High tolerance transdermal patches loaded with caffeine

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ABSTRACT SUMMARY
Caffeine loaded transdermal polyurethane based patches were produced and tested for their in vitro release and in vivo efficacy. The patches were produced by applying a newly developed process (solvent free, no heat exposure) to develop high tolerable patches with a high loading of active.

INTRODUCTION
Caffeine is a phosphodiesterase inhibitor. Despite its pharmaceutical use, recently the active was found to be a promising cosmetic active for the treatment of puffy eyes and cellulite \cite{1}. However, due to its chemical nature the penetration of caffeine into the skin is limited. Therefore, to obtain a sufficient concentration of caffeine in the skin, penetration enhancing methods need to be applied. One possibility is the use of transdermal patches \cite{2}. However, the drawback of many patches is their potential hazard to cause skin irritation, which is caused by residues of organic solvents. In addition these organic solvents need to be removed from the patches after the production, which requires the application of heat, which in turn can lead to the chemical degradation of the active. Recently a new production method for especially skin friendly patches without the use of organic solvents and heat was established \cite{2, 3}. The technology is based on the reaction of polyol and isocyanate to polyurethane (PU) in the presence of the drug and a specially designed coating machine \cite{4}. In addition these patches possess an improved loading capacity when compared to conventional patches. As the skin irritation is often referred to be the “Achilles heel” of these patches, the production of high tolerance skin patches is desired. Therefore the aim of this study was the production of caffeine loaded transdermal patches with high dermal tolerance and a high drug load, when compared to currently marketed patches.

EXPERIMENTAL METHODS
Patches containing 6 % (w/w) caffeine were produced by the reaction of polyol and isocyanate to PU in the presence of the drug \cite{3}. For this Caffeine was mixed with the polyol and the mixture was combined with the isocyanate immediately. The resulting mixture was spread on a PU backing foil using a laboratory technique. The patches were stored at room temperature as “drying temperature”, resulting in a reaction time of 8 min. Oval segments (semi-minor axis = 3 cm, semi-major axis = 4.25 cm) were punched from the resulting web using a die cutter (Arnold & Co. GmbH, Pirmasens, Germany). Drug content was analyzed by HPLC (HP Agilent Series 1100; Column Waters C18). As a reference patch, marketed caffeine patches were used (Cell Patch, Clinians Suisse, Italy). The drug release was studied using a Sotax C7smart Dissolution Tester USP Method 4 (32 °C, 48h) and compared to the marketed product. The in vivo performance to reduce puffy eyes was tested over a period of 3h by applying the patch below the eye on the lower eye lid (Figure 3 middle).

RESULTS AND DISCUSSION
Production of Caffeine loaded patches
For the caffeine a 100% loading efficacy was achieved. However, caffeine could not completely dissolve in the matrix, leading to the appearance of caffeine crystals within the patch (Figure 1). No changes in the appearance of the patch were observed over a storage time of 3 months. The drug content was analyzed and was found to be 6%, hence no chemical degradation
during production occurred. The drug content of the marketed patch was found to be less than 0.2%. Commercial patches with a higher caffeine load were not available.

![Figure 1: Polyurethan (PU) patch loaded with 6 % (w/w) caffeine.](image)

**In vitro dissolution**

The results of the dissolution tests are shown in Fig. 2. The release profiles of the patches were found quite similar by shape, with an initial release of about 25% of the drug during the first 35 min. After 24 h hours about 50% of caffeine from the marketed patch and about 70% of caffeine from the PU patch were released.

![Figure 2: Comparison of dissolution profiles of PU patch loaded with caffeine 6% and marketed patch loaded with about 0.2% caffeine.](image)

**In vivo testing**

The patch was easy to apply, comfortable to wear over a wearing time of 3 hours, and easy to remove without pain. No irritation of skin during or after the treatment was observed. The results showed a reduction in the thickness of the puffy eyes, skin tension and a visible reduction in wrinkles (Figure 3).

![Figure 3: in vivo results – left: eye area prior to treatment; middle – during treatment, right – after treatment. The comparison of the left and right photographs shows a reduction in the thickness of the puffy eyes and a disappearance of wrinkles (c.f. arrows in the images)](image)

**CONCLUSION**

Transdermal patches loaded with 6% (w/w) caffeine were produced. The release profiles of the marketed and the newly developed patch were quite similar. The total release was about 20% higher for the new patch. The loading was about 30fold when compared to the marketed product, thus a 30fold increased caffeine release was obtained. Preliminary in vivo results showed efficient reduction of puffy eyes and a reduction in wrinkles. Further studies will now investigate the skin penetration behavior of caffeine from the patch to optimize the release profile and the in vivo efficacy.

**REFERENCES**


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