Concerns regarding the safety of cumulative exposure to parabens have been raised as a consequence of their estrogenic and endocrine effects. These antibacterial agents are commonly used in food, pharmaceutical and cosmetic products. Preliminary data from animal models has indicated potential links between paraben exposure and various conditions ranging from skin disorders to autism. Oral consumption of parabens is not a cause for concern because they are readily metabolised by the liver and excreted rapidly by the kidney. The presence of parabens in adipose tissue is thought to be due to dermal absorption of parabens where they are incompletely metabolised. Various studies have been performed on paraben absorption; however transdermal permeation of parabens from an emulsion has not been studied to date. In this preliminary study dermal permeation and metabolism across human skin were evaluated for methyl paraben (MP) and butyl paraben (BP) from an emulsion, using Franz Diffusion cell system with analysis by q-ToF (quadrupole time of flight) mass spectrometry. MP was observed to have lower permeation and lower extent of metabolism than BP.

INTRODUCTION

Parabens have been used as preservatives in food, pharmaceutical and cosmetic products for over 50 years (Soni 2005). Humans are exposed to parabens by dermal contact and ingestion. When ingested, parabens are metabolised by the liver, thus higher tissue concentrations of native paraben occur when dermally absorbed. Preliminary animal studies proposed a link between cases of autism and paraben exposure (Ali and Elgoly, 2013; Hegazy et al, 2015) implying that use of paraben-containing formulations on the skin could be a potential ‘risk’ factor. The aim of our study was to examine the extent of diffusion and metabolism of MP and BP via human skin.

MATERIALS AND METHODS

20g of oil-in-water creams were prepared as described in Dodou et al. (2015). Formulations containing 1% w/w paraben (n=3) were prepared by adding the paraben (MP or BP) to the oily phase. Water was then added slowly to the oil phase at the same temperature. A paraben-free cream was used as control.

In-vitro skin permeation studies: Human abdominal skin from one donor (thickness=500µm) was mounted in 8 glass Franz cells (absorption surface area =
Skin samples were placed between the donor and receptor chambers, with the dermis in contact with the receptor medium. The receptor chamber was filled with \(\sim 1.5\) ml of PBS, stirred continuously with a magnetic stirrer while incubated at \(37\pm0.5^\circ\)C. The paraben-free cream was applied to the donor chamber of cell 1 and medicated cream to cells 3-9 \((n=6)\); \(15mg\) of formulation was applied to the donor chamber of each cell, yielding a specific dose of \(75\mu g/cm^2\) of paraben. Receptor fluids were removed at different time intervals \((1, 2, 4, 6, 24\) h) and cells filled with \(\sim 1.5\) ml of fresh preheated PBS. Analysis of paraben and metabolite content in the receptor fluid samples, skin swabs and skin digests was performed via chromatographic separation using a \(4.6mmx50\) mm, \(1.8-mm\) particle size Agilent XDB-C18 column (Agilent Technologies, Santa Clara, CA). The separation was performed isocratically with \(50\%\) A \((10mMol Ammonium Acetate/Water)\) and \(50\%\) B \((10mMol Ammonium Acetate/Methanol)\), at a flow rate of \(0.6\) ml/min, a run time of \(8\) min, autosampler temperature at \(5^\circ\)C and injection volume of \(40ul\). All samples were analyzed on a 1200 Series HPLC system coupled to a 6530 Quadrupole Time of Flight (q-ToF) accurate mass spectrometer system with Jet Stream electrospray source (Agilent Technologies) operated in the negative-ion mode. ESI capillary voltage was set at \(3000\) V and fragmentor at \(100\) V.

### RESULTS AND DISCUSSION

BP showed higher % metabolism to para-hydroxy benzoic acid compared to MP (Figure 1). The higher lag time of BP (1.9 h) compared to MP (0.6 h) (Table 1) was indicative of the quicker diffusion of MP through the skin.

![Fig. 1. % Metabolism of MP and BP.](image)

### CONCLUSIONS

Considering the difference of the extent of skin metabolism between the tested parabens, a systematic study of all parabens would be useful to allow their ranking in terms of potential risk.

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### REFERENCES


