

The Influence of Various Mucoadhesive Polymers on In Vitro Performance of the Resulting Artificial Saliva Pump Spray Formulations

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Abstract

The aim of this study was to investigate the rheological behavior and mucoadhesive nature of saliva substitutes, by incorporating various mucoadhesive polymers into an artificial saliva pump spray formulation. For this purpose various mucoadhesive polymers including cellulosic polymers in the range of 0.1-1.0% and Carbomers such as C974P, C971, C934P and C971 in the range of 0.01-0.1% were added to a formulated aqueous-based artificial saliva pump spray formulation, containing fixed amounts of some essential electrolytes. The pH of the formulations was between 6.3-7.4. The formulations were examined in terms of appearance, taste, odor, spray-ability, short-term thermal and mechanical stability, pH, viscosity and rheological behavior, particle size distribution, as well as invitro mucoadhesive strength (MS). The mucoadhesivity ratio (MR) was also calculated as follows: $MR = MS_{\text{test}} / MS_{\text{control}}$ using natural saliva as the control. Natural saliva showed a pseudoplastic rheological behavior, with a viscosity in the range of 12.85-28.15cP. Hence, artificial saliva samples having viscosities within this range were selected. The rheological behavior and viscosity of the test samples as well as the natural saliva were subsequently determined. Similar to that found for the natural saliva, all the prepared formulations showed a pseudoplastic rheological behavior. Among the polymers, C974P had the highest viscosity (25.97±0.11 cP) and mucoadhesive strength (34.84±0.21 mN/cm²) followed by hydroxypropylmethylcellulose which had a viscosity of 25.48±0.11 cP and a mucoadhesive strength of 34.03±0.24 mN/cm². Furthermore, the mucoadhesivity of C974P containing artificial saliva was 1.186 times greater than natural saliva and 1.387 times more than water. In conclusion, it seems that the presence of mucoadhesive polymers within the artificial saliva pump spray formulations could help to improve the adhesive nature of the formulation to mucosal surfaces, making it even more effective than the natural saliva.

Keywords: Artificial saliva; Pump spray system; Mucoadhesion; Carbomers; Cellulose derivatives; Rheology.

Introduction

Natural saliva is a complex and viscous liquid,

which is secreted from the salivary glands. Each person secretes 1-1.5 liter of saliva per day (1). The density of saliva varies between 1.002-1.0012 g/cm³ and its pH is between 6.7-7.4 (2). Natural saliva contains 99% water; electrolytes such as sodium, potassium, calcium, magnesium,

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iodide, fluoride, phosphate; proteins like mucin and enzymes (1, 3).

Lack or deficiency of saliva could result in xerostomia (dry mouth). The symptoms of this disease include dryness of the tongue, halitosis, dental plaque, difficulty in breathing, speech and swallowing, as well as mouth ulcers and fissures (4, 5). The causes of xerostomia include the use of some drugs such as anticholinergics, antidepressants, antihistamines and antihypertensives; certain diseases such as Sjögren's syndrome and radiotherapy of head and neck regions. Therefore, treatment could be carried out once the main cause of xerostomia has been revealed. In fact palliative therapy, such as the use of artificial saliva could be one of the best ways for relieving the symptoms (5). Artificial saliva could be formulated in the form of aqueous solution, pump spray, aerosol spray, gel, chewing gum, paste, mouth wash and tablet, which can abate the symptoms.

It has been shown that the use of saliva substitutes in patients suffering from dry mouth can diminish the unpleasant symptoms. Furthermore, the results showed that saliva substitute has a remarkable effect on dry mouth compared to drinking water (6).

In another study by Davies et al, the use of artificial saliva pump spray was found to greatly improve the efficacy of the product in comparison to other artificial saliva dosage forms and was also able to produce an excellent degree of patient compliance (7).

Artificial saliva pump spray formulations, beside water as the main vehicle, usually contain a viscosity modifying agent, flavorant, electrolytes, preservative, pH adjusting agent and a colorant (8-10). Water soluble polymers and gums such as cellulose derivatives, carbomers and chitosan have been used as viscosity modifying agents. They also possess mucoadhesive characteristics, which could help to prolong the resistance time of the saliva substitute within the oral cavity, thus improving patient compliance (11). The process of mucoadhesion occurs when a mucoadhesive polymer adheres to a mucosal surface (12). Mucoadhesive polymers are natural or artificial macromolecules that are capable of adhering to the mucosal surfaces of the body, including the ocular, nasal, gastric and buccal mucosa

(13, 14).

Some of the more popular mucoadhesive polymers include cellulose derivatives such as sodium carboxymethyl cellulose (NaCMC), hydroxypropylmethyl cellulose (HPMC) and hydroxyethyl cellulose (HEC); Carbomers such as Carbomer 974P (C974P), Carbomer 934P (C934P), Carbomer 971 (C971) and Carbomer 940 (C940).

The rheological behavior of saliva substitutes and their mucoadhesive nature have not been studied in-dept; hence the aim of this study was to investigate these important properties by incorporating various mucoadhesive polymers into an artificial saliva pump spray formulation.

Experimental

Materials

NaCMC (high viscosity grade) was purchased from ICN, Germany; HEC (high viscosity grade) was purchased from IRV, Germany; HPMC (high viscosity grade) from Acros organics, USA; Carbomers including C974P, C934P, C971 and C940 were obtained from BF Goodrich, England. Hydrochloric acid, potassium chloride, calcium chloride, sodium chloride, sorbitol, dibasic potassium phosphate, magnesium chloride and monobasic potassium phosphate were all purchased from Merck, Germany. Triethanolamine was from Riedel-dehaen, Germany and Parabens were purchased from San.fu.chemical, Taiwan.

Methods

Selection of the pump spray base constituents

Based on previous studies, water was selected as the vehicle to prepare the pump spray formulation (10). In addition, various electrolytes including sodium chloride, potassium chloride, magnesium chloride and monobasic potassium phosphate were dissolved in water (15). Next, different polymers including NaCMC, HPMC, HEC, C974P, C971, C934P and C940 were dissolved in water in amounts mentioned in the literature (12-14, 16). These polymer-containing solutions were individually added and dissolved in the base prepared, as the viscosity adjusting

agent and possibly to improve the mucoadhesive ability of the resulting formulation. Following the preparation of test samples, they were filled in oral type polyethylene pump spray containers (obtained from Pfeiffer Company, Germany). The volume of each puff exited the spray was around 0.13 ml.

Evaluation of the rheological behavior and viscosity

Initially, the rheological behavior and viscosity of the natural saliva was studied. For this purpose, 10 healthy and non-smoking volunteers aged between 24-60 years took part in this study. Each volunteer was asked to provide 3×10 ml of their fresh saliva. Saliva samples were then defrosted by being left standing at room temperature around 30 min.

Next, one milliliter of each of the defrosted saliva samples were placed inside a cone and plate Brookfield DV II viscometer and examined using a CP-42 cone with an angle of 1.565° at 25°C. Different shear rates (SR) and shear stresses (SS) were imposed upon the test samples and the resulting rheogram was constructed. Using the rheograms obtained, the rheological behavior and viscosities of test samples were determined. The same procedure was carried out using the individual polymer-containing artificial saliva samples prepared. Each sample was examined in triplicates.

Particle size determination

In order to determine the mean particle size distribution of the polymer-containing artificial saliva samples, one puff from each sample was individually sprayed on a clean microscope slide from a distance of 15 cm. The slide was then immediately placed under a Karl Zeiss (7082) light microscope fitted with an E34 Graticule and the diameter of 100 particles determined using a magnification of ×1000 at 25°C.

Each sample was examined 3 times.

Spray-ability

In this study the ease of out-flow of the prepared polymer-containing artificial saliva formulations was determined visually upon pressing the pump spray actuator.

Mucoadhesivity

For the purpose of this test an in-house apparatus, used in previous studies (17, 18), was employed a schematic diagram of the test apparatus has been shown in Figure 1.

Fifty µl of each test sample was placed between an upper and a lower platform, each coated with rat buccal mucosa, as the model mucosal membrane.

The test sample was left in contact with the mucosal surface for a period of 2 min, at a temperature of 37°C. The lower platform was then gradually descended at a rate of 2 mm/min until complete separation of the two platforms. The maximum force required to separate the two platforms (i.e. mucoadhesive strength or MS) was taken as the mucoadhesive strength of the test sample. This was calculated as mN/cm². Each sample was examined 3 times, and the mean mucoadhesive strength was determined. In addition, a parameter termed “mucoadhesivity ratio (MR)”, calculated using the formula $MR_{\text{sample/saliva}} = MS_{\text{sample}} / MS_{\text{saliva}}$. MS_{sample} and MS_{saliva} are the mucoadhesive strengths of the test sample and natural saliva, respectively. Also, the mucoadhesivity ratio of test sample to water was determined, using the formula $MR_{\text{water/water}} = MS_{\text{sample}} / MS_{\text{water}}$. In here MS_{water} is the mucoadhesive strength of water (control).

Results and Discussion

As stated before, the aim of this study was to investigate the rheological behavior and mucoadhesive nature of saliva substitutes, following the incorporation of various mucoadhesive polymers into an artificial saliva pump spray formulation. The results obtained would be presented and discussed in the following sections.

Rheological characterization of natural saliva and artificial saliva samples

As could be seen in the rheogram obtained (Figure 2), natural saliva seems to have a non-Newtonian rheological behavior, since it does not follow a linear pattern. Statistical evaluation, using the SPSS version 15.0 statistical software, also confirmed this finding (linearity test,

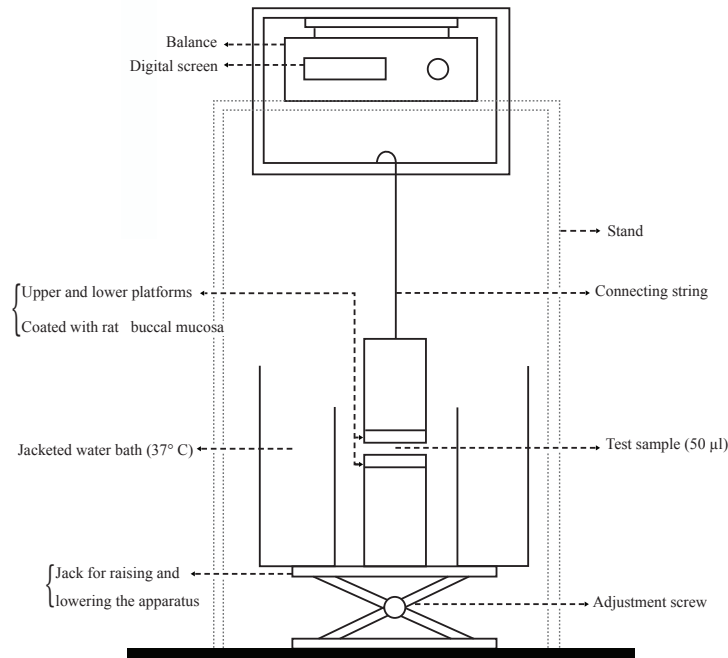


Figure 1. Schematic drawing of the apparatus used for assessing the invitro mucoadhesive strength of polymer containing artificial saliva samples.

$p < 0.05$). Further studies showed the existence of a pseudoplastic rheological behavior in the natural saliva samples. This is because of a shear thinning phenomenon occurring within the saliva glycoprotein network, resulting in a reduction in viscosity following an increased SR or SS.

In order to determine the viscosity of the natural saliva samples, the power law equation

was used. This has been shown in equation 1 (19).

$$SS^n = SR \times \eta \quad \text{Eq. (1)}$$

In equation 1, n (n value) represents the pseudoplasticity index and η is the viscosity coefficient. In order to turn this equation into a linear equation, a logarithmic transformation

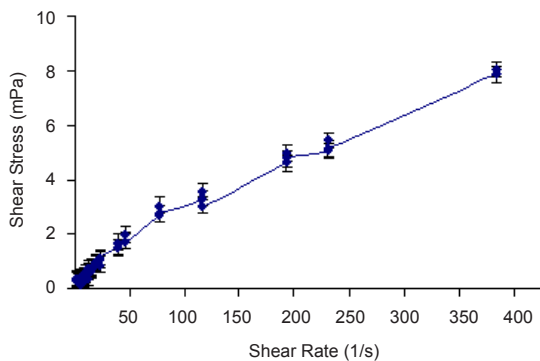


Figure 2. Non-linear rheogram of natural saliva ($n=3$, data points represent mean \pm SD).

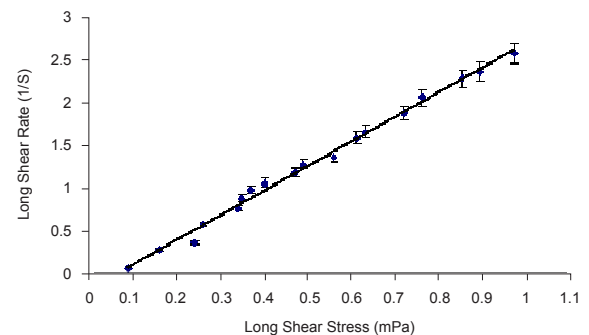


Figure 3. Linear logarithmic rheogram of natural saliva ($n=3$, data points represent mean \pm SD).

Table 1. Viscosities and the pseudoplasticity indices (n values) of natural saliva specimens of 10 human volunteers (n=3, data shown as mean±SD).

| Subject number | Gender | Viscosity (cP) | Pseudoplasticity index |
|----------------|--------|----------------|------------------------|
| 1 | Male | 28.15 ±0.23 | 1.69±0.22 |
| 2 | Male | 25.29 ±0.23 | 1.89±0.14 |
| 3 | Male | 12.85 ±0.27 | 2.19±0.10 |
| 4 | Male | 15.29 ±0.26 | 2.09±0.21 |
| 5 | Male | 22.35 ±0.08 | 1.86±0.23 |
| 6 | Male | 18.32 ±0.12 | 1.98±0.18 |
| 7 | Female | 17.35 ±0.25 | 1.88±0.11 |
| 8 | Female | 22.12 ±0.14 | 2.14±0.19 |
| 9 | Female | 20.56 ±0.12 | 1.56±0.21 |
| 10 | Female | 19.35 ±0.46 | 1.65±0.20 |

was adopted, as shown in equation 2 (19).

$$\text{Log SR} = n \text{ log SS} - \text{log } \eta \quad \text{Eq. (2)}$$

Based on equation 2, the logSS (y-axis) vs. log SR (x-axis) graph was constructed. The resulting rheogram has been shown in Figure 3. The slope of this linearized graph would represent the pseudoplasticity index, found to be equal to 1.88. Since this value is greater than 1, it justifies the presence of a pseudoplastic behavior in the natural saliva samples. Table 1 shows the pseudoplasticity indices and viscosities of natural saliva samples of the human volunteers. Next, in order to determine the viscosity of natural saliva, the intercept was measured, which was found to be 1.30. By taking the anti-logarithm of this

value, the viscosity was determined, and found to be equal to 20.16 cP.

In the next stage, the rheological behavior and viscosity of the polymer-containing artificial saliva formulations prepared were determined. Typical rheograms obtained for cellulose-containing samples and carbomer-containing samples have been shown in Figures 4 and 5. None of the samples showed a linear rheogram, similar to that found for the natural saliva. This would again justify the existence of a non-Newtonian rheological behavior within these samples. Further studies confirmed the presence of a pseudoplastic rheological behavior, as explained for the natural saliva. Using a similar procedure to that of the natural saliva, the pseudoplasticity indices and viscosities of various test samples

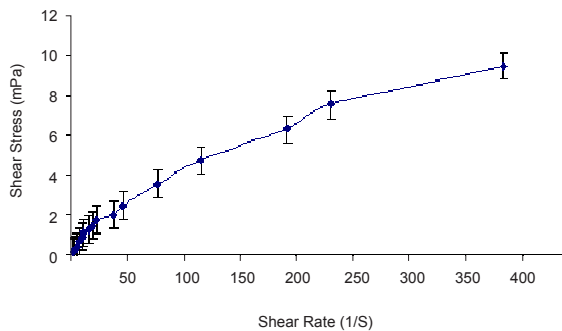


Figure 4. A typical rheogram obtained for the cellulose-containing artificial saliva samples (n=3; data points represent mean±SD).

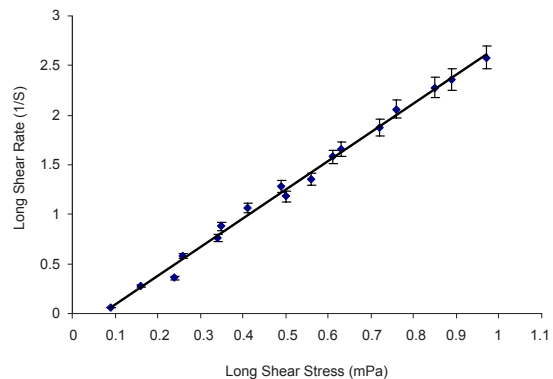


Figure 5. A typical log-log rheogram belonging to the cellulose-containing artificial saliva samples (n=3; data points represent mean±SD).

Table 2. Viscosity and pseudoplasticity indices (n values) of various cellulosic polymer-containing artificial saliva samples (n=3, mean±SD).

| Sample code | Polymer type | Polymer content (%) | n value | Viscosity (cP) |
|-------------|--------------|---------------------|------------|----------------|
| F1 | CMC | 0.1 | 1.215±0.23 | 20.14±0.01 |
| F2 | CMC | 0.2 | 1.261±0.21 | 28.67±0.12 |
| F3 | CMC | 0.3 | 1.357±0.21 | 36.95±0.18 |
| F4 | CMC | 0.4 | 1.281±0.11 | 45.27±0.11 |
| F5 | CMC | 0.5 | 1.231±0.19 | 52.38±0.08 |
| F6 | CMC | 0.6 | 1.184±0.27 | 60.74±0.12 |
| F7 | CMC | 0.7 | 1.285±0.17 | 72.98±0.17 |
| F8 | CMC | 0.8 | 1.352±0.25 | 89.14±0.16 |
| F9 | CMC | 0.9 | 1.421±0.10 | 92.34±0.12 |
| F10 | CMC | 1.0 | 1.479±0.24 | 118.28±0.22 |
| F11 | HPMC | 0.1 | 1.128±0.27 | 11.35±0.84 |
| F12 | HPMC | 0.2 | 1.113±0.22 | 18.21±0.09 |
| F13 | HPMC | 0.3 | 1.185±0.15 | 21.55±0.04 |
| F14 | HPMC | 0.4 | 1.247±0.24 | 25.48±0.11 |
| F15 | HPMC | 0.5 | 1.269±0.17 | 32.66±0.92 |
| F16 | HPMC | 0.6 | 1.215±0.18 | 39.45±0.08 |
| F17 | HPMC | 0.7 | 1.232±0.11 | 46.26±0.10 |
| F18 | HPMC | 0.8 | 1.268±0.12 | 51.12±0.19 |
| F19 | HPMC | 0.9 | 1.381±0.19 | 59.37±0.88 |
| F20 | HPMC | 1.0 | 1.398±0.27 | 65.05±0.05 |
| F21 | HEC | 0.1 | 1.215±0.25 | 6.65±0.25 |
| F22 | HEC | 0.2 | 1.291±0.24 | 11.25±0.12 |
| F23 | HEC | 0.3 | 1.245±0.23 | 16.35±0.78 |
| F24 | HEC | 0.4 | 1.222±0.22 | 21.85±0.28 |
| F25 | HEC | 0.5 | 1.277±0.11 | 28.31±0.25 |
| F26 | HEC | 0.6 | 1.311±0.18 | 33.18±0.18 |
| F27 | HEC | 0.7 | 1.329±0.19 | 41.17±0.09 |
| F28 | HEC | 0.8 | 1.350±0.18 | 49.65±0.03 |
| F29 | HEC | 0.9 | 1.387±0.26 | 53.27±0.09 |
| F30 | HEC | 1.0 | 1.397±0.23 | 60.47±0.12 |

were calculated. The logarithmic rheograms of typical polymer-containing samples are shown in Figures 6 and 7.

As can be seen in tables 2, 3 and 4, all the n values are above 1, confirming the presence of a pseudoplastic behavior. Among the cellulosic polymers, when used in equal amounts (0.1-1%), HPMC gave the highest viscosities followed by HEC and CMC. This difference was also statistically significance ($p < 0.05$,

ANOVA and Tukey post hoc test). Regarding the Carbomers investigated, all had statistically significant ($p < 0.05$, ANOVA) higher viscosity values than the cellulosic polymers, when used in equal amounts. This shows the superiority of Carbomers over the cellulosic polymers in term of viscosity enhancement. Among the Carbomers investigated, C974P had the highest viscosity followed by C971 and C934P. Carbomer C940 had the least viscosity. Again,

Table 3. Viscosity and pseudoplasticity indices (n values) of various Carbomer-containing artificial saliva samples (n=3, mean±SD).

| Sample code | Polymer type | Polymer content (%) | n value | Viscosity (cP) |
|-------------|--------------|---------------------|------------|----------------|
| F51 | C971 | 0.01 | 1.125±0.11 | 1.03±0.92 |
| F52 | C971 | 0.02 | 1.138±0.19 | 2.14±0.01 |
| F53 | C971 | 0.03 | 1.187±0.16 | 4.35±0.12 |
| F54 | C971 | 0.04 | 1.201±0.15 | 6.98±0.12 |
| F55 | C971 | 0.05 | 1.217±0.13 | 8.68±0.10 |
| F56 | C971 | 0.06 | 1.225±0.17 | 11.56±0.04 |
| F57 | C971 | 0.07 | 1.269±0.18 | 19.15±0.07 |
| F58 | C971 | 0.08 | 1.288±0.21 | 23.46±0.18 |
| F59 | C971 | 0.09 | 1.346±0.22 | 28.58±0.09 |
| F60 | C971 | 0.10 | 1.396±0.12 | 32.87±0.10 |
| F61 | C940 | 0.01 | 1.116±0.17 | 1.54±0.01 |
| F62 | C940 | 0.02 | 1.129±0.18 | 2.09±0.15 |
| F63 | C940 | 0.03 | 1.164±0.14 | 2.14±0.19 |
| F64 | C940 | 0.04 | 1.194±0.10 | 3.35±0.55 |
| F65 | C940 | 0.05 | 1.225±0.13 | 4.94±0.05 |
| F66 | C940 | 0.06 | 1.236±0.10 | 6.15±0.09 |
| F67 | C940 | 0.07 | 1.255±0.12 | 8.45±0.12 |
| F68 | C940 | 0.08 | 1.268±0.28 | 11.97±0.95 |
| F69 | C940 | 0.085 | 1.289±0.20 | 17.65±0.08 |
| F70 | C940 | 0.09 | 1.311±0.14 | 21.54±0.12 |

the differences observed in viscosity values were statistically significant ($p < 0.05$, ANOVA). Since the viscosity of natural saliva was found to be within a range of 12.85-28.15 cP, in here artificial saliva samples having viscosities within this range were chosen. These selected

samples have been highlighted in tables 2, 3 and 4.

Figure 8 shows a log-log plot of the changes in viscosity of the selected artificial saliva samples, as well as the natural saliva, against increasing values of SR. Natural saliva shows

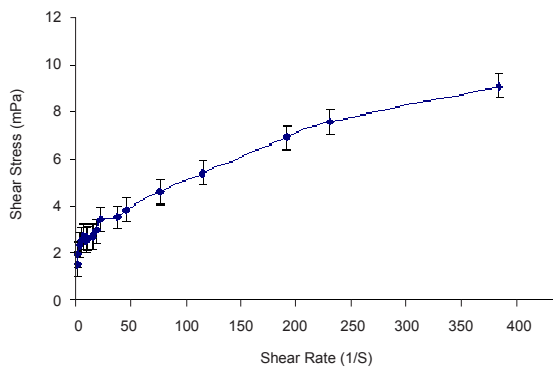


Figure 6. A typical rheogram of Carbomer-containing artificial saliva samples (n=3; data points represent mean±SD).

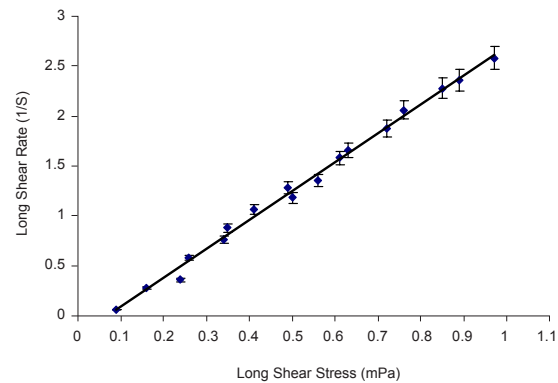


Figure 7. A typical log-log rheogram of Carbomer-containing artificial saliva samples (n=3; data points represent mean±SD).

Table 4. Viscosity and pseudoplasticity indices (n values) of various Carbomer-containing artificial saliva samples (n=3, mean±SD).

| Sample code | Polymer type | Polymer content (%) | n value | Viscosity (cP) |
|-------------|--------------|---------------------|------------|----------------|
| F51 | C971 | 0.01 | 1.125±0.11 | 1.03±0.92 |
| F52 | C971 | 0.02 | 1.138±0.19 | 2.14±0.01 |
| F53 | C971 | 0.03 | 1.187±0.16 | 4.35±0.12 |
| F54 | C971 | 0.04 | 1.201±0.15 | 6.98±0.12 |
| F55 | C971 | 0.05 | 1.217±0.13 | 8.68±0.10 |
| F56 | C971 | 0.06 | 1.225±0.17 | 11.56±0.04 |
| F57 | C971 | 0.07 | 1.269±0.18 | 19.15±0.07 |
| F58 | C971 | 0.08 | 1.288±0.21 | 23.46±0.18 |
| F59 | C971 | 0.09 | 1.346±0.22 | 28.58±0.09 |
| F60 | C971 | 0.10 | 1.396±0.12 | 32.87±0.10 |
| F61 | C940 | 0.01 | 1.116±0.17 | 1.54±0.01 |
| F62 | C940 | 0.02 | 1.129±0.18 | 2.09±0.15 |
| F63 | C940 | 0.03 | 1.164±0.14 | 2.14±0.19 |
| F64 | C940 | 0.04 | 1.194±0.10 | 3.35±0.55 |
| F65 | C940 | 0.05 | 1.225±0.13 | 4.94±0.05 |
| F66 | C940 | 0.06 | 1.236±0.10 | 6.15±0.09 |
| F67 | C940 | 0.07 | 1.255±0.12 | 8.45±0.12 |
| F68 | C940 | 0.08 | 1.268±0.28 | 11.97±0.95 |
| F69 | C940 | 0.085 | 1.289±0.20 | 17.65±0.08 |
| F70 | C940 | 0.09 | 1.311±0.14 | 21.54±0.12 |

a sharp slope, meaning that the viscosity is sharply falling. As a result, the natural saliva

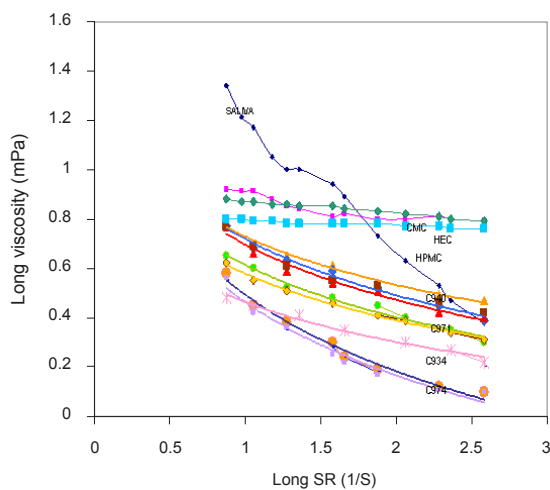


Figure 2. Log-log plot of the changes in viscosity of the selected artificial saliva samples as well as the natural saliva against increasing values of SR (n=3).

would not be able to show a great resistance against removal and dislodgment. In contrast, all the selected polymer-containing artificial saliva samples showed a far less reduction in their viscosity values. This means that the artificial saliva samples are capable of remaining in contact with the buccal mucosa for a longer period of time, as a result of possessing a greater resistance to structural breakdown and displacement. Interestingly, the slopes of viscosity changes for the Carbomers were steeper than the cellulosic polymers investigated. Hence, it is expected that the cellulosic polymers remain in contact with the buccal mucosa longer than Carbomers.

Spray- ability

All the selected polymer-containing artificial saliva samples were found to have good spray-ability and a uniform distribution over the surface of a glass tile. However, the Carbomer containing samples could be sprayed easier than

Table 5. Mean Particle sizes of the selected polymer-containing artificial saliva samples,

| Sample code | Polymer type | Number of particle counted | Range of particles counted (μm) | Mean (μm) | Skewness | Kurtosis |
|-------------|--------------|----------------------------|--|------------------------|------------------|------------------|
| F49 | C974P | 50 | 0.45-1.20 | 0.87 \pm 0.29 | -0.58 \pm 0.32 | -0.78 \pm 0.52 |
| F58 | C971 | 50 | 0.10-2.50 | 1.25 \pm 0.64 | 0.27 \pm 0.28 | 0.56 \pm 0.66 |
| F34 | C934P | 50 | 0.68-1.53 | 1.16 \pm 0.02 | -0.52 \pm 0.33 | 1.85 \pm 0.61 |
| F69 | C940 | 50 | 0.90-1.26 | 1.15 \pm 0.12 | -1.36 \pm 0.30 | 0.95 \pm 0.58 |
| F1 | CMC | 50 | 2.85-4.11 | 3.58 \pm 0.50 | -0.44 \pm 0.29 | -1.16 \pm 0.59 |
| F12 | HPMC | 50 | 1.38-2.56 | 2.11 \pm 0.23 | -0.80 \pm 0.25 | 1.44 \pm 0.60 |
| F24 | HEC | 50 | 3.33-4.25 | 3.87 \pm 0.30 | -0.87 \pm 0.31 | 0.16 \pm 0.62 |

the cellulosic polymer-containing samples. This would mean that all these samples could easily leave the container and spread over the buccal mucosa in a desirably uniform manner.

Particle size distribution

Possession of a suitable mean particle size, with a narrow distribution, would help to improve the efficacy of any spray formulation. The results obtained from this part of the study have been shown in table 5. For the selected polymers, formulation F49 (C974P) had the smallest mean particle size among all the polymers investigated, which was also found to be statistically significant ($p < 0.05$, ANOVA and Tukey post hoc test). In general, by increasing the concentration of polymer, as expected, the mean particle size also increased. For instance, C974P with concentration of 0.086% and a viscosity of 25.97 \pm 0.11 cP, resulted in a mean particle size of 0.87 \pm 0.29 μm .

Moreover, all the Carbomer-containing samples had a significantly ($p < 0.05$, ANOVA

and Tukey post hoc test) smaller particle size than the cellulosic polymers. This complies with the spray-ability findings, in which the Carbomer-containing samples could be spread easier. This means that, the resistance against break up into smaller particles is less in Carbomer-containing samples. Hence, smaller particles could be to resulted after spraying.

The skewness and kurtosis of all the selected samples were reasonably good, meaning that the particle size distribution of the samples tested is narrow. Overall, the best skewness and kurtosis were found with formulations F49 and F58, which contained C974 and C971.

Mucoadhesion

The mucoadhesive strengths of the samples examined have been shown in table 6. For the purpose of comparison, the mucoadhesive strength of natural saliva as well as the purified water have been included in this table.

Overall, C974P had the highest mucoadhesive strength among all the samples investigated,

Table 6. Mucoadhesive strength (MS) and mucoadhesivity ratios ($\text{MR}_{\text{sample/water}}$ and $\text{MR}_{\text{sample/saliva}}$) of the selected polymer-containing artificial saliva samples investigated ($n=3$, mean \pm SD).

| Sample code | Polymer type | MS (mN/cm ²) | $\text{MR}_{\text{sample/water}}$ | $\text{MR}_{\text{sample/saliva}}$ |
|----------------|--------------|--------------------------|-----------------------------------|------------------------------------|
| F1 | CMC | 27.34 \pm 0.12 | 1.12 \pm 0.43 | 1.02 \pm 0.12 |
| F12 | HPMC | 34.03 \pm 0.24 | 1.42 \pm 0.06 | 1.26 \pm 0.51 |
| F24 | HEC | 26.45 \pm 0.14 | 1.01 \pm 0.14 | 0.95 \pm 0.06 |
| F34 | C934P | 29.70 \pm 0.19 | 1.22 \pm 0.34 | 1.10 \pm 0.15 |
| F49 | C974P | 34.84 \pm 0.21 | 1.39 \pm 0.15 | 1.19 \pm 0.12 |
| F58 | C971 | 23.10 \pm 0.09 | 1.36 \pm 0.09 | 0.86 \pm 0.16 |
| F69 | C940 | 27.84 \pm 0.25 | 1.11 \pm 0.45 | 0.86 \pm 0.06 |
| Natural saliva | - | 19.13 \pm 0.09 | 0.75 \pm 0.36 | 1.00 \pm 0.0 |

being statistically significant ($p < 0.05$, ANOVA and Tukey post hoc test), having $MR_{\text{sample/saliva}}$ and $MR_{\text{sample/water}}$ values of 1.19 ± 0.12 and 1.39 ± 0.15 respectively. This means that the presence of C974P could increase the adhesive nature of the artificial saliva sample by 19%, compared to the natural saliva.

Hence, the presence of C974P could improve the adhesion of artificial saliva spray droplets on to the buccal mucosa, helping to keep them in place for a reasonable length of time. Moreover, C974P-containing artificial saliva samples could adhere stronger to the mucosal surface than the natural saliva. Following C974P, HPMC had the second highest mucoadhesive strength (MS). This was then followed by C934P, C940, CMC and HEC. The least mucoadhesive strength was found for C971. In addition, the Carbomer-containing polymers were found to have stronger mucoadhesive strengths, as well as $MR_{\text{sample/saliva}}$ and $MR_{\text{sample/water}}$ values than the cellulosic polymers CMC and HEC. Finally, all the polymers examined were capable of improving the mucoadhesive strength, when compared to the natural saliva (i.e. all the mucoadhesive polymers examined could help to keep the artificial saliva spray droplets in contact with the mucosal surface longer than the natural saliva, providing a greater efficacy and substantivity).

Conclusion

Based on this study, it seems that the presence of mucoadhesive polymers within the artificial saliva pump spray formulations could help to improve the mucosa-adhesive nature of the formulation, making it even more effective than the natural saliva. These polymers could also produce a pseudoplastic rheological behavior within the formulation, which is similar to the natural saliva. This type of rheological behavior also helps to keep the artificial saliva spray formulation in contact with the mucosal surface longer than the natural saliva. Furthermore, it provides a greater resistance against dislodgement. In fact, among all the polymers examined, C974P seems to be the most suitable polymer for the purpose of preparing artificial saliva pump

spray formulations.

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