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RHEOLOGICAL STUDY OF A THERMOREVERSIBLE MORPHINE GEL

DUMORTIER G.*, GROSSIORD J.L.**, ZUBER M.* ,COUARRAZE G.**, CHAUMEIL J.C.*.

* Department of Pharmaceutical Technology and Biopharmacy, Faculty of Pharmacy (ParisV), Paris, France.
** Department of Biophysics, Faculty of Pharmacy (University Paris XI), Châtenay-Malabry, France.
Present Adress:
Gilles Dumortier, Faculté des Sciences Pharmaceutiques et Biologiques, Laboratoire de Pharmacotechnie et Cosmétologie, Département de Pharmacotechnie et Biopharmacie, 4, Avenue de l'Observatoire , Paris 75270, Cedex 06, France.

ABSTRACT

The rheological behavior of a poloxamer 20% thermoreversible gel with morphine or without was studied. Its behavior was newtonian below the transition temperature and became non newtonian above this temperature. The non newtonian part was best fitted with the Herschel-Bulkley equation in comparison with the Casson equation. The sol-gel transition was associated with a drastic increment of the apparent viscosity and a brutal modification of the Herschel-Bulkley equation parameters. Likewise, the oscillatory parameters (the lag phase, the storage modulus and the loss modulus) revealed the great influence of the temperature on the viscoelastic properties of the sample. Different rheological methods have been described in order to determine the transition temperature usable for the control of preparations. The temperature interval corresponding to the sol-gel transition ranged between 22-25°C for the solution with morphine and between 23-26°C for the solution without. Thereby, the addition of morphine acetate did not induce the loss of thermoreversible properties and this preparation could be used as a controlled release system.

INTRODUCTION

Morphine salts are frequently used as an antalgic drug in cancerology. One of the difficulties of its administration corresponds to its very strong and rapid hepatic metabolism which is characterized by an important first hepatic pass. Consequently, the administration of the drug per os every 4 hours is necessary (8, 9).

Recently, many authors evaluated the possibility of using morphine by other routes such as an ophthalmosystemic or a nasal one (1, 8, 9, 12). Their objective was to evaluate the bioavailability of such alternative routes which could be interesting when the oral administration was not possible (in the case of recent digestive surgical intervention or during digestive tumor). Moreover, these routes allow to shunt the first hepatic pass.

The aim of this work was to describe the characteristics of a controlled release system containing morphine acetate. This vehicle corresponding to a thermoreversible poloxamer 407 gel. Poloxamers are non ionic surfactives, and are ethylene oxide - propylene oxide block polymers. The different types of poloxamers vary over a wide range of molecular weight and relative proportions of the two constituents (3, 4, 5, 6). The interest of poloxamer 407 results from its very low toxicity after parenteral delivery and its inertia towards mucosa. Ophthalmic, dermatologic and cosmetic preparations have been evaluated with the aim of prolonging the pharmacologic action of drugs (10, 11, 14, 17, 18, 19, 20, 23).

The phenomenum of thermogelling is perfectly reversible and is characterized by a sol-gel transition temperature. That is to say that below this temperature, the sample is fluid allowing a comfortable and precise delivery; above this transition temperature, the solution becomes gel according to the increment of the local temperature (7).

The thermogelification results from the interactions between the different molecules of poloxamer. The increment of the temperature modifies the hydration spheres around the hydrophobic units which in turn induces higher interactions between these different units (16, 22).

Some works (7, 15, 16) have been carried out on flow curves procedures; however, no work dealt with the fitting of the rheograms and with oscillatory procedures. The oscillatory study enables one to determine the viscoelastic

properties and respects the gel state contrary to flow curves procedure. Moreover, no procedure has been described in order to determine precisely the transition temperature by rheological procedures.
The objective of this work was to determine the rheological properties of a 20% poloxamer 407 solution and to evaluate the effect of 10% morphine acetate. In the first part, a flow curves procedure was used in order to fit the rheogram with the help of different equations. In the second one, an oscillatory procedure was performed in order to determine precisely the viscoelastic behavior as a function of the temperature. Finally, the precise transition temperature was determined with the help of the rheological studies.

EXPERIMENTAL

Preparation of poloxamer - morphine acetate solutions

The choice of the morphine acetate salt was made according to its very important water solubility (soluble 1 in 2.5 of water) which allows to administer the drug in a very small volume. This salt has been used in previous studies for these reasons (8, 9, 12).

The 20% poloxamer 407 solution (with 10% morphine acetate or without) was prepared using the cold method detailed elsewhere (20). The dissolution of the poloxamer 407 with morphine acetate or without was carried out using a volumetric flask (5ml) and distilled water.
Poloxamer 407 (Lutrol FC 127*, Lot n° 7931124) was given by BASF (Düsseldorf, West-Germany) and morphine acetate was purchased from Francopia Laboratories (Paris, France).
Poloxamer 407 has the following formula (3, 4, 5):

$HO(CH_2\text{-}CH_2O)_a\ (CH_2\text{-}CH(CH_3)O)_b\ (CH_2\text{-}CH_2O)_c\ H$
Molecular weight: 12.500
a and c are equivalent and the (a+c)/b ratio is equal to 70/30

Rheological studies.

They were performed with a thermostatized controlled stress rheometer (Carri-Med CS100, Carri-Med Ltd, Vincent Lane, England). The cone and plate geometry was used. The cone has a 4 cm diameter and a 2 degrees angle. The sample volume was equal to 2 ml.

- Flow curves studies.

The rheograms were carried out at 15, 19, 21, 23, 25, 30 and 35°C. Each rheogram was composed of three phases:
* in the first part, the shear stress was continuously increased, for a period of 3 minutes, until a maximal value was attained.
* in the second part, the sample was subjected to a constant shear stress for a period of 2 minutes.
* in the third part, the shear stress was continuously decreased, for a period of 3 minutes, from its maximal value until 0.

The maximal shear stress was chosen in order to obtain a shear rate of about 100 s^{-1} during the second part of the rheogram. The rheogram has been fitted with the help of the Ostwald equation (eqn. 1) which describes a pseudoplastic behavior or with other equations which describes a plastic one (Herschel-Bulkley equation, eqn. 2; and Casson equation, eqn. 3) (21, 24):

$$\tau = K\gamma^n \quad \text{eqn.1}$$

$$\tau - \tau o = K\gamma^n \quad \text{eqn.2}$$

$$\tau^{0.5} = K\gamma^{0.5} + \tau o^{0.5} \quad \text{eqn.3}$$

τ and τo represent the shear stress and the yield value, respectively; γ corresponds to the shear rate. Plastic viscosity was calculated at 10 s^{-1}, and was equal to $(\tau - \tau o)/\gamma$.
The determination of the transition temperature was carried out in two phases. In a first part, the temperature was increased by steps of 1° C, in order to locate the transition interval. In a second part, a very weak shear stress (0.6 N/m^2) was used and temperature was increased by steps of 0.1°C, with the aim of pinpointing the temperature at which the shear rate became non detectable.

This temperature was considered as the transition temperature using the flow curves procedure.

- Oscillatory studies.

The viscoelastic properties can be studied by subjecting the sample to a sinusoidal shear stress τ (24):

$\tau = \tau o \cos(\omega t)$

ω represents the angular frequency, τo the stress amplitude and t the time.

Under the action of τ, a strain appeared which is characterized by a same angular frequency and by a lag phase δ (eqn. 4).

$\gamma = \gamma o \cos(\omega t - \delta)$ (eqn. 4)

γo represents the strain amplitude.

From these different values, two moduli can be calculated: the storage modulus G' and the loss modulus G":

$G' = (\tau o / \gamma o) \cos \delta$

$G'' = (\tau o / \gamma o) \sin \delta$

For an ideally elastic solid, the stress and the strain are in phase ($\delta = 0°$, G" = 0); whereas for a purely newtonian liquid, stress and strain are in quadrature ($\delta = 90°$, G' = 0). G' and G" are related to the elastic stored energy and to the viscous dissipated energy, respectively .

The evolution of the mean oscillatory parameters (the storage modulus, the loss modulus and the lag phase) was studied as a function of the temperature, at a reference angular frequency of 1 Hz and at a strain amplitude of 60 N/m^2.

In a first part, in order to locate the interval of temperature corresponding to the variation of the oscillatory parameters, the temperature was increased by steps of 1 °C. In a second part, with the purpose of determining the beginning of the gelification, the temperature was increased by steps of 0.1 °C, every minute.

The gelification temperature (sol-gel transition) was considered to be the temperature at which the two moduli were equal. The G' and G" crossover has been used by some authors in order to reveal the sol-gel transition (25).

RESULTS AND DISCUSSION

The rheological behavior was either newtonian or non-newtonian depending on the temperature. This evolution was in agreement with the results of Miller and

TABLE 1
Thermorheological behavior of the poloxamer 407 solution with morphine or without

Temp °C	Plastic viscosity (mPa.s) with morphine	without	Rheological behavior with morphine	without
15	47	38	Newtonian r=0.999	Newtonian r=0.999
19	104	96	Newtonian r=0.999	Newtonian r=0.999
21	157	154	Newtonian r=0.999	Newtonian r=0.999
23	12420	25190	"	"
25	37700	93700	"	"
30	96800	132100	"	"
35	89200	140900	"	"

TABLE 2
Herschel-Bulkley parameters resulting from a 20% poloxamer 407 solution with morphine acetate or without.

Temp.	WITHOUT MORPHINE			WITH MORPHINE		
	τo (N/m^2)	K	n	τo (N/m^2)	K	n
23°C	0	7.1	0.55 r=0.994	0	3.6 r=0.996	0.55
25°C	0	61.9	0.19 r=0.995	0	19.8 r=0.994	0.28
30°C	9.1	95.7	0.14 r=0.999	5.0	68.6 r=0.999	0.15
35°C	14.8	104.5	0.13 r=0.999	27.8	60.3 r=0.999	0.17

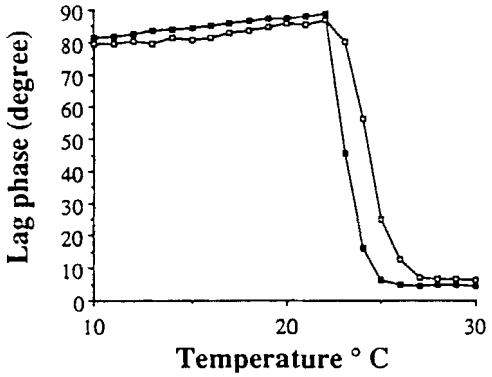

FIGURE 1
Lag phase versus temperature for the 20% poloxamer 407 solution with 10% morphine acetate (■) and without (□).

Drabik (16), of Boye (7) and of Lenearts et al.(15). Although our experiment described more precisely the type of the non-newtonian behavior and its evolution with the temperature. Between 15 and 21°C, both solutions (with morphine or without) had a newtonian behavior. Morphine acetate did not influence the rheological properties of the 20% poloxamer solution (table 1). The viscosity increased slowly with the temperature (table 1). On 23°C and above, the rheological type became suddenly non-newtonian and was characterized by an important measured yield value (table 2).

The rheograms were better fitted by the Herschel-Bulkley equation than by the Casson equation. The calculated yield value and the K value tended to increase with temperature, whilst the n value tended to decrease; then their value tended to plateau out above 25°C (table 2). Between 23 and 25°C, the calculated yield value was considered as negligible, and the behavior was very near to a pseudoplastic one. Above 25°C, a calculated yield value appeared and pointed out a plastic behavior. Nevertheless, the calculated yield value was inferior to the measured yield value. This finding showed the difficulty to determine the rheological type for the poloxamer 407 solution. For some authors, the yield value could not be considered as a very defined parameter and could result from the lack of sensitivity of the apparatus towards infinitesimal shear rate (2).

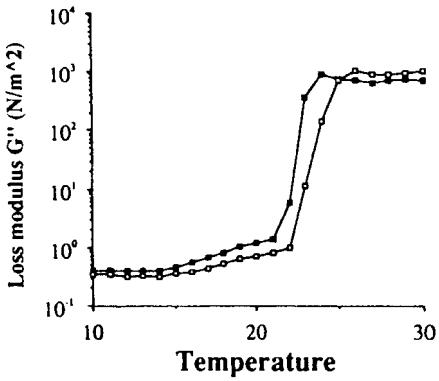

FIGURE 2
Loss modulus versus temperature for the 20% poloxamer 407 solution with 10% morphine acetate (■) and without (□).

The evolution of the lag phase (delta) and the two moduli G' and G" described the viscoelastic behavior of the sample (figure 1, 2, 3). The viscoelastic properties below the sol-gel transition were negligible: G' was close to zero; G" was weakly superior to G' and delta value ranged between 80 and 90°. The thermogelification of the sample with morphine or without was characterized by the increment of the two moduli and G' became superior to G": the sample became viscoelastic but its elastic component was predominant. In the same time, the lag phase value decreased strongly. The addition of the morphine acetate did not influence greatly the profile of this evolution.

The transition temperature corresponds to a range of temperature characterized by a great increment of the apparent viscosity and a drastic modification of the rheological behavior. A precise determination of this parameter needs to choose a defined criterion. The apparition of the measured yield value could be a satisfactory criterion and allowed us to define the transition temperature as equal to 22°4 for the solution with morphine and as equal to 22°8 C for that without. This procedure revealed the loss of newtonian properties; but it did not take into account the possible lag time between the loss of the newtonian properties and the apparition of the measured yield value. Moreover, as it was precendently noted, the yield value did not correspond to a very defined parameter. On the contrary, the oscillatory method pointed out the range of temperature during which a drastic modification was operating. The rough variation of delta and G'

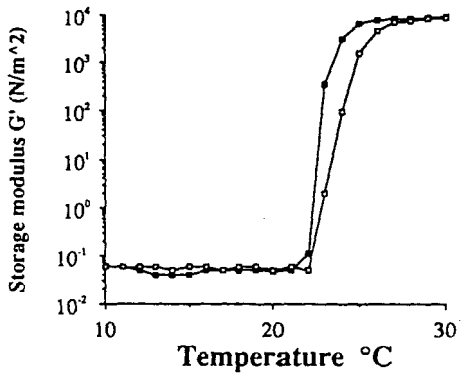

FIGURE 3
Storage modulus versus temperature for the 20% poloxamer 407 solution with 10% morphine acetate (■) and without (□).

was ranged between 22 and 25°C for the solution with morphine and 23 and 26°C for the solution without. The temperature at which the storage modulus became equal to the loss modulus was equal to 23.1°C for the solution with morphine acetate and equal to 24.6° C for that without. These values were slighty superior to those determined with the flow curves procedure because the G' G" crossover criterion pointed out a gel structure whereas the yield value apparition corresponded to the very beginning of the transition. Transition temperature seemed to be weakly decreased by morphine acetate with regard to our results. This weak decrease might be explained by the acid character of the poloxamer-morphine acetate solution (pH equal to 5.5 for the solution with morphine and to 6.9 for that without). Many additives like urea, glycerin, electrolytes (NaCl) or acid compounds (benzoic acid) are able to perturb the hydration sphere, and modify the transition temperature and the rheological properties of poloxamer 407 (13, 22).

Vadnere et al.(22) had described a glass tube method which determined a gel-sol transition temperature; and this one was considered to be very close to the sol-gel transition temperature according to the authors. Nevertheless, it is possible that the gel-sol transition temperature is weakly different to the sol-gel transition temperature. The tube procedure depends on the materials used and does not take into account the possible lag time between the gel-sol transition

and the slipping of the sample on the glass face when the temperature is decreased. On the contrary, rheological studies correspond to sensitive (sensitivity inferior to 0.1°C) and reproducible (C.V. inferior to 2%, n=6) procedures in order to determine the sol-gel transition which is the one observed during the administration of the vehicle.

CONCLUSION

This work enabled us to confirm the interest of 20% poloxamer as a controlled release system. It defined the rheological characteristics of this coumpond and described procedures in order to determine the transition point. This study showed the possible application to morphine preparations. Further studies are needed in order to evaluate its *in vivo* performance.

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REFERENCES

1 Bardin C. Etude du passage de la morphine par voie nasale chez le lapin. Mémoire de Diplôme d'études approfondies de Pharmacotéchnie et Biopharmacie. University of Pharmaceutical Sciences, Paris XI, France.

2 Barnes H.A., Walters K., Rheol. Acta, 24, 323 (1985).

3 BASF Wyandotte Corp. Industrial Chemical group - The wonderful world of Pluronic. - Catalog Card n° 70-150738 (1973).

4 BASF Wyandotte Corp., Industrial Chemical group - Pluronic polyols, toxicity and irritation data. - Publication n° 05-3012 Wyandotte, MI, USA (1973).

5 BASF Wyandotte Corp., Industrial Chemical group - Technical data on Pluronic polyols. - Publication n° 05-796 Wyandotte, MI, USA (1973).

6 BASF Wyandotte Corp., Industrial Chemical group - Technical data on pluronic polyol gels. - Publication n° 0-513 Wyandotte, MI, USA (1973).

7 Boye T.(1986). Développement de nouvelles formes ophtalmiques à libération prolongée et évaluation de la durée de leur activité pharmacologique.Thèse es Sciences Pharmaceutiques, University of Pharmaceutical Sciences, Geneva, Switzerland (1986).

8 Chast, F., Bardin C., Sauvageon-Martre H. and Chaumeil J.C. (1988), in International Conference on Pharmaceutical Sciences and Clinical Pharmacology. Program and abstracts, Jerusalem, Israel, p. 51 (1988).

9 Chast, F., Neil J., Martre H., Astier A., Chaumeil J.C. and Sandouk P.(1987), Act. Pharm. Biol. Clin., 4, 482(1987).

10 Chen-Chow P.C. and Frank S.G., Int. J. Pharm., 8, 89 (1981).

11 Cheng D.C.H., Rheol. Acta, 25, 542 (1986).

12 Dumortier G., Zuber M., Chast F., Sandouk P. and Chaumeil J.C., Int. J. Pharm., 59, 1 (1990).

13 Gilbert J.C., Richardson J.L., Davies M.C. and Palin K.J., J. Contr. Rel., 5, 113 (1987)

14 Hadgraft J.and Howard J.R., J. Pharm. Pharmacol., 34, 3P (1982).

15 Lenearts V.,Triqueneaux C, Quarton M., Rieg-Falson and Couvreur P., Int J. Pharm., 39, 121 (1987).

16 Miller S.C and Drabik B.R. Int. J. Pharm. , 18, 269 (1984).

17 Miller S.C.and Donovan D., Int. J. Pharm., 12, 147 (1982).

18 Miyazaki S., Takeuchi S., Yokouchi C and Takada M., Chem. Pharm. Bull., 32, 4205 (1984).

19 Nalbandia R.M., Henry R.L. and Wilks H.S., J. Biomed. Mater. Res., 6, 583 (1972).

20 Schmolka I.R., J. Biomed. Mat. Res., 6, 571 (1972).

21 Schott H. in Remington's Pharmaceutical Sciences, 16 th edn., Mack Publishing Co., Easton, p. 329 (1980)

22 Vadnere M., Amidon G., Lindenbaum S. and Haslam J.L.,Int. J. Pharm., 22, 207 (1984).

23 Waring G.O. and Harris R.R. in Symposium on ocular therapy, I.H. Leopold and RT.P. Burns (Eds), Vol. 11, John Wiley, New-York,.p.127 (1979).

24 Whorlow R.W. , Rheological techniques, Ellis Horwood (Eds), Chichester U.K.,p.. 33 (1980).

25 Winter H.H.,Polym. Eng. Sci.,27,1698 (1987).