

REFERENCES

- Aarabi, S., Bhatt, K.A., Shi, Y., Paterno, J., Chang, E.I., Loh, S.A., Holmes, J.W., Longaker, M.T., Yee, H., Gurtner, G.C., (2007). Mechanical load initiates hypertrophic scar formation through decreased cellular apoptosis. *The FASEB Journal*, 21, 3250-3261.
- Abergel, R.P., Pizzurro, D., Meeker, C.A., Lask, G., Matsuoka, L.Y., Minor, R.R., Chu, M.L., Uitto, J., (1985). Biochemical composition of the connective tissue in keloids and analysis of collagen metabolism in keloid fibroblast cultures. *J Invest Dermatol*, 84, 384-390.
- Adulyatham, P., Owusu-Apenten, R., (2006). Stabilization and partial purification of a protease from ginger rhizome (*Zingiber officinale* Roscoe). *J Food Sci*, 70, 231-234.
- Afaq, S., Iqbal, J., (2001). Immobilization and stabilization of papain on chelating sepharose: a metal chelate regenerable carrier. *Electron J Biotechn*, 3, 1-5.
- Ajlia, S.A., Majid, F.A., Suvik, A., Effendy, M.A., Nouri, H.S., (2010). Efficacy of papain-based wound cleanser in promoting wound regeneration. *Pak J Biol Sci*, 13, 596-603.
- Alsarra, I.A., Neau, S.H., Howard, M.A., (2004). Effects of preparative parameters on the properties of chitosan hydrogel beads containing *Candida rugosa* lipase. *Biomaterials*, 25, 2645-2655.
- Alster, T., (2003). Laser scar revision: comparison study of 585-nm pulsed dye laser with and without intralesional corticosteroids. *Dermatol Surg*, 29, 25-29.

- Alvarez-Roman, R., Naik, A., Kalia, Y.N., Guy, R.H., Fessi, H., (2004). Enhancement of topical delivery from biodegradable nanoparticles. *Pharm Res*, 21, 1818-1825.
- Aqil, F., Ahmad, I., Mehmood, Z., (2006). Antioxidant and free radical scavenging properties of twelve traditionally used indian medicinal plants. *Turk J Biol*, 30, 177-183.
- Arakawa, M., Hatamochi, A., Mori, Y., Mori, K., Ueki, H., Moriguchi, T., (1996). Reduced collagenase gene expression in fibroblasts from hypertrophic scar tissue. *Br J Dermatol*, 134, 863-868.
- Arora, R., Jain, C.P., (2007). Advances in niosome as a drug carrier: A review. *Asian J Pharm*, 1, 29-39.
- Azarkan, M., El Moussaoui, A., van Wuytsinkel, D., Dehon, G., Looze, Y., (2003). Fractionation and purification of the enzymes stored in the latex of *Carica papaya*. *J Chromatogr B*, 790, 229-238.
- Balitaan, J.N., Steinbrenner, H., Ramos, M.C., (2010). Zymography-based assay for screening potential anti-gelatinase agents using *Serratia marcescens* serralysin. *Philipp Sci Lett*, 3, 100-108
- Banks, P., Bartley, W., Birt, L.M., *The Biochemistry of the Tissues*. John&Wiley, London: 1976
- Barreiro-Iglesias, R., Alvarez-Lorenzo, C., Concheiro, A., (2001). Incorporation of small quantities of surfactants as a way to improve the rheological and diffusional behavior of carbopol gels. *J Control Release*, 77, 59-75.
- Barry, B.W., (2001). Novel mechanisms and devices to enable successful transdermal drug delivery. *Eur J Pharm Sci*, 14, 101-114.

- Barry, B.W., Meyer, M.C., (1979). The rheological properties of carbopol gels I. Continuous shear and creep properties of carbopol gels. *Int J Pharm*, 2, 1-25.
- Bashir, S.J., Maibach, H.I., (2001). *In vivo* irritation, in: Barel, A.O., Paye, M., Maibach, H.I. (Eds.), *Handbook of Cosmetic Science and Technology*. Marcel Dekker, Inc., New York.
- Baumann, L.S., Spencer, J., (1999). The effects of topical vitamin E on the cosmetic appearance of scars. *Dermatol Surg*, 25, 311-315.
- Benoit, J., Cormier, M., Wepierre, J., (1987). Effect of proteins on the assessment of surfactant cytotoxicity by an *in vitro* test: Possible correlations with *in vivo* data. *Toxicol In Vitro*, 1, 91-96.
- Benson, H.A., (2005). Transdermal drug delivery: penetration enhancement techniques. *Curr Drug Deliv*, 2, 23-33.
- Benson, H.A.E., Namjoshi, S., (2008). Proteins and peptides: Strategies for delivery to and across the skin. *J Pharm Sci*, 97, 3591-3610.
- Bergh, B.A.I., Wertz, P.W., Junginger, H.E., Bouwstra, J.A., (2001). Elasticity of vesicles assessed by electron spin resonance, electron microscopy and extrusion measurements. *Int J Pharm*, 217, 13-24.
- Betancourt, T., Doiron, A., Homan, K.A., Brannon-Peppas, L., *Controlled release and nanotechnology*. Springer, New York: 2008
- Beurden, P.A.M.S.-v., Hoff, J.W.V.d., (2005). Zymographic techniques for the analysis of matrix metalloproteinases and their inhibitors. *BioTechniques*, 38, 73-83.

- Bonjoch, N.P., Tamayo, P.R., (2001). Protein content quantification by Bradford method, in: Roger, M.J.R. (Ed.), *Handbook of Plant Ecophysiology Techniques*. Kluwer Academic Publishers, United States of America, pp. 283-295.
- Bougatef, A., Nedjar-Arroume, N., Manni, L., Ravellec, R., Barkia, A., Guillochon, D., Nasri, M., (2010). Purification and identification of novel antioxidant peptides from enzymatic hydrolysates of sardinelle (*Sardinella aurita*) by-products proteins. *Food Chem*, 118, 559-565.
- Bouquet, W., Boterberg, T., Ceelen, W., Pattyn, P., Peeters, M., Bracke, M., Remon, J.P., Vervaet, C., (2009). *In vitro* cytotoxicity of paclitaxel/[beta]-cyclodextrin complexes for HIPEC. *Int J Pharm*, 367, 148-154.
- Cao, X., Li, Z., Song, X., Cui, X., Wei, Y., Cheng, F., Wang, J., (2009). Effects of spacers on surface activities and aggregation properties of anionic gemini surfactants. *J Surfactants Deterg*, 12, 165-172.
- Carafa, M., Marianelli, C., Lucania, G., Marchei, E., Santucci, E., (2004). New vesicular ampicillin-loaded delivery systems for topical application: characterization, *in vitro* permeation experiments and antimicrobial activity. *J Control Release*, 95, 67-74.
- Carafa, M., Santucci, E., Lucania, G., (2002). Lidocaine-loaded non-ionic surfactant vesicles: characterization and *in vitro* permeation studies. *Int J Pharm*, 231, 21-32.
- Carmeliet, P., Moons, L., Herbert, J.-M., Crawley, J., Lupu, F., Lijnen, R., Collen, D., (1997). Urokinase but not tissue plasminogen activator mediates arterial neointima formation in mice. *Circ Res*, 81, 829-839.

- Castro, G.A., Ferreira, L.A., (2008). Novel vesicular and particulate drug delivery systems for topical treatment of acne. *Expt Opin Drug Deliv*, 5, 665-679.
- Cevc, G., Mazgareanu, S., Rother, M., Vierl, U., (2008). Occlusion effect on transcutaneous NSAID delivery from conventional and carrier-based formulations. *Int J Pharm*, 359, 190-197.
- Chaiwut, P., Nitsawang, S., Shank, L., Kanasawud, P., (2007). A comparative study on properties and proteolytic components of papaya peel and latex proteases. *Chiang Mai J. Sci.*, 34, 109-118.
- Chen, H., Yang, W., Chen, H., Liu, L., Gao, F., Yang, X., Jiang, Q., Zhang, Q., Wang, Y., (2009). Surface modification of Mitoxantrone-loaded PLGA nanospheres with chitosan. *Colloid Surface B*, 73, 212-218.
- Chen, M., Li, X.-R., Zhou, Y.-X., Yang, K.-W., Chen, X.-W., Deng, Q., Liu, Y., Ren, L.-J., (2009). Improved absorption of salmon calcitonin by ultraflexible liposomes through intranasal delivery. *Peptides*, 30, 1288-1295
- Chen, Y.M., Liu, H.Y., (1972). Studies on stem bromelain and stem starch from pineapple plants. *TAIWANIA*, 17, 266-276.
- Choe, K.P., Strange, K., (2008). Genome-wide RNAi screen and *in vivo* protein aggregation reporters identify degradation of damaged proteins as an essential hypertonic stress response. *Am J Physiol*, 295, C1488-1498.
- Choi, M.J., Maibach, H.I., (2005). Elastic vesicles as topical/transdermal drug delivery systems. *Int J Cosmetic Sci*, 27, 211-221.
- Chrisostomidis, C., Konofaos, P., Chrisostomidis, G., Vasilopoulou, A., Dimitroulis, D., Frangoulis, M., Papadopoulos, O., (1998). Management of external ear keloids using form-pressure therapy. *Clin Exp Dermatol*, 33, 273-275.

- Chuangsuwanich, A., Gunjittisomrarn, S., (2007). The efficacy of 5% imiquimod cream in the prevention of recurrence of excised keloids. *J Med Assoc Thai*, 90, 1363-1367.
- Chukwuemeka, N.O., Anthonia, A.B., (2010). Antifungal effects of pawpaw seed extracts and papain on post harvest *Carica papaya* L. fruit rot. *Afr J Agr Res*, 5, 1531-1535.
- Claessens, M.M.A.E., Leermakers, F.A.M., Hoekstra, F.A., Stuart, M.A.C., (2007). Entropic stabilization and equilibrium size of lipid vesicles. *Langmuir*, 23, 6315-6320
- Cobbold, C.A., (2001). The role of nitric oxide in the formation of keloid and hypertrophic lesions. *Med Hypotheses*, 57, 497-502.
- Cohen-Sela, E., Chorny, M., Koroukhov, N., Danenberg, H.D., Golom, G., (2009). A new double emulsion solvent diffusion technique for encapsulating hydrophilic molecules in PLGA nanoparticles. *J Control Release* 133, 90-95.
- Cornell, M., Pillai, S., Oresajo, C., (2010). Percutaneous delivery of cosmetic actives to the skin, in: Draehos, Z.D. (Ed.), *Cosmetic Dermatology: Products and Procedures*. Wiley-Blackwell, New Jersey, pp. 62-70.
- Cui, F., Shi, K., Zhang, L., Tao, A., Kawashima, Y., (2006). Biodegradable nanoparticles loaded with insulin-phospholipid complex for oral delivery: Preparation, *in vitro* characterization and *in vivo* evaluation. *J Control Release*, 114, 242–250.
- Cui, Z., Mumper, R.J., (2001). Chitosan-based nanoparticles for topical genetic immunization. *J Control Release*, 75, 409-419.

- Daly, T., Golitz, L., Weston, W., (1986). A double-blind placebo-controlled efficacy study of tretinoin cream 0.05% in the treatment of keloids and hypertrophic scars. *J Invest Dermatol*, 86, 470.
- Dani, B.A., DeLuca, P.P., (2001). Preparation, characterization, and *in vivo* evaluation of salmon calcitonin microspheres. *AAPS PharmsciTech*, 2, 1-7.
- Desai, P., Patlolla, R.R., Singh, M., (2010). Interaction of nanoparticles and cell-penetrating peptides with skin for transdermal drug delivery. *Mol Membr Biol*, 27, 247-259.
- Desser, L., Holomanova, D., Zavadova, E., Pavelka, K., Mohr, T., Herbacek, I., (2001). Oral therapy with proteolytic enzymes decreases excessive TGF-beta levels in human blood. *Cancer Chemother Pharmacol*, 47 Suppl, S10-15.
- Devakate, R.V., Patil, V.V., S.S.Waje, Thorat, B.N., (2009). Purification and drying of bromelain. *Sep Purif Technol*, 64, 259-264.
- Doko, M.B., Bassani, V., Casadebaig, J., Cavailles, L., Jacob, M., (1991). Preparation of proteolytic enzyme extracts from *Ananas comosus* L., Merr. fruit juice using semipermeable membrane, ammonium sulfate extraction, centrifugation and freeze-drying processes. *Int J Pharm*, 76, 199-206.
- Domsalla, A., Melzig, M.F., (2008). Occurrence and properties of proteases in plant latices. *Planta Med*, 74, 699-711.
- Draaijers, L.J., Tempelman, F.R.H., Botman, Y.A.M., Tuinebreijer, W.E., Middelkoop, E., Kreis, R.W., Zuijlen, P.P.M.v., (2004). The patient and observer scar assessment scale: A reliable and feasible tool for scar evaluation. *Plast Reconstr Surg*, 113, 1960-1965.

- Draize, J.H., Woodard, G., Calvery, H.O., (1944). Methods for the study of irritation and toxicity of substances applied to the skin and mucous membranes. *J Pharmacol Exp Ther*, 82.
- Du, Q., Liu, C., Wang, X., (2006). Simulating the deformation of vesicle membranes under elastic bending energy in three dimensions. *J Comput Phys* 212 757-777.
- Duangjit, S., Opanasopit, P., Rojanarata, T., Ngawhirunpat, T., (2011). Characterization and *in vitro* skin permeation of meloxicam-loaded liposomes versus transfersomes. *J Drug Deliv*, 2011, 1-9.
- Duncan, J.A., Bond, J.S., Mason, T., Ludlow, A., Cridland, P., O'Kane, S., Ferguson, M.W., (2006). Visual analogue scale scoring and ranking: a suitable and sensitive method for assessing scar quality? *Plast Reconstr Surg*, 118, 909-918.
- Economides, N., koulaouzidou, E.A., Gogos, C., Kolokouris, I., Beltes, P., Antoniades, D., (2008). Comparative study of the cytotoxic effect of resilon against two cell lines. *Braz Dent J*, 19, 291-295.
- El Moussaoui, A., Nijs, M., Paul, C., Wintjens, R., Vincentelli, J., Azarkan, M., Looze, Y., (2001). Revisiting the enzymes stored in the laticifers of *Carica papaya* in the context of their possible participation in the plant defence mechanism. *Cell Mol Life Sci*, 58, 556-570.
- El Zaafarany, G.M., Awad, G.A.S., Holayel, S.M., Mortada, N.D., (2010). Role of edge activators and surface charge in developing ultradeformable vesicles with enhanced skin delivery. *Int J Pharm*, 397, 164-172.

- Elias, R.J., Kellerby, S.S., Decker, E.A., (2008). Antioxidant activity of proteins and peptides. *Food Sci Nutr*, 48, 430-441.
- Engberts, J.B., Kevelam, J., (1996). Formation and stability of micelles and vesicles. *Curr Opin Colloid Interface Sci*, 1, 779-789.
- Epstein, W.L., (2000). Irritation contact dermatitis: House and garden plants. *J Toxicol Cut Ocular Toxicol*, 19, 207-235.
- Ezeoke, A.C., (1985). Hypersensitivity to paw-paw (*Carica papaya*): report of a case. *Afr J Med Med Sci*, 14, 121-124.
- Farahmand, S., Maibach, H.I., (2009). Transdermal drug pharmacokinetics in man: Interindividual variability and partial prediction. *Int J Pharm*, 367, 1-15.
- Florence, A.T., Attwood, D., *Physicochemical Principles of Pharmacy* Fourth ed. Pharmaceutical Press, UK: 2006
- Francica, J.R., Varela-Rohena, A., Medvec, A., Plesa, G., Riley, J.L., Bates, P., (2010). Steric shielding of surface epitopes and impaired immune recognition induced by the Ebola virus glycoprotein. *PLoS Pathog*, 6, 1-13.
- Fujiwara, M., Muragaki, Y., Ooshima, A., (2005). Keloid-derived fibroblasts show increased secretion of factors involved in collagen turnover and depend on matrix metalloproteinase for migration. *Br J Dermatol*, 153, 295-300.
- Fustier, P., Taherian, A.R., Ramaswamy, H.S., (2010). Emulsion delivery systems for functional foods, in: Smith, J., Charter, E. (Eds.), *Functional Food Product Development*. Blackwell Publishing, Singapore.
- Gajjara, L., Benford, D.J., (1990). Comparison of cultured keratinocytes and fibroblasts as models for irritancy testing *in vitro*. *Toxicol In Vitro*, 4, 280-283

- Galindo-Rodriguez, S., Allémann, E., Fessi, H., Doelker, E., (2004). Physicochemical parameters associated with nanoparticle formation in the salting-out, emulsification-diffusion, and nanoprecipitation methods. *Pharmaceut Res*, 21, 1428-1439.
- Gallarate, M., Chirio, D., Trotta, M., Carlotti, M.E., (2006). Deformable liposomes as topical formulations containing α -tocopherol. *J Disper Sci Technol*, 27, 703-713.
- Gao, W.-P., Bai, Y., Chen, E.-Q., Li, Z.-C., Han, B.-Y., Yang, W.-T., Zhou, Q.-F., (2006). Controlling vesicle formation via interpolymer hydrogen-bonding complexation between poly(ethylene oxide)-block-polybutadiene and poly(acrylic acid) in solution. *Macromolecules*, 39, 4894-4898.
- Gautam, S.S., Mishra, S.K., Dash, V., Goyal, A.K., Rath, G., (2010). Comparative study of extraction, purification and estimation of bromelain from stem and fruit of pineapple plant. *Thai J Pharm Sci*, 34, 67-76.
- Geesink, G.H., Koohmaraie, M., (2000). Ionic strength-induced inactivation of mu-calpain in postmortem muscle. *J Anim Sci*, 78, 2336-2343.
- Genno, M., Yamamoto, R., Kojima, H., Kinishi, H., Klausner, M., (1998). Evaluation of a new alternative to primary Draize skin irritation testing using the EpiDermTM skin model. *Altern Animal Test Experiment*, 5, 195-200.
- Gerze, A., Omay, D., Guvenilir, Y., (2005). Partial purification and characterization of protease enzyme from *Bacillus subtilis megatherium*. *Appl Biochem Biotech*, 121, 335-345.

- Ghahary, A., Shen, Q., Rogers, J.A., Wang, R., Fathi-Afshar, A., Scott, P.G., Tredget, E.E., (1997). Liposome-associated interferon-alpha-2b functions as an anti-fibrogenic factor for human dermal fibroblasts. *J Invest Dermatol*, 109, 55-60.
- Ghahary, A., Shen, Y.J., Nedelec, B., Wang, R., Scott, P.G., Tredget, E.E., (1996). Collagenase production is lower in post-burn hypertrophic scar fibroblasts than in normal fibroblasts and is reduced by insulin-like growth factor-1. *J Invest Dermatol*, 106, 476-481.
- Gibson, N., Shenderova, O., Luo, T.J.M., Moseenkov, S., Bondar, V., Puzyr, A., Purtov, K., Fitzgerald, Z., Brenner, D.W., (2009). Colloidal stability of modified nanodiamond particles. *Diam Relat Mater*, 18, 620-626.
- Glavas-Dodov, M., Goracinova, K., Mladenovska, K., Fredro-Kumbaradzi, E., (2002). Release profile of lidocaine HCl from topical liposomal gel formulation. *Int J Pharm*, 242, 381-384.
- Gulatia, M., Grover, M., Singh, S., Singh, M., (1998). Lipophilic drug derivatives in liposomes. *Int J Pharm*, 165, 129-168.
- Gurung, S., Škalko-Basnet, N., (2009). Wound healing properties of *Carica papaya* latex: *In vivo* evaluation in mice burn model. *J Ethnopharmacol*, 121, 338-341.
- Guterres, S.S., Alves, M.P., Pohlmann, A.R., (2007). Polymeric nanoparticles, nanospheres and nanocapsules, for cutaneous applications. *Drug Target Insights*, 2, 147-157.

- Haas, K., Blom, C., Ende, D.v.d., Duits, M., Haveman, B., Mellema, J., (1997). Rheological behavior of a dispersion of small lipid bilayer vesicles. *Langmuir*, 1, 6658-6668.
- Haiwei, R., (2010). Antioxidant and free radical-scavenging activities of black soybean peptides (BSP). *Int J Agric Biol Eng*, 3, 64-69.
- Hale, L.P., Greer, P.K., Trinh, C.T., James, C.L., (2005). Proteinase activity and stability of natural bromelain preparations. *Int Immunopharmacol*, 5, 783-793.
- Ham, S.W., Kang, M.J., Park, Y.M., Oh, I.Y., Bo Gyun Kim, Im, T.J., Kim, S.H., Choi, Y.W., Lee, J., (2007). Transdermal penetration of synthetic peptides and their penetration enhancement caused by some terpene compounds. *Bul. Korean Chem Soc*, 28, 1535-1538.
- Hamed Mosavian, M.T., Hassan, A., (2010). Making oil-in-water emulsions by ultrasound and stability evaluation using taguchi method. *J Disper Sci Technol*, 31, 293-298.
- Han, B., Goeger, D., Maier, C.S., Gerwick, W.H., (2005). The wewakpeptins, cyclic depsipeptides from a Papua New Guinea collection of the marine cyanobacterium *Lyngbya semiplena*. *J Org Chem*, 70, 3133-3139.
- Han, Y., Tian, H., He, P., Chen, X., Jing, X., (2009). Insulin nanoparticle preparation and encapsulation into poly(lactic-co-glycolic acid) microspheres by using an anhydrous system. *Int J Pharm*, 378, 159-166.
- Hanachi, P., Golkho, S., (2009). Using HPLC to determination the composition and antioxidant activity of *Berberis Vulgaris*. *Eur J Sci Res*, 29, 47-54.

- Haq, I.U., Mukhtar, H., Umber, H., (2006). Production of protease by *Penicillium chrysogenum* through optimization of environmental conditions. *J Agric Soc Sci*, 2, 1813-2235.
- Har-Shai, Y., Amar, M., Sabo, E., (2003). Intralesional cryotherapy for enhancing the involution of hypertrophic scars and keloids. *Plast Reconstr Surg*, 111, 1841-1852.
- Harunari, N., Zhu, K.Q., Armendariz, R.T., Deubner, H., Muangman, P., Carrougher, G.J., Isik, F.F., Gibran, N.S., Engrav, L.H., (2006). Histology of the thick scar on the female, red Duroc pig: Final similarities to human hypertrophic scar. *Burns*, 32, 669-677.
- Hashim, F., El-Ridy, M., Nasr, M., Abdallah, Y., (2010). Preparation and characterization of niosomes containing ribavirin for liver targeting. *Drug Deliv*, 17, 282-282.
- Hashimoto, A., Takeuti, Y., Kawahara, Y., Yasumoto, K., (1991). Proteinase and collagenase activities in ginger rhizome. *J Jpn Soc Nutr Food Sci*, 44, 127-132.
- Hayet, B.K., Rym, N., Ali, B., Sofiane, G., Moncef, N., (2011). Low molecular weight serine protease from the viscera of sardinelle (*Sardinella aurita*) with collagenolytic activity: Purification and characterisation. *Food Chem*, 124, 788-794.
- Hoek, J.B., Cahill, A., Pastorino, J.G., (2002). Alcohol and mitochondria: A dysfunctional relationship. *Gastroenterology*, 122, 2049-2063.

- Honda, K., Okamoto, K., Mochida, Y., Ishioka, K., Oka, M., Maesato, K., Ikee, R., Moriya, H., Hidaka, S., Ohtake, T., Doi, K., Fujita, T., Kobayashi, S., Noiri, E., (2011). A novel mechanism in maggot debridement therapy: protease in excretion/secretion promotes hepatocyte growth factor production. *Am J Physiol Cell Physiol*, 301, C1423-C1430.
- Hosnute, M., Payasli, C., Isikdemir, A., Tekerekoglu, B., (2007). The effects of onion extract on hypertrophic and keloid scars. *J Wound Care*, 16, 251-254.
- Hou, D.Z., Liu, C.K., Ping, Q.N., Liang, X.H., (2007). The entrapped efficiency of BSA liposome. *Yao Xue Xue Bao*, 42, 545-549.
- Hsieh, P.W., Chang, F.R., Wu, C.C., Li, C.M., Wu, K.Y., Chen, S.L., Yen, H.F., Wu, Y.C., (2005). Longicalycinin A, a new cytotoxic cyclic peptide from Dianthus superbus var. longicalycinus (MAXIM.) WILL. *Chem Pharm Bull (Tokyo)*, 53, 336-338.
- Hu, W., Wang, A.-M., Wu, S.-Y., Zhang, B., Liu, S., Gou, Y.-B., Wang, J.-M., (2011). Debriding effect of bromelain on firearm wounds in pigs. *J Trauma*, 71, 966-972.
- Huang, P.-J., Huang, Y.-C., Su, M.-F., Yang, T.-Y., Huang, J.-R., Jiang, C.-P., (2007). *In vitro* observations on the influence of copper peptide aids for the LED Photoirradiation of fibroblast collagen synthesis. *Photomed Laser Surg*, 25, 183-190.
- Jain, G.K., Pathan, S.A., Akhter, S., Ahmad, N., Jain, N., Talegaonkar, S., Khar, R.K., Ahmad, F.J., (2010). Mechanistic study of hydrolytic erosion and drug release behaviour of PLGA nanoparticles: Influence of chitosan. *Polym Degrad Stabil*, 95, 2360-2366.

Jain, S., Tiwary, A.K., Sapra, B., Jain, N.K., (2007). Formulation and Evaluation of Ethosomes for Transdermal Delivery of Lamivudine. *AAPS PharmSciTech* 8, E1-E9.

Jang, J.Y., Kwon, B.S., Lee, H.E., Kim, D.H., Kang, H.K., Kang, J.S., Lee, S., Choi, G.J., (2007). Preparation of biodegradable PLGA nanospheres employing a fast solvent evaporationmethod. *J Ind Eng Chem*, 13, 1043-1046.

Je, J.-Y., Qian, Z.-J., Byun, H.-G., Kim, S.-K., (2007). Purification and characterization of an antioxidant peptide obtained from tuna backbone protein by enzymatic hydrolysis. *Process Biochem*, 42, 840-846.

Jin-Chao, W., Guang-Rong, H., Miao, Y., Yong-Hua, T., (2011). Preparation of angiotensin converting enzyme (ACE) inhibitory peptides from silver carp (*Hypophthalmichthys molitrix*), International Conference on Human Health and Biomedical Engineering, Jilin, China, pp. 856-859.

Jun, S.-Y., Park, P.-J., Jung, W.-K., Kim, S.-K., (2006). Purification and characterization of antioxidative peptide derived from muscle of conger eel (*Conger myriaster*). *Eur Food Res Technol*, 222, 310-315.

Kakar, A.K., Shahzad, M., Haroon, T.S., (2006). Keloids: clinical features and management. *J Pak Assoc Dermatol*, 16, 97-103.

Kamkaen, N., Phuntuwate, W., Samee, W., Boonrod, A., Treesak, C., (2007). The investigation of the rabbit and human skin irritation of herbal anti-wrinkle cream. *Thai Pharmaceutical and Health Science Journal*, 2, 21-25.

- Katayama, K., Anggraeni, H.E., Mori, T., Ahhmed, A.M., Kawahara, S., Sugiyama, M., Nakayama, T., Maruyama, M., Muguruma, M., (2008). Porcine skeletal muscle troponin is a good source of peptides with Angiotensin-I converting enzyme inhibitory activity and antihypertensive effects in spontaneously hypertensive rats. *J Agric Food Chem*, 56, 355-360.
- Kaur, N., Puri, R., Jain, S.K., (2010). Drug-cyclodextrin-vesicles dual carrier approach for skin targeting of anti-acne agent. *AAPS PharmSciTech*, 11, 528-537.
- Kawase, N., Kishi, J., Nakamura, H., Hayakawa, T., (2010). Collagenolytic activity in sonic extracts of *Tannerella forsythia*. *Arch Oral Biol*, 55, 545-549.
- Kawashima, Y., Yamamoto, H., Takeuchi, H., Fujioka, S., Hino, T., (1999). Pulmonary delivery of insulin with nebulized -lactide/glycolide copolymer (PLGA) nanospheres to prolong hypoglycemic effect. *J Control Release*, 62, 279-287.
- Kawashima, Y., Yamamoto, H., Takeuchi, H., Hino, T., Niwa, T., (1998). Properties of a peptide containing dl-lactide/glycolide copolymer nanospheres prepared by novel emulsion solvent diffusion methods. *Eur J Pharm Biopharm*, 45, 41-48.
- Keepers, Y.P., Pizao, P.E., Peters, G.J., van Ark-Otte, J., Winograd, B., Pinedo, H.M., (1991). Comparison of the sulforhodamine B protein and tetrazolium (MTT) assays for *in vitro* chemosensitivity testing. *Eur J Cancer*, 27, 897-900.
- Ketnawa, S., Chaiwut, P., Rawdkuen, S., (2011). Aqueous two-phase extraction of bromelain from pineapple peels ('Phu Lae' cultv.) and its biochemical properties. *Food Sci Biotechnol*, 20, 1219-1226.

- Kim, E.-K., Lee, W.-B., Moon, S.-H., Jeon, Y.-J., Ahn, C.-B., Kim, B., Kim, B.-H., Park, P.-J., Jeon, B.-T., (2009a). Free radical scavenging activity by ESR spectroscopy and neuroprotective effect on H₂O₂-induced damage in PC-12 cells of enzymatic extract from Korean elk velvet antler. *J Food Biochem*, 33, 895-912.
- Kim, H., Taub, I.A., (1991). Specific degradation of myosin in meat by bromelain. *Food Chem*, 40.
- Kim, J.-Y., Kim, J.-K., Park, J.-S., Byun, Y., Kim, C.-K., (2009b). The use of PEGylated liposomes to prolong circulation lifetimes of tissue plasminogen activator. *Biomaterials*, 30, 5751–5756.
- Kim, J.-Y., Yang, H.-J., Kim, K.-S., Chung, Y.-B., (2005). Partial characterization of a 29 kDa cysteine protease purified from *Taenia solium* metacestodes. *Korean J Parasitol*, 43, 157-160.
- Kim, S., Kim, Y., Kim, J.E., Cho, K.H., Chung, J.H., (2008). Berberine inhibits TPA-induced MMP-9 and IL-6 expression in normal human keratinocytes. *Phytomedicine*, 15, 340-347.
- Kim, S.-K., Park, P.-J., Kim, J.-B., Shahidi, F., (2002). Purification and characterization of a collagenolytic protease from the filefish, *Novodon modestrus*. *J Biochem Mol Biol*, 35, 165-171.
- Kim, S.-Y., Je, J.-Y., Kim, S.-K., (2008). Purification and characterization of antioxidant peptide from hoki (*Johnius belengerii*) frame protein by gastrointestinal digestion. *J Nutr Biochem*, 18, 31-38.
- Kleiner, D.E., Stetler-Stevenson, W.G., (1994). Quantitative zymography: detection of picogram quantities of gelatinases. *Anal Biochem*, 218, 325-329.

- Kloeters, O., Tandara, A., Mustoe, T.A., (2007). Hypertrophic scar model in the rabbit ear: a reproducible model for studying scar tissue behavior with new observations on silicone gel sheeting for scar reduction. *Wound Repair Regen*, 15, S40-45.
- Kobayashi, T., Hattori, S., Shinkai, H., (2003). Matrix metalloproteinases-2 and -9 are secreted from human fibroblasts. *Acta Derm Venereol*, 83, 105-107.
- Kojic, Z., Stojanovic, D., Popadic, S., Jokanovic, M., Janackovic, D., (2009). The irritative property of alpha-tricalcium phosphate to the rabbit skin. *Gen Physiol Biophys*, 28 Spec No, 168-173.
- Kolhatkar, R., Kitchens, K., Swaan, P., Ghandehari, H., (2007). Surface Acetylation of Polyamidoamine (PAMAM) Dendrimers Decreases Cytotoxicity while Maintaining Membrane Permeability. *Bioconjugate Chem*, 18, 2054-2060.
- Kongsuwan, A., Suthiluk, P., Theppakorn, T., Srilaong, V., Setha, S., (2009). Bioactive compounds and antioxidant capacities of Phulae and Nanglae pineapple. *As. J. Food Ag-Ind.*, 2, S44-S50.
- Krieger, Y., Bogdanov-Berezovsky, A., Gurfinkel, R., Silberstein, E., Sagi, A., Rosenberg, L., (2012). Efficacy of enzymatic debridement of deeply burned hands. *Burns*, 38, 108-112.
- Kumar, A.B.V., Varadaraj, M.C., Gowda, L.R., Tharanathan, R.N., (2005). Characterization of chito-oligosaccharides prepared by chitosanolysis with the aid of papain and Pronase, and their bactericidal action against *Bacillus cereus* and *Escherichia coli*. *Biochem J*, 391, 167-175.

- Kumar, B., Jain, S.K., Prajapati, S.K., (2011). Effect of penetration enhancer DMSO on *in vitro* skin permeation of acyclovir transdermal microemulsion formulation. *Int J Drug Deliv*, 3, 83-94.
- Lee, E.H., Kim, A., Oh, Y.-K., Kim, C.-K., (2005a). Effect of edge activators on the formation and transfection efficiency of ultradeformable liposomes. *Biomaterials*, 26, 205-210.
- Lee, J.P., Jalili, R.B., Tredget, E.E., Demare, J.R., Ghahary, A., (2005b). Antifibrogenic effects of liposome-encapsulated IFN- α 2b cream on skin wounds in a fibrotic rabbit ear model. *J Interferon Cytokine Res*, 25, 627-631.
- Lee, S.-J., Oh, P.-S., Ko, J.-H., Lim, K.-T., Lim, K., (2006). Protective effect of glycoprotein isolated from *Ulmus davidiana* Nakai on carbon tetrachloride-induced mouse liver injury. *J Pharm Pharmacol*, 58, 143-152.
- Lin, H., Gebhardt, M., Bian, S., Kwon, K.A., Shim, C.-K., Chung, S.-J., Kima, D.-D., (2007). Enhancing effect of surfactants on fexofenadine-HCl transport across the human nasal epithelial cell monolayer. *Int J Pharm*, 330, 23-31.
- Liu, J., Gong, T., Wang, C., Zhong, Z., Zhang, Z., (2007a). Solid lipid nanoparticles loaded with insulin by sodium cholate-phosphatidylcholine-based mixed micelles: Preparation and characterization. *Int J Pharm*, 340, 153-162.
- Liu, J., Zhang, S.M., Chen, P.P., Cheng, L., Zhou, W., Tang, W.X., Chen, Z.W., Ke, C.M., (2007b). Controlled release of insulin from PLGA nanoparticles embedded within PVA hydrogels. *J Mater Sci Mater Med*, 18, 2205-2210.

- Liu, S., Ruibao Zhou, R., Shaojun Tian, S., Junyi Gai, J., (2007c). A study on subunit groups of soybean protein extracts under SDS-PAGE. *J Am Oil Chem Soc*, 89, 793-801.
- Liu, Z., Xiao, H., (2000). Soap-free emulsion copolymerisation of styrene with cationic monomer: effect of ethanol as a cosolvent. *Polymer*, 41, 7023-7031.
- Loan Honeywell-Nguyen, P., de Graaff, A.M., Wouter Groenink, H.W., Bouwstra, J.A., (2002). The *in vivo* and *in vitro* interactions of elastic and rigid vesicles with human skin. *Biochim Biophys Acta*, 1573, 130-140.
- Locatelli, M., Gindro, R., Travaglia, F., Coissson, J.-D., Rinaldi, M., Arlorio, M., (2009). Study of the DPPH-scavenging activity: Development of a free software for the correct interpretation of data. *Food Chem*, 114, 889-897.
- Lopes, P.S., Ruas, G.W., Baby, A.R., Sales, C.A., Pinto, D.O., Watanabe, I.S., Velasco, M.V.R., Kaneko, T.M., (2008). *In vitro* safety assessment of papain on human skin: A qualitative Light and Transmission Electron Microscopy (TEM) study. *Brazilian J Pharm Sci*, 44, 151-156.
- Maestrelli, F., González-Rodríguez, M.L., Rabasco, A.M., Muraa, P., (2006). Effect of preparation technique on the properties of liposomes encapsulating ketoprofen-cyclodextrin complexes aimed for transdermal delivery. *Int J Pharm*, 312, 53-60.
- Maghraby, G.M.M.E., Williams, A.C., Barry, B.W., (2000). Oestradiol skin delivery from ultradeformable liposomes: refinement of surfactant concentration. *Int J Pharm*, 196, 63-74.

- Mahmood, A., Raja, G.K., Mahmood, T., Gulfraz, M., Khanum1, A., (2012). Isolation and characterization of antimicrobial activity conferring component(s) from seeds of bitter gourd (*Momordica charantia*). *J Med Plants Res*, 6, 566-573.
- Mahmood, A.A., Sidik, K., Salmah, I., (2005). Wound healing activity of *Carica papaya* L. aqueous leaf extract in rats. *Int J Mol Med Adv Sci*, 1, 398-401.
- Mainardes, R.M., Evangelista, R.C., (2005). PLGA nanoparticles containing praziquantel: effect of formulation variables on size distribution. *Int J Pharm*, 290, 137-144.
- Majid, F.A.A., Gani, M.A., Talib, S.Z., Hasyim, K.K., (2008). Stability of bromelain-polyphenol complex in pineapple juice. *Jurnal Teknologi*, 49, 27-38.
- Malaekeh-Nikouei, B., Tabassi, S.A.S., Jaafari, M.R., Davies, N.M., (2005). Preparation and characterization of PLGA microspheres loaded by cyclosporine-cyclodextrin complex. *Iran J Pharma Sci*, 1, 195-201.
- Manosroi, A., Chankhampan, C., Manosroi, W., Manosroi, J., (2012a). Enhancement of chemical stability and transdermal absorption of salmon calcitonin loaded in elastic niosomes. *Adv Sci Lett*, 5, 314-319.
- Manosroi, A., Chankhampan, C., Manosroi, W., Manosroi, J., (2012b). Toxicity reduction and MMP-2 stimulation of papain and bromelain loaded in elastic niosomes. *J Biomed Nanotech*, in press.
- Manosroi, A., Chankhampan, C., Ofoghi, H., Manosroi, W., Manosroi, J., (2011a). Low cytotoxic elastic niosomes loaded with salmon calcitonin on human skin fibroblasts. *Hum Exp Toxicol*, in press.

- Manosroi, A., Jantrawut, P., Akihisa, T., Manosroi, W., Manosroi, J., (2011b). *In vitro* and *in vivo* skin anti-aging evaluation of gel containing niosomes loaded with a semi-purified fraction containing gallic acid from *Terminalia chebula* galls. *Pharm Biol*, 49, 1190-1203.
- Manosroi, A., Jantrawut, P., Akihisa, T., Manosroi, W., Manosroi, J., (2010a). *In vitro* anti-aging activities of *Terminalia chebula* gall extract. *Pharm Biol*, 48, 469-481.
- Manosroi, A., Jantrawut, P., Manosroi, J., (2008). Anti-inflammatory activity of gel containing novel elastic niosomes entrapped with diclofenac diethylammonium. *Int J Pharm*, 360, 156-163.
- Manosroi, A., Khanrin, P., Lohcharoenkal, W., Werner, R.G., Götz, F., Manosroi, W., Manosroi, J., (2010b). Transdermal absorption enhancement through rat skin of gallidermin loaded in niosomes. *Int J Pharm*, 392, 304-310.
- Manosroi, A., Khanrin, P., Werner, R.G., Götz, F., Manosroi, W., Manosroi, J., (2010c). Entrapment enhancement of peptide drugs in niosomes. *J Microencapsul*, 27, 272-280.
- Manosroi, A., Khositsuntiwong, N., Götz, F., Werner, R.G., Manosroi, J., (2009). Transdermal enhancement through rat skin of luciferase plasmid DNA entrapped in elastic nanovesicles. *J Liposome Res*, 19, 91-98.
- Manosroi, A., Podjanasoothon, K., Manosroi, J., (2002). Stability and release of topical tranexamic acid liposome formulations. *J Soc Cosmet Chem*, 53, 375-386.

- Manosroi, A., Ruksiriwanich, W., Abe, M., Sakai, H., Manosroi, W., Manosroi, J., (2010d). Biological activities of the rice bran extract and physical characteristics of its entrapment in niosomes by supercritical carbon dioxide fluid. *J Supercrit Fluids*, 54, 137-144.
- Manosroi, J., Khositsuntiwong, N., Manosroi, W., Götz, F., Werner, R.G., Manosroi, A., (2010e). Enhancement of transdermal absorption, gene expression and stability of tyrosinase plasmid (pMEL34)-loaded elastic cationic niosomes: Potential application in vitiligo treatment. *J Pharm Sci*, 99, 3533-3541.
- Manosroi, J., Lohcharoenkal, W., Friedrich Götz, Werner, R.G., Manosroi, W., Manosroi, A., (2011c). Transdermal absorption enhancement of N-Terminal Tat-GFP fusion protein (TG) loaded in novel low-toxic elastic anionic niosomes. *J Pharm Sci*, 100, 1525-1534.
- Manuskiatti, W., Fitzpatrick, R.E., (2002). Treatment response of keloidal and hypertrophic sternotomy scars: comparison among intralesional corticosteroid, 5-fluorouracil, and 585-nm flashlamp-pumped pulsed-dye laser treatments. *Arch Dermatol*, 138, 1149-1155.
- Masdor, N.A., Said, N.A.M., (2011). Partial purification of crude stem bromelain improves its sensitivity as a protease inhibitive assay for heavy metals. *Aust J Basic Appl Sci*, 5, 1295-1298.
- Matsumoto, A., Matsukawa, Y., Suzuki, T., Yoshino, H., (2005). Drug release characteristics of multi-reservoir type microspheres with poly(dl-lactide-co-glycolide) and poly(dl-lactide). *J Control Release*, 106, 172-180.
- Maurer, H.R., (2001). Bromelain: biochemistry, pharmacology and medical use. *Cell. Mol Life Sci*, 58, 1234-1245.

- Maurya, S.D., Aggarwal, S., Tilak, V.K., Dhakar, R.C., Singh, A., Maurya, G., (2010). Enhanced transdermal delivery of indinavir sulfate via transfersomes. *Int J Compr pharm*, 1, 1-7.
- Meenakshi, J., Jayaraman, V., Ramakrishnan, K.M., Babu, M., (2005). Ultrastructural differentiation of abnormal scars. *Ann Burns Fire Disasters*, 13, 83-88.
- Meleleo, D., Gallucci, E., Picciarelli, V., Micelli, S., (2007). Acetyl-[Asn30,Tyr32]-calcitonin fragment 8-32 forms channels in phospholipid planar lipid membranes. *Eur Biophys J*, 36, 763–770.
- Miyajima, M., Koshika, A., Okada, J.i., Ikeda, M., Nishimura, K., (1997). Effect of polymer crystallinity on papaverine release from poly (l-lactic acid) matrix. *J Control Release*, 49, 207-215.
- Moreno, J.J., (2000). Arachidonic acid release and prostaglandin E2 synthesis as irritant index of surfactants in 3T6 fibroblast cultures. *Toxicology*, 143, 275-282.
- Morrow, D.I.J., McCarron, P.A., Woolfson, A.D., Donnelly, R.F., (2007). Innovative strategies for enhancing topical and transdermal drug delivery. *The Open Drug Delivery Journal*, 1, 36-59.
- Mukerjee, A., Vishwanatha, J.K., (2009). Formulation, characterization and evaluation of curcumin-loaded PLGA nanospheres for cancer therapy. *Anticancer Res*, 29, 3867-3875
- Mulinacci, F., Poirier, E., Capelle, M.A.H., Gurny, R., Arvinte, T., (2011). Enhanced physical stability of human calcitonin after methionine oxidation. *Eur J Pharm Biopharm*, 78(2), 229-238.

- Müller-Goymann, C.C., (2004). Physicochemical characterization of colloidal drug delivery systems such as reverse micelles, vesicles, liquid crystals and nanoparticles for topical administration. *Eur J Pharm Biopharm*, 58, 343-356.
- Muneuchi, G., Suzuki, S., Onodera, M., Ito, O., Hata, Y., Igawa, H.H., (2006). Long-term outcome of intralesional injection of triamcinolone acetonide for the treatment of keloid scars in Asian patients. *Scand J Plast Reconstr Surg Hand Surg*, 40, 111-116
- Mustoe, T.A., Cooter, R.D., Gold, M.H., Hobbs, F.D., Ramelet, A.A., Shakespeare, P.G., Stella, M., Teot, L., Wood, F.M., Ziegler, U.E., (2002). International clinical recommendations on scar management. *Plast Reconstr Surg*, 110, 560-571.
- Mutalik, S., (2005). Treatment of keloids and hypertrophic scars. *Indian J Dermatol Venereol Leprol*, 71, 1-6.
- Muthu, M.S., (2009). Nanoparticles based on PLGA and its co-polymer: An overview. *Asian J Pharm*, 3, 266-273.
- Myint, S., Daud, W.R.W., Mohamad, A.B., Kadhum, A.A.H., (1995). Separation and identification of eugenol in ethanol extract of cloves by reversed-phase high-performance liquid chromatography *J Am Oil Chem Soc*, 72, 1231-1233.
- Naeini, F., Najafian, J., Ahmadpour, K., (2006). Bleomycin tattooing as a promising therapeutic modality in large keloids and hypertrophic scars. *Dermatol Surg*, 32, 1023-1030.

- Nakauchi, T., Ando, A., Ueda-Yamada, M., Yamazaki, Y., Uyama, M., Matsumura, M., Ito, S., (2003). Prevention of ornithine cytotoxicity by nonpolar side chain amino acids in retinal pigment epithelial cells. *Invest Ophth Vis Sci*, 44, 5023-5028.
- Nanda, S., Reddy, B.S.N., (2004). Intralesional 5-fluorouracil as a treatment modality of keloids. *Dermatol Surg*, 30, 54-57.
- Nayak, B.s., Pereira, L.P., Maharaj, D., (2007). Wound healing activity of *Carica papaya* L. in experimentally induced diabetic rats. *Indian J Exp Biol*, 45, 739-743.
- Neuman, M.G., Haber, J.A., Malkiewicz, I.M., Cameron, R.G., Katz, G.G., Shear, N.H., (2002). Ethanol signals for apoptosis in cultured skin cells. *Alcohol*, 26, 179-190.
- Nitsawang, S., Hatti-Kaul, R., Kanasawud, P., (2006). Purification of papain from Carica papaya latex: Aqueous two-phase extraction versus two-step salt precipitation. *Enzyme Microb Tech*, 39, 1103-1107.
- Niwa, T., Takeuchi, H., Hino, T., Kawashima, Y., (1995). Stabilization of lactide:glycolide copolymer (PLGA) nanospheres with peptide-drug by freeze-drying. *Yakuzaigaku*, 55, 167–174.
- Niwa, T., Takeuchi, H., Hino, T., Kunou, N., Kawashima, Y., (1994). *In vitro* drug release behavior of D, L-lactide/glycolide copolymer (PLGA) nanospheres with nafarelin acetate prepared by a novel spontaneous emulsification solvent diffusion method. *J Pharm Sci*, 83, 727-732.

- Nobmann, U., Connah, M., Fish, B., Varley, P., Gee, C., Mulot, S., Chen, J., Zhou, L., Lu, Y., Sheng, F., Yi, J., Harding, S.E., (2007). Dynamic light scattering as a relative tool for assessing the molecular integrity and stability of monoclonal antibodies. *Biotechnol Genet Eng*, 24, 117-128.
- Norris, J.R., Ribbons, D.W., *Methods in Microbiology*. Academic press Inc., New York: 1970
- Nutan, M.T.H., Reddy, I.K., (2009). General principles of suspension, in: Kulshreshtha, A.K., Singh, O.N., Wall, G.M. (Eds.), *Pharmaceutical Suspensions*. Springer, London.
- Ogawa, R., Mitsuhashi, K., Hyakusoku, H., Miyashita, T., (2003). Postoperative electron-beam irradiation therapy for keloids and hypertrophic scars: Retrospective study of 147 cases followed for more than 18 Months. *Plast Reconstr Surg*, 111, 547-553.
- Özkan, A., Gübbük, H., Güneş, E., Erdoğan, A., (2011). Antioxidant capacity of juice from different papaya (*Carica papaya L.*) cultivars grown under greenhouse conditions in Turkey. *Turk J Biol*, 35, 619-625.
- Papazisis, K.T., Geromichalos, G.D., Dimitriadis, K.A., Kortsaris, A.H., (1997). Optimization of the sulforhodamine B colorimetric assay. *J Immunol Methods*, 208, 151-158.
- Pardakhty, A., Moazeni, E., Varshosaz, J., Hajhashemi, V., Najafabadi, A.R., (2011). Pharmacokinetic study of niosome-loaded insulin in diabetic rats. *DARU J Pharm Sci*, 19, 404-411.

- Park, P.-J., Lee, S.-H., Byun, H.-G., Kim, S.-H., Kim, S.-K., (2002). Purification and characterization of a collagenase from the Mackerel, *Scomber japonicus*. *J Biochem Mol Biol*, 35, 576-582.
- Peltonen, L., Aitta, J., Hyvönen, S., Karjalainen, M., Hirvonen, J., (2004). Improved Entrapment Efficiency of Hydrophilic Drug Substance During Nanoprecipitation of Poly(l)actide Nanoparticles. *AAPS PharmSciTech*, 5, 1-6.
- Peltonen, L., Koistinen, P., Karjalainen, M., Hakkinen, A., Hirvonen, J., (2002). The effect of cosolvents on the formulation of nanoparticles from low-molecular-weight poly(l)actide. *AAPS PharmSciTech*, 3, E32.
- Pendzhiev, A.M., (2002). Proteolytic enzymes of papaya: Medicinal applications. *Pharm Chem J*, 36, 315-317.
- Pereira-Lachataignerais, J., Pons, R., Panizza, P., Courbin, L., Rouch, J., López, O., (2006). Study and formation of vesicle systems with low polydispersity index by ultrasound method. *Chem Phys Lipids*, 140, 88-97.
- Philips, N., Auler, S., Hugo, R., Gonzalez, S., (2010). Beneficial regulation of matrix metalloproteinases for skin health. *Enzyme Res*, 2011, 1-4.
- Pirvu, C.D., Hlevca, C., Ortan, A., Prisada, R., (2010). Elastic vesicles as drugs carriers through the skin. *Farmacia*, 58, 128-135.
- Polaina, J., MacCabe, A.P., *Industrial Enzymes: Structure, Function and Applications*. Springer, The Netherlands: 2007
- Pople, P., Singh, K., (2006). Development and evaluation of topical formulation containing solid lipid nanoparticles of vitamin A. *AAPS PharmSciTech*, 7, E63-E69.

- Pozzi, D., Caminiti, R., Marianecchi, C., Carafa, M., Santucci, E., Sanctis, S.C.D., Caracciolo, G., (2009). Effect of cholesterol on the formation and hydration behavior of solid-supported niosomal membranes. *Langmuir*, 26, 2268-2273.
- Prakash, A., (2001). The BP and EP Microbial Limit Test, in: Clontz, L. (Ed.), *Microbial Limit and Bioburden Tests: Validation Approaches and Global Requirements*. CRC press, Boston.
- Qi, L.F., Xu, Z.R., Li, Y., Jiang, X., Han, X.Y., (2005). *In vitro* effects of chitosan nanoparticles on proliferation of human gastric carcinoma cell line MGC803 cells. *World J Gastroenterol*, 11, 5136-5141.
- Rahimnejad, M., Mokhtarian, N., Ghasemi, M., (2009). Production of protein nanoparticles for food and drug delivery system. *Afr J Biotechnol*, 8, 4738-4743.
- Ravindra Babu, B., Rastogi , N.K., Raghavarao, K.S., (2008). Liquid-liquid extraction of bromelain and polyphenol oxidase using aqueous two-phase system. *Chem Eng Process*, 47, 83-89.
- Reis, C.P., Neufeld, R.J., Ribeiro, A.n.J., Veiga, F., (2006). Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles. *Nanomed Nanotechnol Biol Med*, 2, 8-21.
- Rhee, G.J., Woo, J.S., Hwang, S.-J., Lee, Y.W., Lee, C.H., (1999). Topical oleo-hydrogel preparation of ketoprofen with enhanced skin permeability. *Drug Dev Ind Pharm*, 25, 717-726.
- Rhett, J.M., Ghatnekar, G.S., Joseph A. Palatinus1, O'Quinn, M., Yost, M.J., Gourdie, R.G., (2008). Novel therapies for scar reduction and regenerative healing of skin wounds. *Trends Biotechnol*, 26,

- Rieux, A.d., Fievez, V., Garinot, M., Schneider, Y.-J., Préat, V., (2006). Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach. *J Control Release*, 116, 1-27.
- Roslan, N.Z.I., Aziz, A.A., Sarmidi, M.R., Azizb, R.A., (2010). Anti-oxidant coated liposome as the delivery system for papain based natural cosmetics, International Conference on Enabling Science and Nanotechnology (ESciNano), Kuala Lumpur, Malaysia.
- Rudenskaya, G.N., Isaev, V.A., Shmojlov, A.M., Karabasova, M.A., Shvets, S.V., Miroshnikov, A.I., Brusov, A.B., (2000). Preparation of proteolytic enzymes from Kamchatka crab *Paralithodes camchatica* hepatopancreas and their application. *Appl Biochem Biotechnol*, 88, 175-183.
- Ruel-Gariépy, E., Leclair, G., Hildgen, P., Gupta, A., Leroux, J.C., (2002). Thermosensitive chitosan-based hydrogel containing liposomes for the delivery of hydrophilic molecules. *J Control Release*, 82, 373-383.
- Rungprom, W., Siwu, E.R.O., Lambert, L.K., Dechsakulwatana, C., Barden, M.C., Kokpol, U., Blanchfield, J.T., Kita, M., Garson, M.J., (2008). Cyclic tetrapeptides from marine bacteria associated with the seaweed *Diginea* sp. and the sponge *Halisarca ectofibrosa*. *Tetrahedron*, 64, 3147-3152.
- Sabeh, F., Li, X.Y., Saunders, T.L., Rowe, R.G., Weiss, S.J., (2009). Secreted versus membrane-anchored collagenases: relative roles in fibroblast-dependent collagenolysis and invasion. *J Biol Chem*, 284, 23001-23011.

- Sairi, M., Yih, L.J., Sarmidi, M.R., (2004). Chemical composition and sensory analysis of fresh pineapple juice and deacidified pineapple juice using electrodialysis, Regional Symposium on Membrane Science and Technology Puteri Pan Pacific Hotel, Johor Bahru, Johor, Malaysia.
- Salata, O., (2004). Applications of nanoparticles in biology and medicine. *J Nanobiotechnology*, 2, 1-6.
- Sangthong, S., Pintathong, P., Rawdkuen, S., Chaiwut, P., (2011). Pineapple waste as a potential source for bromelain extraction, 37th Congress on Science and Technology of Thailand, Centara Grand & Bangkok Convention Centre, Central World, Bangkok, Thailand.
- Santucci, M., Borgognoni, L., Reali, U.M., Gabbiani, G., (2001). Keloids and hypertrophic scars of Caucasians show distinctive morphologic and immunophenotypic profiles. *Virchows Arch*, 438, 457-463.
- Sargeant, J.G., Bowie, H.M., Billington, M.J., (1993). Determination of papain in raw meat by immunoassay. *Meat Sci*, 34, 39-47.
- Saulis, A.S., Chao, J.D., Telser, A., Mogford, J.E., Mustoe, T.A., (2002a). Silicone occlusive treatment of hypertrophic scar in the rabbit model. *Aest Surg J*, 22, 147-153.
- Saulis, A.S., Moqford, J.H., Mustoe, T.A., (2002b). Effect of Mederma on hypertrophic scarring in the rabbit ear model. *Plast Reconstr Surg*, 110(1), 177-186.
- Sharma, M., Sharma, V., Panda, A.K., Majumdar, D.K., (2011). Enteric microsphere formulations of papain for oral delivery. *Yakugaku Zasshi*, 131, 697-709.

- Shoaib, M.H., Tazeen, J., Merchant, H.A., Yousuf, R.I., (2006). Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. *Pak J Pharm Sci*, 19, 119-124.
- Siengdee, P., Nganvongpanit, K., Pothacharoen, P., Chomdej, S., Mekchay, S., Ong-Chai, S., (2010). Effects of bromelain on cellular characteristics and expression of selected genes in canine *in vitro* chondrocyte culture. *Veterinarni Medicina*, 55, 551-560.
- Sigurjónsdóttir, J.F., Loftsson, T., Másson, M., (1999). Influence of cyclodextrins on the stability of the peptide salmon calcitonin in aqueous solution. *Int J Pharm*, 186, 205-213
- Sim, Y.-C., Lee, S.-G., Lee, D.-C., Kang, B.-Y., Park, K.-M., Lee, J.-Y., Kim, M.-S., Chang, I.-S., Rhee, J.-S., (2000). Stabilization of papain and lysozyme for application to cosmetic products. *Biotechnol Lett*, 22, 137-140.
- Singh, M.P., Stefko, J., Lumpkin, J.A., Rosenblatt, J., (1995). The effect of electrostatic charge interactions on release rates of gentamicin from collagen matrices. *Pharm Res*, 12, 1205-1210.
- Smith, P.T., JR, A.D.G., Odman, N., (1993). Isolation and characterization of urease from *Aspergillus niger*. *J Gen Microbiol*, 139, 957-962.
- Soares, P., Coelho, D., Mazzola, P., Silveira, E., Graças, M.d., Carneiro-da-Cunha, Jr., A.P., Tambourgi, E., (2011). Studies on bromelain precipitation by ethanol, poly (ethylene glycol) and ammonium sulphate. *Chem Eng T*, 24, 979-984.
- Sternlicht, M.D., Werb, Z., (2001). How matrix metalloproteinases regulate cell behavior. *Annu Rev Cell Dev Biol*, 17, 463-516.

- Sudjarwo, S.A., (2005). Anti-inflammatory and analgesic effect of bromelain in mice and rats. *Universa Medicina*, 24, 155-160.
- Suetsuna, K., Chen, J.-R., (2002). Isolation and characterization of peptides with antioxidant activity derived from wheat gluten. *Food Sci Technol Res*, 8, 227-230.
- Sun, X., Duan, T.-R., He, Q., Lu, J., Zhang, Z.-R., (2005). PELGE nanoparticles as new carriers for the delivery of plasmid DNA. *Chem Pharm Bull*, 53, 599-603.
- Tahara, K., Sakai, T., Yamamoto, H., Takeuchi, H., Hirashima, N., Kawashima, Y., (2009). Improved cellular uptake of chitosan-modified PLGA nanospheres by A549 cells. *Int J Pharm*, 382, 198-204.
- Tang, Y., Singh, J., (2010). Thermosensitive drug delivery system of salmon calcitonin: *In vitro* release, *in vivo* absorption, bioactivity and therapeutic efficacie. *Pharm Res*, 27, 272-284.
- Tasset, C., Barette, N., Thysman, S., Ketelslegers, J.M., Lemoine, D., Prat, V., (1995). Polyisobutylcyanoacrylate nanoparticles as sustained release system for calcitonin. *J Control Release*, 33, 23-30.
- Thompson, E.H., Wolf, I.D., Allen, C.E., (1973). Ginger rhizome: A new source of proteolytic enzyme. *J Food Sci*, 38, 652-655.
- Thurmond, R.L., Goran Lindblom, Brown, M.F., (1991). Effect of bile salts on monolayer curvature of a phosphatidylethanolamine/water model membrane system. *Biophys J*, 60, 728-732.
- Tochi, B.N., Wang, Z., Xu, S.-Y., Zhang, W., (2008). Therapeutic Application of Pineapple Protease (Bromelain): A Review. *Pak J Nutr*, 7, 513-520.

- Tollefson, T.T., Kamangar, F., Aminpour, S., Lee, A., Durbin-Johnson, B., Tinling, S., (2012). Comparison of effectiveness of silicone gel sheeting with microporous paper tape in the prevention of hypertrophic scarring in a rabbit model. *Arch Facial Plast Surg*, 14, 45-51.
- Touitou, E., Dayan, N., Bergelson, L., Godin, B., Eliaz, M., (2000). Ethosomes-novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. *J Control Release*, 65, 403-418.
- Tredget, E.E., Shankowsky, H.A., Pannu, R., Nedelec, B., Iwashina, T., Ghahary, A., Taerum, T.V., Scott, P.G., (1998). Transforming growth factor-beta in thermally injured patients with hypertrophic scars: effects of interferon alpha-2b. *Plast Reconstr Surg*, 102, 1317-1330.
- Tréhin, R., Krauss, U., Muff, R., Meinecke, M., Beck-Sickinger, A., Merkle, H., (2004). Cellular internalization of human calcitonin derived peptides in MDCK monolayers: a comparative study with Tat(47-57) and penetratin(43-58). *Pharm Res*, 21, 33-42.
- Triglia, D., Braa, S.S., Yonan, C., Naughton, G.K., (1991). *In vitro* toxicity of various classes of test agents using the neutral red assay on a human three-dimensional physiologic skin model. *In Vitro Cell Dev Biol*, 27, 239-244.
- Uchegbu, I.F., Vyas, S.P., (1998). Non-ionic surfactant based vesicles (niosomes) in drug delivery. *Int J Pharm*, 172, 33-70.
- Udenigwe, C.C., Aluko, R.E., (2011). Chemometric analysis of the amino acid requirements of antioxidant food protein hydrolysates. *Int J Mol Sci*, 12, 3148-3161.

- Uhumwangho, M.U., Okor, R.S., (2005). Current trends in the production and biomedical applications of liposomes: A review. *J Biomed Sci*, 4, 9-21.
- Umbach, W., *Cosmetics and Toiletries: Development, Production and Use* Ellis Horwood Ltd., London: 1991.
- Verma, D.D., Fahr, A., (2004). Synergistic penetration enhancement effect of ethanol and phospholipids on the topical delivery of cyclosporin A. *J Control Release*, 97, 55-66.
- Vichai, V., Kirtikara, K., (2006). Sulforhodamine B colorimetric assay for cytotoxicity screening. *Nat Protoc*, 1, 1112-1116.
- Vilaa, A., Sánchez, A., Tobío, M., Calvoa, P., Alonso, M.J., (2002). Design of biodegradable particles for protein delivery *J Control Release*, 78, 15-24.
- Vinardell, M.P., Mitjans, M., (2008). Alternative methods for eye and skin irritation tests: An overview. *J Pharm Sci*, 97, 46-59.
- Wagh, V.D., Deshmukh, O.J., (2010). Niosomes as ophthalmic drug delivery systems: A review. *J Pharm Res*, 3, 1558-1563.
- Wagner, K., Beck-Sickinger, A.G., Huster, D., (2004). Structural investigations of a human calcitonin-derived carrier peptide in a membrane environment by solid-state NMR. *Biochemistry*, 43, 12459-12468.
- Wan, K.C., Evans, J.H., (1999). Free radical involvement in hypertrophic scar formation. *Free Radical Bio Med*, 26, 603-608.
- Wang, A.C., (1988). Molecular basis for cryoprecipitation. *Springer Semin Immunopathol*, 10, 21-31.

- Wei, Y.-J., Yan, X.-Q., Ma, L., Wu, J.-G., Zhang, H., Qin, L.-P., (2011). Oleanolic acid inhibits hypertrophic scarring in the rabbit ear model. *Clin Exp Dermatol*, 36, 528-533.
- Wellisch, G., Cohen, E., Cahane, Z., Horowitz, J., (1984). Simple method for collagenase determination in 38 *Pseudomonas aeruginosa* strains. *J Clin Microbiol*, 20, 1020-1021.
- Werb, Z., Aggeler, J., (1978). Proteases induce secretion of collagenase and plasminogen activator by fibroblasts. *Proc Nati Acad Sci*, 75, 1839-1843.
- Williams, A., *Transdermal and Topical Drug Delivery from Theory to Clinical Practice*. Pharmaceutical Press, USA: 2003
- Wo, Y., Zhang, Z., Zhang, Y., Wang, D., Pu, Z., Su, W., Qian, Y., Li, Y., Cui, D., (2011). Preparation of ethosomes and deformable liposomes encapsulated with 5-fluorouracil and their investigation of permeability and retention in hypertrophic scar. *J Nanosci Nanotechnol*, 11, 7840-7847.
- Wu, H.-C., Chen, H.-M., Shiau, C.-Y., (2003). Free amino acids and peptides as related to antioxidant properties in protein hydrolysates of mackerel (*Scomber austriasicus*). *Food Res Int*, 36, 949-957.
- Wu, J., Wei, X., Wu, Z., Li, S., (2002). An observation of the morphology and the degradation of hypertrophic scar collagen. *Zhonghua Shao Shang Za Zhi*, 18, 296-298.
- Xu, X., Chen, X., Ma, P.a., Wangc, X., Jinga, X., (2008). The release behavior of doxorubicin hydrochloride from medicated fibers prepared by emulsion-electrospinning. *Eur J Pharm Biopharm*, 70, 165-170.

- Xu, X., Chen, X., Wang, Z., Jing, X., (2009). Ultrafine PEG-PLA fibers loaded with both paclitaxel and doxorubicin hydrochloride and their *in vitro* cytotoxicity. *Eur J Pharm Biopharm*, 72, 18-25.
- Xu, X., Chen, X., Xu, X., Lu, T., Wang, X., Yang, L., Jing, X., (2006). BCNU-loaded PEG-PLLA ultrafine fibers and their *in vitro* antitumor activity against Glioma C6 cells. *J Control Release*, 114, 307-316.
- Yang, Y.-Y., Chung, T.-S., Ng, N.P., (2001). Morphology, drug distribution, and *in vitro* release profiles of biodegradable polymeric microspheres containing protein fabricated by double-emulsion solvent extraction/evaporation method. *Biomaterials*, 22, 231-241.
- Yin, J., Noda, Y., Yotsuyanagi, T., (2006). Properties of poly(lactic-co-glycolic acid) nanospheres containing protease inhibitors: Camostat mesilate and nafamostat mesilate. *Int J Pharm*, 314, 46-55.
- Yoshioka, T., Sternberg, B., Moody, M., Florence, A.T., (1992). Niosomes from Span surfactants: Relations between structure and form. *J Pharm Pharmcol Supp*, 44, 1044.
- Yue, P.-F., Lu, X.-Y., Zhang, Z.-Z., Yuan, H.-L., Zhu, W.-F., Zheng, Q., Yang, M., (2009). The study on the entrapment efficiency and *in vitro* release of puerarin submicron emulsion. *AAPS PharmSciTech*, 10, 376-383.
- Zaafarany, G.M.E., Awad, G.A.S., Holayel, S.M., Mortada, N.D., (2010). Role of edge activators and surface charge in developing ultradeformable vesicles with enhanced skin delivery. *Int J Pharm*, 397, 164-172.

- Zhang, J., Zhang, H., Wang, L., Guo, X., Wang, X., Yao, H., (2009). Antioxidant activities of the rice endosperm protein hydrolysate:identification of the active peptide. *Eur Food Res Technol*, 229, 709-719.
- Zhang, Z., Wo, Y., Zhang, Y., Wang, D., He, R., Chen, H., Cui, D., (2012). *In vitro* study of ethosome penetration in human skin and hypertrophic scar tissue. *Nanomed. Nanotechnol Biol Med*, in press.
- Zhilaltsev, I., Maurer, N., Akhong, Q., Leone, R., E, E.L., Wang, J., Semple, S., Cullis, P., (2005). Liposome-encapsulated vincristine, vinblastine and vinorelbine: A comparative study of drug loading and retention. *J Control Release*, 104, 103-111.
- Zhu, K.Q., Carrougher, G.J., Gibran, N.S., F. Frank Isik, Engrav, L.H., (2007). Review of the female Duroc/Yorkshire pig model of human fibroproliferative scarring. *Wound Repair Regen*, 15, S32-S39.
- Zurada, J.M., Kriegel, D., Davis, I.C., (2006). Topical treatments for hypertrophic scars. *J Am Acad Dermatol*, 55, 1024-1031.