Original Article

Design, formulation and evaluation of caffeine chewing gum

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Abstract

Background: Caffeine which exists in drinks such as coffee as well as in drug dosage forms in the global market is among the materials that increase alertness and decrease fatigue. Compared to other forms of caffeine, caffeine gum can create faster and more prominent effects. In this study, the main goal is to design a new formulation of caffeine gum with desirable taste and assess its physicochemical properties.

Materials and Methods: Caffeine gum was prepared by softening of gum bases and then mixing with other formulation ingredients. To decrease the bitterness of caffeine, sugar, aspartame, liquid glucose, sorbitol, manitol, xylitol, and various flavors were used. Caffeine release from gum base was investigated by mechanical chewing set. Content uniformity test was also performed on the gums. The gums were evaluated in terms of organoleptic properties by the Latin-Square design at different stages.

Results: After making 22 formulations of caffeine gums, F_{11} from 20 mg caffeine gums and F_{22} from 50 mg caffeine gums were chosen as the best formulation in organoleptic properties. Both types of gum released about 90% of their own drug content after 30 min. Drug content of 20 and 50 mg caffeine gum was about 18.2-21.3 mg and 45.7-53.6 mg respectively.

Conclusion: In this study, 20 and 50 mg caffeine gums with suitable and desirable properties (i.e., good taste and satisfactory release) were formulated. The best flavor for caffeine gum was cinnamon. Both kinds of 20 and 50 mg gums succeeded in content uniformity test.

Key Words: Caffeine chewing gum, coffee, medicated gum, oral mucosal drug delivery, tea

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INTRODUCTION

Undoubtedly, focusing is essential for any cognitive task especially for learning. However, it is not easy always. For some people, keeping their focus could be a hard task. Focusing is very important for our performance, especially in order to control work flow. To be focused while working, it is necessary to be alert. Focusing in fatigue condition is very hard.[1]

Fatigue can cause various complications and can damage individual's health. It reduces work efficiency and increases accidents. Furthermore, it reduces the interest on work and perform daily activities.[2] Tea and coffee consumption can significantly help refreshment.[3]

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Coffee and black tea are the main sources of caffeine. Behavioral and physiological effects of caffeine have been long documented, thus it is reasonable to assume that the refreshing effects of tea and coffee consumptions are mostly due to their caffeine. It has been proven that caffeinated beverage ingestion is associated with changes in mood state, particularly alertness.[4]

Caffeine is an odorless white powder. It is either anhydrous or can contain one molecule of water.[5] Caffeine is a methylxanthine that, like theophylline, inhibits the phosphodiesterase enzyme and has an antagonistic effect on the central adenosine receptors. Adenosine induces sleep thus caffeine consumption cause sleeplessness.[5,6] Caffeine is a central nervous system (CNS) stimulant which can promote wakefulness and increase mental activity. Moreover, it can stimulate the respiratory center and increase the rate and depth of respiration. However, its bronchodilating properties are weaker than theophylline.[5]

Caffeine can increase the rate of information processing.[3] Drinking a cup of coffee after a meal prevents drowsiness and helps to maintain concentration and alertness.[7] This is important for night shift workers to prevent accidents and errors, especially for the road drivers since the lives of a group of people depend on their wakefulness and alertness.[8] In fact, adenosine is produced during daily activities and binds to its receptors, which results in a fatigue feeling. Due to its similarity to adenosine caffeine sits on these receptors and prevents transmission of the signal. Thus, the person can continue his/her activity for a longer time.[3]

Caffeine facilitates the muscle performance and increases the total muscular work. Caffeine in usual oral dose is used as a mild CNS stimulant. It is also included in oral analgesic drugs such as aspirin and sometimes is combined with ergotamine in preparations for the treatment of migraine. Beverages such as coffee, tea, and cola provide active doses of caffeine.[5] Caffeine is found in the global drug market at 100 and 200 mg tablets and capsules.[9]

Usually caffeine is administered in studies in the form of tablets or capsules containing anhydrous caffeine. However, an alternative novel delivery method via chewing gum may provide some additional advantages.[10] Effects of caffeine observation in caffeinated chewing gum were interesting. Moreover, placebo chewing gum was found to be associated with some positive effects on mood shortly after chewing.[11] Chewing gum is a novel approach of oral transmucosal drug delivery and is a useful means for systemic drug delivery.[12]

It has many advantages compared to other drug-delivery systems, for example: (1) easy to use and requires no water which in turn, increases consumers' compliance, it is suitable for children and patients who have difficulty swallowing tablets, (2) rapid onset of action, (3) lesser side effects because the active substances are absorbed buccally without passing through the primary hepatic metabolism, which can result in a major bioavailability of the active substance, and (4) less risk of overdosing because chewing is necessary to release the active substance from the chewing gums.[13]

Gum chewing is a voluntary physiological motor activity that involves many neuronal pathways. It is associated with many physiological activities, including increased blood flow in the cerebral and orofacial region that may be effective for increased alertness and improved memory.[14]

Active substances that are released from chewing gums are swallowed with saliva and entered into the gastrointestinal track. These substances are either a soluble or a suspension, which in both cases has more rates of absorption than other forms (e.g., tablets).[15] The possibility of controlling the drug release over an extended time and the potential to improve the variability of the drug release and retention times, are other advantages of medicated chewing gums.[12]

The main purpose of this study is to design, formulate and evaluate caffeine gums with suitable taste and quality in order to improve the mood and increase alertness, focus and cognitive performance in people.

MATERIALS AND METHODS

Materials

The substances that were used in this study include four gum bases Elvazti, 487, Fruit C and Stick from Gilan Ghoot Company, (Rasht, Iran) and caffeine, aspartame, glycerin, xylitol, manitol and sorbitol from Sigma-Aldrich Chemie Gmbh, (Steinheim, Germany). Flavors of peppermint, cinnamon, cola, eucalyptus and banana were gifted by Goltash Company (Isfahan, Iran) and flavor of cherry from Farabi Pharmaceutical Company (Isfahan, Iran).

Gum preparation

First, the mixture of gum bases were weighed and carefully put inside a mortar on the water bath at 60°C temperature until it became soft. After softening the gum bases, other ingredients were added at a suitable time with a constant temperature. At first,

the active substance powder (caffeine) with aspartame and xylitol were triturated and then levigated with liquid glucose and glycerin, and were added to the gum bases mixture and mixed thoroughly. Then, a desired amount of sugar was added and mixed thoroughly until a uniformed mixture was achived. At the end of preparation, the temperature of the mixture was set below 40°C and the flavor was added gradually and mixed. When mixing was completed, the gum was placed on a glass plate, and then formatted into small bars with proper thickness and dimension. These gums were placed at the room temperature and packaged.

Sugar coating of caffeine chewing gums

The first sugar-coating layer contained acacia and sugar. Second and third sugar-coating layers consisted of acacia, sugar, and calcium carbonate.

Spectrophotometric analysis in phosphate buffer with pH 6.8

Various concentrations of caffeine prepared; first, the phosphate buffer was added to 10 mg of caffeine in a 100 ml calibration flask to obtain 100 ml solution. Then respectively 0.5, 1, 1.5, 2, 2.5, and 3 ml were taken from this solution and transferred to a 10 ml calibration flask and buffered to 10 ml volume. Thus, 5, 10, 15, 20, 25, and 30 μg/ml concentrations were prepared.

The wavelength at which the most absorbance occurs (λ_{max}) were determined with the 10 μg/ml solution and was 273.2 nm. Then the spectrophotometer was set at this wavelength and the absorbence of prepared concentrations was measured.[16]

In order to determine intraday and interdays variabilities, 3 samples from each concentration were prepared and this test was repeated for 3 consecutive days. After computing the average of absorbencies, a direct linear equation was obtained, and the related curve was plotted.

Evaluation of caffeine release from chewing gum

For this purpose, a device that simulates the action of chewing was used. A piece of gum was placed inside the machine's chamber. The horizontal pistons keep the gum in the right place while it is chewed by the vertical pistons. Notably, the chamber's pH was set at 6.8 using phosphate buffer. The temperature of the chamber was 37 ± 0.5°C and the rate of chewing was 60 rpm.[17]

When the chewing machine started to work under above-mentioned conditions, samples were taken from the chamber at 5, 10, 15, 20, 30, 40 and 50 min. In each sampling, for 20 and 50 mg gums, 1 and 0.5 ml of sample were taken from the chamber, and 1 and 0.5 ml of fresh phosphate buffer at 37°C temperature were added to the chamber, respectively. Furthermore, one placebo gum (gum without drug) was placed in the chewing machine, and samples were taken in above-mentioned times. The samples were buffered up to 10 ml volume with phosphate buffer and their absorbencies were measured by a spectrophotometer set at wavelength 273.2 nm. This procedure was repeated three times. Absorbencies of placebo gum samples were subtracted from the absorbencies of caffeine gums samples. Finally, concentrations and the amount of caffeine that released at each stage were determined by the linear equation of the standard curve.

Spectrophotometric analysis in chloroform

The spectrophotometric analysis in chloroform was done by a method similar to the analysis performed in the phosphate buffer. Here, the wavelength at which the most absorbance occurs (λ_{max}) was determined with the 10 μg/ml solution too, and it was 276.8 nm.

Evaluation of content uniformity in formulated gums

Ten gums were randomly selected from the prepared 20 and 50 mg gums, and were weighed and the amount of their caffeine were measured. In order to determine the amount of caffeine in the gums, each gum was dissolved in 100 ml chloroform. When dissolving was complete, 10 ml of solution was centrifuged using a centrifuge at 3200 rpm. Then 1 and 0.5 ml of the clear solution (for 20 and 50 mg caffeine gum respectively) were removed and buffered up to 10 ml volume and absorbencies of these solutions were measured by the spectrophotometer set at wavelength 276.8 nm. Also, the placebo gum was dissolved in chloroform, and its absorbance was measured using the same method. This absorbance was subtracted from the gums absorbencies.

Evaluation of organoleptic characteristics of prepared gums

The Latin-Square design was used for the evaluation of organoleptic characteristics of the formulations and 20 mg caffeine gums with formulations F_1 to F_{13} were prepared, and given to ten subjects. The subjects were asked for their opinions about the taste, softness/hardness, no stickiness to teeth, and mass volume of the gums. Organoleptic characteristics of 50 mg gums were investigated by ten subjects as well.

In the questionnaire forms, subjects according to the Likert scale as suggested words with scores 1-5 reported their opinions.

Selection of suitable flavoring agents

The Latin-Square design was used for the preliminary evaluation of taste of the formulations too. 20 mg caffeine gums with best formulation based on softness/hardness, no stickiness to teeth and mass volume of gum were

prepared in six flavors (peppermint, eucalyptus, cherry, banana, cola and cinnamon) and were distributed among ten subjects and were asked for their opinions about the flavoring agents. In this investigation, two flavoring agents earned the highest score.

After this stage, some gums from the best formulations in terms of flavor were prepared and given to 20 subjects, and finally, one flavor was selected. In this opinion test, subjects reported their opinions about taste according to the Likert scale as excellent = 5, good = 4, fair = 3, poor = 2, very poor = 1.

RESULTS

Spectrophotometric analysis

After preparation of various concentrations of caffeine in phosphate buffer and measurement of their absorbencies, the absorbance-concentration curve was plotted, and direct linear equation and Regression coefficient (R^2) were obtained. Direct linear equation was $y = 0.053x + 0.004$ and R^2 was 0.999.

Furthermore, after preparation of various concentrations of caffeine in chloroform and measurement of their absorbencies, the absorbance-concentration curve was plotted. Here direct linear equation was $y = 0.048x + 0.004$ and R^2 was 0.999.

Gum preparation

Caffeine gums, 20 and 50 mg, were prepared in 22 formulations and were coated using a sugar coating method [Tables 1 and 2].

In vitro drug release from chewing gum

The release of caffeine from the gum base is shown in Figure 1. Caffeine gums of 20 mg released about 47%, 75% and 88% of their drug and 50 mg gums released about 55%, 78% and 89% of their drug after 10, 20 and 30 min respectively.

Chewing gums weight variation and caffeine content

Weight variation of gums was within the united state pharmacopeia (USP) - recommended limit of ± 5%. The mean drug content was 19.75 ± 1.06 for 20 mg and 48.87 ± 2.76 for 50 mg caffeine chewing gums, all satisfying the criteria commonly required by USP for solid dosage forms. Table 3 shows the content of 10 gums that were randomly selected from 20 and 50 mg caffeine gums.

Evaluation of organoleptic characteristics of caffeine chewing gums

Ten subjects were given 20 mg caffeine gums with F_1 to F_{13} formulations, and their organoleptic characteristics were evaluated. F_{10}, F_{11} and F_{13} formulations earned the highest scores. Results of these investigations were

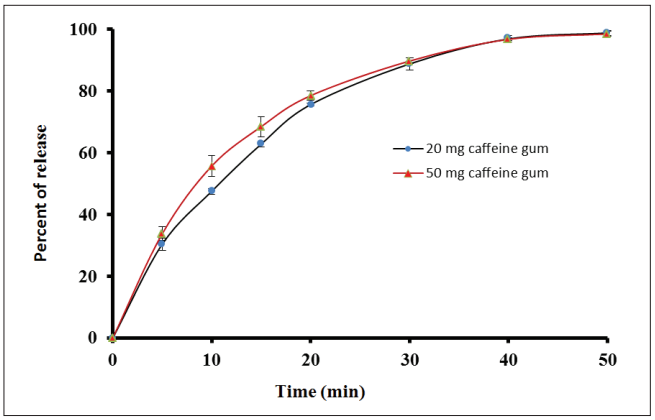

Figure 1: *In vitro* release of caffeine from 20 and 50 mg chewing gum in pH 6.8 phosphate buffer at 37°C

Table 1: Formulations of 20 mg caffeine gums with various ingredients and flavoring agents

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}
Caffeine	20	20	20	20	20	20	20	20	20	20	20	20	20
Gum base													
Elvasti	70	70	70	70	70	70	60	60	60	60	60	60	60
487	70	70	70	70	70	70	60	60	60	60	60	60	60
Stick	70	70	70	70	70	70	80	80	80	80	80	80	80
Fruit C	70	70	70	70	70	70	80	80	80	80	80	80	80
Sugar	500	500	500	500	500	500	500	500	500	500	500	500	500
Liquid glucose	20	20	20	20	20	20	20	20	20	20	20	20	20
Glycerin	20	20	20	20	20	20	20	20	20	20	20	20	20
Aspartame	-	2	2	2	2	2	2	2	2	2	2	2	2
Eucalyptus fla.	-	-	4	-	-	-	-	4	-	-	-	-	-
Peppermint fla.	-	-	-	4	-	-	-	-	4	-	-	-	-
Cherry fla.	-	-	-	-	4	-	-	-	-	4		-	-
Cinnamon fla.	-	-	-	-	-	4	-	-	-	-	4	-	-
Banana fla.	-	-	-	-	-	-	-	-	-	-	-	4	-
Cola fla.	-	-	-	-	-	-	-	-	-	-	-	-	4

shown as average scores in Table 4.

At the next stage, gums were prepared with six flavors and were distributed among ten subjects in order to evaluate the taste of gums and choose the best flavors. The best flavors were cherry and cinnamon. Results of this evaluation were shown in Table 5 as the sum scores out of 50.

At the next stage, two selected flavors were given to 20 subjects, and one flavor (i.e., cinnamon) was selected for rest of the study. Results of this evaluation were shown in Table 6 as the sum scores out of 100.

Ten subjects were given 50 mg caffeine gums with F_{14} to F_{22} formulations, and their organoleptic characteristics were investigated. F_{21} and F_{22} earned most points (F_{22} formulation had more flavoring agent). Results of these investigations were demonstrated in Table 7 as the average scores.

At the next stage, two gums with most scores (F_{21}, F_{22}) were given to 20 subjects in order to be evaluated in terms of taste. Finally, one formulation (F_{22}) was selected. Results of this evaluation were shown in Table 8 as the sum scores out of 100.

DISCUSSION

The pharmacodynamic effects of caffeine depend on its pharmacokinetic properties. A faster rate of absorption as observed with the chewing gum could result in a faster onset of its motive effects. When wakefulness is required caffeine improve efficiency and alertness in individuals who work late at night (e.g., medical and emergency personnel, truckers, and shift workers). Moreover, caffeine decreases physical and mental fatigue. As the onset of action for the gum delivery is within 5-10 min of chewing, the dose of caffeine can be rapidly and easily provided. A second piece of gum can be administered immediately, if a higher dose is needed. In contrast, a time interval must be considered between administrations of other dosage forms of caffeine.[8]

In the present study, all formulations (except F_8) were suitable in terms of either stickiness to teeth or mass volume [Tables 2, 7 and 8]. In terms of hardness/softness, formulations F_1 to F_6 had similar mixtures and ratios of gum bases (i.e., all four gum bases were used equally). In F_7 to F_{13}, gum bases were not used equally and two softer bases (Stick and Fruit C bases) were used more than two harder bases (Elvazti and 487 bases). This mixture of bases earned more points in organoleptic characteristics evaluation thus it was selected for the rest of the study and 50 mg caffeine gums were formulated with it as well [Tables 1, 2, 4 and 7]. In another study, nicotine gum was prepared with equal ratios of these bases, and it had suitable softness and hardness.[17]

The caffeine gums passed the content uniformity test. Drug content of 20 mg was about 18.2-21.3 mg and that of the 50 mg gum was about 45.7-53.6 mg [Table 3]. In the present study, both gum types (20 and 50 mg) were in the acceptable range of content uniformity.[18]

The gum's flavor is a key part in its formulation. If it is undesirable, it influences on person's compliance. Thus, it is very important to use a flavoring agent compatible with other ingredients in the formulation.[15] Selection of a flavoring agent is determined with drug's taste. Usually for covering the bitter taste of drugs, chocolate, peppermint and cherry are used.[19] Also, aspartame as a sweetening agent can cover the bitter taste of drugs. In the other study, sweeteners such as sodium saccharine and liquorice had moderate or no effect on masking the bitter taste of nicotine gums respectively, but aspartame showed the strongest effect on modifying

Table 2: Formulations of 50 mg caffeine gums with various ingredients and sweeteners

Ingredients (mg)	Formulations								
	F_{14}	F_{15}	F_{16}	F_{17}	F_{18}	F_{19}	F_{20}	F_{21}	F_{22}
Caffeine	50	50	50	50	50	50	50	50	50
Gum base									
Elvasti	60	60	60	60	60	60	60	60	60
487	60	60	60	60	60	60	60	60	60
Stick	80	80	80	80	80	80	80	80	80
Fruit C	80	80	80	80	80	80	80	80	80
Sugar	500	500	500	500	500	500	500	500	500
Liquid glucose	20	20	20	20	20	20	20	20	20
Glycerin	20	20	20	20	20	20	20	20	20
Aspartame	2	4	4	4	5	5	5	5	5
Xylitol	-	-	10	20	-	-	-	10	10
Manitol	-	-	10	20	-	10	-	-	-
Sorbitol	-	-	10	20	-	-	10	-	-
Cinnamon fla.	4	4	4	4	4	4	4	4	5

Table 3: Amount of drug content of 10 gums (20 and 50 mg gum)

Caffeine content (mg)	Gum number										Mean±SD
	1	2	3	4	5	6	7	8	9	10	
20 mg gum	19.29	18.79	18.27	20.71	20.58	19.66	21.34	18.57	19.43	20.84	19.75±1.06
50 mg gum	51.83	47.28	50.94	45.74	48.09	46.24	46.28	49.56	49.16	53.64	48.87±2.76

Table 4: Organoleptic characteristics of different 20 mg caffeine chewing gums in 10 subjects at first stage by Latin-Square design

Organoleptic characteristics	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}
Softness/ Hardness*	3.6	3.6	3	4	3.2	3.2	3.8	1	3	3	3	3	3
Stickiness to teeth**	5	5	5	5	5	5	5	1	5	5	5	5	5
Mass volume of gum***	3	3	3	3	3	3	3	3	3	3	3	3	3
Taste****	1.2	3	3.4	3.2	4	4.4	3	3	3.4	4	4.4	3.8	4

*The Softness/hardness was evaluated according to the Likert scale as very hard: 5, Hard: 4, Suitable: 3, Soft: 2, Very soft: 1, **The stickiness to teeth was evaluated according to the Likert scale as never: 5, Rarely: 4, Sometimes: 3, Most of times: 2, Always: 1, ***The mass volume of gum was evaluated according to the Likert scale as far too much: 5, Too much: 4, About right: 3, Too little: 2, Far too little=1, ****The Taste was evaluated according to the Likert scale as excellent: 5, Good: 4, Fair: 3, Poor: 2, Very poor: 1

Table 5: Test evaluation of formulations F_3 and F_9-F_{13} with different flavoring agents in caffeine chewing gums at the second stage by Latin-square design

*Taste evaluation	Formulations					
	F_3	F_9	F_{10}	F_{11}	F_{12}	F_{13}
Flavoring agent	Eucalyptus	Peppermint	Cherry	Cinnamon	Banana	Cola
Sum of score	30	32	40	45	35	38

*The taste was evaluated by 10 subjects using the likert scale as excellent: 5, Good: 4, Fair: 3, Poor: 2, Very poor :1

Table 6: The taste-masking effects of cherry or cinnamon as flavoring agent in caffeine gum formulations at the third stage

*Taste evaluation	Formulations	
	F_{10}	F_{11}
Flavoring agent	Cherry	Cinnamon
Sum of score	59	82

*The taste was evaluated by 20 subjects using the Likert scale as excellent: 5, Good: 4, Fair: 3, Poor: 2, Very poor :1

the bitter taste of it.[17] Generally for this purpose using the sweetening agents and flavoring agents could help to significantly improve the gum's taste. When we evaluated the effects of the flavoring agents on the organoleptic characteristics of the gums, our results showed that generally the flavoring agents had a softening effect on the formulations. However, the peppermint flavor caused the gums to be dry and fragile. Among these flavoring agents, eucalyptus flavor had a strong softening effect such that when added to the F_8 formulation which had a softer base than F_3 formulation. It caused excessive softening of the gum, while other flavors only slightly improved the softness state of the gums [Table 4]. We preferred to use the F_9 formulation for peppermint flavor and F_3 formulation for eucalyptus flavor and for other flavors formulations similar to F_7 were selected, because in the opinion tests formulations with similar gum base as F_7 had better and more suitable

Table 7: Organoleptic characteristics of different 50 mg caffeine chewing gums in 10 subjects at first stage by Latin-square design

Organoleptic characteristics	Formulations								
	F_{14}	F_{15}	F_{16}	F_{17}	F_{18}	F_{19}	F_{20}	F_{21}	F_{22}
Softness/Hardness*	3	3	3	3	3	3	3	3	3
Stickiness to teeth**	5	5	5	5	5	5	5	5	5
Mass volume of gum***	3	3	3	3	3	3	3	3	3
Taste****	1.2	2.2	2.8	3	3.6	3.8	3.8	4.2	4.6

*The Softness/hardness was evaluated according to the Likert scale as very hard: 5, Hard: 4, Suitable: 3, Soft: 2, Very soft: 1, **The stickiness to teeth was evaluated according to the Likert scale as never: 5, Rarely: 4, Sometimes: 3, Most of times: 2, Always=1, ***The mass volume of gum was evaluated according to the Likert scale as far too much: 5, Too much: 4, About right: 3, Too little: 2, Far too little: 1, ****The Taste was evaluated according to the Likert scale as excellent: 5, Good: 4, Fair: 3, Poor: 2, Very poor: 1

Table 8: The taste-masking effects of cinnamon as flavoring agent in caffeine gum formulations

*Taste evaluation	Formulations	
	F_{21}	F_{22}
Cinnamon fla. (mg)	4	5
Sum of score	86	94

*The taste was evaluated by 20 subjects using the Likert scale as excellent: 5, Good: 4, Fair: 3, Poor: 2, Very poor :1

organoleptic properties [Table 5]. Adding flavor to the gum base should be performed in the last stage and at a temperature below 40°C, because a temperature above 40°C causes the flavoring agent to deteriorate. Moreover, adding flavoring agents at a temperature below 40°C may cause softening of the gum. In this investigation, at the first stage, two flavoring agents (i.e., cherry and cinnamon) had higher scores [Table 6]. At the next stage, F_{11} (gum with cinnamon taste) was selected as the best formulation based on the organoleptic characteristic and taste. This formulation was selected for the preparation of 50 mg caffeine gums in the rest of the study. When producing the 50 mg gums, because the amount of caffeine in formulation was higher, we used more aspartame compared to the 20 mg caffeine gum, as well as manitol, sorbitol, xylitol and finally, more flavor until at the end a formulation with suitable taste was achieved [Tables 7 and 8].

Medicated gums are formulated such that they release the maximum amount of their active component in an appropriate time. There are various factors that influence the release and absorption of the drugs, for example, rate and intensity of chewing and the amount of saliva that is produced.[20] The release rate of the drugs from medicated gums depends on their water solubility. Water soluble substances are released from medicated gums completely and rapidly. On the contrary substances that are less soluble in water are released from medicated gums incompletely and slowly.[13] Water solubility of caffeine is 1 in 50.[5] Moreover, it is known that

when a drug has a water solubility between 1 in 10 and 1 in 300, 60% of the drug is released from the gum during 10 min. Accordingly, if these gums are chewed for 15 min, between 50% and 90% of the drug will be released.[15] In this study caffeine was released from the gum base as we expected. After 20 min chewing approximately 75% and 78% of caffeine was released from 20 to 50 mg gums respectively. This increased to about 90% after 30 min chewing for both formulations [Figure 1].

In a study carried out by Gary H. Kamimory and his colleagues, a caffeine gum named Stay Alert® was compared with caffeine capsule in terms of their absorption and bioavailability. They concluded that caffeine with gum form is absorbed at higher rates and provides similar bioavailability. Based on the data from the manufacturing company of this gum, 85% of caffeine was released after 5 min of chewing.[8]

Furthermore, another research performed by Henry T. Tyrpin and his colleagues showed that caffeine has a slow-release rate from the gum such that after 20 min about 88% and after 40 min about 97% of it is released. In this study, the authors stated that to control the release, they had to change the physical properties of caffeine by coating the caffeine particles. Indeed, coating the caffeine particles with methods such as encapsulation or agglomeration can change caffeine release; depending on the type of coating substances and the degree of coating, the release rate could become faster or slower. This could be very effective in decreasing the bitter taste of caffeine.[21] In the present study we used gum bases with different characteristics and ratios and therefore, caffeine release of the gum was controlled. During the preparation of the caffeine gums, triturating caffeine powder with aspartame and xylitol and levigating this mixture in glycerin and liquid glucose resulted in coating of caffeine particles which in turn decreased the bitter taste of it and kept the sweet taste until the end of chewing.

CONCLUSIONS

According to our findings, 20 and 50 mg caffeine gums with suitable organoleptic properties can be prepared. F_{11} of 20 mg gums and F_{22} of 50 mg gums were the best formulations in terms of organoleptic characteristics. Best flavoring agent and sweetener for these gums that could modify bitter taste of caffeine were cinnamon flavor and aspartame sweetener. These gums had desirable release and acceptable content uniformity. Consequently, our study confirmed that gums provide suitable dosage forms for drug delivery of caffeine.

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