

**CHEWING GUM: CONFECTIONARY TO A POPULAR TRANSBUCCAL DOSAGE FORM****BHARAT JHANWAR\*, BHUPENDRA SINGH TOMAR, SURAJPAL VERMA**Department of Quality Assurance, Faculty of Applied Medical Sciences, Lovely Professional University, Phagwara Jalandhar, Punjab, India.  
Email: pharmbharat@gmail.com*Received: 06 March 2017, Revised and Accepted: 10 April 2017***ABSTRACT**

Chewing gum is a highly convenient and controlled release transbuccal drug delivery system taken without water. It is gaining popularity as a self-administrable carrier for the medication used for motion sickness, smoke cessation, hypertension, xerostomia, dental caries, pain, as nutritive and energy supplements. Functional chewing gum favors both local and systemic effects intended to be chewed about half an hour. It has emerged out with a fast onset of action either by direct absorption or swallowed with saliva into gastrointestinal tract. It has better bioavailability that lowers the doses and reduces the gastric side-effects. Gums adhere with ease and compliance of administration to children and dysphagia patients. Chewing gums are formulated using a water-insoluble gum base with water-soluble excipients with the active ingredient in the case of medicated gums. European Pharmacopeia standards used for release studies, there are no other particular official standards. It has attracted the researchers as successful potential drug delivery system in coming future. The present article reviews it as novel drug delivery system including its merits and limitations, material and methods of formulation and evaluation.

**Keywords:** Chewing gum, Transbuccal, Systemic effects, Self-administrable, Gum bases, Novel drug delivery system.© 2017 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2017.v10i6.18307>**INTRODUCTION**

Chewing gum has been used by mankind since ancient times primarily for pleasure. Old dynasty of Mayan Indians chewed tree resins for the aim to keep their breath and teeth hygiene. In old times, it is a well-known fact that chewing gums increase mental performance, verbal and cognitive skills. After the patent in 1869 on chewing gum America has launched Aspergum, a medicated analgesic chewing gum [1,2]. Today, chewing gum is highly accepted as a drug delivery system either for pharmaceutical or nutraceuticals. It has specially recommended in smoking cessation and motion sickness. Gums are the only among all type of delivery systems that can be ingested without the need of water or any skilled person anywhere. In addition, medicated chewing gums are so much useful in the treatment of oral cancer, hypertension, and cardiovascular diseases (CVS) [3,4]. Disadvantage of the buccal route of administration is the inability to maintain the dosage form for a long period that gives birth to the area of the mucoadhesive dosage form for transbuccal drug administration such as chewing gums. Owing to new social and behavioral trends in the past modern age, such as the growing consumer health awareness and increasing attention to safety products, chewing gum has been known for a new image and potential [5]. Chewing gum today is gaining consideration as a vehicle or a delivery system to administer active principles even for over the counter medicines to improve health and nutrition. Chewing gums usually contains insoluble gums and resins as a core material with water-soluble excipients such as humectants, sweeteners, softeners, and flavoring agents with active ingredients. The review found it as a better targeted and controlled release dosage form for an extended period in the local or systemic region [6].

**Oral cavity**

In the aim of mucosal or oral drug delivery necessary to know the morphology of mucosa. It is a thin layer of stratified epithelium covered with mucus and saliva. The mucosa constitutes a resilient barrier to active substances as well as other substances. It has 20-40 layers of cells with a thickness of 450-600  $\mu\text{m}$  with a perfusion rate of 20-40 ml/minutes/100  $\text{cm}^2$  [7]. Submucosa is highly vascular and rapidly removes any permeated active substance to the systemic circulation thus avoiding the first-pass metabolism. A drug can be

administered via oral or peroral route for both the systemic and local effect. There are two principal sites of absorption sublingual and buccal region where the medicine consisting of mucoadhesive polymers used for topical and semi-topical purpose as shown in Fig. 1 [8,9].

**BUCCAL ADMINISTRATION OF DRUGS**

In view of the potential of bypassing, the hepatic first pass metabolism associated with oral administration systemic delivery through skin and mucosa has received attention. Mucosal surfaces at different positions in the body serve as a site of absorption for the drug. Buccal mucosa for drug delivery has excellent accessibility (easy to attach and detach dosage form) with high patient compliance due to painless administration [10]. Robustness of mucosa with a variety of dosage forms makes it an ideal site for absorption of various drugs, especially which extensively metabolized in the liver and required immediate action like cardioselective and antihypertensive drugs [11]. Mucosa is more permeable and perused than the skin but lesser than sublingual membrane because the sublingual membrane is thinner and usually immersed in saliva. Absorption in oral cavity takes place via different phenomena such as simple diffusion (concentration gradient flow), facilitated diffusion (carrier or ion mediated flow), intercellular movements based on molecular weight of substances, and endocytosis [12,13].

**Rational of transbuccal route**

From the viewpoint of drug administration oral mucosa offers various advantages:

- By passing the liver with the help of reticulated vein beneath the mucosa prevents the reduction in the potency or amount.
- Excluding destructive acids of the gastric region and metabolizing enzymes of intestine.
- The better-suited route for the drugs having poor absorption in gastric region.
- Therapeutic concentration can be achieved more rapidly because of no interference due to gastric contents or disease.
- Very first choice of administration for unconscious patients.
- It also allows the opportunity to locally modify tissue permeability inhibit protease activation to reduce immunogenic response. Therefore, selectivity for therapeutic agents can be achieved.

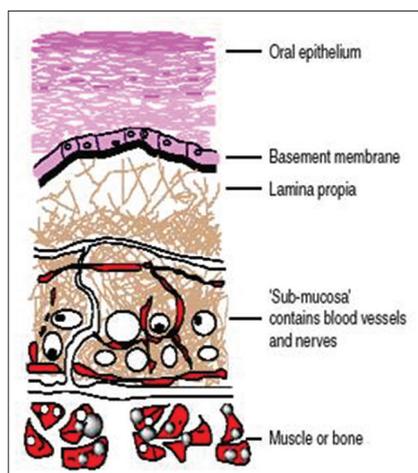


Fig. 1: Cross section of human buccal mucosa

- A passive system so does not require any activation [14,15].
- The degree of perfusion (blood circulation) is very high in comparison of skin [11] and sublingual tissues [16].
- Saliva has a large amount of water in it that is better for drug dissolution, unlike rectal and transdermal route.

#### Limitations of transbuccal route

- This route is suited only for those drugs which absorbed by passive diffusion.
- Unpalatable and noxious drugs which irritate the mucosa not suitable for this route.
- A small dose can be administered because of the lesser surface area (200 cm<sup>2</sup>) of absorption.
- Drug swept off with the swallowed saliva does not follow advantages of the buccal route.
- Ingestion of any other substance parallel may become restricted. It also interferes the drinking and eating habits of the patient for that period [14,17].
- Sure possibility that the patient may swallow.
- Overhydration in cavity forms a slippery surface so the structured integrity of the formulation may get disrupted.
- A major disadvantage of buccal delivery of the drug is the maintenance of the dosage form at the site for an extended period in a particular region of the body. Recent approaches to this cadre are the use of buccal or mucosal adhesive polymers having better drug release [18].

#### CHEWING GUM AS A DRUG DELIVERY SYSTEM

This unique dosage form utilizes the adhesive properties of some water-soluble polymers which can be applied on a wet surface or tissues or the mucosa. Such polymers which have been identified as hydrophilic macromolecules containing numerous hydrogen bond forming groups become adhesive on hydration and are therefore called wet adhesive, bioadhesive, therefore maintains the pharmaceutical dosage form for a clearly defined time at its activity or resorption level [19].

#### Advantage of chewing gums

There are many reasons for choosing chewing gum as a drug delivery system over conventional routes, some of which are described below.

#### Efficacy

It has a very good local effect due to having a long time of chewing and sustaining is there so used in the treatment of diseases in cavity and throat. Low doses are suitable because chewing gums can bypass the hepatic first pass metabolism. Xerostomia or dry mouth is often seen in the case of antidepressants and Sjogren's syndrome, but chewing gum stimulates salivary secretion so beneficial to dental health [20]. Drug can directly absorb through the buccal mucosa for systemic effect

and fast onset of action because drug passed by jugular veins like Dextromethorphan hydrobromide in Pharmagum-M [21,22].

#### Convenience and compliance

Easy to store and less prone to microbial contamination. It is highly acceptable in children and patient with nausea and dysphagia. It is palatable, pleasant and attractive for the lower age. This is the only dosage form conveniently taken anywhere anytime without any water intake that makes it 21<sup>st</sup> century drug delivery system which avails self-administration in current lifestyle [23].

#### Gastric friendly

Gums do not get direct exposure to the gastrointestinal mucosa, so this reduces the side effects of excipients and risk of intolerance of gastric mucosa. Chewing or mastication normally acts as salivary gouge and buffering capacity of saliva reduces the acidity of gastric fluids. The fraction of drug reaching the stomach continuously with the saliva, so the duration of action is increased [24,25].

#### Limitations of chewing gums

- Sorbitol and mannitol present in chewing gums formulation may cause flatulence and diarrhea [20].
- Adherence problem of gums to different degrees to enamel dentures and fillers. Involuntary swallowing sweep off the active principle released into saliva from the site of action [26].
- Salivary dilution decreases the concentration at one place, so variability takes place.
- The pattern of mastication decides the speed and release pattern of the formulation [27].

#### COMPOSITION OF CHEWING GUM

Chewing gum usually consists of water-insoluble and water-soluble portions in appropriate ratio as depicted (Figs. 2 and 3). Active core material usually mixed with the insoluble base material. In the formulation, there are no added preservatives due to low water content [28-33].

#### MANUFACTURING AND METHODS (FIG. 4)

Formulation of medicated or non-medicated chewing gums has following steps and requirements described below:

- Preparation and mixing of the melted gum base materials.
  - The addition of the sweeteners and flavors.
  - These ingredients are mixed together with the gummy base material to produce damp mass. This mass or dough is passed through series of high-pressure rollers to convert it into the ribbon-like structure.
  - Cutting, threading, and wrapping take place as per required size.
- Chewing gum formulation contains the following components as discussed above along with active pharmaceutical ingredients (API) in case of medicated chewing gums. In medicated chewing gums API can be added into base material or coating or into both. The proportion should lie in the range of 0.5-30% of final weight. Coatings can be applied as same as in the case of tablets [33-36].

#### SOURCES OF EDIBLE GUM BASES

Many of plants are huge sources of edible gums that can be used as core material for the formulation. Plants produce latex, resins, gummy secretions, and juices as secondary metabolites which are the mainly used for this purpose. Plant parts useful for the procuring of the gums are trunks roots and barks which also fulfills some other medicinal purpose for formulations. Selection of a useful source of gums depends on its availability, pharmacological effects, and texture.

#### CHEWING GUM BASES

From the old times, natural gums are used; the most popular base is "Chicle." Other than this other synthetic gum bases are also getting popularity nowadays.

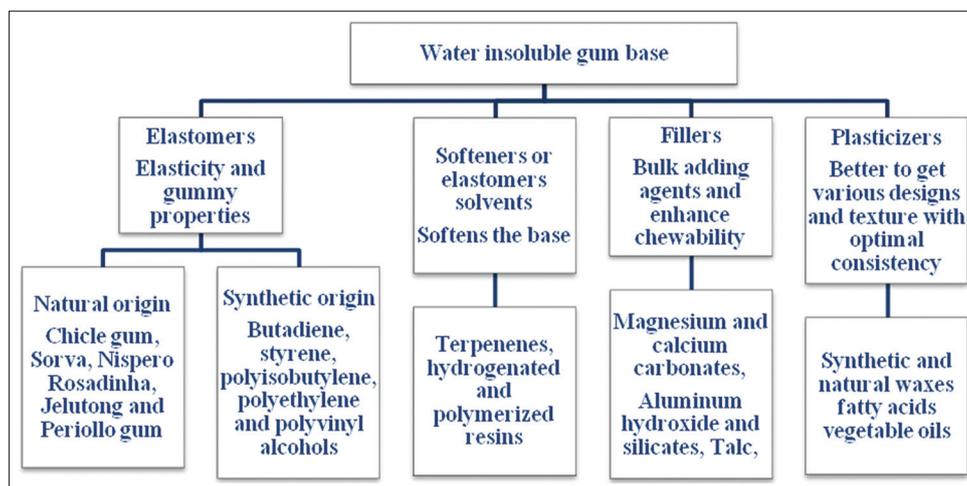


Fig. 2: Different water-insoluble additives in chewing gums

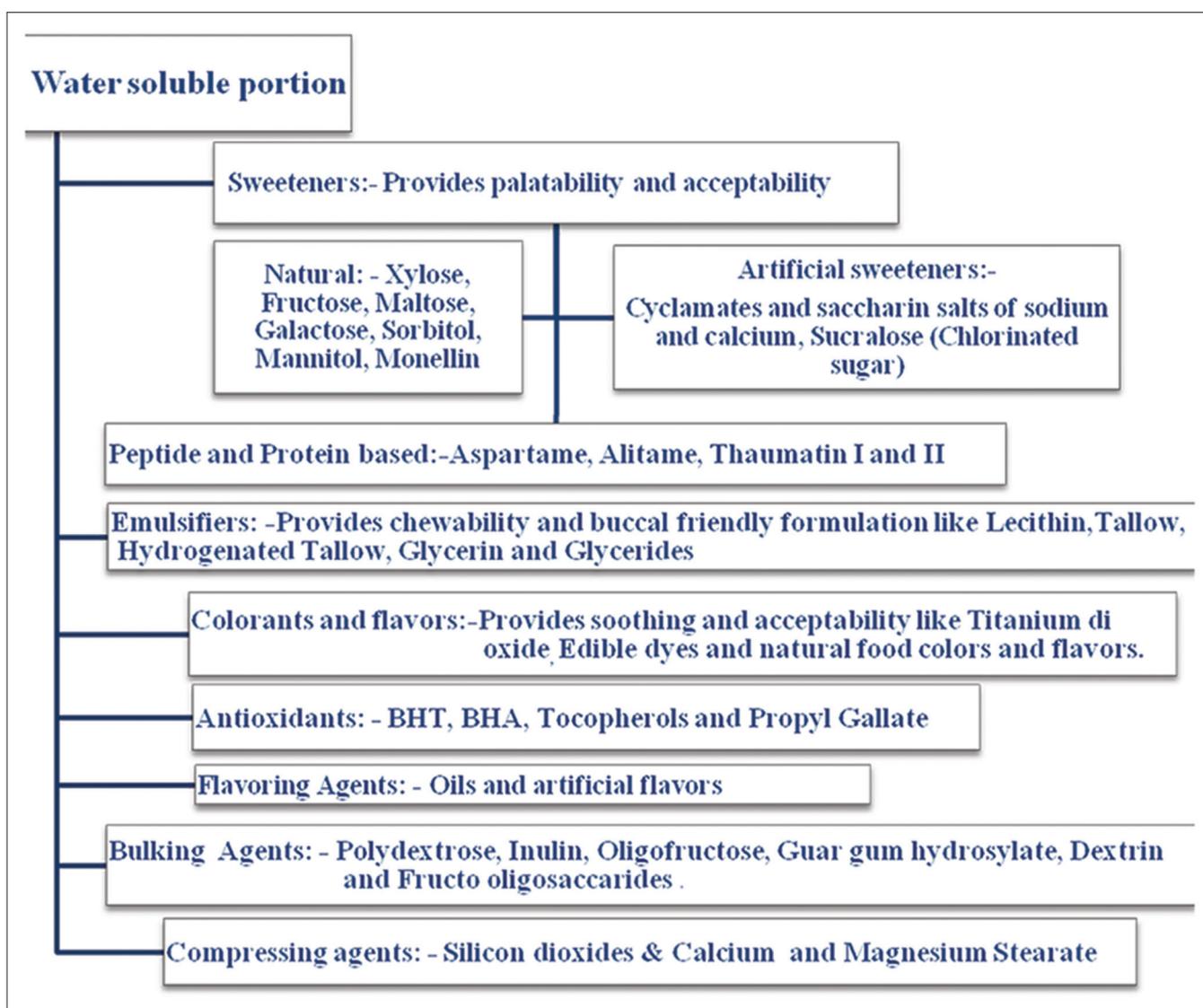


Fig. 3: Different water-soluble additives in chewing gums

**Natural chicle base**

It is a type of latex obtained from the Sapodilla tree by making an incision on the trunk. These incisions followed by the release of gummy secretion that is collected, dried and purified with the help of strong

alkali and then neutralizing. The dried product goes through powdering and the resultant product is insoluble, amorphous powder. Chemically, it is composed of 55% of yellow resin and remaining polyisoprene. Resin consists of Lupeol acetate with a minor amount of amyryna and

**Table 1: Formulation in U.S. patent**

Type of ingredients	Percentage range
Elastomer	8-30
Oleaginous plasticizer	9-40
Mineral adjuvants	10-15
Non-toxic vinyl polymer	16-32
Emulsifier	05-10
Elastomer solvent	2.5-13

**Table 2: Formulation of chewing gum as Indian patent [43]**

Type of ingredients	Percentage range
Isoprene-isobutylene copolymer	6.5
Polyisobutylene	1.4
Polyvinyl acetate (15000)	2.8
Glyceryl esters	6.5
Hydrogenated wood-resin	2.8
Micro crystalline wax	3.0
Low molecular weight polyethylene	6.5
Glyceryl monostearate	5.5
Fats	2.8
Fillers	2.0

**Table 3: ISI classified Rosin grades**

Color grades	Light	Medium	Dark
	X, WW, MG, N	M, K, H	
Softening point	70-75°C	70-75°C	70-75°C
Relatively density	1.05-1.08	1.05 - 1.08	1.05-1.08
Acid value	160	155	155
% Volatile matter (max)	2.0	2.0	2.0
% Ash content	0.05	0.2	0.5
% Insoluble content	0.1	6.0	6.0
% Unsaponified matter	6.0	6.0	6.0

spinasterol acetates. Refined chicle is used for chewing gum base but for those which contains only water-insoluble ingredients [37].

**Synthetic gum bases**

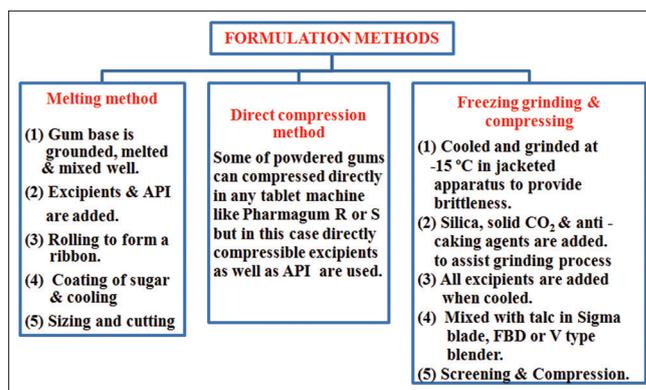
The gum base generally used consists of natural rubbers and mixture with synthetic gum. The most popular synthetic gum bases are derivatives of butadiene. The gum bases usually adhere to dental surfaces. Antiadhesive or anti-sticking agents such as talc and tannic acid [38,39]. The polymer can be used along with polyisoprene or styrene butadiene copolymer. The use of titanium dioxide along with fillers such as calcium carbonate is also reported to produce non-sticky gum [40,41]. Non-sticky bubble-gum can also have some sort of elastomers or fatty acid with oleaginous plasticizers [42]. A U.S. Patent [41] has reviewed online which (4387108) describes the formulation of non-sticky chewing gum with following composition (Tables 1 and 2).

**Rosin**

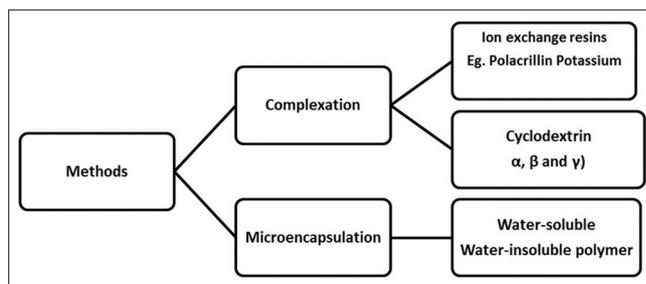
Apart from above conventional gum bases trends rise to use rosin derivatives. Rosin is obtained from Pine trees. It is an oleoresin, solid material which obtained from three ways from the tree:

- Oleoresin exudates of living pine trees.
- Oleoresin contained in aged stumps of the long leaf pines.
- Tall-oil produces rosin as a by-product in the paper industry.

Rosins are chemically made of two components, carboxylic rosin acids and very less of non-acidic material. The acids are divided into two categories that are Asiatic and Pindaric acid. Rosin and its derivatives show a wide number of applications in pharmaceutical field excluding that in transbuccal dosage form formulation. These acids show number or reactions such as esterification, oxidation, hydrogenation,



**Fig. 4: Formulation methods for chewing gums**



**Fig. 5: Methods of improvisation of palatability aspect of gums**

polymerization, and isomerization. Their esters are very useful also in other industries for the purpose of film forming, coating, and varnishing.

Rosin derivatives have different grades as per ISI with certain specifications. It is tabulated as shown in Table 3 [41,42,44].

**Shellac**

It is also known as Lacca or dewaxed orange shellac. Shellac is a refined natural resinous product having a small amount of pigment. Shellac on hydrolysis produces a lot of aliphatic acids and fewer amounts of salicylic acids. The major acids are Aleuntic acid and shellac acid. Different marketed grades of shellac are available. The main grades are orange and bleached shellac. Shellac can also be obtained commercially in pharmaceutical grades in which the appropriate grade of shellac has been dissolved in ethanol [45].

Shellac is thin, hard, brittle, transparent, pale lemon, or brownish yellow-orange flakes. It smelting point range is 115-120°C. All types of shellac discussed above have an acid value from 71% to 91% about [46,47].

**PALATABILITY IN CHEWING GUMS AS BETTER BUCCAL ACCEPTABILITY**

There are several ways to achieve palatability and mask the bitter taste of chewing. Some time chewing also shows absurd taste after chewing long time that is because of losing the sweet taste. The methods are as followed (Fig. 5) [48,49].

**Evaluation of chewing gums**

There are several parameters that can be used for evaluation but not confined anywhere in any monograph about all; European Pharmacopeia suggests, i.e., safety parameters, dissolution parameters, and assay only. Other than those are also given below.

*Organoleptic evaluation*

Appearance, color, flavor, and sweetness index are determined by simple volunteer acceptance or survey in human trials by Likert

score on a scale of 5 points. Artificial tongue simulation can be used as a taster for palatability also [50]. Another important aspect of physical evaluation is the texture profile (TP). It is a sensory analysis and evaluation of characteristics such as hardness, tractability, cohesiveness, and gumminess in the case of gums using the standards of force-time curves. The test consists of compressing the sample twice in a reciprocating motion that imitates the action of the jaw and analyzing the textural parameters. Compression plates and flat surfaces along with standard probe are used for this. The instrument simulates buccal chewing process or mimics the mouth's biting action, therefore also known as two bite test [51].

#### The melting point of gum base

It is determined by any suitable method to know the temperature which the base loses its texture and behaves as a liquid.

#### Excipients evaluation

It is done using Fourier transform infrared spectroscopy (IR) or differential scanning calorimetry techniques to find the interactions in the dosage form.

#### Weight/mass variation

It can carry out as per the guidelines in pharmacopeia for solid dosage form using 10 randomly selected chewing gums.

#### Moisture content

It can be determined IR moisture balance method, desiccation or hot air oven method.

#### Uniformity of drug content

About 10 units from each formulation were individually assayed for active content by the suitable method given in monographs it is done by crushing and dissolving chewing gum in 100 ml of artificial salivary fluid. The solution was then filtered, suitably diluted and read by an instrument like ultraviolet spectroscopy or liquid chromatographic methods [52].

#### In vitro dissolution study

It has been done as per monograph given in European Pharmacopoeia as discussed below also. The mechanism of drug release and release rate kinetics of the drug from the dosage form, the obtained data were fixed in the following model of zero order, first order, Higuchi matrix, Korsmeyer and Peppas model by analyzing the R values and the best fit model [53,54].

#### In vivo dissolution study

The *in vivo* release of therapeutic ingredients from gum base during mastication can be done by appointing sufficient numbers of subjects as and schedule a clinical trial for chew-out studies. Volunteers are asked for a dosage form for a certain period and throw out the residual and exhausted gum base. It is a real-time process, involves saliva stimulation pH variations, buccal absorption and some extent of swallowing. Minimum four human volunteers can be selected (2 male and 2 female). Instruction like mouth rinsing, chewing period already given before trial starts. A sampling of drug meanwhile at different intervals predicted which can be assayed as per need [45,52].

#### In vivo assay of residual gum

After the *in vivo* dissolution by human volunteers, the collected exhausted gum base having a very amount of therapeutic content as per hypothesis are subjected to this test. The residual gums are cut into small pieces, frozen and then ground to a fine powder state. The fine powder is introduced in a suitable solvent and assayed by using the suitable analytical method. The amount of drug released during mastication is calculated by subtracting the amount of residual active

Table 4: ICH\* storage condition for stability testing

Study type	Storage condition (Temperature and Relative humidity)	Minimum time period
Long term	25°C±2: RH*60±5% or 30°C±2: RH 65%±5	12 months
Intermediate	30°C±2: RH 65%±5	06 months
Accelerated	40°C±2: RH 75%±5	06 months

\*ICH: International Conference on Harmonization, RH: Relative humidity

Table 5: Classification of apparatus

Apparatus I	Apparatus II (official)
Chewing gum apparatus	Alternative chewing gum apparatus
Compendial	Non compendial
Christrup and moller	Wennergan

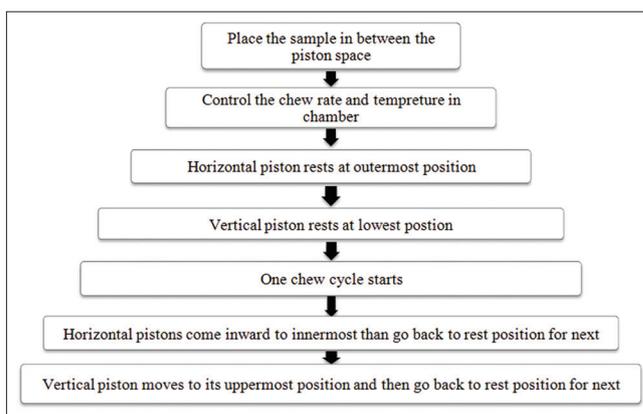


Fig. 6: Working of dissolution apparatus

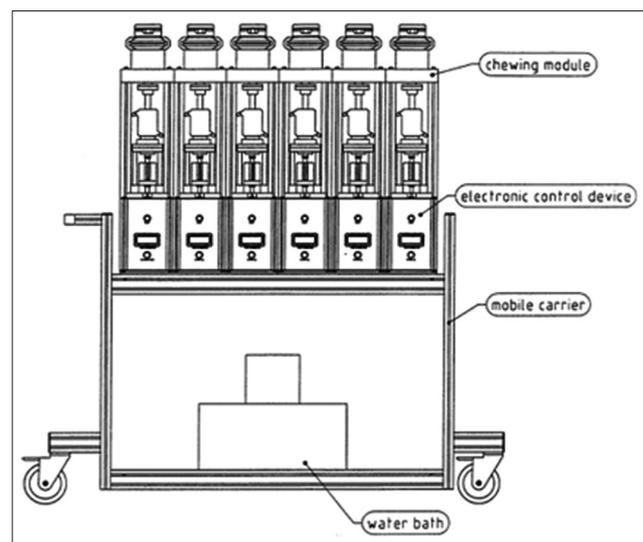


Fig. 7: Six chambered apparatus for *in vitro* dissolution

ingredient present in the gum from the predetermined total therapeutic content of dosage form. The major disadvantage of these studies are difficult to standardize because of high variability in chewing pattern, chewing frequencies, the composition of individual salivary fluid and flow rate of saliva are a few limitations of chew-out studies [55].

#### Stability studies

Accelerated stability studies of any formulation can be carried out as per International Conference on Harmonisation (ICH) Q1A (R2).

Table 6: Comparison of *in vitro* dissolution apparatus

Single cell chamber	Six chambered chewing cell
Batch size: 1 sample at a time	Batch size: 6 samples simultaneously
Two pistons on each side (Teeth or jaw)	Two horizontal pistons (Jaw) and a vertical piston (Tongue)
Brim of the lower surface is angled upward (Cavity) 45 degrees to prevent sliding of gum	A plunger rotates (Mastication) at the rate of 10-40 rpm* while piston is in motion
Movement in one cycle: Piston move toward each other	Upward and one downward stroke simultaneously
Compression between pistons	Compression and rotation
Chewing rate is usually set at 60 per minute	Chewing rate: 7.5-30/minute
Temperature-controlled reservoir	Temperature-controlled reservoir
Dissolution media 20 ml	Dissolution media 20 ml*
pH*: 6-7	pH: 6-7
Temperature: 37°C±5	Temperature: 37°±5
It is less used now days than the six-chambered apparatus	Merits: Faster rate and more reproducible Only commercially available instrument Gum is fixed while mastication goes on

\*pH: Power of hydrogen; ml: Milliliter, rpm: Revolution per minute

Table 7: Artificial saliva medium for dissolution\* [60]

Substance	Quantity (g/l)
KH <sub>2</sub> PO <sub>4</sub>	2.50
Na <sub>2</sub> HPO <sub>4</sub>	0.866
KHCO <sub>3</sub>	1.5
KSCN	0.06
NaCl	0.6
KCl	0.72
MgCl <sub>2</sub>	0.06
CaCl <sub>2</sub>	0.22
Citric acid	0.03

\*pH adjustment by Sodium Hydroxide or Hydrochloric acid, g/l: Gram per liter, KH<sub>2</sub>PO<sub>4</sub>: Monobasic potassium phosphate, Na<sub>2</sub>HPO<sub>4</sub>: Dibasic sodium phosphate, KHCO<sub>3</sub>: Potassium bicarbonate, KSCN: Potassium thiocyanate, NaCl: Sodium chloride, KCl: Potassium chloride, MgCl<sub>2</sub>: Magnesium chloride, CaCl<sub>2</sub>: Calcium chloride

These parameters and data given below can vary as per climatic zones of ICH Guidelines just exemplified for common stability condition in general case of new drug products and drug dosage form. They are kept under such condition and followed by evaluation for any physical deformities, the extent of deterioration and to ensure that the degradation has not exceeded an acceptable level. Storage condition is given (Table 4) [56].

#### DISSOLUTION AND RELEASE STUDIES OF CHEWING DRUG DELIVERY SYSTEM

In European standards classify, the chewing as solid dosage form but it can be put under semisolid dosage forms. It has described an apparatus to study the rate of release. For simulation of buccal mastication or chewing system *in vitro*, a special chewing chamber designed. It contains a buffer solution of same pH and temperature as the mouth. Chewing rate and the angle of force is controlled from outside of the machine. The apparatus are classified as shown in Table 5.

Release profiles for kinetics and release patterns are essential to establish for approval of any new drug delivery systems, but in the case of chewing gums as transbuccal dosage form, a conventional apparatus would not help. There must be some modified apparatus that includes masticator actions in it like above.

Logical sequence of release of API is like first while chewing; then, reaches the saliva followed by systemic absorption or directed to the gut pathway. This study requires human subjects, disability to control the variability in chew pattern, chew speed, saliva flow, and saliva composition [52]. Simulation of this process is published in European Pharmacopoeia.

#### Official chewing gum dissolution apparatus

##### Structure and working

It is a single chamber instrument consists of two horizontal pistons (HP) working like jaw and a third vertical piston (VP) mimics the tongue. The VP moves alternatively with the horizontal one. The HP has some rings attached to it, shape as alphabet "O." Sealing rings of the chamber make it water tight. The HP also rotate oppositely in some case to produce the highest chewing. Chewing chamber has one funnel shape part and two guides which control the movement of HP. The distance between the HP is 50 mm, and the minimum is 0. To 1 mm whereas for VP the impact and rest position has a distance of 22 mm. The temperature of the chamber can be maintained at 37±0.5°C. The variables in hand are chewing rate (up to 60 strokes/minutes), volume of dissolution medium inter-jaw distance and the rate of twisting movement. Chewing chamber capacity is 40 ml but prefers up to half of it with saliva simulation of pH about 6 as in (Table 7). Working of the machine is shown in Fig. 6 [57,58].

##### Apparatus designed by Wennergan (Fig. 7) [59]

Wennergan and his team of scientists have designed a modern dissolution apparatus having one to six chambers with novel simulation of chewing mastication phenomena. The comparative analysis of both apparatus is shown in (Table 6).

#### FACTORS AFFECTING RELEASE OF ACTIVE INGREDIENT

##### Nature of API and gums

Studies must be done on following virtues of API candidates like saliva solubility, pH-independent solubility and nature of drugs either hydrophobic or hydrophilic. API candidates, those are soluble in saliva release immediately whereas hydrophobic candidates will release from gum base material at a slower rate than this. Hydrophilic drug candidates release to the extent of 60-70% in first 10-15 minutes and rest of drug remaining in next 15-20 minutes [55]. Poor water-soluble cyclodextrin and other solubility enhancers or hydrotropic agents can be used. Gums which are hard in nature delay the release that overcomes by adding some excipients such as emulsifiers and softeners or both while formulation. Ion exchange resins and microencapsulation techniques can be used to produce controlled or sustained drug delivery systems [48,49].

##### Contact time

The therapeutic effects on local as well as the systemic side of physiology are dependent on the contact time span of the gum in the buccal cavity. For the optimum effect, it should be in the touch with the site at least for 30 minutes where it is chewed about 60 times/minute.

##### Chewing intensity

Cycle per minute or chewing per minute is known as chewing frequency or chewing intensity. It has a vast effect on drug release and it changes

from person to person. The speed of chewing also has its own effect. As per standard book like European Pharmacopoeia, 60 cycles per minute is optimum for a good release [61].

### Compositional factors

Nature of gum base added ingredients and the respective proportion of both of them has a marked effect on the release. Hydrophilic nature of gum bases will release the API fastly, but hydrophobic bases show delayed release. If the gum base required is added more than the optimum, it will diminish the release up to half of the optimum [62,63].

## THERAPEUTIC APPLICATIONS OF CHEWING GUMS

### Local therapy

Oral diseases are the bull's eye that has to be hit. Chewing gum can release therapeutic ingredients at a controlled rate over a length of time. This effect results in producing a prolonged effect. Sugar-free chewing gums are beneficial. Postprandial intake of this gum can elevate the buccal pH which decreases the chances of dental caries. Therefore, if the aim is to prevent dental caries, sugar-free chewing gums are recommended after meals as a substitute for brushing effect [29]. Fluoride-deficient areas have high chances of dental caries. A comparative study of fluoride containing and placebo chewing gums reveal that medicated gum remineralises and heal the enamel faster than non-functional gums [64,65]. Oral bacterial of fungal infections such as gingivitis, periodontitis, and others can be treated well by using buccal gums of chlorhexidine. Other benefits like reduction of plaque growth and tooth decay [66-68]. Xylitol or birch sugar containing chewing gums are recommended to use in malodor, dental plaque, enamel demineralization, and dental caries [69]. Calcium phosphate is also well used marketed formulation of therapeutic gums for dental caries treatment. Probiotics chewing gums have some beneficial effect on oral [70]. The results indicate that the probiotic gum may affect bacteria that produce malodorous compounds. It can assess by organoleptic score decrement actually compared with placebo [71]. An experimental study claimed that consumption of regular Happydent by subject or Xylitol can significantly decrease *Mutans streptococci* in saliva as well as it also shown detrimental effect on fatality of mother offspring streptococci transmission [72,73]. Clinical trials and experimental study reveal out that patients having candidiasis, Miconazole and their nitrates containing gums are similarly efficient like oral gel formulation, along with its wide acceptability by patient and better release [74,75]. Ascorbic acid intake alone or combination with carbamide in the form of chewing gums is found to decrease oral calculus as per research experiments [76]. Herbal medicines like eucalyptus and green tea extracts are also effective in dental and buccal problems like gingivitis. In one of the clinical trials, eucalyptus extract in chewing gums have shown a significant effect on periodontal health. The parameters such as gingival index, plaque accumulation, bleeding on probing and periodontal probing depth were statistically reduced [77]. Chewing gums have widespread use in oral health and many more to find in future research.

### Systemic therapy

Adopting chewing gums as a delivery system, the systemic delivery of drugs which majorly absorbed from buccal mucosa are also benefitted. If we look from patient side, a list of benefits like rapid and local treatment, level of convenience, zero water for swallowing, no place and time restrictions and lesser gastrointestinal tract (GIT) side effects but strictly adhered with adults. Therapeutic applications of chewing gums in various physiological indications are.

### Pain

Faster analgesic effect is the prime motive of analgesic drugs like in case of, headaches, migraine muscular spasm cold and cough, etc. These conditions require quick absorption of API. Hence, the aim satisfied by using transbuccal drug delivery system of chewing gums [78]. This formulation can also be used in case of severe algesia likewise in experimental study Methadone chewing gum has about equal

bioavailability to the tablet formulation. Drug abusing problems with this study have almost reduced because the active substance can only be released after chewing [79].

### Smoking habits

Since it is known that smoking is an oral, bad and injurious habit for health. To get rid of this, the only possible way is substituting this by any harmless oral habit like chewing. Formulations having Nicotine and Lobeline are found very successful in abandoning smoking [80-82].

### Obesity

Lifestyle-related disease or ailments are on high verge today, in this queue obesity comes at first rank. Chewing of anorectic or fat dissolving substances is in need today [83]. In US 2013, a new "Dietburst" formulation which decreases your diet had launched by Arco Health Ltd. It contains a protein named Slendesta, a natural proteinase kinase inhibitor. Formulations having Guarana, Caffeine and chromium salts can be used and under trail for this purpose. They belong to central nervous system stimulating category but have side effects like stimulating lipolysis, thermogenic, and reduce appetite which ultimately ends with weight loss. Chromium picolinate can improve glycemic index of blood, so it can reduce instant craving for carbohydrates [84,85].

### Postoperative benefits in bowel return

In a case study, based on clinical trial shows that patient undergoes major surgeries which make them bedridden, the patient loses the speed and normal rhythm of bowel evacuation like in the case of surgical correction of scoliosis. As the per the case study results chewing gums can reduce the time but not differ significantly. Chewing gums decreased the time period only by few hours but still a hope that chewing post surgery can facilitate the early return of bowel than control who are not taking these gums [86].

### Motion sickness

Dimenhydrinate salt is the first drug comes into mind for motion sickness. It is in the market already in chewing gum dosage form. It gets absorbed easily from your buccal mucosa and directly goes to your blood stream [87]. According to a health report chewing increases release of digestive juices better digestion, increases the flow of saliva so acting as an antacid and prevents acid reflux ultimately relieves symptoms of motion sickness. Hopeful candidate drugs in future treatment by using gums are Scopolamine, Metoclopramide, and Ondansetron [29,88].

**Table 8: Marketed products an active content**

Product	Drug/contents	Indications
Aspergum	Aspirin	Analgesic
Nicorette, nicotinell	Nicotine	Smoking cessation
Harbitrol (GSK)*	Nicotine and resins	Smoking cessation
Fluorette- novum	Sodium fluoride	Prevention of dental caries
Vitaflor CHX	Chlorhexidine	Antibacterial, gingivitis and dental caries
advanced®, Hexit Stay alert	Caffeine	Lipolytic, thermogenic, anti appetite
Go gum	Guaran	Lipolytic, thermogenic, antiappetite
Chooz	Calcium carbonate	Gatric acidity
Travvel	Dimenhydrinate	Motion sickness
Vitaminize, essentials	A, C, D, E, B, folic acid	Energy and dietary supplement
Stamil	Vitamin C	General health and diet
Happydent/orbit	Calcium phosphate	Tooth glittering and freshening
V-6 strength for teeth	Xylitol and fluoride	Dental strength and dental caries

\*GSK: GlaxoSmithKline

### Sialogogic activity

In the condition of dry mouth or xerostomia chewing gum mastication is the best exercise for stimulation of saliva in the mouth. Therefore, several trials, papers, and reviews have substantiated that gum chewing can relieve in these diseases [89]. Cholinergic drugs and several sugar alcohols can be used as sialogogic. Xerostomia is a condition that can be caused by intake of anticholinergics, antimuscarinic, antihypertensive, antianxiety, antidepressant, antiparkinsons, non-steroidal anti-inflammatory drugs and condition such as Sjogren's syndrome, glandular problems, and radio treatments [62,66,71].

### Hypocalcemia

Several chewing gum formulations containing calcium are available on the market. Adolescents constitute a potential target group for a calcium chewing gum, as the calcium intake of young people is often very low. Calcium chewing gum with a pleasant taste is an attractive and convenient alternative to tablets [90].

### Hypertension and angina pectoris

It is the most common CVS diseases which require constant watching. Most promising K<sup>+</sup> channel openers considered for this is Nicorandil, a potent coronary vasodilator [1]. Current studies are going to develop and evaluate Nicorandil chewing gum as an antihypertensive and antianginal. The aim is to avoid first pass metabolism and getting the rapid onset of action, reduce the dose potency to minimize side effects old age acceptance [91].

### Male enhancement chewing gums

Modern days researchers have brought some extraordinary aspects of therapeutic gums. According to review, "M/S Future Lifestyles LLC, Florida" launched a chewing gum product having an effect on male enhancement. It can be used to increase libido, stamina, and blood flow that ultimately end into size increment lengthening and more powerful erections. The major contents of the chewing gums are some aphrodisiac herbs such as *Pausinystalia yohimbe*, *Turnera diffusa Damiana*, *Lepidium meyenii*, *Panax ginseng* and its varieties. It also includes Orchic powder extract from an animal source, some essential components, and excipients [92].

### Multivitamin chewing gums

Vitamins are very valuable for diet and advances to have been made to provide them in or as a modern and innovative form. Chewing gums can also use as a popular buccal delivery vehicle for multiple vitamins. Vitamins are quickly absorbed by chewing because they immediately enter the bloodstream through the mucous membranes in the mouth and are thus optimally utilized [93]. It helps in provide essential dietary vitamins such as A, C, D, E, B1, B2, B3, B5, B6, B12, folic acid, and biotin. It also serves as breath freshener supported by menthol, spearmint or cinnamon [94].

### MARKETED PRODUCTS AND BRANDS OF THERAPEUTIC GUMS

There are several worldwide products acceptable as chewing gums containing medicinally active substances for different local as well as systemic action also known as functional gums. Some of them are given in Table 8 [95].

### GUMS AS FASHION IN LIFESTYLE

Mainly non-medicated gums that are chewed regularly just a trend point of view in youngster lifestyle especially in western countries have some serious and long-term side effects on physiology. According to article by chewing or gums as an addiction has following side effects listed below.

#### Demotivate healthy eating habits and appetite

Chewing reduces the food cravings which logically help to avoid eating unhealthy foods but it also is known by literature that it diminish

appetite and push to eat less nutritious food than those of non-gum-chewers. They were less likely to eat fruits and vegetable, because of that inherent minty flavors which make them taste bitter.

#### Muscular disorder in jaw

It's regular use, especially from one side of buccal cavity imbalances the jaw muscle. A person is only using certain set of muscle for a long time which ends up into arthralgia, headaches, dental pain and pain in the ear. Teenagers are notorious for gum chewing and popping; they are the major affected segment of the population.

#### GIT problems

It can cause an intake of excess air which results in abdominal pain, swollen belly. Pseudo signals of food intake generated which stimulate secretion of enzymes and acids, but nothing to digest actually. High ingestion of polyols like Xylitol or Sorbitol as a major ingredient in therapeutic gums can cause laxative effects [96].

#### Dental erosion

It is actually a process of incremental decalcification. Sugar-containing therapeutic gums is the most harmful thing for teeth whereas sugar-free gums are less likely to deteriorate the teeth. They also have some mild ill effects because of their acidic flavorings and preservatives.

#### Problems due to artificial sweeteners

As we know that transbuccal means dosage form which is directly contacted with oral mucosa as well as systemic circulation, therefore it also increases the chances of penetration of such toxic or carcinogenic excipients into the blood stream. Saccharin, cyclamates, and aspartames are among them. Sweeteners are unavoidable in the buccal dosage form as a fact. Aspartame biotransformed into formaldehyde and methyl alcohol which are carcinogen and poison for body, respectively. It also produces some signs of headaches. Sucralose is the other one which shows signs of anemia, infertility, abortions in some animal studies.

#### Problems due to some other dangerous excipients

Listed below some of the chewing gums additives that must be avoided straight forward while taking or formulating gums.

- Butylated hydroxytoluene: Kidney, liver damage, and carcinogenic
- Calcium casein peptone: Autoimmunity disorders and poison
- Gum base (petroleum derived): Carcinogenic
- Titanium dioxide: Autoimmune disorder, asthma and Crohn's disease.

#### Interferes the root canal therapy and dental fillings [97,98]

Chewing gum regular basis can have drastic and ill effects on patient who had undergone root canal or dental filling like therapy. It leaches out the mercury amalgam or the filling from dental cavity into your body. It has some late shown effects like oxidative stress on tissues [97,98].

### CONCLUSIONS AND FUTURE PROSPECTS

Novel things discovered or introduced should always acceptable, admissible and affordable and adequately effective for the common one. Previously, chewing gum was mainly considered a confectionery product; however, fluoride chewing gum, and especially nicotine chewing gum which was launched in the 1970s, enlighten the way for a more general acceptance of chewing gum as a drug delivery system. Therapeutic gums are actually a modified release systems adhering to the most convenient and compliant way of drug dosing. The inclusion of medical chewing gum in the European Pharmacopoeia (under medicated chewing gum) in 1998 has further contributed to full acceptance worldwide. Medical chewing gum meets the high-quality standards of the pharmaceutical industry and can be formulated to obtain different release profiles of active substances, thus enabling distinct patient group targeting. A few decades ago, the only treatment for some diseases was surgical procedures (e.g., gastric ulcers); however, today more and more diseases are treated by medication. This trend is likely to continue as sophisticated research methods allow the development of medication for an increasing number of diseases. At the

same time, there is a demand for efficient and convenient drug delivery systems. In general, it takes time for a new drug delivery system to establish itself on the market and gain acceptance by both professionals and patients. Health enclosed in gum suitable attract the patient and provide added value to the customer as well as differentiating market trend set. Medicated chewing gum is a valid alternative to standard, chewable or orally disintegrating tablet presentations. Now, these therapeutic gums are intervening into sex enchantments, erectile dysfunction and oral contraceptives category as for those who hate swallowing the drugs. There are also some scopes for chewing gum for research in the treatment of amnesia, Alzheimer and memory defects. No solid evidence is available that chewing gums increases aspects of mental performance, but there are some experiments and running clinical trials that shows practicing gum can improve episodic memory, working memory, and mood and also act as stress relief. Some trials also show that chewing action (gum) also helps in attaining the normal bowel evacuation and early intestinal stimulation after cesarean section in women. There is a lot of scopes to produce therapeutic gums containing memory enhancing herbs, anxiolytics and drugs acting on the recovery of normal bowel evacuation for future research. Chewing gums as we discussed are very potential in targeting oral diseases and disorders presently as well as a marvelous futuristic approach for aiming the systemic ailments.

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