J. Appl. Cosmetol. 22, 35-42 (January/March 2004)

INFLUENCE OF POLYALCOHOLS AND SURFACTANTS ON SKIN PENETRATION OF FLAVONOIDS FROM THE EMULSION

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Received: *February 2004 - Presented at the "All for Cosmetics Conference", Warsaw 19-20 November, 2003*

Key words: *Flavonoids; Skin permeation; Polyalcohols; Surfactants; Diffusion cell*

Summary

It has been proven that common cosmetic ingredients - polyalcohols and surfactants can influence the permeation process of flavonoids from O/W model emulsion.
The experiments have shown that permeation rate of selected flavonoids decreases with increasing length of surfactant's oxyethylene chain. The highest permeability coefficient was calculated for the emulsion containing polyoxyethylene 12 cetostearyl ether.
It has been documented that investigated polyalcohols increase permeation rate of both quercetin and rutin. The substance increasing permeability coefficients of flavonoids very effectively is 1,2-propylene glycol. Investigations introduced in this paper have evidenced that permeation coefficients of flavonoids increase with increasing molecular weight of polyethylene glycols up to the value 1500. It has been also confirmed that the penetration ability of flavonoids depends on concentration of applied cosmetic additives.
Results presented in this paper through a new light on the problem of formulating products containing flavonoids and posses many practical aspects. To elucidate the mechanisms that are involved in the processes described above the investigation on the model solution should be done. It has been proven that process of skin penetration of flavonoids can be controlled by proper selection of other cosmetic additives. The careful addition of adequate hydrophilic substance and application of suitable surfactant can increase the permeation rate of flavonoids from the emulsion system what finally results in better cosmetic activity of these active substances.

Riassunto

È stato dimostrato come i polialcoli ed i tensioattivi siano in grado di influenzare il processo di penetrazione dei flavonoidi da un modello di emulsione olio/acqua.
Le prove sperimentali hanno dimostrato che il grado di penetrazione dei flavonoidi selezionati, di-

minuisce con l'aumentare della catena ossietilenica dei tensioattivi. L'emulsione contenente l'etere poliossietilen 12 ceto-stearilico ha dimostrato di possedere il più alto coefficiente di penetrazione.
È stato documentato che i polialcoli studiati incrementano il grado di penetrazione sia della quercitina che della rutina. In particolare il 1,2 propilenglicol incrementa molto il coefficiente di permeabilità dei flavonoidi.
Gli studi condotti con questo lavoro hanno posto in evidenza come i coefficienti di permeazione dei flavonoidi si incrementino con l'aumentare del peso molecolare dei glicoli polietilenici fino al valore 1500.
È stato confermato che l'abilità penetrativa dei flavonoidi dipende dalla concentrazione di questi additivi utilizzati.
I risultati presentati in questo lavoro pongono una nuova luce sul problema della formulazione dei prodotti cosmetici contenenti flavonoidi anche da un punto di vista pratico.
Per delucidare i meccanismi coinvolti in questo processo è necessario studiare a fondo il tipo di emulsioni adottate soprattutto per quanto riguarda la fase acquosa. Infatti si è potuto verificare come il processo di penetrazione dei flavonoidi possa essere controllato adottando una scelta oculata delle materie prime.
L'aggiunta oculata di una sostanza idrofila e l'applicazione di un adeguato tensioattivo può incrementare il grado di penetrazione dei flavonoidi inseriti nell'emulsione, migliorando in modo sensibile l'attività del prodotto formulato

INTRODUCTION

Skin penetration ability of active substances is one of the most important problems in modern cosmetology. Investigations undertaken by scientists in this field are important factor in development of cosmetic industry.

It has been documented, that activity of the substance depends strictly on its skin penetration ability [1]. To be effective, the compound must overcome the skin barrier, which is *stratum corneum* and reach the proper skin layer. The very common active substances that found wide application in cosmetology are flavonoids - perfect antioxidants, anti-inflammatory agents and enzyme activity modifiers [2-5]. Unfortunately, the literature concerning skin permeation of these compounds is very narrow what convinced us to investigate this problem.

One of the most common cosmetic delivery system is an emulsion [6-9]. Wide research has been done in the field of permeation of substances from the emulsion but none of them concerns flavonoids. This paper focuses on the problem of skin penetration of selected flavonoids - quercetin (1) and rutin (2) from the O/W emulsion.

Model system that has been applied in this research is composed of liposome model membrane mounted in Frantz diffusion cell (Figure 1) [10].

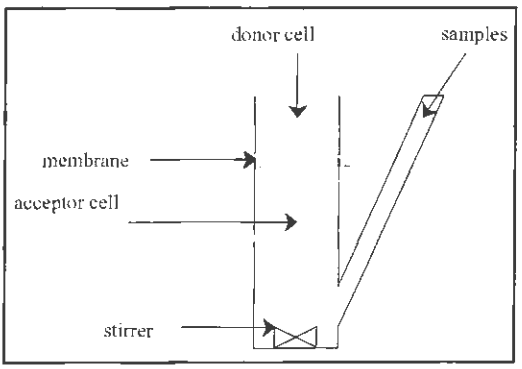


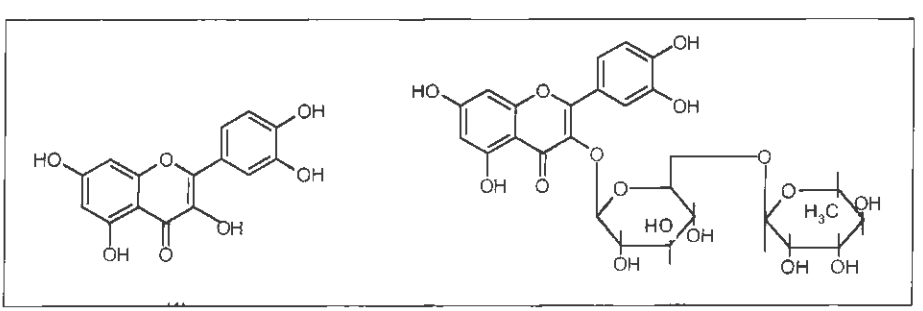
Fig. 1 Frantz diffusion cell.

The literature reports that common cosmetic ingredients - polyalcohols can influence the permeation process [11-14]. The other group of substances influencing skin penetration of chemical compounds are surface active agents [15-18]. Flavonoids are very often a part of complicated cosmetic system containing polyalcohols as well as surface active agents what convinced us to undertake research in this field. The matter of this paper is an influence of selected polyalcohols and nonionic surfactants on penetration ability of flavonoids from O/W emulsion.

Materials and methods

Materials

Rutin and quercetin were purchased from Sigma - Aldrich. PEG 400 and PEG 1500 were obtained from Clariant. Glycerine, 1,2-propylene glycol and 1,2- butylene glycol were supplied



by Fluka. Polyoxyethylene 12 cetostearyl ether, polyoxyethylene 20 cetostearyl ether and polyoxyethylene 30 cetostearyl ether (Eumulgin B1, Eumulgin B2 and Eumulgin B3 respectively) were obtained from Cognis. Polyester membrane (radius – 12mm, diameter of pores – 0,4 micrometer, thickness – 12 micrometers) was purchased from The Institute of Chemistry and Nuclear Technique in Warsaw.

Model membrane and permeation process

Liposomes composed of the *stratum corneum* lipids were sandwiched between two polyester membranes and dried in the room temperature for 24 hours. After mounting in Frantz diffusion cell the acceptor cell was filled with 15 ml of phosphate buffer, pH 7.4. 1 g of O/W emulsion containing quercetin or rutin was placed in the donor cell. Diffusion cell has been placed on the magnetic stirrer and samples were collected during 72 hours.

Concentration of flavonoids was determined by spectrophotometric methods.

Permeability coefficient (Kp) was calculated according to the following equation:

$$Kp = \frac{J}{C_v}$$

where:

Kp- permeability coefficient

J- flux at the steady state

C_v - concentration of flavonoid in the donor solution

Components of model emulsion

- Glyceryl Stearate (Cutina GMS) - 8 %
- Hexyldecanol, Hexyldecyl Laurate (Cetiol PGL) -20 %
- Emulsifier - Ceteareth-12 (Eumulgin B_1) or Ceteareth-20(Eumulgin B_2) or Ceteareth-30(Eumulgin B_3) - 3%
- Polyalcohols: glycerin or 1,2-propylene glycol or 1,2-butylene glycol or PEG - 3%
- Methylchloroisothiazolinone, Methylisothiazolinone (Kathon CG) - 0.1%
- Water - q.s.

RESULTS AND DISCUSSION

Influence of cosmetic additives on transport of flavonoids

The emulsifier

Surface active agents are substances influencing the permeation process of other compounds through the stratum corneum and membranes modeling stratum corneum. Polyoxyethylene cetostearyl ethers of different oxyethylene chain length have been employed to investigate the influence of the emulsifier on the migration rate of flavonoids. The schematic formula of these compounds has been introduced below:

$R\text{-}(OCH_2CH_2)_nOH$ R= blend of cetyl and stearyl radicals, n = 12, 20 or 30

The influence of these nonionic surfactants on the permeability coefficients of flavonoids is presented at the Figure 2.

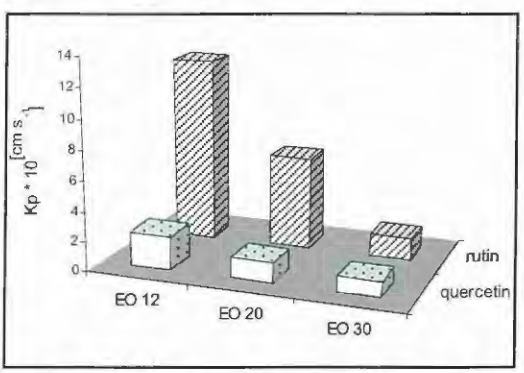


Fig. 2 Influence of oxyethylene chain length on permeation rate of flavonoids.

Table I

Influence of EO chain length on permeability coefficients of flavonoids.

EO CHAIN LENGTH	$KP_Q \cdot 10^7$ [CM S-1]	$KP_R \cdot 10^7$ [CM S-1]
12	2.23	12.34
20	1.32	6.20
30	0.99	1.48

The experiments introduced above have proven that length of oxyethylene chain in the emulsifier plays significant role in the permeation process. The influence of nonoinic surfactants is more visible in the case of rutin (Table 1).

where:
Kp_Q and Kp_R – permeability coefficients for quercetin and rutin respectively.

Permeability coefficients of investigated flavonoids decrease with increasing length of oxyethylene chain. The highest permeability coefficient can be observed for the system that contains polyoxyethylene 12 cetostearyl ether in the case of both flavonoids. Polyoxyethylene 30 cetostearyl ether is the emulsifier for witch the permeation rate of quercetin as well as rutin was the lowest.

Polyalcohols

Other group of substances influencing permeation ability of chemical compounds are polyalcohols. The literature reports that cosmetic additives such as 1,2-propylene glycol (PG), glycerine and 1,2- butylene glycol (BG) can play a significant role in process of skin penetration.
This paper introduces the influence of polyalcohols mentioned above on permeation rate of quercetin and rutin from O/W emulsion through the model membrane mounted in Frantz diffusion cell. Results of the experiments have been presented at the Figure 3.

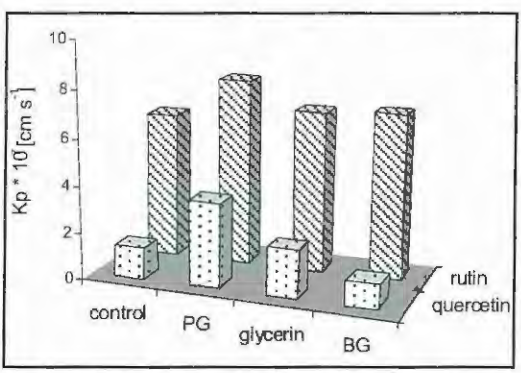


Fig. 3 Influence of polyalcohols on permeation rate of flavonoids from O/W emulsion.

It has been observed that influence of investigated polyalcohols is different for quercetin and for rutin. Permeation coefficient calculated for rutin is more than 4 times higher than for quercetin. The presence of polyalcohols influences mainly transport process of quercetin. Differences between emulsion containing polyalcohols and control emulsion have been introduced in the Table II.

Table II

Differences between Kp of flavonoids in emulsion containing polyalcohols and Kp in control emulsion.

polyalcohol	$\Delta Kp_Q \cdot 10^7$ [cm s-1]	$\Delta Kp_R \cdot 10^7$ [cm s-1]
control	-	-
1,2- propylene glycol	2.25	1.69
glycerin	0.70	0.61
1,2- butylene glycol	-0.31	0.79

Where:

ΔKp = Kp in the presence of polyalcohol – Kp in the absence of polyalcohol

control – system without polyalcohol

It has been proven that all probed polyalcohols (except for 1,2-butylene glycol in the case of quercetin) increase permeation rate of flavonoids. 1,2-propylene glycol is the substance that very effectively increases permeation coefficient of both quercetin and rutin. Less influence can be observed for glycerine.

Cosmetic additives of hydrophilic character are present in emulsions in different concentration. Furthermore, after appliction onto the skin the contents of particular chemicals change. Further part of our research comprised the determination of polyalcohol concentration influence on the penetration ability of flavonoids. 1,2-propylene glycol has been selected as a representative substance. Results of these experiments have been presented at the diagram below (Figure 4).

As drown at the Figure 4, the permeation rate of both flavonoids depends on concentration of 1,2-propylene glycol. Increase in propylene glycol concentration results in increasing value of permeation coefficient for rutin. Different character of the curve can be observed for quercetin. Permeation coefficient of this substance increases with increasing concentration of polyalcohol up to 3%. Permeation coefficient of quercetin decreases when PG concentration is 3-12% and increases for concentration higher than 12%.

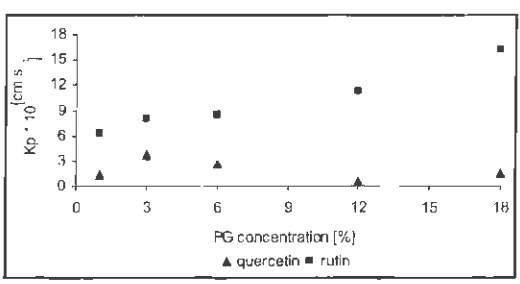


Fig. 4 Influence of 1,2-propyene glycol concentration on permeability coefficient of flavonoids from O/W emulsion.

Polyethylene glycols (PEG)

The next stage of this research aimed at determination of permeation coefficient of quercetin and rutin in the presence of common cosmetic ingredients - polyethylene glycols (PEG). The results of these experiments can be sketched according to the following diagram (Figure 5).

The analysis of Figure 4 revealed the influence of polyethylene glycols' molecular weight on permeation coefficients of quercetin as well as

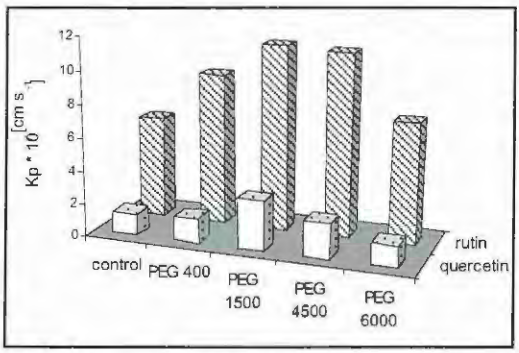


Fig. 5 Influence of polyethylene glycols of different molecular weight on permeation ability of flavonoids.

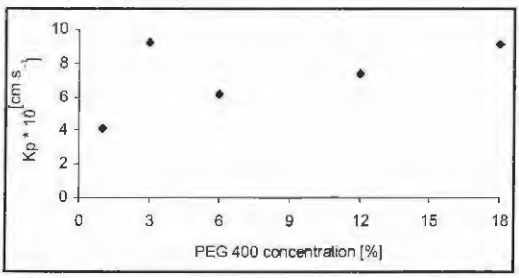


Fig. 6 Influence of PEG 400 concentration on permeability coefficient of rutin from O/W emulsion.

rutin. One can notice that investigated polyethylene glycols increase the permeation rate of flavonoids from O/W emulsion (Table III).

Where:

ΔKp = Kp in the presence of PEG – Kp in the absence of PEG

control – system without PEG

Permeability coefficients increase with increasing molecular weight up to value 1500. In the range of molecular weight 1500-6000 decreasing tendency of permeation coefficients can be observed. The effect of polyethylene glycols concentration on transport process of rutin was investigated employing PEG 400 as a model substance. The results of this research can be presented according to the Figure 6.

It has been proven that addition of PEG 400 to the O/W emulsion containing rutin causes the increase in permeation rate of this substance. The highest permeability coefficient value can be observed for the system containing 3% PEG 400.

Table III

Differences between Kp of flavonoids in emulsion containing PEG and Kp in control emulsion.

PEG's molecular weight	$\Delta Kp_Q \cdot 10^7$ [cm s-1]	$\Delta Kp_R \cdot 10^7$ [cm s-1]
control	-	-
400	0.15	2.99
1500	1.66	5.08
4500	0.83	4.84
6000	0.00	1.07

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