and proteins from the erythrocytes[24], therefore, one of the mechanisms of the enhancement of 5-FU penetration is to be lipid extraction from the skin by the complex, but the effect can not be compared with oil's, according to the fact that there is very weak enhancing action in the case of pure β-Cd.

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桉叶油及其β-环糊精包合物对5-氟脲嘧啶经离体大鼠皮肤渗透的促进作用

达尤·阿博杜拉 平其能 刘国杰

(中国药科大学药剂学教研室,南京 210009)

摘 要 研究了桉叶油及其β-环糊精(β-CD)包合物对5-氟脲嘧啶(5-FU)经皮渗透的影响。渗透实验在离体大鼠皮肤上进行,桉叶油的增渗约60倍,单纯β-CD几乎无促进作用。在扩散池中加入桉叶油及其β-CD包合物与仅用桉叶油相比,水溶性5-FU具有更高的渗透系数和更持久的作用。研究表明桉叶油及其β-CD包合物增加药物在皮肤中的分配系数,但扩散系数增加更为显著,证明促进剂通过改善扩散和分配两种机理发挥作用,其中以扩散过程为主。

关键词 5-FU; 桉叶油; 环糊精包合物; 皮肤渗透; 促进剂

Enhancing Effect of Eucalyptus Oil, and Its β-Cyclodextrin Complex on the Permeation of 5-Fluorouracil Through Excised Rat Skin

Dayo Abdullah, Ping Qineng, Liu Guojie
Department of Pharmaceutics, China Pharmaceutical University, Nanjing 210009

Abstract The effects of eucalyptus oil(oil) and its complex with β-cyclodextrin(complex) on the percutaneous absorption of 5-fluorouracil(5-FU) were investigated. Permeation experiments were performed on the excised rat skins and the enhancers varied in their activities. The oil caused about 60 fold increase. β-cyclodextrin was less effective than the complex. Treating the skin with the oil and addition of the complex in donor phase gives higher permeability coefficients of the aqueous 5-FU than treating the skin with oil alone. With the oil and the complex, increased partition coefficients were observed but the diffusion coefficient values obtained were comparatively higher. The mode of action of these accelerants may be described by combined processes of partition and diffusion, the diffusion process being dominant.

Key words 5-Fluorouracil; Eucalyptus oil; Cyclodextrins complex; Skin permeation; Enhancer

Introduction

The skin has become a matter of interest in the pharmaceutical field because of its potency as the route of systemic administration[1]. However, the difficulty to employ the transdermal route for a systemic administration, is that the skin is essentially a barrier against penetration and permeation of the external substances, including drugs for therapeutic uses[2]. One of the available methods to improve the transdermal transport is to reduce this barrier function of the skin by the aid of penetration enhancers or accelerants[3].

An ideal penetration enhancer is pharmacologically inert and cosmetically acceptable, and has yet intermediate and reversible action[3~5]. Essential oils are the volatile, fragrant substances residing in the flowers, fruit, leaves, and roots of many plants. Numerous essential oils have been employed as perfumes, flavorings and medicines for centuries. They are a complex mixture of compounds, including nitrogen and sulfur-containing molecules, aromatic chemicals, and terpenes. Terpenes may be divided as acyclic, monocyclic, bicyclic and so on, and have wide varied uses[6]. Eucalyptus oil has been employed in ointments as a topical counter-irritant and together with menthol as an inhalation[7].

Cyclodextrins(Cds) have been one of the subjects of interest for numerous industries including those engaged in the pharmaceutical field[8]. This is due to their particular structures which impart interesting physiochemical properties. Today Cds are known for their ability to molecularely encapsulate a wide variety of the drugs into their hydrophobic cavity, resulting in the enhancement of water solubility and drug dissolution rate. Though various studies of the effects of Cds on the drug absorption from the gastrointestinal tract have been carried out, there has been little information on the utilities of the Cds as the additives for topical preparations.

In the present study, 5-fluorouracil(5-FU) was chosen as penetrant and the effects of eucalyptus oil(Oil), and β-cyclodextrin(β-Cd) on the percutaneous penetration of dissolved drug has been investigated. As the essential oils are volatile in nature, an attempt was made to make the complex of eucalyptus oil with β-cyclodextrin(complex), and the enhancing effect of complex towards 5-FU was also investigated.

Materials and methods

Materials 5-FU was obtained from Shanghai

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12th Pharmaceutical Manufacturing Factory, Shanghai. Eucalyptus oil was obtained from Da Qun Chemical Manufacturing Factory, Guangzhou, and β-Cd from Suzhou Weijing Factory, Suzhou.

All the other chemicals and reagents used were of the reagent grade obtained commercially.

Complex formation β-Cd (4 g) was dissolved in 50 ml of water around 50℃ and 1 ml of eucalyptus oil was added and stirred for 2.5 h at the same temperature. The mixture was filtered and the residue (complex) was washed with 5 ml of absolute alcohol, 3 times. Finally kept in desicator until dried.

The physical mixture of the eucalyptus oil and β-Cd were also prepared in the same ratio by gradually mixing both, and the mixture was stored in desicator till further use.

Evaluation of inclusion complex The inclusion complex, free β-Cd, eucalyptus oil and the physical mixture were subjected to DSC studies using a home made DSC setup (CDR-I; Shanghai Tianping Instrument Factory, Shanghai). The empty alumina pan was used as a reference at scanning rate of 20℃/min.

Skin preparation Male white rats (SD) weighing 190 to 240 g were used. The animals were sacrificed and hairs from the abdominal side were clipped. The clipped abdominal skin was excised from the animal and the subcutaneous fat on the dermal side was removed. The skins were floated on normal saline for 12 h before use to ensure full tissue hydration.

The samples of full thickness skin without stratum corneum were prepared by the tape stripping method as described by Williams and Barry[9].

Permeation experiments A two chamber cell system with a diffusional area of 2.01 cm^2 was used. The receptor cell was filled with 16.5 ml of normal saline solution, and stirred at 100 rpm. The donor cell receives 1 ml of the saturated solution of 5-FU. To ensure full saturation of the donor solution a crystal of 5-FU was placed in the donor compartment. The receiving cell was maintained at (37 ± 0.5)℃, while the donor cell was exposed to the ambient temperature. At appropriate times 4 ml of solution was withdrawn from the receptor compartment, and 1 ml was used for analysis. After sampling, 4 ml of fresh normal saline was added to the receptor to keep the volume constant.

To determine the enhancing effect of the oil, β-Cd and complex, the skins were prepared in the same way and mounted between the donor and receptor compartments. Here, donor compartment receives 150 μl of the oil, β-Cd (saturated solution), or complex (complex in water at saturated concentration of β-Cd). After 12 h treatment, the excessive enhancer was removed by swabbing with tissue paper and 5-FU permeation was determined as described above.

To determine the effect of the complex as a mixture with 5-FU solution, the skin was treated with the oil and in the donor compartment saturated solution of 5-FU containing complex, at saturated point of the β-cd, was added. This system will be described here as oil/complex in donor phase (Oil/CDP).

Amount of 5-FU in skin The amount of the drug in the skin was determined, as described by Tenjarla et al[10]. At the end of experiment the exposed skin was cut, the surface was washed carefully with water to remove excess drug on the surface, blotted dry, weighed and cut into small pieces. The tissue was homogenized with 4 ml of ethyl acetate thrice. The homogenates were mixed, filtered, and the ethyl acetate evaporated to dryness. The residue was reconstituted with 2 ml of water and analyzed for the drug content by HPLC.

Analysis of 5-FU The concentration of 5-FU in receptor solution was determined by HPLC. Shimadzu LC-5A system equipped with UV detector was used. A Zorbax ODS column (4.6 mm × 25 cm) was employed. The eluting solvent was water and the flow rate was 0.8 ml/min. Detection was done at 266 nm. The retention time of 5-FU was 7.2 min.

One ml of methanol was added to 1 ml of 24 h skin eluted solution, which already contained a measured amount of 5-FU, giving a final concentration of 1, 2.5, 5, 10 and 20 μg per ml. The solution was vortex stirred and centrifuged at 6000 r/min for 10 min, at room temperature. The 20 μl of resulting supernatant was injected into the HPLC.

Solubility studies To determine the solubility of 5-FU in oil, an excess of 5-FU was added to 5 ml of the oil, heated to (37 ± 0.5)℃, vortex stirred and equilibrated for 24 h. A 0.5 ml of

sample was taken, filtered through 0.8 μm filter, diluted to 10 ml with ethyl acetate and analyzed by HPLC.

To determine the effect of β-Cd on the solubility of 5-FU, the method as described by Higuchi and Conners was used[11]. Excess amount of β-Cd was dissolved in water. The samples were shaken at (37±0.5)℃ for 24 h until the system reached equilibrium. After equilibration the sample was filtered through 0.8 μm filter and the portions of final solutions were analyzed for drug content by HPLC.

Permeation data analysis The flux of 5-FU was calculated from a calibrated curve of the cumulative amount permeated vs time plot. The slope of the linear portion of the plot is equal to the flux. The permeability coefficient (K_P) of the drug was calculated from the following equation[10]:

$$K_P = \frac{J}{C}$$

Where J is the flux and C is the concentration of drug added to the skin. As a measure of the penetration activity of the enhancers, the enhancement ratio(ER) was calculated as[12]:

$$ER = \frac{K_P \text{ after application of penetration enhancer}}{K_P \text{ before application of penetration enhancer}}$$

The partition coefficient of the drug is expressed by the equation[13]:

$$P_C = \frac{\text{mg of drug/mg of the skin}}{\text{mg of drug/mg of the solvent}}$$

The diffusion coefficient was calculated, using the equation[14]:

$$D = \frac{K_P \cdot h}{P_C}$$

Where K_P is the mean permeability coefficient and h is the thickness of hydrated stratum corneum(taken as 3×10^{-3} cm)[15].

Results and discussion

Fig 1. shows the DSC curves of β-Cd, oil, physical mixture and complex. β-Cd showed a prominent peak at 100℃. Eucalyptus oil showed a peak at 145℃. With physical mixture, the prominent peaks of β-Cd were also observed but no any peak was observed for the oil, showing a partial complexion of β-Cd with the oil. However, in case of the complex, the peaks of β-Cd and the oil both were totally absent, showing a strong complexion. Using oil separation method, as described by Chinese Pharmacopoeia[16], it was found by determination that 1 g of the complex contained 0.133 ml of oil.

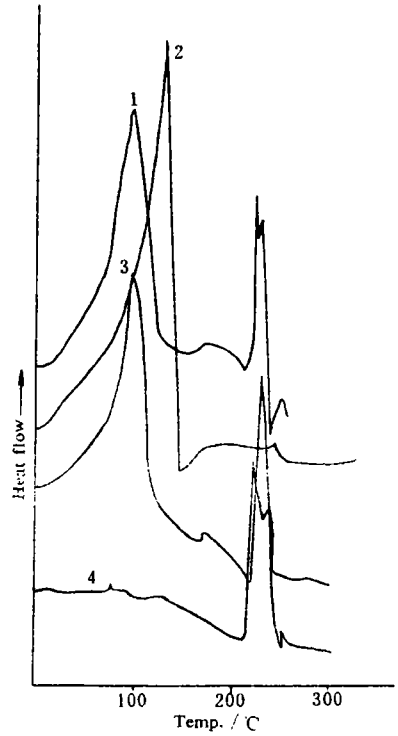

Fig 1. DSC curves of oil/β-Cd complex at a scanning speed of 20 ℃/min.
β-Cd(1); oil(2); physical mixture(3); complex(4)

The permeability coefficients and the enhancement ratios of 5-FU before and after the treatment of the skin with the enhancers indicated the obvious enhancing effect (Tab 1). The mean control value for K_P of 5-FU in the untreated skin at (37±0.5)℃ is(1.053±0.02)×10^{-3} cm/h, with a lag time of 4 h.

Tab 1. Mean flux, permeability coefficients(K_P) and enhancement ratios(ER) of 5-FU in rat skin before and after treatment with enhancers ($\bar{x}\pm s$, $n=3$)

Enhancer	Flux, μg/cm² · h	K_P, cm/h(10^{-3})	ER
Control	13.0±0.28	1.053±0.02	——
Oil	786.0±11.4	62.80±10.0	59.63
Stripped control	2188.4±12.6	175.07±1.0	166.25
Stripped treated	2572.9±34.4	205.80±0.27	195.44 (1.175)*
β-Cd	23.2±0.31	1.86±0.25	1.768
Complex	157.7±0.54	12.62±0.43	11.98
Oil/CDP	1055.3±14.2	84.30±1.14	80.05

*Values when stripped untreated rat skin was taken as control

In Fig 2. the total amount of the penetrant that appeared in the receptor fluid was plotted as

a function of time. Following skin treatment with a enhancer, the lag time for 5-FU falls. The steady state permeation was observed only for 4～6 h when oil was used as enhancer, and when stripped stratum corneum was used the steady state permeation was observed only for 2 ～3 h, which may contribute to accumulation of the higher concentrations of 5-FU in the receiver compartment and/or the wash up effect of the enhancer in the diffusion cell. However, in case of β-Cd and the complex, the steady state permeation was observed for more than 24 h.

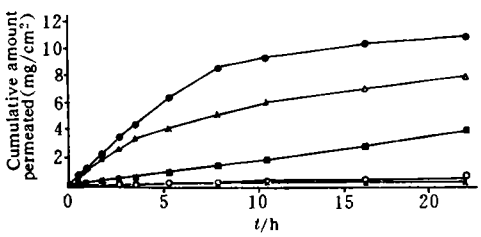

Fig 2. Effect of the enhancers on 5-FU permeation across rat skin
Control(—×—); β-Cd(—○—); Complex(—■—); Oil(—△—); Oil/CDP(—●—)

Fig 2. shows comparative permeation profiles for β-Cd, complex, oil and oil/CDP system. The oil clearly increased the drug permeation (ER = 59. 63) ($P<0.01$). β-Cd showed a very little effect on the drug permeation (ER = 1. 768). The effect of the complex was found to be less than the oil, but more than the β-Cd (ER = 11. 98). Treating the skin with the oil and incorporating the complex in the donor phase give more enhanced permeation than the oil only (ER = 80. 05), and significally prolonged the enhancing time of the oil.

Removing the stratum corneum completely eliminated the barrier properties of the skin. Permeation profiles with and without treating the skin with the oil through stripped stratum corneum are shown in Fig 3. A little difference was observed between the treated and untreated stripped membranes, as ER values obtained were 166. 25 and 195. 44, respectively, when the full skin was taken as a control. When the stripped untreated membrane was taken as a control ER for treated stripped membrane was 1. 175 only.

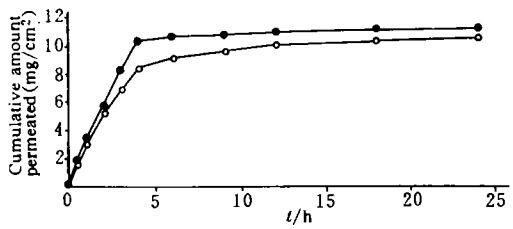

Fig 3. Typical permeation profiles of 5-FU through stripped stratum corneum rat skin
Control(—○—); Treated(—●—)

The partitioning results are shown in Tab 2. The treatment of skin with the enhancers used generally increased the partitioning of the drug into the skin membrane as illustrated by the partition ratio, P_R[13,14], where:

$$P_R = \frac{P_C \text{ after enhancer treatment}}{P_C \text{ with untreated skin}}$$

Tab 2. Mean partition coefficients(P_C), diffusion coefficients(D), partition ratios(P_R) and diffusion ratios(D_R) of 5-FU into fullyhydrated membranes($\bar{x}\pm s$, $n=3$)

Enhancer	P_C, $\times 10^{-3}$	D, cm/h($\times 10^{-5}$)	P_R	D_R
Control	46. 94±4. 3	6. 7±0. 4	1. 0	1. 0
Oil	98. 80±13	193±272. 1	28. 6	
Stripped control	7. 47±0. 1	7020±41	0. 15	1038. 46
Stripped treated	17. 15±0. 6	3599±5. 3	0. 36±2. 29[a]	532. 39(0. 51)[a]
β-Cd	54. 27±3. 0	10. 2±0. 1	1. 15	1. 5
Complex	95. 95±1. 7	39. 6±0. 1	2. 0	5. 8
Oil/CDP	90. 49±5. 7	357. 7±4. 7	1. 92	52. 91

[a]Values when stripped untreated rat skin was taken as control

The treatment of the skin with the oil and the complex doubles that partitioning, and P_R values obtained were 2. 1 and 2. 0 respectively, but in the case of β-Cd no any significant increase was observed ($P_R = 1.15$). The partition ratios obtained with the stripped untreated and stripped treated skin were less than the unity when full thickness skin was taken as a control,

and more than double when stripped untreated membrane was taken as a control.

From the diffusion coefficient values (Tab 2), it can be seen that the use of the enhancers has decreased the resistance to the diffusion of the drug, as the mean untreated diffusion coefficient value of 5-FU is $(6.76 \pm 0.4) \times 10^{-5}$ cm^2/h only. The increase in diffusivity of 5-FU in the skin may be expressed as a diffusivity ratio, D_R[14]:

$$D_R = \frac{\text{diffusivity of 5-FU after treatment}}{\text{diffusivity of 5-FU before treatment}}$$

The solubility of the 5-FU in the oil, as determined, is about 0.046 mg/ml. 5-FU is much less soluble in the enhancer than in the donor phase, water. The solubility of 5-FU in water is 12.5 mg/ml[17]. Fig 4. shows the effect of β-Cd on the solubility of 5-FU. No any profound effect of β-Cd was observed on the solubility of 5-FU. Therefore, the enhanced permeation of 5-FU is not related with its solubility, but only with the efficiency of oil on skin.

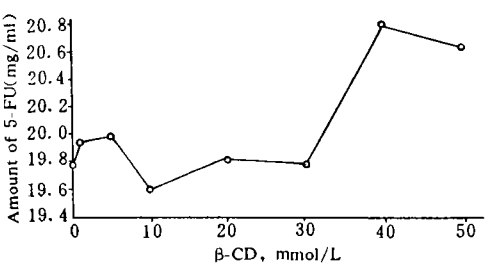

Fig 4. Phase solubility diagram of 5-FU/β-Cd system at (37± 0.5)℃

Some essential oils and their terpene constituents have recently been investigated as potential enhancers. The eucalyptus oil and camphor increased the total flux of nicotine permeating excised hairless mouse skin[18]. The eucalyptus oil and others have increased the permeation of 5-FU in excised human skin[19]. In our previous studies, oils of eucalyptus, peppermint and turpentine were investigated for their enhancing effect towards 5-FU, using excised rat skin[20]

In the present studies eucalyptus oil was found to be most active. No any lag time was observed. The eucalyptus oil increased the penetration of polar drug 5-FU, by aprox. 60 fold.

The effects of β-Cd and di-*O*-methyl-β-Cd on the percutaneous absorption of butylparaben, indomethacin and sulfanilic acid have been investigated[21]. β-Cd has enhanced the bioavailablity of the tolnaftate percutaneously[22]. In our studies β-Cd itself showed a very little effect on the drug permeability, as only 1.76 fold increase was observed, but in case of the complex aprox. 12 fold increase was observed. On the other hand, in case of Oil/CDP system an aprox. 81 fold increase in the drug flux was observed. Therefore, from these results it can be seen that the eucalyptus oil can be complexed with β-Cd and the complex can be used as a good enhancer. Complex can also be useful to prevent oil from volatilization, and thus the oil can stand on the site of action for longer periods, resulting in prolonged and controlled release of drug. Furthermore, the complex may also be easily incorporated into the transdermal formulations.

Removal of the stratum corneum has completely eliminated the resistance to the drug permeation and is in good agreement with all the published data, that the main resistance to the permeation of hydrophilic drugs lies in the stratum corneum[4,9,23]. It can be seen that the oil and its complex have only the enhancing effect towards the stratum corneum.

The partition ratios calculated suggest that the enhancers increased the partition of 5-FU into the skin. As the drug is less soluble in the oil than water, the increased partition of 5-FU in skin can be contributed to the structure modification of stratum corneum lipid-bilayers. Therefore, we conclude that the enhanced permeation of the 5-FU may be produced not only by increasing the partition of drug into stratum corneum, but also by modifying the intercellular lipids, disrupting their highly ordered structure, thus increasing the diffusion of 5-FU through the membrane, as observed by comparatively increased diffusivity ratios (Tab 2). Furthermore, the latter is more important than the former in permeation, because the increased amounts of 5-FU in the skin may also be the retention of the drug by the skin. Same may be true in the case of β-Cd and the complex, as β-Cd has no any effect on the solubility of 5-FU. It has been reported that Cds cause the release of some membrane components such as cholesterol, phospholipids

and proteins from the erythrocytes[24], therefore, one of the mechanisms of the enhancement of 5-FU penetration is to be lipid extraction from the skin by the complex, but the effect can not be compared with oil's, according to the fact that there is very weak enhancing action in the case of pure β-Cd.

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达尤·阿博杜拉 平其能 刘国杰

(中国药科大学药剂学教研室,南京 210009)

摘 要 研究了桉叶油及其β-环糊精(β-CD)包合物对5-氟脲嘧啶(5-FU)经皮渗透的影响。渗透实验在离体大鼠皮肤上进行,桉叶油的增渗约60倍,单纯β-CD几乎无促进作用。在扩散池中加入桉叶油及其β-CD包合物与仅用桉叶油相比,水溶性5-FU具有更高的渗透系数和更持久的作用。研究表明桉叶油及其β-CD包合物增加药物在皮肤中的分配系数,但扩散系数增加更为显著,证明促进剂通过改善扩散和分配两种机理发挥作用,其中以扩散过程为主。

关键词 5-FU; 桉叶油; 环糊精包合物; 皮肤渗透; 促进剂