

嘉南藥理科技大學教師補助專題研究計畫成果報告

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題目：化妝品塑身燃脂霜中氨茶鹼經皮吸收代謝之研究

一、中文摘要

研究含皮膚促進劑之各種基劑與皮膚接觸後，以 ATR (attenuated total reflection) 傅立葉轉換紅外線光譜儀 (FTIR) 測定氨茶鹼在皮膚之傳送。由於存在光譜帶的 N-H 鍵頻率特性，可提供氨茶鹼在皮膚的吸收。研究三種皮膚促進劑(植物油、精油及親油性物質)，以親油性物質 β -cyclodextrin 對氨茶鹼促進吸收最大。

關鍵詞：

經皮吸收，氨茶鹼
促進劑，傅立葉轉換
紅外線，減弱全反射

Abstract

The delivery of aminophylline from several vehicles, including those containing penetration enhancers, was investigated in human skin. The skin after contact with the aminophylline formulation was examined by attenuated total reflection (ATR) - Fourier transform infrared (FTIR) spectroscopy. The presence of spectral bands at frequencies characteristic of N-H bonds provides evidence for the adsorption of the aminophylline on skin. Of the three kinds penetration enhancers (plant oils, essential oils and lipophilicities) were studied, β -cyclodextrin exhibited the largest increase in transdermal delivery when various enhancers were used.

Keywords:

Percutaneous absorption; aminophylline; enhancers; FT-IR; ATR.

二、緣由與目的

減肥塑身霜的成份源自於一種氣喘治療藥物，必須經由醫師開立處方才能使用的氨茶鹼(Aminophylline)。氨茶鹼為黃票哈甲基(methylxanthine)衍生物，即茶鹼(theophylline)與乙二胺以 2:1 比例所形成的複鹽。可以提高茶鹼的水溶性，並促進生體可用率(bioavailability)及動力學性質。過去的研究着重於藥物口服或注射方式經腸胃吸引後，測尿液或血液中氨茶鹼及其代謝物含量。至今，有關基劑配方影響氨茶鹼釋放[1-3]和經皮吸收[4-6]之研究仍然很少。定量茶鹼或氨茶鹼分析方法多數為液相層析法配合紫外光[7-20]、電化學[21-24]檢測器及免疫技術[25-26]。僅一篇用傅立葉轉換紅外線光譜儀 (FTIR) 測茶鹼 IR 吸收帶的波長特性，提供形成新化合物的診斷值。減弱全反射 (attenuated total reflection, ATR)- FTIR (Fourier transform infrared) 可評估皮膚接觸藥物後，某鍵結頻率特性，提供藥物在皮膚的吸引。FTIR 的分析技術為非破壞性，適合活體研究。所以本研究以 ATR- FTIR 評估氨茶鹼在各種配方中經皮吸收之變化量。

三、結果與討論 實驗條件

a. 塑身燃脂霜製品 (fat-burning preparations) (含 5 % 氨茶鹼) :
配方 (A) 含促進劑植物油 W/O 乳霜;
配方 (B) 促進劑含植物精油 W/O 乳霜;
配方 (C) 不含促進劑 W/O 乳霜。

b. 被實驗者 (subjects)
六個健康自願者參與研究，他們年齡在 20-23 歲多，體重公斤。調製含 5 % 氨茶鹼配方，使用於人體皮膚長 7.5 cm 寬 1.8 cm。經適當間隔時間，利用 ATR-FTIR 光譜儀偵測表皮的氨茶鹼含量。經二小時後，以吸附膠帶施力 15 秒，重覆此操作數次。再以 ATR-FTIR 測留在皮膚上氨茶鹼剩餘含量。

參考文獻

1. Y. Kasuya, T. Ohno, N. Kubota, H. Takahashi, and H. Hirayama, New method for bioavailability assessment of slow-release preparations of theophylline, *J. Pharmacokin. Biopharm.* 13, 571-587 (1985).
2. C. A. Lau-Cam and R. W. Roos, Simultaneous high performance liquid chromatographic determination of theophylline and ethylenediamine in aminophylline dosage forms as their dansyl derivatives, *J. Lig. Chromatogr.* 14, 1939-1956 (1991).
3. J. T. Stewart, F. W. Warren, and S. M. Johnson, Stability of cefuroxime sodium and aminophylline or theophylline, *Am. J. Hosp Pharm.* 51, 809-11 (1994).
4. T. Elka, L. S. Francesca, S. E. Naomi, B. Y. Ramy and F. Boris, Enhanced permeation of theophylline through the skin and its effect on fibroblast proliferation, *Int. J. Pharm.* 70, 159-166 (1991).
5. J. I. Ademola, R. C. Wester and H. I. Maibach, Cutaneous metabolism of theophylline by the human skin, *J. Invest Dermatol.* 98, 310-314 (1992).
6. R. Kadir, D. stempler, Z. Liron and S. Cohen, Penetration of theophylline and adenosine into excised human skin from binary and ternary vehicles: Effect of a nonionic surfactant, *J. Pharm. Sci.* 78, 149-153 (1989).
7. J. J. Lauff, Ion-pair high performance liquid Chromatographic procedure for the quantitative analysis of theophylline in serum samples, *J. Chromatogr.* 417, 99-109 (1987).
8. D. F. Mathis, Extraction of acetaminophen and theophylline from post-mortem tissues and urine for high-performance liquid chromatographic analysis, *J. chromatogr.* 439, 466-469 (1988).
9. T. E. B. Leakey, Simultaneous analysis of theophylline, caffeine and eight of their metabolic products in human plasma by gradient high-performance liquid chromatography, *J. Chromatogr.* 507, 199-220 (1990).
10. J. Blanchard, S. Harvey and W. J. Morgan, A rapid and specific high-performance liquid chromatographic assay for theophylline in biological fluids, *J. Chromatogr. Sci.* 28, 303-306 (1990).
11. J. Blanchard, C. W. Weber and Luz. E. Shearer, HPLC analysis of methylxanthines in human breast milk, *J. Chromatogr. Sci.* 28, 640-642 (1990).
12. P. Parra, A. Limon, S. Ferre, T. Guix, F. Jane, High-performance liquid chromatographic separation of caffeine,

- theophylline , theobromine and paraxathine in rat brain and serum, *J. Chromatogr.* 570, 185-190 (1991).
13. M. A. Sarkar, H. T. Karnes, High performance liquid chromatographic determination of theophylline metabolites in human liver microsomes, *Biomed. Chromatogr.* 5, 38-42 (1991).
 14. P. J. Helmsing, HPLC determination of caffeine and theophylline by direct serum injection, *Clin. Chem.* 39, 1348-1349 (1993).
 15. J. D. Daris, L. Aarons and J. B. Houston, Simultaneous assay of fluoroquinolones and theophylline in plasma by high-performance liquid chromatography, *J. Chromatogr.* 621, 105-109 (1993).
 16. B. B. Rasmussen, K. K. Nielsen, and K. Brosen, Determination of theophylline metabolites in human liver microsomes by high-performance liquid chromatography, *Anal. Biochem.* 222, 9-13 (1994).
 17. H. Konishi, and A. Yamaji, Measurement of theophylline metabolites produced by reaction with hepatic microsome by high-performance liquid chromatography following solid phase extraction, *Biomed. Chromatogr.* 8, 189-192 (1994).
 18. G. Carlucci, P. Mazzeo, and G. Palumbo. Simultaneous determination of rifloxacin and theophylline by high-performance liquid chromatography in human plasma, *Analys* , 120, 2493-2495 (1995).
 19. M. A. Radwan, HPLC assay of theophylline and Zidovudine in rat serum, *J. Liq. Chromatogr.* 18, 3301-3309 (1995).
 20. J. Kizu, S. Watanabe, N. Yasuno. Y. Arakawa, S. Uzu, S. Kanda, F. Komoda, T. Iawta, H. Hayakawa, T. Hayakawa, and K. Imai, Development and Clinical application of high-performance liquid chromatography for the simultaneous determination of plasma levels of theophylline and its metabolites without interference from caffeine, *Biomed. Chromatogr.* 13, 15-23 (1999).
 21. P. Augustijns and N. Verbeke, A microassay method for the determination of theophylline in biological samples using HPLC with electrochemical detection, *J. Liq. Chromatogr.* 15, 1303-1313 (1992).
 22. N. N. Chernysheva, I. F. Abdullin, and G. K. Budnikov, Coulometric determination of purine alkaloid series with electrogenerated chlorine, *J. Anal. Chem.* 56, 745-747 (2001).
 23. M. Stredansky, A. Pizzariello, S. Miertus, and J. Svorc, Selective and sensitive biosensor for theophyllin based on xanthine oxidase electrode, *Anal. Biochem.* 285, 225-229 (2000).
 24. G. Chen, Q. Chu, L. Zhang, J. Ye, Separation of six purine bases by capillary electrophoresis with electrochemical detection, *Anal. Chim. Acta*, 457, 225-233 (2002).
 25. D. Habel, S. Guermouche and M. H. Guermouche, Direct determination of theophylline in human serum by high-performance liquid chromatography using Zwitterionic micellar mobile phase. Comparison with an enzyme multiplied immunoassay technique, *Analyst*, 118, 1511-1513 (1993).
 26. C. M. Rico, Mdel Pilar. Fernandez, Ana M. Gutireez, M. Concepcion, P. Conde and C. Camara, Development of a flow fluoroimmunosensor for determination of theophylline, *Analyst*, 120, 2589-2591 (1995).
 27. J. Madarasz, P. Bombicz, K. Jarmi, M. Ban, G. Pokol and S. Gal, Thermal, FTIR and XRD study on some 1:1 molecular compounds of theophylline, *J. Therm. Anal. Cal.* 69, 281-290 (2002).



Table 1 Aminophylline absorbances observed in spectra (ATR-FTIR) of fat-burning sample on the human skin.

Functionality		Absorption Frequencies (cm^{-1})	Absorbance band chosen for quantitation
N – H	Primary amine stretch	3493 , 3380	—
	Primary amine bend	1560	1560
O – H	Stretch (broad)	3398	—
C – H	Aliphatic carbons stretch	2921 , 2849	—
C = O	Ring	1701	—
	Ring conjugated	1649	—
C = C	Ring	1605 , 1525 , 1495	—

Table 2 Changes in N-H bending absorbance peak height after treatment with 5 % aminophylline in combination with 40 % plant oils.

Plant oils	% Decrease	
	30 min	60 min
Corn germ oil	3.73	14.90
Olive oil	— ^a	2.47

^a No change

Table 3 Changes in N-H bending absorbance peak height after 60 min treatment with 5 % aminophylline 30 % / corn germ oil / 10 % essential oil.

Essential oils	% Decrease
Jobba oil	28.53
Peppermint oil	24.58
Ylang oil	9.67
Lilacin oil	21.46

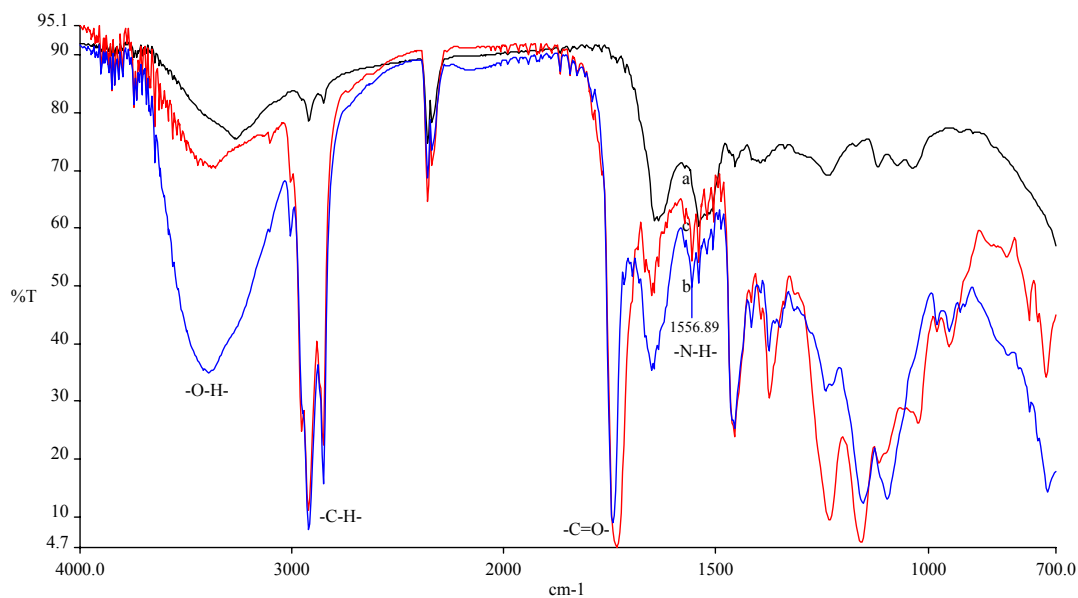


Fig.1 ATR-FTIR spectra of human skin treated with 34.25 mg/cm² and without fat-burning cream containing 5% aminophylline / 30% corn germ oil (a) untreated cream (b) treated cream at 0 min for N-H bending characteristic (c) at 60 min for N-H bending characteristic.

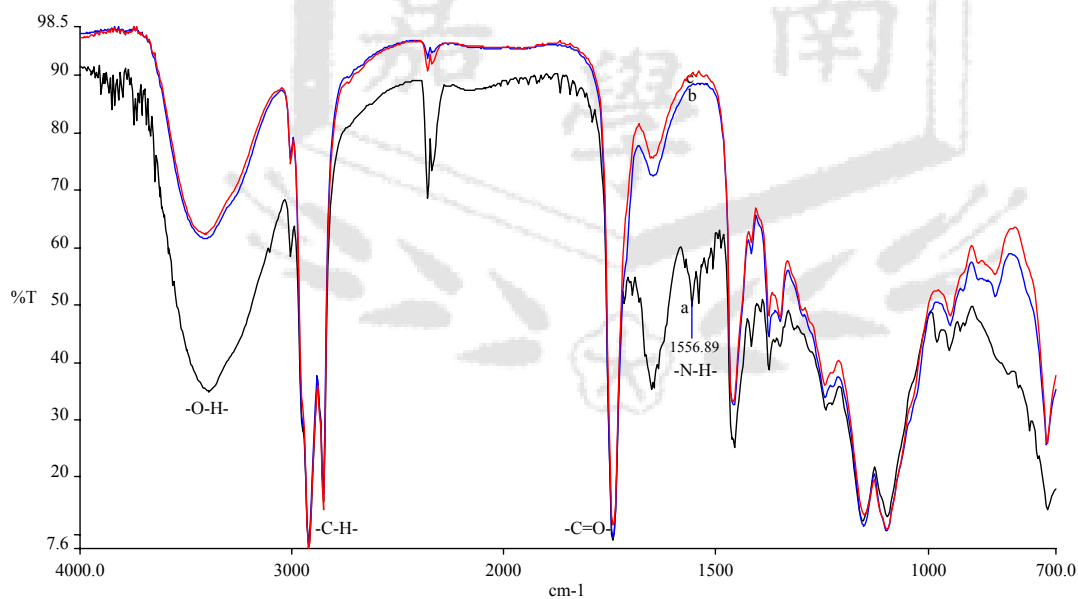


Fig.2 ATR-FTIR spectra of aminophylline stratum corneum treated with cream and essential oils (a) 5% aminophylline / 30% corn germ oil (b) 10% peppermint oil / 30% corn germ oil (c) 10% jojoba oil / 30% corn germ oil.

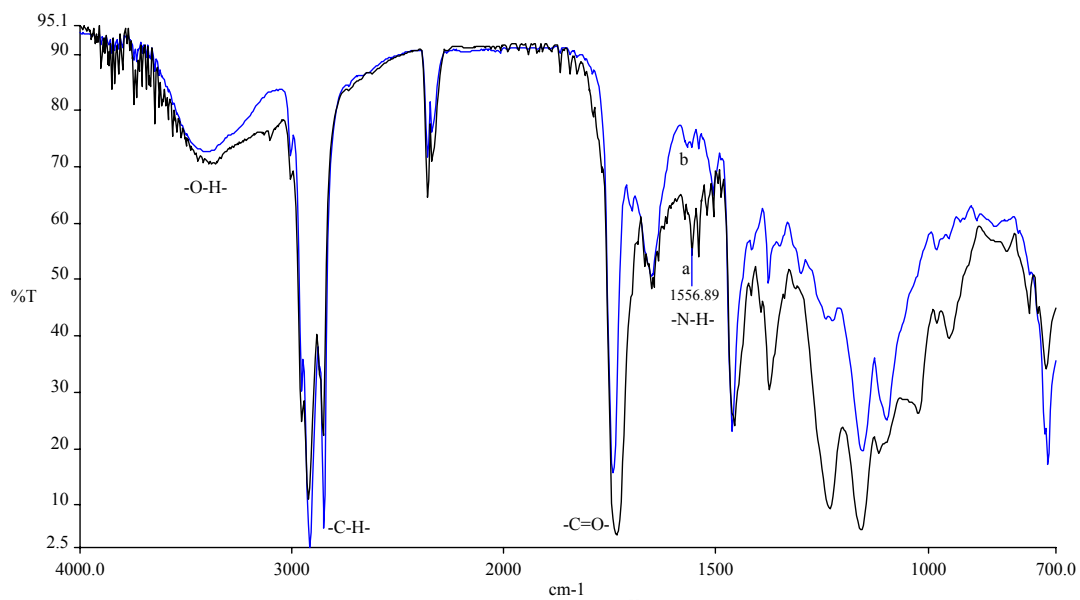


Fig.3 Percutaneous absorption of aminophylline after application of a formulation of 30 % corn germ oil / 10% jojoba oil cream (a) with and (b) without 5% β -cyclodextrin (penetration enhancer).

