STABILITY ASPECTS OF POLOXAMER 407-BASED DRUG DELIVERY SYSTEMS IN PHOTODYNAMIC THERAPY

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Introduction

Previously it could be shown that a poloxamer-407 (POX) semisolid system was able to enhance permeation of 5-aminolaevulinic acid (5-ALA) through excised human stratum corneum [1]. This permeation enhancement was due to a synergistic effect of all the components [2].

In the present study a pseudo ternary phase diagram was established in order to find out which systems have an adequate consistency for dermal application and are stable over one year storage. Such systems are intended to be used as vehicles for 5-ALA in permeation studies.

Experimental methods

Material

Lutrol® F127 (POX) and dimethyl isosorbide (DMIS) were kindly provided by Dolorgiet (St. Augustin , Bonn). Isopropyl alcohol (IPA) and medium chain triglycerides (miglyol 840 = MCT) were purchased from Merck KG (Darmstadt, Germany). Water was used in double distilled quality.

Methods

- **Preparation of the systems**

Preparation of all semisolid and liquid systems was performed with a Cito Unguator 2000 (GAKO Konietzko GmbH, Bamberg, Germany). First POX and then all other components were weighed into a jar designed for the apparatus. This mixture was automatically stirred at 1450 rpm for 1.5 min.

As shown in figure 1 a pseudo ternary phase diagram was established with a fixed combination of 1:1 (w/w) of IPA and DMIS, a fixed ratio of 4:1 (w/w) POX to MCT and water. Formulations were stored in a climate room at 20 °C.

- **Macroscopical Characterization**

Examination was performed 24 hours after preparation since former studies of our group have shown that the systems need a certain time to equilibrate [2] and included the inspection of consistency and homogeneity of the formulations. This was performed by taking a small sample (approximately the tip of a spatula) and spreading it over a microscope slide.

- **Polarising Microscopy**

Selected samples were investigated one day, three, nine and twelve months after preparation under a polarising microscope Leica DM LM (Leica Microsystems GmbH, Wetzlar, Germany) in order to characterize their texture. Digital photographs were taken with an Olympus DP12 (Olympus, Hamburg, Germany).

- **Wide Angle X-Ray Diffraction (WAXD)**

X-rays with a wavelength of $\lambda = 0{,}1542$ nm were generated by the x-ray generator PW3040/60 which was connected to an x-ray tube PW3373/00 with cupper anode. Measurements of selected systems were performed with a goniometer (all PANalytical/Almelo, Netherlands) operated at a high voltage of 40 kV and an anode current of 40mA from 3 to 45 ° 2θ.

References

[1] Gruening, N., Mueller-Goymann, C. C. Physicochemical characterisation of a novel thermogelling formulation for percutaneous penetration of 5-aminolevulinic acid. Journal of Pharmaceutical Sciences, 97(6), 2311-2323 (2008).

[2] Gruening, N. Entwicklung und Charakterisierung eines halbfesten Systems zur Verbesserung der Permeation von 5-Aminolävulinsäure durch exzidiertes humanes Stratum Corneum. Dissertation (2007).

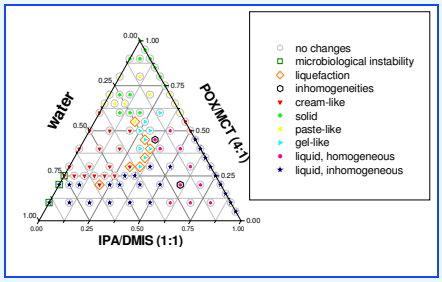

Figure 1 – Macroscopical characterization in a pseudo ternary phase diagram showing consistency and stability of systems upon storage.

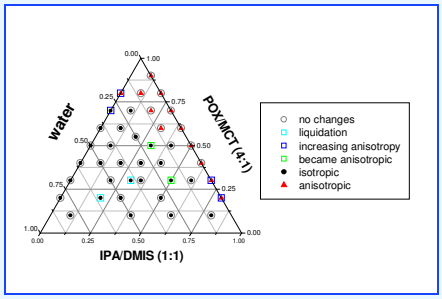

Figure 2 - Pseudo ternary phase diagram showing selected systems analyzed by polarising microscopy.

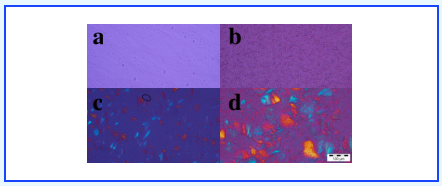

Figure 3 – Phenomena observed by polarising microscopy: a-b liquefaction of a cream, c-d increasing size of crystals.

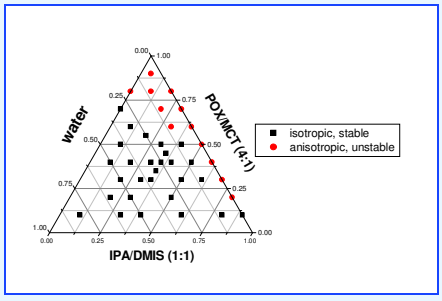

Figure 4 - Pseudo ternary phase diagram presenting selected systems analyzed by WAXD.

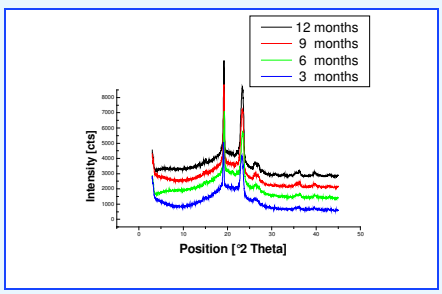

Figure 5 – WAXD-data on increasing crystallinity over time of storage.

Results and discussion

- **Macroscopical Characterization**

As shown in figure 1 a variety of consistencies was identified one day after preparation in the pseudo ternary phase diagram ranging from liquids at lower POX/MCT concentrations to paste-like or waxy systems at higher POX/MCT contents. An interesting region for dermal application with cream- and gel-like formulations could be found between 20-60 % (w/w) POX/MCT, 0-30 % (w/w) IPA/DMIS and 20-75 % (w/w) water. Liquid homogeneous systems represented a second area of importance for the same purpose. Outside of these limits formulations did not have an appropriate consistency or showed instabilities directly after preparation.

Upon storage three kinds of instabilities could be observed:

- microbiological instability for three systems without IPA/DMIS at low POX/MCT contents
- liquefaction for almost all gel-like formulations below 50 % (w/w) POX/MCT as well as one paste-like and one cream-like system
- inhomogeneity for two liquid homogeneous preparations

All remaining systems did not change their initial states.

- **Polarising Microscopy**

In terms of optical characteristics a clear border between isotropic and anisotropic systems could be found at 10 % water (w/w) for POX/MCT concentrations above 50 % (w/w) as shown in figure 2. Beneath this concentration just systems without water were anisotropic.

After one year storage the majority of the formulations remained stable. Nevertheless three different phenomena could be distinguished:

- liquefaction evidenced by losing the cream structure and therefore showing droplets (figure 3a, 3b)
- increasing crystallinity visible as larger crystals (figure 3c, 3d)
- anisotropic systems upon storage

- **WAXD**

Results obtained by WAXD (figure 4) showed also a clear border between amorphous and crystalline systems. This was in accordance with polarising microscopy results at 10 % water (w/w) for high POX/MCT contents (above 50 % (w/w)) and at 0 % water (w/w) for systems below 50 % (POX/MCT).

While isotropic preparations did not exhibit remarkable changes at all, anisotropic ones increased in crystallinity over time (figure 5).

Conclusions

An area of potential vehicles for 5-ALA with adequate consistency for dermal application upon storage could be determined in the established pseudo ternary phase diagram.

Instability of gel-like formulations appeared to be due to relatively high IPA/DMIS content, since this solvent combination turned out to be a bad solvent for POX.

Water seemed to be a decisive parameter regarding increasing crystallinity since only formulations with sufficient water (beyond 10 % (w/w)) were stable over time.