

抗生素藥物配方與分析之研究

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摘要

近年來，畜牧水產業等生產趨向企業化經營，故採取大群密集化飼養為必然之發展，隨著飼養密集化之要求，預防與治療的工作相當重要。常用之動物用藥如抗生素及磺胺系列可對畜牧水產業等具有其治療功效，還兼具預防等功能。而 diaveridine 及 sulfadiazine 的應用範圍最廣，可治療土壤絲菌病、沙眼、包含體結膜炎，以及對本類藥物敏感之細菌如沙氏桿菌、革蘭氏陽性及陰性菌等所引起之各種感染。本研究探討 diaveridine 及 sulfadiazine 之物理化學性質及物理化學安定性與其分析方法，並完成 diaveridine 及 sulfadiazine 二物之生理可接受鹽類之製備。目標亦將對抗氧化劑、界面活性劑及各添加物對 diaveridine 及 sulfadiazine 之安定性及水溶性之影響。最後期望可獲得具水溶性、穩定之 diaveridine 及 sulfadiazine 動物用藥配方，以提供工業上生產，更為往後國內從事動物用藥品之配方研究發展有所貢獻。另一研究 acetaminophen, aspirinum aluminum, ethoxybenzamide, codeine phosphate, thiamine disulfide, potassium guaiacol sulfonate, caffeine anhydrous, chlorpheniramine maleate 等為市售綜合感冒藥劑中較常見之主要成分，本文中所報導乃利用離子配高效液相層析法同時分析此八種成分，並探討逆離子種類、濃度及 pH 之影響。結果顯示使用 Vercopak C-18 (4.6x250 mm) 層析管，並以含 sodium 1-pentanesulfonate (PICB-5)/sodium 1-heptanesulfonate (PICB-7), pH 為 3.0 之逆離子緩衝劑與甲醇作梯度沖提，流速為 1 毫升/分鐘，測定波長設定為 280 nm。此方法分析市售三種感冒劑及一合成混合物（含以上八種成分）可得到相當好的結果。

關鍵詞：配方；分析；抗生素

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參考文獻

- 參考文獻 1. 王文憲 (民83), 藥理學精義, 合記圖書, 台北, 頁 150. 2. 朱慶基 (民82), 動物用藥品配方設計及實例探討-動物用藥之配方設計, 農委會, 台北, 頁103-160. 3. 李煥燦及李匡邦 (民64), 化學藥理學, 文和印刷, 台北, 頁87-90. 4. 吳慧眼、程亦妮、張夢玲、林雨平 (民83), 感冒藥糖漿有效成分定量-實驗室間測試研究, 食品藥物分析, 2(1), 頁 63-69. 5. 拓人 (民68), 養豬與磺胺劑之應用, 畜牧半月刊, 10 (7), 頁 60-66. 6. 邵丹平 (民78), 新藥物治療法, 藝軒出版社, 台北, 頁258, 812. 7. 林立 (民68), 磺胺劑分類簡介, 畜牧半月刊, 22(3), 頁 72. 8. 林達雄 (民62), 磺胺劑在養豬上之臨床應用, 中國畜牧雜誌, 5 (9), 頁 30-32. 9. 施筱梅 (民77), 開發中國家動物藥品銷售潛力, 農牧旬刊, 73 (3), 頁 112-113. 10. 陳甘霖 (民82), 藥品之研發工作內容, 動物用藥之配方設計, 農委會, 頁1-6. 11. 陳昭姿 (民83), 藥師說藥, 吳氏圖書, 台北, 頁 27-28. 12. 莊萬發 (民74), 最新高速液體層析法, 復漢出版社, 台南, 頁 324-338. 13. 許興智及陳甘霖 (民80), 藥劑的安定性及配方的篩選, 華榮圖書, 頁 161-168. 14. 集大成 (民70), 磺胺劑在家畜的應用, 農牧旬刊, 頁103-106. 15. 葉明功、王大鵬及蘇德政 (民74), 藥品安定性之探討, 國防醫學, 頁 80-88. 16. 潘子明、陳坤雄 (民81), 豬肉中殘留磺胺劑快速分析法之研究, 食品科學, 19 (3), 頁358-374. 17. 劉興華、趙國芳及揚筱蕙 (民83), 醫護藥物學, 偉華書局, 頁 260. 18. 譚柱光 (民83), 實用藥物治療手冊, 金名圖書, 台北, 頁 520. 19. 蕭水銀 (民78), 生化藥理學論集, 聯經出版社, 台北, 頁 121-122. 20. 鐘柄泓、詹素妃、李安榮及鄒台黎 (民77), 離子配對高效液相層析法及其在藥品分析上之應用, Journal of Chinese Pharmaceutical, 40(2), 頁 53-75. 21. Austin, R. L., Lily, C. H., Marsha, S. M., Charles, R. S. and Steven, A. B. (1990) Multiresidue method for the determination of sulfonamides in Pork tissue. Journal of Agricultural Food Chemistry, 36, 423-426. 22. Batha, A., Billiet, H. A., Galan, L. and Vigh, G. (1984) Studies in reversed-phase ion-pair Chromatography, III. The effect of counter ion concentration. Journal of Chromatography, 291, 91-102. 23. Bidlingmeyer, B. A. and Warren, F. V. J., (1982) Effect of ionic strength on retention and detector response in reversed-phase ion-pair liquid chromatography with ultraviolet-absorbing ion interaction reagents. Analytical Chemistry, 84(13), 2351-2356. 24. Billiet, H. A., Vuik, J., Strasters, J. K. and Galan, L. (1987) Simultaneous optimization of reagent concentration and pH in reversed-phase ion-pairing chromatography. Journal of Chromatography, 384, 153-162. 25. Carola, H. (1986) Increasing solubility of enoxacin and Norfloxacin by means of salt formation. Journal of parenteral Sciences & Technology, 40(2), 70-72. 26. Carroll, P. T., Robb, C. A., Tippett, L. O. and Langston, J. B. (1971) Antibacterial activity of diaveridine, trimethoprim, and selected sulfonamides in prostatic fluid. Investigative Urology, 8(6), 686-694. 27. Chang, C. H., Hsien, C. H., Lu, D. W. and Kao, K. D. (1992) Stability Studies of topical carbonic anhydrase inhibitor 6-Hydroxyethoxy-2-benzothiazole Sulfonamide. Journal of Pharmaceutical Sciences, 81(3), 299-302. 28. Chung, I. H., Ralph, J. B., Hui, S. W., Youcef, R. and Charles, R. W. (1991) Formulation, stability, and antitumor activity of 1-β-D-arabinofuranosylctosine conjugate of thioether phospholipid. Cancer Research, 50(15), 4401-4406. 29. Chung, P. -H., Chan, S. -F., Lee, A. -R. and Tsou, T. -L. (1987) Ion-pair high-performance liquid chromatography and its application in drug analysis. The Chinese Pharmaceutical Journal, 40(2), 53-57. 30. Elvira, A. F., Shirley, D. and George, H. (1951) 2,4-Diaminopyrimidines as antimalarials. II. 5-Benzyl derivatives. Journal of American Chemical Society, 73, 3758-3762. 31. Fransson, B., Ragnarsson, U. and Zetterqvist, O. (1982) Separation of basic, hydrophilic peptides by reversed-phase ion pair Chromatography. Analytical Biochemistry, 126, 174-178. 32. Gupta, V. D. (1979) Simultaneous quantitation of acetaminophen, aspirin, caffeine, codeine phosphate, phenacetin, and salicylamide by high-pressure liquid chromatography. Journal of Pharmaceutical Science, 68(1), 97-103. 33. Gupta V. D. (1980) high-pressure liquid chromatography determination of salicylic acid in aspirin powder and pharmaceutical dosage forms. Journal of Pharmaceutical Sciences. 69(1), 110-113. 34. Gurmukh, D. C. and Bhogi, B. (1995) Particle size reduction of emulsions by formulation design-II: Effect of oil and surfactant concentration. Research Article, 49(2), 71-76. 35. Haikala, V., Marvola, M. and Sothmann A. (1987) Formulation

studies of a new noscapine embonate preparation. *Drug Development and Industrial Pharmacy*, 13(7), 1159-1169. 36. Harou, Y. (1991) Mutagenicity of the coccidiostat diaverdine in the salmonella/ mammalian microsome assay. *Mutation Research*, 261, 149-152. 37. Hoffer, M., Grwberg, E., Mitrovic, M. and Bossi, C. (1971) An Improved synthesis of diaveridine, trimethoprim and closely related 2, 4- diaminopyrimidines, *Journal of Medicinal Chemistry*, 14(5), 462-463. 38. Ibrahim, F. B. (1993) Simultaneous determination and separation of several barbiturates and analgesic products by ion-pair high-performance liquid chromatography. *Journal of Liquid Chromatography*, 16(3), 2835-2851. 39. Lee, A. R., Sung, K. S. and Huang, W. H. (1993) Simultaneous quantitation of caffeine, ethoxybenzamide and propyphenazone in oral analgesic tablets by high-pressure liquid chromatography. *Journal of Food and Drug Analysis*, 1(4), 351-356. 40. Ling, Y. L. and Alan, B. (1980) Specific and sensitive method for the determination of aspirin and salicylic acid in plasma using reversed-phase high-performance liquid chromatography. *Journal of Chromatography*, 181, 473-477. 41. McSharryw, W. O. and Savage, I. V. E. (1980) Simultaneous high-pressure liquid chromatographic determination of acetaminophen, guaifenesin, and dextromethorphan hydrobromide in cough syrup. *Journal of Pharmaceutical Science*, 69(2), 212-215. 42. Michael, F. P., Linda, C. F., Allyn, R. B. and Willam, L. (1988) Formulation of vaccine adjuvant muramyl dipeptides (MDP). 2. The thermal reactivity and pH of maximum stability of MDP compounds in aqueous solution. *Pharmaceutical Research*, 5(8), 528-532. 43. Nivaud-Guerent, E., Guernet, M., Ivanovic, D. and Medenica, M. (1994) Effect of eluent pH on the ionic and molecular forms of the non-steroidal anti-inflammatory agents in reversed-phase high-performance liquid chromatography. *Journal of Liquid Chromatography*, 17(11), 2343-2357. 44. Norman, J. (1966) A comparison of the toxicity of the coccidiostats diaveridine and pyrimethamine in the chick and the effect of an antibiotic on the anti-folic activity of pyrimethamine. *Research Science*, 7, 196-206. 45. Pandit, N. K., Strykowski, J. M., McNally, E. J. and Waldbillig, A. M. (1985) Surfactant solutions as media for dissolution testing of a poorly water-soluble drug. *Drug Development and Industrial Pharmacy*, 11(9), 1797-1818. 46. Paul, S., Richard, B. (1983) A new synthesis of 5-benzylpyrimidines. *Journal of Organic Chemistry*, 28, 1983-1988. 47. Peng, G. W., Gadalla, M. A. F., Smith, V., Peng, A. and Chiou, L. (1978) Simple and rapid high-pressure liquid chromatographic simultaneous determination of aspirin, salicylic acid, and salicylic acid in plasma. *Journal of Pharmaceutical Science*, 67(5), 710-712. 48. Reepmeyer, J. C. and Kirchhoefer, R. D. (1979) Isolation of salicylic acid, acetylsalicylic acid, and acetylsalicylic anhydride from aspirin tablets by extraction and high-pressure liquid chromatography. *Journal of Pharmaceutical Science*, 68(9), 1167-1169. 49. Richard, B. S., San, D., Raza, A. and Francisco (1980) Topical antibiotic therapy of acne. *Cutis*, 25, 216-248. 50. Stephen, M. B., Lyle, D. B. and Donald, C. (1977) pharmaceutical salts, *Journal of Pharmaceutical Sciences*, 66(1), 2-16. 51. Su, D. J. and Yen, M. K. (1989) Simultaneous determination of caffeine, ethoxybenzamide and Isopropylantipyrine in tablets by high-performance liquid chromatography. *The Chinese Pharmaceutical Journal*, 41(3), 209-213. 52. Thuro, C. J., Johnson, J. B., valenting, W. and Vance, J. J. (1964) Extrapolation of Appearance of tablets and powers from accelerated storage test. *Journal of Pharmaceutical Sciences*, 53(9), 1050-1054. 53. Tomlinson, E., Jefferies, T. M. and Riley, C. M. (1978) Ion-pair high-performance liquid chromatography. *Journal of Chromatography*, 159, 315-358. 54. Toshiyuki, S., Sachko, M. and Tameyuki, A. (1980) Determination of residual diaveridine and sulfaquinoxaline in hen's egg, chicken plasma and tissues by high-performance liquid chromatography. *Chemical of Pharmaceutical Bull*, 29(8), 2290-2295. 55. McSharry, W. O. and Savage, V. E. (1980) Simultaneous high-pressure liquid chromatographic determination of acetaminophen, guaifenesin, and dextromethorphan hydrobromide in cough syrup, *Journal of Pharmaceutical Sciences*, 69(2), 212-215. 56. Wolfgang, G. (1986) Stability testing in industry for worldwide marketing. *Drug Development and Industrial Pharmacy*, 12(8?), 1259-1292. 57. Yutaka, A., Kozo, T., Yoshiharu, M. and Tsuneji, N. (1985) Computer Optimization of the formulation of acrylic plaster. *Chemical of Pharmaceutical*, 33(10), 4536-4534.