e-ISSN: 2248-9126
Vol 5 | Issue 4 | 2015 |233-239. Print ISSN: 2248-9118

Indian Journal of Pharmaceutical Science & Research

www.ijpsrjournal.com

MEDICATED CHEWING GUM – A COMPLIANT DRUG DELIVERY

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ABSTRACT

Medicated chewing gums are one of the very compliant dosage forms. These drug delivery systems have gained a wide range of acceptability over past few decades owing to its ease of administration and local effects. No intake of water is required for these delivery systems and comparatively less gastro-intestinal irritation occurs. Moreover, these dosage forms are excellent drug delivery systems when it comes to freshening of breaths and cleansing of teeth. Advances have been seen in these formulations over past few decades, due to consumer satisfaction and increasing demands by mass population. Different technologies have been used to manufacture and evaluate these drug delivery systems.

Keywords: Gum base, Elastomers, Chewing test, *In vitro* release, Oral effects.

INTRODUCTION

Owing to major drug delivery by the oral route, scientists and researchers have made huge advances in this field of drug delivery to ensure patients safe and efficient delivery with no or minimum side effects at site of action. Itis due to these efforts that chewing gums (CG) are nowadays formulated by incorporating various drugs and effects have been observed. The first commercial chewing gum "State of Maine pure spruce gum" was marketed in 1948 in the U.S.A. The first patent was filed in 1869. The gum was intended as dentifrices but it has never been marketed. The first Medicated chewing gum "Aspergum" was launched in 1928.Also, work has been done to formulate the modified release drug delivery systems pertaining to these dosage forms. It occupies a major space in nutraceuticals ingredients as a delivery vehicle, e.g. (Cafosa is part of the Wrigley/Mars group of companies that are leading the chewing gum market supplying gum base for confectionery, nutraceutical and pharmaceutical applications).It has been observed experimentally that gums release drugs at desired rate and it can be compared with modified release drug deliveries. These drug delivery system permits more rapid therapeutic action compared to per-oral dosage forms. Drugs that have been incorporated till date include mouth freshners, anti-nausea and motion sickness (Quease Ease). Most of the chewing gum was usedfor smoking cessation (containing the nicotine) and also used for oral and dental hygiene (consisting of fluoride and carbamideetc).

A proprietary technology for directly compressible Gumbase (zenara) [1] have been developed which enabled formulation of the product in a conventional pharmaceutical facility instead of extrusion and it ensures consistent product and greater manufacturing efficiency. These are believed to manifest its position as a convenient and advantageous drug delivery system as it meets the high quality standards of Pharmaceutical industry and can be formulated to obtain different release profiles of active substances. Chewing gum can be retained in the oral cavity for a long period and, if the drug is readily absorbed across oral mucosa, chewing gum can provide a fast onset time for a systemic effect and the potential for avoidance of gastrointestinal and hepatic first pass metabolism of susceptible drugs. Generally, medicated chewing gum has a good stability, the medicine can be taken easily and directly without the prerequisite of water, and if required, prompt discontinuation of medication is possible. Physiochemical

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properties of the drug like aqueous stability, pKa value, distribution between gum/ saliva, product properties like, composition, mass, manufacturing process and the process of chewing i.e. chewing time, chewing rate, affects the release of drugs from the medicated chewing gum. Varying the formulation and manufacturing process, chewing gum as a drug delivery system can be formulated for an extended period of time [2,3].

The anecdotal effect of chewing gum on weight loss has also been studied recently. Though there are many other interesting anecdotal effects that result from gum chewing, such as the easing of blocked ears. It can be used either for local (mucosal) treatment of mouth disease or for systemic (transmucosal) delivery by direct intraoral absorption through the buccal mucosa. The medicated chewing gums may be coated, for example, if necessary to protect from humidity and light. Unless otherwise justified and authorised, a suitable test is carried out to demonstrate the appropriate release of the active ingredients. There is an increasing need to reformulate existing drugs into novel system or protect product patents thereby delaying, reducing or avoiding generic dependence. By formulating the drugs in MCG composition re-vitalization of old products and re-formulation of new patented products is possible to distinguish from future generics competition in the market.

During chewing the drug contained in the gum is released into the saliva. The released drug has got two fates; either it could be absorbed through the oral mucosa or may reach the stomach for GI absorption. These meet the same high-quality standards as tablets and can be formulated to obtain different release profiles of active substances, thus enabling distinct patient group targeting. In addition to offering competitive marketing advantages, a chewing gum formulation offers a vast number of clinical benefits.

Generally, chewing gum is a combination of a water-insoluble phase, known as gum base, and some other ingredients. These include powdered sugar whose amount and grain size determine the brittleness of the resulting gum, corn syrup and/or glucose which serve as humectants and coat the sugar particles to stabilize their suspension and keep the gum flexible, various softeners, food colourants, preservatives, flavourants etc. The drug product is intended to be chewed in the oral cavity for a specific period of time, after which the insoluble gum base is discarded.

There is no doubt that chewing gum is an important factor in confectionery and that it can be expected to have an influence on dental health. Chewing gum was initially sweetened with sugar, which contributed to dental caries. Today, however, more than 50% of chewing gum sold in Europe is sweetened with sugar substitutes (polyols).

Clinical evidence shows that sugar substituted chewing gum does not lead to caries, because the polyolsdo not lead to a clinically relevant production of metabolic acids in dental plaque. At the same time, however, chewing stimulates the flow of saliva, thus strengthening its protective properties, i.e., its buffering capacity, mineral supersaturating, and cleansing, antimicrobial, and agglutinating actions. Clearly, this suggests a beneficial effect from the chewing of sugar-free gum.

COMPONENTS

Chewing gum is a mixture of natural or synthetic gums, plastisizers and resins, sweetened with sugar, corn syrup, artificial sweeteners and may also contain coloring agents and flavor. The basic raw material for all CG is natural gum Chicle, obtained from the sapodilla tree. Chicle is very expensive and difficult to procure, therefore other natural gum or synthetic materials like polyvinylacetate and similar polymers can be used as given base [4].

IDEAL REQUIREMENTS FOR DRUG PROFILE

1. The drug should not have any type of disagreeable taste, since, it can affect patient compliance.
2. The particle size of the drug should be kept below approximately 100 mcm to avoid unpleasant gritty feeling during chewing. Decrease in particle size can be effective in increasing absorption of drug.
3. Drug should have high salivary solubility.
4. The solubility of drug should be pH independent.

COMPOSITION OF GUM BASE

A gum base comprises of a complex mixture of elastomers, plasticizers, resins, emulsifiers and fats, fillers or texturizers, sweetners, flavoring agents, anti-caking agent, and grinding agents [5, 6].

1. Elastomers: They provide elasticity, gummy texture and cohesion to the chewing gum. Some are natural elastomers and synthetic elastomers.

a) Natural elastomers e.g. Jelutong, Chicle etc.

b) Synthetic elastomers e.g. polyisobutylene and butyl rubber are used.

2. Plastisizers: These are used to regulate cohesiveness of product. These are again divided into natural and synthetic.

a) Natural Plastisizers e.g. glycerol esters or partially hydrogenated rosin or glycerol esters of polymerized esters.

b) Synthetic Plastisizers: e.g. Terpene resins derived from α-pinene. Some refers to d-limonene also.

3. Resins: A masticating substance and other as binding agent between elastomers and fillers. They contribute to the balance between the properties of elasticity and plasticity. Glycerol esters from pine resins are examples of natural resins. Synthetic resin like polyvinyl acetate can be used. It reduces the tendency of the gum to adhere to the teeth and to be divided into pieces during chewing. It has

only a slight taste, its stability is good and it is available in range of different molecular weights.
4. Emulsifiers and fats: These are used to soften the mixture and give the required chewing consistency and mouth feel. Emulsifiers promote the uptake of saliva into the chewing gum during mastication. Monoglycerides, diglycerides and partly hardened vegetable and animal fat are examples. Softeners include Glycerin, Mono/ di/ tri-Glycerides, Fatty acids like Stearic acid, Palmitic acid, etc.
5. Fillers or Texturizers: They provide the right texture, improve chewability, and provide reasonable size of the gum lump with low dose drug for the gum base. Commonly used fillers are Magnesium and Calcium Carbonate.
6. Antioxidants: They may be added to protect the gum base and flavors from oxidation. Ascorbic acid, tocopherol, butylhdroxytoluene have been used.
7. Sweetners: They are divided as aqueous sweetners and bulk sweetners.
a) Aqueous Sweetners: These are used as softeners to blend the ingredients and retain moisture. These include Sorbitol, hydrogenated Starch hydrolysates and Corn Syrups. Corn syrup keeps gum fresh and flexible.
b) Bulk Sweetners include Sugar and Sugarless components.
b) 1) Sugar components are Sucrose, Dextrose, Maltose, Dextrin etc.
b) 2) Sugarless components are sugar alcohols such as Sorbitol, Mannitol, hydrogenated Starch hydrolysate. High intensity artificial Sweetners can also be included to provide longer lasting sweetness and flavor perception e.g. Sucralose.
8.Flavouring Agents: A variety of flavouring agents are used to improve flavour in chewing gum includes essential oils, such as Citrus oil, Peppermint oil, Spearmint oil, etc.
9. Anti-caking agent: An anti-caking agent such as precipitated silicon dioxide can be mixed with chewing gum composition and solid carbon dioxide prior to grinding. This helps to prevent agglomeration of the subsequently ground chewing gum particles.
10. Grinding agents: To prevent the gum from sticking to the grinding apparatus 2-8% w/w of grinding aid such as alkaline metal phosphate, an alkaline earth metal phosphate or malto dextrin can be incorporated. However practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionisable therapeutic agents.

MANUFACTURING PROCESSES

Different methods employed for the manufacturing of CG can be broadly classified into three main classes [7, 8] as follows:

1) Conventional/ traditional (melting) method
2) Cooling, grinding and tabletting method
3. Direct Compression method

1. Conventional/ traditional Method:

Components of gum base are softened or melted and placed in a kettle mixer to which sweetners, syrups, active ingredients and other excipients are added at a definite time. The gum is then sent through a series of rollers that form into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavor. In a carefully controlled room, the gum is cooled for upto 48 hours. This allows the gum to set properly. Finally the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity.

Limitations

Elevated temperature used in melting restricts the use of this method for thermo labile drugs. Lack of precise form, shape or weight of dosage form are other limitations.

2. (a). Cooling, grinding and tabletting method:

This method can be divided into two steps:

(a) Cooling and Grinding

The CG composition (base) is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle during the subsequent grinding step without adhesion to the grinding apparatus. The temperature required for cooling is determined in part by the composition of the CG and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperature of the refrigerated mixture is around -15^{0}C or lower. Amongst the various coolants like liquid nitrogen, hydrocarbon slush, use of solid carbon dioxide is preferred as it can give temperatures as low as -78.5^{o}C, it sublimes readily on warming the mixture, is not absorbed by the chewing gum composition, does not interact adversely with the processing apparatus and does not leave behind any residue which may be undesirable or potentially hazardous. The refrigerated composition is then crushed or ground to obtain minute fragments of finely ground pieces of the composition. Alternatively, the steps of cooling the chewing gum composition can be combined into a single step. As an example, cooling the grinding apparatus itself which can be done by contacting the grinding apparatus with a coolant or by placing the grinding apparatus in a cooling jacket of liquid nitrogen or other cold liquid. For more efficient cooling, the chewing gum composition can be pre cooled prior to cooling to the refrigeration temperature. Sometimes a mixture of chewing gum composition, solid carbon dioxide and precipitated silica is ground in a mill grinder in a first grinding step. Additional solid carbon dioxide and silica are added to the ground composition, and the composition is further ground in a second grinding step. This two step grinding process advantageously keeps the chewing gum composition at a very low temperature. The presence of solid carbon dioxide also serves to enhance the efficiency of the

grinding process. The same process can be made multiple by incorporating additional carbon dioxide and/or precipitated silica at each step. After the composition is ground to a powder, the coolant can be removed by evaporation. Alternatively it has been found that such a powdered mass when warmed to room temperature from the refrigerated state, it becomes cross linked or self adhere together to form an integrated body which incorporates minute air bubbles in the texture between the particles. This provides a chewing gum product that is light and gives a soft chewing impression when chewed.

(b) Tabletting

After, the coolant has been removed from the powder, the powder is mixed with other ingredients such as binders, lubricants, coating agents, sweeteners etc, all of which are compatible with the components of the chewing gum base in a suitable blender such as sigma mill or a high shear mixer. Alternatively a Fluidized Bed Reactor (FBR) can be used. The use of FBR is advantageous as it partially rebuilds the powder into granules, as well as coats the powder particles or granules with a coating agent thereby minimizing undesirable particle agglomeration. The granules so obtained can be mixed with antiadherents like talc. The mixture can be blended in a V type blender, screened and staged for compression. Compression can be carried out by any conventional process like punching.

Direct Compression Chewing Gum

Direct compression chewing gum can be directly compressed on a traditional tabletting machine, thus enabling rapid and low cost development of a gum delivery system. This method has been used by few industries and for specialized gums only.Examples of gums: Lactose, Pharmagum.

FACTORS AFFECTING RELEASE OF ACTIVE INGREDIENT

1. Contact Time: The local or systemic effect is dependent on time of contact of MCG in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use [9].
2. Physicochemical properties of active ingredient: Physicochemical properties of active ingredient plays very important role in release of drug from MCG. The saliva soluble ingredients will be immediately released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly.
3. Inter individual variability: The chewing frequency and chewing intensity which affect the drug release from MCG may vary from person to person. *In-vitro* study prescribed by European Pharmacopoeia suggest 60 cycles per minute chewing rate for proper release of active ingredient.

4. Formulation factor: Composition and amount of gum base affect rate of release of active ingredient. If lipophilic fraction of gum is increased, the release rate is decreased

QUALITY CONTROL TESTS

Uniformity of content

Unless otherwise prescribed or justified and authorized, medicated chewing gum with content of 2 mg or less than 2 percent of total mass comply with test for uniformity of content of single dose preparation. If the preparation contains more than one active substance, the requirements applies only to that active substance, which corresponds to the above condition [9,10].

Uniformity of mass

Uncoated medicated chewing gum and, unless otherwise justified and authorized, coated medicated chewing comply with the test for uniformity of mass of single dose preparations. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required [11].

Drug release from medicated chewing gum

It has been reported commercially that the drug release from medicated chewing gum as per the specification given in European Pharmacopoeia and is determined by applying a mechanical kneading procedure to a piece of gum placed in a small chewing chamber containing a known volume of buffer solution [12].

IN- VITRO STUDIES

Apparatus 1: Chewing Gum Apparatus.

The chewing apparatus for medicated chewing gum was adopted by Ph. Eur. in 2000 (European Pharmacopoeia. Suppl. General Chapter 2.9.25, 2000). Figure 1 shows the construction of the apparatus. The chewing apparatus comprises a chewing chamber, two horizontal pistons, and a third vertical piston (tongue). The vertical piston operates alternatively with the two horizontal pistons and makes sure the gum stays in the right place between chews.

If necessary, it is feasible to construct the machine so that at the end of the chew the horizontal pistons rotate around their own axes in opposite directions to each other to obtain maximum chewing. The working procedure of this chewing apparatus is described in Ph. Eur. (European Pharmacopoeia. General Monograph 2.9.25, 2000, 2005, 2008). Several studies have been carried out using the Ph. Eur. apparatus, and the results indicate the methodology is rugged and reproducible.

Alternative 2. Alternative Chewing Gum Apparatus, Non compendia - Wennergren. .Fig no.2

One of the compendia apparatus commercially available was designed by Wennergren. The chewing procedure consists of reciprocations of the lower surface (twisting) movement of the upper surface that provides mastication of the chewing gum and at the same time adequateagitation of the test medium. The upper jaw has a

flat surface that is parallel to the central part of the lower surface. The small brim of the lower surface (45 degrees) so that the lower surface functions as a small bowl with a flat bottom. The influences of different operational parameters of the chewing gum apparatus on drug release have been carefully investigated [13].

In vivo 'chew-out' studies

The in vivo release of active ingredient from chewing gum during mastication can be studied by recruiting a panel of sufficient numbers of tasters and scheduled chew-out studies. For the duration of the chewing process the drug contained within the MCG is released in the saliva and then it is either absorbed through oral mucosa or, if swallowed, it is absorbed through the gastrointestinal tract.

A. Release of drug in saliva: Panel of volunteers is asked to chew the drug delivery device for a certain period of time and to assess the remaining quantity of active substance in the residual gum. In this way, the gums are really chewed and the formulation is subjected not only to the mechanical stresses of an artificial machine but also it undergoes all the phenomena involved in this process (increase of salivary secretion, saliva pH variation, swallowing and absorption by the oral mucosa, etc.) which can strongly influence the performance of the dosage form and the amount and rate of drug release. Optimized formulation with good consistency can be selected for the release of drug in saliva. Minimum four human volunteers can be selected (two male and two female). Volunteers are instructed to rinse their mouth with distilled water and allowed to chewing the medicated chewing gum for 15 minutes, so that its maximum release has to be taken. Sample of saliva are taken after 2, 4, 6, 8, 10, 12, 14, 15 min. The saliva samples are made diluted in required solvent and absorbance is analyzed by suitable analytical method.

Dissolution test of residual medicated chewing gum

In this experiment, gums are tested by a panel of volunteers to verify the drug release process from the drug delivery system. Each person chews one sample of the tableted gum for different time periods (1, 5, 10, 15 min). The residual gums are cut into small pieces, frozen and then ground till obtaining a fine powder. The residual drug content is determined by using suitable analytical method. The amount of drug released during mastication is calculated by subtracting the amount of residual active ingredient present in the gum from the total content, whereas pharmacokinetics can be determined from withdrawn blood samples at specific time intervals. The prerequisites of human volunteers, person-to-person variability in the chewing pattern, chewing frequencies, composition of individual salivary fluid and flow rate of saliva are a few limitations of chew-out studies [14].

Urinary excretion profile of medicated chewing gum

This method can be applicable only to those drugs which are excreted via urine. In that minimum four healthy human volunteer are selected for the study of formulations. Volunteers are strictly instructed that they should not take any medicine in the last 48 hour. They are fasted overnight, and emptied their bladder in the volumetric flask. Sample collection starts from blank of zero hour urine. Then sample collection is done on the 15 min, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 24 hour intervals after administration of medicated chewing gum. The volunteers are asked to drink water at regular intervals of 30 min. and urine samples are analyzed by suitable analytical methods [15].

APPLICATIONS

Being used as an alternative to buccal, sublingual and chewable tablets which are intended to act systemically because active ingredient is released more uniformly and cover greater area of absorption in oral cavity. Oral diseases are prevented or cured with MCG. MCGs can be used for systemic effect in conditions like vitamin C deficiency, pain & fever, alertness, motion sickness, smoking cessation, as well as for local effect in conditions like plaque acid neutralization, fresh breath, dental caries, antiplaque, fungal, and bacterial infections. Prevention and cure of oral diseases is a prime target for chewing gum formulations [16].

Local Therapy

Chewing Gum can control the release rate of active substances providing a prolonged local effect. It also re-elevates plaque pH which lowers intensity and frequency of dental caries. Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia. Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal infections. It can also be used for inhibition of plaque growth.

Systemic therapy

Chewing gum can be used in treatment of minor pains, headache and muscular aches. Xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety, etc are all indications for which chewing gum is a means of drug delivery.

Table 1. Various merits and demerits of Medicated chewing gum

Merits	Demerits
Avoids First Pass Metabolism and thus increases the bioavailability of drugs.	Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers.
Excellent for acute medication.	Prolonged chewing of gum may result in pain in facial muscles and

	ear ache in children.
Counteracts dry mouth, prevents candidiasis and dental caries.	Sorbitol present in MCG formulation may cause flatulence, diarrhea.
The treatment can be terminated at any time, if required.	Risk of over dosage with MCG compared with chewable tablets or lozenges that can be consumed in a considerable number and within much shorter period of time.

Fig 1. Chewing gum apparatus

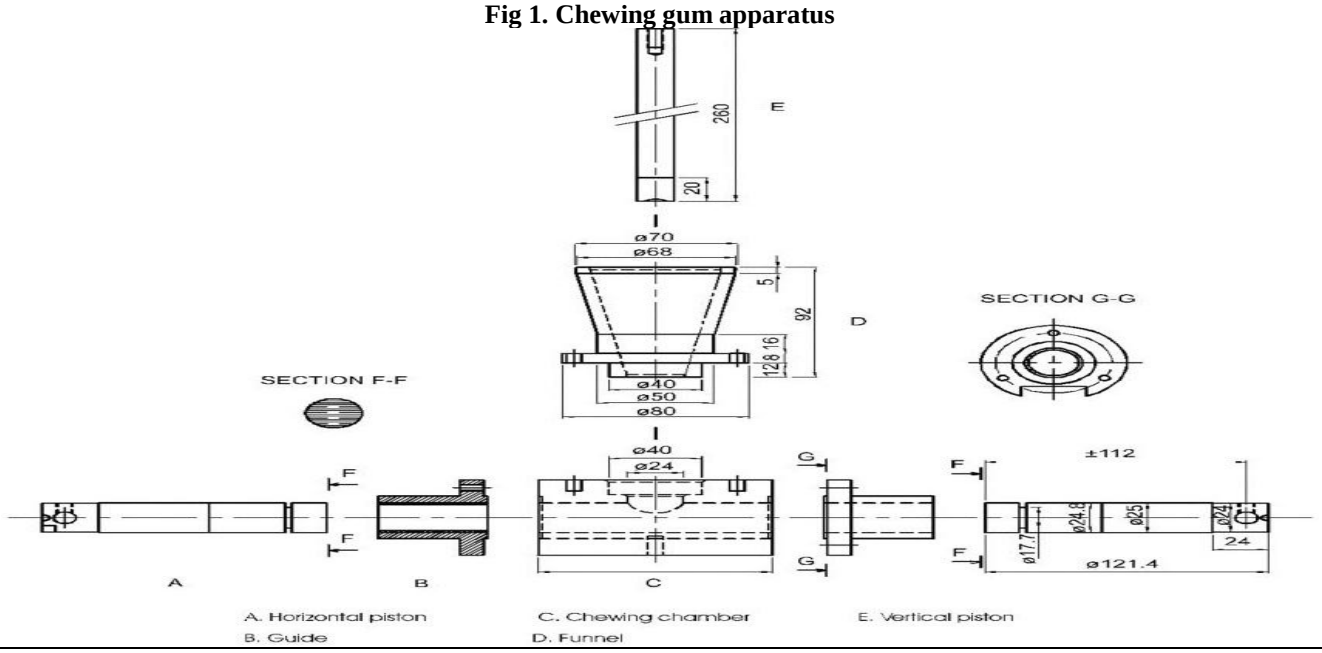
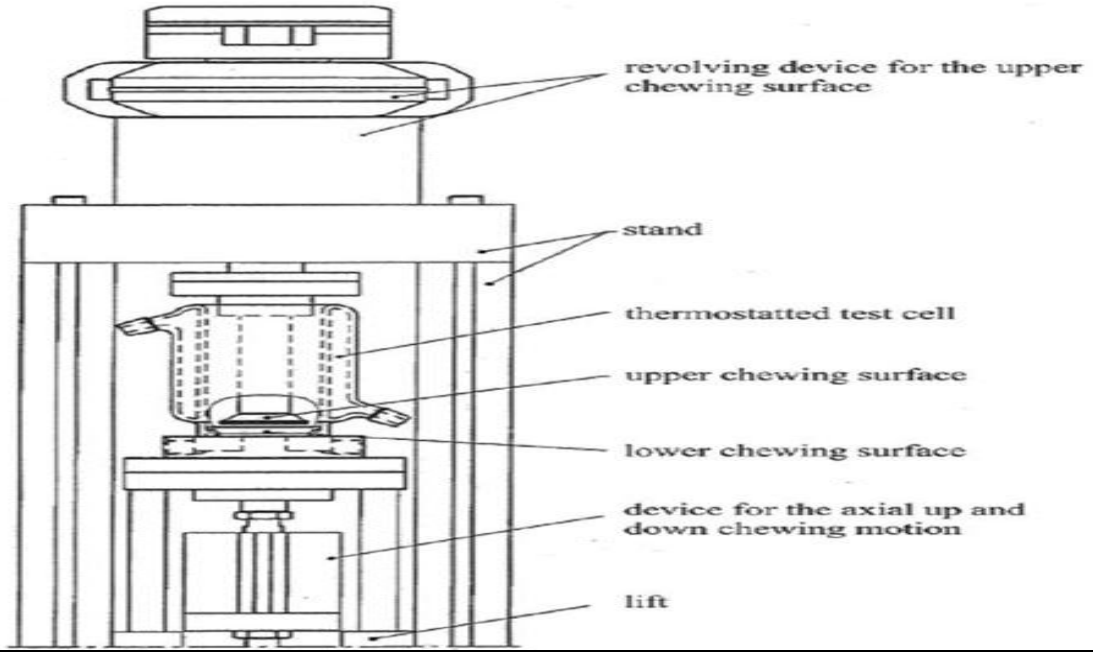


Fig. 2: Wennergren chewing apparatus



CONCLUSION

For most of drugs there are realistic possibilities of formulating them into a suitable chewing gum delivery system, although active agents with an extremely bitter taste may not be suitable candidates. Dental health chewing gum for caries prevention has come to stay and the indications are that it will be accepted widely in future. Chewing gum for smoking cessation will also remain

despite the fact that nicotine patches have grown in popularity lately. MCG has a good potential to become a convenient alternative approach to improve patient compliance. The delivery system can be used successfully for local as well as systemic delivery of drug.

ACKNOWLEDGEMENTS

I like to thank my institution for providing me with facilities, so, that I was able to complete my manuscript in time. I extend my thank towards my fellow ones to helping me in directly in my work. I would also extend my token of thank for my parents too.

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