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Rheological, mucoadhesive and release properties of Pluronic F-127 gel and Pluronic F-127/polycarbophil mixed gel systems

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This study was designed to combine the mucoadhesive property of Noveon® and the thermosensitive property of Pluronic® F-127 into one gel system. A rheological study of Pluronic aqueous sols (10–35%), Noveon® gels (0.5–2%) and of mixed gels containing Pluronic (10–17.5%) and polycarbophil (0.5–2.5%) was conducted at different temperatures (15–35 °C). The viscosity of Pluronic sols increased with an increase in temperature and the mixed gels had thermoreversible property. The viscosity of mixed gels was higher than that of the Pluronic sols containing only Pluronic because of the increase in total polymer concentration. No interaction was found between –COOH groups of Noveon and Pluronic molecules at the studied concentrations of polymers; the viscosity of mixed gels containing un-neutralized Noveon was lower than that of the neutralized mixed gels. The effect of Pluronic® F-127 on the mucoadhesive property of Noveon was investigated. The mucoadhesive properties of Pluronic and Noveon gels were compared by a force of detachment test. It was found that Pluronic and Noveon gels showed approximately the same mucoadhesive strength. However, there were significant differences in the viscosity of Noveon and Pluronic gels. The adhesive force of the mixed gel was almost same as that of the Noveon gel. The Pluronic did not affect the adhesive power of Noveon and the increased viscosity did not affect the bioadhesive force of the mixed gels. In spite of increasing viscosity of the gel, the percentage of released model material (mannitol) increased with increasing temperature. This is based on the previously reported observation that the interaction between the Pluronic molecules squeezed mannitol molecules out of the polymer chains. The mannitol release obeyed zero-order kinetics and the flux values of mixed gels at 15 and 35 °C were very similar. The Noveon chains among Pluronic chains probably hindered the diffusion of mannitol molecules and the release was thus controlled by Noveon. The combination of a thermosensitive polymer like Pluronic and a bioadhesive polymer like Noveon appears promising from a pharmaceutical viewpoint. These gel systems may find use in the development of bioadhesive, thermosensitive and controlled release formulations.

1. Introduction

Pluronic® F-127, also known as "poloxamer 407", consists of approximately 70% ethylene oxide and 30% of propylene oxide by weight. This product is called block polymer because it is composed of a propylene oxide block surrounded by two ethylene oxide blocks. It is reported to be the least toxic of commercially available poloxamers (BASF 1996). The polymer is soluble in water and a 20–35% (w/w) aqueous solution of this compound is a clear, viscous liquid at refrigerator temperature. It exhibits the property of reverse thermal gelation. At low temperatures, the polymeric solution is a liquid and at higher temperatures, the polymer chains form a gel structure. It was shown that Pluronic® F-127 formed a gel in water at a concentration of 20% and a temperature above 25 °C (Schmolka 1972; Schmolka 1991; Malmsten and Lindman 1993).

This compound has a potential use as a controlled drug delivery system, which is liquid at room temperature or lower, but forms a gel at body temperature. The polymer has thus been examined as a vehicle for ophthalmic application (artificial tears, ophthalmic drug delivery) (Warring and Harris 1979; Miller and Donovan 1982); as an artificial skin for the treatment of burns (Schmolka 1972); as a vehicle for parenteral administration (Katakam et al. 1997; Johnston et al. 1992; Johnston and Miller 1989; Collet et al. 1985); as a vehicle for extra vascular administration (Fults and Johnston 1990); and as a potential topical vehicle (DiBiase and Rhodes 1996; Chi and Jun 1990). Pluronic® F-127 is also an emulsifying, solubilizing and stabilizing agent (DiBiase and Rhodes 1996; Schmolka 1967; Wang and Johnston 1995; Saettone et al. 1988).

Mucoadhesive polymers have been studied for prolonging the contact time between dosage form and the mucosa (Ch'ng et al. 1985). In particular, poly(acrylic acid) poly-

mers are well established as good mucoadhesive materials. Polycarbophil (Noveon® AA-1, Carbopol® EX-55) is an insoluble, water swellable and highly mucoadhesive poly(acrylic acid) polymer (Park and Robinson 1985). However, the release characteristics of polycarbophil gel are not unique for sustained release drug delivery.

Previous studies have shown Pluronic possesses bioadhesive properties (Charrueou et al. 2001; Juhasz et al. 1991). In this research, we aimed to combine the mucoadhesive property of Noveon and the thermoreversible property of Pluronic into one gel system. No studies have yet been published reporting on the mucoadhesive, rheologic and release properties of a mixed gel containing Pluronic F-127 and Noveon. We were interested to know the release characteristics and mucoadhesive properties of polycarbophil, and how the thermoreversible property of Pluronic F-127 gels would change.

The purpose of the present study was to investigate a) the viscosity characteristics, mucoadhesive properties and release properties of mixed gels containing Pluronic and polycarbophil, b) the release characteristics of gels containing only Pluronic F-127 at two temperatures, c) the effect of a second polymer (Pluronic) on the mucoadhesion of polycarbophil, d) the mucoadhesive property of Pluronic F-127 in comparison with polycarbophil.

2. Investigations, results and discussion

2.1. Viscosity

The viscosity data of gels containing only Pluronic at different concentrations is shown in Table 1. All Pluronic sols were viscous liquids at refrigerator temperature. Pluronic solutions of 10, 12.5 and 15% exhibited newtonian flow for three temperatures (25, 30 and 35 °C); the systems were too soft and remained as a liquid and no gel formation was observed. The same results were reported by Choi et al. (1998), Guzman et al. (1994), Tung (1994), and Miller and Drabik (1984). The flow curve of 15% Pluronic at 35 °C showed non-newtonian behavior. When newtonian viscosity values were investigated, no significant difference was observed between temperatures for 10, 12 and 15% Pluronic, demonstrating that the temperature does not dramatically affect the viscosity of non-concentrate solutions of Pluronic; the Pluronic micelles were monomolecular form and the sol system had relatively low viscosity. For 15% Pluronic solution at 35 °C, there was a dramatic increase in viscosity because of the formation of the gel structure.

At concentrations of Pluronic above 15%, the viscosity increased significantly and exhibited non-newtonian rheologic behavior at all temperatures. They formed a semisolid gel at the experimental temperatures. The viscosity versus shear rate curves of the gels at various temperatures showed shear thinning property. An increasing concentration of Pluronic resulted in a large increase in resistance to flow, primarily due to entanglement of molecule chains.

When Pluronic is added to water, the polymer dissolves because of formation of hydrogen bonds between the poly(oxyethylene) unit and water molecules. At lower concentrations (10, 12 and 15%), a monomolecular micelle forms. At a higher concentration, a polymolecular micelle forms and several micelles come together and minimize their interaction with water. Thus the viscosity increases with increasing concentration (Schmolka 1991; Vadnere et al. 1984).

With an increase in temperature, Pluronic sols exhibited an increase in viscosity (Table 1). The same condition has previously been described (Schmolka 1991; Malmsten and Lindman 1993; Vadnere et al. 1984; Tung 1994; Atwood et al. 1985; Lenaerts et al. 1987). According to these studies, the interaction between Pluronic molecules or micelles is responsible for the formation of the gel structure. At a lower temperature, water molecules around the polymer chain are ordered and the hydrophilic interaction between poly(oxyethylene) (POE) units of Pluronic molecules and water molecules is dominant. With increasing temperature, hydrophobic interaction between poly(oxy-propylene) (POP) units of Pluronic molecules dominate, polymer chains approach closer and squeezed ordered water molecules (dehydration processes). The viscosity of the gel increased and the high viscosity or rigid gel formed.

Table 1: Viscosity values (Pa · s) of Pluronic gels and Noveon els at onstant shear rate (0.5 s^{-1})

	15 °C	25 °C	30 °C	35 °C
Pluronic (%)				
10	–	0.0104	0.0117	0.0129
12.5	–	0.0239	0.0322	0.0351
15	–	0.0616	0.0899	18.9
17.5	168.2	248.6	396.7	590.0
20	–	487.1	690.4	765.8
25	–	1144.9	1692.2	1893.1
30	–	1702.2	2568.4	3412.1
35	1119.8	1867.9	3477.3	4135
Noveon (%)				
0.5	160.7	–	–	130.6
1	283.7	–	–	233.5
2	386.6	–	–	343.9

Noveon gels produced non-newtonian behavior at the investigated shear rates. Only three concentrations of Noveon gel at 15 and 35 °C were examined. The viscosity of Noveon gel decreased as was expected with increasing temperature. The viscosity of polymer dispersion was lower at 35 °C in comparison with the values measured at 15 °C. The viscosity of Noveon sol also reduced as the concentration of polymer concentration decreased because of expansion of the Noveon chains diluted. Noveon formed a strong gel at neutral pH. The neutralization of carboxylic groups provided a strong network. Noveon sols (un-neutralized) at pH 3 (0.5 and 2%) were also not easy flowing and the gel structure was weaker than with neutralized gel.

Throughout these experiments, the effect of Noveon and Pluronic on the viscosity characteristics of mixed gels was studied. Every mixed gel used in this study had a different Pluronic concentration. First, the mixed gels containing 1% Noveon were prepared and their viscosity was measured. The percentage of Pluronic in the mixed gel was then kept constant at 17.5%, while the Noveon concentration was varied (Table 2). It can be seen that the viscosity of gels increased with increasing Noveon or Pluronic concentrations and with increasing temperature.

Table 2 shows the influence of the presence of Noveon on the viscosity of Pluronic. The incorporation of Noveon gel into a Pluronic sol dramatically altered the viscosity; a considerable increase was observed with increasing amounts of Noveon.

It was also observed that mixed gels had a thermoreversible property at 25, 30 and 35 °C. The result of this phenomenon was an increase in viscosity upon heating. Noveon did not modify the responsiveness of the thermosensitive property of Pluronic sols.

There were no significant viscosity differences among the three temperatures for mixed gels containing 10% Pluro-

Table 2: Viscosity values (Pa · s) of mixed gels at constant shear rate (0.5 s^{-1})

Pluronic (%)	Noveon (%)	15 °C	25 °C	30 °C	35 °C
10	1	–	24.6	24.1	24.9
12.5	1	–	150.7	165.7	183.8
15	1	–	183.9	554.9	740.7
17.5	1	459.5	823.5	1074.6	1240.3
17.5	0.5	374.1	–	–	1064.5
17.5	2	559.9	–	–	1443.6
17.5	2.5	604.7	–	–	1501.9
17.5	0.5*	171.5	–	–	453.3
17.5	2*	225.4	–	–	580.8

*pH = 3 (un-neutralized Noveon gel)

nic and 12.5% Pluronic. Pluronic molecules in these mixed gels were probably monomolecular micelles, and Noveon molecules entered among the Pluronic chains. Therefore, Noveon chains blocked the interaction between Pluronic chains with increasing temperature. An increase in viscosity with increasing temperature became apparent for mixed gels containing 15% and 17.5% Pluronic. At concentrations of 15% and higher of pure Pluronic sols, polymolecular micelles were present and started considerable interaction between chains and micelles.

After combination of Pluronic gel and Noveon gel to prepare mixed gels, it was observed that their viscosity was very high and that the mixed gels had elastic property. This was confirmed by viscosity measurements. A much higher viscosity was found for the mixed gels in comparison with the Pluronic and Noveon gels separately, showing the formation of a strong gel network. The change in viscosity led us to postulate that the probable Noveon/Pluronic interaction and the carboxyl group of Noveon could have caused the interaction with the Pluronic molecule. Therefore, we chose to investigate the possible interaction between Pluronic and non-neutralized Noveon or the effect of the −COOH group. Un-neutralized mixed gels were prepared containing 17.5% Pluronic and un-neutralized Noveon gel (0.5% or 2%) and the viscosity of these gels at different temperatures was measured. The pH value of these mixed gels was about 5. At this pH, there is complete ionization of −COOH groups of Noveon; it has been shown previously that hydrogen bonding cannot occur in this condition (Lenaerts et al. 1987; Cole and Whateley 1996).

The viscosity of un-neutralized mixed gels was lower than that of neutralized mixed gel containing the same concentration of Pluronic (17.5%) and of Noveon (0.5 and 2%). The lower viscosity of Noveon gel caused the decreased viscosity of Pluronic gel, since the viscosity of un-neutralized Noveon gel was lower than that of neutralized Noveon gel. While the viscosity of pure Pluronic gel (17.5%) was 590 Pa · s at 35 °C, the viscosity decreased to 453 Pa · s when non-neutralized Noveon gel was added. Thus, it was decided that there is no interaction between Pluronic molecule and −COOH groups of Noveon. The possible interaction between Noveon and Pluronic molecules may be a hydrophobic interaction, as previously suggested (Cole and Whateley 1996).

It was apparent that the viscosity of mixed gels containing 17.5% Pluronic increased with increasing Noveon concentration and the increase seems to be close to linear for 15 °C (Table 2). The interpenetration of Noveon molecules had a marked effect on the viscosity of Pluronic gel. When this was investigated, there was a significant difference between viscosity values at different temperatures for the same Noveon concentration. It was concluded that Noveon did not alter the thermal sensivity of Pluronic gels and increasing Noveon concentration did not damage the thermoreversible property of mixed gels. During the mixing of Noveon and Pluronic gels to prepare mixed gels, probably Noveon molecules become associated with cavities between polymolecular Pluronic micelles. Thus, the interaction between Pluronic molecules of micelle was not hindered and the viscosity increased with increasing temperature.

2.2. Mucoadhesion

The purpose of the mucoadhesion experiments was to examine the adhesion power of Pluronic and compare it with Noveon, which is known as an excellent mucoadhesive polymer. Therefore, Noveon gel was used as a reference material. It is known that the mucoadhesion of Noveon is related to the pH of gel and medium. Bioadhesion occurs only when carboxylic groups of Noveon are in the acid form (Park and Robinson 1985). Therefore, first mucoadhesion experiments were done with un-neutralized 2% Noveon gel (pH = 3) at USP simulated gastric fluid (pH 1.2). Unfortunately, this gel immediately disintegrated in this medium, and the detachment force could not be measured. We then decided to use neutralized 2% Noveon gel (pH = 6) at pH 1.2 gastric solution because the viscosity of neutralized Noveon gel is higher than the un-neutralized gel.

Thirty-five percent Pluronic gel was chosen because it has the highest viscosity among the other Pluronic gels. The adhesion power of the mixed gel was also measured. These gels did not disintegrate during adhesion measurement at gastric solution. Table 3 shows the mucoadhesion power of the gel samples.

Although some of the neutralized 2% Noveon gel had disintegrated in gastric solution, the detachment force could be measured and was calculated as 119.8 mg/cm^2. This value seems reasonable. Park and Robinson reported a similar result in 1985 for fully hydrated polycarbophil in pH 6 buffer solution.

The mucoadhesive capacity of Pluronic gel was investigated and compared with Noveon gel. The force of detachment for Pluronic gel (35%) was found to be approximately the same as for polycarbophil gel ($p > 0.05$), even though there was a significant difference between the viscosity of Noveon gel and Pluronic gel. It was thought that the Pluronic chains were sufficiently elastic to interpenetrate the mucus layer of the stomach.

The effect of Pluronic on the bioadhesive property of Noveon was also studied. As can be seen in Table 3, Pluronic showed little effect in this regard. The adhesive force of the mixed gel was not different from that of Noveon gel or Pluronic gel ($p > 0.05$), whereas the viscosity of the mixed gel was higher than the others. This showed that Pluronic gel does not affect the adhesive force of Noveon gel. These results demonstrate that an increased viscosity does not affect bioadhesive force for these gel systems.

Table 3: Mucoadhesion for gel samples (mg/cm^2 to separate tissue)

	at pH 1.2 gastric sol.
2% Noveon*	119.8 (± 9.83)
35% Pluronic*	123.4 (± 7.99)
Mixed (17.5% Pluronic and 1% Noveon)	186.1 (± 14.1)

*pH = 6, Noveon gel has 30 mg Noveon and Pluronic gel has 525 mg Pluronic

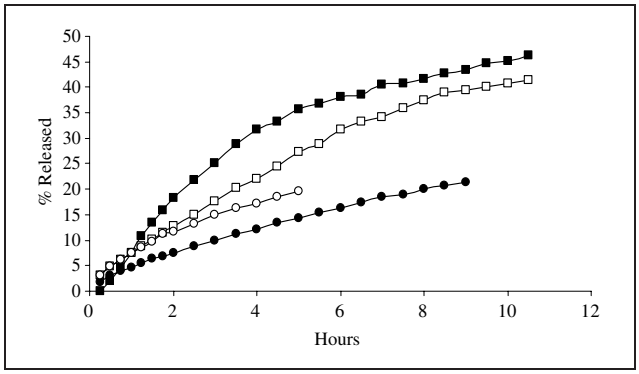

Fig. 1: Release profile of 17.5% and 35% pure Pluronic gels at 15 and 35 °C
–■– 17.5% Pluronic, 15 °C; –□– 17.5% Pluronic, 35 °C; –●– 35% Pluronic, 15 °C; –○– 35% Pluronic, 35 °C

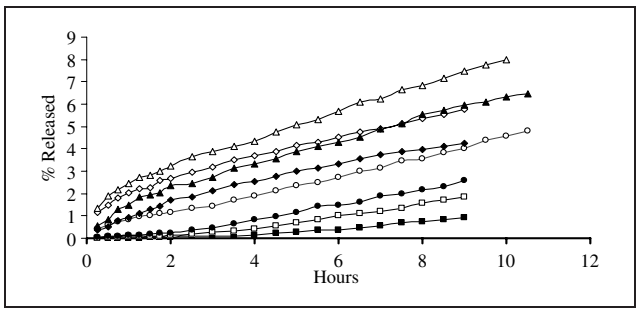

Fig. 2: Release profile of mixed gels with 17.5% Pluronic, and different % of Noveon
–■– 2.5% Noveon, 15 °C; –□– 2.5% Noveon, 35 °C; –●– 2% Noveon, 15 °C; –○– 2% Noveon, 35 °C; –◆– 1% Noveon, 15 °C; –◇– 1% Noveon, 35 °C; –▲– 0.5% Noveon, 15 °C; –△– 0.5% Noveon, 35 °C

2.3. Release

Mannitol release from mixed gels, pure Pluronic gels (17.5 and 35%) and pure Noveon gels (0.5, 1 and 2%) was evaluated at two temperatures (15 and 35 °C). Fig. 1 shows the release from pure Pluronic gels, Fig. 2 from mixed gels, and Fig. 3 from pure Noveon gels as a function of time. The amount of mannitol release (dpm/cm^2) was plotted as a function of time; a straight line was obtained and the flux values were calculated from the slope of lines.

During the release studies, the release media was mixed in order to obtain an homogeneous phase. The diffusion of mannitol through the membrane was not a rate-limiting step, and thus the release and flux were only affected by the gel viscosity at the same temperature. The viscosity of gel systems was high due to the formation of a three-dimensional network, and the polymer chains probably prevented the movement of molecules.

The release experiments showed the effect of the concentration of polymers on the release of mannitol at two temperatures. The cumulative percentage of mannitol released as a function of time is shown in Figs. 1 and 3. With all gels the mannitol released increased linearly with time ($r^2 > 0.988$) and the release was relatively constant (zero-order). As can be expected the flux of drug decreased as the pure Pluronic or Noveon concentration in gel increased at the same temperatures (Table 4). As the amounts of polymer increased due to reductions in aqueous pathway, the structure of the gels was a barrier to the release of mannitol. Similar observations were reported by Moore et al. (2000) and Bhardwaj and Blanchard (1996).

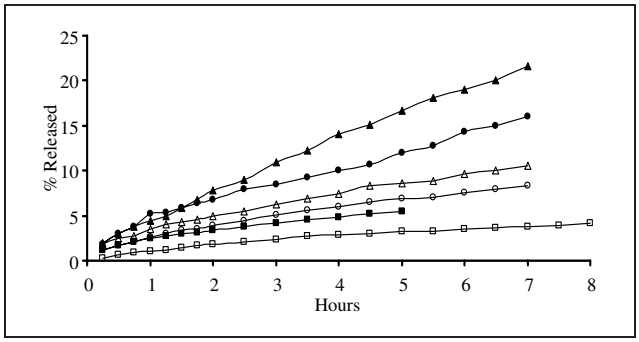

Fig. 3: Release profile of pure Noveon gels 15 and 35 °C
–▲– 0.5% Noveon, 35 °C; –●– 1% Noveon, 35 °C; –△– 0.5% Noveon, 15 °C; –○– 1% Noveon, 15 °C; –■– 2% Noveon, 35 °C; –□– 2% Noveon, 15 °C

The flux of mannitol from pure Noveon gels decreased with increasing Noveon concentration and increased with elevating temperature. This can be attributed to the increase in gel viscosity and the thermodynamic activity of mannitol (Fig. 3, Table 4).

Pluronic gels (17.5 and 35%) demonstrated similar release profiles at both temperatures (Fig. 1). However, there was a significant difference in the mannitol release behavior between 15 and 35 °C. After five hours, the mannitol release percentage reached 14.4% at 15 °C and 19.7% at 35 °C for 35% pluronic gel, and 35.7% at 15 °C and 27.3% at 35 °C for 17.5% pluronic gel.

As the concentration of pluronic was increased from 17.5 to 35% at 35 °C, the flux of mannitol decreased. This was probably due to the increase in number and size of micelles within the gel structure.

In this study, the Pluronic gel (17.5%) used was a viscous liquid form at 15 °C, and a gel form at 35 °C. Therefore, the released percentage of mannitol at 15 °C was higher than at 35 °C for 17.5% Pluronic gel.

Thirty-five percent Pluronic gel was soft at 15 °C and a rigid gel at 35 °C. At this temperature, this concentration of Pluronic in water exhibited reverse thermal behavior and its viscosity increased as temperature rose. When the release profiles of 35% Pluronic gel were investigated, it was observed that the released amount of mannitol at 35 °C was higher than at 15 °C, despite the rising viscosity of gel at higher temperature. The flux value also increased

Table 4: Flux data of the gels (dpm/cm^2/min)

Pluronic (%)	Noveon (%)	15 °C	35 °C
Neutralized mixed gels			
17.5	0.5 (pH: 6)	1283.4 (± 150.4)	1485.4 (± 76.9)
17.5	1 (pH: 6)	1016.1 (± 68.4)	1135.1 (± 187.6)
17.5	2 (pH: 6)	682.6 (± 39.1)	964.1 (± 143.9)
17.5	2.5 (pH: 6)	237.2 (± 29.8)	487.8 (± 72.1)
Un-neutralized mixed gels			
17.5	0.5 (pH: 3)	4303.8 (± 248.5)	4306.8 (± 248.6)
17.5	2 (pH: 3)	2740.3 (± 158.2)	2918.4 (± 168.5)
Pure gels			
17.5	–	10071.9 (± 1510.4) (viscous liquid)	9140.8 (± 826.9)
35	–	5228.1 (± 398.9)	7853.3 (± 858.9)
–	0.5 (pH: 6)	1852.6 (± 95.8)	4328.7 (± 250.1)
–	1 (pH: 6)	1519.9 (± 87.4)	2838.1 (± 65.6)
–	2 (pH: 6)	1185.3 (± 129.7)	1981.2 (± 19.8)

Mean ± SE, n = 3

when temperature was raised from 15 to 35 °C (Table 4). Despite a 3.7-fold increase in viscosity, the flux value of mannitol was increased 1.5-fold. As previously observed by several authors (Lu and Jun 1998; Chi and Jun 1991; Suh and Jun 1996), no correlation was found between viscosity and flux. It was concluded that the flux of mannitol was largely dependent on the temperature rather than on the viscosity of Pluronic gel and that there was a negative correlation between flux of mannitol and viscosity of gel.

Previous studies have shown the same result: the viscosity of Pluronic gel increased with increasing temperature and the release amount, release rate or diffusion coefficient also increased (Chi and Jun 1991; Chen-Chow and Frank 1981; Miyazaki et al. 1984; Juhasz et al. 1989; Veyries et al. 1999). This can be explained as follows: the molecule to be released diffuses through water channels in the gel structure and the viscosity of water in these water channels will decrease with increasing temperature, since Pluronic F127 gels are isotropic liquid crystals. Lenaerts et al. (1987) showed that Pluronic F127 gels have no crystalline or pseudo-crystalline arrangement. Another hypothesis has been presented as further clarification: the cores of the Pluronic micelles undergo dehydration with rising temperature (Vadnere et al. 1984; Atwood et al. 1985; Juhasz et al. 1989). This induced a redistribution of drug in colloidal solution and the molecules were expelled into the outer compartment. Therefore, the diffusion coefficient of the drug increased. These researchers found that the relationship between diffusion coefficient and temperature is quite similar in water and gel but that these parameters depend on temperature.

In this study, Pluronic gel (35%) was mixed with neutralized Noveon gel containing different concentrations of Noveon (1, 2, 4 and 5%). Thus, every mixed gel contained same Pluronic concentration (17.5%) and a different Noveon concentration (0.5, 1, 2 and 2.5%). The effect of temperature on mannitol release from mixed gels was studied at 15 and 35 °C.

First Noveon gels were neutralized and then mixed with Pluronic gel. The release profiles of mixed gels are shown in Fig. 2. The release percentage of mannitol at 35 °C was higher than at 15 °C for mixed gels containing the same Noveon concentration. When we investigated the viscosity of the gels (Table 2), we observed that the viscosity values at 35 °C were higher than at 15 °C. Naturally, it was thought that the released percent of mannitol at 35 °C could be lower than at 15 °C; however, the opposite occurred. As mentioned before (Table 2), the mixed gels had thermoreversible properties and this was not disrupted by Noveon. The hydrophobic interaction between Pluronic molecules increased at 35 °C and the mannitol molecules among the pluronic chains were squeezed out of the chains and micelles. Thus in spite of increasing viscosity, the amount of released mannitol increased.

When release profiles were investigated (Fig. 1), the release of mannitol from pure Pluronic gels was comparatively fast and, the release percentage was found to be retarded as Noveon was added. The released percent of mannitol considerably decreased with increasing Noveon concentration (Fig. 2). This was logical because viscosity values increased with increasing Noveon concentration. The high Noveon amount in the mixed gel probably modified the size of the water-filled regions. A reduction in the gel-free volume decreased the amount of mannitol released. Therefore, flux value of mixed gels decreased with increasing Noveon concentration at both temperatures (15 and 35 °C) (Table 4, Fig. 3). The investigated gels can thus be considered a potential medium for delayed release in biological environment.

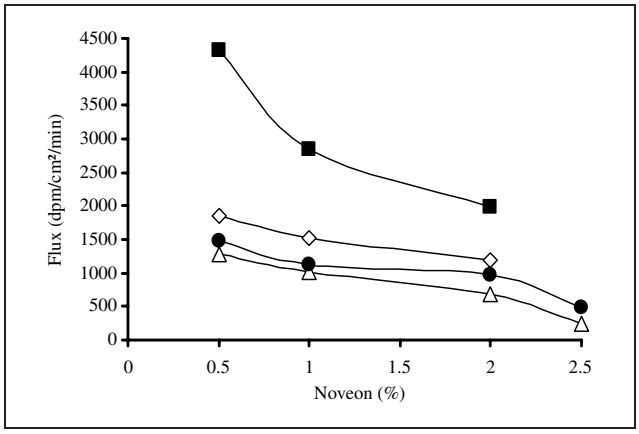

Fig. 4: Flux values for mixed gels and neutralized Noveon gels as function of Noveon concentration
–◇– 15 °C, neutralized Noveon gel; –■– 35 °C, neutralized Noveon gel; –△– 15 °C, mixed gel; –●– 35 °C, mixed gel

When the flux values of each mixed gel at the two temperatures were investigated (Table 4), there were no significant differences among them. However, these gels had thermoreversible properties and there were significant differences in their viscosity. In our opinion, with increasing temperature, pluronic chains close and mannitol molecules between the Pluronic chains are squeezed out. However, the Noveon molecules present among the Pluronic micelles and Noveon chains hindered the release of mannitol molecules. Thus, Noveon chains controlled the release of mannitol. To prove this case the flux value of the mixed gel and Noveon gels at 15 and 35 °C were plotted versus the Noveon concentration. As shown in Fig. 4, the slope of Noveon gels line at 15 °C was very close to that of mixed gels. It was presumed that the release of mannitol was controlled by Noveon.

In addition, the release of mixed gels prepared using un-neutralized Noveon gel was also investigated. The pH value of un-neutralized Noveon gels was 3.0 and the pH value of the mixed gel was 5.0. The flux value of the un-neutralized mixed gel containing the same percent of Pluronic and Noveon was higher than that of the neutralized mixed gel (Table 4) since the viscosity of the mixed gel containing un-neutralized Noveon gel was lower than the other mixed gel containing neutralized Noveon gel.

3. Experimental

3.1. Materials

Pluronic® F127 (poloxamer 407 NF) was obtained as a gift from BASF Corp., New Jersey, USA. Polycarbophil (Noveon® AA-1) was supplied by B.F. Goodrich, Ohio, USA. Sodium hydroxide (Aldrich Chemical Comp. Inc.) was used as a neutralizing agent. D-Mannitol – ^{14}C (Sigma, 30484-0) was chosen as a model active material because of its water-soluble characteristics.

3.2. Methods

3.2.1. Preparation of polycarbophil gels

Un-neutralized gels of 0.5 and 2% polycarbophil were prepared by dispersing in water. After continuous stirring at high rpm for 30 min, the gel samples were left to hydrate completely for 24 h. The pH value of un-neutralized gels was 3. Neutralized gels of polycarbophil were prepared with a sodium hydroxide solution. First, polycarbophil powder was added to 80% of distilled water with agitation. After dispersing polycarbophil, the required alkali solution was added and diluted with distilled water to reach desired weight. Neutralized gels were in the pH range of 6 to 7.

3.2.2. Preparation of Pluronic gels/sols

Different concentrations of Pluronic gels were prepared by the cold process (Schmolka 1972). First, a weighted amount of Pluronic was slowly added to cold weighted distilled water at about 4 °C with mild agitation. This mixture was kept refrigerated and sealed overnight in order to produce a clear solution. The pH of this solution was 6 at refrigerator temperature. The preparation of gel at 35% concentration was more difficult, requiring three days to complete.

3.2.3. Preparation of mixed gel systems

The mixed gels were prepared by mixing one unit Pluronic gel and one unit polycarbophil gel. The Pluronic and Noveon concentration of each mixed gel is shown in Table 1. Before each experiment, mixed gels and other gels were centrifuged at 4000 rpm over 15 minutes to remove air bubbles.

3.2.4. Measurement of viscosity

Viscosity measurement was performed with a rotational viscometer (Haake Rotovisco RV12, Programmer PG142, M-500). This viscometer is equipped with a temperature control unit so that the temperatures of the samples were adjusted to 15, 25, 30 and 35 °C by circulating the water through the thermostated water jacket. Two different cup and rotor sensor systems (NV and SV) were used depending on the viscosity of the sample. The sensor system was filled with sample and was allocated for about 10 min to equilibrate to experimental temperature. The NV sensor system was used for measuring of fluid sols (10%, 12.5% and 15% Pluronic sols) and three different types of SV sensor systems were examined for gels. A wall slip problem was observed in the SVI and SVII sensor systems and the torque measured reduced to about zero. No wall slip problem was present however in the SVIIP sensor system due to the grooves on the surface of cup and rotor. This sensor system improved the adhesion between the gel and surfaces of the sensor system for all gels. Before each viscosity experiment, Pluronic gels were stored in a refrigerator for 1 h to convert the gel form to flowing liquid and were then poured into the cub. The mixed gels and Noveon gels were centrifuged to remove air bubbles and then poured into the cub. Viscosity measurements for each gel were replicated three times and the mean values presented.

3.2.5. Measurement of mucoadhesion

Adhesion power (mg/cm^2) was measured using a precision balance (Roller Smith, Biolar Inc., North Grafton, MA, USA). The fundus of freshly excised rabbit stomach was used as a tissue. The mucoadhesive property of gel samples was tested according to the method described by Park and Robinson (1985). 1.5 g of gel was used for adhesion experiment.

3.2.6. Measurement of mannitol release rate from gels

The release of mannitol was studied at 37 °C using the Franz Diffusion Cell (FDC-400, Crown Glass Company, Inc. New Jersey, USA). Before each release experiment, 1 g gel at 4 °C was mixed with radioactive mannitol solution over 2 min. The gel was then refrigerated for 30 min to remove air bubbles (for Noveon gel) or to turn into a free-flowing liquid (for mixed gels and Pluronic gels). The temperature of the Franz Cell was adjusted to 15 and 35 °C to evaluate the effect of gelation properties of Pluronic and mixed gels on mannitol release.
The receptor volume of the diffusion cell was 4 mL and distilled water was used as a receptor solution. Membrane filter (0.8 μm/pore size, mixed esters of cellulose, AAWP025, Millipore) was used between donor and receptor compartment. The receptor phase was stirred with a magnetic stirring bar and sampled over 8 h. Receiver samples were diluted in a 4 ml scintillation cocktail and analyzed by evaluation of total radioactivity (dpm) in a liquid scintillation counter (Beckman-LS6000IC,USA). All experiments were carried out in triplicate and the average values were plotted.

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