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The Influence of the Type and Concentration of Alcohol on the Rheological and Mucoadhesive Properties of Carpobol 940 Hydroalcoholic Gels

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ABSTRACT

The objective of this work was to study the influence of type and concentration of the alcohol (ethyl alcohol and isopropyl alcohol) on the rheological and mucoadhesive properties of carbopol 940 gel formulations. The rheological and mucoadhesive properties of the systems were investigated by means of rheological analysis. The mucoadhesive properties were demonstrated by viscosity enhancement ($\eta_{enhance}$), bioadhesion force (F_b) and relative viscosity (η_{rel}). The viscosity, flow index and consistency index were found to be significantly influenced by type and concentration of alcohol added. Flow index was directly related to alcohol concentration while the consistency index was inversely related to alcohol concentration. The force of bioadhesion was found to be promoted by increasing concentration of ethyl alcohol up to 50% and isopropyl alcohol up to 30%. It was concluded that the optimum concentration of the alcohol in hydroalcholic systems is 30% and this concentration provide higher viscosity of Cp 940 gel with ethyl alcohol while with isopropyl alcohol provide strong mucoadhesive properties.

Keywords: Carbopol 940, Hydroalcoholic gels, Rheological properties, Mucoadhesive properties.

INTRODUCTION

Gels are widely recognized as valuable dosage forms in order to deliver various drugs through different routes of administration. According to the ″Encyclopedia of Polymer Science and Engineering″ a gel is a cross – linked polymer network swollen in a liquid medium. Its properties depend on the interaction of these two components [1].

According to its phenomenological characteristics a gel is better defined as a soft, solid or solid like material consisting of two or more components, one of which is a liquid, present in

substantial quantity [2]. Hydrogels in particular have been widely utilized in the medical and pharmaceutical fields for their biocompatibility and their similarity to natural tissue [3-4].

Carbopols, which are very high molecular weight polymers of acrylic acid, have been used mainly in liquid or semi- solid pharmaceutical formulations, as a thickening and viscosity agent, in order to modify the flow characteristics; they are also used for their mucoadhesive properties [5].

Aqueous gel vehicles containing water, propylene glycol and alcohol in different concentrations and gelled with carbopols are classed as water soluble bases [6]. Simple gelled mixtures of water and alcohol in proportions varying to suit specific cases, are also extensively used, and are often referred to as hydroalcoholic gels. Bases of this kind may be formulated to optimize non – polar drug delivery [7]. However, although alcohols are useful to increase solubility of non-polar drugs, their use as cosolvents with hydrophilic polymers is often limited. The rheological behavior of polymer solutions is determined not only by polymer – polymer conformation and entanglement, but also by concentration and polymer - solvent effects. Therefore, the gelation process in hydroalcoholic mixtures is also a function of alcohol – polymer intermolecular interactions and consequently , the alcohol content used in the design and development of technologically adequate hydroalcoholic gelled bases is often limited by the compatibility of the gelling agent with non- aqueous solvent [8].

The objective of this work was to study the effect of the type and concentration of incorporated alcohol (ethyl and isopropyl alcohol) on the physical properties e.g. spreadability, rheological properties and mucoadhesive properties of carbopol gel formulations.

MATERIALS AND METHODS

2.1. Materials

Carbopol 940 (Cp 940) by BF Goodrich, Co, USA, Propylene glycol (PG) was provided by Biochemica, Switzerland. Methylparaben and propylparaben by Merck LTD, UK, Triethanolamine and Mucin, Type II: Crude from procine stomach, were purchased from Sigma, USA.

2.2. Preparation of hydroalcoholic carbopol gels

Table (1) shows the composition of prepared carbopol gels. Appropriate amount of Cp 940 (0.5% w/w) was dispersed into a beaker containing the calculated amount of purified water, stirred using magnetic stirrer until no lumps were observed. PG 10% was added during stirring. Stirring speed was then reduced to allow foam to break. The calculated amount of alcohol was added. Adequate amount of triethanolamine was added to neutralize the free carboxylic acid groups of Cp 940 to pH 6 ± 0.5. All samples were allowed to equilibrate for 48 hr at room temperature prior to the evaluation of their properties [9].

2.3. Spreadability Test

The spreadability is represented by the thickness of the film that the preparation leaves on the skin. The spreadability of the gel formulations was determined 48 hr after preparation, by measuring the spreading diameter of 1 g of the gel between two glass plates (20 × 20 cm^2) after 1

min. The standardized weight tied on the upper plate was 100g. The spreadability [10] was calculated by using the formula S = m. l /t, where S is spreadability, m is the weight tied to the upper slide, l is the length of the glass slide, and t is the time taken.

Table (1): Composition of the prepared Carbopol 940 Gels

Formulation Code	Composition in % w/w				
	Cp 940	PG	Ethyl alcohol	Isopropyl alcohol	Triethanolamine
F1	0.5	-	-	-	q.s.
F2	0.5	10	-	-	q.s.
F3	0.5	10	10	-	q.s.
F4	0.5	10	30	-	q.s.
F5	0.5	10	50	-	q.s.
F6	0.5	10	-	10	q.s.
F7	0.5	10	-	30	q.s.
F8	0.5	10	-	50	q.s.

N.B.:- All formulations contain 0.02% propyl paraben and 0.2% methyl paraben. Water was added to make 100 g of each gel formula.

2.4. Rheological analysis

The study of the rheological profile of the different gel formulations was carried out using a rotational Brookfield viscometer (USA) DVIII of cone and plate structure [11]. The viscosity (η) and the shear stress (τ) of gel formulations of different composition were measured as a function of shear rate (γ). The flow behavior index or non-Newtonian index (n) and consistency index (K_c) can be derived from the power law expressed in Eq.(1) [12].

$$\tau = K_c \gamma^n \quad (1),$$

where τ is the shear stress and γ is the shear rate. The flow behavior index (n) can be calculated from the plots of shear stress versus shear rate. The consistency index (k_c) was then estimated at a shear rate of 20 s^{-1}. Samples were left for 1 minute before measuring or decreasing the shear rate. The spindle was kept to rotate for 1 minute before measuring the shear stress and viscosity. The test was done in triplicates [13].

2.5. Mucoadhesion analysis

Mucoadhesive characteristics of prepared Cp 940 gels were evaluated through a method reported in the literature [14]. This method is based on the evaluation of the rheological synergism existing between the mucoadhesive polymers and mucin. A substantial number of studies have investigated the rheological properties of mucin- polymer mixtures, in particular synergistic increases in viscosity upon mixing, as a method for studying mucoadhesive interactions [15 and 16]. Specified amount of mucin (1.5 g) was mixed with an equal quantity of distilled water, adjusted to the required pH using 0.1 M NaOH or 0.1M HCl, and finally diluted with distilled water to 4.5 g. The expected viscosity (η_{exp}), viscosity enhancement or synergism ($\eta_{enhance}$) and relative viscosity enhancement (η_{rel}) of the combination systems of polymer and mucin are expressed in Eqs. (2- 4):

$$\eta_{exp} = \eta_p + \eta_m \quad (2)$$

$$\eta_{enhance} = \eta_{obs} - \eta_{exp} \quad (3)$$

$\eta_{rel} = \eta_{obs} / \eta_{exp}$ (4)

Where η_p and η_m are the individual viscosities of the polymer and mucin , respectively.

Consequently, the force of bioadhesion (F_b) represents the additional intermolecular frictional force per unit area and can be determined by Eq. (5):

$F_b = \eta_{enhance} \times \gamma$ (5)

Where γ represents the shear rate at which viscosity value was calculated (7.5 s^{-1}) [17].

3. Data analysis and statistical evaluation

The results obtained were statistically analyzed by an unpaired two – tail t- test to determine whether the results were significantly differ or not.

RESULTS AND DISCUSSION

The results of spreadability in table (2) reveal that the spreadability was significantly increased ($p < 0.05$) by increasing alcohol concentration in the formulations.

Table (2): Spreadability , flow behavior index (n) and consistency index (k_c) of prepared Cp 940 gels

Cp 940 gel Formulation	Spreadability (gm.cm/sec) (mean ± SD)*	Flow behavior index, n	Consistency index, k_c (mPa.s)
with 10% ethanol	3.81 ± 0.165	0.194	1257.8
with 30% ethanol	4 ± 0.153	0.215	1214.1
with 50% ethanol	4.4 ± 0.096	0.266	652.2
with 10% isopropyl alcohol	3.9 ± 0.1	0.34	696.3
with 30% isopropyl alcohol	4.1 ± 0.103	0.39	542.8
with 50% isopropyl alcohol	4.22 ± 0.1096	0.47	304.6

** no. of trials = 3*

The rheological behavior of all gel formulations was investigated. The viscosity of different Cp 940 gels in hydroalcoholic vehicle were summarized as shown in Table 3 and compared with the values of control Cp 940 gels containing the same concentration of carbopol alone without PG and that containing the same concentration of Cp 940 with 10% PG.

The results of Cp 940 gels when compared with that of the two control gels (F_1 and F_2), indicated that the incorporation of PG significantly increases ($p < 0.05$) the viscosity of Cp 940 gel formulations. This may be explained due to the intermolecular hydrogen bonding between Cp 940 and PG which increases the rigidity of the structure. This is in agreement with Kedar Chikhalikar et.al [18] who reported that, **t**he combination of a carboxyl group of carbopol and one or more hydroxyl donors (polyols) will result in thickening the gel because of the formation

of hydrogen bonds. In addition the presence of PG provides a steric hindering to curling or collapse of carbopol chains (Figures 1&2).

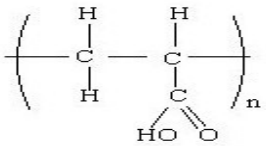


Figure (1) The chemical structure of Carbopol

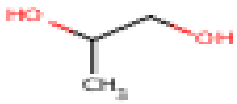


Figure (2) The chemical structure of PG

The results in table 3 and figure 3 show increase in viscosity by increasing the concentration of ethyl alcohol up to 30% in presence of PG (10%).This could be due to increase the possibility of formation of hydrogen bonding.

In a poor solvent, the polymer chain would be more or less tightly coiled, preferring self-interactions to interaction with the solvent [19]. The degree of hydration will hence determine the extent of weak secondary bonds between Cp 940 and PG. As a consequence, the rigidity of the structure increases and the donor effect of PG hydrogen bonds dominate. However, when ethyl alcohol concentration increases up to 50%, an inverse effect is produced.

This could be due to the addition of ethyl alcohol; it disrupts the interaction between Cp 940 and water molecules with its subsequent transformation into adverse solvent, which means that its dehydrating effect on the polymer diminishes the viscosity.

On the other hand, for Cp 940 gel formulations containing isopropyl alcohol, the experimental results presented in table 3 and figure 4, indicate that, the viscosity of Cp 940 gel formulations decreases by increasing the concentration of incorporated isopropyl alcohol. This may be explained as the presence of methyl group as side chain in isopropyl alcohol (secondary alcohol), decreases the possibility of close approach of other molecules and affect the formation of hydrogen bonds (Fig. 5 chemical structure of isopropyl alcohol).

As a result, the intermolecular hydrogen bonding between isopropyl alcohol molecules and PG is less than ethyl alcohol, thus the dehydrating effect of isopropyl alcohol will be more dominant and as a result the viscosity was significantly decreased.

The results of calculated consistency indexes shown in table 2, were found to be inversely related to alcohol (ethyl or isopropyl) content in Cp 940 hydroalcoholic gel formulations. The decrease is more pronounced between 30 and 50 % alcohol concentrations, than between 10 and 30 % alcohol concentrations. Fig. 6 shows, experimental K_c values plotted as a function of type and concentration of incorporated alcohol.

Table (3) viscosity values (cps) of prepared hydroalcoholic Cp 940 gels

Rpm	Average viscosity of carbopol gel formulations (cps)							
	Cp 940 alone	with 10% PG	with ethyl alcohol			with isopropyl alcohol		
			10%	30%	50%	10%	30%	50%
10	15675	17304	16514	19567	10066	9515	8729	6213
20	8890	9604	9594	10813	6878	5544	4053	4757
40	5338	5755	5340	6134	3579	4011	3630	3401
60	4008	4207	3749	4548	2621	3152	3093	2910
80	3135	3383	3077	3492	2153	2418	2537	2212
100	2619	2850	2672	3043	1809	1887	1879	1754
80	3026	3314	2979	3417	2104	2084	2025	2054
60	3691	4061	3526	4391	2608	2543	2503	2464
40	5001	5477	4738	5937	3441	3637	3421	3460
20	8512	9287	8179	9909	5846	6999	6645	6409
10	14605	15716	13269	16850	10066	13762	12870	12425

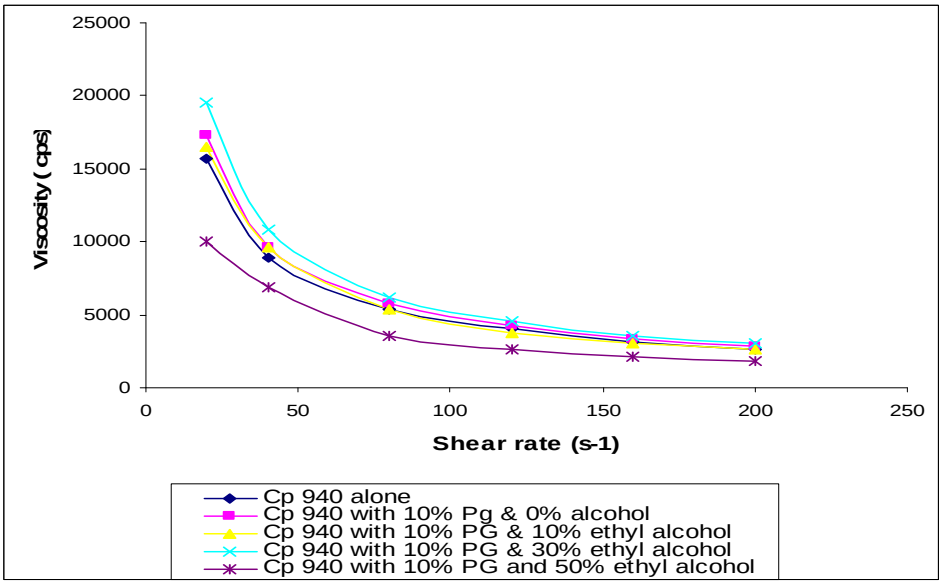
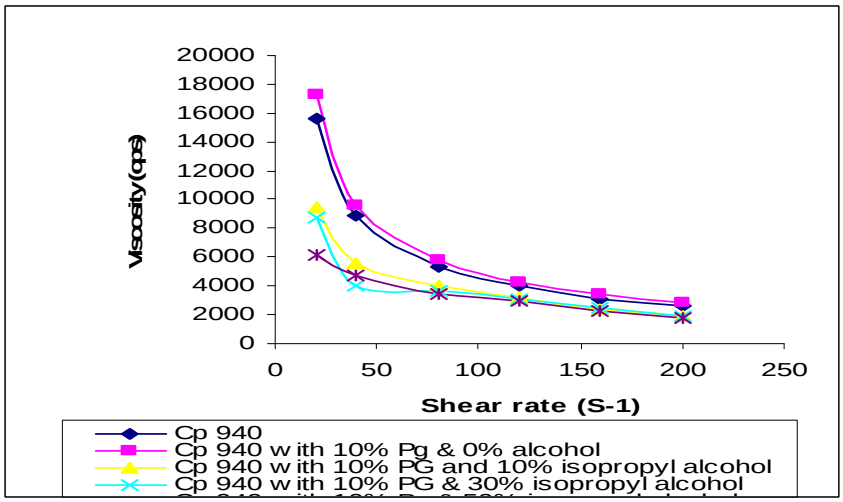


Fig. (3) Viscosity and shear rate interrelation for Cp940 gels containing different concentrations of ethyl alcohol



Figure(4): Viscosity and shear rate interrelation for Cp940 gels containing different concentrations of isopropyl alcohol

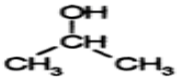


Figure 5: Chemical structure of isopropyl alcohol.

Power law flow indexes were also estimated as a function of type and concentration of alcohol. The values of flow behavior indexes (n) in table 2 were found to be directly related to alcohol concentration incorporated in Cp 940 gel formulations. Figure 7 illustrates (n) values plotted as a function of type and concentration of incorporated alcohol.

The exponent ″n″ from power law model is an indication of departure from Newtonian behavior. For pseudoplastic flow, $0 < n < 1$, for dilatant flow $n > 1$ and $n = 1$ for Newtonian flow [10]. In all prepared Cp 940 gels pesudoplastic flow was obtained ($n < 1$).

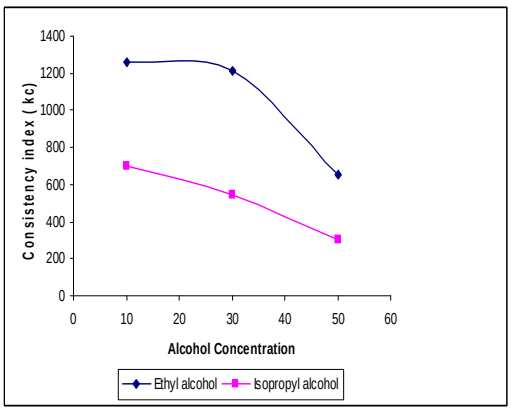


Fig.6. Correlation between experimental Kc values and type and concentration of incorporated alcohol.

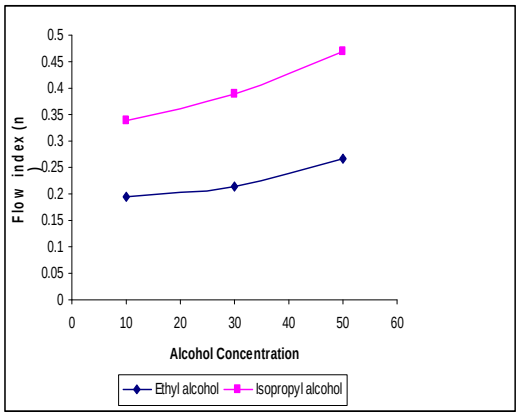


Fig.7. Correlation between experimental n values and type and concentration of incorporated alcohol.

The expected viscosity (η_{exp}), viscosity enhancement ($\eta_{enhance}$) and relative viscosity enhancement (η_{rel}) of the combination systems of Cp 940 gel formulation and mucin and finally bioadhesion force (F_b) calculated at a shear rate equal to 7.5 s^{-1} are summarized in table 4.

Table (4) Mucoadhesion viscosity parameters for various Cp 940 gels mixed with mucin

% of alcohol in Cp940 gels	η_{obs} (Pa.s)	η_{exp} (Pa.s)	$\eta_{enhance}$ (Pa.s)	η_{rel} (Pa.s)	Bioadhesion force F_b (Pa)
10 % ethanol	6.1	5.8	0.3	1.1	2.4
30 % ethanol	6.5	5.8	0.7	1.1	5.3
50 % ethanol	8.4	6.8	1.6	1.2	12.0
10 % isopropyl alcohol	3.96	2.4	1.5	1.6	11.5
30 % isopropyl alcohol	12.63	9.1	3.5	1.4	26.2
50 % isopropyl alcohol	8.47	7.3	1.1	1.2	8.6

For Cp 940 gels containing ethyl alcohol their observed viscosity η_{obs} was higher than the expected viscosity η_{exp}. Bioadhesive force (F_b) between the Cp940 gels containing ethyl alcohol and mucin was significantly increased by increasing the alcohol concentration, as shown in fig. 8. This could be explained due to the dehydrating effect of alcohols, as polymers may lose some of their mucoadhesive strength upon overhydration and produce only limited gel strenghthening when mixed with mucin [20]. In addition, possibility of hydrogen bond formation between ethyl alcohol and mucin. This may be explained in terms of the co-operative nature of interactions.

While for Cp 940 gels containing isopropyl alcohol up to 30%, the bioadhesive force (F_b) was increased as the concentration of isopropyl alcohol from 10% to 30% (fig.9). This could be explained as previously mentioned due to steric hindering which decrease the possibility of hydrogen bond formation between PG and isopropyl alcohol. As a result, the dehydrating effect of isopropyl alcohol will be more dominant. However, for Cp 940 gel containing 50% isopropyl alcohol, it was observed that the bioadhesive force (F_b) decreased to 8.6 Pa. It is thought that an optimum water concentration has been reported [21], for hydrocolloid particles to develop maximum adhesive strength.

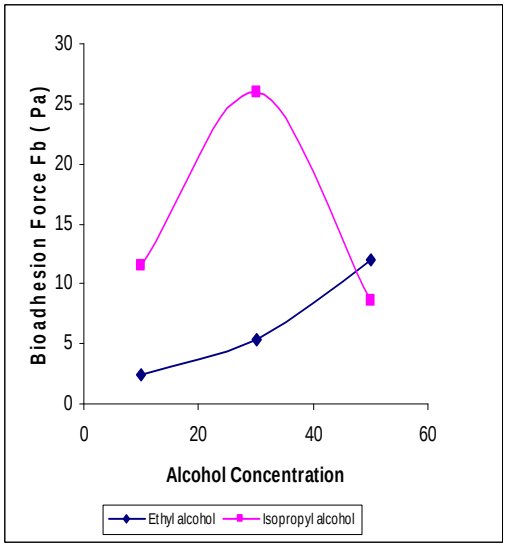


Figure 8: Bioadhesive force of Cp 940 gels mixed with mucin dispersion

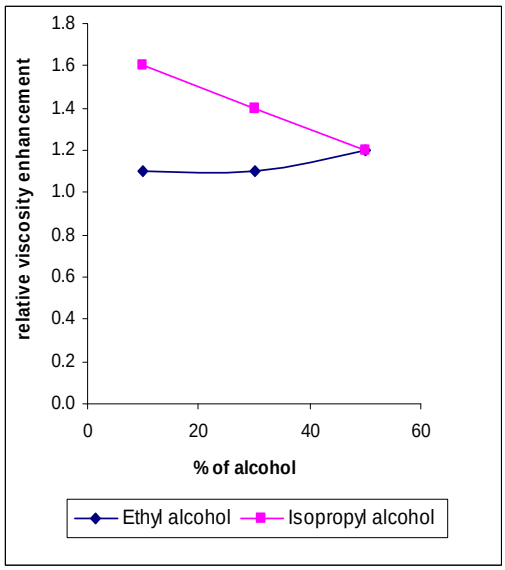


Figure 9: Relative viscosity enhancement of Cp 940 gels mixed with mucin dispersion

The magnitude of the rheological synergism can be represented by the consideration of the relative viscosity enhancement (η_{rel}) as shown in Eq. (4). This equation could allow the viscosity enhancement effect to be expressed as a proportion of the unmixed materials viscosities. If η_{rel} =1 this means there is no interaction between the polymer and mucin.

A higher value of η_{rel} shows rheological synergism between the polymer and mucin and is indicative of potentially mucoadhesive association between them. The calculated η_{rel} is shown in table 3 and figure 9. It is found that for Cp 940 gels containing ethyl alcohol the increase of η_{rel} is somewhat limited as a plateau was observed. While for Cp 940 gels containing isopropyl alcohol the value of η_{rel} was decreased by increasing the concentration of isopropyl alcohol (> 30%).

Figures (10 and 11) show the relationship between alcohol concentration, rhelogical properties (viscosity) and mucoadhesive properties (bioadhesion force and relative viscosity). The figures demonstrate that, increasing ethyl alcohol concentration up to 50% seems to promote the mucoadhesive properties of prepared Cp 940 gels , while isopropyl alcohol promote the mucoadhesive properties up to 30% alcohol concentration. But , even, on increasing ethyl alcohol concentration up to 50% the bioadhesion force still has lower value (12 Pa) than that of 30% isopropyl alcohol (26.2 Pa).

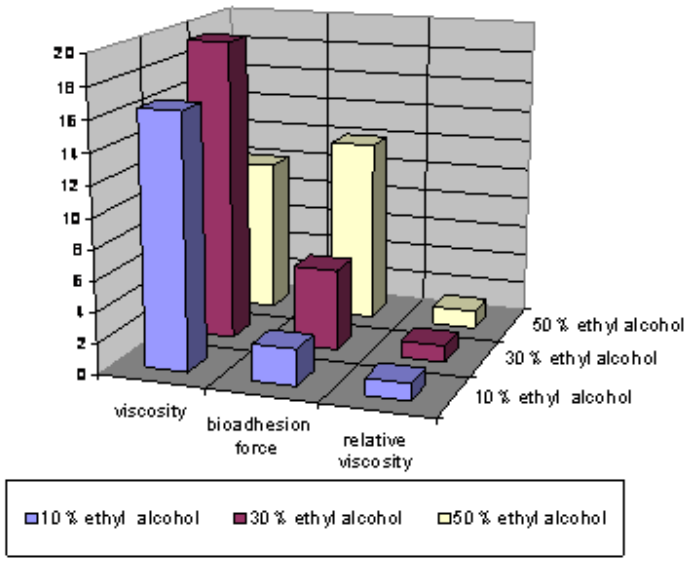


Figure (10): The Relationship between ethyl alcohol Concentration, Rheological properties (viscosity) and mucoadhesive properties of prepared Cp 940 Gels.

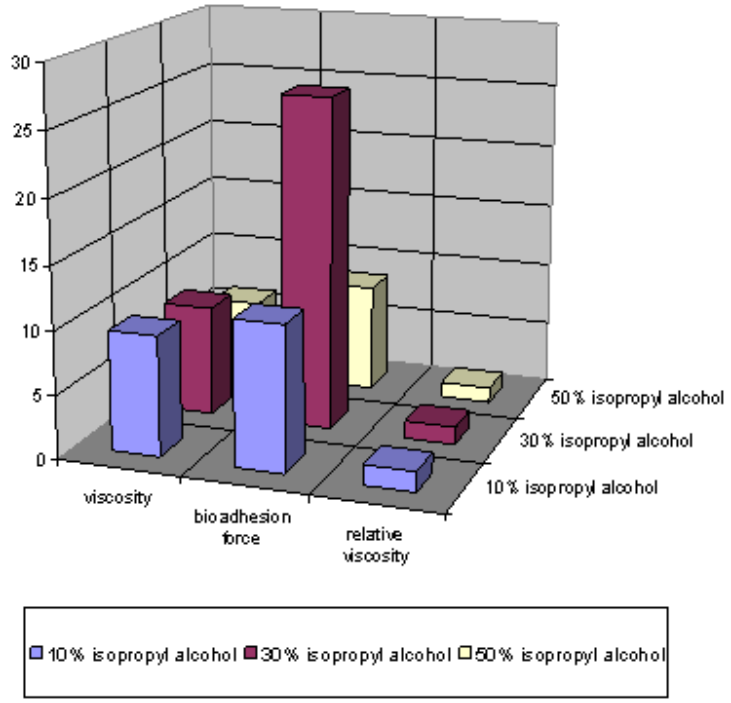


Figure (11): The Relationship between isopropyl alcohol Concentration, Rheological properties (viscosity) and mucoadhesive properties of prepared Cp 940 Gels.

CONCLUSION

In the present study, it was shown that the type and concentration of the incorporated alcohols (ethyl and isopropyl alcohol) significantly affect the rheological and mucoadhesive properties of prepared Cp 940 gels. Isopropyl alcohol provides substantial advantage over ethyl alcohol in promoting the mucoadhesive properties of Cp 940 gels up to 30%.

On the basis of the results of the rheological and mucoadhesive properties that are demonstrated and discussed in this work, we conclude that 30% is the optimum concentration of ethyl alcohol in hydroalcoholic systems when higher viscosity of the gel was required, and 30% also for isopropyl alcohol when strong mucoadhesive properties is required for Cp 940 gel formulations.

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