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Research Article

Grewia Gum 2: Mucoadhesive Properties of Compacts and Gels

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Abstract

Purpose: *To compare the mucoadhesive performance of grewia polysaccharide gum with those of guar gum, carboxymethylcellulose, hydroxypropyl methylcellulose and carbopol 971P.*
Methods: *Grewia polysaccharide gum compacts or gels as well as those of guar gum, carboxymethylcellulose, hydroxypropyl methylcellulose or carbopol 971P were prepared. Texturometric and tensile analysis of the polymer gels and compacts were carried out using a software-controlled penetrometre, TA.XTPlus texture analyzer. The polymer gels were evaluated for hardness, stickiness, work of cohesion and work of adhesion. Furthermore, the detachment force of the polymer compacts from a mucin substrate was evaluated.*
Results: *The work of adhesion of guar gels was significantly greater than that of grewia gels ($p < 0.001$) but the latter showed a significantly greater work of adhesion than carboxymethylcellulose gels ($p < 0.05$) and hydroxypropyl methylcellulose gels ($p < 0.001$). However, the work of cohesion for grewia/mucin gel mixture was significantly greater ($p < 0.001$) than those of carboxymethylcellulose/mucin, hydroxypropyl methylcellulose/mucin and carbopol 971P/mucin gel blends. The difference between the mucoadhesive performance of grewia compacts and those of hydroxypropyl methylcellulose and carbopol 971P compacts was insignificant ($p > 0.05$).*
Conclusion: *Grewia polysaccharide gum demonstrated good mucoadhesive properties, comparable to those of carbopol 971P, carboxymethylcellulose, guar gum and hydroxypropyl methylcellulose, and therefore, should be suitable for the formulation of retentive drug delivery devices.*

Keywords*: Grewia polysaccharide gum, Texture analyzer, Mucoadhesive performance, Work of cohesion/adhesion.*

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INTRODUCTION

Bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time [1]. When applied to mucosal epithelia, a bioadhesive polymer may adhere primarily to the mucus layer by a phenomenon known as mucoadhesion [2]. Mucoadhesive delivery systems have been proposed as effective dosage forms for controlled delivery of various drugs via buccal, ocular, rectal, vaginal, nasal, and sublingual routes [1,2]. Where such polymers are used in eye, nose, vaginal, buccal and rectal formulations, they may also be suitable for oral controlled delivery [3]. Tragacanth, a plant gum, has been used as a bioadhesive polymer to promote dosage form residence time as well as to improve intimacy of contact with various absorptive surfaces of biological systems [3].

Several approaches have been used to evaluate *in vitro* interaction between mucin and mucoadhesive systems and for measuring the mucoadhesive potential of candidate delivery platforms [2]. One such approach is to determine the adhesive strength between the polymer and the attached substrate. This can be determined by measuring the force required to detach one entity from the other through the application of an external force in the form of a shearing, tensile or peeling force. A number of these techniques have been reported [4].

A new technique for mucoadhesion testing using the TA.XT2 texture analyzer and porcine stomach tissue has been validated [5]. The use of the technique provides a more advanced and accurate method for evaluating the mucoadhesive properties of materials. The effect of various instrumental parameters on candidate mucoadhesive polymers has been studied [6] and the results indicate that variables such as contact force, contact time and the speed of removal of the probe from the mucosal tissue can influence the mucoadhesive performance of a system.

Grewia polysaccharide gum is obtained by extraction from the pulverized inner stem bark of the plant *Grewia mollis* Juss, (Family, Tiliaceae). The gum has been characterized for its physicochemical properties [7,8]. The mechanical properties of grewia gum tablets have also been reported [9]. Although the potential of grewia gum as a bioadhesive excipient has also been reported [10,11], a systematic comparison of the mucoadhesive performance of the gum itself (compact or gel) with other well known agents such as guar gum, carboxymethylcellulose (CMC), hydroxypropyl methylcellulose (HPMC) and carbopol 971P (CBP 971P) has, to the best of our knowledge, not been carried out. Therefore, the objective of this study was to use a texture analyzer to evaluate and compare the mucoadhesive performance of grewia polysaccharide gum with those of CBP 971P, HPMC, CMC and guar gum in terms of gel/mucin interaction and compact/mucin adhesion.

EXPERIMENTAL

Materials

Carbopol 971P (Noveon) was a gift from Lubrizol Advanced Materials, Cleveland, USA. Mucin from porcine stomach type II and guar gum were procured from Sigma-Aldrich, UK). HPMC (Methocel® - K100 premium LVCR) was a gift from Colorcon, Dartford Kent, UK. CMC (Blanose® – Type 7M1F-PHARM) was a gift from Aqualon, Wilmington, USA. Grewia polysaccharide gum was extracted and air-dried as reported [8].

Extraction and purification of grewia polysaccharide gum

Grewia polysaccharide gum was extracted as detailed previously [8]. Briefly, the dried and pulverized inner stem bark of *Grewia mollis* shrub (2000 g) was dispersed in 0.1 %w/v sodium metabisulphite and allowed to hydrate for 48 h. The mixture was then stirred for 2 h and passed through muslin to

remove extraneous solid matter. The filtrate was treated with 20 mL of 0.1M NaOH to precipitate and isolate alkali insoluble impurities, and centrifuged at 3,000 rpm for 10 min. The supernatant was then treated with acidified ethanol, (containing 10 mL of 0.1M HCl) to isolate acid insoluble impurities, and centrifuged again as described above. The supernatant was treated with absolute ethanol and the resultant precipitate washed several times until only clear absolute ethanol was recovered. The precipitate was wet-milled and then passed through muslin before air-drying the product. The air-dried product was dry-milled before further drying at 50 ^{o}C in an oven for 24 h.

Preparation of polymer compacts

The polymer (300 mg), in each case, was compressed on a KBr press by the application of 2 ton load for 2 min. The compact diameter was 13 mm providing a theoretical surface contact area of 1.33 cm^2. Given the possibility of different surface porosities between the top and bottom surfaces, the same surface (bottom) of the compressed polymer discs was used in all mucoadhesion experiments.

Preparation of polymer gels, polymer/ mucin gels and mucin gels

The gels (3 %w/w) of the polymers - carbopol 971P, HPMC, CMC, guar gum and grewia polysaccharide gum - were prepared by dispersing the polymer in distilled water with the aid of a paddle stirrer mixer for 10 min. The gel samples were left to hydrate for 24 h and then centrifuged at 3000 rpm for 10 min to remove trapped air. Gel mixtures of polymer/mucin were prepared by mixing 10 g of mucin with 100 ml of 3 %w/w dispersion of polymer and allowed to hydrate for 12 h. All samples containing mucin were stored at 4 ^{o}C pending use. Mucin gel was prepared by dispersing mucin powder in distilled water to give 10 or 30 % w/w dispersion. Prior to evaluation of mucoadhesion, the viscosity of the gels was measured using a Brookfield viscometer (DV-1+version 5, Brookfield Engineering Labs, USA).

Texture analysis of polymer gels

Mucoadhesive studies were carried out on the polymer gels, 10 % mucin gel and compacts according to the methods of Tamburic and Craig [12], with slight modification, using a software-controlled penetrometer, TA.XTPlus texture analyzer (Stable MicroSystems, UK), equipped with a 5 kg load cell and 10 mm plastic cylindrical probe. The resistance to penetration and withdrawal of the probe was measured at a pre-test speed of 2 mm/s, test speed of 1 mm/s, post-test speed of 10 mm/s and acquisition rate of 100 points/s. The penetration depth of the probe into the gel was fixed at 5 mm. Trigger type was set to auto-0.01g while tare mode was set to auto with the option of return to start. Approximately 0.2 mL of 30 % mucin gel was uniformly spread over the probe which was then brought into contact with the polymer gel and held for 60 s.

Tensile analysis of polymer compacts

The polymer compacts were fixed to the lower platform of the texture analyzer with a contact adhesive. The compact was first wetted with 0.1 ml of distilled water and left to hydrate for 1 min prior to measurement. A contact force of 0.5 N was applied for 60 s upon contact of the surface of the compact with the mucin-covered probe (20 mm aluminium cylinder). Other settings for the detachment force measurements were pretest speed, 1 mm/s; test speed, 0.5 mm/s; post-test speed, 10 mm/s; and acquisition rate, 500 points/s.

Statistical analysis

The data were subjected to one-way ANOVA at 95 % confidence interval using Instat software (GraphPad, San Diego, CA, USA).

RESULTS

Tensile properties of polymer compacts

Figure 1 shows the detachment profiles of the polymer compacts. Guar gum compacts were too fragile to withstand the 0.5 N contact force applied by the texture analyzer. The detachment force is represented by the negative force on the force-time or force-distance profile. The positive horizontal line on the force-time profile (not shown) shows the application of contact force of 0.5 N for 60 s. Thereafter the probe was withdrawn and the amount of force required to detach the mucin covered probe from the polymer compact is displayed as a profile of force against time or distance.

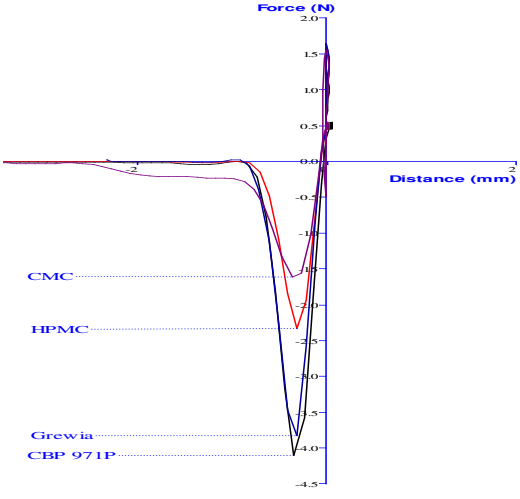

Figure 1: Detachment force profile of force versus distance for polymer compacts

The work of adhesion to the mucin-covered 20 mm aluminium cylinder probe was 1.45 ± 0.26, 1.23 ± 0.26, 0.93 ± 0.28 and 0.64 ± 0.24 Nmm for CBP 971P, grewia gum, HPMC and CMC, respectively.

There were no significant differences (p < 0.05) between the mucoadhesive performance of grewia compacts and those of HPMC and CBP 971P compacts (Fig 1). Grewia compacts had significantly greater mucoadhesive performance (p < 0.05) than CMC compacts.

Texture analysis of polymer gels

Figure 2*a* presents the penetration/ withdrawal profiles of the individual polymer gels (3 %w/w) while the penetration/ withdrawal profiles of the polymer/mucin mixtures are shown in Figure 2*b*. At time 0, the 10 mm plastic cylindrical probe touched the surface of the sample and progressed to a depth of 5 mm inside the gel system at a speed of 1 mm/s. The Fig also shows a sharp drop in the positive profile as the probe is withdrawn from the sample at a speed of 10 mm/s. The resistance to penetration of the gel by the probe is recorded as resistance force (+ peak) and the work performed (+ area) along with the withdrawal parameters (- peak and - area). The value of the positive area (+ area) and of the negative area (-area) corresponds to the work of cohesion of the sample and the work of adhesion to the probe, respectively, while the values of the positive (+) peak and of the negative (-) peaks correspond to hardness and stickiness (or adhesiveness) of the sample, respectively. The values of the positive area (cohesive work) and positive peak (cohesiveness or hardness) and the percent increase for all the samples are shown in Tables 1. The corresponding values for the work of adhesion (- area) and maximum adhesiveness or stickiness (- peak) are shown in Table 2.

The effect of polymer interaction with mucin on the viscosity of the polymer gels is shown in Figure 3. Guar gel showed the highest resistance to penetration. At 3 %w/w, the dispersion of guar gum exhibited the highest viscosity of the polymers studied (Fig. 3). The work of cohesion for guar and CBP 971P gels were significantly higher than that for grewia gel (p< 0.001 and 0.01, respectively) while the work of cohesion of grewia gel was not significantly different from that of HPMC or CMC gel (p > 0.05). However, the interaction

Table 1: Increase in work of cohesion (positive area under the penetration/withdrawal curve) and increase in maximum cohesive force or hardness (positive peak of the penetration/withdrawal curve) (mean ± s.d., n = 10)

Gel	+ Area (N.s) polymer gel ($x10^{-2}$)	+ Area (N.s) polymer/ mucin mixture ($x10^{-2}$)	Change (%)	+ peak (N) polymer gel ($x10^{-2}$)	+ peak (N) polymer mucin mixture ($x10^{-2}$)	Change (%)
CBP 971P	5.4±0.010	1.4±0.001	-74.1	3.4±0.004	0.9±0.000	-72.1
CMC	1.4±0.001	2.3±0.010	64.3	0.9±0.001	1.6±0.003	70.2
HPMC	1.5±0.001	2.0±0.001	33.3	0.9±0.001	1.3±0.000	41.3
Guar	29.3±0.040	9.1±0.010	-68.9	19.2±0.020	5.6±0.004	-70.8
Grewia	2.5±0.001	3.9±0.002	56.0	1.7±0.001	2.6±0.001	56.7
Mucin	1.6±0.001	1.6±0.001	0.0	1.3±0.001	1.3±0.001	0.0

Table 2: Change in work of adhesion (negative area under the penetration/withdrawal curve) and change in maximum adhesive force or stickiness (negative peak of the penetration/withdrawal curve) (mean ± s.d., n = 10)

Polymer	- Area (N.s) polymer gel ($x10^{-2}$)	- Area (N.s) polymer mucin mixture ($x10^{-2}$)	Change (%)	- peak (N) polymer gel ($x10^{-2}$)	- peak (N) polymer mucin mixture ($x10^{-2}$)	Change (%)
CBP 971P	1.3±0.002	0.3±0.001	-77.4	2.5±0.002	0.6±0.000	-74.8
CMC	0.2±0.001	1.6±0.010	700.0	0.6±0.001	2.2±0.007	266.0
HPMC	0.2±0.001	1.5±0.002	572.7	0.6±0.001	1.9±0.001	202.7
Guar	5.6±0.010	4.4±0.003	-21.4	15.5±0.011	7.0±0.003	-54.6
Grewia	0.9±0.002	1.9±0.003	107.8	1.5±0.000	2.9±0.001	93.3
Mucin	0.2±0.001	0.2±0.001	0.0	0.6±0.000	0.6±0.000	0.0

between mucin and polymer gels resulted in a higher work of cohesion for the grewia/ mucin gel mixture, significantly higher than CMC/mucin, HPMC/mucin and CBP 971P/mucin gel mixtures ($P < 0.001$). Although there was a decrease in the work of cohesion when guar gel was mixed with mucin, the resultant mixture still had a work of cohesion higher than all the other polymer/mucin gel mixtures ($P<0.001$). Similar results were obtained for the maximum cohesive forces for polymer gels and polymer/mucin gel mixtures (Table 1).

Table 2 shows the effect of interaction of the polymers with mucin on the adhesiveness (stickiness) and work of adhesion of the polymer gels. The data indicate that grewia performed similarly to CBP 971P ($p > 0.05$). However, the work of adhesion of guar gum was significantly greater than that of grewia gel ($p < 0.001$) which in turn was significantly greater than those of CMC ($p < 0.05$) and HPMC ($p < 0.001$). Thus, the rank order of work of adhesion is guar gum > CBP 971P = grewia > HPMC = CMC. Interaction with mucin also resulted in decreased work of adhesion for CBP 971P/mucin and guar/mucin gels while also leading to increased work of adhesion for grewia/mucin, CMC/mucin and HPMC/mucin gel. Hence, the work of adhesion of grewia/mucin gels

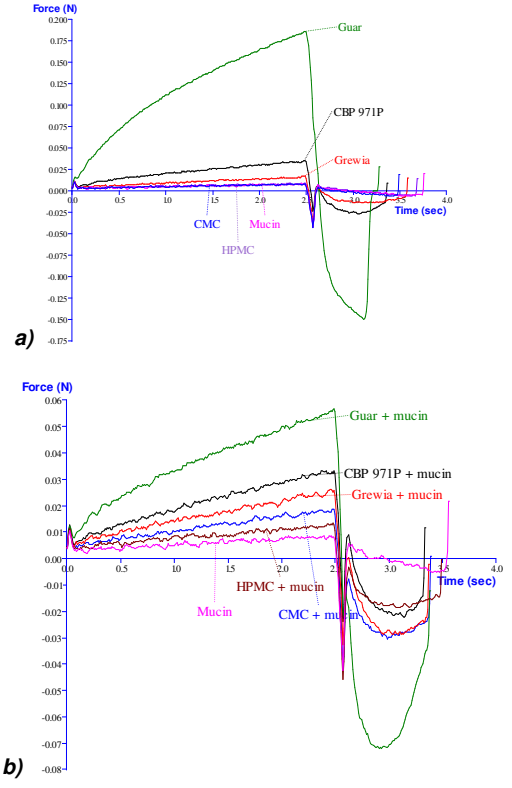

Figure 2: *a)* Penetration/withdrawal profiles obtained by texture analyzer for polymer and mucin gels; *b)* Penetration/withdrawal profiles obtained by texture analyzer for the polymer/mucin mixtures and mucin gel

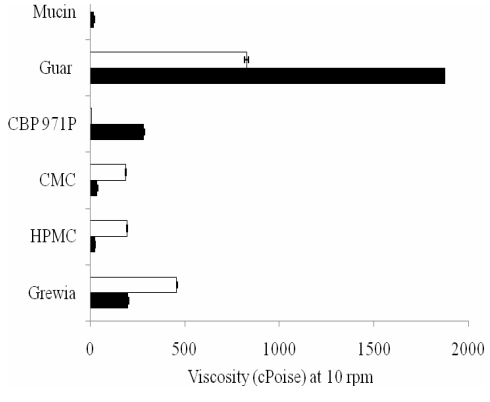

Figure 3: Effect of mucin-polymer interaction on the viscosity of = 3 %w/w polymer gel (■); and 3 % w/w polymer gel + mucin (□) dispersion (n = 5).

was significantly higher ($p < 0.001$) than that of CBP 971P/mucin gel. There was no significant difference between the work of adhesion of grewia/mucin, CMC/mucin and HPMC/mucin gels. Thus, the rank order of work of adhesion is guar gum > grewia gum = HPMC = CMC > CBP 971P. As was the case with work of cohesion, work of adhesion of guar/mucin gel was higher than that of grewia/mucin gel although interaction of guar gum with mucin resulted in a decrease of 21.4 %.

As Table 2 shows, the rank order of maximum adhesive force (stickiness) of the polymer gels is guar > CBP 971P > grewia > HPMC = CMC. Guar gum and CBP 971P gels were significantly more adhesive ($p < 0.001$) than grewia gum gels which in turn was significantly greater ($P < 0.01$) than HPMC or CMC. Following interaction of the polymer gels with mucin, adhesiveness (stickiness) of CMC and HPMC remained unchanged ($p > 0.05$) while that of CBP 971P decreased by 74.8 %. The adhesiveness of grewia gel remained significantly greater ($p < 0.001$) than those of HPMC and CMC.

The effect of the polymer interaction with mucin on polymer gel viscosity is displayed in Fig 3 and it also shows the relationship between work of cohesion and viscosity of the gels. The interaction with mucin lowered the viscosity of guar and CBP 971P gels but enhanced the viscosity of CMC, HPMC and grewia polysaccharide gels. Similar findings in respect of CBP 971P/mucin gels have previously been reported [12].

DISCUSSION

Tensile tests on polymer compacts

Detachment force studies have been used as a direct measure of mucoadhesivity or mucoadhesive performance of a material [13]. This parameter measures the force required to separate the surface of a mucoadhesive material from that of the mucoadhesive substrate.

If cohesive forces within the mucus gel are generally stronger than the adhesive forces between mucoadhesive material and mucus, then fracture will tend to occur at the adhesion interface. However, fracture may occur within the mucus gel or within the polymer compact itself, if cohesive forces are weaker than mucoadhesive forces [14]. This latter situation would tend to give rise to artificially low detachment force and accounts for the low work of adhesion measured for CMC compacts. This is shown by broad detachment profile (Fig 1). Rupture might have occurred within the CMC compacts resulting in the low detachment forces observed. The surfaces of grewia compacts were visibly rougher than those of HPMC and CBP 971P compacts and this would impact on adhesion to the mucin-covered probe. This is because tissue surface roughness is an important factor for mucoadhesion and rough polymer surfaces may favour more intimate contact between mucin and polymer than smooth polymer surfaces [3].

The work of adhesion of grewia gum to the mucin covered probe was the same as that of HPMC or CBP ($p > 0.05$), implying comparable mucoadhesive potentials.

Texture analysis of polymer gels

Texture analysis, a penetrometry technique often used in mechanical characterization of food materials, has emerged as a useful tool for pharmaceutical gel characterization [15,16]. The technique reported by Jones *et al*. [5] was used in this study to evaluate the mucoadhesive performance of the polymer gels and polymer/mucin mixtures.

The main physical mechanism of mucoadhesion is chain flexibility, with flexible polymer chains favouring interpenetration between polymer chains and mucus to a depth sufficient to create a strong adhesive bond [17]. Consequently, cross-linking (the formation of covalent bonds between chains) or covalent attachment of large sized ligands may lead to a reduction in chain flexibility and hence a decrease in mucoadhesion. Carbopol 971P is cross-linked with allyl pentaerythritol and polymerized in ethyl acetate. This may explain the decrease in work of adhesion observed for carbopol 971P and guar gum.

The viscosity of polymer/mucin mixtures increases with increasing molecular mass [18] and shorter chain length polymers with inherent poor gel forming properties are less effective in promoting gel strengthening [19]. The much higher viscosities of grewia/mucin, CMC/mucin and HPMC/mucin gel mixtures are attributable to the formation of bonds between the polymer and mucin. The type or nature of bond formed depends on the polymer type or the inherent functional groups present. The formation of disulphide bonds which are covalent in nature have been reported to be accountable for the enhanced mucoadhesive properties of thiomers such as carbopol 971P [20]. Earlier, Mortazavi and Smart reported the formation of hydrogen bonds between polymer and mucus as essential for the mucoadhesion process [19]. The possession of hydroxyl and carboxyl functional groups by grewia gum [8] would enhance formation of hydrogen bonds between the gum and mucus, and may be responsible for the good mucoadhesive performance of grewia gum. The good mucoadhesive performance of HPMC and guar may also be attributed to the same factor (presence of hydroxyl and carboxyl groups).

CONCLUSION

Carbopol 971P, guar gum, CMC and HPMC are considered to have excellent mucoadhesive performance as both gels and compacts [20]. The results from the present study suggest that grewia gum, a high molecular weight polymer that hydrates in water over time to form highly viscous dispersions, possesses good mucoadhesive performance comparable to those of carbopol 971P, CMC, guar and HPMC. Further studies will be required to develop and standardize

the material for actual application in the formulation of dosage forms

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