



Science

## POLOXAMER 407 GEL FOR TOPICAL ADMINISTRATION: INFLUENCE OF ACETIC ACID AND DEMINERALIZED WATER ON THE BEHAVIOR OF THE GEL OBTAINED

Dally Li <sup>\*1</sup>, Lia Gja <sup>1</sup>, N'guessan A <sup>1</sup>, Aka Any-Grah <sup>1</sup>, Tuo A <sup>1</sup>, N'guessan C <sup>1</sup>, Koffi Aa <sup>1</sup>  
<sup>1</sup> Department of Pharmacy Galenic, School of Pharmacy, University of Félix Houphouët Boigny,  
Côte d'Ivoire.01 BP V 34 Abidjan

---

### Abstract

**Background:** Poloxamers are low-toxicity copolymers whose aqueous solutions can pass reversibly from the ground state to the gel state at temperatures approaching body temperature, which is of interest for their use as a reservoir system of active principle. Understand the effect of the type of solvent on the rheological characteristics of the gel obtained.

**Methods:** Various formulations of Poloxamer 407 gel at 16% and 17,5% were prepared and evaluated successively in acetic acid and demineralised water. The main evaluation parameters were the gelling temperature ( $T_{gel}$ ) and the concentration of these different solvents.

**Results:** The  $T_{gel}$  at 16% F127 in demineralised water and 0.1M acetic acid was  $27^{\circ} \pm 0.3$  and 17.5% at  $25^{\circ}$  to  $29^{\circ}C \pm 0.1$ . in 0.1M and 16 % acetic acid, there is no marked gelation. At 17.5% F127 in acetic acid, gelation was observed and the  $T_{gel}$  was higher than with F127 in deionized water.

**Conclusion:** The gelation process is favored by increasing the concentration of F127 and is substantially disadvantaged by 0.1M acetic acid.

**Keywords:** Thermosensitive; Poloxamer; Gel; Topical Administration.

**Cite This Article:** Dally Li, Lia Gja, N'guessan A, Aka Any-Grah, Tuo A, N'guessan C, and Koffi Aa. (2019). "POLOXAMER 407 GEL FOR TOPICAL ADMINISTRATION: INFLUENCE OF ACETIC ACID AND DEMINERALIZED WATER ON THE BEHAVIOR OF THE GEL OBTAINED." *International Journal of Research - Granthaalayah*, 7(6), 270-275. <https://doi.org/10.5281/zenodo.3332636>.

---

### 1. Introduction

Buruli ulcer (BU) is a disease of chronic evolution and some aspects of its pathophysiology are still unknown until today. It is a complex disease that makes its therapeutic management even more difficult. The goal of treatment for BU is that it is not only effective but also simple, reproducible in rural areas, less costly than excision-graft treatment with reduced hospital stay [1]. At present, surgical treatment is the treatment most often applied in health facilities in developing countries. But some parts of the affected population remain inaccessible to the health network for

several reasons: health center too far from the village, means of travel inexistent or too expensive, cost of care too high, stigmatization of the disease [2]. In order to develop a topical treatment of Buruli ulcer, we are interested in thermogelling and bioadhesive systems based on poloxamer F127. These polymers are not very toxic and their aqueous solutions can pass reversibly from the ground state to the gel state at temperatures close to body temperature [6] which is of interest for their use as a reservoir system of principle active. It is therefore advisable to study these systems in order to explain their behavior and also to improve them in order to obtain satisfactory materials for the pharmacy in the field of controlled release. Poloxamer would allow easy administration in the liquid state and gelation at body temperature. The intended application would be the treatment of certain skin ulcers including Buruli ulcer (which is a cutaneous disease caused by *Mycobacterium ulcerans* and is manifested by ulcers occurring on the skin). The objective of this study was to characterize from a rheological point of view the formulations obtained in order to determine their possible gelling temperature and to evaluate the influence of the solvent on the gelation.

## 2. Materials and Methods

### 2.1. Materials Used for the Gels Formulation

The poloxamer 407 was provided to us by BASF. He has for reference Art : 51632903, Batch WPHB615B (67056 Ludwigshafen, Germany). 99-100% RECTAPUR™ acetic acid with a molecular weight of 60.05 g / mol, density  $d = 1.05$  code 20 103.295 Lot L212 was used for the preparation of a 0.1M aqueous solution which served as dissolution solvent. For all preparations we used RIOS 5 purified ultrapure water and Synergy 185 (Millipore®) with a reverse osmosis system.

### 2.2. Methods

#### 2.2.1. Preparation of the Studied Systems

The poloxamer solutions were prepared in 0.1M acetic acid and in demineralized water. The preparation of the Poloxamer solutions was cold in 0.1M acetic acid or deionized water. Two 32% and 35% (g / g) stock solutions were prepared. 16% and 17.5% solutions were prepared by dilution of this stock solution either in 0.1M acetic acid or in demineralized water.

#### 2.2.2. Rheological Study of Solutions

It has been shown that the sol-gel transition of Poloxamers is reversible with temperature [4] and is accompanied by an abrupt change of the rheological characteristics of systems [5]. We therefore carried out a rheological study in dynamic mode in order to determine the gelling temperature ( $T_{gel}$ ). Samples placed in the cone / plane geometry are at rest at zero shear rate until thermal equilibrium is obtained. We conduct a temperature scan between 5° C and 70° C at a rate of 1° C / min to determine the variations of  $G'$  and  $G''$  as a function of temperature at a constant shear stress and a frequency of 1Hz. The shear stress chosen is 30 N / m<sup>2</sup>. A previous study carried out at the laboratory made it possible to select this value in order to carry out measurements in the linear regime. Two are mainly of interest to us: they are the elastic and viscous modules,  $G'$  and  $G''$ :

$$G' = G^* \cdot \cos \delta \quad (\text{Equation 1})$$

$$G'' = G^* \cdot \sin \delta \quad (\text{Equation 2})$$

$$G^* = \tau_0 / \gamma_0$$

Where  $\tau_0$  and  $\gamma_0$  represent respectively the maximum amplitudes of the stress and the strain.  $G'$  is proportional to the elastic energy stored and restored during a period, and  $G''$  to the energy dissipated by friction during the same period.  $G'$  and  $G''$  have the dimension of a constraint and express themselves in Pascal (Pa) or  $\text{N} / \text{m}^2$ .  $G'$  and  $G''$  are therefore measured as a function of temperature at a constant frequency and under a fixed stress. Gelling corresponds to the sudden increase of  $G'$  and  $G''$ .

### 2.3. Equipment

For all measurements we used a Carri-Med CSL100 rotary rheometer (Rhéo, Champlan, France). It is an imposed stress rheometer equipped with a cone / plane geometry (4 cm diameter,  $2^\circ$  angle and  $54 \mu\text{m}$  gap). The temperature is controlled using a Peltier diode system. We took care for each measurement to use a protective dome with a water tank to prevent evaporation in the sample. The set of results presented is an average based on two to three measurements.

## 3. Results and Discussions

### 3.1. Formulation of Systems

The various systems prepared and their macroscopic appearance are summarized in Table 1. The observations were made at  $4.5^\circ \text{C}$ .

Table 1: Aspects Of The Different Solutions Prepared At  $4.5^\circ \text{C}$

Systems studied	Aspect of preparations
F127 at 32% in demineralised water	Viscous, transparent
F127 at 32% in 0.1M acetic acid	Viscous, transparent
F127 at 35% in demineralised water	Very viscous, transparent
F127 at 35% in 0.1M acetic acid	Very viscous, transparent

### 3.2. Summary of Gelling Temperatures of Preparations

Table 2 below gives a summary of the gelation temperatures of our different systems.

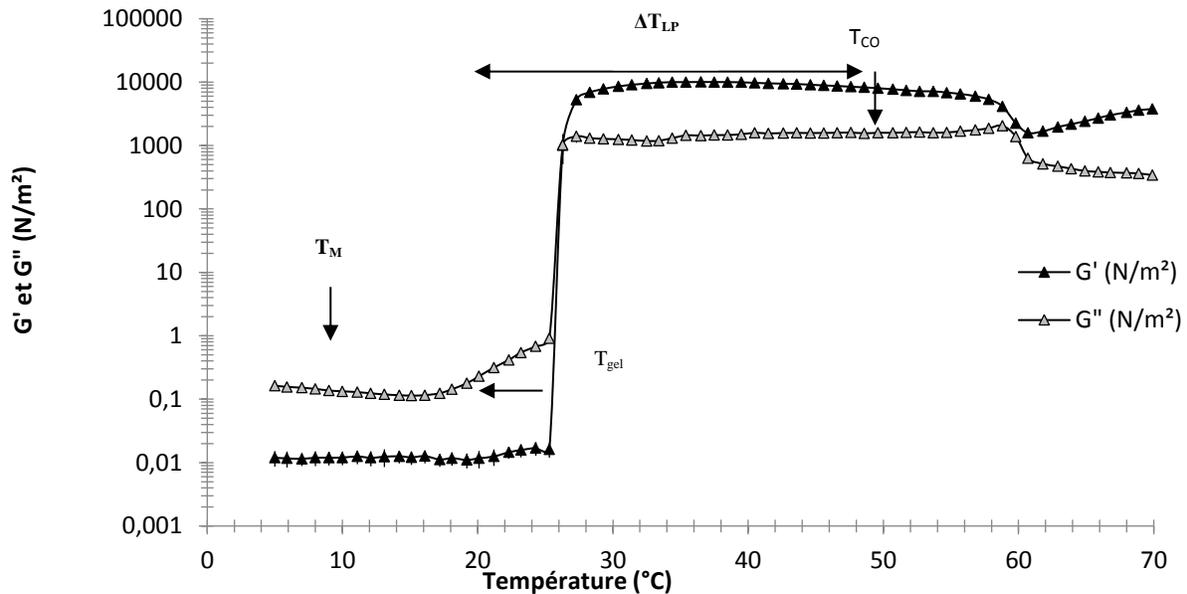
### 3.3. Study of Gels Based on Poloxamer 407

#### 3.3.1. In Demineralised Water

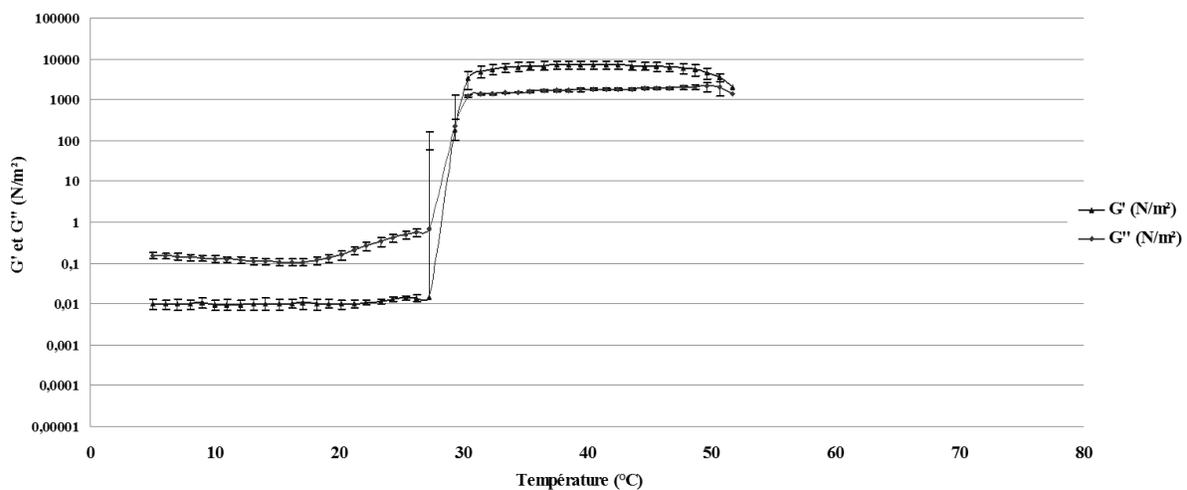
**Picture 1** shows the variations of  $G'$  and  $G''$  as a function of the temperature at the concentration of 17.5%. This curve is representative of all the curves obtained with all the systems studied. The variations of  $G'$  and  $G''$  obtained at 16% of poloxamer are given in **Picture 1**. The  $T_{\text{gel}}$  values for its systems are summarized in **Table 2**.

Table 2: Summary of gelation temperatures

Solutions	Gelation temperature (T <sub>gel</sub> )
F127 at 16% in demineralised water	27.4° C ± 0.1° C
F127 at 16% in 0.1M acetic acid	Difficult to determine
F127 at 17.5% in demineralised water	25.3° C ± 0.1° C
F127 at 17.5% in 0.1M acetic acid	29.3° C ± 0.1° C



Picture 1: Variations of G' and G'' as a function of temperature for the solution of F127 at 17.5% in demineralized water (temperature sweep at a rate of 1° C / min under a stress of 30N / m<sup>2</sup> and at a frequency of 1Hz).



Picture 2: Variations of G' and G'' as a function of temperature for the solution of F127 at 16% in demineralised water (temperature sweep at a rate of 1° C / min under a stress of 30 N / m<sup>2</sup> and at a temperature of frequency of 1Hz).

### 3.3.1.1. Description of the Behavior of Systems in Water

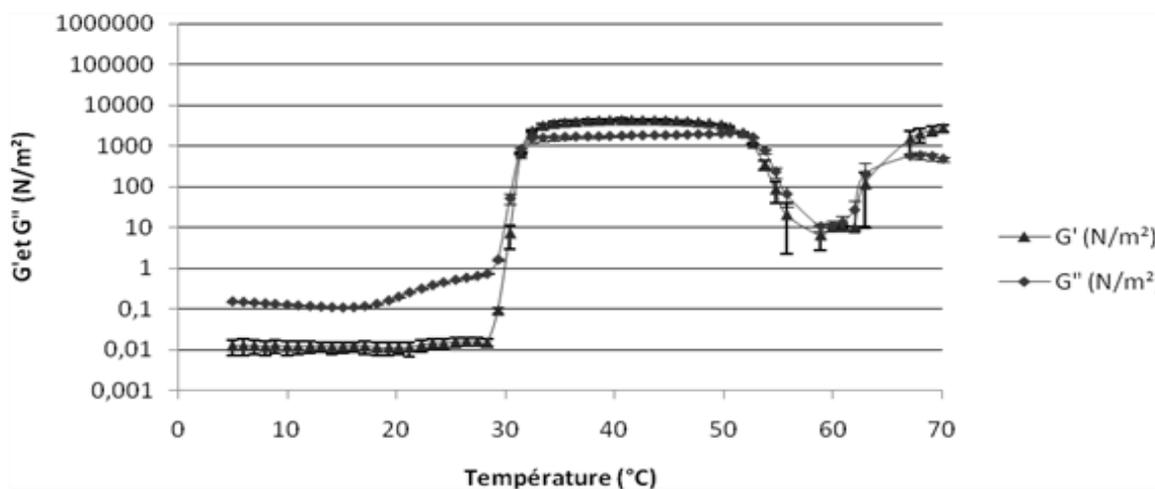
Before  $T_{gel}$ , the viscous and elastic modulus are weak,  $G''$  is superior to  $G'$ : the system behaves like a viscous liquid. Between 5 and 20° C,  $G''$  is above  $G'$ ; and  $G''$  decreases as a function of temperature: this behavior corresponds to the decrease in the viscosity of simple liquids with temperature. The poloxamer is in the form of unimeros which when the temperature increases are in a less and less good solvent. From a temperature denoted  $T_M$ ,  $G''$  increases slightly. This increase is attributed to the formation of micelles. At  $T_{gel}$  we have a sharp increase of  $G'$  and  $G''$  and then we have after  $T_{gel}$ ,  $G'$  is superior to  $G''$ : the system behaves like an elastic gel. This gelation is attributed to the crystallization of micelles. We then observe a plateau, the temperature range of this plateau is noted  $\Delta T_{LP}$ , then at a temperature noted  $T_{CO}$ , a decrease of  $G'$  and  $G''$  which could be due to a reorganization of the micelles in another crystalline form.

### 3.3.1.2. Influence of the Poloxamer's Concentration

When the concentration of poloxamer increases, the micelles that form are closer and therefore interact and crystallize at lower temperatures, hence the drop in the gelation temperature observed for the concentration of 17.5% F127 (Table II). This effect has already been reported by **Minatchy (2006)** and **Alexandridis et al, (1994)**.

### 3.3.2. In Acetic Acid

At 16% there is no marked gelation and the results are not very reproducible (results not shown). It would seem that we are right at the limit concentration to observe gelling in acetic acid. **Picture 3** shows the variations of  $G'$  and  $G''$  as a function of temperature at a concentration of 17.5% F127 in 0.1M acetic acid.



Picture 3: Variations of  $G'$  and  $G''$  as a function of temperature for the solution of F127 at 17.5% in 0.1M acetic acid (temperature sweep at a rate of 1 ° C / min under a stress of 30N / m<sup>2</sup> and at a frequency of 1 Hz).

At 17.5% F127 in acetic acid, gelation was observed and the  $T_{gel}$  was higher than with F127 in demineralized water (**Table II**). Acetic acid as a solvent would therefore disadvantage gelation. The description of the curve is similar to that observed for **Picture 1**.

#### 4. Conclusion

This study has made it possible to demonstrate that the gelation process is favored by increasing the concentration of F127 and is significantly disadvantaged by 0.1M acetic acid. The gelling temperature of F127 mixtures is essentially controlled by P oloxamer. The presence of acetic acid would cause disruption of the micelles resulting in a slight increase in the gelation temperature. As the concentration of poloxamer increases, the micelles that form are closer, interact and then crystallize at lower temperatures.

#### References

- [1] Ahoua, L (2002). Facteurs de risque de l'UB en Côte d'Ivoire : résultats d'une enquête réalisée en Aout 2001. Thèse 2002. Institut Pasteur de Cote d'Ivoire. 21-10-2002.
- [2] Ahoua L (2004). Prise en charge de l'Ulcère de Buruli. Médicaments disponibles : perspectives. Epicentre.
- [3] Alexandris P., Holtzwarth JF, Hatton TA (1994) "Micellization of Poly (ethylene oxide) -Poly (propyl oxide) triblock copolymers in aqueous solutions: Thermodynamic of copolymer association". *Macrom* .27 : 2414-2425
- [4] Attwood D., JH Collet, Tait CJ (1985) "The micellar properties of poly (oxyethylene) -poly (oxypropylene) copolymer Pluronic F127 in water and electrolyte solution." *Int. J. of Pharma*. 26 : 25-33
- [5] Cho CW, Shin SC and Oh IJ (1997) "Thermorheologic properties of aqueous solutions and gels of poloxamer 407." *Drug. dev. Ind. Pharm*. 23 (12) : 1227-1232
- [6] Gilbert JC, Hadgraft J., Bye A., Brookes LG (1996) "Drug release from Pluronic F-127 gels." *Int. J. of Pharma*. 32 : 223-228
- [7] Minatchy C. (2006) Rep ort of research master : "Thermosensitive gels based on poloxamer: from molecular organization to adhesion properties". Center for Pharmaceutical Studies - University of Paris XI

---

\*Corresponding author.

E-mail address: dismaelfr@ yahoo.fr/ jliafr@ yahoo.fr