Rheological Studies of Interferon Creams

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Abstract:
The determination of flow curves and the apparent viscosity curves at 28°C of creams containing human leukocyte alpha interferon as active principle is presented in this paper. These creams are used for the treatment of papiloma virus and herpes simplex. It is demonstrated that their behaviour corresponds to a thixotropic fluid. The Herschel-Bulkley model parameters are presented and discussed as an indicator of the grade of thixotropy. Apparent viscosity plotted as a function of shear rate and storage time allows defining the time period in which the samples recover their initial structure. Additionally it was concluded that for determining the quality of the product, the acceptance limit of the viscosity should be specified for a given shear rate.

Zusammenfassung:
Die Fliess- und die Viskositätkurven für Formulierungen mit menschlichen Leukozyt-Alpha-Interferon als Wirkstoff wurden bei 28°C vermessen. Die Formulierungen werden vorallem bei der Behandlung des Papiloma Viruses und gegen Herpes Simplex eingesetzt. Das beobachtete Fliessverhalten zeigt thixotrope Eigenschaften und das Herschel-Bulkley Modell wurde daher gewählt, um Fliesskurven und Thixotropie zu beschreiben. So wurde die Zeitspanne des reversiblen Strukturaufbaues durch die Analyse der Viskositätswerte als Funktion der Scherrate und der Lagerzeit bestimmt. Für die Anwendung der Formulierung konnte weiterhin ein Viskositätsgrenzwert als Qualitätsmerkmal erarbeitet werden.

Résumé:
La détermination des courbes d'écoulement et des courbes de viscosité apparente à 28°C, pour des crèmes contenant du leucocyte alpha interférant comme un principe actif, est présentée dans cet article. Ces crèmes sont utilisées pour le traitement du virus papiloma et de l'herpes simplex. Il est démontré que leur comportement correspond à celui d'un fluide thixotrope. Les paramètres du modèle Herschel-Bulkley sont présentés et discutés en tant que indicateurs du degré de thixotropie. La viscosité apparente représentée en fonction de la vitesse de cisaillement et du temps de stockage permet de définir la période de temps durant laquelle les échantillons recouvrent leur structure initiale. De plus, nous concluons que pour déterminer la qualité du produit, la limite d'acceptabilité de la viscosité doit être spécifiée pour une vitesse de cisaillement donnée.

Key words: Rheology, viscosity, interferon creams, flow curves, thixotropy

1 INTRODUCTION

Alpha-interferons (IFN-α) are groups of glycoproteins produced by different tissues in responses to an inductor agent. Their mass molar is between 16 and 27.6 kDalton and each one is constituted by 165 - 166 amino acids. These molecules, with antiviral, antiproliferative (antitumoral) and inmunomodulator actions have been considered recently as biotechnonogical products that had high impact in the market during the last decade. As a consequence, such products sustain an increasing trend in the commercial world considering a sales over 3 billion dollars. These aspects facilitate the introduction of new formulations and pharmaceutical formulations in which they are used [1].

Scientific researches have demonstrated the effectiveness of a topical application of human leukocyte alpha interferon (M = 19.6kDalton) in the treatment of illnesses caused by papiloma virus and herpes simplex of high incidence in different population groups [2 - 6]. At the moment, research groups are developing new creams, ointments and gels with interferon as active principle. One of the factors to study in

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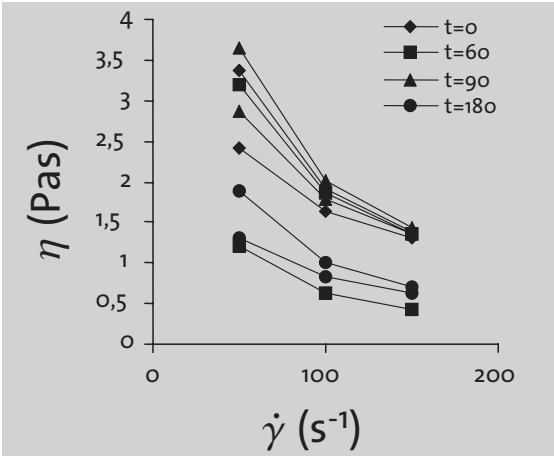
Table 2 (left above): Thixotopy degree %.

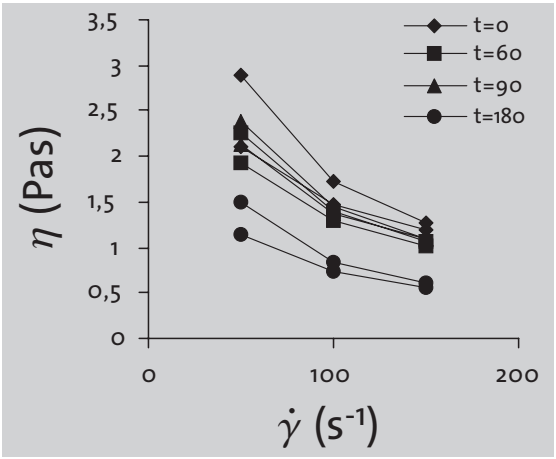
Figure 3 (right above): Apparent viscosity versus shear rate for sample D at different storage times.

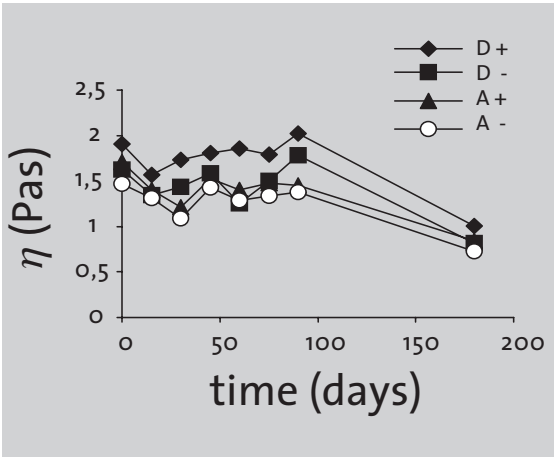
Figure 4 (left below): Apparent viscosity versus shear rate for sample A at different storage times.

Figure 5 (right below): Apparent viscosity versus storage time for sample D and A at 100s^{-1}.

t [days]	Sample D	Sample A
0	19	18.3
15	16.4	7.8
30	20.2	12
45	13.8	8.1
60	13.9	10.3
75	19.2	11.3
90	14.7	7.1
180	23	16.4







the grade of thixotropy is bigger for the samples with higher content of active principle.

3.2 INFLUENCE OF SHEAR RATE AND STORAGE TIME ON APPARENT VISCOSITY

In Figs. 3 and 4 the apparent viscosity is presented as a function of the shear rate for different storage times for samples D and A, respectively. Changes in apparent viscosity were observed when shear rate and storage time changed. This behaviour was similar for the remaining samples.

The decrease of apparent viscosity as the shear rate increased was caused by the impairment of the structure that confers the plastic character and its later molecular orientation. It was observed that the curve obtained decreasing shear rates does not correspond with the one obtained increasing shear rates, which is characteristic of a thixotropic behaviour.

The values of apparent viscosity for the 100000 UI/g samples were between 5 - 15 Pas for shear rate interval between 10 and 100 s^{-1}, while for the 20000 UI/g samples the range of 3 - 10 Pas for an identical shear rate interval was obtained. It can be concluded that apparent viscosity depends on the content of active principle in the sample. The shear rate interval selected was the typical for pharmaceutical applications. In Fig. 5 the dependence of apparent viscosity, calculated at 100 s^{-1}, with the storage time is presented for the samples D and A. Also shown in Fig. 5 is shown how a recovery of the initial value of viscosity takes place after approximately 60 days (sample D). For samples E and F this behaviour was repeated (values are not shown). For samples A, B and C the recovery was not total, but a tendency in decreasing the apparent viscosity with the increase of time until the day 45 exists. Starting from this value the viscosity begins to increase although it is not reaching its initial value (only sample A shown in Fig. 5).

4 CONCLUSIONS

The following conclusions can be extracted from this study. The rheological behavior of the creams containing human leukocyte alpha interferon is in general non-Newtonian fluid and of real plastic character that depends on time (thixotropic flow). Such behaviour can be described using the Herschel-Bulkley model. For a concentration of 100000 UI/g the yield stress and the consistency index are larger than for the concentration 20000 UI/g. The grade of

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thixotropy increases with the concentration of active principle. For the samples of active principle concentration 100000 UI/g the values of apparent viscosity are in the range 5 - 15 Pas while for the samples with 20000 UI/g these values are between 3 - 10 Pas. The higher limits of the interval are presenting values at the lowest accessible shear rate. The samples with lower concentration present a tendency to recover the initial structure after approximately 45 days although the recovery is not achieved totally. The samples of higher concentration recover the initial structure after 60 days. The Herschel-Bulkley predicted value of apparent viscosity can be included as a quality parameter for alpha interferon creams. Changes in formulations need new determination of flow curves because of the dependence of apparent viscosity with concentration.

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