Design, Formulation and Evaluation of Medicinal Chewing Gum by the Extract of *Salvadora persica L.*

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ABSTRACT: Dental caries is one of the common hygienic problems. Salvadora persica L. Or Miswak is rich in fluorine and many anti-bacterial agents. Fluoride helps to prevent dental caries. Chewing gum as a preparation to prevent tooth decay and improve oral health can be supplied to the pharmaceutical market. This study aimed to evaluate the organoleptic, physicochemical and mechanical characteristics of the gum, the product designed to provide the consumer's optimal. The plant was prepared from Hormozgan State. Its stems and twigs were ground; then percolated at 25° C. Liquid glucose, glycerin, various sweeteners, plant extracts and flavorings have been added to the softened gum base at the proper temperature. In order to evaluate the organoleptic characteristics of the product, Latin square was designed. Weight variation and content uniformity were determined. Fluoride release has been studied by means of the mechanical chewing device in phosphate buffer with the pH adjusted at 6.8. The mechanical properties of the product were evaluated by using a tensile testing machine. The amount of fluoride per gram of extract was 0.111 ± 0.017 µg. Organoleptic properties were evaluated at 3 stages in the volunteers. The average weight of the chewing gum for F11 to F15 was 832.0 ± 2.9, 829.0 ± 2.2, 833.3 ± 3.9, 829.2 ± 3.2 and 828.0 ± 3.8 mg respectively. The mean amount of fluoride in the gums form F11 to F15 was 94.1 ± 5.7%, 92.3 ± 5.7%, 96.5 ± 4.7%, 93.9 ± 4.4% and 95.6 ± 3.8% of the claim respectively. F11 to F15 after 15 minutes released 62%, 73%, 80%, 69%, 73%, and finally 85%, 92%, 97%, 94%, 95% of their fluoride in the release medium respectively. The mechanical testing was performed. Parameters such as yield strength, ultimate strength, toughness, elongation, and modulus of elasticity are calculated. In this study S. persica L. is extracted and formulated into chewing gum with favorable taste and suitable organoleptic properties as F12. The best sweetener for persica gum is xylitol and peppermint is the best flavoring agent. It is succeeded in the content uniformity, release and mechanical tests.

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Key Words: Medicated chewing gum, dental caries, fluoride, oral health, *Salvadora persica L.*, fluoride ion selective electrode, tensile test.

INTRODUCTION

Localized destruction of susceptible dental hard tissues is induced by the fermentation of dietary carbohydrates by some bacteria called dental caries. [1,2] Nowadays the more emphasis is on prevention rather than the cure. [3] To prevent tooth decay, several factors such as the amount of fluoride intake, good health and decreasing the carbohydrates consumed by the bacteria is important. [4] Fluoride is the most important factor in preventing dental caries. This effect is related to its presence in the hydroxyapatite crystals, the prevention of demineralization of teeth and stimulating teeth remineralization. [3,5] Moreover it is effective on the metabolism of cariogenic bacteria. [3]

S. persica L. is a small evergreen shrub with the white branches and aromatic root. [6] Its roots, stems and branches for centuries have been used for oral hygiene. It is commonly used in the Middle East, Asia, Africa and South America. [6,7,8] The World Health Organization (WHO) has recommended and encouraged the use of chewing sticks as an effective oral hygiene tool in areas where it is traditionally grown. [9] In addition, whitening the teeth, improving the memory, freshening the breathing, calming the bile, drying up the phlegm, strengthening the gums, sharpening the vision and increasing the appetite are the

other benefit of this plant. [10] Extracts from its roots and stems contain the powerful antimicrobial substances such as sulfur. Moreover Trimethylamine, benzyl isothiosyanate, Salvadorine, beta cholesterol, tannins, saponines, sodium chloride, potassium chloride, vitamin C, flavonoids and sterols are associated with anti-bacterial effects. Significant amounts of silica can help to remove plaque mechanically. [11] Fluoride is also found in considerable quantities, [12] which is easily dissolved and released in water. [6,13,14] Slightly bitter taste of the extract is due to its volatile oils that helps saliva to flow and buffer it. [15]

Chewing gum is one of the new forms of medication that can be used for local and systemic drug delivery. [16] Gum advantages over the other delivery methods include no needing to water or liquids to eat, [16] increasing the systemic effects, [17] low dose administration, [18] faster onset of action, [16,18] good stability, relieving of dry mouth, strengthening the mastication muscles and prevention of dental caries. [18,19] However, complications such as adhesion to dentures, breaking the filling teeth by severe gum, muscle and jaw joint pain and rarely hypertrophy of masticatory muscle, have been reported. [20]

Drugs such as nicotine, caffeine, sodium fluoride, dimenhydrinate, acetyl salicylic acid, vitamin C and chlorhexidine are formulated in the form of chewing gum. [16,20] Chewing gum contains a chewable base including elastomers, resins, waxes, fats and emulsifiers and several non chewable components include fillers, softeners, sweeteners and flavors. [18,19] Medicinal gum should release the drug content in duration to 20-30 minutes. Drug solubility in water, formulation and method of gum preparation are the factors influencing the drug release rate. [20]

One of the most concerns associated with the use of fluoride products is the fluorosis phenomenon. The total amount of fluoride ingested is the most important risk factor in this issue. It has been proven the plasma fluoride levels mildly increased after consumption of chewing gum containing fluoride. Thus the chewing gum is considered the less harmful dosage form to deliver fluoride to the teeth topically. [22] Studies recommended the use of products with low concentrations of fluoride, that lead to low but uniform levels of fluoride in saliva. It is the most effective way to prevent tooth decay. [3]

This chewing gum is designed for the first time to promote oral health, accordingly non- cariogenic sweeteners were used in formulating it. It has been proven that consumption of sugar-free gum raises the pH of dental plaque. Low pH of dental plaque plays an important role in developing dental caries. So to prevent tooth decay the use of such chewing gum after eating is recommended. [21] In addition sucrose is high in calories and lead to obesity and are not suitable for diabetic people. Polyols are the examples of non-cariogenic sugar. They are less sweet than the sucrose, but their taste is also neutral and pleasant. Endothermic dissolution is another features, that will lead to a sense of coolness in the mouth. The amount of coolness depends on some factors such as dissolution heat, dissolution rates at oral temperature (36.4° C) and the particle size of sweetener. Usually in making of gum, xylitol is used for the reason of the maximum cooling effect. Its application in peppermint-flavored products is essential. Xylitol is not fermented by *Streptococcus mutans*; accordingly it can inhibit its growth in saliva. Xylitol can decrease the amount of insoluble polysaccharidic plaque, making it less adhesive and easier to remove by brushing the teeth. Aspartame is used in trace amounts approximately 0.05% of the gum weight. Mannitol and maltitol are also found in sugar-free chewing gum composition. [23] There are many studies showing that Miswak has strong anti caries effects due to the large amounts of fluoride [24,25,26,27] and antimicrobial agents [28,29] in it.

The purpose of this study is to prepare the persica gum with desirable physicochemical properties and customer-friendly features in order to prevent tooth decay and benefit from the other properties of this plant like aids in digestion.

MATERIALS AND METHODS

Materials

Stems and twigs of *S. persica L.* which grows wild near Bandar Abbas were collected in October 2003 (Hormozgan, Iran). The plant identification as *S. persica L.* was confirmed by Mahboobeh Khatamsaz at the Tehran Research Institue of forests and rangelands, where its voucher herbarium specimen were deposited (Tehran, Iran). The gum bases including Elvazti, 487, stick and fruit C were purchased from the Gilan Ghoot Company (Rasht, Iran). Flavoring agent of peppermint, banana and cinnamon gifted from the Goltash Company (Isfahan, Iran). Cherry and tutti-frutti were produced by the Farabi Pharmaceutical Company (Isfahan, Iran). Xylitol, maltitol, mannitol, glycerin, aspartame, and other ingredients were pharmaceutical grade.

Extraction of the plant and fluoride assay

300 grams of stems and twigs of *S. persica L.* were milled by means of industrial mixer and percolated with 70% ethanol. The extract was concentrated by the rotary set at 45°C. Fluoride measurements were made using a fluoride ion selective electrode (Ion-Check 45, Radiometer Analytical, USA).

In the direct method, the sample was diluted with double deionized water in 1:10 ratio. TISAB III solution is then added in a 1:1 ratio. The sample is placed directly under the electrode and the concentration is recorded. In the diffusion method, 1 ml of the diluted sample is transferred to a petri dish. 50 µl of 0.05 N sodium hydroxide solution as a trap solution, and 1ml of 3 N sulfuric acid that is saturated by HMDS (Hexamethyldisiloxane) were placed. HMDS increases the fluoride diffusion rate by forming the volatile and hydrophobic TMFS (Trimethylfluorosilane). Samples have been covered with parafilm for 24 hours. TMFS released from acidic sample and trapped in sodium hydroxide. Samples are recovered, then buffered at pH, 5.2 by 25 µl of 0.1 N acetic acid and 25 µl of TISAB III. Finally reached at a volume of 100 ml by double deionized water, and placed under the electrode. [30] The determination of fluoride was performed by direct and diffusion methods.

Gum preparation

Persica chewing gum was formulated by the gum bases, liquid glucose, glycerin, non sugar sweeteners (xylitol, maltitol, mannitol, aspartame) and a flavoring agent. The combination of the bases were softened in a water bath at 60°C. Liquid glucose, glycerin, sweeteners, plant extract, and finally flavors were added at 40 °C (Table 1). Homogeneous mixture was extended on a glass plate. Then it was cut in small pieces and kept for 48 hours at room temperature.

Evaluating the organoleptic characteristics

To evaluate organoleptic features of this product, the Latin square was designed. 10 healthy volunteers were asked to chew the gum (F_1–F_{15}) for 20 minutes and give comments on the hardness/softness, adhesion to teeth, the volume of the gum mass and taste according the Likert scale on the evaluation forms. The candidates should then wash their mouth and try the next gum after 20 minutes (Table 2).

Weight variation

20 gums from each formulation F_{11} to F_{15} were selected separately. They were weighed and the mean of weight and standard deviation were calculated.

Uniformity of content

10 gums from each formulation F_{11} to F_{15} were randomly selected [31] and were weighed. Each gum separately was dissolved in 50 ml of chloroform. After they were dissolved completely, 100 ml of phosphate buffer with adjusted pH in 6.8 were added to extract the fluoride salts in the aqueous phase. The amount of fluoride was measured by fluoride ion selective electrode device as before.

In vitro drug release

The release of fluoride from the dosage form, was performed by means of a mechanical chewing device, that mimics human behavior's chewing. The device includes a compartment for keeping the release medium and a piston that hits the gum randomly in different directions. 50 ml of phosphate buffer with pH=6.8 instead of saliva were used as the release medium. Warm water is circulated around the chamber to maintain a constant ambient temperature at 37° C. The piston strikes on the gum 60 beats per minute. [17] After the startup of the machine, 1 ml of the medium in the chamber was sampled at 5, 10, 15, 30 and 45 minutes. In each sampling, 1 ml of the medium was replaced with a new isothermal buffer. The amount of fluoride is measured as before. The test was performed for 3 gums of each formulation (Figures 1,2).

Evaluation of the mechanical properties

Tensile test is one of the most common tests to evaluate the mechanical properties of materials. Because the tensile strength is easy to determine and is a quite reproducible property, it is useful for the purposes of specifications and for quality control of a product. A tensile load is applied to the specimen until it fractures. [32] The test for a number of formulations with different sweeteners and the gum bases (F_5, F_6, F_{11}-F_{14}) is performed by the tensile testing machine (SANTAM ENG DESIGN CO. LTD.). For each sample, thickness, width, gauge length and speed must be set accurately. Mechanical parameters such as yield strength, ultimate strength, toughness, percentage of elongation, and modulus of elasticity were calculated. [33] The parameters were presented in Table 3. The experiment was carried out for 3 samples of each formulation (Figure 3).

Effect of different flavors

To evaluate the taste of the persica gum, some formulations that have desirable organoleptic and physicochemical features were made with 5 kinds of flavors such as banana, peppermint, cherry, cinnamon and tutti-frutti. They have been given to 20 subjects and were evaluated according to the Likert scale as excellent = 5, good = 4, moderate = 3, poor = 2, very poor = 1 (Table 4). Finally the previous formulations that had the greatest reception by consumers, were given to 30 volunteers and were analyzed as before to select the best flavors (Table 5).

RESULTS

Extraction

The weight of herbal extracts was 112.4 g. It had a volume of 110 ml. Fluoride was measured by the fluoride ion selective electrode set. The amount of fluoride in the extract was reported as 0.111 ± 0.017 µg/g by diffusion method and 0.098±0.004 µg/g with direct method.

Evaluating the organoleptic characteristics

In evaluating the hardness and softness of the product, F_1 and F_2 earned the lowest scores (table 2) and were very soft. F_5, F_6 and F_{10} with the scores of 46, 44 and 40 were the hardest formulations. Other formulations earning the scores of 28 to 38 in terms of softness and hardness were used to make the final formulations. F_1 and F_2 were stuck to the teeth. None of the other formulations showed the sticking to the teeth problem. All formulations except F_1 and F_2 had the suitable mass volume. Gum was formulated by combining a variety of different flavors and sweeteners. F_2 and F_1 with the scores of 10 and 12 had the worst taste. F_{12} and F_{13} with the scores of 50 and 46 were the most delicious gums (Table 2).

Physicochemical evaluation

Weight variation of the gums was investigated according to the USP recommended limit of ±5%. The mean weight of the gums from the F_{11} to F_{15} was 832.0 ± 2.9, 829.0 ± 3.2, 833.3 ± 3.9, 829.0 ± 2.2 and 828.0 ± 3.8 mg. The mean drug content of 10 gums that were randomly selected from each series of formulations F_{11} to F_{15} was 94.1± 5.7%, 92.3 ± 5.7%, 96.5 ± 4.7%, 93.9 ± 4.4% and 95.6 ± 3.8% of the claim. All results satisfied the criteria which are commonly required by USP for solid dosage forms.

In vitro drug release from medicinal chewing gum

Charts of fluoride release from the formulation 11 to 15 are seen (Figures 1&2). F_{11}, F_{12} and F_{13} were released 62%, 73% and 80% of their fluoride content after 15 minutes.

The drug release after 45 minutes reached to 85%, 92% and 97% respectively (Figure 1). Release drug from F_{14} and F_{15} after 15 minutes, were 69% and 73% of the gum fluoride content. At the end of chewing time, each gum released 94% and 95% of its fluoride in the release medium respectively (Figure 2).

Evaluating the mechanical properties of the formulations

F_5, F_6 and F_{11} to F_{14} were mechanically tested. Diagrams of tensile test are shown in figure 3. F_5, F_6, F_{11}, F_{12}, F_{13} and F_{14} up to 0.09, 0.06, 0.02, 0.03, 0.02 and 0.02 MPa showed the elastic deformation as the yield strength respectively. F_5, F_6 and F_{11} to F_{14} supported the maximum stress until fractured as 0.13 , 0.10, 0.05, 0.06, 0.04 and 0.04 MPa, respectively. Percentage of elongation is measured for samples and the results for F_5, F_6 and F_{11} to F_{14} are 6.46%, 6.56%, 9.00%, 5.73%, 8.41% and 7.15% respectively. F_5, F_6 and F_{11} to F_{14} absorbed respectively 66.7, 63.2 , 39.6 , 26.9 , 31.5 and 57.4 joules of energy till fractured. Modulus of elasticity were calculated for F_5, F_6 and F_{11} to F_{14} as 27.3, 8.04, 12.10, 13.22, 10.26 and 5.4 MPa respectively (Table 3).

Selection of the best flavoring agent

According to the Table 4, banana earned 54 points and was the worst flavor. Tutti-frutti with 62 points was not very interesting. Cinnamon by gaining 74 points was good. Peppermint and cherry flavors with 94 and 88 points were desirable to cover the plant extracts taste. The ratings were up 100. Peppermint (F_{12}) with 134 points in comparison with the cherry (F_{13}) had the highest acceptance level. The ratings were up 150 (Table 5).

DISCUSSION

There are many studies about the use of *S. persica L.* in the oral health and traditional medicine. It also has a special place in Islam. [11,34,35] This study focused on the fluoride content of the extract. Persica chewing gum was designed to deliver fluoride to dental tissues; Moreover, it is acceptable to the consumers.

The analysis of the hydro-alcoholic extract of the plant showed that 1 g of *S. persica L.* contains 0.04 µg of fluoride. Another study reported the amount of fluoride in 1g of the plant 0.07 µg. [15] Different results can be due to differences in climate condition (Iran and Saudi Arabia) and the method of fluoride determination.

Persica chewing gum contains the extract of the plant to 10% by weight. Chewing gum can be a good carrier for delivering fluoride to the tooth. Nowadays, to prevent dental caries fluoride products are prescribed frequently. Although these products are beneficial, but an increase in fluoride intake may put a person at risk of fluorosis. When fluoride interacts with mineralizing tissues, causing changes in the mineralization process and fluorosis occurs. The result is porosity in dental enamel. Dental fluorosis is related to the total fluoride exposure to the developing dentition. [36] Our medicinal gum has the smaller amount of fluoride than the fluoride products available in the market. Chewing gum is considered a fancy refreshment which is highly interested in children. They are the most group exposed to the risk of fluorosis, who may chew a lot of gum daily. Therefore, you can prescribe this useful chewing gum with a higher level of certainty.

We use 4 kinds of gum bases with different physical characteristics. Elvazti and 487 are hard and stick and fruit C are the soft base. F_1 and F_2 with more amounts of the softer bases were built. They were too soft. The volume was little and it stuck to the teeth. In order to solve this problem, some formulations were designed. The equal amounts of gum bases were used ($F_3 - F_4$). They were to some extent hard. The suitable volume and no stickiness to teeth have been reported for F_3 and F_4. In the next formulations the Elvazeti and 487 decreases and the same amount is added to the stick base. The gums possess a good volume and do not attach to the teeth, but were stiff and chewing them was boring (F_5 and F_6). The same change was done with the fruit C base. The consumers were satisfied. The Less amount of change in gum bases was the other attempt and having no enough softness (F_9 and F_{10}). F_{12} is the best formulation. It has the desire softness, favorable volume and no stickiness to the teeth (Table 2). The amount of gum bases can be changed for other chewing gums, as in the making 2 and 4 mg nicotine gum, the same amount of gum bases is used. [37]

Different sweeteners in the gum making process are used. Maltitol is as sweet as 0.9 of the sucrose. It is expected that F_1 had a good taste, but consumers were not satisfied. Mannitol is as sweet as 0.5 of the sucrose, so it is a weak sweetener (F_2). The next formulations had a relatively good taste by adding them aspartame ($F_3 - F_4$). F_5 was made with xylitol and maltitol in the ratio of 2:1 and F_6 made by xylitol and mannitol in the ratio of 2:1 with 1 mg of aspartame, they tasted good. F_7 and F_8 were made by elimination of aspartame from F_5 and F_6, were delicious. Xylitol plus 1 mg aspartame used in the preparation of F_9, it was so sweet. To produce the F_{10} xylitol was used alone, the taste was excellent. Xylitol is as sweet as 0.95 of the sucrose. The cooling effect of the sweeteners is another feature affects on the sweetener utility, which plays an important role in the product taste. The heat of dissolution for maltitol is -16.3 cal/g at room temperature. While the heat of dissolution for xylitol is -36.6 cal/g. When maltitol is dissolved in the mouth, it causes to absorb less heat from the oral cavity compared to xylitol. The result is the less desirable taste, as in F_2 maltitol did not taste good.

Several flavors were thought to be compatible with the taste of *S. persica L.* selected. Peppermint and cherry were the best flavors to cover the taste of *S. persica L.*extract well. Cinnamon and tutti-frutti were fairly desirable and banana was bad. Peppermint was the most acceptable flavor. The kind and amount of sweeteners and flavors depend on the dosage form, active substance and its application. Products such as gum is chewed for several minutes, compared to products that should be swallowed. Thus its flavor should be delicious and extended. For bitter drugs such as nicotine, aspartame is used as the main sweetener, and eucalyptus was the best flavors respectively. [37] In our study the extract of the plant was

not too bitter, so xylitol could cover its unpleasant taste. Persica gum was produced with xylitol and peppermint.

To study the effect of gum bases and sweeteners on the drug release profile, 5 formulations are made by the use of different types of gum bases and sweetener. Fluoride salts are freely soluble in water and fortunately there is no need to increase the drug release. The effect of gum bases on drug release from chewing gum was investigated. 3 formulations with different amounts of the gum bases were built. F_{12} and F_{13} released 73% and 80% of their fluoride content after 15 minutes and 92% and 97% at the end. F_{11} was more difficult than F_{12} and F_{13}. It released 62% and 85% of its drug at the same time. It was concluded that the hard gum leds to lower drug release. Release charts of F_{12} and F_{13} also indicated the base type having no effect on the drug release. Then drug release has been studied with various sweeteners. Release charts of chewing gum with xylitol, mannitol and maltitol is approximately overlapped. To verify the release test, results are compared with the sodium fluoride chewing gum. [38] Sodium fluoride gum released 22%, 68% and 94% of the fluoride content at regular intervals 5, 15 and 30 minutes. It confirms the research hypothesis.

Formulations with different ratios of gum bases and sweeteners were made and the mechanical properties investigated. The maximum amount of stress, material reversibly can undergo or deformed elastically called yield strength. The part of the stress-strain curve up to the yielding point is called the elastic region. Elastic deformation is nearly recoverable. In the elastic region, stress and strain are related to each other linearly by this equation $\sigma = Ee$.

Stress $\sigma = P/A_0$ (Load/Initial cross-sectional area)

Strain $e = \Delta l/l_0$ (Elongation/Initial gauge length)

The linearity constant E is called the elastic modulus which is specific for each type of material because it is determined by the linkage between atoms of each material. F_5 has the most yield strength and is more elastic than the others. Stick base had the highest elasticity (F_5 – F_6). Plastic deformation starts at the yield stress. The part of the stress - strain diagram after the yielding point is the plastic region. Plastic deformation is permanent. Tensile Strength is the maximum stress that the material can support till fractured. F_5 and F_6 supported the most stress, the stiffest formulation. Other formulation endured almost the same stress. Area under the stress - strain curve up to the fracture point expresses the amount of energy required to break material called the toughness. F_5 and F_6 are the toughest. Ductility is the degree of plastic deformation that a material can withstand before fracture. It can be expressed in terms of the percentage of elongation. F_{11} had the most plastic changes and F_{12} deformed plastically in minimum. So, fruit C base with the least elasticity and ductility, is better to be increased in order to increase the softness of chewing gum.

CONCLUSION

The results of mechanical testing recommend the fruit C base to increase the gum softness. Chewing gum has an optimal drug release. Content uniformity and weight variation tests are passed. In evaluating the organoleptic characteristics, F_{12} by combination of xylitol and peppermint possesses the desired organoleptic characteristics. Considering the results of this study, *S. presica L.* can be formulated in the form of medicinal gum to deliver fluoride to the teeth. Our study can confirm the gum as a drug delivery system.

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Table 1: Formulation of persica chewing gum with different ratios of gum bases and sweeteners

Ingredients (mg)	Formulation														
	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}
S. persica L. extract	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80
Elvazti	60	60	70	70	60	70	60	70	65	70	70	60	70	60	60
487	60	60	70	70	70	60	70	60	70	65	70	70	60	70	70
Stick	80	80	70	70	80	80	70	70	70	70	70	70	70	70	70
Fruit C	80	80	70	70	70	70	80	80	75	75	70	80	80	80	80
Xylitol	200	200	200	200	300	300	300	300	400	400	400	400	400	300	300
Liquid glucose	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Glycerol	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Maltitol	200	-	200	-	100	-	100	-	-	-	-	-	-	100	-
Mannitol	-	200	-	200	-	100	-	100	-	-	-	-	-	-	100
Aspartame	-	-	2	2	1	1	-	-	1	-	-	-	-	-	-
Banana	20	20	20	20	20	20	-	-	-	-	20	-	-	-	-
Peppermint	-	-	-	-	-	-	20	-	-	-	-	20	-	-	-
Cherry	-	-	-	-	-	-	-	20	-	-	-	-	20	-	-
Cinnamon	-	-	-	-	-	-	-	-	20	-	-	-	-	20	-
Tutti-frutti	-	-	-	-	-	-	-	-	-	20	-	-	-	-	20

Table 2: Organoleptic properties of different persica chewing gums in 10 volunteers by Latin-Square design (1st Stage)

Organoleptic properties	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}
Softness/Hardness[1]	14	14	36	36	44	42	30	28	40	40	36	30	28	30	28
Adhering to teeth[2]	20	20	50	50	50	50	50	50	50	50	50	50	50	50	50
Gum mass volume[3]	12	12	26	26	28	26	26	26	26	24	26	26	26	28	26
Taste[4]	12	10	24	26	30	30	40	42	46	42	32	50	46	46	42

[1]The Softness/Hardness was assessed according to the Likert scale as very hard = 5, hard = 4, proper softness = 3, soft = 2, very soft =1

[2]The adhering to the teeth was assessed according to the Likert scale as never = 5, rarely = 4, sometimes = 3, often=2, always = 1

[3]The Mass volume of gum was assessed according to the Likert scale as too bulky = 5, bulky = 4, proper volume = 3, little= 2, very little = 1

[4]The Taste was assessed according to the Likert scale as excellent = 5, good = 4, moderate= 3, poor = 2, very poor = 1

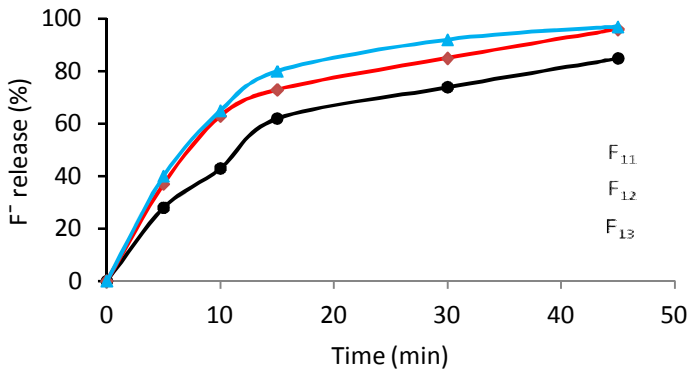

Figure 1: *In vitro* release of F^- from chewing gum with different ratio of gum bases in pH 6.8 phosphate buffer at 37º C

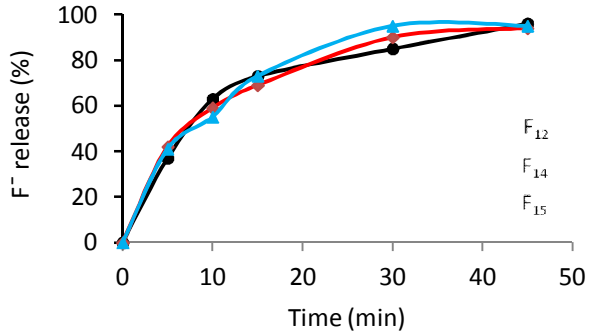

Figure 2: *In vitro* release of F^- from chewing gum with different sweeteners in pH 6.8 phosphate buffer at 37º C

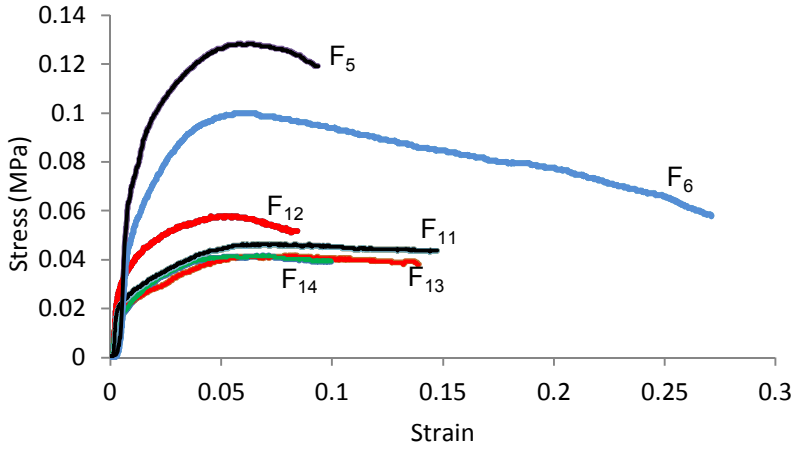

Figure 3: The mechanical evaluation of F_5, F_6 and $F_{11} - F_{14}$ at speed of 10 mm/min

Table 3: The most important parameters during tensile test

Parameters / Formulations	Yield strength (MPa)	Tensile strength (MPa)	Elongation (%)	Energy (J)	Elastic modulus	Time (Min)
F_5	0.09	0.13	6.46	66.7	27.30	0:3:57
F_6	0.06	0.10	6.56	63.2	8.04	0:3:77
F_{11}	0.02	0.05	9.00	39.6	12.10	0:14:13
F_{12}	0.03	0.06	5.73	26.9	13.22	0:11:45
F_{13}	0.02	0.04	8.41	31.5	10.26	0:17:74
F_{14}	0.02	0.04	7.15	57.4	5.40	0:18:09

Table 4: Taste assessment of formulations with flavorings banana, cherry, cinnamon and tutti-frutti in 20 volunteers by Latin-Square design (2nd Stage)

Taste assessment[1]	Formulation				
	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}
Sum of scores	54	94	88	74	62

[1]The taste was assessed using the Likert scale as excellent = 5, good = 4, moderate= 3, poor = 2, very poor = 1

Table 5: The taste-masking effects of cherry or peppermint as flavoring agent in *S. persica L.* chewing gum in 30 volunteers by Latin-Square design (3rd Stage)

Taste assessment[1]	Formulation	
	F_{12}	F_{13}
Sum of scores	134	123

[1]The taste was assessed using the Likert scale as excellent = 5, good = 4, moderate = 3, poor = 2, very poor = 1