Studies on the Formation and Analysis of Antibacterical

江佳惠、施英隆 ; 王三郎

E-mail: 8812469@mail.dyu.edu.tw

ABSTRACT

Althouth considered to be powerful veterinary medicines, diaveridine and sulfadiazine suffer from low water solubility that reduce their effectiveness. it is necessary to formulate these two drugs to enhance their water solubility and effectiveness. this study has focused on the development of an ideal formulation for these two drugs in hope to solve their solubility problem. In the context, several physical proerties of these two drug were reported, which includes thermal stability by DSC, UV absorbance, specific rotation, ect.. The analytical conditions for TLC, HPLC were also described. These two drugs were found stable at long exposure of light, heat and various pH. Nevertheless, The attempt to increase their solubility by addition of surfactant or salt formation were not yet successful. The ideal formation for two drugs is still to be seen. A method for simultaneous analysis of acetaminophen, aspirinum aluminum, ethoxybenzamide, codeine phosphate, thiamine disulfide, potassium guaiacol sulfonate, caffeine anhydrous, chlorpheniramine maleate, the common ingredients present in cold medicine was described. The method was based on reversed-phase ion- pairing high-pressure liquid chromatography. The best separation was achieved on a Vercopak C-18 column with a gradient elution, using a solvent system containing a acetate buffer (1:1, sodium pentane sulfonate (PICB-5)/sodium 1-heptanesulfonate (PICB-7), 5mM, with acetic acid to pH 3), and the methanol as mobile phase at a flow rate 1 ml/ min, and a detection fixed wavelength of 280 mn. The method gave excellent results for three commerical products and a synthetic mixture containing eight major ingredients. The effects of the counter-ion concentration and the pH on the separation were also discussed.

Keywords : formulation ; analysis ; antibacterial

Table of Contents

目錄 封面內頁 簽名頁 授權書.....iii 中文摘要.....v 英文摘要.....vii 誌謝.....ix 目錄.....x 圖目錄.....xii 表目錄.....xiv 第一章 抗生素配方之研究.....1 1.1 前言.....1 1.2 文獻回顧.....3 1.2.1 化學療法之發展.....3 1.2.2 磺胺劑之分類.....5 1.2.3 磺胺劑在家畜的應用.....6 1.2.4 磺胺嘧啶特性及功用.....7 1.2.5 麗馬林特性及功用.....10 1.2.6 動物用藥製劑配方設計.....11 1.2.7 配分應考慮之因素.....12 1.3 材料與分法.....16 1.3.1 化學藥品.....16 1.3.2 儀器與設備.....17 1.3.3 實驗方法.....17 1.4 結果與討論.....25 1.5 結論.....63 第二章 利用離子配高效液相層析法同時分析綜合感冒藥劑中常見之八種主要成分.....65 2.1 前言.....65 2.2 文獻回顧.....67 2.2.1 治療感冒之藥物種類與功用.....67 2.2.2 離子配層析法之演進.....69 2.2.3 離子配層析法分類.....70 2.2.4 離子配層析法的優點.....71 2.2.5 離子配層析法之離子配模式.....72 2.2.6 離子配高效液相層析控制變因.....74 2.3 實驗材料與方法.....78 2.3.1 材料與方法.....78 2.3.2 實驗儀器.....78 2.3.3 實驗方法.....78 2.4 結果與方法.....82 2.4.1 pH值對分離效果之影響.....82 2.4.2 在 PH 值為 3.0時之離子配試劑濃度對分離效果之影響.....84 2.4.3 利用最佳分離條件分析合成混合物及市售感冒劑之檢品.....87 2.5 結論.....92 參考文獻.....94 圖目錄 圖一、磺胺嘧啶與麗馬林 DSC 圖.....26 圖二、磺胺嘧啶與麗馬林溶解度.....38 圖三、磺胺嘧啶對 pH 之穩定度.....39 圖四、麗馬林在不同 pH 之穩定度.....40 圖五、磺胺嘧啶與麗馬林對光照之穩定度.....42 圖六、磺胺嘧啶在 60℃ 之穩定度.....43 圖七、磺胺嘧啶在 80℃ 之穩定度.....44 圖八、麗馬林在 60℃ 之穩定度.....45 圖九、麗馬林在 80℃ 之穩定度.....46 圖十、磺胺嘧啶對不同比例助溶劑（丙二醇及甘油）之溶解度.....49 圖十一、麗馬林對不同比例助溶劑（propylene glycol 及 glycerin）之溶解

度.....50 圖十二、磺胺嘧啶與乙醇胺及二酸狻基乙胺之溶解度.....51 圖十三、磺胺嘧啶對不同比例乙醇胺之穩定性.....52 圖十四、磺胺嘧啶對不同比例二基乙之穩定性.....53 圖十五、麗馬林對檸檬酸及酒石酸溶解度.....55 圖十六、麗馬林對不同比例檸檬酸之穩定性.....56 圖十七、麗馬林對不同比例酒石酸之穩定性.....57 圖十八、磺胺嘧啶 - 麗馬林鹽類之溶解度.....58 圖十九、麗馬林無機鹽類之溶解度.....59 圖二十、磺胺嘧啶 tween80, SDS之溶解度.....61 圖二十一、麗馬林 tween80, SDS之溶解度.....62 圖二十二、離子配試劑種類與 pH 值對分析之影響.....83 圖二十三、不同離子配試劑濃度對分析之影響.....86 圖二十四、合成混和物之分析圖.....88 圖二十五、得適可感冒膠囊之分析圖.....89 圖二十六、斯斯感冒膠囊之分析圖.....91 圖二十七、治痛單糖漿之分析圖.....91 表目錄 表一、磺胺嘧啶與麗馬林對有機溶劑之溶解情形.....28 表二、pH 值及磷酸緩衝溶液體積對 10 毫升磺胺嘧啶之溶解度分析.....29 表三、pH 值及磷酸緩衝溶液體積對 10 毫升麗馬林之溶解度分析.....31 表四、磺胺嘧啶對乙醇胺配方溶解度之定性分析.....32 表五、磺胺嘧啶對二狻基乙胺配方溶解度之定性分析 （1）表五之一、磺胺嘧啶 200 毫克，於 5 毫升水中之溶解情形.....33 （2）表五之二、磺胺嘧啶 200 毫克之溶解情形.....33 表六、麗馬林對檸檬酸配方溶解度之定性分析 （1）表六之一、麗馬林 40 毫克，於 5 毫升水中之溶解情形.....34 （2）表六之二、麗馬林 40 毫克之溶解情形.....34 表七、麗馬林對酒石酸配方溶解度之定性分析 （1）表七之一、麗馬林 40 毫克，於 5 毫升水中之溶解情形.....35 （2）表七之二、麗馬林 40 毫克之溶解情形.....35 表八、磺胺嘧啶與麗馬林之鹽類混和溶解度之情形.....37 表九、酸、鹼及胺基酸之鹽類對溶解度之影響.....47 表十、高效液相層析梯度衝提條件.....81

REFERENCES

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 reagwnts. 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. Investgative Ubology., 8(6), 686-694. 27. Chaing, C. H., Hsien, C. H., Lu, D. W. and Kao, K. D.(1992) Stability Stusies of topical carbonic anhydrase inhibitor 6-Hydroxyethoxy-2-benzothiazole Sulfonamide. Journal of Pharmaceutical Sicences, 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 coujugate of thioether phospholipid. Canacer 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 Chemicla Society, 73, 3758-3762. 31. Fransson, B., Ragnarsson, U. and Zetterqvist, O. (1982) Separation of basic, hydrophillic peptides by revered- phase ion pair Chromatography. Analytial of 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 pharmacetical dosage forms..Journal of Phamaceutical 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 concetration. Research Article, 49(2), 71-76. 35. Haikala, V., Marvola, M. and Sothmann A. (1987) Formulation studiesof 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 Brossi, C. (1971) An Inprored 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 chormatography. Journal of Chormatography, 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 Pharmacetical Science, 69(2), 212-215. 42. Michael, F. P., Linda, C. F., Allyn, R. B. and WillIam, L. (1988) Formulation of vaccine adjuvant muramyldipeptides (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) Surfanct 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 salicyluric acid in plasma. Journal Pharmaceatical Science, 67(5), 710-712. 48. Reepmeyer, J. C. and Kirchhoefer, R. D. (1979) Isolation of salicylsalicylic acid, acetylsalicylic acid, and acetylsalicylic anhydride from aspirin tablets by extraction and high-pressure liquid chromatography. Journal Pharmaceatical 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-perforance liquid chromatograpy. Journal Chromatography, 159, 315-358. 54. Toshiyuki, S., Sachko, M. and Tameyuki, A. (1980) Determination of residual diaveridine and sulfaquinoxaline in hen's egg, chichen plasma and tissues by high-performance liquid chromatography. Chemical of Pharmaceutical Bull, 29(8), 2290-2295. 55. McSharry, W. O. and Savagei, 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 worldeide 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.