99.

Tinu, T., Thomas, L., and Kumar, B. A. (2013). Polymers Used in Ophthalmic in Situ Gelling System. *International Journal of Pharmaceutical Sciences Review and Research, 20*(1).

Todica, M., Pop, C. V., Udrescu, L., and Pop, M. (2010). Rheological Behavior of Some Aqueous Gels of Carbopol with Pharmaceutical Applications. *Chinese Physics Letters, 27*(1), 018301-018304.

Trivedy, P. and Teitelbaum, J. (2015). Eosinophilic Esophagitis in Children. *Pediatric Drugs*, 1-11.

Trommer, H. and Neubert, R. (2006). Overcoming the Stratum Corneum: The Modulation of Skin Penetration. *Skin Pharmacology and Physiology, 19*, 106-121.

Trottet, L., Merly, C., Mirza, M., Hadgraft, J., and Davis, A. F. (2004). Effect of Finite Doses of Propylene Glycol on Enhancement of in Vitro Percutaneous Permeation of Loperamide Hydrochloride. *International Journal of Pharmaceutics, 274*(1–2), 213-219.

Turi, C. E., Axwik, K. E., Smith, A., Jones, A. M. P., Saxena, P. K., and Murch, S. J. (2014). Galanthamine, an Anti-Cholinesterase Drug, Effects Plant Growth and Development in Artemisia Tridentata Nutt. Via Modulation of Auxin and Neurotransmitter Signaling. *Plant Signaling and Behavior, 9*(3), e28645-1-12.

Ubaidulla, U., Reddy, M. S., Ruckmani, K., Ahmad, F., and Khar, R. (2007). Transdermal Therapeutic System of Carvedilol: Effect of Hydrophilic and Hydrophobic Matrix on in Vitro and in Vivo Characteristics. *AAPS PharmSciTech, 8*(1), E13-E20.

Ünal, M., Ak, A., Topuz, V., and Erdal, H. (2013). *Artificial Neural Networks Optimization of Pid Controllers Using Ant Colony and Genetic Algorithms* (Vol. 449, pp. 5-17). Berlin Heidelberg: Springer.

Unal, M., Onat, M., Demetgul, M., and Kucuk, H. (2014). Fault Diagnosis of Rolling Bearings Using a Genetic Algorithm Optimized Neural Network. *Measurement, 58*(0), 187-196.

Vilar, G., Tulla-Puche, J., and Albericio, F. (2012). Polymers and Drug Delivery Systems. *Current Drug Delivery, 9*(4), 367-394.

Vishwanath, K. P. and Kandasamy, A. (2010). Inertia Effects in Circular Squeeze Film Bearing Using Herschel–Bulkley Lubricants. *Applied Mathematical Modelling, 34*(1), 219-227.

Waghmare, N., Waghmare, P., Wani, S., and Yerawar, A. (2011). Development of Isotretinoin Gel for the Treatment of Acne Vulgaris. *Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2*(1), 220-230.

Wang, L., Yin, Z.-Q., Cai, Y., Zhang, X.-Q., Yao, X.-S., and Ye, W.-C. (2010). Amaryllidaceae Alkaloids from the Bulbs of Lycoris Radiata. *Biochemical Systematics and Ecology, 38*(3), 444-446.

Wang, Y. and Burgess, D. J. (2013). Influence of Storage Temperature and Moisture on the Performance of Microsphere/Hydrogel Composites. *International Journal of Pharmaceutics, 454*(1), 310-315.

Whitehead, K., Shen, Z., and Mitragotri, S. (2004). Oral Delivery of Macromolecules Using Intestinal Patches: Applications for Insulin Delivery. *Journal of Controlled Release, 98*(1), 37-45.

Williams, A. C. and Barry, B. W. (2012). Penetration Enhancers. *Advanced Drug Delivery Reviews, 64, Supplement*(0), 128-137.

Winnik, F. M. (1999). Elements of Polymer Science. In E. D. Goddard and J. V. Grubber (Eds.), *Principles of Polymer Science and Technology in Cosmetics and Personal Care* (pp. 1-50). New York: Marcel Dekker.

Woodruff-Pak, D. S., Vogel, R. W., and Wenk, G. L. (2001). Galantamine: Effect on Nicotinic Receptor Binding, Acetylcholinesterase Inhibition, and Learning. *Proceedings of the National Academy of Sciences USA, 98*(4), 2089-2094.

Wu, C. L., Chau, K. W., and Fan, C. (2010). Prediction of Rainfall Time Series Using Modular Artificial Neural Networks Coupled with Data-Preprocessing Techniques. *Journal of Hydrology, 389*(1–2), 146-167.

Wu, J. S., Kim, A. M., Bleher, R., Myers, B. D., Marvin, R. G., Inada, H., Nakamura, K., Zhang, X. F., Roth, E., Li, S. Y., Woodruff, T. K., O'Halloran, T. V., and Dravid, V. P. (2013). Imaging and Elemental Mapping of Biological Specimens with a Dual-Eds Dedicated Scanning Transmission Electron Microscope. *Ultramicroscopy, 128*, 24-31.

Xu, H., Timares, L., and Elmets, C. A. (2013). Host Defenses in the Skin. In R. R. Rich, T. A. Fleisher, W. T. Shearer, H. W. S. Jr., A. J. Frew and C. M. Weyand (Eds.), *Clinical Immunology, Principles and Practice* (4th ed., pp. 228-239). UK: Elsevier

Xu, L., Grandi, N., Del Vecchio, C., Mandas, D., Corona, A., Piano, D., Esposito, F., Parolin, C., and Tramontano, E. (2015). From the Traditional Chinese Medicine Plant Schisandra Chinensis New Scaffolds Effective on HIV-1 Reverse Transcriptase Resistant to Non-Nucleoside Inhibitors. *Journal of Microbiology, 53*(4), 288-293.

Yamamoto, K., Tanei, Z.-i., Hashimoto, T., Wakabayashi, T., Okuno, H., Naka, Y., Yizhar, O., Fenno, Lief E., Fukayama, M., Bito, H., Cirrito, John R., Holtzman, David M., Deisseroth, K., and Iwatsubo, T. (2015). Chronic Optogenetic Activation Augments Aβ Pathology in a Mouse Model of Alzheimer Disease. *Cell Reports, 11*(6), 859-865.

Yang, W. N., Ma, K. G., Chen, X. L., Shi, L. L., Bu, G., Hu, X. D., Han, H., Liu, Y., and Qian, Y. H. (2014). Mitogen-Activated Protein Kinase Signaling Pathways Are Involved in Regulating A7 Nicotinic Acetylcholine Receptor-Mediated Amyloid-B Uptake in SH-SY5Y Cells. *Neuroscience, 278*(0), 276-290.

Yang, Z., Teng, Y., Wang, H., and Hou, H. (2013). Enhancement of Skin Permeation of Bufalin by Limonene Via Reservoir Type Transdermal Patch: Formulation Design and Biopharmaceutical Evaluation. *International Journal of Pharmaceutics, 447*(1–2), 231-240.

Young, P. A., Young, P. H., and Tolbert, D. L. (2008). Aging of the Nervous Sytem: Dementia. *Basic Clinical Neuroscience* (2nd ed., pp. 309-312). United States: Lippincott Williams & Wilkins.

Zaid, A. N., Al-Ramahi, R. J., Ghoush, A. A., Qaddumi, A., and Zaaror, Y. A. (2013). Weight and Content Uniformity of Lorazepam Half-Tablets: A Study of Correlation of a Low Drug Content Product. *Saudi Pharmaceutical Journal, 21*(1), 71-75.

Zainol, S., Basri, M., Basri, H. B., Shamsuddin, A. F., Abdul-Gani, S. S., Karjiban, R. A., and Abdul-Malek, E. (2012). Formulation Optimization of a Palm-Based Nanoemulsion System Containing Levodopa. *International Journal of Molecular Sciences, 13*(10), 13049-13064.

Zhang, Z. and Feng, S.-S. (2006). The Drug Encapsulation Efficiency, in Vitro Drug Release, Cellular Uptake and Cytotoxicity of Paclitaxel-Loaded Poly(Lactide)–Tocopheryl Polyethylene Glycol Succinate Nanoparticles. *Biomaterials, 27*(21), 4025-4033.

Zhao, B., Summers, F. A., and Mason, R. P. (2012). Photooxidation of Amplex Red to Resorufin: Implications of Exposing the Amplex Red Assay to Light. *Free Radical Biology and Medicine, 53*(5), 1080-1087.

Zhu, J. and Kringos, N. (2015). Towards the Development of a Viscoelastic Model for Phase Separation in Polymer-Modified Bitumen. *Road Materials and Pavement Design, 16*(sup1), 39-49.

Zhu, Q., Lu, S., Ma, D., Zhang, L., and Hu, J. (2010). Preparation of Galantamine Hydrobromide Patch and Its Release and Transdermal Properties in Vitro. *Pharmaceutical Care and Research, 2*, 135-137.

Zivin, K., Yosef, M., Miller, E. M., Valenstein, M., Duffy, S., Kales, H. C., Vijan, S., and Kim, H. M. (2015). Associations between Depression and All-Cause and Cause-Specific Risk of Death: A Retrospective Cohort Study in the Veterans Health Administration. *Journal of Psychosomatic Research, 78*(4), 324-331.

Zorec, B., Jelenc, J., Miklavčič, D., and Pavšelj, N. (2015). Ultrasound and Electric Pulses for Transdermal Drug Delivery Enhancement: Ex Vivo Assessment of Methods with in Vivo Oriented Experimental Protocols. *International Journal of Pharmaceutics, 490*(1–2), 65-73.