Original Article

Design, formulation and evaluation of *Aloe vera* chewing gum

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Abstract

Background: *Aloe vera* has antioxidant, antiinflammatory, healing, antiseptic, anticancer and antidiabetic effects. The aim of the present study was to design and evaluate the formulation of *Aloe vera* chewing gum with an appropriate taste and quality with the indications for healing oral wounds, such as lichen planus, mouth sores caused by cancer chemotherapy and mouth abscesses as well as reducing mouth dryness caused by chemotherapy.

Materials and Methods: In *Aloe vera* powder, the carbohydrate content was determined according to mannose and phenolic compounds in terms of gallic acid. *Aloe vera* powder, sugar, liquid glucose, glycerin, sweeteners and different flavors were added to the soft gum bases. In *Aloe vera* chewing gum formulation, 10% of dried *Aloe vera* extract entered the gum base. Then the chewing gum was cut into pieces of suitable sizes. Weight uniformity, content uniformity, the organoleptic properties evaluation, releasing the active ingredient in the phosphate buffer (pH, 6.8) and taste evaluation were examined by Latin square method.

Results: One gram of *Aloe vera* powder contained 5.16 ± 0.25 mg/g of phenolic compounds and 104.63 ± 4.72 mg/g of carbohydrates. After making 16 *Aloe vera* chewing gum formulations, the F_{16} formulation was selected as the best formulation according to its physicochemical and organoleptic properties. In fact F_{16} formulation has suitable hardness, lack of adhesion to the tooth and appropriate size and taste; and after 30 min, it released more than 90% of its drug content.

Conclusion: After assessments made, the F_{16} formulation with maltitol, aspartame and sugar sweeteners was selected as the best formulation. Among various flavors used, peppermint flavor which had the most acceptance between consumers was selected.

Key words: *Aloe vera* chewing gum, lichen planus ulcer, mouth ulcers, phenolic compounds, wounds caused by cancer chemotherapy

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INTRODUCTION

The scientific name of *Aloe vera* is *Aloe barbadensis Miller*. This plant belongs to the *Liliaceae* family.[1] There are more than 300 species of plants which are used for therapeutic, cosmetic and nutraceutical

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purposes.[2] *Aloe vera* is separated to latex and gel products. *Aloe vera* latex, which is the bitter yellow extraction, comes from pericyclic tubules of the outer skin leaf. *Aloe vera* colorless gel is extracted from inner fresh leaf.[3] *Aloe vera* is orally used to control digestive problems, including constipation, anorexia, irritable bowel syndrome and colitis, asthma, diabetes and strengthening the immune system. It is also topically used to treat eczema, burns, acne, dermatitis and psoriasis. It stimulates cell regeneration. *Aloe vera* contains various compounds such as vitamins, sugars, enzymes, minerals, lignin, saponins, salicylic acids, amino acids and anthraquinone.[1,4]

The healing properties of *Aloe vera* improve the skin which is exposed to ultraviolet (UV) and gamma rays. It has antiinflammatory, antiseptic, antiviral, antibacterial, antitumor, moisturizing, antiaging, hypoglycemic, antidiabetic, cytotoxic, and antioxidants effects. It is also used against cardiovascular diseases.[5]

In recent decades, the scientific studies on *Aloe vera* due to the above mentioned properties have attracted more attention.[6] Researchers have greatly proven therapeutic claims about *Aloe vera* since 1986.[7] *Aloe vera* has been used for therapeutic purposes in many cultures, such as Greece, Egypt, Mexico, India, China and Japan for 1000 of years.[5]

Several products containing *Aloe vera* include juices, gel capsule, pills, creams, lotions, soaps, shampoos, toothpaste, mouthwash, hair styling, body shampoos, hand washing liquids and etc., have been marketed.[8]

Pharmaceutical chewing gums are produced in a solid form and a single dose. Their base mainly consists of gum base. This form of medication contains one or more active ingredients that are released by chewing. Pharmaceutical applications of pharmaceutical chewing gums include topical treatment of oral diseases and systemic delivery after absorption through the buccal mucosa or the gastrointestinal route.[9]

The benefits of chewing gum include consumption without water,[10] high acceptance by children,[10] low side effects, suitable stability,[11] high bioavailability, rapid onset effect[10] and relieving the mouth dryness by stimulating saliva.[10,12]

Formulation of pharmaceutical chewing gums contain pharmaceutical active ingredients, gum bases, fillers, elastomers, plasticizers, softeners, emulsifiers, sweeteners and flavors.[13] Factors affecting drug release in this type of dosage form include physicochemical properties of the active ingredient, chewing gum properties and related factors with strength and number of masticatory movements.[10,14]

Some of the formulated drugs in the form of chewing gum include fluoride, chlorhexidine, nicotine, aspirin, caffeine, and dimenhydrinate.[15]

It has been reported that some active principles of *Aloe vera* have antiinflammatory and wound healing effects in some of the phases of the inflammation. The polysaccharide of aloe mucilage gel is determined as active ingredient for antiinflammatory effects and has an immunomodulatory role.[16] Thus, according to what was mentioned, oral *Aloe vera* can be used as a wound healer for oral wounds.

To heal mouth sores, such as lichen planus, ulcers and abscesses caused by cancer chemotherapy, oral products such as mouthwash are used. Recently, one study examined the effects of 70% *Aloe vera* extract in the form of mouthwash for the treatment of mucositis caused by radiotherapy[17] and another study examined the effects of 80% *Aloe vera* extract in the form of mouthwash to treat lichen planus.[18]

The aim of this study was to design and to evaluate the formulation of *Aloe vera* chewing gum with an appropriate taste and quality with the indications for healing oral wounds, such as lichen planus, mouth sores caused by cancer chemotherapy and mouth abscesses as well as reducing mouth dryness caused by chemotherapy.

MATERIALS AND METHODS

Materials

Aloe vera powder was provided from Barij Essence Pharmaceutical Company (Isfahan, Iran). Gum bases of elvasti, 487, stick, fruit C were provided from Gilan Ghoot Company (Rasht, Iran). Flavors of eucalyptus, peppermint, banana, cola and cinnamon were provided by Goltash Company (Isfahan, Iran) and cherry flavor from Farabi Pharmaceutical Company (Isfahan, Iran). Glycerin, aspartame, maltitol, xylitol, anthrone reagent, sulfuric acid, chloroform, Folin–Ciocalteu's phenol reagent, gallic acid and sodium carbonate were purchased from Merck Company (Germany).

Methods

Determination of carbohydrates by mannose

To determine the amount of carbohydrates by mannose, a colorimetric method was applied using anthrone. Anthrone reagent prepared by dissolving pure anthrone in concentrated sulfuric acid and mannose was used as the standard material. Reagent

was poured into a test tube with cap, and then the tube was placed in an ice water bath. After cooling, the sample solution was slowly poured over it and was thoroughly mixed for 5 min. Then it was placed in boiling water bath for 10 min and immediately the test tube was entered in ice-cold water bath, then the absorption was read against a control in wavelength of 623.2 nm.[19]

Determination of phenolic compounds

Folin–Ciocalteu method which is a colorimetric assay was used to determine the polyphenol content of a substance. Gallic acid was used as a standard phenol. The sample solutions were poured into a test tube and after adding water, Folin–Ciocalteu's phenol reagent was added and shaken completely. Wait 30 s to 8 min and then a solution of sodium carbonate is added and well shaken. The tubes were maintained for 2 h at 20°C (or 30 min at 40°C) and after that absorption for each solution was read at a 765 nm wavelength and by using the data, absorption curve was plotted against concentration.[19-21]

Preparation of Aloe vera chewing gum

Aloe vera chewing gum was formulated using a mixture of gum bases, sugar, liquid glucose, glycerin, sweeteners (xylitol, maltitol, aspartame) and flavors such as eucalyptus, peppermint, cola, banana, cinnamon and cherries.

In formulation of *Aloe vera* chewing gum, 10% of *Aloe vera* dried extract is entered into the gum bases.

The gum base mixture is softened at the temperature of 70°C. *Aloe vera* powder, sugar, liquid glucose, glycerin and other ingredients are added to the base. Finally, at the temperature of 40°C, flavors were added and the mixture of chewing gum was cut into pieces of appropriate sizes [Table 1].

The best formulation in terms of organoleptic properties was selected and the flavors of eucalyptus, mint, cola, banana, cinnamon and cherry were added to it and the best among them was selected [Table 2].

Weight variations

Twenty chewing gums from each formulation were weighed. Mean and standard deviation of the weights were calculated.[9]

Content uniformity

Ten chewing gums were randomly selected.[9] At first, the chewing gum was dissolved in chloroform. Then the phosphate buffer with (pH, 6.8) was used to extract the drug into the aqueous phase. The carbohydrates value was measured on the amount of mannose absorption in the 623.2 nm by UV spectrophotometer.

Drug release

In order to study drug releasing from the gum base European Pharmacopoeia has suggested the device that simulates the act of chewing.[22] The device includes the following sections: The device includes a piston to enter the stroke, a chamber including the medium and chewing gum, circulation pipe with 37°C water around the chamber in order to provide oral temperature, engine and water bath.[23]

One milliliter of the sample was removed from the chamber at 5, 10, 15, 30, 40 min by pipette and 1 mL of phosphate buffer (pH, 6.8) at 37°C was added to the chamber. A placebo chewing gum (without medication) was also placed on the masticatory apparatus. And at the mentioned time they were sampled. The absorption was measured in 623.2 nm. This experiment was repeated 3 times for each formulation.

Table 1: Formulations of *Aloe vera* chewing gum with different ingredients

Ingredients (mg)	Formulations																	
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}	F_{16}	F_{17}	F_{18}
Elvasti base	70	70	65	70	70	65	65	65	65	65	65	65	65	65	65	65	55	75
487 base	70	70	75	70	70	75	75	75	75	75	75	75	75	75	75	75	65	85
Stick base	70	70	75	75	65	70	70	70	70	70	70	70	70	70	70	70	80	60
Fruit C base	70	70	65	65	75	70	70	70	70	70	70	70	70	70	70	70	80	60
Sugar	-	300	300	300	300	300	-	-	50	50	100	100	100	100	50	50	50	50
Maltitol	-	-	-	-	-	-	-	300	250	-	-	200	-	200	-	250	250	250
Xylitol	-	-	-	-	-	-	300	-	-	250	200	-	200	-	250	-	-	-
Aspartame	-	-	-	-	-	-	-	-	-	-	-	-	1	1	2	2	2	2
Aloe vera	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Flavoring agent	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Glycerol	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Liquid glucose	400	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation of the organoleptic properties of the Aloe vera chewing gum

In order to evaluate the organoleptic properties of *Aloe vera* chewing gum that contains hardness and softness, suitable mass volume, lack of stickiness to the teeth and suitable taste, samples with different combining base, sweeteners and flavors were prepared and in the first phase were tested by volunteers. Thus, in the first phase the 10 volunteers were asked to chew gum for 20 min and tell their comments about the hardness and softness, lack of stickiness to the teeth, volume and taste of the chewing gum.

Flavor evaluation of the Aloe vera chewing gum

Different flavors were added to the best formulation in terms of organoleptic properties. According to the Latin square method, based on the panel test, 20 people were volunteers and asked their opinions about different flavors. Two superior flavors were given to 30 other volunteers to choose the best one.

Evaluation of mechanical properties of the Aloe vera chewing gum

Tensile test was used for F_{16}, F_{17} and F_{18} formulations with different bases by universal testing machine (STM, Santam, Iran). Each sample of gum in the form of a dumbbell with 13 mm width and 3 mm thickness were prepared and with 30 mm gauge space, tensile test was performed. The tension velocity for samples was 50 mm/min.

RESULTS

Analysis of the *Aloe vera* powder

One gram of *Aloe vera* powder contained 5.16 ± 0.25 mg/g of phenolic compounds and 104.63 ± 4.72 mg/g of carbohydrates.

Analysis of the *Aloe vera* chewing gum

Uniformity of content for F_{16} formulation, which was selected as the best formulation, was 10.68 ± 1.69 mg according by mannose and its weight variation was 903.10 ± 4.92 mg.

Releasing of carbohydrates based on mannose from formulations with different gum bases ratios and different sweeteners were shown in Figures 1 and 2 respectively. As can be observed, after 30 min, about 90% of the drug content of the formulations was released.

Table 2: Formulations of *Aloe vera* chewing gum by altering the flavoring agent in the formulation F_{16}

Formulations	Flavoring agent
F_{19}	Cherry
F_{20}	Banana
F_{21}	Eucalyptus
F_{22}	Peppermint
F_{23}	Cinnamon
F_{24}	Cola

The organoleptic properties of *Aloe vera* chewing gum depend on using excipients. The F_{16} formulation had the highest acceptance according to the hardness and softness properties, lack of stickiness to tooth, volume and taste [Table 3].

The F_{16} formulation which was prepared with different flavors that mint and cinnamon (F_{22}, F_{23}) had the highest approval rating among volunteers [Table 4]. Of these two flavors, the mint flavor (F_{22}) won the most points [Table 5].

The results of the tensile test for F_{16}, F_{17} and F_{18} formulations with different ratios of the gum bases were shown in Figure 3.

DISCUSSION

Due to the properties of *Aloe vera*, aloe chewing gum can be formulated as a medication for oral wound healing.

In present study, in comparison with mouthwash form it was preferred to use chewing gum (as a drug delivery system) due to: More attractive and easier usage for the convenience and hold of increased consumption, more safety, lower overdose risk, releasing drug within a longer time (for the mouthwash about 30 s and for the chewing gum about 30–45 min) and controlled releasing of the drug.[24]

Kolahi-Kazerani *et al*. reported that the profile of the drug releasing in form of the chewing gum was appropriate and this form was considered as a

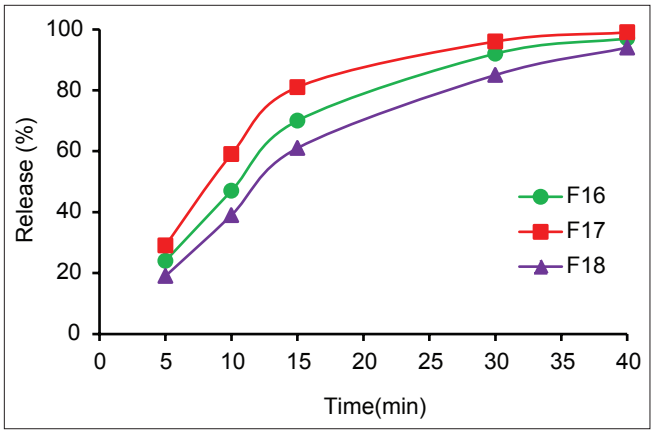

Figure 1: *In vitro* release of *Aloe vera* chewing gum formulations with various gum bases according to mannose in pH, 6.8 phosphate buffer at 37°C

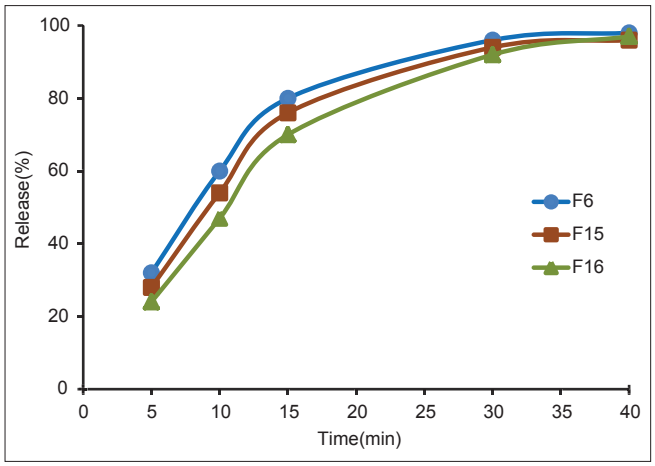

Figure 2: *In vitro* release of *Aloe vera* chewing gum formulations with various sweeteners according to mannose in pH, 6.8 phosphate buffer at 37°C

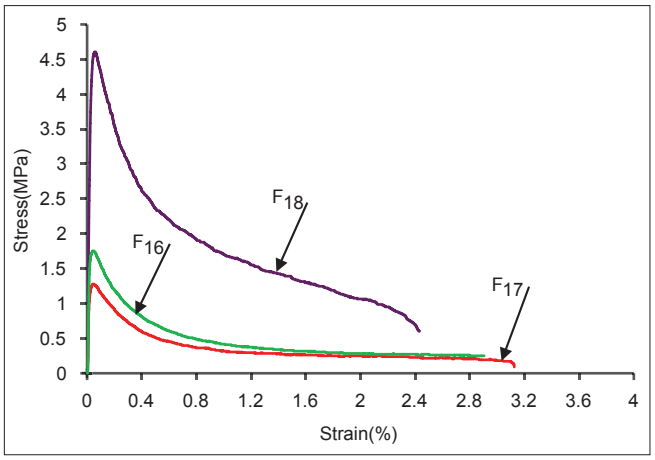

Figure 3: Tensile behavior of F_{16}, F_{17}, and F_{18} formulations with various gum bases

better choice than mouthwash form because of above reasons.[24]

One gram of *Aloe vera* powder contained 5.16 ± 0.25 mg/g of phenolic compounds and 104.63 ± 4.72 mg/g of carbohydrates.

In Cock and Ruebhart study, the carbohydrates content and phenolic compounds were reported 201 mg/g and 46.8 mg/g respectively.[19] The differences between the values obtained in our study and the mentioned article can be due to different sources of *Aloe A. vera*, plant growth conditions, the method of preparing powders, the extraction type and the measurement methods.

In the preparation of *Aloe vera* chewing gum, four gum base types were used. The gum bases of elvasti, 487, stick and fruit C have different hardness. Elvasti and 487 compared with the stick and fruit C are more rigid. The hardness and softness of each chewing gum can be set by changing the amount of these bases to select the best formulation in terms of hardness and softness. Among F_1 to F_6 formulations, F_6 formulation had better organoleptic properties [Table 1]. Because of this advantage, F_6 formulation was selected to continue and formulations of F_7 to F_{16} were made by the same percentage. In this study for the preparation of *Aloe vera* chewing gum formulations, *Aloe vera* powder, sugar, maltitol, xylitol, aspartame, liquid glucose, glycerol and various flavors with the specified percentages were added to the gum bases. Using a combination of sweetener such as xylitol, maltitol and aspartame along with sugar was useful. The F_{16} formulation prepared by combining sweeteners including sugar, aspartame and maltitol was the best formulation of flavors. Theresa Cea and Glass study showed that the aspartame in chewing gum increased the stability of the sweet flavour.[25]

In order to find the effects of flavors on the organoleptic properties, in general, the flavors had the effects of softening on the formulation. Pepperint, cinnamon, cherry, cola, banana and eucalyptus flavors were used and among them mint had the greatest acceptance among the volunteers.

Aslani and Jalilian prepared the caffeine chewing gum and in their study the volunteers were selected cinnamon flavor as the best one.[26]

On the other hand, in another study which was conducted by Aslani and Rafiei to make the nicotine chewing gum, cherry and eucalyptus flavors were selected as the best flavors.[23]

In another study by Aslani *et al.*, to make green tea chewing gum, mint and cinnamon flavors were selected by volunteers.[27]

Since the test for uniformity of content and the acceptable range of it for pharmaceutical chewing gum are not available specifically, therefore, the uniformity of content test for the tablet by European Pharmacopoeia test was used to examine the content uniformity of *Aloe vera* chewing gum. Content uniformity test was separately carried out on 10 samples of F_{16} formulation. The mean of carbohydrate concentration was calculated in terms of mannose. According to the results, the content uniformity was in the acceptable range.

Pharmaceutical chewing gums are formulated in such a ways that release the maximum of its active ingredient at the appropriate time. Factors such as

Table 3: The averages of scores allocated by volunteers for organoleptic properties of *Aloe vera* chewing gum formulations by 10 volunteers

Organoleptic properties	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}	F_{16}	F_{17}	F_{18}
Gum volume[1]	2.2	2.9	2.9	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Softness and Hardness[2]	4.5	3.4	2.1	3.2	3.2	3	3	3	3	3	3	3	3	3	3	3	1.9	4.2
No stickiness[3]	4.6	4.4	3	4.8	4.9	5	5	5	5	5	5	5	5	5	5	5	2.3	5
Taste[4]	2.3	3	3	3	3	3.1	3.2	3.2	3.3	2.5	3.4	2.7	4	4.1	4.3	4.4	4.4	4.4

[1]The bulk volume of gum was evaluated as Huge-5, much-4, right-3, little-2, very little-1, [2]The Softness/Hardness was evaluated as very hard-5, hard-4, suitable-3, soft-2, very soft-1, [3]The stickiness to teeth was evaluated as never sticks-5, rarely sticks-4, sometimes sticks-3, mostly sticks-2, always sticks-1, [4]The taste was evaluated as excellent-5, good-4, fair-3, poor-2, very poor-1

Table 4: The scores allocated by 30 volunteers for each taste of best *Aloe vera* chewing gum formulations

Score	Formulations					
	F_{19}	F_{20}	F_{21}	F_{22}	F_{23}	F_{24}
1	2	2	6	-	-	3
2	5	3	10	-	2	10
3	9	10	3	3	1	5
4	4	5	1	15	16	2
5	-	-	-	2	1	-
Mode	3	3	2	4	4	2
Mean	2.75	2.90	1.95	3.95	3.80	2.30

The taste was evaluated as excellent-5, good-4, fair-3, poor-2, very poor-1. Flavoring agents used in F_{19}-F_{24} formulations were cherry, banana, eucalyptus, peppermint, cinnamon and cola respectively.

Table 5: The scores allocated by 30 volunteers for top tastes of best *Aloe vera* chewing gum formulations

Score	Peppermint	Cinnamon
1	-	3
2	-	2
3	2	19
4	25	5
5	3	1
Mode	4	3
Mean	4.03	2.96

The taste was evaluated as excellent = 5, good-4, fair-3, poor-2, very poor-1

speed and the intensity of chewing and the amount of saliva production affect the releasing and absorption of oral drugs.[12]

Drug releasing rate from pharmaceutical chewing gum depends on their dissolution in water. Soluble substances in water are rapidly, and sparingly dissolve but insoluble substances in water are slowly released from the pharmaceutical gum bases.[28]

In releasing test of samples with different percentage of gum bases [Figure 1], we observed that chewing gum samples with a higher percentage of softer bases (F_{17}) had more releasing amount in compare with F_{16} and F_{18} with a lower percentage of softer bases at the same time. In contrast, the releasing of F_{18} sample which had a higher percentage of the hard bases was less than the other two samples at the same time.

As seen in Figure 2, the amount of sample releasing with different types of sweeteners was almost identical.

In the present study, the releasing of carbohydrates by mannose after 30 min, from chewing gums with different bases such as F_{16}, F_{17} and F_{18} were 92%, 96% and 85% respectively. In F_6, F_{15} and F_{16} chewing gums with different sweeteners over than 90% of carbohydrate were released after 30 min.

In the study conducted by Aslani and Jalilian, the release of caffeine in chewing gum at 10, 20 and 30 min were reported 55%, 78% and 89% respectively.[26]

Also, in the study conducted by Aslani and Rafiei, the release of nicotine from 2 to 4 mg chewing gums at 20 min was reported 83% and 79% respectively.[23]

By examining the graph of stress strain of F_{16}, F_{17} and F_{18} formulations with different bases composition, as can be seen in Figure 3, all three formulations had the linear elastic behavior because of the effect of strain. By increasing the strain, it entered the linear area, and then by increasing the strain, the yield point was reached. Then, by increasing the strain, the samples showed plastic behavior and before reaching the stage of hardening because of the stress the rupture occurred. The F_{18} formulation containing higher elvazti and 487 bases had higher yield point than the other two formulations and the F_{17} formulation containing higher stick and fruit C bases had lower yield point than the other two formulations. It is expected that the F_{18} chewing gum due to the higher yield point is more lasting during the chewing and because of long linear region is more elastic. However, the F_{17} formulation due to lower yield point loses the ability of chewing in the mouth sooner and by considering the short linear region has a greater plasticity and the F_{16} formulation behaves intermediately. The results of the study conducted by Aslani *et al.* support the results obtained in this study.[27]

CONCLUSION

According to the findings of the present study, *Aloe vera* chewing gum can be formulated with appropriate

organoleptic properties and the best formulation considering the organoleptic properties was F_{16} formulation. Based on the views of participants, from six flavors which tested at first mint and cinnamon were selected as better flavors and in next stage between these two mint was chosen as the best flavoring agent.

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Conflicts of interest

There are no conflicts of interest.

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