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Effect of Carbopol and Polyvinylpyrrolidone on the Mechanical, Rheological, and Release Properties of Bioadhesive Polyethylene Glycol Gels

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ABSTRACT This study examined the mechanical (hardness, compressibility, adhesiveness, and cohesiveness) and rheological (zero-rate viscosity and thixotropy) properties of polyethylene glycol (PEG) gels that contain different ratios of Carbopol 934P (CP) and polyvinylpyrrolidone K90 (PVP). Mechanical properties were examined using a texture analyzer (TA-XT2), and rheological properties were examined using a rheometer (Rheomat 115A). In addition, lidocaine release from gels was evaluated using a release apparatus simulating the buccal condition. The results indicated that an increase in CP concentration significantly increased gel compressibility, hardness, and adhesiveness, factors that affect ease of gel removal from container, ease of gel application onto mucosal membrane, and gel bioadhesion. However, CP concentration was negatively correlated with gel cohesiveness, a factor representing structural reformation. In contrast, PVP concentration was negatively correlated with gel hardness and compressibility, but positively correlated with gel cohesiveness. All PEG gels exhibited pseudoplastic flow with thixotropy, indicating a general loss of consistency with increased shearing stress. Drug release $T_{50\%}$ was affected by the flow rate of the simulated saliva solution. A reduction in the flow rate caused a slower drug release and hence a higher $T_{50\%}$ value. In addition, drug release was significantly reduced as the concentrations of CP and PVP increased because of the increase in zero-rate viscosity of the gels. Response surfaces and contour plots of the dependent variables further substantiated that various combinations of CP and PVP in the PEG gels offered a wide range of mechanical, rheological, and drug-release characteristics. A combination of CP and PVP with complementary physical properties resulted in a prolonged buccal drug delivery.

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INTRODUCTION

Drug delivery via buccal mucosa offers distinct advantages over peroral administration [1-5]. Recent studies by Jones et al. [6] suggest that bioadhesive formulations designed for buccal application should exhibit suitable rheological and mechanical properties, including pseudoplastic or plastic flow with thixotrophy, ease of application, good spreadability, appropriate hardness, and prolonged residence time in the oral cavity. These properties may affect the ultimate performance of the preparations and their acceptance by patients.

The Franz diffusion cell apparatus [7], the paddle method of the JPXII dissolution test apparatus [8], and a two-port cylinder suspended in a dissolution test apparatus [9] are methods used to study drug

release from buccal dosage forms. However, these methods may not simulate the buccal condition for testing the bioadhesive buccal gel. Mumtaz and Ch'ng [10] reported the design of a dissolution apparatus suitable for an in-situ release study of bioadhesive buccal tablets. Nevertheless, a dissolution test apparatus suitable for the assessment of drug release from bioadhesive buccal gel preparations has not been reported.

Hydrophilic polymers have been used mainly to improve the bioadhesive properties of buccal preparations. Polymers such as Carbopol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, polyvinylpyrrolidone, and their combinations were evaluated for their mucoadhesive strength and bioadhesive potential [11-17]. Some of these polymers were also used to formulate various buccoadhesive delivery systems, such as controlled-release systems [14, 17], patch formulations [15], and oramucosal devices containing fast-release and slow-release layers [16]. On the other hand, polyethylene glycol is commonly used as a base for cream, gel, and ointment preparations because of its physical characteristics and the versatile consistencies that can be obtained by mixing different proportions of its liquid and waxy forms. The current literature contains little information on mucoadhesive polyethylene glycol gels containing Carbopol and polyvinylpyrrolidone.

This study formulated bioadhesive polyethylene glycol gels containing Carbopol 934P and polyvinylpyrrolidone K-90 and examined how these two polymers could modify the mechanical and rheological properties of the gel preparations. In addition, drug release was investigated using a fabricated drug-release apparatus simulating buccal conditions. The relationship between mechanical and rheological properties and drug release was measured, and the effects of the concentrations of Carbopol 934P and polyvinylpyrrolidone K-90 on the various parameters were expressed using response surface and contour plots.

MATERIALS AND METHODS

Materials

The materials used for preparing the bioadhesive gels were Carbopol 934P (CP; B. F. Goodrich, Cleveland, OH), polyvinylpyrrolidone K-90 (PVP; a gift from ISP Technologies Inc., Wayne, NJ), polyethylene glycol 400 (PEG 400; BDH Laboratories Supplies, Poole, UK), and polyethylene glycol 4000 (PEG 4000; MERCK, Darmstadt, Germany).

The model drug was lidocaine HCl (BP grade). All materials were used as received.

Preparation of Oral Gel

PEG 400 and PEG 4000 were combined in an evaporating dish at 70±1°C and cooled to room temperature. The resulting gel was transferred onto a glass slab and levigated homogeneously with a known amount of CP and PVP. Formulations comprising constant amounts of PEG 400 and PEG 4000 (6 parts to 2 parts) but different ratios of CP and PVP were prepared (see **Table 1**). Narrow concentration ranges of CP and PVP were used, because the PEG gels became hard and were difficult to spread at higher concentrations.

Texture Profile Analysis

The mechanical properties of each formulation were determined using a texture analyzer (Model TA-XT 2, Stable Micro Systems, Surrey, UK) at 28±1°C. Each gel sample was packed to a fixed height of 6 cm in a universal bottle. A stainless steel probe of 1 cm diameter was compressed twice into the formulation at a defined rate of 4 mm/s to a depth of 1.5 cm, with a delay period of 30 seconds between the two compressions. Data collection and calculation were performed using the XTRA Dimension software package of the instrument. Four parameters (hardness, compressibility, adhesiveness, and cohesiveness) were used to characterize the gel. A minimum of 3 analyses were recorded for each gel formulation.

Evaluation of Rheological Properties

The rheograms of the bioadhesive gels were obtained at 28 +/- 0.1°C using a rheometer (Rheomat Model 115A, Mettler-Toledo, Switzerland) equipped with a cone and plate measuring system (Contraves CP 150, Mettler-Toledo, Switzerland). The dimension of the measuring cone CP 6 was 50 mm and the angle of the cone was 2°. Sample was carefully applied onto the plate using a spatula, ensuring that formulation shearing did not occur. The following parameters used to investigate flow profile, zero-rate viscosity, and thixotropy:

Preshearing time of 5 seconds, followed by ascending curve time of 120 seconds at a maximum shear rate of 100 s^{-1} followed by a hold time of 10 seconds at a minimum shear rate of 0 s^{-1} and then a descending time of 120 seconds. The rheograms obtained were the average of at least 2 determinations.

Drug-Release Studies

Ten percent wt/wt of lidocaine HCl was incorporated into the various gel formulations and was used in the drug-release studies. The design of the drug-release cell was a modified version of the apparatus used by Mumtaz and Ch'ng [10]. It consisted of a semicircular glass tube of 9 cm length and 3 cm diameter. A small inlet tube (0.5 cm diameter) was attached to the upper end of the cell and an outlet tube of the same diameter was attached to the lower end of the cell. Fresh chicken pouch membrane of uniform thickness, devoid of fatty tissue material, was folded onto a glass slide 2.1 cm wide, 3.6 cm long, and 0.5 cm thick. A 0.5 g of gel sample was evenly applied onto the membrane with a defined area of 0.8 cm x 3 cm. The glass slide was subsequently assembled in the drug-release cell and the latter was held vertically at 90° by a clamp attached to a retort stand, over a USP dissolution test vessel equipped with a paddle stirrer rotating at 100 rpm. Simulated saliva solution (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8 g of NaCl in 1 liter of distilled water, pH 6.75) at 37 ± 0.5°C in the dissolution vessel was circulated through the drug-release cell over the gel and chicken pouch membrane at a predetermined rate using a peristaltic pump. A diagrammatic representation of the experimental setup used in the drug-release study is shown in **Figure 1.**

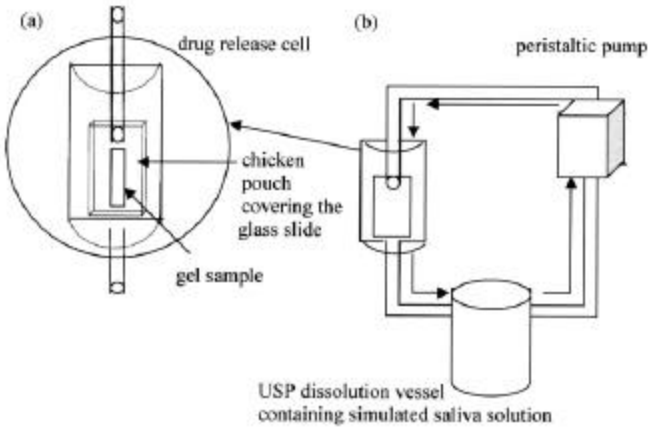

Figure 1. Schematic diagram of the dissolution apparatus used in the drug-release study. (a) Drug-release cell. (b) Flow diagram of the dissolution apparatus.

A 4-mL sample was collected at various time intervals and the lidocaine concentration was measured spectrophotometrically at 261.5 nm (Model U-2000, Hitachi, Japan). Drug release $T_{50\%}$ is defined as 50% of lidocaine HCl released from the gel during the drug-release study.

Statistical Analysis

The effects of the concentration of CP and PVP on the mechanical properties, rheological properties, and $T_{50\%}$ were evaluated using multivariate tests. The results were also subjected to bivariate correlation statistical treatment. The regression polynomial was calculated using SPSS statistical software and was applied to approximate the response surface and contour plots using the PC-based software Mathematica.

RESULTS AND DISCUSSION

Results of the multivariate analysis indicated that CP and PVP concentrations generally had significant effects on the mechanical and rheological characteristics as well as the drug release ($T_{50\%}$) of the PEG gels. A statistical interaction was observed between CP and PVP concentrations with respect to gel hardness, compressibility, and adhesiveness ($P<0.05$). Regression polynomials for the individual dependent variables (compressibility, hardness, adhesiveness, cohesiveness, drug release $T_{50\%}$, or zero-rate viscosity) were calculated and applied to approximate the

response surfaces and contour plots. The general model as shown below was generated to fit the various data:

$$y = \alpha_0 + \alpha_1 x_1 + \alpha_2 x_2 + \alpha_3 x_1 x_2 + \alpha_4 x_2^2 + \alpha_5 x_1 x_2^2 + \alpha_6 x_1^3 x_2^2 + \alpha_7 x_1^3 x_2 + \alpha_8 x_1 x_2^3 + \alpha_9 x_1^4 + \alpha_{10} x_2^4 \quad (1)$$

where y = dependent variable (compressibility, hardness, adhesiveness,

cohesiveness, drug release $T_{50\%}$ or zero-rate viscosity)

$\alpha_0 ... \alpha_{10}$ = regression coefficients of the independent variable (x_1, x_2)

x_1 = concentration of CP

x_2 = concentration of PVP

Mechanical Properties

Texture profile analysis (TPA) has been used to characterize the mechanical properties of pharmaceutical gels and semisolid systems [6, 18, 19]. This simple and rapid technique could provide information related to the gel mechanical parameters, such as hardness, adhesiveness, compressibility, and cohesiveness. Ideally, formulations designed for buccal drug delivery should have low hardness and compressibility, yet high adhesiveness and cohesiveness. Low gel hardness and compressibility will ensure that minimum work is required for gel removal from the container and administration onto the oral mucosal epithelium, while high gel adhesiveness and cohesiveness will ensure prolonged adhesion of the gel onto the oral mucosa and a complete structural recovery of the gel following application. The mechanical properties of the PEG gels are shown in **Table 1.**

The final models for gel compressibility and hardness are as follows:

$$\text{Compressibility} = 4.103 + 60.546x_1 - 16.56x_2 - 279.992x_1x_2 + 29.3x_2^2 + 151.075x_1x_2^2 - 39333.333x_1^3x_2^2 + 25106.667x_1^3x_2 + 226.083x_1x_2^3 - 5412.865x_1^4 - 14.529x_2^4$$

(2) ($r^2 = 0.941$)

$$\text{Hardness} = 1.727 + 24.639x_1 - 6.333x_2 - 124.979x_1x_2 + 11.738x_2^2 + 82.423x_1x_2^2 - 14388.148x_1^3x_2^2 + 9179.852x_1^3x_2 + 74.306x_1x_2^3 - 215.205x_1^4 - 5.938x_2^4$$

(3) ($r^2 = 0.977$)

Table 1. Mechanical, Rheological and Drug Release Properties of PEG Gel formulations*

Code	CP**	PVP***	Hardness N	Adhesiveness N mm	Compressibility N mm	Cohesiveness	Zero-rate Viscosity (Pa.s)	Drug release $T_{50\%}$ (min)
A	0	0	1.8± 0.4	4.0± 1.8	4.5± 1.1	0.6± 0.0	3.6± 0.6	2.7± 0.1
B	0	0.2	1.0± 0.2	2.2± 0.1	2.3± 0.7	0.7± 0.2	5.1± 1.5	2.9± 0.4
C	0	0.5	1.1± 0.7	2.9± 1.4	2.1± 1.5	1.0± 0.2	5.1± 3.0	3.5± 0.3
D	0	1	1.3± 0.2	3.2± 0.3	2.6± 0.6	1.0± 0.2	7.0± 2.2	6.3± 0.7
E	0.1	0	4.3± 0.5	7.3± 2.1	10.1 ±2.7	0.7± 0.1	4.3± 0.4	2.9± 0.1
F	0.1	0.2	2.6± 0.0	6.6± 0.8	6.6± 0.5	0.6± 0.1	9.6± 0.5	4.2± 0.1
G	0.1	0.5	1.3± 0.2	3.8± 1.1	3.3± 1.0	0.8± 0.1	9.3± 0.2	6.1± 1.5
H	0.1	1	1.6± 0.2	4.1± 0.2	3.5± 0.6	0.9± 0.2	10.4 ±3.0	6.7± 1.2
I	0.15	0	5.3± 0.1	5.9± 1.3	10.5 ±1.2	0.6± 0.0	6.1± 2.2	3.5± 0.9
J	0.15	0.2	5.6± 0.4	9.9± 2.6	12.9 ±2.3	0.6± 0.2	10.0 ±1.3	5.2± 0.7
K	0.15	0.5	3.2± 0.4	8.2± 1.1	6.6± 0.3	0.8± 0.0	10.8 ±0.5	8.1± 0.7

* Each formulation contained 6 parts PEG 400 & 2 parts of PEG 4000

** Parts of CP added to the PEG 400 & PEG 4000 gel

*** Parts of PVP added to the PEG 400 & PEG 4000 gel

The corresponding response surfaces and contour plots (**Figures 2** and **3**) show that at PVP concentrations below 0.6 parts, an increase in CP concentration increased gel compressibility and hardness. At PVP concentrations above 0.6 parts, an increase in CP concentration decreased gel compressibility and hardness.

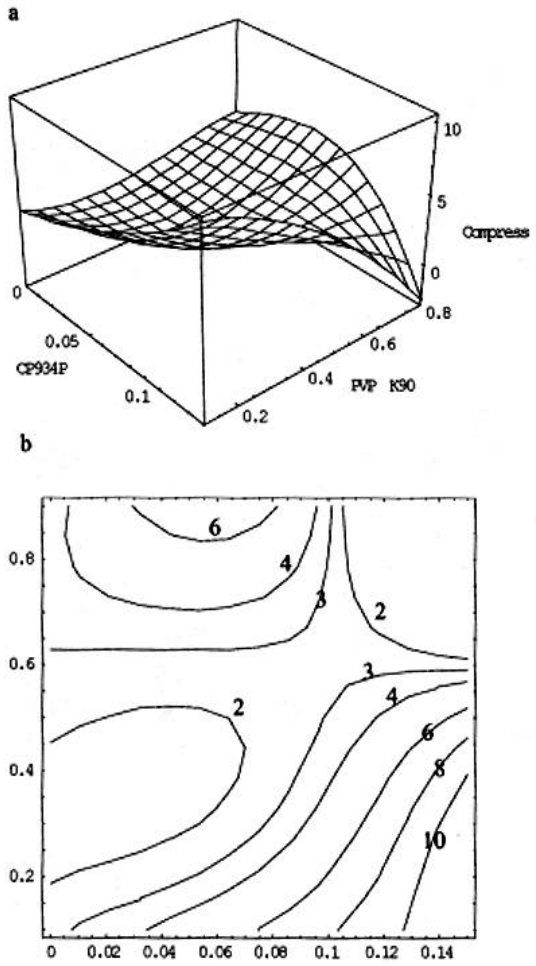

Figure 2. Estimated response surface (a) and contour plot (b) illustrating the relationship between compressibility of gel and CP and PVP concentrations.

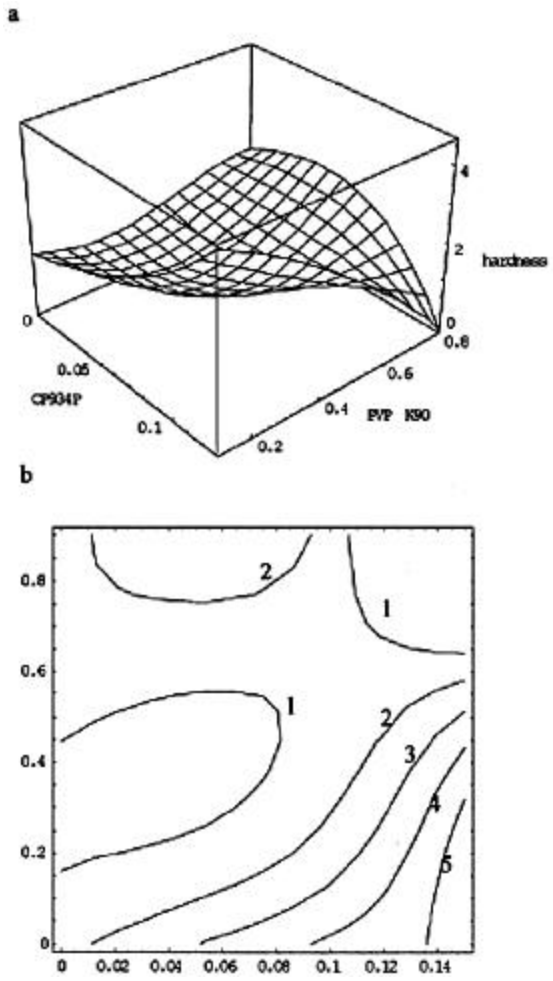

Figure 3. Estimated response surface (a) and contour plot (b) illustrating the relationship between hardness of gel and CP and PVP concentrations.

Pearson correlation coefficients indicated that CP concentration was positively correlated with compressibility and hardness (P<0.01) (**Table 2**), while PVP concentration was negatively correlated with gel compressibility and hardness (P<0.01). Additionally, compressibility and hardness were positively correlated with adhesiveness (P<0.01) but inversely correlated with cohesivenss (P<0.01).

Jones et al. [6] reported the effect of polymer concentration on product compression characteristics. They found that the product compressibility and hardness were dependent on the concentrations of hydroxyethylcellulose, polyvinylpyrrolidone, and polycarbophil in the hydrogel formulations. In this study, it was apparent that both the concentration and type of polymer affected product hardness and compressibility. A combination of CP and PVP in an appropriate ratio produced PEG gel preparations with suitable compressibility and hardness.

Adhesive characteristic is an important parameter in the design of an oral gel, since a desirable gel contact and retention at the mucosal surface will ensure better clinical efficacy. The final model for gel adhesiveness follows:

$$\text{Adhesiveness} = 3.78+55.904x_1-14.598x_2-139.252x_1x_2+28.234x_2^2-185.744x_1x_2^2-20174.815x_1^3x_2^2+19150.519x_1^3x_2+301.972x_1x_2^3-12336.842x_1^4-14.446x_2^4 \quad (4)$$

($r^2 = 0.867$)

Table 2 . Pearson's Correlation Coefficients for the Mechanical, Rheological and Drug Release Properties of PEG Gel Formulations

	CP	PVP	Adhesiveness	Cohesiveness	Hardness	Compressibility	Zero-rate Viscosity	$T_{50\%}$
CP	1.00	-0.18	0.76 **	-0.42*	0.75**	0.73**	0.58**	0.38*
PVP	-0.18	1.00	-0.34	0.68**	-0.49**	-0.51**	0.42	0.69**
Adhesiveness	0.76*	-0.34	1.00	-0.49**	0.83**	0.85**	0.45*	0.16
Cohesiveness	-0.42*	0.68**	-0.49**	1.00	-0.61**	-0.67**	0.05	0.35*
Hardness	0.75**	-0.49**	0.83**	-0.61**	1.00	0.98**	0.14	-0.03
Compress-ibility	0.73**	-0.51**	0.85**	-0.67**	0.98**	1.00	0.15	-0.06
Zero-rate Viscosity	0.58**	0.42	0.45*	0.05	0.14	0.15	1.00	0.70**
$T_{50\%}$	0.38*	0.69**	0.16	0.35*	-0.03	-0.06	0.70**	1.00

* Correlation is significant at the 0.05 levels
** Correlation is significant at the 0.01 levels
Other correlations are not significant

The corresponding response surface and contour plots are shown in **Figure 4.**

In general, an increase in CP concentration increased the gel's adhesiveness, while the concentration of PVP did not significantly affect adhesiveness. Pearson correlation coefficients indicated that CP concentration was positively correlated with adhesiveness (P<0.01), but the correlation with PVP concentration was insignificant (P>0.05) (**Table 2**).

Adhesiveness in gel texture analysis is the measurement of work needed to overcome the attractive forces between the gel and the analytical probe. The increase in gel adhesiveness caused by an increase in CP (but not PVP) concentration might be attributed to the greater ability of CP to chemically interact with the probe.

Cohesiveness is a parameter related to the structural reformation following successive shearing stress during application. The final model for gel cohesiveness was as follows:

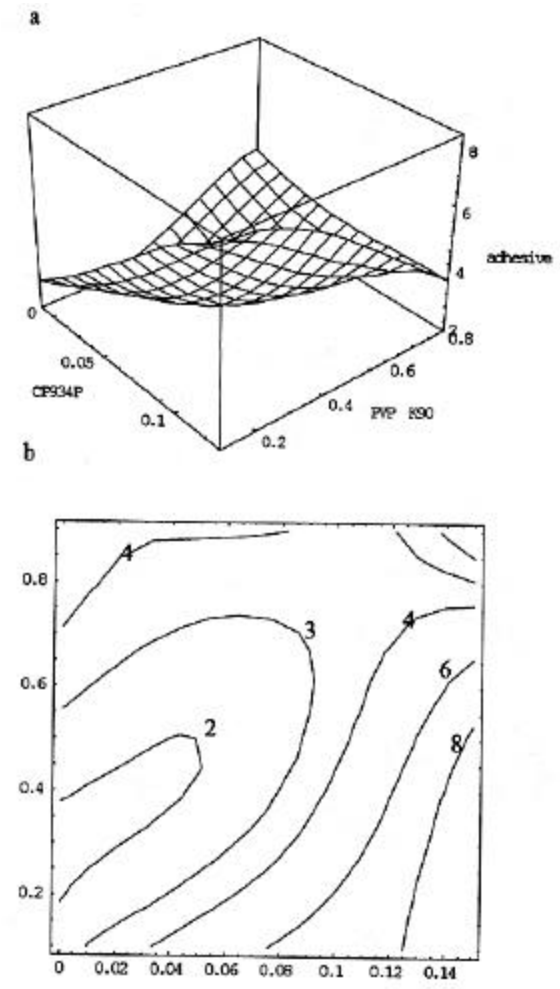

Figure 4. Estimated response surface (a) and contour plot (b) illustrating the relationship between adhesiveness of gel and CP and PVP concentrations.

$$\text{Cohesiveness} = 0.673+0.255x_1+0.214x_2-10.654x_1x_2+1.223x_2^2+8.261x_1x_2^2-391.111x_1^3x_2^2+371.556x_1^3x_2+1.722x_1x_2^3-191.813x_1^4-1.114x_2^4 \quad (5)$$

($r^2 = 0.675$)

The response surface and contour plot in **Figure 5** indicates that an increase in CP concentration caused a reduction in cohesiveness.

This was due to the increase in dispersed solids in the gel, which caused the gel to become less coherent. In contrast, gel cohesiveness was augmented with an increase in PVP. Pearson correlation coefficients also indicated that CP concentration was inversely correlated with cohesiveness (P<0.05) but was positively correlated with PVP concentration (P<0.01) (**Table 2**).

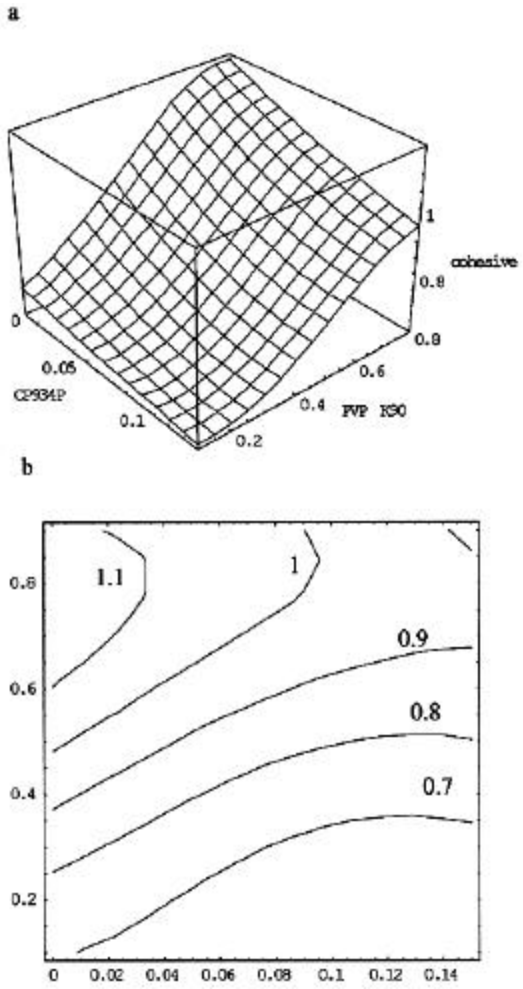

Figure 5. Estimated response surface (a) and contour plot (b) illustrating the relationship between cohesiveness of gel and CP and PVP concentrations.

In this study, cohesiveness was a measure of the ratio of work required during the second compression cycle to that of the first compression cycle. At a constant CP concentration and an increase in PVP concentration, more work was needed to compress the gel during the second compression cycle than the first cycle, indicating that the gel structure became more coherent.

Rheological Properties

All the gel formulations demonstrated pseudoplastic flow with thixotropy. A typical example of the flow curve of the gel formulations is shown in **Figure 6.**

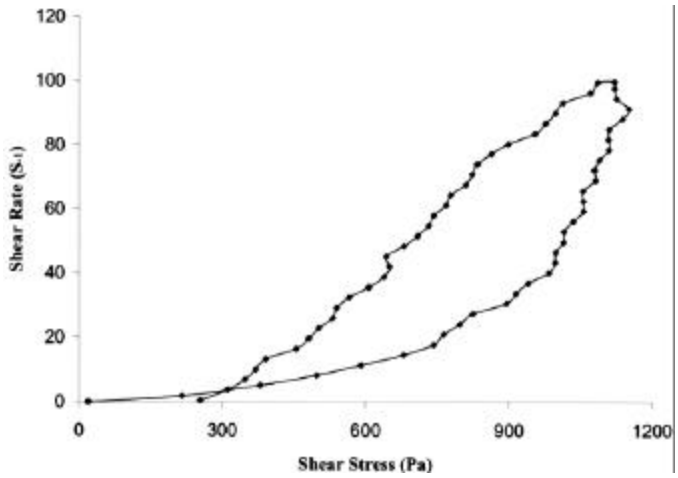

Figure 6. Flow curve for formulation K. Error bars were excluded for clarity.

Shear thinning phenomenon, an advantageous property for buccal gel, was observed for all the gels tested. An increase in shear stress reduced the consistency of the gels. The presence of the hysteresis loop indicated that a breakdown in structure occurred, and the area within the loop might be used as an index of the degree of breakdown of the gel. The result of zero-rate viscosity of the gel is shown in **Table 1**. The final model for gel zero-rate viscosity follows:

Zero-rate viscosity= $3.585+3.326x_1+11.585x_2+439.486x_1x_2-20.203x_2^2-894.111x_1x_2^2$ - $13103.556x_1^3x_2^2+21951.111x_1^3x_2+393x_1x_2^3+3873.684x_1^4+11.973x_2^4$ (6) ($r^2 = 0.814$)

The corresponding response surface and contour plot are shown in **Figure 7.** An increase in CP concentration increased zero-rate viscosity, whereas an increase in PVP concentration had inconsistent effects on zero-rate viscosity. Pearson correlation coefficients indicated that CP concentration was positively correlated with zero-rate viscosity ($P<0.01$), but the correlation with PVP concentration was insignificant ($P>0.05$) (**Table 2**).

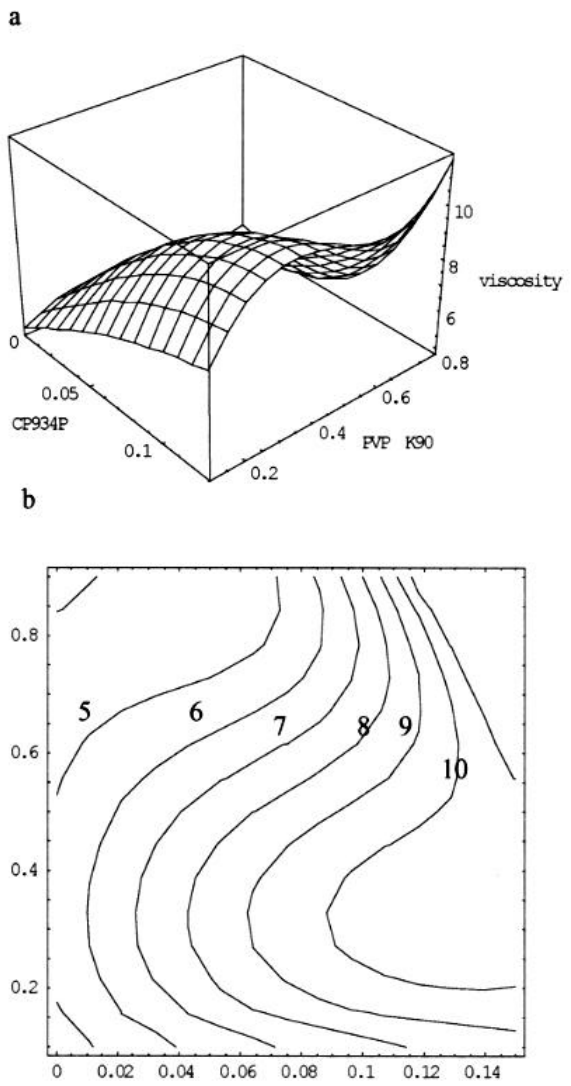

Figure 7. Estimated response surface (a) and contour plot (b) illustrating the relationship between zero-rate viscosity of gel and CP and PVP concentrations.

Zero-rate viscosity was also positively correlated with gel adhesiveness ($P<0.05$) and $T_{50\%}$ ($P<0.01$) (**Table 2**), but it was not correlated with other mechanical properties ($P>0.05$) (gel hardness, compressibility, and cohesiveness), or PVP concentration ($P>0.05$). Although previous research noted the importance of viscosity on compression characteristics of aqueous mucoadhesive gels [6], this study found no indications that an increase in the viscosity of PEG gels was correlated with the hardness and compressibility of the product.

Drug-Release Study

The drug-release cell used in this study was designed to simulate the buccal condition as closely as possible. The glass slide was designed so that it could be assembled centrally in the curved wall of the semicylindrical outer cell, below the inlet tube and above the outlet tube, without dislodging. Since the membrane could be applied evenly and folded over the edges of the glass slide, fastening of the membrane to the glass slide was unnecessary.

Animal mucosa of rat, chicken, hamster, rabbit, dog, monkey, and pig have been used in other buccal drug absorption or permeation studies [20-24]. Freshly slaughtered and conditioned chicken pouch membrane was used in this study because of its availability and the consistency of the tissue.

The $T_{50\%}$ values presented in **Table 1** were obtained at a flow rate of 4 mL/min. At this flow rate, $T_{50\%}$ values ranged from 2.7 to 8.1 minutes. However, the effects of CP and PVP concentrations on $T_{50\%}$ values were statistically significant ($P<0.01$). The final model for gel $T_{50\%}$ follows:

$$\text{Drug release } T_{50\%} = 2.7 - 0.17x_1 + 0.56x2 + 67.7x_1x_2 + 1.555x_2^2 + 1.433x_1x_2^2 + 3066.667x_1^3x_2^2 - 1480x_1^3x_2 - 83x_1x_2^3 + 1936.842x_1^4 + 1.511x_2^4 \quad (7)$$

($r^2 = 0.890$)

The response surface and contour plot in **Figure 8** show that an increase in both CP and PVP concentrations increased the $T_{50\%}$ values. Pearson correlation coefficients further supported this finding. $T_{50\%}$ was positively correlated with CP concentration ($P<0.05$) and PVP concentration ($P<0.01$) and also with cohesiveness ($P<0.05$) and zero-rate viscosity ($P<0.01$) (**Table 2**).

During the drug-release study, gel samples were exposed to a constant flow of simulated saliva solution (4 mL/min). In the presence of an aqueous medium, PEG gel base dissolved gradually, while CP and PVP swelled and formed a viscous barrier to drug release. With time, the polymeric barrier was eroded away and complete drug release was achieved. For all the gel formulations studied, more than 95% of drug was released within 30 minutes.

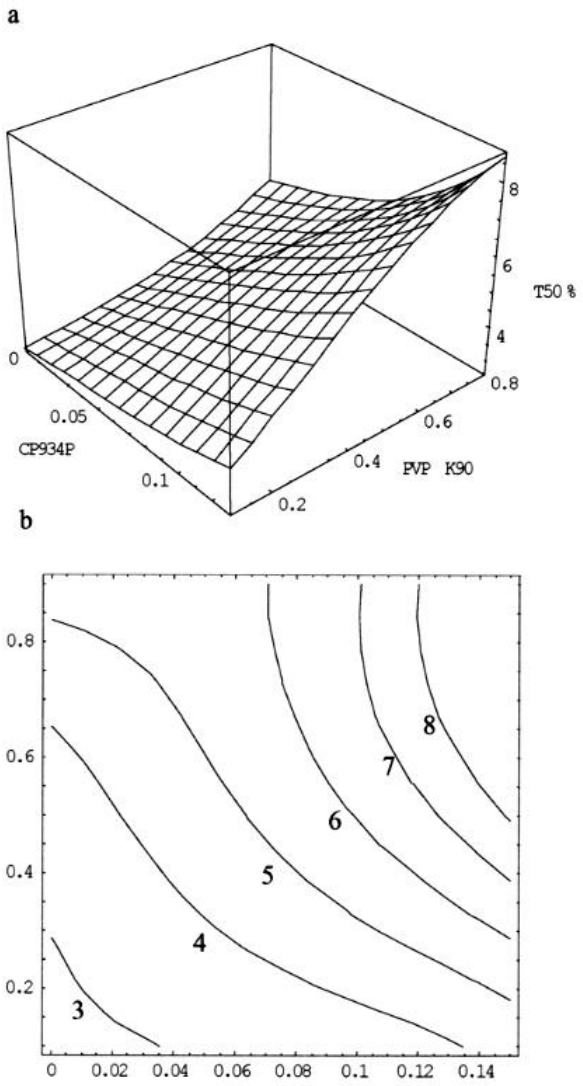

Figure 8. Estimated response surface (a) and contour plot (b) illustrating the relationship between drug release $T_{50\%}$ of gel and CP and PVP concentrations.

Humans produce about 1 liter of saliva per day. The resting flow of saliva is 0.5 mL/min, while under maximal stimulation of the parasympathetic system it can increase to more than 7 mL/min [25]. To study the effect of saliva flow rate on drug release, the test was repeated with 3 different flow rates (1, 2, and 4 mL/min) of simulated saliva solution using formulation K as shown in Table 1. The results showed that an increase in flow rate caused a decrease in $T_{50\%}$ values, indicating a faster drug release. At flow rates of 1, 2, and 4 mL/min, $T_{50\%}$ values were 15.3, 13.5, and 8.1 minutes respectively (P<0.01).

CONCLUSIONS

PEG gels containing various ratios of CP and PVP offer a wide range of mechanical, rheological, and drug-release characteristics. A combination of CP and PVP with complementary physical properties resulted in prolonged buccal drug delivery. Gel formulation K was found to be the most suitable gel carrier due to its favorable mechanical properties of low hardness and compressibility, but maximal adhesiveness and cohesiveness. Even though texture analysis offered an understanding of the mechanical properties of bioadhesive gels, drug release was better correlated with gel rheology. Clinical performance and patient acceptance of the gel preparation in healthy human volunteers should be evaluated in the future.

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