

DAFTAR PUSTAKA

1. Harris M, Zimmet P. Classification of Diabetes Mellitus and Other Categories of Glucose Intolerance. 2nd ed. Chichester: Wiley; 1997. 9-23.
2. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels: International Diabetes Federation; 2013. 23,34.
3. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the Year 2000 and Projections for 2030. *Diabetes Care*. 2004; 27(5): 1047-1053.
4. Milner B, Marc J, Janez A, Pfeifer M. Molecular Mechanisms of Insulin Resistance and Associated Diseases. *Clin Chim Acta*. 2007; 375(1-2): 20-35.
5. Jung UJ, Lee MK, Jeong KS, Choi MS. The Hypoglycemic Effects of Hesperidin and Naringin are Partly Mediated by Hepatic Glucose-Regulating Enzymes in C57BL/KsJ-db/db Mice. *J Nutr*. 2004; 134(10): 2499-2503.
6. Ahmed OM, Ayman MM, Adel AM, Mohamed BA. Antidiabetic Effects of Hesperidin and Naringin in Type 2 Diabetic Rats. *Diabetol Croat*. 2012; 41(2): 53-67.
7. Garg A, Garg S, Zaneveld LJ, Singla AK. Chemistry and Pharmacology of The Citrus Bioflavonoid Hesperidin, Review Article. *Phytother Res*. 2001; 15(8): 655-669.
8. Sansone F, Alessandra R, Pasquale DG, Francesco DS, Rita PA, Maria RL. Hesperidin Gastroresistant Microparticles by Spray-Drying: Preparation, Characterization, and Dissolution Profiles. *AAPS PharmSciTech*. 2009; 10(2): 391-401.
9. Majumdar S, Srirangam R. Solubility, Stability, Physicochemical Characteristics and In Vitro Ocular Tissue Permeability of Hesperidin : A Natural Bioflavonoid. *Pharm Res*. 2009; 26(5): 1217-1225.
10. Serra H, Mendes T, Bronze MR, Simplicio AL. Prediction of Intestinal Absorption and Metabolism of Pharmacologically Active Flavones and Flavonones. *Bioorg Med Chem*. 2008; 16(7): 4009-4018.

11. Sarmento, B, A. Riberio, F. Veiga, P. Sampaio, R. Neufeld, D. Ferreira. Alginate/Chitosan Nanoparticles are Effective for Oral Insulin Delivery. *Pharm Res.* 2007; 24(12): 2198-2206.
12. Marschütz MK, Caliceti P, Bernkop-Schnürch A. Oral Peptide Drug Delivery: Polymer-Inhibitor Conjugates Protecting Insulin from Enzymatic Degradation In Vitro. *Biomaterials*, 2000; 21(14): 1499-1507.
13. Liu L, Sheardown H. Glucose Permeable Poly(Dimethyl Siloxane) Poly (N-Isopropyl Acrylamide) Network Polymers as Ophthalmic *Biomaterials*. *Biomaterials*, 2005; 26(3): 233-244.
14. Zhang XZ, Wu DQ, Chu CC. Synthesis, Characterization and Controlled Drug Release of Thermosensitive IPN-PNIPAAm Hydrogels. *Biomaterials*, 2004; 25(17): 3793-3805.
15. Thirawong N, Thongborisute J, Takeuchi H, Sriamornsak P. Improved Intestinal Absorption of Calcitonin by Mucoadhesive Delivery of Novel Pectin-Liposome Nanocomplexes. *J Control Release*. 2008; 125(3): 236-245.
16. Han HK, Shin HJ, Ha DH. Improved Oral Bioavailability of Alendronate Via the Mucoadhesive Liposomal Delivery System. *Eur J Pharm Sci.* 2012; 46(5): 500-507.
17. Narayanan RP, Melman G, Letourneau NJ, Mendelson NL, Melman A. Photodegradable Iron (III) Cross-Linked Alginate Gels. *Biomacromolecules*. 2012; 13(8): 2465–2471.
18. Skjåk-Bræk G, Grasdalen, H.; Smidsrød, O. Inhomogeneous Polysaccharide Ionic Gels. *Carbohydr Polym.* 1989; 10(1): 31–54.
19. Ghosal, K., Ray, S.D. Alginate/Hydrophobic HPMN (60M) Particulate Systems : New Matrix for Site-Specific and Controlled Drug Delivery. *Braz J Pharm Sci.* 2011; 47(4): 833-844.
20. Karewicz A, Zasada K, Bielska D, Douglas TE, Jansen JA, Leeuwenburgh SC, Nowakowska M. Alginate-Hydroxy Propyl Cellulose Hydrogel Microbeads for Alkaline Phosphatase Encapsulation. *J Microencapsul.* 2014; 31(1): 68-76.

21. Hua S, Ma H, Li X, Yang H, Wang A. pH-Sensitive Sodium Alginate/Poly(Vinyl Alcohol) Hydrogel Beads Prepared by Combined Ca^{2+} Crosslinking and Freeze-Thawing Cycles for Controlled Release of Diclofenac Sodium. *Int J Biol Macromol.* 2010; 46(5): 517-523.
22. Jao WC, Chen HC, Lin CH, Yang MC. The Controlled Release Behavior and pH and Thermo-Sensitivity of Alginate/ Poly(Vinyl Alcohol) Blended Hydrogels. *Polym Adv Technol.* 2009; 20(8): 680–668.
23. Rajendran A., Basu SK. Alginate-Chitosan Particulate System for Sustained Release of Nimodipine. *Trop J Pharm Res.* 2009; 8(5): 433-440.
24. Wittaya-Areekul S, Kruenate J, Prahsarn C. Preparation and In Vitro Evaluation of Mucoadhesive Properties of Alginate/Chitosan Microparticles Containing Prednisolone. *Int J Pharm.* 2006; 312(1-2): 113-118.
25. Gupta P, Vermani K, Garg S. Hydrogels : Form Controlled Release to pH-Responsive Drug Delivery. *Drug Discov Today.* 2002; 15,7(10): 569-579.
26. Déat-Lainé E, Valérie H, Ghislain G, Jean-Francois J, Jean-Michel C, Muriel S, Eric B. Efficacy of Mucoadhesive Hydrogel Microparticles of Whye Protein and Alginate for Oral Insulin Delivery. *Pharm Res.* 2013; 30(3): 721-734.
27. Taberner TS, Martín-Villodre A, Pla-Delfina JM, Herráez JV. Consistency of Carbopol 971-P NF Gels and Influence of Soluble and Cross-Linked PVP. *Int J Pharm.* 2002; 233(1-2): 43–50.
28. Dogra S. A Chitosan-Polymer Hydrogel Bead System For A Metformin HCl Controlled Release Oral Dosage Form. *Thesis.* The University of Toledo. 2011. 18, 66.
29. Srilatha D, Nasare M, Nagasandhya B, Prasad V, Diwan P. Development and Validation of UV Spectrophotometric Method for Simultaneous Estimation of Hesperidin and Diosmin in the Pharmaceutical Dosage Form. *ISRN Spectroscopy.* 2013; 1(1): 1-4.
30. Kuntić V, Pejić N, Mićić S. Direct Spectrophotometric Determination of Hesperidin in Pharmaceutical Preparations. *Acta Chim Slov.* 2012; 59(2): 436-441.

31. Evans WC. Trease and Evans' Pharmacognosy. 15th ed. Edinburgh: W.B. Saunders; 2002. 246.
32. Barthe GA, Jourdan PS, McIntosh CA, Mansell RL. Radioimmunoassay for the Quantitative Determination of Hesperidin and Analysis of Its Distribution in Citrus sinensis. *Phytochemistry*. 1988; 27(1): 249-254.
33. Preston RK, Avakian S, Beiler JM, Moss JN, Martin GJ. In-Vivo and In-Vitro Inhibition of Hyaluronidase by Organic Phosphates. *Exp Med Surg*. 1953; 11(1): 1-8.
34. Budavari S. The Merck Index. New Jersey: Merck and Co, Inc. 1996.
35. Higby RH. The Chemical Nature of Hesperidin and Its Experimental Medicinal Use as a Source of Vitamin-P. Review Article. *J Am Pharm Assoc Sci*. 1941; 30(12): 629-635.
36. King FE, Robertson A. Natural Glucosides. *J Chem Soc*. 1931; 2: 1704-1709.
37. Kim M, Kometani T, Okada S, Shimuzu M. Permeation of Hesperidin Glycosides Across Caco-2 Cell Monolayers Via the Paracellular Pathway. *Biosci Biotechnol Biochem*. 1999; 63(12): 2183-2188.
38. Booth AN, Jones FT, DeEds F. Metabolic Fate of Hesperidin, Eriodictyol, Homoeriodictyol and Diosmin. *J Biol Chem*. 1958; 230(2): 661-668.
39. Meyer OC. 1994. Safety and Security of Daflon-500 mg in Venous Insufficiency and in Haemorrhoids Disease. *Angiology*. 1994; 45(6): 579-584.
40. Tanaka Y, Gong JP, Osada Y. Novel Hydrogels with Excellent Mechanism Performance. *Prog Polym Sci*. 2005; 30(1): 1-9.
41. Eposito E, Carotta V, Scabbitta A. Cutaneous and Transdermal Delivery: Processes and System of Delivery. USA: Marcel Dekker. 1996.
42. Hoare, TR, Kohane DS. Hydrogels in Drug Delivery: Progress and Challenges. *Polymer*. 2008; 49(8); 1993-2007.
43. Peppas NA, Huang Y, Torres-Lugo M, Ward JH, Zhang J. Physicochemical, Foundations and Structural Design of Hydrogels in Medicine and Biology. *Annu Rev Biomed Eng*. 2000; 2: 9-29.

44. Chen L, Tian Z, Du Y. Synthesis and pH Sensitivity of Carboxymethyl Chitosan-Based Polyampholyte Hydrogels for Protein Carrier Matrices. *Biomaterials*. 2004; 25(17): 3725-3732.
45. Li Q, Wang J, Shahani S, Sun DDN, Sharma B, Elisseeff JH, Leong KW. Biodegradable and Photocrosslinkable Polyphosphoester Hydrogel. *Biomaterials*. 2006; 27(17): 1027-1034.
46. Barbucci R. Hydrogels: Biological Properties and Application. Milan: Springer; 2009.
47. Zarzycki R, Modrzejewska Z, Nawrotek K. Drug Release From Hydrogel Matrices. *Eco Chem Eng*. 2010; 17(2): 117-136.
48. Hennink WE, Nostrum CFV. Novel Crosslinking Methods to Design Hydrogels. *Adv Drug Deliv Rev*. 2002; 54(1): 13-36.
49. Barbucci R, Leone G, Vecchiullo A. Novel Carboxymethylcellulose-Based Microporous Hydrogels Suitable for Drug Delivery. *J Biomater Sci Polym Ed*. 2004; 15(5): 607-619.
50. Fei B, Wach RA, Mitomo H, Yoshii F, Kume T. Hydrogel of Biodegradable Cellulose Derivatives. *J Appl Polym Sci*. 2000; 78(2): 278-283.
51. Liu P, Peng J, Li J, Wu J. Radiation Crosslinking of CMC-Na at Low Dose and Its Application as Substitute for Hydrogel. *Radiat Phys Chem*. 2002; 72(5): 635-638.
52. Said HM, Alla SGA, El-Naggar AWM. Synthesis and Characterization of Novel Gels Based on Carboxymethyl Cellulose/Acrylic Acid Prepared by Electron Beam Irradiation. *React Func Polym*. 2004; 61(3): 397-404.
53. Peppas NA. Physiologically Responsive Gels. *J Bioac Compat Polym*. 1991; 6(3): 241-246.
54. He, H. Multifnctional Medical Device Based on pH-Sensitive Hydrogels for Controlled Drug Delivery. *Dissertation*. The Ohio State University. 2006. 8-10, 38,39, 56.
55. Hariharan D, Peppas NA. Characterization, Dynamic Swelling Behavior and Solute Transport in Cationic Networks with Application to the Development of Swelling-Controlled Release Systems. *Polymer*. 1996; 37(1): 149-158.

56. Tangri P, Madhav NVS. Oral Mucoadhesive Drug Delivery System. Review Article. *Intr J Biopharm.* 2011; 2(1): 36-46.
57. Grabovac V, Guggi D, Bernkop-Schnurch A. Mucoadhesive Polymers: Strategies, Achievements and Future Challenges. *Adv Drug Deliv Rev.* 2005; 57(11): 1713–1723.
58. Rajput GC, Majmudar FD, Patel JK, Patel KN, Thakor RS, Patel BP, Rajgor NB. Stomach Spesific Mucoadhesive Tablet as Controlled Drug Delivery System, Review Article. *Int. J Pharm Bio Res.* 2010; 1(1): 30-41.
59. Akiyama Y, Lueben HL, de Boer AG, Verhoef JC, Junginger HE. Novel Peroral Dosage Form with Protease Inhibitory Activities. II. Design of Fast Dissolving Poly(Acrylate) and Controlled Drug Releasing Capsule Formulation with Trypsin Inhibiting Properties. *Int J Pharm.* 1996; 138(1): 13-23.
60. Ramadas M, Paul W, Dileep KJ, Anitha Y, Sharma CP. Lipoinulin Encapsulated Alginate-Chitosan Capsule: Intestinal Delivery in Diabetic Rats. *J Microencapsul.* 2000; 17(4): 405-411.
61. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 6th ed. London: Pharmaceutical Press; 2009. 89-90, 159-161, 622-624.
62. Vennat B, Lardy F, Arvouet-Grand A, Pourrat A. Comparative Texturometric Analysis of Hydrogels Based on Cellulose Derivatives, Carragenates, and Alginates: Evaluation of Adhesiveness. *Drug Dev Ind Pharm.* 1998; 24(1): 27–35.
63. Tonnesen HH, Karlsen J. Alginate in Drug Delivery Systems. *Drug Dev Ind Pharm.* 2002; 28(6): 621–630.
64. Holte Ø, Onsøyen E, Myrvold R, Karlsen J. Sustained Release of Water-Soluble Drug from Directly Compressed Alginate. *Eur J Pharm Sci.* 2003; 20(4–5): 403–407.
65. Stevens MM, Qanadilo HF, Langer R, Shastri, VP. A Rapid-Curing Alginate Gel System: Utility in Periosteum-Derived Cartilage Tissue Engineering. *Biomaterials.* 2004; (25): 887–894.

66. Kuo CK, Ma PX. Ionically Crosslinked Alginate Hydrogels as Scaffolds for Tissue Engineering: Part 1. Structure, Gelation Rate and Mechanical Properties. *Biomaterials* 2001; 22(6): 511–521.
67. Yogeshkumar NG, Gurav AS, Yadav AV. Chitosan and Its Application, Review Article. *Int J Res Pharm Bio.* 2013; 4(1): 312-331.
68. Li Q, Dunn ET, Grandmaison EW, Goosen MFA. Application and Properties of Chitosan. *J Bioact Compat Polym.* 1992; 7(4): 370–397.
69. He P, Stanley SD, Lisbeth I. In Vitro Evaluation of the Mucoadhesive Properties of Chitosan Microspheres. *Int J Pharm.* 1998; 166(1): 75–88.
70. Artursson P, Lindmark T, Davis SS, Illum L. Effect of Chitosan on the Permeability of Monolayers of Intestinal Epithelial Cells (Caco-2). *Pharm Res.* 1994; 11(9): 1358–1361.
71. Kuo CK, Ma PX. Maintaining Dimensions and Mechanical Properties of Ionically Crosslinked Alginate Hydrogel Scaffolds In Vitro. *J Biomed Mater Res.* 2007; 84(4): 899-907.
72. Simpson NE, Stabler CL, Sambanis A, Constantinidis I. The Role of the CaCl₂-Guluronic Acid Interaction on Alginate Encapsulated bTC3 Cells. *Biomaterials.* 2004; 25(13): 2603-2610.
73. Todd RG, Wade A. The Pharmaceutical Codex. 11th ed. London : Pharmaceutical Press; 1979. 125.
74. Montgomery DG. Design and Analysis of Experiments. 5th ed. New York: Wiley; 2001. 170-107.
75. Caze J. Erwing's Analytical Instrumentation Handbook. 3rd ed. New York: Marcel Dekker; 2005. 127-139.
76. Orchin M, Macomber RS, Pinhas AR, Wison RM. The Vocabulary and Concepts of Organic Chemistry. 2nd ed. New York: Wiley; 2005. 725.
77. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A Clinical Prospective on Mucoadhesive Buccal Drug Delivery Systems. *J Biomed Res.* 2014; 28(2): 81-97.

78. Ramasamy N, Gopal V. Characteristic Features of Polymers Used Mucoadhesive Buccal Delivery. *Int J Bio Pharm Res.* 2013; 4(12): 1165-1170.
79. Dolatabdi-Farahani T, Ebrahim VF, Hamid M. Swelling Behaviour of Alginate-N,O-Carboxymethyl Chitosan Gel Beads Coated by Chitosan. *Iran Polym J.* 2006; 15(5): 405-415.
80. Abu-Jdayil B, Fara DA. Modification of the Rheological Behaviour of Sodium Alginate by Chitosan and Multivalent Electrolytes. *Ital J Food Sci.* 2013; 25(2): 196-201.
81. Honary S, Maleki M, Karami M. The Effect of Chitosan Molecular Weight on the Properties of Alginate/Chitosan Microparticles Containing Prendisolone. *Trop J Pharm Res.* 2009; 8(1): 53-61.
82. Hyunh-Ba K. Handbook of Stability Testing in Pharmaceutical Development: Regulation, Methodologies, and Best Practice. Newark : Springer; 2008. 167.
83. Jahari B, Rafie F, Davaran S. Preparation and Characterization of a Novel Smart Polymeric Hydrogel for Drug Delivery of Insulin. *Bioimpacts.* 2011; 1(2): 135-143.
84. El-Leithy ES, Shaker DS, Ghobrab MK, Abdel-Rashid RS. Evaluation of Mucoadhesive Hydrogels Loaded with Diclofenac Sodium-Chitosan Microsphere for Rectal Administration. *AAPS PharmSciTech.* 2010; 11(4): 1695-1702.
85. Pratima NA, Shailee T, Smrutigandha K. Mucoadhesive : As Oral Controlled Gastroretentive Drug Delivery System, Review Article. *Int J Res Pharm Sci.* 2012; 2(3): 32-59.
86. Lin YH, Liang HF, Chung CK, Chen MC, Sung HW. Physically Crosslinked Alginate/N,O-Carboxymethyl Chitosan Hydrogels with Calcium for Oral Delivery of Protein Drugs. *Biomaterials.* 2005; 26(14): 2105-2113.
87. Morsch YA, Donati I, Strand BL, Skjak-Braek G. Effect of Ca^{2+} , Ba^{2+} , and Sr^{2+} on Alginate Microbeads. *Biomacromolecules.* 2006; 7(1): 1471-1480

88. Sahasthian T, Praphairaksit N, Muangsin N. Mucoadhesive and Floating Chitosan-coated Alginate Beads for the Controlles Gastric Release of Amoxicillin. *Arch Pharm Res.* 2010; 33(6): 889-899.
89. Motwari SK, Chopra S, Talegaonkar S, Kohli K, Ahmed FJ, Khar RK. Chitosan-Sodium Alginate Nanoparticles as Submicroscopic Reservoirs for Ocular Delivery: Formulation, Optimisation and *In Vitro* Characterisation. *Eur J Pharm Biopharm.* 2008; 68(1): 513-525.
90. Takka S, Gürel A. Evaluation of Chitosan/Alginate Beads Using Experimental Design: Formulation and *In Vitro* Characterization. *AAPS PharmSciTech.* 2010; 2(1): 460-466.
91. El-Rasoul SA, Ahmed MM. Chitosan Polymer as a Coat of Calcium Alginate Microcapsules loaded by Non-Steroidal Anti-Inflammatory Drug. *Bull Pharm Sci.* 2010; 33(2): 179-186.
92. Hoffman AS. Hydrogels for Biomedical Application, Review Article. *Adv Drug Deliv.* 2002; 43(5): 3-12.
93. Meng X, Li P, Wei Q, Zhang HX. pH Sensitive Alginate-Chitosan Hydrogel Beads for Carvedilol Delivery. *Pharm Dev Tech.* 2011; 16(1): 22-28.
94. Pasparakis G, Bouropoulos N. Swelling Studies and In Vitro Release of Verapamil From Calcium Alginate and Calcium-Chitosan Beads. *Int J Pharm.* 2006; 323(3): 34-42.
95. Colinet I, Dulong V, Mocanu G, Picton L, Cerf DL. Effect of Chitosan Coating on the Swelling and Controlled Release of a Porrly Water-Soluble Drug From an Amphiphilic and pH-Sensitive Hydrogel. *Int J Bio Macro.* 2010; 47(201): 120-125.
96. Tavakol M, Vasheghani-Farahani E, Hashemi-Najafabadi S. The Effect of Polymer and CaCl_2 Concentrations on the Sulfazalazine Release from Alginate-N,O-Carboxymethyl Chitosan Beads. *Biomaterials.* 2013; 17(5): 2-10.
97. Bajpai SK, Sharma S. Investigation of Swelling with Ca^{2+} and Ba^{2+} Ions. *React Funct Polym.* 2004; 59(16): 129-140.

98. Bajpai SK, Tankhiwale R. Investigation of Water Uptake Behavior and Stability of Calcium Alginate/Chitosan Bi-Polymeric Beads: Part-1. *React Funct Polym.* 2006; 66(25): 645-658.
99. Kim WT, Chung H, Shin IS, Yam, KL, Chung DH. Characterization of Calcium Alginate and Chitosan-Treated Calcium Alginate Gel Beads Entrapping Allyl Isothiocyanate. *Carbohydr Polym.* 2007; 71(2008): 566-573.
100. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. *In Vitro* Evaluation of Mucoadhesive Properties of Chitosan and Some Other Natural Polymers. *Int J Pharm.* 1992; 78(1): 43-48.
101. He P, Davis SS, Illum L. *In Vitro* Evaluation of the Mucoadhesive Properties of Chitosan Microspheres. *Int J Pharm.* 1998; 166(1): 75-88.
102. Deacon MP, Davis SS, White RJ, Nordman H, Carlstedt I, Errington N, et.al. Are Chitosan-Mucin Interactions Specific to Different Regions of the Stomach? Velocity Ultracentrifugation offers a Clue. *Carbohydr Polym.* 1999; 38(1): 235-238.
103. Poojari R, Srivastava R. Composite Alginate Microspheres as the Next-Generation Egg-Box Carriers for Biomacromolecules Delivery, Review Article. *Drug Deliv.* 2013; 1(1): 1-16.
104. Patil DA, Patil GB, Deshmukh PK, Belgamwar VS, Fursule RA. Chitosan Coated Mucoadhesive Multiparticulate Drug Delivery System for Glicazide. *Asian J Pharm Clin Res.* 2009; 2(2): 62-68.
105. Elzatahry AA, Eldin MSM, Soliman EA, Hassan EA. Evaluation of Alginate-Chitosan Bioadhesive Beads as Drug Delivery for Controlled Release of Theophylline. *J Appl Pol Sci.* 2013; 111(2009): 2452-2459.
106. Costa P, Lobo JMS. Modeling and Comparison of Dissolution Profiles, Review Article. *Eur J Pharm Sci.* 2001; 13(1): 123-133.
107. Lowman AM, Peppas NA. Hydrogels. In : Mathiowitz E, editor. Encyclopedia of Controlled Drug Delivery. New York: Wiley; 1999. 397-418.

108.Buxton R. Design Expert 7: Introduction, Mathematics Learning Support [Internet]; London: Stat-Ease, Inc; 2007 [dicitasi 7 Juli 2015]. Tersedia dari: http://mls/boro.ac.uk/resources/statistics/design_expert.7.pdf.