Original Article

Preliminary investigation of *in-vitro* bioadhesive properties of selected natural gums

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ABSTRACT

Objective: The aim was to investigate the suitability of hydrophilic natural gums, namely – konjac glucomannan gum (KG), Tara gallactomannan gum (TG) andxanthan gum (XG); and their combination, as bioadhesive polymers.
Materials and Methods: Bioadhesive strength of the gums and their combination was investigated using texture analyzer employing chicken pouch as biological membrane.
Results: It was observed that the bioadhesive strength was enhanced by the increase in contact time between the tablets under test and biological membrane. Different gums and their combination produced significantly different bioadhesive strength, and were ranked in the order of: XG > KG40H > KG40H + XG > KG32H > KG32H + XG + TG > KG32H + XG > XG + TG > KG40H + XG + TG.
Conclusions: From these preliminary studies, it can be concluded that KG and XG are capable to be employed as bioadhesive polymers in drug delivery systems and chicken pouch an easily available, having uniform surface thus producing reproducible results, can be used as model mucosa.

Key words: Bioadhesion, chicken pouch, konjac glucomannan gum, Tara gallactomannan gum, xanthan gum

INTRODUCTION

Bioadhesion is, where two surfaces, one of which is a mucous membrane and the other synthetic or biological macromolecules, adhere to each other. This has been of interest in the pharmaceutical sciences in order to enhance localized drug delivery, or to deliver difficult molecules (proteins and oligonucleotides) into the systemic circulation. Bioadhesive drug delivery, a vital route of drug administration, has been extensively reviewed by many researchers.[1-3] Since, bioadhesion can prolong the residence time of dosage form at the absorption site, better drug absorption can be attained. Khutoryanskiy elaborated the history of bioadhesive drug delivery system in his review article.[1] Sticking of any drug dosage form to the biological membranes, in the gastrointestinal tract or any other body cavity, can be described as bioadhesion and/or mucoadhesion. The occurrence of the interaction between polymer and epithelial surface is generally referred as bioadhesion. The same interaction when occurs with the mucus layer of the biological membrane, is referred as mucoadhesion. In general, bioadhesion is deeper than mucoadhesion, although these two terms are used interchangeably.[4] Different bioadhesive mucosal dosage forms have been developed, such as adhesive tablets,[5,6] microspheres,[7] mucoadhesive nanoparticles,[8] gels,[9] ointments,[9] mucoadhesive liposomes,[10] patches,[11] and films.[12,13]

Many polymers, particularly hydrophilic polymers have been examined for bioadhesive properties. A bioadhesive material is defined as a substance that is capable of interacting with biological materials and being retained on them or holding them together for an extended period.[14] The goal of the development of bioadhesive material is to duplicate, mimic or improve biological adhesion. It should be durable at application site, degradable, and nontoxic.[15] Some of the commonly used polymers for mucoadhesive drug delivery systems

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are cellulose derivatives, carbomer and polycarbophil, sodium alginate, chitosan, and pectin.

For successful application of bioadhesive drug delivery systems, the adhesive strength determination is essential. Various methods have been developed to determine the *in-vitro* bioadhesive strength. Some of these included adhesion weight method,[16] Wilhelmy plate method,[17] fluorescent probe method,[18] the texture analyzer method,[19] flow channel techniques,[20] tensile testing method,[21] and colloidal gold staining method.[22] Texture analyzer method has gained popularity among the researchers and has been used as a routine quality control tool in the development of bioadhesive delivery systems.

Different animal tissues have been used as model membranes. These include rat intestine,[23] rabbit stomach,[12] bovine sublingual mucosa,[7] porcine buccal mucosa,[24] sheep buccal mucosa,[25] and porcine gastric mucosa.[26] The use of chicken pouch[11,27,28] and cow intestine[27] as biological membrane has been reported.

In this study, cheap and easily available mucosal membrane, chicken pouch having a nonkeratinized and uniform surface morphology, was used in bioadhesive strength measurement.

The aim of this study was to investigate the bioadhesive properties of three selected natural gums, namely - konjac glucomannan gum (KG), Tara galactomannan gum (TG), and xanthan gum (XG). The gums were evaluated alone and in different combinations. Binary and ternary combinations were made in order to check if there is any synergism effect. The bioadhesion test was performed to measure the adhesive strength of the natural gums to the mucosa. KG is a water soluble hydrocolloid, forming a highly viscous solution with a pH between 5.0 and 7.0. It fulfills most of the factors required for an ideal bioadhesive polymer, which makes it a suitable candidate as a bioadhesive polymer.[29] TG has the ability to form viscous hydrogel on contact with an aqueous medium, and thus help in mucoadhesion. XG has been used to increase the bioadhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems.[30,31]

MATERIALS AND METHODS

Materials

Konjac gum 32H (KG32H) (viscosity grade: 32,000 mPa s for 1% solution at 30°C) and KG40H (viscosity grade: 40,000 mPa s for 1% solution at 30°C) were gift from Hubei Yizhi Konjac Biotechnology Co., Ltd., China. XG was purchased from Deosen Biochemicals Ltd., China. TG was a gift from Silvateam, California, USA. All other chemicals and materials were used as received.

Tablet preparation

Tablets were prepared of pure KG32H, KG40H, TG, XG and their combinations. In case of binary combination (1:1) of each gum and for ternary combination (1:1:1) of each gum was carefully weighed, passed through 60 mesh size sieve, thoroughly mixed in KENWOOD (KM010, UK) mixer and then compressed using a single punch tableting machine (Korsch-Berlin, Germany) with 10 mm flat round punches. Each tablet was having 300 mg average weight, and a constant compression force of 80 kN was employed.

Determination of weight uniformity

Ten tablets from each natural gum were evaluated. Each tablet was weighed individually using an analytical balance (A-160, Denver Instrument Company, Colorado, USA) and then the average weight per tablet was determined. The weight variation of each tablet against the average value was calculated.

Determination of hardness

The hardness of 10 tablets was examined using Tablet Hardness Tester (Model YD-2, Vanguard Pharmaceutical Machinery Inc., USA). The point of fracture of the tablet was taken as the crushing strength or hardness value of the tablets.

Determination of thickness

The thickness was determined using a digital Vernier caliper (Mitutoyo, Japan). Ten individual tablets of each formulation were used for the determination.

Determination of friability

Ten tablets were weighed and placed into a tablet friability tester (Model CS-1, Vanguard Pharmaceutical Machinery Inc., USA). The samples underwent 25 rotations/min, for 4 min, and were then re-weighed. This process was repeated for all formulations and the percentage friability value was calculated using the equation below.

$$\text{Friability } (\%) = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100 \quad (1)$$

The lot of tablets that loses < 1% of the original weight is considered acceptable British Pharmacopoeia, 2010.[32]

Biological membrane treatment

The biological membrane, chicken pouch was obtained from a local slaughter house and transported in cold normal saline solution. The inverted surfaces of the biological membranes were frozen at − 20°C in normal saline after cleaning, washing and removal of its contents and fats. The biological membranes were thawed to room temperature before use. The tissues were rinsed with distilled water and mounted onto a mucoadhesive test rig. Distilled water of 250 µL was pipetted onto the surface of the biological tissue before the commencement of the experiment to standardize the hydration of the mucosa.

Bioadhesive strength measurement

The bioadhesive strength of the tablets was measured using Texture Analyser (TA.XTPlus, Stable Micro Systems, Haslemere, Surrey, UK), with a 5 kg load cell and equipped with mucoadhesive test rig. The preserved biological membranes were thawed to room temperature before use. Distilled water of 250 µL was pipetted onto the surface of the biological tissue before the commencement of the experiment to standardize the hydration of the mucosa. The tablet was attached to the underside of the upper cylindrical probe with double-sided adhesive tape. The probe was lowered onto the surface of the tissue at a constant speed of 0.5 mm/s and contact force of 0.5 N. These values for contact force and probe withdrawal speed were chosen based on the previous work done by Wong *et al.* 1999[28] After remaining in contact for 300 s, the probe was then removed vertically upwards at a constant speed of 0.5 mm/s to a distance of 15 mm. Work of adhesion (WOA) (mJ/cm^2) and peak detachment force (PDF) (N/cm^2) were calculated from force–distance plot using Texture Exponent 32 version 1.0.0.6.8 beta software package of the instrument. For each polymer, measurements were repeated 3 times. All readings were taken at a room temperature of 28°C and relative humidity of 60–70%.

Effect of contact time on bioadhesive strength

The effect of contact time on bioadhesive strength of natural gums was investigated using chicken pouch as a biological membrane. For this part of study XG, due to its preestablished bioadhesive properties,[30,31] was preferred over the other two gums. Seven different time points of 60, 120, 180, 300, 420, 540, and 660 s were employed. The setup of the texture analyzer instrument was same as described earlier, with a probe speed of 0.5 mm/s and a contact force of 0.5 N.

Statistical analysis

Work of adhesion and PDF results were analyzed using one-way analysis of variance. Whenever, a statistically significant difference ($P < 0.05$) was obtained, Tukey-honestly significant difference (HSD) test was then performed. Statistical Procedure for Social Sciences (SPSS) software (version 16, SPSS Inc., USA) was used for the statistical analyses.

RESULTS AND DISCUSSION

Evaluation of physical properties of the adhesive tablets

Some physical tests were performed on the tablets before the bioadhesive strength measurements. These tests are crucial as they can affect the bioadhesive strength measurement. The results of weight, thickness, hardness and friability are summarized in Table 1. XG tablets are of highest hardness and lowest friability values, followed by binary combination of XG + KG and then KG alone. Conversely, TG demonstrated poor compressibility and tablets prepared were low in hardness. The tablet was friable and ruptured during friability study. The friability result of TG tablet was not presented in Table 1. When used in combination with other gums TG negatively affects the hardness and friability of XG and KG as evident from the results of binary and ternary combinations of TG.

Measurement of *in-vitro* bioadhesive strength of natural gums

Peak detachment force and WOA are the two parameters that are used for bioadhesive strength measurement. WOA was reported to be more consistent and precise predictor of bioadhesion.[28,33] The WOA is the area under the force–distance curve while, PDF is

Table 1: Physical tests of tablets prepared from KG, XG, and TG and their combination (mean±SD, *n*=10)

Natural gums	Weight (g)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
KG32H	299±0.07	3.03±0.01	16.40±0.55	0.49
KG40H	303±0.05	3.01±0.06	15.48±1.23	0.39
XG	303±0.06	2.95±0.05	19.39±0.51	0.06
TG	299±0.08	3.25±0.12	1.97±0.54	-
KG32H+XG	304±0.06	2.89±0.01	17.30±2.00	0.42
KG40H+XG	300±0.07	2.81±0.06	17.78±0.94	0.44
KG32H+TG	303±0.08	3.16±0.04	2.08±0.49	2.64
KG40H+TG	298±0.09	3.18±0.05	2.02±0.56	2.49
XG+TG	302±0.06	3.17±0.05	5.18±0.35	0.80
KG32H+XG+TG	296±0.05	2.98±0.05	4.93±0.53	0.76
KG40H+XG+TG	303±0.07	3.10±0.05	4.86±0.51	0.75

KG=Konjac glucomannan gum, XG=Xanthan gum, TG=Tara gallactomannan gum, SD=Standard deviation

the maximum force required for detaching the dosage form from the biological membrane.[13]

Table 2 shows the results of WOA, PDF and the statistical analysis results of individual natural gum and their combination. It could be observed from Table 2 that XG and KG40H exhibited comparatively higher WOA and PDF than the others.

The mean WOA results of KG32H, KG40H, XG, KG32H/XG (KG32H + XG), KG40H/XG (KG40H + XG), XG/TG (XG + TG), KG32H/XG/TG (KG32H + XG + TG) and KG40H/XG/TG (KG40H + XG + TG) were 1.64 ± 0.24, 4.26 ± 1.28, 5.57 ± 1.23, 1.16 ± 0.25, 1.65 ± 0.36, 1.10 ± 0.73, 1.33 ± 0.32, and 0.93 ± 0.28 mJ. XG was found to demonstrate the highest WOA, followed by KG40H, KG40H/XG (KG40H + XG), KG32H, KG32H/XG/TG (KG32H + XG + TG), KG32H/XG (KG32H + XG), XG/TG (XG + TG), and finally KG40H/XG/TG (KG40H + XG + TG).

On the other hand, when the PDF was used for comparison, the trend was similar, except XG and KG40H. XG recorded a higher WOA but slightly lower PDF when compared with KG40H. The mean PDF results of KG32H, KG40H, XG, KG32H + XG, KG40H + XG, XG + TG, KG32H + XG + TG and KG40H + XG + TG were 2.71 ± 0.54, 3.51 ± 0.21, 3.50 ± 0.12, 2.77 ± 0.49, 3.38 ± 0.15, 2.84 ± 0.51, 3.12 ± 0.16, and 2.12 ± 0.41 N.

When the WOA as well as PDF results of the various natural gums were compared, and analyzed statistically, the difference in the values was found to be significant ($P < 0.05$). Tukey-HSD test showed that the bioadhesive values between XG and KG40H were not significantly different but were significantly higher than the rest of natural gums in pairwise comparison. The bioadhesive strength of all other gums and their combination was not significantly different. Figures 1 and 2 are

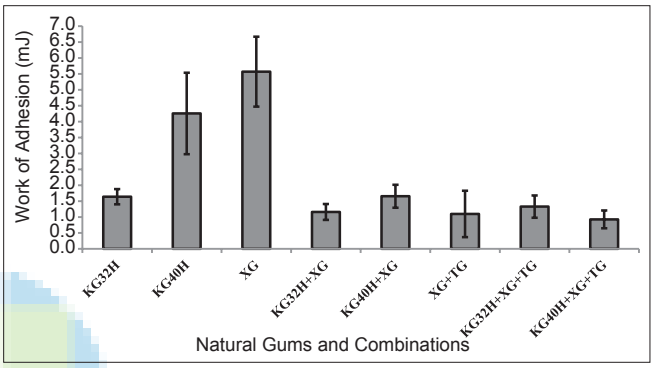

Figure 1: Work of adhesion of natural gums and their combination. Mean ± standard deviation, *n* = 3

Table 2: Bioadhesive strength measurement of tablets prepared from different natural gums and their combination (mean±SD, *n*=3)

Natural gums	Chicken pouch	
	Work of adhesion (mJ)	Peak detachment force (*n*)
KG32H	1.64±0.24	2.71±0.49
KG40H	4.26±1.28	3.51±0.19
XG	5.57±1.23	3.50±0.11
KG32H+XG	1.16±0.25	2.77±0.44
KG40H+XG	1.65±0.36	3.38±0.14
XG+TG	1.10±0.73	2.84±0.46
KG32H+XG+TG	1.33±0.35	3.12±0.15
KG40H+XG+TG	0.93±0.28	2.12±0.36
Statistical significance	*P*<0.05	*P*<0.05
Tukey-HSD (multiple comparison)	KG32H and KG40H (*P*<0.007)	KG40H and KG40H+XG+TG (*P*<0.005)
	KG32H and XG (*P*<0.001)	XG and KG40H+XG+TG (*P*<0.006)
	KG40H and KG32H+XG (*P*<0.002)	KG40H+XG and KG40H+XG+TG (*P*<0.012)
	KG40H and KG40H+XG (*P*<0.008)	
	KG40H and XG+TG (*P*<0.001)	
	KG40H and KG32H+XG+TG (*P*<0.003)	
	KG40H and KG40H+XG+TG (*P*<0.001)	
	XG and KG32H+XG (*P*<0.001)	
	XG and KG40H+XG (*P*<0.001)	
	XG and XG+TG (*P*<0.001)	
	XG and KG32H+XG+TG (*P*<0.001)	
	XG and KG40H+XG+TG (*P*<0.001)	

SD=Standard deviation, XG=Xanthan gum, KG=Konjac glucomannan gum, TG=Tara gum, HSD=Honestly significant difference

the graphical presentations of the data of the WOA and PDF.

According to Sudhakar *et al.*,[4] there are some basic properties which a bioadhesive polymer must possess to show a good mucoadhesive profile. These properties are high molecular weight up to 100,000 Da and above, optimum pH, polymer chain flexibility, spatial conformation (molecular arrangement of a polymer), optimum concentration of polymer, optimum cross-linked density of polymer, charge and degree of ionization of polymer, optimum hydration of polymer, certain contact force[28] and duration of its application and high initial contact time.

The average molecular weight values of KG, XG, and TG, are about 1,320,000 Da,[34] 2,000,000 Da,[35] and 600,000 Da[36] respectively. XG exhibits the highest molecular weight, followed by KG and lastly TG. In the present study, molecular weight of the natural gums could be the determining factor affecting the bioadhesion strength. This finding is in agreement with Huntsberger.[37] He reported that adhesive strength increased as the molecular weight of adhesive polymer increased. Tobyn[38] also found that the molecular weight of the polyacrylic acid crucially influenced the work of detachment between the polymer and pig gastric tissue. Increase in molecular weight of polymer led to an increase in the internal cohesion of the molecules, which augmented the mucoadhesion.

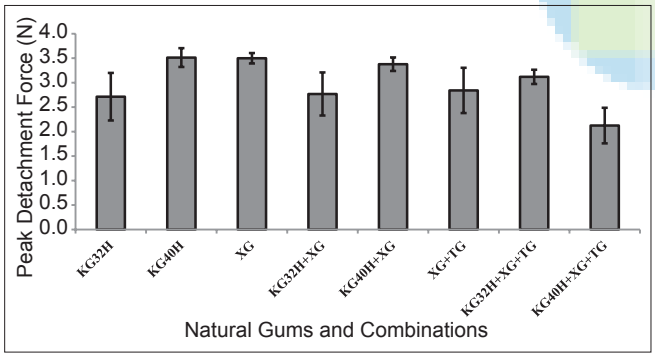

Figure 2: Peak detachment force results of natural gums and their combination. Mean ± standard deviation, *n* = 3

Among the three polymers studied, XG produced the highest bioadhesion. This could be attributed to its high molecular weight, high swellability rate and wetting properties that contributed to the strong entanglement and interpenetration with biological membrane. The swelling properties of bioadhesive polymers were reported to be crucial for bioadhesivness.[8]

Konjac gum, which is naturally acetylated, nonionic, high molecular weight (~1,320,000), having highest viscosity (40,000 mPa s [1% solution at 30°C]) among the natural gums and is water soluble hydrocolloid. Soluble in hot or cold water is forming a highly viscous solution with a pH between 5.0 and 7.0 and satisfies many of the properties required for a good bioadhesive polymer. Further, chemical modification would be applied to improve the functional properties of natural polysaccharides. Kobayashi *et al.*[39] introduced carboxymethyl group to KG and studied rheological properties of KG to explore new applications of this unique natural gum. Since the carboxyl group also plays an important role in mucoadhesion of the polymers. This type of chemical modifications will result in the enhancement of the bioadhesive properties of KG.

Tara galactomannan gum was not used for further study due to its poor compressibility and powder erosion from the tablet surfaces during the adhesive strength measurement, as was observed during this study. Figure 3 shows the pictures of TG tablet during bioadhesive strength measurement, the surface of tablet detached and layer of powder adhered on the biological membrane when the tablet was removed from the surface.

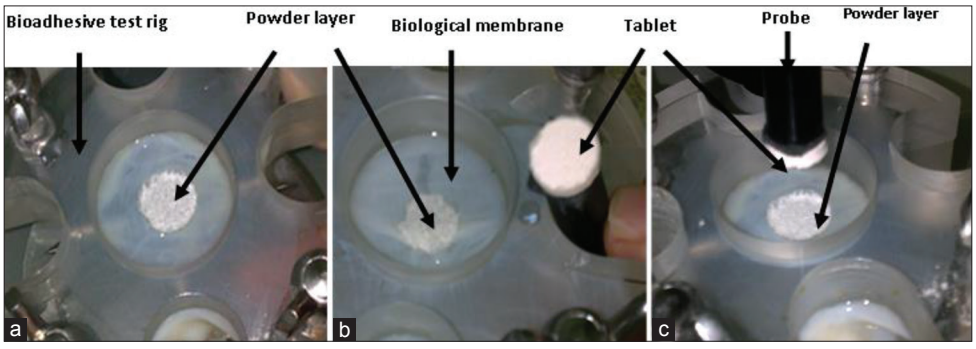

Figure 3: Pictures of (a) surface layer of Tara gallactomannan gum (TG) tablet left adhered on the tissue, (b) surface layer of TG/konjac glucomannan gum (KG) 32H tablet left adhered on the tissue, and (c) surface layer of TG/KG40H tablet left adhered on the tissue after detachment

Effect of contact time on bioadhesion

Table 3 and Figure 4 present the bioadhesive strength of XG for different contact time. The bioadhesion strength increased when the contact time was increased. It could be observed that the increase in bioadhesive strength followed almost similar pattern for both WOA and PDF.

Table 3: Influence of different contact time on work of adhesion and peak detachment force of tablets prepared with natural gums and their combination (mean±SD, *n*=3)

Time (s)	Work of adhesion (mJ)	Peak detachment force (*n*)
60	0.94±0.59	1.38±0.72
120	1.35±0.64	2.14±0.48
180	1.49±0.46	2.71±0.16
300	2.37±0.66	3.39±0.58
420	2.52±0.55	3.73±0.24
540	5.53±1.60	4.50±0.29
660	5.84±1.70	4.56±0.56
Statistical analysis	*P*<0.05	*P*<0.05
Tukey-HSD (multiple comparison)	60 and 540 (*P*<0.001)	60 and 180 (*P*=0.002)
	60 and 660 (*P*<0.001)	60 and 300 (*P*<0.001)
	120 and 540 (*P*<0.001)	60 and 420 (*P*<0.001)
	120 and 660 (*P*<0.001)	60 and 540 (*P*<0.001)
	180 and 540 (*P*<0.001)	60 and 660 (*P*<0.001)
	180 and 660 (*P*<0.001)	120 and 300 (*P*=0.005)
	300 and 540 (*P*<0.001)	120 and 420 (*P*<0.001)
	300 and 660 (*P*<0.001)	120 and 540 (*P*<0.001)
	420 and 540 (*P*<0.001)	120 and 660 (*P*<0.001)
	420 and 660 (*P*<0.001)	180 and 420 (*P*=0.028)
		180 and 540 (*P*<0.001)
		180 and 660 (*P*<0.001)
		300 and 540 (*P*=0.014)
		300 and 660 (*P*=0.008)

HSD=Honestly significant difference, SD=Standard deviation

A contact time of 300 s was reported for bio/mucoadhesive measurements.[40,41] In this study, three time points below and three time points above 300 s were employed to evaluate the effect of contact time. The results obtained were statistically significant ($P < 0.05$). Tukey-HSD test revealed that increase contact time from 300 s to 420 s had no significant effect on bioadhesive strength but there was a drastic increase in bioadhesive strength from 420 s to 540 s. There was no statistically significant difference in bioadhesive strength with further increase in contact time from 540 s to 660 s.

Figure 4 infers that both, WOA and the PDF, were increased with an increase in the contact time. The findings obtained in this part of study were in good agreement with the results of Tobyn,[19] Wong *et al.*,[28] and Hamzah.[27] It has been proposed by Duchene *et al*. that mucoadhesion process starts with the establishment of intimate contact between the surfaces of the dosage form and mucosa, followed by the polymer penetration into the mucosal surface and thus form secondary chemical bonds.[42] Contact time is a key factor in bioadhesion as adequate contact time ensures sufficient hydration and consequently swelling of the polymer, increases interpenetration of the two substrates, tablet and biological surface, and establishment of noncovalent interaction and thus upholds mucoadhesion.[28]

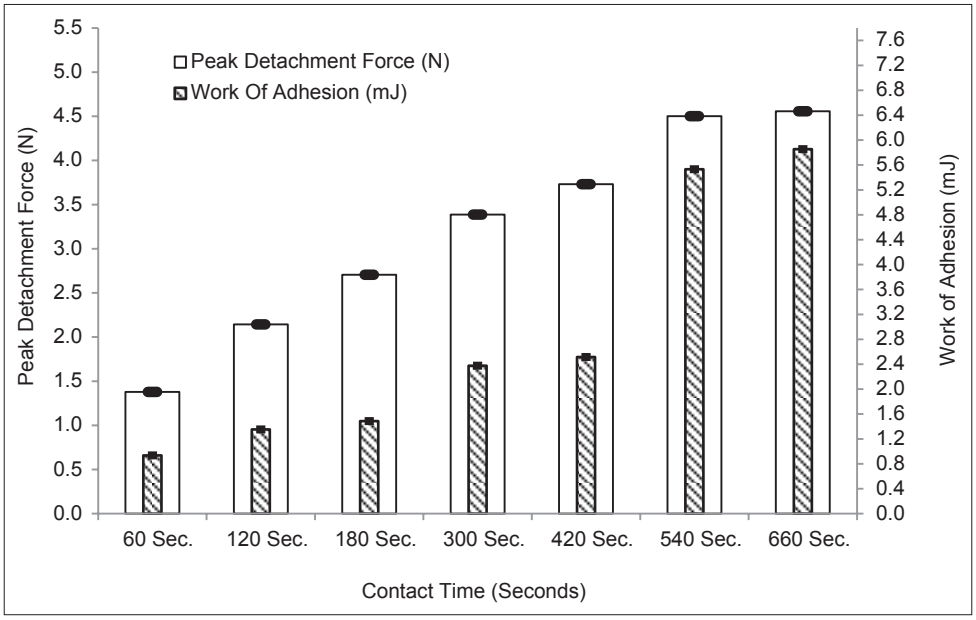

Figure 4: Influence of contact time on work of adhesion and peak detachment force for xanthan gum. Mean ± standard deviation, *n* = 3

CONCLUSIONS

It is concluded that the two gums, KG and XG-either alone or in combination, may be used in bioadhesive drug delivery system. As chicken pouch showed reproducible results, it could be an attractive alternative biological membrane in bioadhesion strength measurement.

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