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# Characterization of a pseudo ternary phase diagram of poloxamer 407 systems for potential application of 5-aminolevulinic acid in photodynamic therapy

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ABSTRACT

A poloxamer 407 (POX) gel containing dimethyl isosorbide (DMIS), isopropyl alcohol (IPA), propylene glycol dicaprylocaprate (MIG) and water has been suggested in a previous study for permeation enhancement of 5-aminolevulinic acid (ALA) across isolated human stratum corneum. The purpose of this study was to characterize other formulations coming from the same pseudo ternary phase diagram as the "Thermogel" in order to find out which of them show appropriate characteristics to be used as a vehicle for ALA since it could be shown that variation of the ingredients' content had an influence on the permeation rate. A pseudo ternary phase diagram was developed with water, a fixed combination of 1:1 of IPA and DMIS and a fixed ratio of 4:1 POX to MIG. The systems were categorized according to their consistencies and ringing gel characteristics with special emphasis on appropriate formulations for dermal application. Polarizing microscopy enabled a clear differentiation between isotropic and anisotropic systems. Wide angle X-ray diffraction analyzes confirmed that anisotropy was due to crystalline POX. Furthermore both methods showed that IPA/DMIS was an inferior solvent mixture for POX related to water.



## 1. Introduction

Poloxamer 407 (POX), a polyoxyethylene–polyoxypropylene block copolymer, forming gels of thermoreversible characteristics (Kim et al., 2000; Gilbert et al., 1986) and featuring the best toxicological data among this kind of block copolymers (Schmolka, 1972) has widely been studied in the last years. Due to these favorable properties a variety of pharmaceutical applications as drug carriers for different purposes has been studied. For example a buccal application for triamcinolone acetonide (Shin and Kim, 2000), a rectal formulation for quinine (Fawaz et al., 2004), an ophthalmic gel for pilocarpine (Desai and Blanchard, 2000) and a liposomal intramuscular gel for the administration of ibuprofen (Paavola et al., 2000) have been considered. The major interest has though been focused on the topical and dermal application of POX systems. Many different active pharmaceutical ingredients (APIs) as well as vehicles and techniques have been examined for this purpose. Several authors incorporated analgesic drugs in POX gels and reported advantages on application and release characteristics (Fang et al., 2002; El-Kattan et al., 2000; Escobar-Chavez et al., 2005). Furthermore classical APIs for dermal application such as antibiotics (Zhang et al., 2002) and antiseptic drugs (Gilbert et al., 1986) were investigated, even a transdermal application by means of iontophoresis for drugs like insulin (Pillai and Panchagnula, 2003) and vasopressin (Nair and Panchagnula, 2003) was considered.

In a previous study from our group a POX hydrogel (thermogel) of a complex composition has been proposed for the topical application of 5-aminolevulinic acid (ALA) for the treatment of skin diseases like actinic keratosis and superficial skin cancer (Grüning and Müller-Goymann, 2008). Although esterification of ALA improves its penetration (Winkler and Müller-Goymann, 2005; Uehlinger et al., 2000; De Rosa et al., 2003), prodrugs need to be metabolized into the active form prior to the patient's exposure to the appropriate irradiation in the photodynamic therapy (PDT). The interval between topical application and irradiation takes up to several hours. That is why the topical application of ALA in novel vehicles is still of major interest in terms of providing permeation enhancement and reducing the time between administration and irradiation in PDT. Since a commercial formulation of the NSAID ibuprofen, Dolgit® Mikrogel, enhanced the permeation of ALA (Winkler and Müller-Goymann, 2005), an ibuprofen-free system containing the same excipients, named thermogel, was developed and compared to the commercial formulation as well as to water containing hydrophilic ointment (Wasserhaltige Hydrophile Salbe, WHS) from the German Pharmacopeia and Basiscreme DAC from the German Drug Code. The latter

*Abbreviations:* ALA, 5-aminolevulinic acid; APIs, active pharmaceutical ingredients; DMIS, dimethyl isosorbide; MIG, propylene glycol dicaprylocaprate; NSAID, non-steroidal anti-inflammatory drug; IPA, isopropyl alcohol; PDT, photodynamic therapy; PEO, polyoxyethylene; PLM, polarizing microscopy; POX, poloxamer 407; PPO, polyoxypropylene; WAXD, wide angle X-ray diffraction; WHS, water containing hydrophilic ointment.

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are bases commonly used in retail pharmacies for the application of ALA (Grüning and Müller-Goymann, 2008). The thermogel showed a 19.5-fold increase of ALA's permeation coefficient across isolated human stratum corneum compared to that from WHS. This novel thermogelling formulation contained 20% POX, 12.5% isopropyl alcohol (IPA), 12.5% dimethyl isosorbide (DMIS), 5% propylene glycol dicaprylocaprate (MIG) and 50% water (all w/w) and showed thermoreversible characteristics: in the refrigerator e.g. at 4 °C it was in the liquid state and above 13 °C (determined by means of oscillation rheometry upon increasing the temperature) it turned semisolid (Grüning, 2007). This gelation was completely reversible and occurred repeatedly upon adjusting the temperature accordingly.

Furthermore it could be demonstrated that POX hydrogels containing either none, one or two additives were inferior in terms of permeation enhancement and that a system containing all ingredients in a different ratio from that mentioned above was even able to enhance permeation compared to thermogel (Grüning, 2007). Thus a synergistic effect of the ingredients regarding the permeation was suggested.

The aim of this study was to establish a pseudo ternary phase diagram of water and fixed combinations of POX/MIG (4:1) and IPA/DMIS (1:1) in order to identify systems of appropriate consistencies for dermal application of APIs including ALA and to characterize them macroscopically as well as by polarizing microscopy (PLM) and wide angle X-ray diffraction (WAXD).

## 2. Materials and methods

### 2.1. Materials

Poloxamer 407 Ph. Eur. (POX) is a surface active polyoxyethylene–polyoxypropylene block copolymer ($PEO_{100}$–$PPO_{56}$–$PEO_{100}$) being responsible for the stabilization and consistency of the formulations. Dimethyl isosorbide (DMIS) is a solvent and solubilising agent and was also included in the formulations. Both were kindly provided by Dolorgiet (St. Augustin, Bonn, Germany). Miglyol® 840 (MIG) is the trade name of propylene glycol dicaprylocaprate Ph. Eur. and was purchased from Sasol Germany GmbH (Witten, Germany). Isopropyl alcohol (IPA) was incorporated as a penetration enhancer and was purchased from Merck KG (Darmstadt, Germany). Water was used in double distilled quality.

### 2.2. Methods

#### 2.2.1. Manufacture of the systems

The manufacture of all systems was performed with a Cito Unguator 2000 (GAKO Konietzko GmbH, Bamberg, Germany). First POX and then all the 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 Fig. 1, a fixed combination of 1:1 (w/w) of IPA and DMIS and a fixed ratio of 4:1 (w/w) POX to MIG as well as double distilled water were used in order to establish the pseudo ternary phase diagram. Formulations covering the whole area of the phase diagram were manufactured and equilibrated at 20 °C in a climate cabinet until examination. All the systems were allowed for at least 24 h of equilibration because of literature reports that a few hours (POX gels) up to 3 days (w/o cream) were required until the structure of a semisolid system was built up (Grüning, 2007; Brämer and Daniels, 2005).

The concentrations are given as mass percentages of the respective ingredients. For denomination of the systems the first two ciphers refer to the POX/MIG concentration, the second two represent the IPA/DMIS content, while the amount of water is adding up to 100% and is not represented in the term.

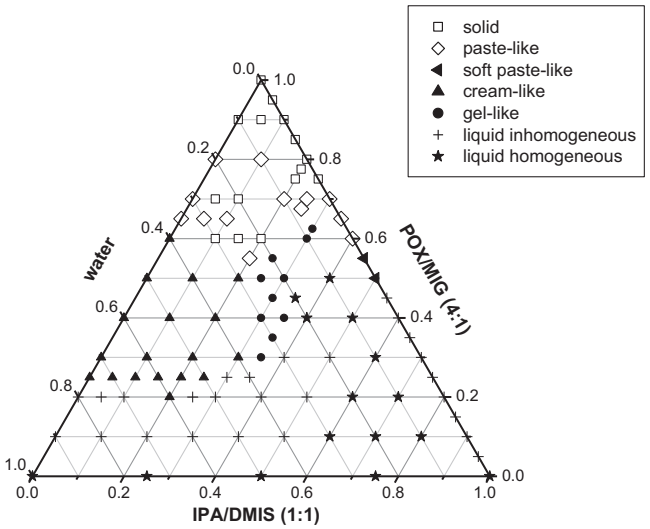


**Fig. 1.** Macroscopical characterization in terms of consistency one day after manufacture represented in a pseudo ternary phase diagram.

#### 2.2.2. Macroscopical examination

Macroscopical examination at 20 °C included the inspection of consistency and homogeneity of the formulations after 1 day up to 12 months with following intervals: 1 day (at least 24 h), 1, 3, 6, 9 and 12 months. The macroscopical examination of the consistency was performed by taking a small sample (approximately the tip of a spatula) and spreading it over a microscope slide. Ringing gel characteristics were analyzed after the same intervals by agitating the unguator jar and determining if resonance effects could be recognized.

#### 2.2.3. Polarizing microscopy (PLM)

All samples were investigated 24 h after manufacture under a polarizing microscope Leica DM LM (Leica Microsystems GmbH, Wetzlar, Germany) in order to characterize their microscopical structure and texture. Digital photographs were taken with an Olympus DP12 (Olympus, Hamburg, Germany).

#### 2.2.4. Wide angle X-ray diffraction (WAXD)

X-rays with a wavelength of $\lambda = 0.1542$ nm were generated by an X-ray generator PW3040/60 which was connected to an X-ray tube PW3373/00 with copper anode. Measurements of all the systems were performed with a goniometer (all PANalytical/Almelo, Netherlands) operated at a high voltage of 40 kV and an anode current of 40 mA in a range between 3 and 45° ($2\theta$).

The results were analyzed with the software X'Pert HighScore Version 2.1. For crystalline samples a calculation of crystallinity was performed after generating a baseline with a predetermined curvature factor individually for each diffractogram. For this purpose the software proposed a curved baseline which separated the sharp reflections of the crystalline amounts from the diffuse halo of the amorphous material. It was assumed that the area below the baseline represented the amorphous fraction, while the area above the baseline constituted the crystalline portion of the sample (compare with Fig. 2). In addition the calculated crystallinity value of POX was set to a relative crystallinity of 1.0 to compare decreasing crystallinities of the complex systems with additional components.

## 3. Results and discussion

### 3.1. Macroscopical examination

For the characterization of the systems a macroscopical examination was performed which included the determination of ringing

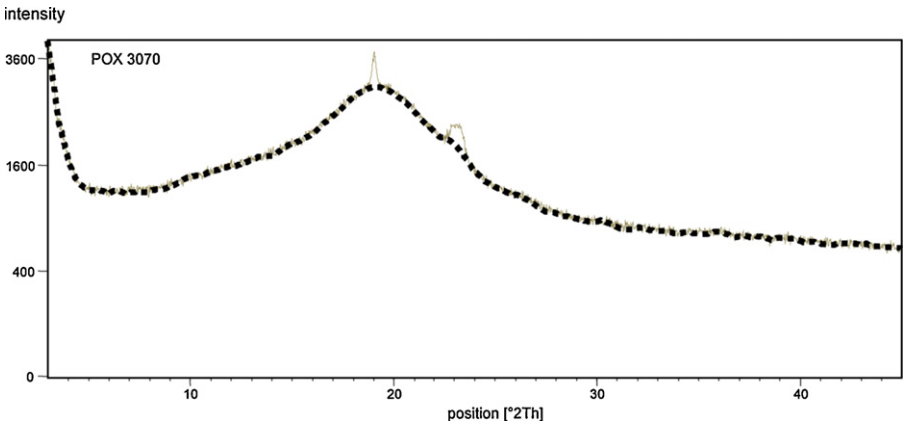


**Fig. 2.** Estimation of a calculated baseline with a curvature factor of 50 (■) from a WAXD diffractogram (– –). The area below the baseline is assumed to represent the amorphous fraction whereas the area above it is assigned to the crystalline amount of the sample.

gel characteristics. The appearance of the gels varied during the first 24 h. Since it took a few hours after manufacture until the structure of the gel was completely built up, all the determinations were made after at least 24 h of storage at 20 °C. The pseudo ternary phase diagram in Fig. 1 presenting the consistency of the formulations was established 24 h after manufacture. A variety of consistencies was identified ranging from solid/paste-like systems to liquids. Solid and paste-like systems were located at high POX/MIG concentrations with at least 55% POX/MIG. The other components ranged from 0 to 35% for water and 0 to 40% for IPA/DMIS. It was rather difficult to differentiate solid and paste-like consistencies. Solid ones had a more waxy character, appearing dry and difficult to spread. In fact some pressure was needed to spread the system over the microscope slide in order to be examined. In contrast, paste-like systems had a wet appearance with grains as in a highly concentrated suspension (probably unswollen POX). For these systems less pressure was needed to spread them over a microscope slide. Solid and paste-like systems did not meet the requirements for dermal application such as a good homogeneous appearance, a soft consistency and an easy spreadability. Neither did the two systems referred to as soft paste-like (POX5050, POX 5545). The high consistency was probably due to the low amount of polar liquid components, which was not enough for the swelling or dissolution of the high POX amount.

Cream-like formulations (Fig. 1) could be found between 20–60% POX/MIG, 30–75% water and 0–30% IPA/DMIS. This region was of bigger interest, because of the appropriate consistency and appearance of the formulations. It showed homogeneous semisolid systems which could easily be spread. Adjacent to this group a small region of gel-like formulations could be found (Fig. 1). Nearly all of the latter had also an appropriate consistency while being translucent or almost transparent in contrast to the cream-like preparations. The gel-like region was situated within a small region in the middle of the phase diagram at following concentrations: POX/MIG, 30–62.5%; IPA/DMIS, 25–35% and water 7.5–35%.

The largest region belonged to liquid systems, which could be separated in two groups: the first one consisted of liquid formulations showing inhomogeneities a few hours after manufacture and the second one included homogeneous and stable systems upon storage (see below for results on stability). The number of inhomogeneous formulations was larger than that of the homogeneous ones being situated between 0–30% POX/MIG, 0–50% IPA/DMIS and from 20 to 90% of water as well as at the water-free side of the phase diagram at low POX/MIG concentrations (<50%) and high IPA/DMIS concentrations (>50%), whereas the homogeneous systems were found between 10–50% POX/MIG, 35–80% IPA/DMIS

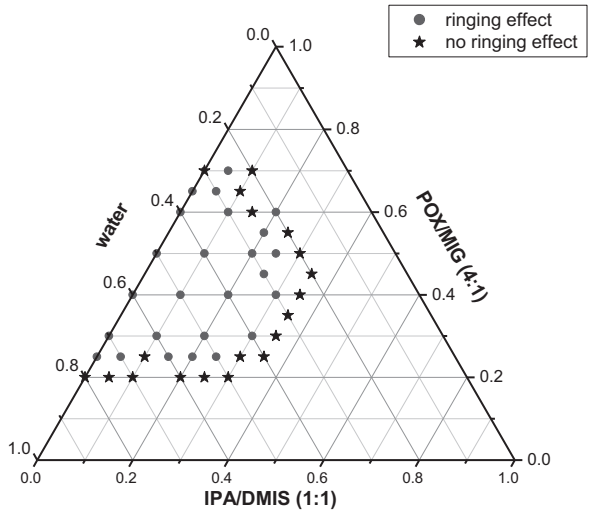


**Fig. 3.** Pseudo ternary phase diagram representing formulations with or without ringing gel characteristics.

and 10–30% water as well as across the IPA/DMIS-water side of the phase diagram (Fig. 1). Some formulations among the inhomogeneous liquids could gel around human skin temperature (30–34 °C) and thus could be used for dermal application of APIs. For example POX2000 is liquid below 25 °C and gels at approximately 29 °C. Furthermore the incorporation of an active substance into the liquid state would be another advantage of such systems.

The results obtained by determining ringing gel characteristics are shown in Fig. 3. The area containing ringing formulations was observed at 25–70% POX/MIG, 0–30% IPA/DMIS and 20–75% water and contained thus almost all cream-like systems as well as some gel-like, paste-like and solid formulations. Since thermogel represented a ringing gel of a cubic liquid crystalline microstructure (data not shown), the latter phenomenon was considered an interesting property in terms of permeation enhancement of ALA (Grüning, 2007). In the literature permeation enhancement has already been related to cubic liquid crystalline structures (Lopes et al., 2006).

A 12-month stability study was performed in unguator jars at 20 °C for selected systems from the pseudo ternary phase diagram. The majority of the systems were stable at 20 °C over a period of 12 months. Only a few systems changed their appearances after 6 or 9 months, respectively. From the group of the solid and

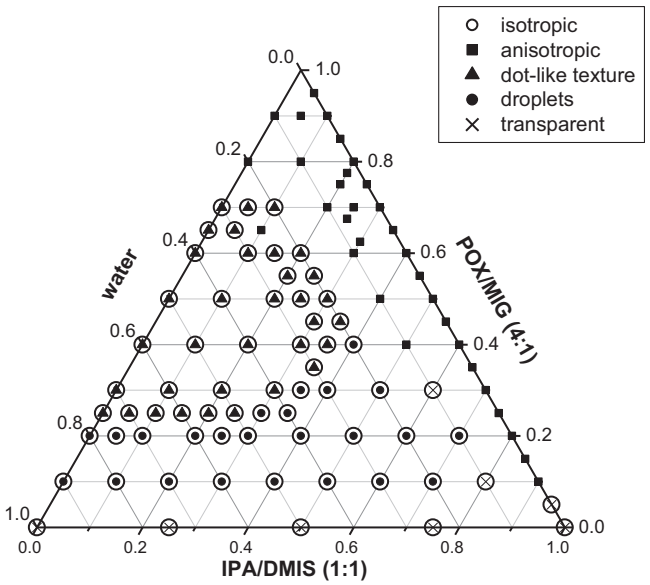


**Fig. 4.** Results of polarizing microscopy showing a clear differentiation between isotropic and anisotropic systems as well as different structures among the isotropic systems.

paste-like systems, one system (POX5520) liquefied after 9 months of storage. Cream-like systems were also very stable. Only two cream-like systems liquefied during storage after 6 months (POX2020 and POX3030); in addition POX2500 showed microbial growth due to its high water content as no preservatives had been added. Four out of nine gel-like formulations (POX3035, POX3535, POX4035, POX4530) liquefied after six months of storage.

### 3.2. Polarizing microscopy (PLM)

This technique was used in order to determine isotropy/anisotropy of the systems. In this manner the presence of anisotropic crystalline or liquid crystalline textures (except for isotropic cubic liquid crystals) can be analyzed. As shown in Fig. 4, a large number of isotropic formulations were located within the pseudo ternary phase diagram. Anisotropy was related to a low water content since anisotropic systems were mostly located at water concentrations between 0% and 10% and only two anisotropic systems with high POX contents, i.e. POX8000 and POX6510 (with 20% and 25% water, respectively) were both anisotropic despite a water content above 10%. At lower POX/MIG concentrations (<40%) even 10% water was sufficient to hinder anisotropy. The anisotropic region among the POX/MIG–IPA/DMIS axis showed differences in the amount and appearance of anisotropy (Fig. 5A–C). At higher POX/MIG concentrations there were bigger structures/crystals covering the whole area. These got smaller and fewer by increasing IPA/DMIS concentration and disappeared at 95% IPA/DMIS. This fact pointed out IPA/DMIS to be a worse solvent mixture for POX than water. Parallel to the POX/MIG-IPA/DMIS axis at 10% water content, a similar effect could be observed: at high POX/MIG concentrations the samples could not be levelled to an appropriate thickness because of the almost solid consistency, so that anisotropic structures could be recognized over the whole area. At concentrations from 60% POX/MIG and below the anisotropic textures became fewer and disappeared at 30% POX/MIG.

On the POX/MIG-water side of the phase diagram a change in microscopical appearance of the systems could be observed too (Fig. 5D–F). At low concentrations of POX/MIG (<10%) big droplets representing an unstable emulsion (not shown) dominated. The droplets got smaller by increasing POX/MIG concentration (20%, Fig. 5D) and were followed by cream-like systems (25% < POX/MIG < 60%, Fig. 1), while in those cream-like systems tiny droplets (“dots”) could be recognized (Fig. 5E). The area of “dots” included POX/MIG concentrations from 25 to 70% (Figs. 4 and 5E). The anisotropic state was observed at higher POX/MIG contents (80%, Fig. 5F). These anisotropic textures were though not as pronounced as the ones at the other axis confirming IPA/DMIS to be a worse solvent mixture in relation to water (compare Fig. 5C and F).

The third axis of the phase diagram represented homogeneous aqueous systems of water and IPA/DMIS and was thus not interesting for further investigation due to the lack of POX and MIG.

Within the pseudo ternary phase diagram a large number of formulations showing droplets could be observed coinciding with the liquid region and partially overlapping with the cream-like and gel-like areas (Fig. 4). Cream-like and gel-like systems showed mainly a so called “dot-like texture”, because the size of the droplets was too small to be resolved. Three transparent liquid systems could be observed in the pseudo ternary phase diagram consisting of four (POX0595) or all five components (POX1080 and POX3060).

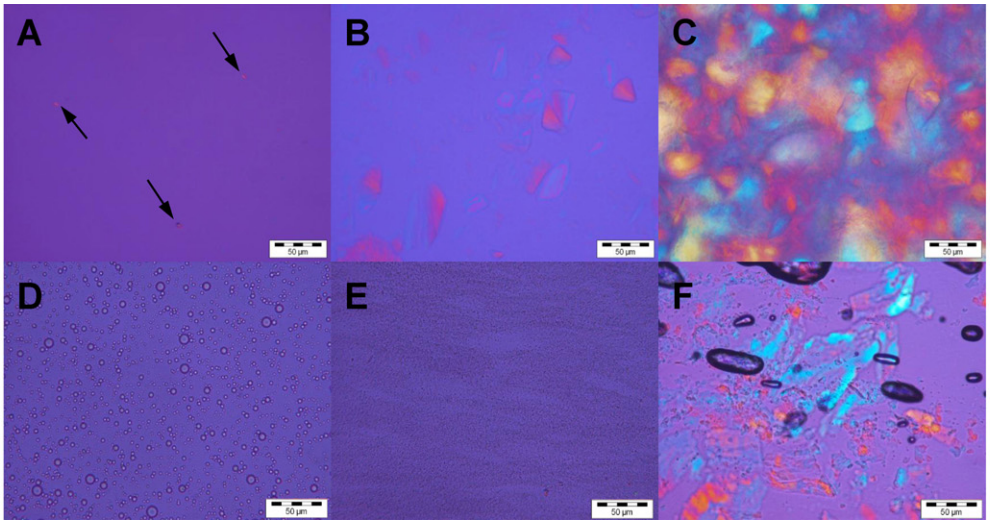


**Fig. 5.** Different structures resulting from polarizing microscopy (A, POX1090; B, POX3070; C, POX5050; D, POX2000; E, POX3000; F, POX8000), arrows mark small POX crystals, scale bar: 50 μm.

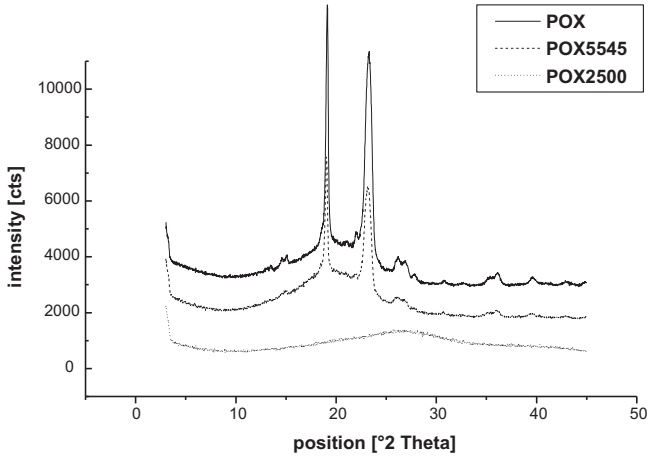


**Fig. 6.** Wide angle X-ray diffractogram of pure POX crystals and two different POX systems; POX5545 and POX2500 representing a crystalline and an X-ray amorphous diffractogram, respectively.

### 3.3. Wide angle X-ray diffraction (WAXD)

The results obtained by means of WAXD were similar to those determined by PLM and allowed to identify the anisotropic area from Fig. 4 as crystalline, since all the formulations in this area evidenced at least one reflection. The WAXD reflections could be assigned to one or both main reflections of crystalline POX at about 19 and 23° (2$\theta$) (Fig. 6). Besides, in accordance with PLM, a clear differentiation between X-ray amorphous and crystalline systems could be observed (Fig. 7) at 10% water for high POX/MIG concentrations (crystalline state ≥ 50% POX/MIG) and at the water-free side of the phase diagram for systems with less than 20% POX/MIG being X-ray amorphous. The non-crystalline, i.e. X-ray amorphous state was reflected by a broad deviation from the baseline, a so called amorphous halo. Concerning the X-ray amorphous systems within the pseudo ternary phase diagram a shift of the amorphous halo's position was observed from approximately 20–28° (2$\theta$) with increasing water content (Fig. 8). Pure water exhibits a halo around 28° (2$\theta$), whereas the amorphous halos of MIG and the mixture of IPA/DMIS (1:1) are located at around 20° (2$\theta$). Therefore the form and position of the halo of the X-ray amorphous systems resulted from the combination of the halos of the excipients. The X-ray amorphous systems with a halo around 26–28° (2$\theta$) contained at least 55% water, while the ones with halos around 19 to 20° (2$\theta$) had either a high POX/MIG or IPA/DMIS concentration (Fig. 7).

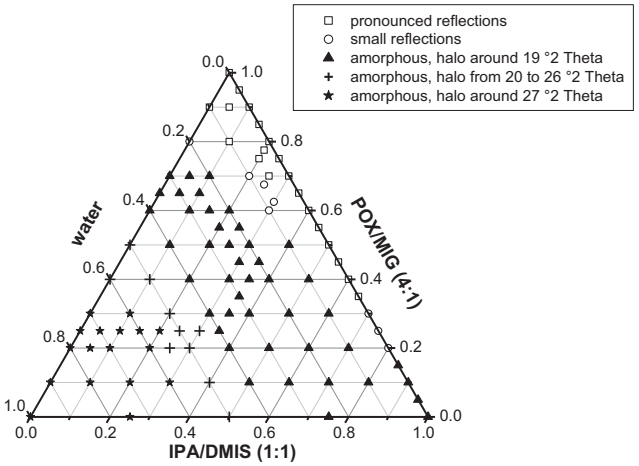


**Fig. 7.** WAXD results presented in a pseudo ternary phase diagram.

**Table 1**
Calculated and relative crystallinity of pure poloxamer 407 (POX), POX/MIG (4:1) and complex formulations thereof without water.

| Formulation | Crystallinity [%] | Relative crystallinity |
|---|---|---|
| POX | 33.89 | 1.00 |
| POX/MIG (4:1) | 25.94 | 0.77 |
| POX9505 | 25.38 | 0.75 |
| POX9010 | 24.69 | 0.73 |
| POX8515 | 23.70 | 0.70 |
| POX8020 | 19.67 | 0.58 |
| POX7525 | 19.80 | 0.58 |
| POX7030 | 17.10 | 0.50 |
| POX6535 | 13.92 | 0.41 |
| POX6040 | 12.97 | 0.38 |
| POX5545 | 12.33 | 0.36 |
| POX5050 | 10.46 | 0.31 |
| POX4555 | 7.40 | 0.22 |
| POX4060 | 6.14 | 0.18 |
| POX3565 | 4.52 | 0.13 |
| POX3070 | 1.63 | 0.05 |
| POX2575 | 1.62 | 0.05 |
| POX2080 | 1.00 | 0.03 |

The determination of crystallinity of the systems without water showed a decrease in crystallinity upon decreasing the POX/MIG concentration (Table 1), with pure POX showing the highest crystalline amount (33.89%). This unexpected low value was due to the calculated baseline hinting at a high amount of disordered POX molecules in the pure compound. To clearly show a decrease in crystallinity upon addition of IPA/DMIS the calculated value of POX was set to a relative crystallinity of 1.0. The relative crystallinities of the quaternary systems (POX/MIG/IPA/DMIS) are also included in Table 1. They decreased down to 0.03 (POX2080) with increasing IPA/DMIS concentrations. Fig. 9 shows a fairly linear correlation ($R$ = 0.9928) between relative crystallinity and IPA/DMIS content for those systems. The intersection of the least squares fit with the abscissa was extrapolated being at approximately 83.5% IPA/DMIS and providing information about the solubility of POX in the solvent mixture of IPA/DMIS in the presence of MIG. This WAXD-determined concentration is lower, but in the same order of magnitude as that from PLM (between 90 and 95%). The difference between both values is due to the different resolutions of the applied methods, with PLM being the more sensitive one (Latsch et al., 2004).

With regard to the last three data points in Fig. 9 (POX3070, POX2575 and POX2080, with 70%, 75% and 80% IPA/DMIS, respectively) the relative crystallinity is virtually the same. Probably the resolution of WAXD was insufficient to identify the crystalline POX

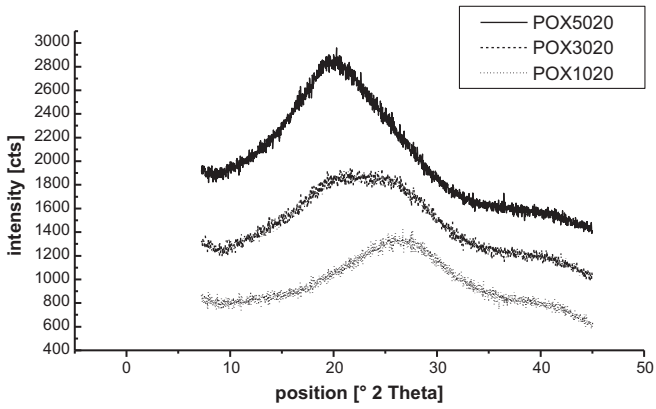


**Fig. 8.** WAXD diffractograms of three systems of different water contents from 30 to 70% showing the shift of the amorphous halo from approximately 20–28° (2$\theta$) with increasing water content.

**Table 2**
Influence of water on the calculated and relative crystallinities of anisotropic systems of complex compositions.

| Formulation | Water content [%] | Crystallinity [%] | Relative crystallinity |
|---|---|---|---|
| POX9010 | 0 | 24.69 | 0.73 |
| POX9005 | 5 | 19.51 | 0.58 |
| POX9000 | 10 | 15.61 | 0.46 |
| POX8020 | 0 | 19.67 | 0.58 |
| POX8010 | 10 | 10.18 | 0.30 |
| POX8000 | 20 | 2.29 | 0.07 |
| POX77.5/20 | 2.5 | 11.26 | 0.33 |
| POX7520 | 5 | 7.29 | 0.22 |
| POX7030 | 0 | 17.1 | 0.50 |
| POX7025 | 5 | 5.37 | 0.16 |
| POX7020 | 10 | 2.95 | 0.09 |
| POX67.5/25 | 7.5 | 1.23 | 0.04 |
| POX62.5/30 | 7.5 | 1.82 | 0.05 |
| POX6030 | 10 | 1.45 | 0.04 |

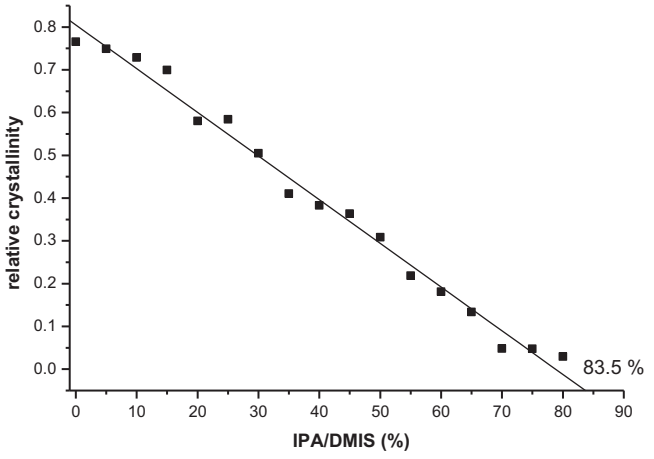


**Fig. 9.** Correlation between relative crystallinity and IPA/DMIS content for the quaternary systems (POX/MIG/IPA/DMIS).

confirming superiority of the PLM resolution. However, analytical variance of the results has to be considered, too, especially in terms of separating the crystalline part of the diffractogram from the X-ray amorphous halo. Yet, the relative crystallinities corroborate that IPA/DMIS has an inferior dissolving potency for POX compared to water. As shown in Table 2 and Fig. 10, increasing the water content of the formulations with 90%, 80% and 70% POX/MIG led to a decrease in relative crystallinity: for POX/MIG 90% series it decreased from about 0.73 to approximately 0.46 by increasing the water content from 0 to 10%. POX/MIG 80% series showed a decrease in relative crystallinity from 0.58 to 0.07 by modifying water content from 0 to 20%. Finally POX/MIG 70% series exhibited a reduction in relative crystallinity from 0.50 to 0.09 by increasing water concentration from 0 to 10%. As expected, an increasing content of water which is a good solvent for POX and a decrease in POX/MIG content decreased the relative crystallinity. Furthermore, the decline in crystallinity was the stronger the higher the content of IPA/DMIS was (compare POX/MIG 70% series versus POX/MIG 90% series), although the latter is an inferior solvent for POX compared to water. This may be interpreted as a mutual interaction of water, IPA and DMIS resulting in a superior solubilization of POX.

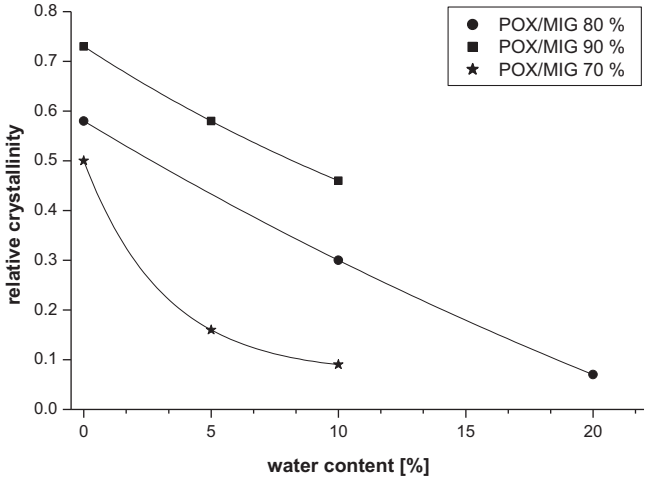


**Fig. 10.** Correlation between relative crystallinity and water content for systems containing 90%, 80% and 70% POX/MIG, respectively.

## 4. Conclusions

This study investigated a pseudo ternary phase diagram of water and fixed combinations of POX/MIG (4:1) and IPA/DMIS (1:1) macroscopically as well as by means of PLM and WAXD. An area could be identified containing formulations (gel- and cream-like) for appropriate dermal application, whereas other systems were either too hard or liquid and thus inappropriate for this purpose. Some of the liquid inhomogeneous systems could also gel around body temperature and could thus be used as vehicles for dermal application of active pharmaceutical ingredients like ALA. The majority of the semisolid systems exhibited ringing gel characteristics. By means of PLM it could be shown that most of the formulations were isotropic and could be clearly separated from the anisotropic ones which were situated at the water free side of the phase diagram only as well as at 10% water and high POX/MIG concentrations. WAXD confirmed that all the anisotropic formulations contained crystalline amounts due to the incorporated POX. In this respect water content was suggested to be the decisive parameter for anisotropy/crystallinity. The X-ray amorphous systems reflected by a broad deviation from the baseline showed a shift of the halo's position from 20 to 28° ($2\theta$) with increasing water content. This shift was related to the content of the components (besides POX), since water causes an amorphous halo at around 28° ($2\theta$) whereas MIG and the mixture of IPA/DMIS cause a halo located around 20° ($2\theta$). Furthermore with the calculation of crystallinity and relative crystallinity it could be demonstrated that IPA/DMIS was an inferior solvent mixture for POX related to water. A selection of the above mentioned systems is subjected to the subsequent studies in terms of rheology and permeation across isolated human stratum corneum. In this context two model drugs (ALA and lidocaine) have been incorporated into a selection of the systems presented. The results will be submitted in a subsequent contribution.

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