

Pharmaceutical Technology Division¹, Department of Pharmacy, University of Helsinki, Orion Corporation, Espoo², Viikki Drug Discovery Technology Center³, University of Helsinki, Finland

Development of indomethacin Carbopol ETD 2001 gels and the influence of storage time and temperature on their stability

A. M. SHAWESH¹, AM. KAUKONEN¹, S. KALLIOINEN², O. ANTIKAINEN¹, J. YLIRUUSI^{1,3}

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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_s86@yahoo.ca*

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We investigated the development of a topical indomethacin gel formulation of suitable consistency using Carbopol ETD 2001 as the gelling agent. Topical gel formulations containing 1% w/w indomethacin (IND), 1% w/w Carbopol ETDTM 2001 (C2001), 1% of triethanolamine (TEA), 30% hexylene glycol (HG) and 10% polyethylene glycol (PEG 300) were prepared with excipients Tween[®] 80, PVP 25, both Tween 80 and PVP 25 or neither agent. These four gel formulations were tested after a period of 1 and 4 weeks at storage temperature of 6 °C, 20 ± 2 °C and 45 °C. Physical evaluation of the stability of these gels was carried out by microscopic and rheological tests, measurement of pH and by visual inspection. Rheological properties were studied using the cone and plate method at shear rates of 600 to 6000 1/s. Viscosities corresponding to shear rates were also calculated. Our results indicated that C2001 could be used as a gelling agent for IND in topical preparations. IND-C2001 gels were clear and exhibited an acceptable appearance; gel behaviour was non-Newtonian and pseudoplastic. The addition of either Tween 80 or PVP 25 to the base gel formulation significantly increased the shear stresses and viscosity of the gels. These novel formulations exhibited good physical stability throughout the 4-week examination periods as inferred from pH measurements and microscopic examination. Additionally, the non-Newtonian pseudoplastic behaviour of the gels was maintained throughout storage, with only a minimal decrease in gel viscosity after 4 weeks. Differences in consistencies of the four formulations, although initially apparent, were no longer evident after 4 weeks of storage for all temperature conditions examined. Gels stored at high temperature (45 °C) developed a dark yellow color and decreased in viscosity compared to other storage temperature.

1. Introduction

Carbopols are acrylic acid polymers widely used as pharmaceutical excipients. They disperse in water to form acidic colloidal solutions of low viscosity and when neutralised produce highly viscous gels [1]. This gel formation is dependent on the electrostatic repulsion between the anionic groups and results in the molecules becoming extended and rigid. On addition of basic materials the dissociation of the carboxyl groups is enhanced and the viscosity of the systems increases. However, on addition of further quantities of base the viscosity may decrease due to screening of the carboxyl groups [2]. The viscosity reaches a maximum at pH values between 6 and 11, but is considerably reduced if the pH is less than 3 or greater than 12 [1].

Carbomers have been used to prepare topical gel formulation for (IND) by several investigators [3–8] because they exhibit high viscosities at low concentrations. Moreover, they are quite stable when heat is applied with negligible batch-to-batch variability. Carbomer gels are unaffected by aging and do not support bacterial or fungal growth. They

have excellent patient acceptability due to their appearance and because they are non-toxic and non-irritating [1].

C2001 resin is chemically similar to standard Carbopol resins and can be used in topical formulations in the place of Carbopol (940, 980, 934, 2984 or 5984). C2001 is different from Carbopols as it is produced with a proprietary polymerization aid in the toxicologically preferred cosolvent system [9]. C2001 has recently been commercialized and is patent-pending. This Carbopol resin provides dispersions in water that are easy to mix, less susceptible to lumping and much lower in viscosity prior to neutralization [9]. Following neutralization, C2001 yields perfectly homogeneous and transparent hydrogels [10].

In the present investigation, C2001 was used as gel-forming polymer for a model IND. In recent years, many gelled water-soluble bases have been formulated to optimize topical drug delivery, but exhaustive rheological studies of these systems have not been undertaken. The rheological properties of Carbopols are of great importance, and may lead to the possible use of rheological parameters to optimize topical drug delivery for dermatological formulations [6, 10–18].

Table 1: Composition of 1% w/w IND-C2001gels

Formulation	IND	HG	PEG	Carbopol 2001	TEA	Tween	PVP	Sterile Water
F I	1	30	10	1	1	—	—	57
F II	1	30	10	1	1	1	—	56
F III	1	30	10	1	1	—	1	56
F IV	1	30	10	1	1	1	1	55

Studies [10–18] of the rheological behaviour of Carbopol gels in topical formulations have examined a number of variables, including changes in the concentration of polymer, degrees of neutralization, mechanical properties (agitation time, temperature, shear rate and shear stress). However, the studies did not examine the stability of the gels as a function of storage time and condition. During manufacture and storage of pharmaceuticals it is of great importance to know how the flow properties of dispersed systems are affected by changes in temperature and time. The assessment of physical stability should be done on the finished product as it sets after preparation, thereby taking into account all ingredients.

In this study, gel formulations (Table 1) contained constant concentrations of 1% w/w IND, 1% w/w C2001 as a gel-forming agent, 1% w/w of the organic base TEA as a neutralizer and 30% w/w HG and 10% w/w PEG 300 as solvents. Four different gel formulations were created by adding either 1% w/w of Tween 80, 1% PVP 25, both Tween 80 and PVP 25, or neither excipients. Tests were done on the four gels formulations after a storage period of 1 and 4 weeks at 6 °C, 20 ± 2 °C and 45 °C.

The objectives of this investigation were to develop formulae suitable for topical therapeutic use of IND-C2001 and to study the effect of the four formulations on the physical characteristics of the gels (macroscopic inspection, pH, crystallization and rheological properties). In addition, we examined the influence of storage time and storage conditions on these characteristics.

2. Investigations, results and discussion

The results of the consistency of the gels are summarized in Table 2. After gel preparation and storage of the gels at 20 ± 2 °C for 24 h, all of the gels were semisolid, compact, yellow, clear, and transparent in appearance. A smooth, thin film was formed on application to the skin which was readily removed with water. No crystals were observed in any of the gels. Formulation I was the least viscous gel. Because this gel did not contain additives the water content was higher than other gels, and may explain the lower viscosity. The effect of storage on the appearance and consistency of the gels is presented in Table 2. All gels presented good stability. Therefore, no macroscopic physical changes were observed during storage. Additionally, these gels did not show any sign of phase separation or microbial contamination. It was noted that formulation I was very compact, i.e., it was a highly structured semisolid after 1 week storage under all storage temperatures.

The gels remained yellowish and transparent at 6 °C and 20 ± 2 °C during 4 weeks of storage. However, a yellow to dark yellow color appeared in all formulations stored at 45 °C for 4 weeks. The changes in the color of the gels was most likely due to ion bonding or hydrolysis of some IND, which is known to darken slightly at high tempera-

Table 2: Influence of storage time and condition on the characteristics of IND-C2001 gels

Formulation	Storage time	Storage temperature	Consistency	PH
Gel I	Initial		1	5.83
			2	5.85
	1 week	+6 °C	2	5.84
		20 ± 2 °C	2	5.88
		+45 °C	2	5.88
			2	5.88
			2	5.89
			1	5.90
Gel II	Initial		2	5.90
			2	5.92
	1 week	+6 °C	2	5.91
		20 ± 2 °C	2	5.94
		+45 °C	2	5.94
			2	5.93
			2	5.92
			1	5.95
Gel III	Initial		2	5.89
			2	5.90
	1 week	+6 °C	2	5.91
		20 ± 2 °C	2	5.91
		+45 °C	2	5.91
			2	5.93
			2	5.92
			1	5.93
Gel IV	Initial		2	6.05
			2	6.07
	1 week	+6 °C	2	6.05
		20 ± 2 °C	2	6.09
		+45 °C	2	6.09
			2	6.08
			2	6.05
			1	6.10

tures. This observation was also noted in a previous study [19].

Microscopic analysis did not reveal any changes in gels. No IND crystals were observed microscopically after gel preparation or during 4 weeks of storage at 6 °C, 20 ± 2 °C and 45 °C. These results were attributed to the use of two solvents (HG and PEG 300) which were required to obtain a clear gel in which IND was completely solubilized. The choice of these solvents was related to our previous work [20], which showed that the solvents HG and PEG 300 gave the best solubility for IND. Using PVP as an excipient also improves the solubility of IND [20]. PVP has been used as a drug crystallization inhibitor in pharmaceutical formulations for many years. Ziller and Rupprecht suggested that the inhibitory effect of PVP on drug crystallization in aqueous suspension may be primarily attributed to the protective PVP layers adsorbed on the crystal surfaces [21].

pH measurement data (Table 2) indicated that Tween 80 and PVP had no significant effect on the pH of the formulations. The pH values were between 5.8 and 6.1 after gel preparation and for all storage temperatures and times. The pH values of each formulation did not change during the storage period (Table 2). These results indicate that there was no degradation of IND from the gel and that there was no hydrolysis of IND. No changes occurred within the mild acidic pH range which is suitable for human skin.

As can be seen in Figs. 1, 2–5a, b, the flow curves obtained for the four IND-C2001 gels studied were qualitatively similar with characteristics of a non-Newtonian system with pseudoplastic flow. In all cases, shear stress was

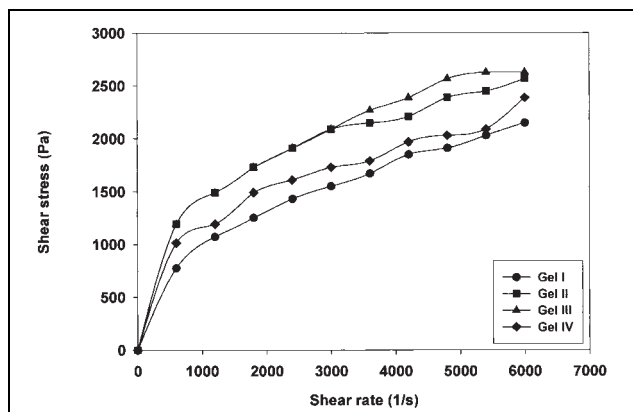


Fig. 1: Rheogram of IND-C2001 gels I, II, III and IV after preparation

found to increase with shear rate. Fig. 1 shows the rheograms obtained for the four formulations (I–V) just after gel preparation. As shown in the figure, all gels demonstrated a linear relationship between shear stress and shear rate. Therefore, the results obtained from these formulations appear to be dependent on the stress used. The rheogram of gel I lies markedly below that of the gels containing additives Tween (gel II) or PVP (gel III) or Tween and PVP (gel IV). Another very important finding was that the combination of Tween and PVP in the formulation (IV) was associated with a decrease in the shear stresses. However, the shear stresses of the rheogram for formulation I were much lower than those for formulations II–IV. This indicated that the deformation of this network required much greater shear stresses than those needed to deform gel I.

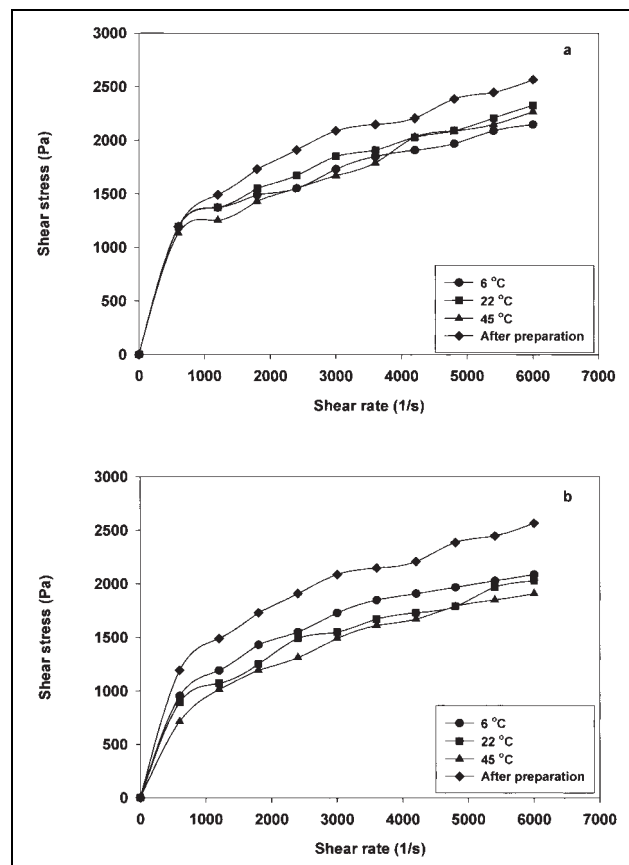


Fig. 3a, b: Effect of storage temperature on the rheograms of IND-C2001 gel II, a: after 1 week, b: after 4 weeks

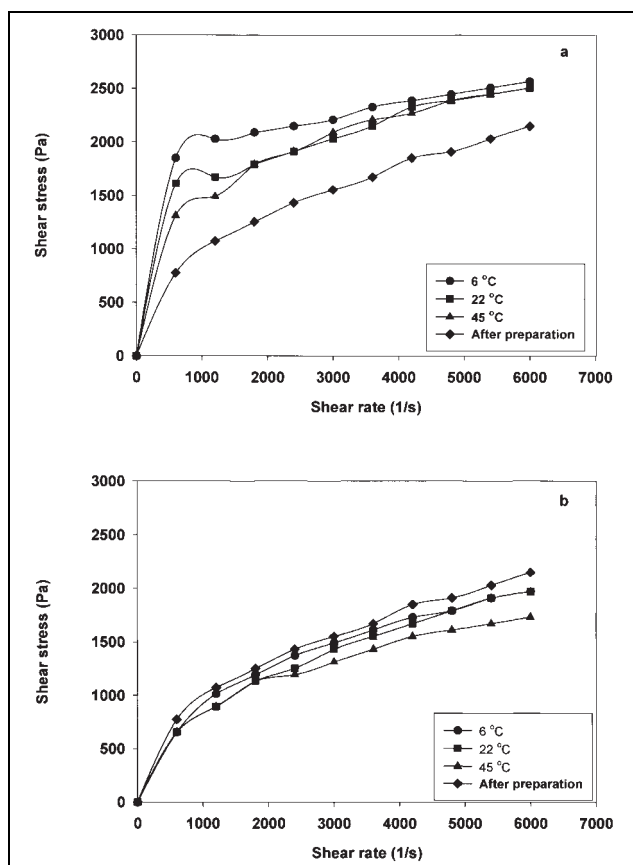


Fig. 2a, b: Effect of storage temperature on the rheograms of IND-C2001 gel I, a: after 1 week, b: after 4 weeks

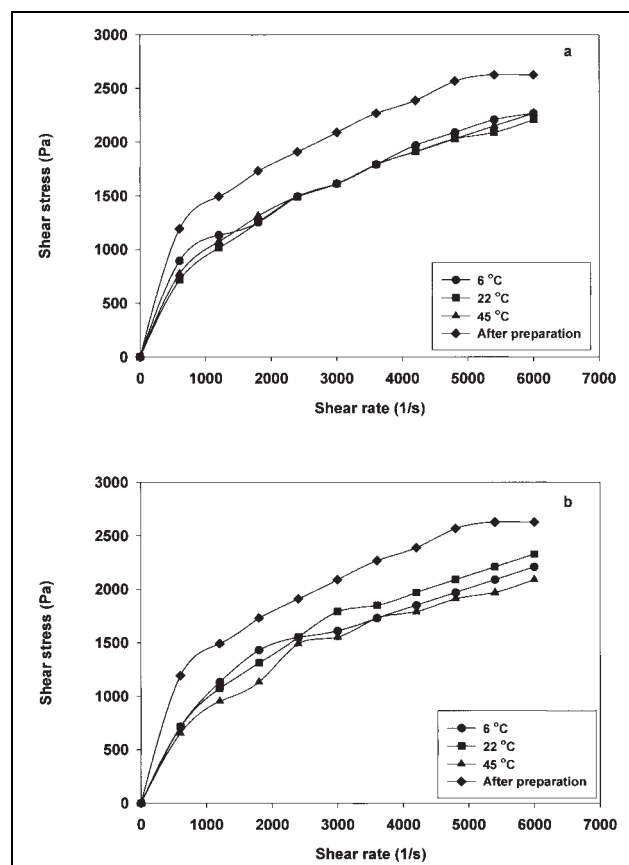


Fig. 4a, b: Effect of storage temperature on the rheograms of IND-C2001 gel III, a: after 1 week, b: after 4 weeks

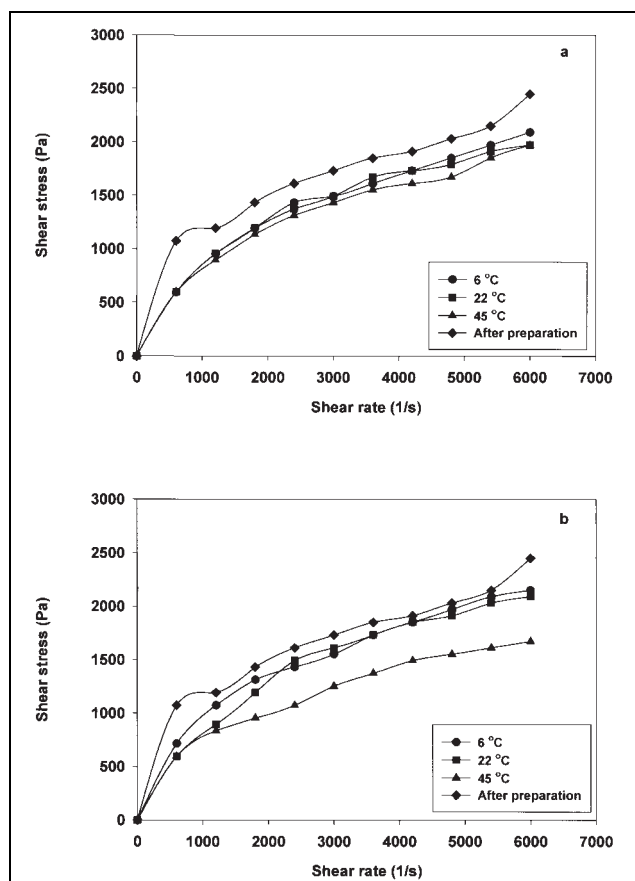


Fig. 5a, b: Effect of storage temperature on the rheograms of IND-C2001 gel IV, a: after 1 week, b: after 4 weeks

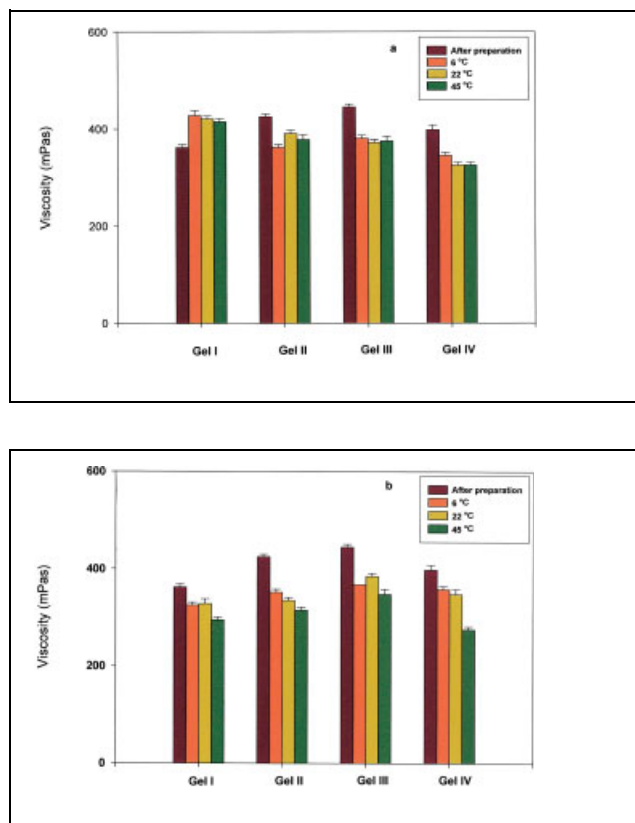


Fig. 6a, b: Viscosities of the IND-C2001 gels on a higher rate (6000 1/s), a: after 1 week, b: after 4 weeks

The effect of storage time on the rheograms of the gels was clearly indicated (Figs. 2–5a, b). For formulation I (Fig. 2a) the shear stresses increased after one week of storage for all storage temperatures. The deviation from the initial rheogram was greater and is probably because the basic network had not been formed before the determination of the first rheogram. The shear stress was decreased after 4 weeks of storage. In Fig. 3–5a, b the shear stresses for formulations II–IV were decreased after 1 and 4 weeks of storage independently of storage temperature. No structural breakdown occurred under these shearing conditions.

The viscosity values of the gels (Table 3) were calculated from the rheograms of shear rates (600, 1800, 3000, 4200 and 6000 1/s) [22].

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

where

$$\text{Shear stress } \tau = A \cdot \% \tau \cdot S_{\tau} \text{ [Pa]}$$

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

A = shear stress factor = 85.300

$\% \tau$ = preset shear stress value at the RV 100 given as 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 the RV 100 given as percentage of maximum shear rate.

We noted a decrease in viscosity of the gels as the shear rate increased, thus indicating the non-Newtonian, pseudo-plastic character of the tested gels (Table 3). This finding is a commercial requirement, as high viscosity at high shear rates will result in irritation. If, on the other hand, the viscosity is too low then increased liquification will occur. To decrease the liquification of the gel on the skin the viscosity at low shear should be high. Marked differences were noted in viscosity between the four IND-C 2001 formulations after gel preparation. The lowest viscosity values were obtained with the gel that did not contain additives (gel I). However, formulation III, which contained PVP, had the highest values, due to PVP's viscosity-increasing properties [1]. We noted an increase in the viscosity of gels II–IV due to presence of additives (Tween or PVP or Tween with PVP). Formulation II, which contained 1% Tween (polysorbate is a hydrophilic nonionic surfactant) also had a high viscosity value with low shear rates (Table 3). It is possible, however, that polyoxyethylene chains of polysorbate 80, which are known to have high hydration properties [1], have caused hydration of the C 2001 polymer chains and hence the increase in viscosity. The combination of Tween with PVP in formulation IV resulted in a lower viscosity than formulations II and III.

After 1 week of storage the viscosity of gel I had increased for all storage conditions while the viscosities of formulations II–IV were decreased after 1 week for all storage temperatures. In other words, these changes in the viscosities of the formulations occurred independently of storage temperature during the first week of storage. The net increase of the viscosity of gel I stored for 1 week at all storage temperatures could be explained by a total structurization of the gel. Viscosity was lower after 4 weeks than it was initially or after 1 week of storage at each storage temperature investigated.

In conclusion, this study has demonstrated that IND-C2001 formulations generate semi-solid, clear, transparent and compact gels. According to both rheogram analysis and viscosity measurements, all IND-C2001 gels exhibited

Table 3: Viscosity values of IND-C2001 gels measured with different shear rates from 600 to 6000 s⁻¹

Formulation	Storage time	Storage temperature	Viscosity (mpa*s) (shear rates)						
			600 s ⁻¹	1800 s ⁻¹	3000 s ⁻¹	4200 s ⁻¹	6000 s ⁻¹		
Gel I	Initial		1360	708	524	436	362		
		+ 6 °C	3019	1150	730	564	428		
		20 ± 2 °C	2720	1006	683	554	421		
		+45 °C	2156	973	703	545	415		
	4 weeks	+ 6 °C	1095	675	504	412	325		
		20 ± 2°C	1095	619	491	403	328		
		+45 °C	1128	641	445	374	295		
		Gel II	Initial		2024	973	690	535	425
				+ 6 °C	1990	818	564	460	362
20 ± 2 °C	1957			851	604	479	391		
+45 °C	1791			807	564	483	378		
4 weeks	+ 6 °C		1592	796	577	455	352		
	20 ± 2 °C		1493	708	511	417	335		
	+45 °C		1227	652	491	403	315		
	Gel III		Initial		1957	951	697	564	445
				+ 6 °C	1493	708	544	474	381
20 ± 2 °C		1128		708	544	450	372		
+45 °C		1261		741	544	450	375		
4 weeks		+ 6 °C	1227	785	544	450	368		
		20 ± 2 °C	1227	719	590	464	385		
		+45 °C	1062	641	511	422	348		
		Gel IV	Initial		1758	818	577	460	398
				+ 6 °C	1028	652	491	408	345
20 ± 2°C	995			652	491	408	325		
+45 °C	995			619	464	384	325		
4 weeks	+ 6 °C		1227	719	524	445	358		
	20 ± 2 °C		995	652	524	436	348		
	+45 °C		995	542	425	355	275		

a non-Newtonian pseudoplastic behaviour. Significantly, the excipients Tween and PVP increased the consistency of the gels. The additive PVP (gel III) caused the greatest increase in gel viscosity and the additive Tween (gel II) caused a lesser increase in gel viscosity; the combination of both Tween and PVP (gel IV) was associated with significantly smaller increases in gel viscosity compared to either Tween or PVP when added separately. Gels of least viscosity were obtained when neither excipients was added to the formulation (gel I).

All gels tested exhibited good stability, although a decrease in the consistency of the gels and the appearance of a pale to dark yellow color was observed in all samples stored for 4 weeks at 45 °C. Additionally, the viscosity of all gels decreased with increasing storage time. After 4 weeks of storage for all temperature conditions examined the consistency differences initially noted between the four gel formulations were no longer evident.

3. Experimental

3.1. Materials

Indomethacin (IND) (particle size 5 µm) was supplied by Orion Corporation, Espoo, Finland. Carbopol® ETD 2001 (C2001) was obtained from B. F. Goodrich Chemical Co., Calvert City, KY. Hexylene glycol (HG), polyethylene glycol 300 (PEG 300) and Tween® 80 were supplied by Fluka Chemical, Switzerland. Polyvinyl pyrrolidone (PVP) Plasdane®, K-25 was supplied by GAF Chemicals, USA. Triethanolamine (TEA), British Pharmacopeal grade (BP-93, analysis nr. 173597).

3.2. Preparation of gel formulations

The composition of the IND-C2001 gels is summarized in Table 1. The weighed amounts of C2001 were added slowly in small increments into a

vortex of the appropriate quantity of sterile water. A magnetic stirrer ensured constant stirring. After all the resin was added the stirring was continued at a reduced speed in order to prevent the entrapment of air. The resulting dispersion was stored at rest and in darkness for 24 h to obtain homogenous solutions. Required amounts of HG and PEG were mixed together. These solvents were then added into IND to dissolve. The drug-solvent solution was then added slowly to the mixture in small portions with constant stirring until homogeneity was achieved. The required quantity of TEA was then added to the mixture to increase the pH and initiate the gel formation. The final gel formulations were packed in amber glass containers and stored in a dark place at room temperature (20 ± 2 °C) for 24 h before being stored at one of three different temperatures (6 °C, 20 ± 2 °C and 45 °C).

3.3. Stability study

The stabilities of the gels were examined during a 4 week period under three different conditions. Measurements were made 24 h after gel preparation (initial) and after 1 and 4 weeks of storage. The storage conditions studied were cold (6 °C), room temperature (20 ± 2 °C) and accelerated conditions (45 °C).

3.3.1. Visual inspection

The appearance of the model formulations was inspected for changes in colour and clarity of the gel. The consistency was assigned as semi-solid (1) or more viscous semi-solid (2).

3.3.2. Microscopy

The gels were analysed for the presence of crystals by observing them with an optical microscope (Olympus VANOX-T, Tokyo, Japan). The magnification was 500X.

3.3.3. pH

The pH was measured in each gel using a portable pH meter (PHM 80, Copenhagen, Denmark). The meter was calibrated before each use with buffered solutions at pH 4 and 7 at room temperature (20 ± 2 °C).

3.3.4. Rheological characteristics

The rheograms were measured initially, after one week and after four weeks of storage by the cone and plate method (Haake Rotovisco sensor PKI/0.5 degree PK100/RV100, Haake GmbH, Karlsruhe, Germany). Determinations were done at 20.0 ± 0.1 °C. A sample of approximately 1 g was carefully placed on the plate. The measuring time was 2 min during which the shear rate was increased from zero to 6000 1/s. The viscosities were calculated from the rheograms at all shear rates. All determinations were performed in triplicate.

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