



# The development and *in vitro* evaluation of benzydamine hydrochloride medicated chewing gum formulations

Özlem Akbal\*, Erdal Cevher, Ahmet Oğul Araman

Department of Pharmaceutical Technology, Faculty of Pharmacy, İstanbul University, 34116, İstanbul, Turkey

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## ABSTRACT

The objective of this study was to develop a chewing gum formulation for benzydamine hydrochloride (BN) and evaluate the effect of different co-compression agents on physicochemical parameters and *in vitro* drug release profile. BN has been utilized in symptomatic treatment for pain and irritations of the mouth and throat. Chewing gum formulations of BN were produced using direct compression method. In fabricated chewing gums, except pharmacopeia analysis, physical and structural analysis like thickness, weight variation, elasticity and compressibility were evaluated. The release of BN from the gum was studied using the chewing apparatus which have been designed for procuring the release of BN from the chewing gum. The quantity of BN present in the chewing gum and the release medium were quantified by spectrophotometric method. Gum formulations showed promising *in vitro* release profiles, in which 80–90% BN was released in a sustained manner over 20 min of chewing time. In addition, it was observed that the drug release was fitted into matrix diffusion kinetic and revealed a non-Fickian drug release mechanism. This study suggests that BN in a gum formulation is a suitable dosage form for the delivery in the oral cavity, thereby and serving as an instant analgesic.

**Keywords:** Benzydamine hydrochloride, medicated chewing gum, mastication apparatus

## INTRODUCTION

Benzydamine hydrochloride (BN), a tertiary amine derivative, is a non-steroidal anti-inflammatory agent that possesses analgesic, anesthetic, anti-inflammatory, anti-pyretic and anti-microbial properties. However its oral, topical and oro-mucosal dosage forms are currently available in the market, it is commonly in use for the relief of inflammatory conditions of the oral cavity soft tissues and skin.

In a mouth-rinse formulation as a concentration of 0.15 % BN, its use has been indicated in the cure for recurring oral disorders as aphthous stomatitis, burning mouth syndrome, sore throat and radiation-induced oral mucositis (Herrera 2005).

Since the ancient times, chewing gum has been used world-wide, however the concept of using chewing gum as a drug delivery system has been implemented for more than 100 years. *Aspergum*, which contains acetyl salicylic acid, is the first medical chewing gum (Noehr-Jensen et al. 2006). It was marketed in 1924 in the USA and is still in the market. Chewing gums gained broader attention as a drug delivery system with the introduction of nicotine containing chewing gums into the market in 1978 (Rowe 2003). Twenty years later, in 1998, drug containing chewing gums were included in the European Pharmacopoeia with the name: '*medicated chewing gum*' (European Pharmacopoeia 9<sup>th</sup> edition ).

The definition of medicated chewing gum in the European Pharmacopoeia is stated as; "a single-dose, solid preparation with tasteless masticatory gum base, mainly consisting of gum which is intended to be chewed and not swallowed, providing a slow steady release of the medicine contained", and it is intended to be used as "local treatment of mouth diseases or systemic delivery after absorption through the buccal mucosa or from the gastrointestinal tract" (Herrera 2005). Medical chewing gums have

### \* Address for Correspondence:

Özlem Akbal, e-mail: ozlemakbal@istanbul.edu.tr

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been formulated with different kinds of drugs beside nicotine (Cherukuri et al. 2000; Morjaria et al. 2009) and aspirin (Woodford and Lesko 1981) such as nystatin (Andersen et al. 1990), miconazole (Pedersen and Rassing 1990), caffeine (Tyrpin et al. 2002), antacids (Zyck et al. 2003), anti-microbial decapeptide (Dong et al. 2005), ondansetron hydrochloride (Nagaich et al. 2010), cetirizine (Stojanov et al. 2012; Swamy et al. 2012), dextromethorphan hydrobromide (Swamy et al. 2012), dimenhydrinate hydrochloride (Mehta and Trivedi 2011).

Medicated chewing gums have so many benefits compared to other conventional oral mucosal dosage forms that are intended to be used for local treatment of mouth diseases like gingivitis and dry mouth syndrome (Maggi et al. 2005). Chewing gums are also useful for providing tooth hygiene and caries-prevention by activating the masseter muscles and stimulating secretion of saliva that contains rich bicarbonate ions, in which increase in plaque pH reduce the risk of caries formation (Abelson et al. 1990; Dodds et al. 1991). Chewing gum can be retained in oral cavity for long times and with the help of the saliva circulation within the mouth, drug could be effectively distributed inside the whole mouth. As a dosage form, gum could be taken easily and discretely without any need of water intake and also in any case prompt discontinuation of medication is possible. Besides, the use of chewing gum as a drug delivery system can also improve patient acceptance and compliance. In addition to offering clinical benefits, medicated chewing gums have also good physical and chemical stability during the use and the storage as well (Maggi et al. 2005).

Chewing gum consists basically of a neutral and tasteless masticatory gum-base and several non-masticatory ingredients, such as fillers, softeners, sweeteners, flavouring and texture regulating agents (Rassing 1992; Eisenstadt et al. 1998). All excipients in the gum formulation gives different properties to the formulation like anti-sticking effect to the teeth, long lasting flavor and improved texture. After non-sugar gums gain attention, combinations of sorbitol, xylitol, mannitol, aspartame and acesulfame potassium is started to use in sugar free gums and medicated gums (Maggi et al. 2005).

There are three main methods given in the literature which are properly used for production of medicated chewing gums named as; conventional and direct compression method and ion exchange method which is specialized for nicotine containing chewing gum. Among these three methods, direct compression which is developed in compliance with the conventional tablet compression technology brought advantages as; the easiness of production steps, cost and time effectiveness, by using low temperatures allows us to use sensitive bioactive and phytochemical components by this way it can prevent the potential stability problems, low moisture prolong the shelf life of the active in the gum and higher dosage of active could be formulated within gum. However, the main drawback of these methods is the sticking effect of the gum base to the compression punches of the tableting equipment. This problem originates from the adhesive nature of the gum base, major component of the formulation; due to this reason, production speed should be held at slow and cooling proce-

dures could be applied optionally. To prevent any sticking problems, whole tableting machines and their tools should be kept at temperatures below 18°C during the production process. And it should be noted that the temperature should not be as low to interfere the production procedure of medicated chewing gums therefore the temperature should be held above 10-12°C (Testa 1999; Mostafavi et al. 2014).

The recommended solution to overcome the sticking problem is using co-compression agents as glidants and lubricants in different manners but in some formulations it causes organoleptic problems and it could change the release profile of the drug from the chewing gum so it is crucial to find the exact amount for each ingredient in the formulation receipt.

The primary objective of this work was to develop a chewing gum formulation for BN and investigate the influence of different lubricants on physicochemical parameters and drug release profile.

## MATERIALS AND METHODS

### Materials

Benzylamine hydrochloride was a gift sample, provided by Santa Farma (Istanbul, Turkey). Health in Gum, compressible gum base powder mixture was obtained from Cafosa Gum S.A. (Barcelona, Spain) as a sample gift, Colloidal silicon dioxide from Evonik Industries (Germany), and the other chemicals provided as a gift sample from Roquette (France). All the other components are in the analytical grade.

### Methods

#### Chewing gum mastication apparatus

A chewing gum mastication apparatus was designed to simulate the chewing behaviour for the release of benzylamine from the gums. The designated apparatus was used to evaluate the releasing pattern of the drug from gum. Briefly, the fully stainless steel wall of the vessel was used to be able to keep the temperature equal inside the whole vessel during the mastication of gum samples.

The instrumental settings were adjustable for temperature and mastication rate. In the present experiment the following settings and conditions were used. Temperature of the test medium was set at 37°C; 10 ml of artificial saliva buffer, pH

**Table 1. Composition of artificial saliva\***

Composition	Amount (g/L)
Potassium chloride	0.720
Sodium chloride	0.600
Calcium chloride dihydrate	0.220
Citric acid	0.030
Potassium thiocyanate	0.060
Potassium bicarbonate	1.500
Potassium phosphate monobasic	0.680
Sodium phosphate dibasic	0.886
* Swamy et al. 2012	

6.75, (Table 1) was used as the volume of the test medium. 50 strokes per minute was implemented for chewing frequency. The distance between the upper and lower jaws set was at 1.6 mm and total chewing time was 60 min. Aliquots of 1 ml were withdrawn from each time point from the chamber at 0, 5, 10, 15, 30 and 60 min during the *in vitro* releasing procedure. The samples were diluted for analyzing the drug concentrations in the test medium (Kvist et al. 2000).

### Spectrophotometric analysis

Spectrophotometric measurements of BN samples were carried out using the UV-1601 model UV-VIS spectrophotometer with 1 cm quartz cell. A standard stock solution of BN reference standard (100 µg/mL) was prepared in a 10 mL calibrated flask in artificial buffer (pH 6.75). A validation set, consisting of six solutions in working range of 1-60 µg/mL, was freshly prepared and scanned in UV region. This process was repeated three times for each concentration. The absorption maxima, observed at 308 nm, was recorded and plotted against concentration, which followed the Beer and Lambert's law and gave a straight line ( $R^2 = 0.9998$ ).

### Preparation of Benzydamine Hydrochloride chewing gum

Direct compression method was used to produce twenty seven chewing gum powder formulations containing BN. Formulation of chewing gum mainly consisted of gum base powder, fillers, active ingredients (drug), and flavoring agents as shown in Table 2. At the first stage of production steps, BN was mixed with aspartame- acesulfame potassium (1:2 ratio) as a suitable sweetener by using cubic shaker for 15 min. Then this mixture was directly mixed with compressible gum base powder for another 10 min. Since BN has slightly bitter taste, menthol flavor (0.5 %) was used to mask its bitterness and unpleasant taste. Gum powder mixture which was obtained by adding co-compression agents to previous powder mixture, became ready for compression. Gums were compressed in oval shapes, in every piece of which 2.3 g of powder was weighed by using Korch EK-0 model hydraulic tablet compression machine. To prevent probable sticking problems, not only whole tabletting machines and their tools were kept at temperatures below 18°C, but also co-compression agents as glidants; colloidal silicon dioxide and lubricants; magnesium stearat in different manners were used during the production process.

### Determination of pre-compression parameters

The formulated chewing gum granules for each formulation in Table 2 were evaluated for pre-compression parameters such as bulk Density (*V<sub>b</sub>*), tapped density (*V<sub>t</sub>*), Hausner's ratio (*H*) and Carr's Index (*I*) which are indicative parameters for flow and compressibility (European pharmacopoeia, 9<sup>th</sup> edition).

$$\text{Bulk Density (V}_b\text{)} = \frac{\text{Mass}}{\text{Bulk Volume}}$$

$$\text{Tapped Density (V}_t\text{)} = \frac{\text{Mass}}{\text{Tapped Volume}}$$

$$\text{Hausner's Ratio (H)} = \frac{V_t}{V_b}$$

$$\text{Carr's Index (I)} = \frac{V_t - V_b}{V_t} * 100$$

Table 2. Selection and optimization of excipient in Benzydamine Hydrochloride chewing gum formulation

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26	F27	
Gum Base Composition (HiG PWD-01) (%)	93	93	93	93	93	93	93	93	93	95	95	95	95	95	95	95	95	95	97	97	97	97	97	97	97	97	97	97
Benzydamine Hydrochloride (%)	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13
Magnesium Stearat (%)	0.25	0.5	0.75	0.25	0.5	0.75	0.25	0.5	0.75	0.25	0.5	0.75	0.25	0.5	0.75	0.25	0.5	0.75	0.25	0.5	0.75	0.25	0.5	0.75	0.25	0.5	0.75	0.75
Aerosil 200® (%)	0.5	0.5	0.5	1	1	1	1.5	1.5	1.5	0.5	0.5	0.5	1	1	1	1.5	1.5	1.5	0.5	0.5	0.5	1	1	1	1.5	1.5	1.5	1.5
Aspartame-Acesulfam K (1:2,%)	5.25	5.0	4.75	4.75	4.25	4.25	4.25	4.0	3.75	3.25	3.0	2.75	2.75	2.5	2.25	2.25	2.0	1.75	1.25	1.0	0.75	0.75	0.5	0.25	0.25	0	0	0
Menthol (%)	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87

### Determination of post-compression parameters

The chewing gum tablets, shown in Table 2, were subjected to weight variation test as uniformity of mass and drug content, tablet breaking force/hardness and friability determination.

#### Uniformity of mass

Uniformity of mass is mainly implemented for non-coated compressed dosage forms. Ten units of gums were taken randomly from different gum formulations and weighed individually. The arithmetic mean weight was used to calculate the results. The dosage form formulation comply with the test; on condition that, not more than two of the individual masses deviate more than 5%, from the average mass (European pharmacopoeia, 9<sup>th</sup> edition).

#### Uniformity of drug content

Ten units of chewing gum from randomly selected formulations from Table 2 were used to determine drug content in prepared chewing gums. Each gum piece was crushed separately and transferred into a 10 mL volumetric flask and 10 mL artificial saliva was added. After 1 h mixing with magnetic stirrer, 1 mL of sample was taken and diluted with artificial saliva to 10 mL. The absorbance of solution was measured spectrophotometrically at 308 nm. The standard curve was used to calculate BN concentration. The formulation complies with the pharmacopoeial test limits, only if the individual drug content result is between 85% and 115% of the average content (European pharmacopoeia, 9<sup>th</sup> edition).

#### Friability

To evaluate friability of compressed gums, ten units of gum formulations from the twenty seven formulations were randomly chosen and attentively de-dusted prior to test. Then gums were accurately weighed and placed in the drum of a Sotax<sup>®</sup> HT-1 Friabilator. The drum was rotated 100 times at 25 rpm, and then gums were removed from the drum. Loose dust was removed from the gums as mentioned above and reweighed accurately. The difference in two weights represents the friability of formulation. A maximum loss of mass (obtained from a single test or from the mean of three tests) not greater than 1.0% is considered admissible (European pharmacopoeia, 9<sup>th</sup> edition).

#### *In vitro* drug release from chewing gum

The standardized equipment for disintegration, dissolution and drug release testing, used for the conventional oral dosage forms could not be considered as appropriate for the medicated chewing gums because the drug release process from medicated chewing gum is quite different compared to other conventional oral dosage forms fundamentally. For evaluation of the drug release from chewing gum, both of the dosage form and the chewing activity would influence the drug release which should be considered in release studies. Furthermore, gums are not intended to dissolve/disintegrate by themselves so a mechanical force inside the mouth is needed to cause the active release drug from the chewing gum (Liljewall 1992). Therefore, the European Pharmacopoeia guidelines recommend to use of a specific device for *in vitro* release studies from medicated gum formulations which is able to simulate the human chewing behavior (European pharmacopoeia, 9<sup>th</sup> edition). But high cost of

the equipment prompt most of the research groups to find alternative solutions as designing new equipment which can fulfil researchers needs (Gajendran et al. 2008).

In the current study, all twenty seven BN chewing gums have been tested by using the mastication apparatus. Artificial saliva (10 mL) was placed to mouth stimulating part of mastication apparatus and a prepared chewing gum was placed on its pre-designed place in the apparatus. The ragged piston, designed to simulate the teeth, was adjusted. The mechanical mixer (as a motor) was attuned on 50 rounds per minute. The masticating apparatus was started to release the drug from the chewing gum by mechanical forces.

Aliquots of 1 ml were withdrawn from each sample at 5, 10, 15, 20, 30, 40, 50 and 60 min. during the releasing test and diluted to 10 mL for spectrophotometric analysis. The medium was replaced by an artificial saliva (pH 6.75 at 37°C) after each sampling. The experiments were replicated with placebo chewing gums as well. The percentage 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.

#### *In vitro* drug release kinetics

For understanding the mechanism of drug release and release rate kinetics of the drug from the dosage form, the obtained data was fitted into the equations belongs to zero order, first order, Higuchi matrix, Krosmeier & Peppas model by analyzing the values, the best fit model was selected (Peppas 1985; Swamy et al. 2010)

#### Influence of co-compression agents on *in vitro* drug release profile

In this study, beside keeping the environmental temperature of production below 18°C, various amounts of co-compression agents were also employed to overcome the sticking problem during the production of the chewing gums. While using co-compression agents in the production, their effect on release profiles should be taken into consideration. Therefore, quantity bound effect of these agents on the release profiles within the study evaluated.

#### Statistical analysis

All testing is performed in accordance with the pharmacopoeia requirements. In any cases in which the statistical analyses were required, the paired t-test was performed. A significant difference was  $p < 0.05$  used.

## RESULTS

Gum formulations were visually inspected and physically evaluated for appearance, color, stickiness, and plasticity, which seem suitable. All gums were prepared in an oval-shape with 2 cm diameter and 1 cm thickness and the prepared gums had smooth and soft surface.

The physical parameters of the granules for all the formulated batches exhibited good flow properties, which is indicated by the bulk and tapped density in the range of 0.465 g/mL to 0.575 g/mL and 0.540 g/mL to 0.610 g/mL respectively.

The Carr's index was found to be in the range of 5.263 % to 9.615 % and Hausner's ratio was in the range of 1.044 -1.093, which is found to be acceptable.

The mean weight of 20 chewing gum tablets from each twenty-seven formulation were determined. None of the tablets deviated by more than 5% from the mean weight, indicating that all the formulations fulfilled the pharmacopeial limits for weight variation.

The hardness of the compressed chewing gum formulation was found to be in range of 9.8 to 11.7 kg/cm<sup>2</sup>. All the formulations were found to conform to pharmacopeial limits of the label claim.

Randomly selected medicated chewing gum formulations passed tests for uniformity of mass with an average mass of 2301.4 mg and non of the formulations were deviated from ±5% of average mass of chewing gums.

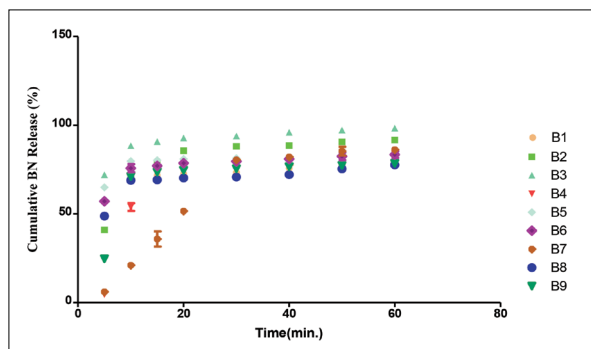
All 10 units of medicated chewing gums from twenty seven formulations, which were sampled randomly, have shown suitable uniformity of content results as contents of BN in all 10 gum formulations have fallen within a compliance limit of 85–115% and the average content of BN was found to be 2.98 mg ± 0.34%.

In friability test, after 100 rotations, the total weight loss of 10 units of medicated chewing gums were found to be 0.36% which was less than the compliance limit of 1.0 %; so selected gum formulations have passed in the friability test.

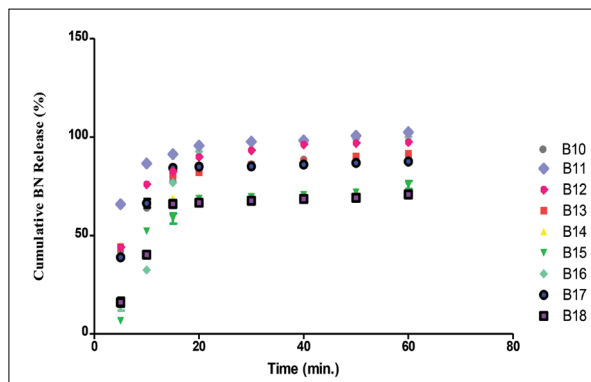
As the instrumental settings, the chewing frequency, temperature of the test medium, distance between the upper and lower jaws, and chewing times are four factors which may affect the drug release from the gum base, optimised prior to release test.

Chewing gum formulations containing BN as active substance were prepared with different ratio of compressible gum base powder, sweetening and co-compressing agents. Within this study, we mainly evaluated the effect of the compressible gum base powder co-compression agents' ratio on *in vitro* release profile. The rate and amount of drug released from the gum formulations was determined in artificial saliva (pH 6.75), due to the pH of the saliva is between 6.3 -7.2. Drug release was tested for all formulations that is shown in Table 2 and the mean releasing percentage and the related standard deviations are shown in Figures 1-3.

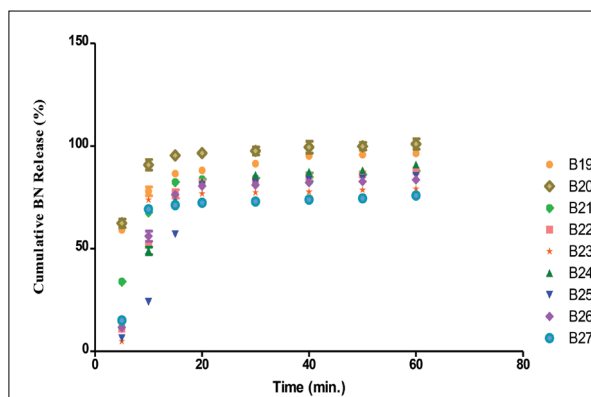
The release profile obtained after chewing are a proof of the efficiency of this dosage form, as the BN content in the residual gum decreased by increasing the mastication time for all the formulations. Contrary to the expectations, while formulation F7 which is produced with lower amounts of gum base powder and higher amount of aspartame-acesulfame and colloidal silicon dioxide, showed slower release profile; formulation F20 which is prepared with higher amount of gum base powder, showed faster release and released the 65% of the BN within 5 min. and 96,5 % in 20 min. However, formulation F22 that is prepared with lowest amount of lubricant and high amount of glidant showed the gradually increasing release profile. After 5 min was about 15% and after 20 min, the release of the BN was reached about 93%. This finding may propose a longer oral presence of BN in oral cavity as a chewing gum formulation.



**Figure 1.** *In vitro* release profile of 93% gum base powder containing gum formulations with different ratio of magnesium stearate vs aerosil 200 (Mean SD, n=3)



**Figure 2.** *In vitro* release profile of 95% gum base powder containing gum formulations with different ratio of magnesium stearate vs aerosil 200 (Mean SD, n=3)



**Figure 3.** *In vitro* release profile of 97% gum base powder containing gum formulations with different ratio of magnesium stearate vs aerosil 200 (Mean SD, n=3)

In all formulations, the determination coefficient ( $r^2$ ) values of Korsmeyer Peppas model were close to 1. The diffusion coefficients ( $n$ ) values ranged from 0.5113 to 0.9988. Since the  $r^2$  values of Korsmeyer Peppas matrix were close to 1, the drug release follows matrix diffusion kinetics. Hence it was concluded that diffusion was the mechanism of the drug release from the medicated chewing gums. Further, observed diffusion coefficient values are indicative of the fact that the drug release from the formulation follows non-Fickian transport mechanism.

**Table 3. In vitro Release Kinetics \*\***

Mathematical models	Equation
Zero order	$F=k_0t$
First order	$\ln(1-F)=-k_1t$
Higuchi	$F=k_h t^{1/2}$
Korsmeyer-Peppas	$F=k_K \cdot t^n$

\*F denotes fraction of drug released up to time t.  $k_0$ ,  $k_1$ ,  $k_h$ ,  $k_{1/2}$ ,  $k_{K,P}$  are constant of the mathematical models. n is the release exponent for the Korsmeyer-Peppas model \*\*[Peppas 1985]

These results provide a proof that this dosage form is a good administration system which is able to guarantee a fast and complete drug release after a reasonable chewing time.

## DISCUSSION

At first glance, chewing gums are mainly considered as a confectionery product. However, after medicated chewing gums had become available in the pharmaceutical market, chewing gum paved the way for a more general acceptance as a drug delivery system (Mostafavi et al. 2014). Nowadays, this new drug delivery system has established itself on the market and achieved a reasonable acceptance by both professionals and patients (Rathbone et al. 2002; Rassing et al. 2003). Beside this, when local effect is targeted, chewing gums gain more attention as a drug delivery tool.

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 (Maggi et al. 2005).

Drug delivery from a medicated chewing gum has completely different dynamics compared to conventional oro-mucosal drug delivery systems. While assessing drug release from chewing gum, chewing activity of the patient should be considered as one of the main factors that has a great influence on drug release. Releasing of the active substance from gum formulation is not performed by disintegrating and/or dissolving by the gum itself, therefore a mechanical treatment of the dosage form is essential.

It is observed from the study that, drug release from the gum to saliva is affected from 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 (European Pharmacopoeia, 9<sup>th</sup> edition). Thus, a specific mastication device was employed for performing drug release to simulate human chewing behavior. However, in some formulations, the co-compression agents caused sandy effect and reduced the chewability of gum formulations and ratio between the gum base: glidant: lubricant has a great influence on *in vitro* release profiles of

the gum formulations therefore the affect of anti-adherence agents on release profile assessed.

Consequently, F22 formulation which is consist of %97 gum base, % 13 BN, %0,5 magnesium stearate, %1 Aerosil, %0.75 Aspartame-Asesulfam K (1:2) and %87 menthol, was selected due to its *in vitro* release profile and *in vitro* release characteristics.

## CONCLUSION

The study accomplishes the probability of the formulation of the directly compressible chewing gum of BN using Health in Gum (gum base powder) with the improved taste and compressibility by using combination of the sweeteners and co-compression agents. It will give quick analgesic effect. Moreover, it can be taken anywhere anytime without preventing patient from living an active life which promotes very high patient acceptance and higher patient compliance.

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