

# Formulation development and evaluation of metformin chewing gum with bitter taste masking

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## Abstract

**Background:** Medicated gums are intended to be chewed and act either locally, absorbed via the buccal mucosa or swallowed with saliva. We prepared the metformin gum to overcome its side effects including vomiting, diarrhea, and abdomen discomfort. Furthermore, it could be useful for those who have swallowing problems.

**Materials and Methods:** Metformin hydrochloride (250 mg) with suitable sweeteners was mixed manually for 5 min. This mixture was spray dried, freeze dried, or directly mixed with chewing gum base. Glycerin, xylitol, and menthol were added and the produced paste was kept in the freezer for 2 h to be stable. As the metformin shows bitter taste, we tried to mask this unpleasant taste with using different methods explained. The releasing pattern was evaluated by using a mechanical chewing machine. The best formulation with the optimized releasing pattern, suitable physicochemical properties and pleasant taste were selected. Content uniformity, releasing percent, and other physicochemical properties were identified as well. Taste, flavor, and appearance characteristics were evaluated by using a self-made questionnaire based on the hedonic test method.

**Results:** The chewing gum dosage content was about 86.2%. The release rate of metformin chewing gum was about 70% after 5 min of mastication. Masking the bitter taste of drug was achieved by using acesulfame-isomalt as sweeteners and prepared it by freeze drying equipment.

**Conclusion:** Metformin chewing gum had suitable appearance and appropriate *in vitro* characteristics that follow the pharmacopeia suggestions. This chewable gum showed bitterness suppression with a suitable release rate.

**Key words:** Acesulfame-isomalt, freeze drying, hedonic test, medicated chewing gum, metformin

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## INTRODUCTION

Aspirin chewing gum was the first medicated chewing gum produced in the United States. Since then, the medicinal chewing gums have been available in the market. Nicotine gum was introduced during the 1970s in which the potential of chewing gum as a drug delivery system was recognized. The commission of European Council has accepted it as a drug delivery system since 1991.<sup>[1]</sup>

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By using a medicated gum, a drug is released in the mouth from gum and can act either locally, or systemically in which the drug can be absorbed via the buccal mucosa or swallowed with saliva.<sup>[2]</sup> Using chewing gum increases the saliva and amplifies buffer system in mouth that helps to neutralize the acidic situation and increase rebuilding the external coverage of teeth.<sup>[3,4]</sup> Medicated gums can be used for the delivery of dental products in the mouth as an alternative to mouthwashes or can be used for some diseases such as xerostomia or for other systemic diseases.<sup>[5]</sup> This dosage form is intended to be chewed for 10–30 min for active ingredient to dissolve in the saliva prior to swallowing. It is a convenient dosage form, because it is administered without water, comforted to stop drug delivery at any time and it is carryable.

Some chewing gums introduced for their systemic effects are pain killers,<sup>[6]</sup> vitamins such as vitamin C,<sup>[7]</sup> alertness enhancers,<sup>[8]</sup> motion sickness removal,<sup>[9]</sup> and smoking cessation gums.<sup>[10]</sup>

If a drug is absorbed buccally or by sublingual blood vessels, as it may be a case for metformin, the first-pass metabolism can be avoided and a faster onset of action might be possible. Associated increases in bioavailability facilitate the use of lower doses and may reduce the incidence of gastric side-effects, a possible benefit for developing the metformin gum.

Metformin is a crystalline white powder that is highly soluble in water made it a good candidate for developing medicated chewing gum as the drug is released in saliva.

It is used to regulate blood glucose levels by decreasing hepatic glucose production and hepatic glucose output. It belongs to the biguanides class of antidiabetic drug and improves the insulin sensitivity of cells. Metformin also slows glucose absorption from the gastrointestinal tract.

Although it is a popular medicine for type 2 diabetes, millions of people do not use it because of its side effects, including gastrointestinal disturbance, large pill size, and unpleasant bitter taste especially for the children. It is believed that abrupt release of active drug in gastrointestinal tract causes the side effects such as vomiting, diarrhea, abdomen discomfort.<sup>[11]</sup>

In this study, the metformin chewing gum was prepared with the acceptable taste to increase its compliance and decrease its adverse effects in patients.

## MATERIALS AND METHODS

### Chemicals

Metformin powder and the chewing gum base were kindly provided by Minoos Industrial Company (Tehran, I.R Iran). Glycerin, aspartame, sodium hydroxide, potassium hydrogen phosphate, sodium saccharine, potassium acesulfame, chloroform, and dichloro-methane (Merck Chemical Company, Germany) were purchased from market. Spearmint essence was bought from Parea-Quinica Company (Spain).

### Instrumentations

A mastication device designed to simulate the mastication of metformin chewing gum in human. This device was used to evaluate the releasing pattern of the drug from gum.<sup>[12]</sup> Briefly, the fully transparent wall of the vessel used to be able to inspect visually during the mastication of samples. The test vessel consists of transparent glass chamber; upper and lower jaws simulator; setting of twisting angle; a place for the chewing gum; circulation of thermostat controlled water. The instrumental settings were adjustable for different gum formulations but in the present experiment the following settings and conditions were used. Temperature of the test medium was set at 37°C; 40 ml of phosphate buffered saline PBS (pH 6.8) was used as the volume of the test medium. 50 strokes per minute used for chewing frequency. The distance between the upper and lower jaws set at 1.6 mm and total chewing time was 45 min. Aliquots of 1 ml were withdrawn from each tests chamber at 5, 10, 20, and 60 min during the *in vitro* releasing procedure. The samples were diluted for analyzing the drug concentrations in the medium.

### Spectrophotometric analysis

Spectrophotometric measurements of metformin samples were carried out using the Shimadzu UV-1240 model UV-VIS spectrophotometer with 1 cm quartz cell. A standard stock solution of metformin hydrochloride reference standard (100 µg/ml) was prepared in a 100 ml calibrated flask in phosphate buffer (pH 6.8). A validation set consisting of six solutions in working range of 5–30 µg/ml was freshly prepared and scanned in the UV region. This process was repeated three times for each concentration. The absorption maxima observed at 233.4 nm was recorded and plotted against concentration, which followed the Beer and Lambert's law and gave a straight line ( $R^2=0.998$ ).

### Preparation of metformin hydrochloride chewing gum

Metformin was mixed with acesulfam-isomalt as the suitable sweeteners manually. This mixture was then either freeze dried, spray dried, or directly mixed

with chewing gum base in 65°C. Glycerin, xylitol, and menthol were added and the produced paste was kept in the freezer (-4°C) for 2 h to be stable. As the metformin has bitter taste, we tried to mask this unpleasant taste with using different methods which is explained in drug taste masking section.

Due to the absence of any reported method for hardness of gum, it was decided to visually and physically evaluate this value.

### Dosage content

To determine drug content in chewing gum, nine chewing gum units of selected formulation were used. Each unit was crushed separately, transferred to a decanting vessel and 250 ml chloroform was added. Within 24 h, 250 ml phosphate buffer (pH 6.8) was added in several times to extract the drug. The absorbance of solution was measured spectrophotometrically at 233.4 nm. Then the metformin concentration was measured using the standard curve.

### Weight variation

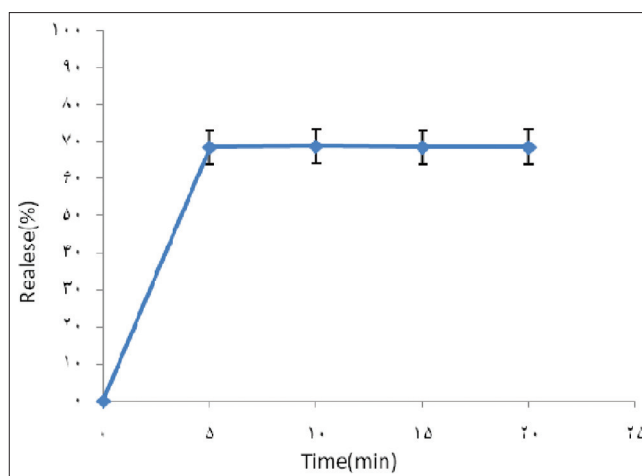
Weight variation of the selected formulation was done by the method described in United State Pharmacopoeia for metformin tablets.<sup>[13]</sup>

### Drug release from chewing gum

The drug release evaluation for medicated chewing gum is completely different from conventional oral formulations. For chewing gum evaluation, both of the dosage form and the chewing activity would influence the drug release. Furthermore, gums are not intended to disintegrate and dissolve by stomach environment, but a mechanical crushing of the chewing gum is also required<sup>[14]</sup> for drug delivery. Therefore, equipments used for other oral dosage form delivery are not suitable for drug release testing of chewing gum. For this situation, the European Pharmacopoeia guidelines recommend the employment of a particular device for gum formulations which is able to simulate the human chewing behavior.<sup>[15]</sup>

In the current experiment, three metformin chewing gums have been tested by using the mastication device. Phosphate buffer (30 ml) was placed to the dilution container of mastication device and a designed chewing gum was fixed on its predesigned place in the machine. The piston was adjusted on chewing gum. The mechanical mixer (as a motor) was attuned on 60 rounds per minute. The masticating machine was started to release the drug from the chewing gum.<sup>[12]</sup>

Aliquots of 1 ml were withdrawn from each test cell at 5, 10, 15, 20, and 60 min during the releasing testing procedure. The medium was replaced by a phosphate buffer (pH 6.8 in 37°C) after each sampling time. The



**Figure 1:** Metformin release profile from optimized chewing gum formulation (Mean SD, n=3).

experiments were replicated on three placebo chewing gums as well. The percent of drug released during the mastication process was calculated by subtracting the absorbance of the active ingredient present in the gum from the absorbance of the placebo gum. The mean releasing percent and the related standard deviations are shown in Figure 1.

### Drug taste masking

Taste masking agents can be classified according to basic drug that is to be masked. Flavoring agents are either natural or synthetic in nature. Natural flavors are usually distilled fractions of natural materials such as peppermint, balsam, clove, and lemon oil which are available as concentrated extracts, alcoholic or aqueous solutions. For formulations which are intended to be chewed or dissolved in the mouth, clove oil or calcium carbonate is useful. Aspartame, sodium saccharine, acesulfame, and isomalt are the sweeteners used to mask the bitter taste of drugs as well. Furthermore, various methods are used to mask the bitter tastes of drug.<sup>[16-19]</sup>

In this study, we employed various sweeteners to mask the bitter taste of metformin. However, the sweeteners we used either were unable to mask the bitter taste of metformin powder or were interfering with the absorbance of metformin. After assigning the suitable sweeteners and acesulfame-isomalt mixture, different methods to make a proper formulation were employed. Methods we employed to mask the taste of metformin were as follow.

### Trituration method

Aspartame, sodium saccharine, and the mixture of acesulfame-isomalt were used to mask the bitter taste of metformin by simple mixing. To achieve the pleasant taste, drug was mixed with each of mentioned

sweeteners in separate experiments to cover the bitter taste by coating the drug molecules. As the bitter taste was not alleviated, the spray drying method was employed.<sup>[20]</sup>

### Spray drying method

One gram of metformin plus 2 g of acesulfame–isomalt, with equal weight, were dissolved in 20 ml of water. The resulting solution was transferred to a mini spray dryer machine with temperature adjusted to 115°C. The aspirator set at 60% pumped by 8% and the spray pressure was set at 40 bars. The resulting powder achieved showed much more acceptable taste as it was compared to the triturating method. Besides, using this method less material was wasted. However, much sweeteners and drug powders were stuck to the chamber of the mini spray drying machine, so this method was not acceptable and it did not provide enough medicated powder.

### Freeze drying method

Similar to the previous method 1 g of metformin plus 2 g of acesulfame-isomalt were dissolved in 20 ml of water and frozen. It was left in the freezer for 24 h and the mixture was transferred to the freeze dryer apparatus for 48 h, 2002, p 537. The resulting powder had an acceptable taste without the previous problems and it provided the suitable amount of masked powder therefore this method were used for further studies.

### Evaluating the taste and features of metformin chewing gum

Consumer sensory evaluation is the use of consumer sense to establish food preferences.<sup>[18,21]</sup> Testing the end user preferences has been suggested as a measure of consumer product acceptance. To minimize the rate of failure for marketing a new product, it is essential to carry out a market survey to the perception of the end user for the new product. In this regard, we measured the taste of the prepared formulation and compared it to the available gum in the market (CHIEC® chewing gum with the mint taste). To perform the taste measurement, a self-made questionnaire based on the sensory test was used.<sup>[22,23]</sup> The questionnaire was distributed among 12 volunteers randomly. It contained two parts; in the first part, features of chewing gum were measured and in the second part, the formulated product was compared with the chewing gum available in the market.

Twelve healthy man volunteered in the age group of 20–23 years were enrolled in this study as the panel. After gum preparation, each volunteer was chewed either the formulated gum or the gum obtained from the market for 10 min. Taste preference was determined by the sensation tests as compared between two formulations.<sup>[18]</sup> Participants evaluated the different

statement [Table 2] with a score from one (1) to five (5), where a score of one (1) equaled “strongly disagree” and five (5) equaling “strongly agree”. This numerical scale was validated by testing samples randomly. The oral cavity was rinsed with water before using the second sample to avoid bias. The wash out period between testing different samples was at least 15 min.

### Statistical analysis

All testing is performed according to pharmacopoeia requirements. In any cases in which the statistical analyses were required the paired *t*-test was performed. A significant difference was set at 0.05. Furthermore, the hedonic test was used to evaluate the taste of the formulated gum by a self-made questionnaire.

## RESULTS

### Preparation and evaluation of chewing gum

Gums were prepared according to Table 1 without any problem. It did not require any change in ratio of excipients. Among prepared formulations, number 7 had the best characteristic, thus it was selected for further studies. Gums prepared were smooth and soft and it did not coated as for experimental purpose. Weight variation was within limit of  $\pm 5\%$ . It seems that the gums had suitable hardness as they were chewed by volunteers. All formulations were visually inspected and physically evaluated for appearance, color, stickiness, and plasticity which seem suitable. As the last formulation (#7) found the suitable taste, it was selected for further studies.

### Drug releasing from chewing gum

As the instrumental settings may affect the drug release profile, we find the instrumentation to be suitable as it was explained in method.

The rate and amount of drug released from the selected gum was determined in phosphate buffer (pH 6.8), because the pH of the saliva is in the range of 6.3 to 7.2. Drug release was tested for all formulations explained in Table 1. For the first set of formulation using aspartame, it was found that this sweetener interferes with the absorbance of metformin. In fact, drug and aspartame showed the same absorbance at 233.4 nm. The same problem was observed after using sodium saccharin as well. Therefore, we used acesulfame-isomalt which showed no interfering problem with metformin. From this study, it was found that drug release from the selected formulation after 5 min was about 70%. This finding may propose a longer oral presence of metformin in oral cavity. Figure 1 shows the drug release from the selected chewing gum in 20 min.



**Table 1: Various formulations of metformin chewing gum (Number 7 is the selected formulation)**

Gum Base (g)	Glycerin (g)	Xyletol (g)	Aspartame (g)	Saccharin (g)	Acesulfam and Isomalt (g)	Metformin (g)	Menthol (mg)
2.25	0.5	0.25	0.22	—	—	0.5	4.5
2.25	0.5	0.25	0.22	—	—	0.25	4.5
2.25	0.5	0.25	—	0.22	—	0.25	4.5
2.25	0.5	0.25	—	0.22	—	0.25	4.5
2.25	0.5	0.25	—	—	0.5	0.25	4.5
2.25	0.5	0.25	—	—	0.5	0.25	4.5
2.25	0.5	0.25	—	—	0.5	0.25	4.5

**Table 2: Different statements used to evaluate the preference of metformin chewing gum as compared to an available gum in the market**

Questions	Scores
The prepared gum shows an appropriate taste	3.5
The prepared gum smells good	4.3
The prepared gum is chewed easily	4.4
The prepared gum is smooth and soft	3.75
Sample masks the taste of metformin	4.08
Two samples tastes equally	3
Two samples smells similarly	4
Two samples needs equal force for chewing	4.5
Two samples has an appropriate appearance	3.6
In overall two samples looks equally	4.25

### Dosage content

To determine drug content in selected chewing gums, 9 units was taken randomly. All gums contained about 250 mg of metformin. The mean drug content value obtained was  $86 \pm 6\%$  which was found satisfactorily within limits.

### Effect of sweetening agents on bitter taste

The taste masking test was carried out using the sensory test method.<sup>[18]</sup> For this experiment, the formulation 7 was used and the preference tastes of the chewable gums were compared. In comparison between these two gums, volunteers find them to be comparable. The results are shown in Table 2.

## DISCUSSION

Chewing gums at the first glance are mainly considered as a confectionery product. However, medicated chewing gums available in the market paved the way for a more general acceptance of such gums as a drug delivery system. Nowadays, this new drug delivery system has established itself on the market and achieved a reasonable acceptance by both professionals and patients.<sup>[24,25]</sup> This drug delivery system can be designed in a way to be a suitable dosage form for children as well. On the other hand, if a drug absorbed buccally, due to the buccal mucosa which is a well-vascularized tissue, it may pass the first-pass metabolism and a faster onset of action is achieved. In this case, increases in bioavailability of a drug would

facilitate the use of lower doses and may reduce the incidence of gastric side-effects, a potential benefit for metformin gum.

Various formulations should be prepared and tested to provide a chewing gum with acceptable organoleptic and technological properties. A pleasant taste is a prerequisite for this dosage form. An optimal chewing volume, a long-lasting taste, anti-adherent properties to the teeth, and acceptable pharmaceutical properties such as fast and complete drug release from the prepared formulation must be considered as well. Metformin is a drug with the bitter taste and the first problem were encountered in this study was masking the bitter taste. Different pharmaceutical approaches are used to mask the taste of bitter drugs including use of flavors and sweeteners,<sup>[26,27]</sup> coating of drugs using a suitable polymers,<sup>[28]</sup> taste masking by a spray drying technique,<sup>[29]</sup> complex formation with ion exchange resin,<sup>[30]</sup> taste masking by inclusion complex formation,<sup>[31]</sup> forming solid dispersion,<sup>[32]</sup> microencapsulation technique,<sup>[26]</sup> multiple emulsion preparation,<sup>[27]</sup> liposome formation, and pro-drug approach.<sup>[33]</sup>

All gums were prepared in a cubic shape with 2 cm diameter and 1 cm thickness. Formulation 7 was used in this experiment. Prepared gums were a little harder than a pastilles candy, and they were easily crushed by bite; however, their hardness was not measured in detail.

In this study, we were supposed to mask the bitter taste of metformin by using various sweeteners. As we are making a new formulation for diabetes, we had limitation in using sugar or other sweeteners with the sugar. Aspartame, sodium saccharine, acesulfame-isomalt had no interfering with blood glucose and are suitable for making such formulation. To mask the bitter taste of drug, the simplest method in which the plain mixing of sweeteners and drug powder is mixed was employed. Aspartame and saccharin tended to suppress bitter taste; however, they were interfering with the metformin absorbance at 233.4 nm. Due to this interference we were unable to employ these sweeteners therefore, acesulfam-isomalt

were used. Acesulfam-isomalt had no interfering with the drug absorbance but it did not mask the drug taste by simple mixing. At this stage, spray drying was the first method considered for drug coating as it was reported that spray drying may overcome this problem.<sup>[16]</sup> Spray drying was a suitable method for making microspheres by coating the drug powder. Although the drug powder was coated very well, but it was stuck to the chamber of machine and the yield of the final preparation was very low. At this point, it was decided to utilize the freeze dryer to coat the metformin powder. By using this method, the drug was coated successfully and the bitter taste was masked.

### Drug-release testing

Drug delivery from a medicated chewing gum is completely different when compared to conventional oral drug delivery systems. For chewing gums, chewing activity of the patient should also be simulated as it can influence drug release. Drug releasing from gums is not performed by disintegrating and/or dissolving by itself but a mechanical treatment of the dosage form is required<sup>[14]</sup> to make the drug to be released. It seems that transition from the gum base to the active drug is influenced by mechanical forces, temperature, and water permeation. In fact, under sink conditions, the rate of drug release is directly related to the chewing frequency and solubility of drug in buccal cavity and is indirectly related to the mass of the gum base. Therefore, we should employ a specific device for drug release which simulates human chewing behavior.<sup>[15]</sup> We adopted a similar device to determine the release rate from metformin chewing gums formulations.

The release profile indicated that formulation # 7 released about 70% of metformin from the gum base in the releasing chamber of employed device. Figure 1 shows the results of the dissolution test performed on the chewing gum for 5, 10, 15, and 20 min. The chewing frequency, temperature of the test medium, distance between the upper and lower jaws, and chewing times are four factors which may affect the drug release from the gum base. Although 70% of metformin is released in *in vitro*, a longer oral presence of metformin in oral cavity maybe achieved. Additionally, we may change the drug release by changing these factors *in vitro*.

The average dosage content of metformin chewing gum was about  $86 \pm 6$  % which is in the range of dosage content mentioned in the pharmacopeia for oral dosage forms. This value is in a lower limit of drug releasing from the tablets. It should be considered that this amount is released in *in vitro* and the mastication of the gum in the mouth and the oral cavity environment which is similar to sink condition is completely different from the *in vitro* experiment.

### Bitterness evaluation

Bitterness evaluation results were made by the consents of volunteers enrolled in this study. In sensory testing, volunteers are employed as an instrument to measure characteristics or preference levels and product differences.

For comparing two products, a hedonic test is employed, which explores volunteer's likings or preference levels of the products. Volunteers' should have some criteria in common, such as willingness to participate, availability, and freedom from food allergies.

Using a Likert taste preference scale, participants evaluated the statements explained in table two. The formulation #7 had a mean Likert score of 4, showing that the prepared formulation is acceptable for volunteers. As this formulation was compared to available brand gum the mean Likert score was about 3.9 with no statistical difference between these two formulations with regard to the taste and the appearance.

### CONCLUSION

The present study revealed that metformin would be a suitable drug for making it as a new dosage form such as a chewable gum. The chewable gum prepared by the freeze dryer and the mixture of acesulfame-isomalt as sweetening agents showed bitterness suppression. Those prepared either by the simple mixing or by the spray dryer with the same sweetening agent were not comfortable in taking and the bitterness did not mask. Formulation #7 was the most excellent chewable gum for taste balance and oral feeling and good drug release.

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