

CHAPTER 6

REFERENCES

1. O'Byrne, K. J. & Dalgleish, A. G. Chronic immune activation and inflammation as the cause of malignancy. *Br. J. Cancer* **85**, 473–83 (2001).
2. Hoyert, D. L. & Xu, J. Deaths: preliminary data for 2011. *Natl. Vital Stat. Rep.* **61**, 1–51 (2012).
3. Bastard, J.-P. *et al.* Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur. Cytokine Netw.* **17**, 4–12 (2006).
4. Cao, J. J. Effects of obesity on bone metabolism. *J. Orthop. Surg. Res.* **6**, 30 (2011).
5. Jha, R. K., Ma, Q., Sha, H. & Palikhe, M. Acute pancreatitis: a literature review. *Med Sci Monit* **15**, RA147–56 (2009).
6. Ferrucci, L. *et al.* Proinflammatory state, hepcidin, and anemia in older persons. *Blood* **115**, 3810–3816 (2010).
7. Glorieux, G., Cohen, G., Jankowski, J. & Vanholder, R. Platelet/leukocyte activation, inflammation, and uremia. *Semin. Dial.* **22**, 423–427 (2009).
8. Kundu, J. K. & Surh, Y. J. Inflammation: Gearing the journey to cancer. *Mutation Research - Reviews in Mutation Research* **659**, 15–30 (2008).
9. Murphy, S. L., Xu, J. & Kochanek, K. D. Deaths: final data for 2010. *Natl. Vital Stat. Rep.* **61**, 1–117 (2013).
10. Singh, T. & Newman, A. B. Inflammatory markers in population studies of aging. *Ageing Research Reviews* **10**, 319–329 (2011).
11. Singh, G. & Triadafilopoulos, G. Epidemiology of NSAID induced gastrointestinal complications. *J. Rheumatol. Suppl.* **56**, 18–24 (1999).
12. Paul, a. D. & Chauhan, C. K. Study of usage pattern of nonsteroidal anti-inflammatory drugs (NSAIDs) among different practice categories in Indian clinical setting. *Eur. J. Clin. Pharmacol.* **60**, 889–892 (2005).
13. Dhikav, V., Singh, S., Pande, S., Chawla, A. & Anand, K. S. Non-Steroidal Drug-induced Gastrointestinal Toxicity : Mechanisms And Management. *Clin. Med. (Northfield. Il).* **4**, 315–322 (2003).
14. Gandhi, M. N., Challa, S. R., Prasanth, P. & Gandhi, T. R. Role of leukotrienes in NSAID induced gastric ulceration and inflammation in wistar rats. *Asian Pacific J. Trop. Dis.* **2**, 215–219 (2012).
15. Ilic, S. *et al.* Pentadecapeptide BPC 157 and its effects on a NSAID toxicity model: diclofenac-induced gastrointestinal, liver, and encephalopathy lesions. *Life Sci.* **88**, 535–42 (2011).

16. Wallace, J. L., McKnight, W., Reuter, B. K. & Vergnolle, N. NSAID-induced gastric damage in rats: requirement for inhibition of both cyclooxygenase 1 and 2. *Gastroenterology* **119**, 706–714 (2000).
17. Tu, C. & Louie, A. Y. Nanoformulations for molecular MRI. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **4**, 448–57
18. Wischke, C. & Schwendeman, S. P. Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles. *International Journal of Pharmaceutics* **364**, 298–327 (2008).
19. Nils Ove Gustavsson, Monica Jonsson, Per Berden, Timo Laakso, M. R. Starch.pdf.
20. Zhang, N., Wardwell, P. R. & Bader, R. A. Polysaccharide-based micelles for drug delivery. *Pharmaceutics* **5**, 329–352 (2013).
21. Liu, Z., Jiao, Y., Wang, Y., Zhou, C. & Zhang, Z. Polysaccharides-based nanoparticles as drug delivery systems. *Advanced Drug Delivery Reviews* **60**, 1650–1662 (2008).
22. Saravanakumar, G., Jo, D.-G. & H. Park, J. Polysaccharide-Based Nanoparticles: A Versatile Platform for Drug Delivery and Biomedical Imaging. *Current Medicinal Chemistry* **19**, 3212–3229 (2012).
23. Jayakumar, R., Menon, D., Manzoor, K., Nair, S. V. & Tamura, H. Biomedical applications of chitin and chitosan based nanomaterials—A short review. *Carbohydrate Polymers* **82**, 227–232 (2010).
24. Agnihotri, S. A., Mallikarjuna, N. N. & Aminabhavi, T. M. Recent advances on chitosan-based micro- and nanoparticles in drug delivery. *J. Control. Release* **100**, 5–28 (2004).
25. Liu, L., Fishman, M. L. & Hicks, K. B. Pectin in controlled drug delivery – a review. *Cellulose* **14**, 15–24 (2006).
26. Zhang, J. & Ma, P. X. Cyclodextrin-based supramolecular systems for drug delivery: Recent progress and future perspective. *Adv. Drug Deliv. Rev.* **65**, 1215–1233 (2013).
27. Rodrigues, A. & Emeje, M. Recent applications of starch derivatives in nanodrug delivery. *Carbohydr. Polym.* **87**, 987–994 (2012).
28. Le Corre, D., Bras, J. & Dufresne, A. Starch nanoparticles: A review. *Biomacromolecules* **11**, 1139–1153 (2010).

29. Simi, C. K. & Emilia Abraham, T. Hydrophobic grafted and cross-linked starch nanoparticles for drug delivery. *Bioprocess Biosyst. Eng.* **30**, 173–180 (2007).
30. Teramoto, N., Motoyama, T., Yosomiya, R. & Shibata, M. Synthesis and properties of thermoplastic propyl-etherified amylose. *Eur. Polym. J.* **38**, 1365–1369 (2002).
31. Tan, Y. *et al.* Fabrication of Size-Controlled Starch-Based Nanospheres by Nanoprecipitation. *ACS Appl. Mater. Interfaces* **1**, 956–959 (2009).
32. Jain, A. K., Khar, R. K., Ahmed, F. J. & Diwan, P. V. Effective insulin delivery using starch nanoparticles as a potential trans-nasal mucoadhesive carrier. *Eur. J. Pharm. Biopharm.* **69**, 426–435 (2008).
33. Santander-ortega, M. J. *et al.* Nanoparticles made from novel starch derivatives for transdermal drug delivery. *J. Control. Release* **141**, 85–92 (2010).
34. Besheer, A., Hause, G. & Ma, K. Hydrophobically Modified Hydroxyethyl Starch : Synthesis , Characterization , and Aqueous Self-Assembly into Nano-Sized Polymeric Micelles and Vesicles. 359–367 (2007).
35. Medzhitov, R. Origin and physiological roles of inflammation. *Nature* **454**, 428–435 (2008).
36. Guo, S. & Dipietro, L. A. Factors affecting wound healing. *J. Dent. Res.* **89**, 219–229 (2010).
37. Gabay, C. & Kushner, I. Acute-phase proteins and other systemic responses to inflammation. *N. Engl. J. Med.* **340**, 448–454 (1999).
38. Lawrence, T., Willoughby, D. A. & Gilroy, D. W. Anti-inflammatory lipid mediators and insights into the resolution of inflammation. *Nat. Rev. Immunol.* **2**, 787–795 (2002).
39. Coussens, L. M. & Werb, Z. Inflammation and cancer. *Nature* **420**, 860–867 (2002).
40. Alegre, J. *et al.* Pleural-fluid myeloperoxidase in complicated and noncomplicated parapneumonic pleural effusions. *Eur. Respir. J.* **19**, 320–325 (2002).
41. Haslett, C. *et al.* Granulocyte apoptosis and the control of inflammation. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **345**, 327–333 (1994).
42. Buttarello, M. & Plebani, M. Automated blood cell counts: State of the art. *American Journal of Clinical Pathology* **130**, 104–116 (2008).

43. Zimmermann, N., Hershey, G. K., Foster, P. S. & Rothenberg, M. E. Chemokines in asthma: Cooperative interaction between chemokines and IL-13. *Journal of Allergy and Clinical Immunology* **111**, 227–243 (2003).
44. Weyrich, A. S. & Zimmerman, G. A. Platelets: Signaling cells in the immune continuum. *Trends in Immunology* **25**, 489–495 (2004).
45. Kosone, T. *et al.* Hepatocyte growth factor accelerates thrombopoiesis in transgenic mice. *Lab. Invest.* **87**, 284–291 (2007).
46. Savill, J. & Fadok, V. Corpse clearance defines the meaning of cell death. *Nature* **407**, 784–788 (2000).
47. Fadok, V. A. *et al.* Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF- β , PGE₂, and PAF. *J. Clin. Invest.* **101**, 890–898 (1998).
48. Huynh, M. L. N., Fadok, V. A. & Henson, P. M. Phosphatidylserine-dependent ingestion of apoptotic cells promotes TGF- β 1 secretion and the resolution of inflammation. *J. Clin. Invest.* **109**, 41–50 (2002).
49. Van Lent, P. L. *et al.* Uptake of apoptotic leukocytes by synovial lining macrophages inhibits immune complex-mediated arthritis. *J. Leukoc. Biol.* **70**, 708–714 (2001).
50. Dibbert, B. *et al.* Cytokine-mediated Bax deficiency and consequent delayed neutrophil apoptosis: a general mechanism to accumulate effector cells in inflammation. *Proc. Natl. Acad. Sci. U. S. A.* **96**, 13330–13335 (1999).
51. William Vandivier, R. *et al.* Elastase-mediated phosphatidylserine receptor cleavage impairs apoptotic cell clearance in cystic fibrosis and bronchiectasis. *J. Clin. Invest.* **109**, 661–670 (2002).
52. Larsen, G. L. & Henson, P. M. Mediators of inflammation. *Annu. Rev. Immunol.* **1**, 335–59 (1983).
53. Shanley, T. P., Warner, R. L. & Ward, P. A. The role of cytokines and adhesion molecules in the development of inflammatory injury. *Mol. Med. Today* **1**, 40–45 (1995).
54. Green, S. *et al.* Partial purification of a serum factor that causes necrosis of tumors. *Proc. Natl. Acad. Sci. U. S. A.* **73**, 381–385 (1976).
55. Sethi, G., Sung, B. & Aggarwal, B. B. TNF: a master switch for inflammation to cancer. *Front. Biosci.* **13**, 5094–5107 (2008).

56. Lawrence, T., Gilroy, D. W., Colville-Nash, P. R. & Willoughby, D. A. Possible new role for NF- κ B in the resolution of inflammation. *Nat. Med.* **7**, 1291–1297 (2001).
57. Sarada, S. *et al.* Role of oxidative stress and NF κ B in hypoxia-induced pulmonary edema. *Exp. Biol. Med. (Maywood)*. **233**, 1088–1098 (2008).
58. Bashir, M. M., Sharma, M. R. & Werth, V. P. TNF- α production in the skin. *Archives of Dermatological Research* **301**, 87–91 (2009).
59. Schmid, H. *et al.* Modular activation of nuclear factor-kappaB transcriptional programs in human diabetic nephropathy. *Diabetes* **55**, 2993–3003 (2006).
60. Goulding, N. J. *et al.* Anti-inflammatory lipocortin 1 production of peripheral blood leucocytes in response to hydrocortisone. *Lancet* **335**, 1416–1418 (1990).
61. Meyer, O. Anti-CRP antibodies in systemic lupus erythematosus. *Joint. Bone. Spine* **77**, 384–389 (2010).
62. Windgassen, E. B., Funtowicz, L., Lunsford, T. N., Harris, L. A. & Mulvagh, S. L. C-reactive protein and high-sensitivity C-reactive protein: an update for clinicians. *Postgrad. Med.* **123**, 114–119 (2011).
63. Kaptoge, S. *et al.* C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* **375**, 132–140 (2010).
64. Acevedo, M. *et al.* C-reactive protein and atrial fibrillation: ‘Evidence for the presence of inflammation in the perpetuation of the arrhythmia’. *Int. J. Cardiol.* **108**, 326–331 (2006).
65. Folsom, A. R., Aleksic, N., Catellier, D., Juneja, H. S. & Wu, K. K. C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study. *Am Hear. J* **144**, 233–238 (2002).
66. Nesto, R. C-reactive protein, its role in inflammation, Type 2 diabetes and cardiovascular disease, and the effects of insulin-sensitizing treatment with thiazolidinediones. *Diabetic Medicine* **21**, 810–817 (2004).
67. Gentry PA. in *The clinical chemistry of laboratory animals 2nd edn.* Taylor and Francis, Philadelphia 336–398 (1999).
68. Holgate, S. T. The pathophysiology of bronchial asthma and targets for its drug treatment. *Agents Actions* **18**, 281–287 (1986).

69. Kushner, I., Rzewnicki, D. & Samols, D. What does minor elevation of C-reactive protein signify? *American Journal of Medicine* **119**, (2006).
70. Murphy, K., Travers, P. & Walport, M. *Janeway's Immunobiology*. Garland Science **7**, (2008).
71. Morgan, B. P., Marchbank, K. J., Longhi, M. P., Harris, C. L. & Gallimore, A. M. Complement: Central to innate immunity and bridging to adaptive responses. in *Immunology Letters* **97**, 171–179 (2005).
72. Tanaka, A., Araki, H., Komoike, Y., Hase, S. & Takeuchi, K. Inhibition of both COX-1 and COX-2 is required for development of gastric damage in response to nonsteroidal antiinflammatory drugs. in *Journal of Physiology Paris* **95**, 21–27 (2001).
73. Lichtenberger, L. M., Zhou, Y., Dial, E. J. & Raphael, R. M. NSAID injury to the gastrointestinal tract: evidence that NSAIDs interact with phospholipids to weaken the hydrophobic surface barrier and induce the formation of unstable pores in membranes. *J. Pharm. Pharmacol.* **58**, 1421–1428 (2006).
74. Rafferty, P. & Holgate, S. T. *Terfenadine (Seldane) is a potent and selective histamine H1 receptor antagonist in asthmatic airways*. *The American review of respiratory disease* **135**, (1987).
75. Markiewski, M. M., Nilsson, B., Ekdahl, K. N., Mollnes, T. E. & Lambris, J. D. Complement and coagulation: strangers or partners in crime? *Trends Immunol.* **28**, 184–192 (2007).
76. Sitrin, R. G., Pan, P. M., Srikanth, S. & Todd, R. F. Fibrinogen activates NF-kappa B transcription factors in mononuclear phagocytes. *J. Immunol.* **161**, 1462–1470 (1998).
77. Paraskevas, K. I., Baker, D. M., Vrentzos, G. E. & Mikhailidis, D. P. The role of fibrinogen and fibrinolysis in peripheral arterial disease. *Thromb. Res.* **122**, 1–12 (2008).
78. Sandborn, W. J. *et al.* Early symptomatic response and mucosal healing with mesalazine rectal suspension therapy in active distal ulcerative colitis - Additional results from two controlled studies. *Aliment. Pharmacol. Ther.* **34**, 747–756 (2011).
79. Sutherland, L. & Macdonald, J. K. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst. Rev.* CD000544 (2006).

80. Eaden, J., Abrams, K., Ekbom, A., Jackson, E. & Mayberry, J. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment. Pharmacol. Ther.* **14**, 145–153 (2000).
81. Hanauer, S. B. *et al.* Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. *Lancet* **359**, 1541–1549 (2002).
82. Lochs, H. *et al.* Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI. *Gastroenterology* **118**, (2000).
83. Modigliani, R. *et al.* Mesalamine in Crohn's disease with steroid-induced remission: Effect on steroid withdrawal and remission maintenance. *Gastroenterology* **110**, 688–693 (1996).
84. Summers, R. W. *et al.* National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* **77**, (1979).
85. Loftus, E. V, Kane, S. V & Bjorkman, D. Systematic review: short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. *Aliment. Pharmacol. Ther.* **19**, 179–189 (2004).
86. Ransford, R. A. J. & Langman, M. J. S. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut* **51**, 536–539 (2002).
87. Van Staa, T. P., Travis, S., Leufkens, H. G. M. & Logan, R. F. 5-Aminosalicylic acids and the risk of renal disease: A large British epidemiologic study. *Gastroenterology* **126**, 1733–1739 (2004).
88. Franchimont, D., Kino, T., Galon, J., Meduri, G. U. & Chrousos, G. Glucocorticoids and inflammation revisited: The state of the art - NIH Clinical Staff Conference. *NeuroImmunoModulation* **10**, 247–260 (2002).
89. Steinhart, A. H., Ewe, K., Griffiths, A. M., Modigliani, R. & Thomsen, O. O. Corticosteroids for maintaining remission of Crohn's disease. *Cochrane Database Syst. Rev.* CD000301 (2001).
90. Lennard-Jones, J. E., Longmore, A. J., Newell, A. C., Wilson, C. W. & Jones, F. A. An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as out-patient treatment for ulcerative colitis. *Gut* **1**, 217–222 (1960).
91. J. Treib, Baron, J. & Grauer, M T, R. G. S. An international view of hydroxyethyl starches. *Intensive Care Med.* **25**, 258–268 (1999).

92. Malchow, H. *et al.* *European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment.* *Gastroenterology* **86**, (1984).
93. Modigliani, R. *et al.* *Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives.* *Gastroenterology* **98**, (1990).
94. Kane, S. V *et al.* Systematic review: the effectiveness of budesonide therapy for Crohn's disease. *Aliment. Pharmacol. Ther.* **16**, 1509–1517 (2002).
95. Aronoff, D. M. & Neilson, E. G. Antipyretics: Mechanisms of action and clinical use in fever suppression. *American Journal of Medicine* **111**, 304–315 (2001).
96. Koeberle, A. & Werz, O. Inhibitors of the microsomal prostaglandin E(2) synthase-1 as alternative to non steroidal anti-inflammatory drugs (NSAIDs)--a critical review. *Curr. Med. Chem.* **16**, 4274–4296 (2009).
97. Nabulsi, M. Is combining or alternating antipyretic therapy more beneficial than monotherapy for febrile children? *BMJ* **339**, b3540 (2009).
98. Coceani, F., Bishai, I., Lees, J. & Sirko, S. Prostaglandin E2 and fever: A continuing debate. *Yale Journal of Biology and Medicine* **59**, 169–174 (1986).
99. Rainsford, K. D. Ibuprofen: Pharmacology, efficacy and safety. *Inflammopharmacology* **17**, 275–342 (2009).
100. Warden, S. J. Prophylactic use of NSAIDs by athletes: a risk/benefit assessment. *Phys. Sportsmed.* **38**, 132–138 (2010).
101. Towheed, T. E. *et al.* Acetaminophen for osteoarthritis. *Cochrane Database Syst. Rev.* CD004257 (2006).
102. Gøtzsche, P. C. Methodology and overt and hidden bias in reports of 196 double-blind trials of nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Control. Clin. Trials* **10**, 31–56 (1989).
103. Traversa, G. *et al.* Gastroduodenal toxicity of different nonsteroidal antiinflammatory drugs. *Epidemiology* **6**, 49–54 (1995).
104. Tadataka, Yamada David , Alpers, Anthony, Kalloo. Textbook of Gastroenterology, 2 Volume Set, 5th Edition -. at <<http://as.wiley.com/WileyCDA/WileyTitle/productCd-1405169117.html>>

105. Higuchi, K. *et al.* Present status and strategy of NSAIDs-induced small bowel injury. *J. Gastroenterol.* **44**, 879–888 (2009).
106. Rutgeerts, P., Van Assche, G. & Vermeire, S. Optimizing Anti-TNF treatment in inflammatory bowel disease. *Gastroenterology* **126**, 1593–1610 (2004).
107. Targan, S. R. *et al.* A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N. Engl. J. Med.* **337**, 1029–1035 (1997).
108. Koenders, M. I. & Joosten, L. A. B. Potential new targets in arthritis therapy: interleukin (IL)-17 and its relation to tumour necrosis factor and IL-1 in experimental arthritis. 14–16 (2006). doi:10.1136/ard.2006.058529
109. Present, D. H. *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *N. Engl. J. Med.* **340**, 1398–1405 (1999).
110. Sands, B. E. *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N. Engl. J. Med.* **350**, 876–885 (2004).
111. Ljung, T. *et al.* Infliximab in inflammatory bowel disease: Clinical outcome in a population based cohort from Stockholm County. *Gut* **53**, 849–853 (2004).
112. Colombel, J. F. *et al.* The Safety Profile of Infliximab in Patients with Crohn's Disease: The Mayo Clinic Experience in 500 Patients. *Gastroenterology* **126**, 19–31 (2004).
113. Siu, S. S., Yeung, J. H. & Lau, T. K. A study on placental transfer of diclofenac in first trimester of human pregnancy. *Hum. Reprod.* **15**, 2423–2425 (2000).
114. Kudo, C. *et al.* Diclofenac inhibits proliferation and differentiation of neural stem cells. *Biochem. Pharmacol.* **66**, 289–295 (2003).
115. Chang, J.-K., Wang, G.-J., Tsai, S.-T. & Ho, M.-L. Nonsteroidal anti-inflammatory drug effects on osteoblastic cell cycle, cytotoxicity, and cell death. *Connect. Tissue Res.* **46**, 200–210 (2005).
116. Ericson, A. & Källén, B. A. Nonsteroidal anti-inflammatory drugs in early pregnancy. *Reprod. Toxicol.* **15**, 371–5 (2001).
117. Bardell, E. COX-2 inhibitors--implementation of the NICE guidelines. *Rheumatology* **41**, 590–592 (2002).

118. Ford-Hutchinson, A. W., Brunet, G., Savard, P. & Charleson, S. Leukotriene B₄, polymorphonuclear leukocytes and inflammatory exudates in the rat. *Prostaglandins* **28**, 13–27 (1984).
119. Ricciotti, E. & Fitzgerald, G. A. Prostaglandins and inflammation. *Arterioscler. Thromb. Vasc. Biol.* **31**, 986–1000 (2011).
120. Tomlinson, R. V & Ringold, H. J. Relationship between inhibition of prostaglandin synthesis and drug efficacy: support for the current theory on mode of action of aspirin-like drugs. *Biochem. Biophys. Res. Commun.* **46**, 552–559 (1972).
121. Flower, R. J. Drugs Which Inhibit Prostaglandin Biosynthesis. *Pharmacol. Rev.* **26**, 33–67 (1974).
122. Whittle, B. J. R. Gastrointestinal effects of nonsteroidal anti-inflammatory drugs. *Fundam. Clin. Pharmacol.* **17**, 301–313 (2003).
123. Simon, L. S. *et al.* Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* **282**, 1921–1928 (1999).
124. Singh, G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. in *American Journal of Medicine* **105**, (1998).
125. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. The Dutch TIA Trial Study Group. *N. Engl. J. Med.* **325**, 1261–1266 (1991).
126. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. The SALT Collaborative Group. *Lancet (London, England)* **338**, 1345–1349 (1991).
127. Schjerning Olsen, A.-M. *et al.* Association of NSAID Use With Risk of Bleeding and Cardiovascular Events in Patients Receiving Antithrombotic Therapy After Myocardial Infarction. *JAMA* **313**, 805 (2015).
128. Tomisato, W. *et al.* Role of direct cytotoxic effects of NSAIDs in the induction of gastric lesions. *Biochem. Pharmacol.* **67**, 575–585 (2004).
129. Bjarnason, I., Scarpignato, C., Takeuchi, K. & Rainsford, K. D. Determinants of the short-term gastric damage caused by NSAIDs in man. *Aliment. Pharmacol. Ther.* **26**, 95–106 (2007).
130. Orrenius, S. Reactive oxygen species in mitochondria-mediated cell death. *Drug Metab. Rev.* **39**, 443–455 (2007).

131. Darling, R. L. *et al.* The effects of aspirin on gastric mucosal integrity, surface hydrophobicity, and prostaglandin metabolism in cyclooxygenase knockout mice. *Gastroenterology* **127**, 94–104 (2004).
132. Naito, Y. & Yoshikawa, T. Oxidative stress involvement and gene expression in indomethacin-induced gastropathy. *Redox Rep.* **11**, 243–253 (2006).
133. Chattopadhyay, I., Bandyopadhyay, U., Biswas, K., Maity, P. & Banerjee, R. K. Indomethacin inactivates gastric peroxidase to induce reactive-oxygen-mediated gastric mucosal injury and curcumin protects it by preventing peroxidase inactivation and scavenging reactive oxygen. *Free Radic. Biol. Med.* **40**, 1397–1408 (2006).
134. Gretzer, B., Maricic, N., Respondek, M., Schuligoi, R. & Peskar, B. M. Effects of specific inhibition of cyclo-oxygenase-1 and cyclo-oxygenase-2 in the rat stomach with normal mucosa and after acid challenge. *Br. J. Pharmacol.* **132**, 1565–1573 (2001).
135. Ehrlich, K., Sicking, C., Respondek, M. & Peskar, B. M. Interaction of cyclooxygenase isoenzymes, nitric oxide, and afferent neurons in gastric mucosal defense in rats. *J. Pharmacol. Exp. Ther.* **308**, 277–283 (2004).
136. Schmassmann, A. *et al.* Role of the different isoforms of cyclooxygenase and nitric oxide synthase during gastric ulcer healing in cyclooxygenase-1 and -2 knockout mice. *Am. J. Physiol.* **290**, G747–56 (2006).
137. Bhandari, P., Bateman, A. C., Mehta, R. L. & Patel, P. Mucosal expression of cyclooxygenase isoforms 1 and 2 is increased with worsening damage to the gastric mucosa. *Histopathology* **46**, 280–286 (2005).
138. Starodub, O. T., Demitrack, E. S., Baumgartner, H. K. & Montrose, M. H. Disruption of the Cox-1 gene slows repair of microscopic lesions in the mouse gastric epithelium. *Am. J. Physiol. Cell Physiol.* **294**, C223–32 (2008).
139. DIKMAN, A. *et al.* A randomized, placebo-controlled study of the effects of naproxen, aspirin, celecoxib or clopidogrel on gastroduodenal mucosal healing. *Aliment. Pharmacol. Ther.* **29**, 781–791 (2009).
140. Rostom, A. *et al.* in *Cochrane Database of Systematic Reviews* (ed. Rostom, A.) (John Wiley & Sons, Ltd, 2002). doi:10.1002/14651858.CD002296
141. Hooper, L. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. *BMJ* **329**, 948–0 (2004).

142. Bombardier, C. *et al.* Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis. *N. Engl. J. Med.* **343**, 1520–1528 (2000).
143. Schnitzer, T. J. Update on guidelines for the treatment of chronic musculoskeletal pain. *Clin. Rheumatol.* **25 Suppl 1**, S22–9 (2006).
144. McEwen, J. *Therapeutic Goods Administration, Department of Health and Ageing. Expanded information on Cox-2 inhibitors for doctors and pharmacists.* at <<http://www.tga.gov.au/media-release/expanded-information-cox-2-inhibitors-doctors-and-pharmacists-amended>>
145. *Expanded information on Cox-2 inhibitors for doctors and pharmacists (amended*) | Therapeutic Goods Administration (TGA).* at <<http://www.tga.gov.au/media-release/expanded-information-cox-2-inhibitors-doctors-and-pharmacists-amended>>
146. *COX-2 selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).* (2005). at <<http://www.fda.gov/drugs/drugsafety/postmarketdrugsafety/informationforpatientsandproviders/ucm103420.htm>>
147. Bresalier, R. S. *et al.* Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial. *N. Engl. J. Med.* **352**, 1092–1102 (2005).
148. Solomon, S. D. *et al.* Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention. *N. Engl. J. Med.* **352**, 1071–1080 (2005).
149. P, M. & D, H. Cardiovascular risk and inhibition of cyclooxygenase: A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* **296**, 1633–1644 (2006).
150. Hernández-Díaz, S., Varas-Lorenzo, C. & García Rodríguez, L. A. Non-Steroidal Antiinflammatory Drugs and the Risk of Acute Myocardial Infarction. *Basic Clin. Pharmacol. Toxicol.* **98**, 266–274 (2006).
151. McGettigan, P. & Henry, D. Use of Non-Steroidal Anti-Inflammatory Drugs That Elevate Cardiovascular Risk: An Examination of Sales and Essential Medicines Lists in Low-, Middle-, and High-Income Countries. *PLoS Med.* **10**, e1001388 (2013).
152. Scholer, D. W., Ku, E. C., Boettcher, I. & Schweizer, A. Pharmacology of diclofenac sodium. *Am. J. Med.* **80**, 34–38 (1986).

153. Savaşer, A., Özkan, Y. & İşimer, A. Preparation and in vitro evaluation of sustained release tablet formulations of diclofenac sodium. *Farm.* **60**, 171–177 (2005).
154. Gan, T. J. Diclofenac: an update on its mechanism of action and safety profile. *Curr. Med. Res. Opin.* **26**, 1715–1731 (2010).
155. Ortiz, M. I. *et al.* Pharmacological evidence for the activation of K⁺ channels by diclofenac. *Eur. J. Pharmacol.* **438**, 85–91 (2002).
156. Lee, H. M. *et al.* Diclofenac inhibition of sodium currents in rat dorsal root ganglion neurons. *Brain Res.* **992**, 120–127 (2003).
157. Dietrich, T., Leeson, R., Gugliotta, B. & Petersen, B. Efficacy and safety of low dose subcutaneous diclofenac in the management of acute pain: a randomized double-blind trial. *Pain Pract.* **14**, 315–23 (2014).
158. Chiarello, E., Bernasconi, S., Gugliotta, B. & Giannini, S. Subcutaneous injection of diclofenac for the treatment of pain following minor orthopedic surgery (DIRECT study): a randomized trial. *Pain Pract.* **15**, 31–9 (2015).
159. Brack, A., Rittner, H. L. & Schäfer, M. Non-opioid analgesics for perioperative pain therapy. Risks and rational basis for use. *Anaesthesist* **53**, 263–280 (2004).
160. McCormack, P. L. & Scott, L. J. Diclofenac sodium injection (Dyloject): in postoperative pain. *Drugs* **68**, 123–130 (2008).
161. Arora, P. & Mukherjee, B. Design, development, physicochemical, and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt. *J. Pharm. Sci.* **91**, 2076–2089 (2002).
162. Ahire, B. R. *et al.* Solubility Enhancement of Poorly Water Soluble Drug by Solid Dispersion Techniques. **2**, 2007–2015 (2015).
163. Singhal, S., Lohar, V. K. & Arora, V. Hot Melt Extrusion Technique. *WebmedCentral Pharm. Sci.* **2**, 1–20 (2011).
164. Kumar, R. *et al.* Supramolecular Assemblies Based on Copolymers of PEG600 and Functionalized Aromatic Diesters for Drug Delivery Applications. *J. Am. Chem. Soc.* **126**, 10640–10644 (2004).
165. Sravana, M., Srivalli, P. & Rajeev, T. A Novel Approach for Improvement of Solubility and Bioavailability of Poorly Soluble Drugs : Lquisolid Compact Technique. *Int. J. Res. Pharm. Biomed. Sci.* **3**, 1621–1632 (2012).

166. Jain, P., Goel, A., Sharma, S. & Parmar, M. Solubility enhancement techniques with special emphasis on hydrotrophy. *Pharma Professional's Res.* **1**, 34–45 (2010).
167. Bernard, S., Mathew, M. & Senthilkumar, K. L. Spectrophotometric method of estimation of Amlodipine besylate using hydrotropic solubilization. *J. Appl. Pharm. Sci.* **01**, 177–180 (2011).
168. Deshmukh, V., Deshmukh, T., Deshmukh, M. & Jadhav, P. Design and Development of Melt Sonocrystallization Technique for Carbamazepine. *Indian J. Pharm. Educ. Res.* **47**, 199–205 (2013).
169. Chaudhari, P. D. & Uttekar, P. S. Melt-Sonocrystallization : A Novel Particle Engineering Technique for Solubility Enhancement . *Int. J. PharmTech Res.* **1**, 111–120 (2009).
170. Crison, J. R. & Amidon, G. L. Method and formulation for increasing the bioavailability of poorly water-soluble drugs. (1999). at <<http://www.google.co.in/patents/US5993858>>
171. Vippagunta, S. R., Wang, Z., Hornung, S. & Krill, S. L. Factors affecting the formation of eutectic solid dispersions and their dissolution behavior. *J. Pharm. Sci.* **96**, 294–304 (2007).
172. Patil, J. S., Kadam, D. V, Marapur, S. C. & Kamalapur, M. V. Inclusion complex system ; A novel technique to improve the solubility and bioavailability of poorly soluble drugs: A review *Int. J. Res. Pharm. Sci. Rev. Res.* **2**, 29–34 (2010).
173. Sano, A., Kuriki, T., Handa, T., Takeuchi, H. & Kawashima, Y. Particle design of tolbutamide in the presence of soluble polymer or surfactant by the spherical crystallization technique: Improvement of dissolution rate. *J. Pharm. Sci.* **76**, 471–474 (1987).
174. Rajanikant, P., Nirav, P., Patel, N. M. & Patel, M. M. A novel approach for dissolution enhancement of Ibuprofen by preparing floating granules. *Int. J. Res. Pharm. Sci.* 57–64 (2010).
175. Patravale, V. B., Date, A. A. & Kulkarni, R. M. Nanosuspensions: a promising drug delivery strategy. *J. Pharm. Pharmacol.* **56**, 827–840 (2004).
176. Koo, O. M., Rubinstein, I. & Onyuksel, H. Role of nanotechnology in targeted drug delivery and imaging: a concise review. *Nanomedicine Nanotechnology, Biol. Med.* **1**, 193–212 (2015).
177. West, J. L. & Halas, N. J. Applications of nanotechnology to biotechnology: Commentary. *Curr. Opin. Biotechnol.* **11**, 215–217 (2000).

178. LaVan, D. A., Lynn, D. M. & Langer, R. Moving smaller in drug discovery and delivery. *Nat Rev Drug Discov* **1**, 77–84 (2002).
179. Sahoo, S. K. & Labhasetwar, V. Nanotech approaches to drug delivery and imaging. *Drug Discov. Today* **8**, 1112–1120 (2003).
180. Ryan, S. M. & Brayden, D. J. Progress in the delivery of nanoparticle constructs: towards clinical translation. *Curr. Opin. Pharmacol.* **18**, 120–8 (2014).
181. Min, Y., Caster, J. M., Eblan, M. J. & Wang, A. Z. Clinical Translation of Nanomedicine. *Chem. Rev.* 150619062806005 (2015). doi:10.1021/acs.chemrev.5b00116
182. Duncan, R. The dawning era of polymer therapeutics. *Nat Rev Drug Discov* **2**, 347–360 (2003).
183. Gref, R. *et al.* Biodegradable long-circulating polymeric nanospheres. *Science* (80-.). **263**, 1600–1603 (1994).
184. Panyam, J. & Labhasetwar, V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. *Adv. Drug Deliv. Rev.* **55**, 329–347 (2003).
185. Soppimath, K. S., Aminabhavi, T. M., Kulkarni, A. R. & Rudzinski, W. E. Biodegradable polymeric nanoparticles as drug delivery devices. *J. Control. Release* **70**, 1–20 (2001).
186. Vasir, J. K. & Labhasetwar, V. Biodegradable nanoparticles for cytosolic delivery of therapeutics. *Adv. Drug Deliv. Rev.* **59**, 718–728 (2007).
187. Zhang, L. *et al.* Nanoparticles in Medicine: Therapeutic Applications and Developments. *Clin. Pharmacol. Ther.* **83**, 761–769 (2008).
188. Hu, L., Tang, X. & Cui, F. Solid lipid nanoparticles (SLNs) to improve oral bioavailability of poorly soluble drugs. *J. Pharm. Pharmacol.* **56**, 1527–1535 (2004).
189. Jabr-Milane, L. S., van Vlerken, L. E., Yadav, S. & Amiji, M. M. Multi-functional nanocarriers to overcome tumor drug resistance. *Cancer Treat. Rev.* **34**, 592–602 (2008).
190. Faraji, A. H. & Wipf, P. Nanoparticles in cellular drug delivery. *Bioorg. Med. Chem.* **17**, 2950–2962 (2009).
191. Cho, K., Wang, X., Nie, S., Chen, Z. (Georgia) & Shin, D. M. Therapeutic Nanoparticles for Drug Delivery in Cancer. *Clin. Cancer Res.* **14**, 1310–1316 (2008).

192. Pinto Reis, C., Neufeld, R. J., Ribeiro, A. J. & Veiga, F. Nanoencapsulation II. Biomedical applications and current status of peptide and protein nanoparticulate delivery systems. *Nanomedicine Nanotechnology, Biol. Med.* **2**, 53–65 (2015).
193. Uhrich, K. E., Cannizzaro, S. M., Langer, R. S. & Shakesheff, K. M. Polymeric Systems for Controlled Drug Release. *Chem. Rev.* **99**, 3181–3198 (1999).
194. Barratt, G. M. Therapeutic applications of colloidal drug carriers. *Pharm. Sci. Technol. Today* **3**, 163–171 (2000).
195. Barratt, G. Colloidal drug carriers: achievements and perspectives. *Cell. Mol. Life Sci.* **60**, 21–37 (2003).
196. Couvereur, P., Barratt, G., Fattal, E., Legrand, P. & Vauthier, C. Nanocapsule technology: a review. *Crit. Rev. Ther. Drug Carrier Syst.* **19**, 99–134 (2002).
197. Kumari, A., Yadav, S. K. & Yadav, S. C. Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids Surfaces B Biointerfaces* **75**, 1–18 (2010).
198. Peracchia, M. T. *et al.* PEG-coated nanospheres from amphiphilic diblock and multiblock copolymers: Investigation of their drug encapsulation and release characteristics¹. *J. Control. Release* **46**, 223–231 (1997).
199. Redhead, H. M., Davis, S. S. & Illum, L. Drug delivery in poly(lactide-co-glycolide) nanoparticles surface modified with poloxamer 407 and poloxamine 908: in vitro characterisation and in vivo evaluation. *J. Control. Release* **70**, 353–363 (2001).
200. Ishihara, T., Kubota, T., Choi, T. & Higaki, M. Treatment of Experimental Arthritis with Stealth-Type Polymeric Nanoparticles Encapsulating Betamethasone Phosphate. *J. Pharmacol. Exp. Ther.* **329**, 412–417 (2009).
201. Conn, R. E. *et al.* Safety assessment of polylactide (PLA) for use as a food-contact polymer. *Food Chem. Toxicol.* **33**, 273–283 (1995).
202. Wang, C. & Pham, P.-T. Polymers for viral gene delivery. *Expert Opin. Drug Deliv.* **5**, 385–401 (2008).
203. Mizrahy, S. & Peer, D. Polysaccharides as building blocks for nanotherapeutics. *Chem. Soc. Rev.* **41**, 2623–2640 (2012).
204. Robertson, M. I. Regulatory issues with excipients. *Int. J. Pharm.* **187**, 273–276 (1999).

205. Jansook, P. & Loftsson, T. CDs as solubilizers: Effects of excipients and competing drugs. *Int. J. Pharm.* **379**, 32–40 (2009).
206. Killen, B. U. & Corrigan, O. I. Effect of soluble filler on drug release from stearic acid based compacts. *Int. J. Pharm.* **316**, 47–51 (2006).
207. Langoth, N., Kalbe, J. & Bernkop-Schnürch, A. Development of buccal drug delivery systems based on a thiolated polymer. *Int. J. Pharm.* **252**, 141–148 (2003).
208. Lemieux, M., Gosselin, P. & Alexandru, M. Carboxymethyl high amylose starch as excipient for controlled drug release : Mechanistic study and the influence of degree of substitution. *Int. J. Pharm.* **382**, 172–182 (2009).
209. Li, S., Lin, S., Daggy, B. P., Mirchandani, H. L. & Chien, Y. W. Effect of HPMC and Carbopol on the release and floating properties of Gastric Floating Drug Delivery System using factorial design. *Int. J. Pharm.* **253**, 13–22 (2003).
210. Massicotte, L. P., Baille, W. E. & Mateescu, M. A. Carboxylated high amylose starch as pharmaceutical excipients: Structural insights and formulation of pancreatic enzymes. *Int. J. Pharm.* **356**, 212–223 (2008).
211. Munday, D. L. & Cox, P. J. Compressed xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms. *Int. J. Pharm.* **203**, 179–192 (2000).
212. Nykänen, P. *et al.* Citric acid as excipient in multiple-unit enteric-coated tablets for targeting drugs on the colon. *Int. J. Pharm.* **229**, 155–162 (2001).
213. Williams, H. D., Ward, R., Culy, A., Hardy, I. J. & Melia, C. D. Designing HPMC matrices with improved resistance to dissolved sugar. *Int. J. Pharm.* **401**, 51–59 (2010).
214. Park, K. Nanotechnology: What it can do for drug delivery. *Journal of controlled release* **120**, 1–3 (2007).
215. Sajilata, M. G., Singhal, R. S. & Kulkarni, P. R. Resistant Starch?A Review. *Compr. Rev. Food Sci. Food Saf.* **5**, 1–17 (2006).
216. Angellier, H., Choisnard, L., Molina-Boisseau, S., Ozil, P. & Dufresne, A. Optimization of the Preparation of Aqueous Suspensions of Waxy Maize Starch Nanocrystals Using a Response Surface Methodology. *Biomacromolecules* **5**, 1545–1551 (2004).
217. Giezen, Franciscus, E. Biopolymer nanoparticles.pdf.

218. Shi, A., Li, D., Wang, L., Li, B. & Adhikari, B. Preparation of starch-based nanoparticles through high-pressure homogenization and miniemulsion cross-linking: Influence of various process parameters on particle size and stability. *Carbohydr. Polym.* **83**, 1604–1610 (2011).
219. Danmi, Y. U., Suyao, X., Chunyi, T., Lin, C. & Xuanming, L. I. U. Dialdehyde starch nanoparticles : Preparation and application in drug carrier. *Chinese Sci. Bull.* **52**, 2913–2918 (2007).
220. Xiao, S. *et al.* Preparation of folate-conjugated starch nanoparticles and its application to tumor-targeted drug delivery vector. *Chinese Sci. Bull.* **51**, 1693–1697 (2006).
221. Athira, G. K. & Jyothi, A. N. Preparation and characterization of curcumin loaded cassava starch nanoparticles with improved cellular absorption. **6**, 171–176 (2014).
222. Dumitriu, S. *Polysaccharides in Medicinal Applications*. (CRC Press, 1996). at <<https://books.google.co.in/books>>
223. Brecher, M. E., Owen, H. G. & Bandarenko, N. Alternatives to albumin: Starch replacement for plasma exchange. *J. Clin. Apher.* **12**, 146–153 (1997).
224. Wing, R. E., Maiti, S. & Doane, W. M. Effectiveness of Jet-Cooked Pearl Cornstarch as a Controlled Release Matrix. *Starch - Stärke* **39**, 422–425 (1987).
225. Trimnell, D. & Shasha, B. S. Autoencapsulation: A new method for entrapping pesticides within starch. *J. Control. Release* **7**, 25–31 (1988).
226. Wing, R. E., Maiti, S. & Doane, W. M. Amylose content of starch controls the release of encapsulated bioactive agents. *J. Control. Release* **7**, 33–37 (1988).
227. Reed, J. P., Hall, F. R. & Trimnell, D. Effect of Encapsulating Thiocarbamate Herbicides Within Starch for Overcoming Enhanced Degradation in Soils. *Starch - Stärke* **41**, 184–186 (1989).
228. Heller, J., Pangburn, S. H. & Roskos, K. V. Development of enzymatically degradable protective coatings for use in triggered drug delivery systems: derivatized starch hydrogels. *Biomaterials* **11**, 345–350 (1990).
229. Lévy, M.-C. & Andry, M.-C. Microcapsules prepared through interfacial cross-linking of starch derivatives. *Int. J. Pharm.* **62**, 27–35 (1990).
230. Evans, I. D. & Haisman, D. R. Rheology of gelatinised starch suspensions. *J. Texture Stud.* **10**, 347–370 (1980).

231. Bagley, E. B. & Christianson, D. D. Swelling capacity of starch and its relationship to suspension viscosity-effect of cooking time, temperature and concentration. *J. Texture Stud.* **13**, 115–126 (1982).
232. Byrappa, K., Ohara, S. & Adschiri, T. Nanoparticles synthesis using supercritical fluid technology – towards biomedical applications. *Adv. Drug Deliv. Rev.* **60**, 299–327 (2008).
233. Heath, J. R. & Davis, M. E. Nanotechnology and Cancer. *Annu. Rev. Med.* **59**, 251–265 (2008).
234. Linkov, I., Satterstrom, F. K. & Corey, L. M. Nanotoxicology and nanomedicine : making hard decisions. **4**, 167–171 (2008).
235. Ashammakhi, N., Wimpenny, I., Nikkola, L. & Yang, Y. Electrospinning: Methods and development of biodegradable nanofibres for drug release. *Journal of Biomedical Nanotechnology* **5**, 1–19 (2009).
236. Koo, Y.-E. L. *et al.* Brain cancer diagnosis and therapy with nanoplatfoms. *Adv. Drug Deliv. Rev.* **58**, 1556–1577 (2006).
237. Briones, E., Colino, C. I. & Lanao, J. M. Delivery systems to increase the selectivity of antibiotics in phagocytic cells. *J. Control. Release* **125**, 210–227 (2008).
238. Torchilin, V. P. Multifunctional nanocarriers. *Adv. Drug Deliv. Rev.* **64**, 302–315 (2012).
239. Jin, S. & Ye, K. Nanoparticle-Mediated Drug Delivery and Gene Therapy. *Biotechnol. Prog.* **23**, 32–41 (2007).
240. Sun, Q., Radosz, M. & Shen, Y. Challenges in design of translational nanocarriers. *J. Control. Release* **164**, 156–169 (2012).
241. Dunn, P. *et al.* Bone Marrow Failure and Myelofibrosis in a Case of PVP Storage Disease. *Am. J. Hematol.* **71**, 68–71 (1998).
242. Schneider, P., Korolenko, T. A. & Busch, U. A review of drug-induced lysosomal disorders of the liver in man and laboratory animals. *Microsc. Res. Tech.* **36**, 253–275 (1997).
243. Tyrrell, Z. L., Shen, Y. & Radosz, M. Fabrication of micellar nanoparticles for drug delivery through the self-assembly of block copolymers. *Prog. Polym. Sci.* **35**, 1128–1143 (2010).
244. Irfan, M. & Seiler, M. Encapsulation Using Hyperbranched Polymers: From Research and Technologies to Emerging Applications. *Ind. Eng. Chem. Res.* **49**, 1169–1196 (2010).

245. Huh, K. M. *et al.* Hydrotropic polymer micelle system for delivery of paclitaxel. *J. Control. Release* **101**, 59–68 (2005).
246. Vail, D. M., Kravis, L. D., Cooley, A. J., Chun, R. & MacEwen, E. G. Preclinical trial of doxorubicin entrapped in sterically stabilized liposomes in dogs with spontaneously arising malignant tumors. *Cancer Chemother. Pharmacol.* **39**, 410–416 (1997).
247. Kim, S. Y. & Lee, Y. M. Taxol-loaded block copolymer nanospheres composed of methoxy poly(ethylene glycol) and poly(ϵ -caprolactone) as novel anticancer drug carriers. *Biomaterials* **22**, 1697–1704 (2001).
248. Szebeni, J. Complement activation-related pseudoallergy: A new class of drug-induced acute immune toxicity. *Toxicology* **216**, 106–121 (2005).
249. Szebeni, J. *et al.* Role of complement activation in hypersensitivity reactions to doxil and hynic peg liposomes: experimental and clinical studies. *J. Liposome Res.* **12**, 165–172 (2002).
250. Radomski, A. *et al.* Nanoparticle-induced platelet aggregation and vascular thrombosis. *Br. J. Pharmacol.* **146**, 882–893 (2005).
251. Anderson N Banker GS. *The theory and practice of industrial pharmacy.* (Lea & Febiger, 2013). at <<http://www.isbnsearch.org/isbn/8123922892>>
252. Batzri, S. & Korn, E. D. Single bilayer liposomes prepared without sonication. *Biochim. Biophys. Acta - Biomembr.* **298**, 1015–1019 (1973).
253. Woo, K. & Seib, P. A. Cross-linking of wheat starch and hydroxypropylated wheat starch in alkaline slurry with sodium trimetaphosphate. *Carbohydr. Polym.* **33**, 263–271 (1997).
254. Gui-Jie, M., Peng, W., Xiang-Sheng, M., Xing, Z. & Tong, Z. Crosslinking of corn starch with sodium trimetaphosphate in solid state by microwave irradiation. *J. Appl. Polym. Sci.* **102**, 5854–5860 (2006).
255. Chaovanalikit, A., Dougherty, M. P., Camire, M. E. & Briggs, J. Ascorbic Acid Fortification Reduces Anthocyanins in Extruded Blueberry-Corn Cereals. *J. Food Sci.* **68**, 2136–2140 (2003).
256. Kytariolos, J. *et al.* Stability and physicochemical characterization of novel milk-based oral formulations. *Int. J. Pharm.* **444**, 128–138 (2013).
257. Kutuzov, N. P. *et al.* ATP-induced lipid membrane reordering in the myelinated nerve fiber identified using Raman spectroscopy. *Laser Phys. Lett.* **10**, 75606 (2013).

258. Stolzing, A., Naaldijk, Y., Fedorova, V. & Sethe, S. Hydroxyethylstarch in cryopreservation – Mechanisms, benefits and problems. *Transfus. Apher. Sci.* **46**, 137–147 (2012).
259. Cedervall, T. *et al.* Understanding the nanoparticle-protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proc. Natl. Acad. Sci.* **104**, 2050–2055 (2007).
260. Capron, I., Robert, P., Colonna, P., Brogly, M. & Planchot, V. Starch in rubbery and glassy states by FTIR spectroscopy. *Carbohydr. Polym.* **68**, 249–259 (2007).
261. Li, B. *et al.* Physical properties and loading capacity of starch-based microparticles crosslinked with trisodium trimetaphosphate. *J. Food Eng.* **92**, 255–260 (2009).
262. Whittinghill, J. M., Norton, J. & Proctor, A. Stability determination of soy lecithin-based emulsions by Fourier transform infrared spectroscopy. *J. Am. Oil Chem. Soc.* **77**, 37–42 (2000).
263. Singhvi, G. & Singh, M. Review: in vitro drug release characterization models. *Int J Pharm Stud Res* **II**, 77–84 (2011).
264. Raval, A., Parikh, J. & Engineer, C. Mechanism and in Vitro Release Kinetic Study of Sirolimus from a Biodegradable Polymeric Matrix Coated Cardiovascular Stent. *Ind. Eng. Chem. Res.* **50**, 9539–9549 (2011).
265. Grassi, M. & Grassi, G. Mathematical Modelling and Controlled Drug Delivery: Matrix Systems. *Curr. Drug Deliv.* **2**, 97–116 (2005).
266. Shoaib, M. H., Tazeen, J., Merchant, H. a, Yousuf, R. I. & Shoaib, M Harris; Tazeen, Jaweria; Merchant, H. a. Evaluation of Drug Release Kinetics From Ibuprofen Matrix Tablets Using Hpmc. *Pak. J. Pharm. Sci.* **19**, 119–124 (2006).
267. Suvakantha Dash, Padala Narasimha Murthy, Lilakantha Nath, P. C. Review: kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol. Pharm.* **67**, 217–223 (2010).
268. Narayanan, D. *et al.* Poly-(ethylene glycol) modified gelatin nanoparticles for sustained delivery of the anti-inflammatory drug Ibuprofen-Sodium: An in vitro and in vivo analysis. *Nanomedicine Nanotechnology, Biol. Med.* **9**, 818–828 (2013).
269. Motwani, S. K. *et al.* Chitosan–sodium alginate nanoparticles as submicroscopic reservoirs for ocular delivery: Formulation, optimisation and in vitro characterisation. *Eur. J. Pharm. Biopharm.* **68**, 513–525 (2008).

270. Williams, D. F. On the mechanisms of biocompatibility. *Biomaterials* **29**, 2941–2953 (2008).
271. Benesch, J. & Tengvall, P. Blood protein adsorption onto chitosan. *Biomaterials* **23**, 2561–2568 (2002).
272. *Food and Drug Administration*. 'Single dose acute toxicity testing for pharmaceuticals'. (1996).
273. Harboe, M. A Method for Determination of Hemoglobin in Plasma by Near-Ultraviolet Spectrophotometry. *Scand. J. Clin. & Lab. Investig.* **11**, 66–70 (1959).
274. Alexis, F., Pridgen, E., Molnar, L. K. & Farokhzad, O. C. Factors Affecting the Clearance and Biodistribution of Polymeric Nanoparticles. *Mol. Pharm.* **5**, 505–515 (2008).
275. Nel, A. E. *et al.* Understanding biophysicochemical interactions at the nano–bio interface. *Nat. Publ. Gr.* **8**, 543–557 (2009).
276. Baier, R. E. Key Events in Blood Interactions at Nonphysiologic Interfaces — A Personal Primer. *Artif. Organs* **2**, 422–426 (1978).
277. Amiji, M. M. Permeability and blood compatibility properties of chitosan-poly(ethylene oxide) blend membranes for haemodialysis. *Biomaterials* **16**, 593–599 (1995).
278. Klokkevold, P. R., Lew, D. S., Ellis, D. G. & Bertolami, C. N. Effect of chitosan on lingual hemostasis in rabbits. *J. Oral Maxillofac. Surg.* **49**, 858–863 (1991).
279. Malette, W. G., Quigley, H. J., Gaines, R. D., Johnson, N. D. & Rainer, W. G. Chitosan: A New Hemostatic. *Ann. Thorac. Surg.* **36**, 55–58 (1983).
280. Strauss, R. G., Stump, D. C., Henriksen, R. A. & Saunders, R. Effects of hydroxyethyl starch on fibrinogen, fibrin clot formation, and fibrinolysis. *Transfusion* **25**, 230–234 (1985).
281. BIMC Colorectal Surgery - Drs . Martz and Melstrom Aspirin and blood thinner list.
282. Jamnicki, M. *et al.* Compromised Blood Coagulation. *Anesth. Analg.* **87**, 989–993 (1998).
283. Entholzner, E. K. *et al.* Coagulation effects of a recently developed hydroxyethyl starch (HES 130/0.4) compared to hydroxyethyl starches with higher molecular weight. *Acta Anaesthesiol. Scand.* **44**, 1116–1121 (2000).

284. Franz, A. *et al.* The Effects of Hydroxyethyl Starches of Varying Molecular Weights on Platelet Function. *Anesth. Analg.* 1402–1407 (2001). doi:10.1097/0000539-200106000-00008
285. Lin, W.-W. & Karin, M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J. Clin. Invest.* **117**, 1175–1183 (2007).
286. Gupta, S. C., Sundaram, C., Reuter, S. & Aggarwal, B. B. Inhibiting NF- κ B activation by small molecules as a therapeutic strategy. *Biochim. Biophys. Acta - Gene Regul. Mech.* **1799**, 775–787 (2010).
287. Zolnik, B. S., González-Fernández, Á., Sadrieh, N. & Dobrovolskaia, M. A. Minireview: Nanoparticles and the Immune System. *Endocrinology* **151**, 458–465 (2010).
288. Laxenaire, M. C. Drugs and other agents involved in anaphylactic shock occurring during anaesthesia. A French multicenter epidemiological inquiry. *Ann. Fr. Anesth. Reanim.* **12**, 91–96 (1993).
289. Tolman, K. G. Hepatotoxicity of non-narcotic analgesics. *Am. J. Med.* **105**, 13S–19S (2015).
290. Vane, J. R. & Botting, R. M. Mechanism of Action of Anti-Inflammatory Drugs. *Scand. J. Rheumatol.* **25**, 9–21 (1996).
291. Ponsoda, X. *et al.* The use of cultured hepatocytes to investigate the mechanisms of drug hepatotoxicity. *Cell Biol. and Toxicol.* **13**, 331–338 (1997).
292. Kretzrommel, A. & Boelsterli, U. A. Diclofenac Covalent Protein Binding Is Dependent on Acyl Glucuronide Formation and Is Inversely Related to P450-Mediated Acute Cell Injury in Cultured Rat Hepatocytes. *Toxicol. Appl. Pharmacol.* **120**, 155–161 (1993).
293. Thanagari, B. S. *et al.* Haemato-biochemical alterations induced by Diclofenac sodium toxicity in Swiss albino mice One of the commonly used painkillers , Diclofenac is a phenyl acetic acid derivative and is mostly available in the form of Diclofenac sodium . sufficient reports a. *Vet. World* **5**, 417–419 (2012).
294. Kappus, H. Overview of enzyme systems involved in bioreduction of drugs and in redox cycling. *Biochem. Pharmacol.* **35**, 1–6 (1986).
295. Uyemura, S. A., Santos, A. C., Mingatto, F. E., Jordani, M. C. & Curti, C. Diclofenac Sodium and Mefenamic Acid: Potent Inducers of the Membrane Permeability Transition in Renal Cortex Mitochondria. *Arch. Biochem. Biophys.* **342**, 231–235 (1997).

296. Hussain, I., Khan, M. Z., Khan, A., Javed, I. & Saleemi, M. K. Toxicological effects of diclofenac in four avian species. *Avian Pathol.* **37**, 315–321 (2008).
297. El-Ashmawy, Z. K. E.-M. & I. M. Hepato-Renal and Hematological Effects of Diclofenac Sodium in Rats. *Glob. J. Pharmacol.* **7**, 123–132 (2013).
298. Munir, M. A., Enany, N. & Zhang, J.-M. Nonopioid analgesics. *Med. Clin. North Am.* **91**, 97–111 (2007).
299. Jones, R., Rubin, G., Berenbaum, F. & Scheiman, J. Gastrointestinal and Cardiovascular Risks of Nonsteroidal Anti-inflammatory Drugs. *Am. J. Med.* **121**, 464–474 (2008).
300. Beck, W. S., Schneider, H. T., Dietzel, K., Nuernberg, B. & Brune, K. Gastrointestinal ulcerations induced by anti-inflammatory drugs in rats. *Arch. Toxicol.* **64**, 210–217 (1990).
301. Moghimi, S. M. & Hunter, A. C. Poloxamers and poloxamines in nanoparticle engineering and experimental medicine. *Trends Biotechnol.* **18**, 412–420 (2000).
302. Farokhzad, O. C. & Langer, R. Nanomedicine: Developing smarter therapeutic and diagnostic modalities. *Adv. Drug Deliv. Rev.* **58**, 1456–1459 (2006).
303. Shaffer, C. Nanomedicine transforms drug delivery. *Drug Discov. Today* **10**, 1581–1582 (2005).
304. Alexis, F. *et al.* New frontiers in nanotechnology for cancer treatment. *Urol. Oncol. Semin. Orig. Investig.* **26**, 74–85 (2008).
305. Moghimi, S. M., Hunter, A. C. & Murray, J. C. Long-circulating and target-specific nanoparticles: theory to practice. *Pharmacol. Rev.* **53**, 283–318 (2001).
306. Nel, A. Toxic Potential of Materials at the Nanolevel. *Science (80-)*. **311**, 622–627 (2006).
307. He, C., Hu, Y., Yin, L., Tang, C. & Yin, C. Effects of particle size and surface charge on cellular uptake and biodistribution of polymeric nanoparticles. *Biomaterials* **31**, 3657–3666 (2010).
308. Schipper, M. L. *et al.* Particle Size, Surface Coating, and PEGylation Influence the Biodistribution of Quantum Dots in Living Mice. *Small* **5**, 126–134 (2009).

309. Veronese, F. M. & Harris, J. M. Introduction and overview of peptide and protein pegylation. *Adv. Drug Deliv. Rev.* **54**, 453–456 (2002).
310. Park, J. *et al.* PEGylated PLGA nanoparticles for the improved delivery of doxorubicin. *Nanomedicine Nanotechnology, Biol. Med.* **5**, 410–418 (2009).
311. Medicines, V. COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS. *Distribution* (2004).
312. International, T. & Excipients, P. The IPEC Excipient Information Package (EIP): Template and User Guide. (2009).
313. Kutscher, H. L. *et al.* Threshold size for optimal passive pulmonary targeting and retention of rigid microparticles in rats. *J. Control. Release* **143**, 31–37 (2010).
314. Bertrand, N., Fleischer, J. G., Wasan, K. M. & Leroux, J.-C. Pharmacokinetics and biodistribution of N-isopropylacrylamide copolymers for the design of pH-sensitive liposomes. *Biomaterials* **30**, 2598–2605 (2009).
315. Chollet, P., Favrot, M. C., Hurbin, A. & Coll, J.-L. Side-effects of a systemic injection of linear polyethylenimine–DNA complexes. *J. Gene Med.* **4**, 84–91 (2002).
316. Merkel, T. J. *et al.* Using mechanobiological mimicry of red blood cells to extend circulation times of hydrogel microparticles. *Proc. Natl. Acad. Sci.* **108**, 586–591 (2011).
317. Cavalli, R., Peira, E., Caputo, O. & Gasco, M. R. Solid lipid nanoparticles as carriers of hydrocortisone and progesterone complexes with β -cyclodextrins. *Int. J. Pharm.* **182**, 59–69 (1999).
318. Tang, S. Y., Sivakumar, M., Ng, A. M.-H. & Shridharan, P. Anti-inflammatory and analgesic activity of novel oral aspirin-loaded nanoemulsion and nano multiple emulsion formulations generated using ultrasound cavitation. *Int. J. Pharm.* **430**, 299–306 (2012).
319. Hemmila, M. R. *et al.* Topical nanoemulsion therapy reduces bacterial wound infection and inflammation after burn injury. *Surgery* **148**, 499–509 (2010).
320. Garg, V., Jain, G. K., Nirmal, J. & Kohli, K. Topical tacrolimus nanoemulsion, a promising therapeutic approach for uveitis. *Med. Hypotheses* **81**, 901–904 (2013).