Pharmaceutical Technology Division[1], Department of Pharmacy, University of Helsinki, Orion Corporation[2], Espoo, Orion Corporation[3], Turku, and Viikki Drug Discovery Technology Center[4], University of Helsinki, Finland

Pluronic F-127 gels as a vehicle for topical formulations of indomethacin and rheological behaviour of these formulations

A. Shawesh[1], S. Kallioinen[2], L. Hellén[3], O. Antikainen[1] and J. Yliruusi[1, 4]

Topical gel formulations containing a non-steroidal anti-inflammatory drug, indomethacin (IND), were prepared using 20% w/w Lutrol PF-127 as a gel-forming agent, and 16, 20 and 24% w/w Hexylene glycol (HG) or polyethylene glycol 300 (PEG) as solvents. 1% w/w Tween® 80 and 1% w/w PVP 25 were added as excipients. The effects of the amounts of solvent and excipients on the physical characteristics of IND gel such as consistency, appearance, crystallization, pH and viscosity were studied. The results indicated that 1% w/w IND is able to form a structural gel. The viscosity values were calculated from the rheograms which were determined by a Haake Rotovisco sensor at a shear rate of 10000 1/s. Viscosities corresponding to shear rates of 1000, 3000, 6000 and 9000 1/s were also calculated. Yield points were approximated from the rheograms. Although all IND gels maintained their pseudoplastic flow behaviour, their viscosities decreased markedly with increasing shear rates. Furthermore, increasing the amount of HG or PEG gave a more viscous gel except for the 24 w/w% HG gels which turned a jelly with or without either Tween® or PVP. The difference in viscosities was explained by the changes in the gel compositions. 20% of PEG-1% PVP ranked first in viscosity followed by 16% PEG-1% PVP, 16% PEG-1% Tween®, 24% PEG, 20% PEG-1% Tween® and 16% HG-1% PVP. The results indicate that the excipients influence the physical characteristics of the gels. The optimum concentration for gels manifesting as strength of gel was 20% PEG in combination with 1% PVP which had the highest viscosity and yield value at a low shear rate.

1. Introduction

Indomethacin (IND), a methyl imidazole acetic acid derivative introduced in 1962, is one of the most effective non-steroidal anti-inflammatory drugs (NSAIDs) in clinical use. It benefits rheumatoid arthritis patients by relieving pain, reducing swelling and tenderness of the joints and increasing grip strength [1]. Unfortunately, side-effects, primarily in the central nervous system and gastrointestinal tract, are often seen after the administration of oral immediate-release formulations of this potent drug [1].

To overcome the disadvantages of IND, several attempts have been made to develop a topical dosage form having local activity without systemic toxicity [2, 3]. Ishihama et al. [2] showed that topically applied IND ointment penetrated the skin as deep as 5 mm, and the concentration of IND in the muscle increased to a constant level after multiple applications [2].

Pluronic F-127 (PF-127 or Poloxamer 407), a gelling agent, is a polyoxyethylene: polyoxy-propylene block copolymer, which consists of approximately 70% w/w ethylene oxide and 30% propylene oxide [4]. This surface-active polymer is known for its very low toxicity and low skin irritation, excellent compatibility with other chemicals, high solubilizing capacity for different drugs [4] and good drug release characteristics [5–9]. A previous study [10] predicted that the time required for 10% IND degradation is 2.7 years in 20% w/v PF-127 gel at pH 7.00 and 20 °C, while in an aqueous solution it is only 48 days. Thus, PF-127 appears a potential vehicle for topical drug delivery systems [10]. In addition, PF-127 is a surface-active agent and forms non-ionic micelles in aqueous solutions and gels [6]. It is particularly useful as a gel base because of its unique property of reverse thermal behaviour (20–30% PF-127 gels are fluid at 4–5 °C, but highly viscous at room temperature and body temperature) [5, 6].

A thickening or gelling agent is usually and preferably included to facilitate the application of the formulation to the skin. The amount of the thickening agent is not particularly critical and can be selected to provide the desired product consistency or viscosity to allow for easy application to the skin without being too watery or loose so that it will stay where applied [11]. In the development of topical dosage forms, several desirable attributes that contribute to ultimate patient acceptability and clinical efficacy of the product may be defined. These include ease of removal of product from the container, good spreadability on the skin, good bioadhesion (to ensure retention at the site of application), acceptable viscosity, drug release and drug absorption [12]. Although rheological properties of pharmaceutical semisolids have been the subject of considerable interest during the last few decades, rheological characterization of such polymeric materials can be important as it provides fundamental information required for the assessment of some of the final properties of a product, e.g. consistency, quality and storage stability [1, 13].

NSAIDs, in general, are poorly soluble in water. In order to use them topically, they need to be dissolved in an organic solvent, or solubilized with a surfactant. For a topical gel formulation, the concentration of the active ingredient IND is such that all is in solution and a minimum amount of solvent is used to dissolve the IND.

The selection of an appropriate solvent can ensure minimum tissue irritation at the site of application. Our previous study [14] showed that the solvents hexylene glycol (HG) and polyethylene glycol 300 (PEG) give the best solubility for IND.

In this study, topical gel formulations of 1% w/w IND were prepared, using 20% w/w PF-127 as a gel-forming agent. The vehicle for any of the gels included glycol, HG and PEG 300 in different amounts (16, 20 and 24% w/w) as solvents and 1% w/w of Tween® 80 or PVP25 as excipients to improve the gel formulations (Table 1).

The physical characteristics of the gels (appearance, consistency, crystallization, pH and rheology) are also discussed.

Table 1: Indomethacin gel formulations 1% w/w containing Lutrol PF-127

No.	IND	PF-127	HG	PEG 300	PVP 25	Tween 80	Sterile Water
1	–	20	16	–	–	–	64
2	1	20	16	–	–	–	63
3	1	20	16	–	1	–	62
4	1	20	16	–	–	1	62
5	1	20	20	–	–	–	59
6	1	20	20	–	1	–	58
7	1	20	20	–	–	1	58
8	1	20	24	–	–	–	55
9	1	20	24	–	1	–	54
10	1	20	24	–	–	1	54
11	1	20	–	16	–	–	63
12	1	20	–	16	1	–	62
13	1	20	–	16	–	1	62
14	1	20	–	20	–	–	59
15	1	20	–	20	1	–	58
16	1	20	–	20	–	1	58
17	1	20	–	24	–	–	55
18	1	20	–	24	1	–	54
19	1	20	–	24	–	1	54
20	–	20	–	16	–	–	64

The aims of this study were to investigate the use of 20% w/w PF-127 as a gel base for IND and to determine its rheological properties, and to evaluate the effects of the solvents HG and PEG 300 at different concentrations and of the excipients Tween® and PVP on the physical characteristics of the gels.

2. Investigations, results and discussion

2.1. Physical properties

In a first approach the influence of IND on the appearance and consistency of the PF-127 gels were investigated (Table 2). After storage at 20 ± 2 °C for 24 h, all the gels were semisolid, yellow, clear and transparent in appearance, except for the HG placebo gel (1) and 24% w/w HG gels (8, 9 and 10) which had a jelly form. This was attributed to the large amount of HG in the formulations 8, 9 and 10.

A thin and smooth film was formed on application to the skin which was readily washable with water. No crystals were observed after 24 h of preparation, which indicates that the amounts of HG and PEG used were able to solubilize the IND.

Table 2: Evaluation of 1% Indomethacin-Lutrol gel formulations 24 hours after preparation

No.	Consistency	pH
1	Liquid	7.37
2	Semisolid	4.68
3	Semisolid	4.58
4	Semisolid	4.73
5	Semisolid	4.67
6	Semisolid	4.52
7	Semisolid	4.75
8	Liquid	4.62
9	Liquid	4.53
10	Liquid	4.72
11	Semisolid	5.02
12	Semisolid	5.02
13	Semisolid	5.00
14	Semisolid	5.15
15	Semisolid	5.20
16	Semisolid	5.14
17	Semisolid	5.25
18	Semisolid	5.20
19	Semisolid	5.30
20	Semisolid	6.79

The pH of the IND gels containing HG ranged between 4.5 and 4.7, while that of the placebo gel was 7.37. This decrease might be explained by the acid character of the IND (pK_α 4.5, which means that 50% of IND is in ionized form). The pH values of the IND gels containing PEG 300 ranged between 5.00 and 5.30, while that of the placebo gel was 6.79. The results of pH measurements indicate that the amount and the type of the solvents did not affect significantly the pH of the gels.

The addition of Tween® and PVP kept the pH in the same range. Nevertheless, the pH values of all the dermatological preparations were compatible with the skin pH which ranges from 4.5 to 6.5 depending on the body area [15].

2.2. Viscosity and rheology

The viscosity values obtained for the different variables (shear rate and shear stress) were graphically represented at different shear rates as described previously [16].

$$\eta = \tau / D \ [\mathrm{Pa \cdot s}] \qquad (1)$$

Where:

shear stress $\tau = A \cdot \%\tau \cdot S_\tau$ [Pa]

shear rate $D = M \cdot \%D \cdot S_D$ [S^{-1}]

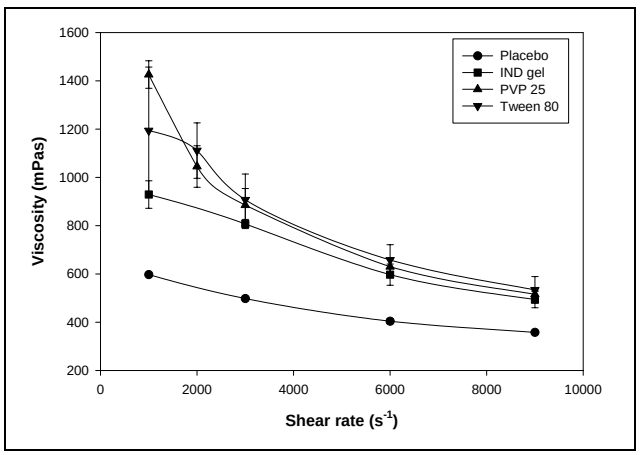

Fig. 1: Viscosity of Pluronic F-127 gels with HG 16% as a function of shear rate

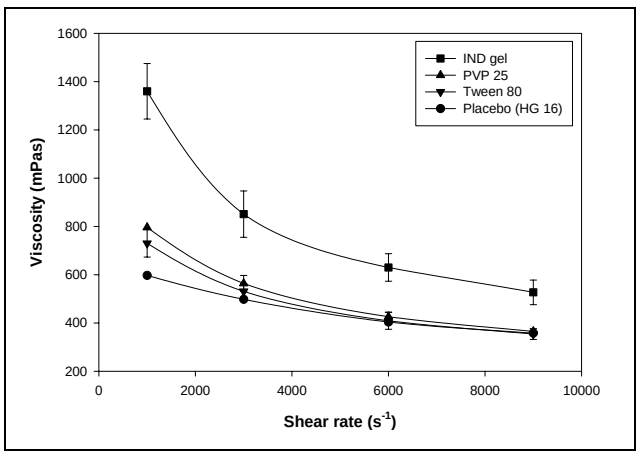

Fig. 2: Viscosity of Pluronic F-127 gels with HG 20% as a function of shear rate

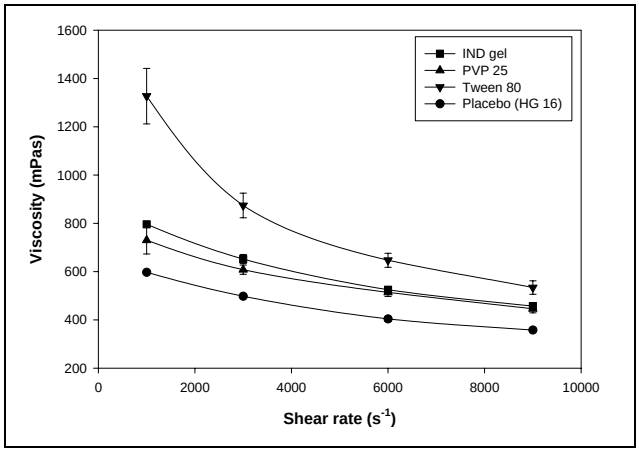

Fig. 3: Viscosity of Pluronic F-127 gels with HG 24% as a function of shear rate

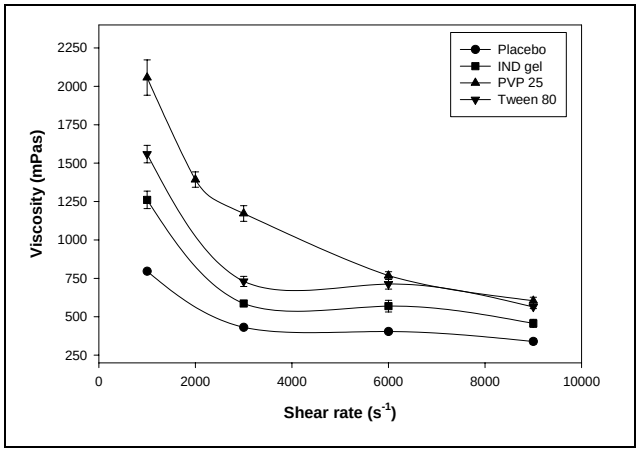

Fig. 5: Viscosity of Pluronic F-127 gels with PEG 20% as a function of shear rate

A = shear stress factor = 85.300
%τ = preset shear stress value at RV 100 given as a percentage of maximum shear stress.
S_τ, S_D: scale values, taken from the recorded flow curve
M = shear rate factor = 60.000
%D = preset shear rate value at RV 100 given as a percentage of maximum shear rate.

The viscosity of the PF-127 gels was plotted against the shear rate, giving non-linear relationships (Figs. 1–6). In all cases the gels exhibited a non-Newtonian flow behaviour. The graphs showed a pseudoplastic behaviour with the yield point of the PF-127 gel preparations, indicating that some intermolecular interactions were present [17]. However, at a shear rate of 1000 1/s the viscosity of all gels was the highest. With increasing shear rates the viscosity decreased markedly. Technically this can mean [18–19] that for a given force or pressure more material can be made to flow, or the energy can be reduced to sustain a given flow rate. Materials which are thinning due to increasing shear rates are called "pseudoplastic". Typical pseudoplastic preparations contain entwinted long-chain molecules or other aggregated structures. As the shearing stress increases, the aggregates progressively disrupt and polymer molecules begin to align their long axes in the direction of flow and, correspondingly, a sizable internal resistance against flow, i.e. a high viscosity [18]. With increasing shear rate the particle or molecular alignments allow particles and molecules to slip past each other more easily and this shows up as reduced viscosity [18]. At high shear rates, pseudoplastic flow behaves similarly to Newtonian flow and has a constant independent of shear rate [18–19].

In the gel containing 16% HG (placebo gel), the relationship between viscosity and all shear rates seems to be almost linear. With IND, the viscosities increased, followed by a sharp decrease until a minimum value was reached (Figs. 1–3). Our findings of the inverse relation between shear rate and viscosity of the gels are in agreement with a previous study [20] which showed that viscosity decreases as the shear rate increases. In the gel containing 16% HG-1% PVP (Fig. 1) the viscosity was the highest at a shear rate of 1000 1/s, which could be explained by the characteristic properties of PVP as a viscosity-increasing agent, whereas, in the gel containing 20% HG (Fig. 2) the viscosities were higher when only IND was used. When 20% HG, Tween® or PVP gels were used (Fig. 2), a small increase in viscosity was noticed. The viscosities of the gel containing 24% HG-1% Tween® (Fig. 3) were high, but this gel had a jelly form, which might be attributed to the amount of HG as mentioned above or due to the presence of Tween® 80 as an additive which was able to break the network of the gel structure.

At high shear rates the viscosity of the gels containing PEG (Figs. 4–6) was higher than those of the gels containing HG, including the placebo gel. This can be attributed to the molecular weight of HG (= 118.18) which is

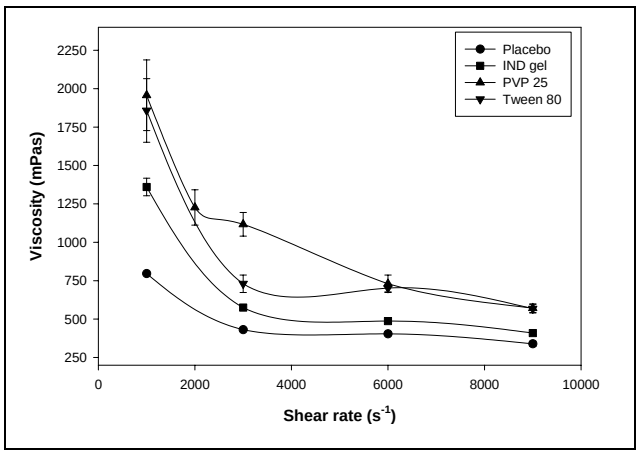

Fig. 4: Viscosity of Pluronic F-127 gels with PEG 16% as a function of shear rate

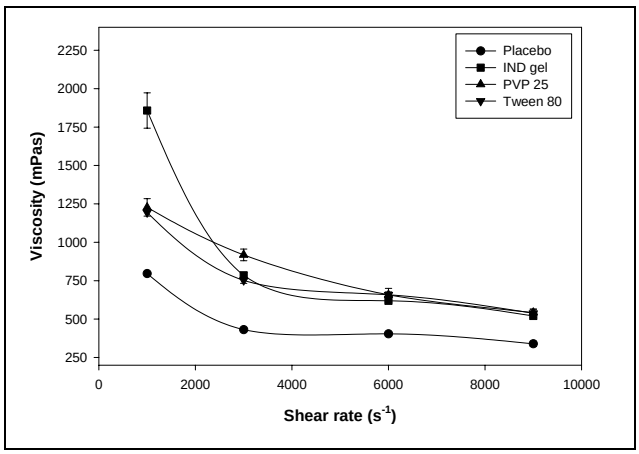

Fig. 6: Viscosity of Pluronic F-127 gels with PEG 24% as a function of shear rate

lower than that of PEG 300 (~300). The viscosities of IND-PEG gels increased markedly with the use of PVP or Tween® (Figs. 4–6). These results indicate that PVP and Tween® exert a positive effect on IND gels when the amounts of PEG are low (16 and 20%).

On the other hand, the highest viscosities were recorded when the gel containted PEG 20%-1% PVP (gel-15), followed by 16% PEG-1% PVP (gel-12).

Kassem and Mattha [21] explained the behaviour of PVP by the hydrodynamic theory of rod-shaped particles. The PVP molecule is a tightly coiled one. In theory it could be inferred that the viscosity of the rods decreases as the rate of shear increases. This is due to the fact that the particles are more and more flow oriented. The orientation becomes more pronounced at higher shear rates, which could in theory result in a lower viscosity [21].

Additives such as acids, humectants, alcohols, glycols and surfactants have been shown to affect the viscosity of the PF-127 gel [4]. Our results clearly show that the viscosities of the placebo gels were low at all shear rates but these viscosities increased with the addition of additives like IND, Tween® 80 and PVP 25 as shown in Figs. 1–6. The results obtained by viscosity measurements for PF-127 gel/Tween® support the fact that the viscosity increases in the presence of a non-ionic surfactant. This behaviour has been attributed to the interactions of the surfactant micelles with polymer chains. The surfactant micelles solubilize the polymer chains which belong to the polymer macromolecules and so increase the cross-linking of the system which is then quantified by increased rheological parameters. On the other hand, the subsequent decrease in viscosity is attributed to the disruption of inter-polymer bonds as the stoichiometry between micelles and polymer hydrophobic tails change (i.e. when the polymer hydrophobic sites become saturated with surfactant micelles). Shearing of micelles between the polymer chains is no longer a necessity and, consequently, the connectivity of the system drops and the viscosity decreases [19, 22]. It is possible, however, that the polyoxyethylene chains of Tween® 80, which are known to have high hydration properties, have caused minor dehydration of the polymer chains, and hence a slight decrease in viscosity [23].

The yield values (i.e. the values at which the formulations start flowing) were estimated at low shear rates. No yield values were seen in the placebo gels and the gels containing 24% HG. The gel containing 20% PEG-1% PVP had the highest yield value (200 ± 57.0) which was twice as high as that of the 16% HG-1% PVP (100 ± 0.0). Thus it can be concluded that the structure of the gel containing 20% PEG-1% PVP was the strongest.

A high yield value may help to maintain the gel on the skin so that it does not run off after application. When the preparation spread over the diseased area, the imposed shearing forces exceed the yield value and the application flows [24].

Statistical analysis (Student's t-test) was made with Systat®, Windows version 5.0 (Table 3). It showed that the additives PVP and Tween® had a significant influence on the viscosities of the gels ($p < 0.01$).

In conclusion, 20% w/w PF-127 solutions did show the ability to form a gel with 1% IND under test conditions. All these gels were semi-solid, except the 24% HG gels which had a jelly form. The pH values of these gels in a range between 4.52 and 5.30 were compatible with the skin pH. Although the viscosity of these gels varied with the gel compostions, they all exhibited a pseudoplastic flow behaviour. Thus the viscosity increased with increasing amount of HG and PEG. On the other hand, the highest viscosties were recorded when the gel containted PEG 20%-1% PVP (gel-15), followed by the gel containing 16% PEG-1% PVP (gel-12). The effect of the presence of PVP and Tween® on the viscosties of these gels was observed with HG 16% and PEG 16 and 20%. These results indicate that the PEG gels are stronger than the HG gels.

Table 3: Summary of statistical analysis of 1% w/w indomethacin gel formulations (n = 3)

Formulation	1000 s-1	3000 s-1	6000 s-1	9000 s-1
2 VS 3	**	–	–	–
2 VS 4	–	–	–	–
3 VS 4	–	–	–	–
5 VS 6	***	***	**	***
5 VS 7	***	***	***	***
6 VS 7	–	–	–	–
8 VS 9	–	–	–	–
8 VS 10	***	**	–	–
9 VS 10	***	***	–	*
11 VS 12	**	***	**	***
11 VS 13	*	*	**	***
12 VS 13	–	***	–	–
14 VS 15	***	***	**	***
14 VS 16	*	**	*	***
15 VS 16	–	***	–	–
17 VS 18	**	–	–	–
17 VS 19	***	–	–	–
18 VS 19	–	–	–	–

* = $P < 0.05$
** = $P < 0.01$
*** = $P < 0.001$
– = no significant difference

3. Experimental

3.1. Materials

Indomethacin (IND, particle size <5μ) was supplied by Orion Corporation, Espoo, Finland. Pluronic PF-127 (Basf Chemicals, Germany); hexylene glycol HG, polyethylene glycol 300 PEG, Tween® 80 (Fluka Chemical, Switzerland), and Polyvinyl pyrrolidone (PVP) Plasdone®, K-25 (GAF Chemicals, New Jersey, USA).

3.2. Preparation of pluronic gels

The composition of the different IND gels is shown in Table 1. The gels were prepared by the cold method described by Schmolka in 1972. The weighed amount of PF-127 was slowly added to cold water (4–6 °C) under constant agitation. Thereafter the dispersion was stored overnight in a refrigerator. With time, a clear, viscous solution was formed.

IND was dissolved previously in the solvents (HG, PEG). The solution of IND was added to the viscous solution of Pluronic by mixing gently to facilitate the formation of IND gel. The gels were packed in Amber glass containers and stored at room temperature (20 ± 2 °C) for 24 h before analyses.

3.3. Testing methods

3.3.1. Visual appearance of gels

The visual appearance of the model formulations was assigned according to whether or not a yellowish, clear gel was visible and to a liquid or semisolid consistency.

3.3.2. Microscopic examination

The solubility of IND in the solvent as manifested by the presence of crystals was evaluated by optical microscopy (Olympus VANOX-T, Tokyo, Japan). The magnification was 500X.

3.3.3. pH Measurements

A portable pH meter (PHM 80, Copenhagen, Denmark) was used to measure the pH of the gels at room temperature (20 ± 2 °C).

3.3.4. Rheological characteristics

The rheograms were measured by the cone and plate method (Haake Rotovisco sensor PKI/0.5 degree PK100/RV100, Haake GmbH, Karlsruhe, Germany) at $20.0 \pm 0.1\,^{\circ}C$. A sample of approximately 1 g was carefully placed on the plate. The measuring time was two minutes during which the shear rate was increased from zero to 10000 1/s. The viscosities were calculated from the rheograms at shear rates of 1000, 2000, 3000, 6000 and 9000 1/s. Also the yield points were approximated from the rheograms. All determinations were performed in triplicate.

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Amna M. Shawesh
Department of Pharmacy
Pharmaceutical Technology Division
University of Helsinki
P.O.Box 56
FIN-00014 Helsinki
Finland
Amna.shawesh@helsinki.fi