INTERNATIONAL RESEARCH JOURNAL OF PHARMACY ISSN 2230 – 8407
Available online www.irjponline.com Review Article

CHEWING GUM: A MODERN ERA OF DRUG DELIVERY

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Article Received on: 12/08/11 Revised on: 21/09/11 Approved for publication: 16/10/11

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ABSTRACT
Chewing gum as a drug delivery system has many advantages over other oral dosage forms and oral route is the most preferred route amongst the patient and clinicians because the first pass metabolism can be avoided by the absorption of drug through buccal mucosa in the systemic circulation. It can be applied to cure and prevent the dental caries, pain, smoking cessation, obesity, xerostomia, motion sickness, acidity and specially diabetes. It has many advantages like fast onset of action, no first pass metabolism, patient compliance, taste masking, reduced risk of erosion of gastric mucosa, overdose and some marketing advantages. This review indicates that further study on medicated chewing gum can be used to improve it as a modern drug delivery.

KEY WORDS: Medicated chewing gum, buccal mucosa, first-pass metabolism, xerostomia.

INTRODUCTION

Medicated chewing gum is solid, single-dose preparations that have to be chewed & not swallowed; chewing gums contain one or more active ingredient that is released by chewing. A medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the remaining mass is discarded. During the chewing process the drug contained in the gum product is released from the mass into saliva & could be absorbed through the oral mucosa or swallowed reaching stomach for gastro-intestinal absorption.

Empiric findings had shown that people chewing gum was better at keeping awake and alert, and that gum chewing eased tension. The acceptance of this somewhat anecdotally understood effect achieved a better scientific basis in the summer 2002 when L Wilkinson and co-workers published a study of 75 healthy volunteers who were led through a number of cognitive, recognition, and memory tests. The results provided the first evidence that the chewing of gum can improve episodic memory and working memory[1].

Today chewing gum is convenient drug delivery system which is appropriate for a wide range of active substances[2]. Many therapeutic agents are absorbed in the oral cavity. For the drugs having significant buccal absorption, dosage forms such as Lozenges, Chewable tablets and Chewing gum permits more rapid therapeutic action compared to per-oral dosage forms[3]. Chewable tablets and chewing gum have been very well received by the parents for use in children with full dentition. Children in particular may consider chewing gum as a more preferred method of drug administration compared with oral liquids and tablets. The use of chewing gum is feasible in local treatment of diseases of oral cavity as well as treatment of systemic conditions.

Chewing gum has been used for centuries to clean the mouth and to freshen up the breath[4]. The first patent for the production of chewing gum was filed in 1869 and was issued to Mr. W. F. Semple in Ohio under U. S. Patent No. 98,304. A chewing gum containing Acetyl Salicylic Acid was commercially introduced in 1928[5]. In 1991, Chewing gum was approved as a term for pharmaceutical dosage form by the commission of European Council[6].

CHEWING GUM AS A DRUG DELIVERY SYSTEM

The advantages of utilizing a chewing gum drug delivery system are highlighted by T Imfeld in his 1999 review of gum chewing and oral health. There are two absorption pathways which are possible to introduce the active ingredient into the systemic circulation giving rise to a systemic effect. Drug absorbed directly via the buccal membrane avoids metabolism in the G.I tract & the first-pass effect of the liver; it might therefore be to administer a reduce dose in chewing gum compared to other oral delivery system[7].

(A). Local effect

To obtain the optimal local effect to treat a health condition requires that the relevant active substance be available at a therapeutic level near or within the tissue being treated, regardless of the delivery system. For the treatment of oral cavity conditions, it is beneficial to achieve a therapeutic level of active substance in the saliva, and different formulations (e.g. oral gel, mouth rinse) have been created to meet this goal. Chewing gum is an ideal drug delivery system for this treatment area; the active substances are released as the gum is chewed, thus providing the potential for a high level of active substance to obtain local effect in the oral cavity. It is possible to design a chewing gum that releases active substances over a prolonged period. The "Oral health and caries prevention" and "Oral fungal infection" provide a more comprehensive review of the advantages of chewing gum drug delivery systems for the local treatment of oral health conditions[8].

(B). Systemic effect

Systemic effects of active substances released from chewing gum can be achieved in two ways: in the "traditional" way, by swallowing the active substance, or buccally via absorption through the oral mucosa. The latter is of special interest. As buccal absorption avoids first-pass hepatic metabolism of the active substance, it could provide better bioavailability.[7] Buccal absorption may also lead to fast onset of the active substance as the vascular supply of the buccal mucosa is rich and lead directly into the systemic circulation. Chewing gum promotes buccal absorption by releasing active substances at carefully controlled rates, thus allowing for extended exposure in the oral cavity. There are several methods for examining buccal absorption; these methods are described by MR Rassing and co-workers. The buccal absorption of nicotine has been studied extensively and is, therefore, a good example of buccal absorption obtained when using chewing gum as a drug delivery system[9, 10].

OTHER ASPECTS OF CHEWING GUM

As suggested above, it is obvious that the length of time that patients chew becomes important when using chewing gum as a drug delivery system. In order to receive the full benefit from either buccal absorption or local effect, a certain concentration level in the oral cavity has to be maintained for a period of time[11]. The question is, therefore, what prescribed chewing duration will the typical patient accept; A study of 4,064 Americans between the ages of 12 and 55 answered this question to some degree. Participants were

asked about their gum chewing habits, and results showed that mean chewing time was 36 minutes – a sufficient time to obtain local effect or buccal absorption of an active substance.

MERITS OF CHEWING GUM

1. Dose not requires water to swallow. Hence, it can be taken anywhere[12].
2. Advantageous for patients having difficulty in swallowing[5].
3. Excellent for acute medication.
4. Counteracts dry mouth, prevents candidiasis and caries[12].
5. Highly acceptable by children.
6. Avoids First Pass Metabolism and thus increases the bioavailability of drugs[5].
7. Fast onset due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation[12].
8. Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients.
9. Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa[5].
10. Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.
11. Aspirin, Dimenhydrinate and Caffeine shows faster absorption through chewing gum than tablets.

DEMERITS OF CHEWING GUMS

1. Risk of over dosage with chewing gum compared with chewable tablets or lozenges that can be consumed in a considerable number and within much shorter period of time[4].
2. Sorbitol present in chewing gum formulation may cause flatulence, diarrhea[13].
3. Additives in gum like flavoring agent, Cinnamon can cause Ulcers in oral cavity and Licorice cause Hypertension.
4. Chlorhexidine oromucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue[14].
5. Chewing gums have been shown to adhere to different degrees to enamel dentures and fillers[15].
6. Prolong chewing on gum may result in pain in facial muscles and earache in children. [16].

COMPONENTS OF CHEWING GUM

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

Typically Chewing gum comprises two parts.

1. Water insoluble chewable gum base portion[17].
2. Water-soluble bulk portion[17].

1. Water insoluble gum base generally comprises Elastomer, Resins, Fats and Oils, and Inorganic fillers[5, 17].

a) Elastomer: Elastomer provides elasticity and controls gummy texture.

Natural elastomer: Natural rubbers like Latex or Natural gums such as Jelutong, Lechi Caspi, Perillo, and Chicle.

b) Plasticizers: These are used to regulate cohesiveness of product. These are again divided into Natural and Synthetic.

Natural Plasticizers include Natural rosin esters like Glycerol Esters or partially hydrogenated Rosin, Glycerol Esters of Polymerized Esters, Glycerol Esters of Partially demonized Rosin & Pentaerythritol Esters of Rosin.

Synthetic Plasticizers include Terpene Resins derived from α-pinene and/or d-limonene.

c) Fillers or Texturizers: Provide texture, improve chewability, provide reasonable size of the gumlump with low dose drug. Commonly used fillers are Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminum Silicate, Clay, Alumina, Talc, Titanium Oxide & Mono/ di/ tri Calcium Phosphate.

2. Water soluble portions contain Bulk Sweeteners, High intensity Sweeteners, Flavoring agents, Softeners, Emulsifiers, and Colors & Antioxidants.

a) Softeners and Emulsifiers: These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. Softeners include Glycerin, Lecithin, Tallow, Hydrogenated Tallow, Mono/ di/ tri-Glycerides, Fatty acids like Stearic acid, Palmitic acid, Oleic acid and Linoleic acid.

b) Colorants and Whiteners may include FD & C type dyes and lakes, fruit and vegetable extracts, Titanium Dioxide.

c) Sweeteners: These are of two types, Aqueous and Bulk.

Aqueous Sweeteners can be 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. Bulk Sweeteners include Sugar and Sugarless components. Sugar Components include Saccharides like Sucrose, Dextrose, Maltose, Dextrin, Fructose, Galactose, Corn Syrup. Sugarless Components include sugar alcohols such as Sorbitol, Mannitol, Xylitol, hydrogenated Starch hydrolysate. High intensity artificial Sweeteners can also be included to provide longer lasting sweetness and flavor perception e.g. Sucralose, Aspartame, salt of Acesulfame, Alitame, Saccharin, Glycerrhizin, Dihydrochalcones.

d) Bulking agents: These are used if low calorie gum is desired. Examples of low caloric bulking agents include Polydextrose, Oligofructose, Inulin, Fructooligosaccharides, Guargum hydrolysate, Indigestible Dextrin.

e) Flavoring Agents: A variety of flavoring agents are used to improve flavor in chewing gum includes essential oils, such as Citrus oil, fruit essences, Peppermint oil, Spearmint oil, Mint oil, Clove oil & Oil of Wintergreen. Artificial flavoring agents can also be used.

f) Active Component: In medicated chewing gum active pharmacological agent may be present in core or coat or in both. The proportion of which may vary from 0.5-30% of final gum weight. A small, unionized, lipophilic and enzymatically stable active agent is likely to be absorbed more readily. A saliva soluble ingredient will be completely released within 10-15 minutes of chewing whereas lipid soluble ingredient will dissolve in the gum base and thereafter be slowly and completely absorbed.

MANUFACTURING PROCESSES

Different methods employed for the manufacturing of chewing gum can be broadly classified into three main classes namely.

1. Conventional/ traditional Method (Melting).
2. Freezing, 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 sweeteners, 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 [3,6].

Limitations[6,18]:

1. Elevated temperature used in melting restricts the use of this method for thermo labile drugs.
2. Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.
3. Lack of precise form, shape or weight of dosage form.
4. Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.
5. Such a chewing gum composition is difficult to form into chewing gum tablets because of their moisture content (2-8%). If attempted to grind and tablet such a composition would jam the grinding machine, stick to blades, screens adhere to punches and would be difficult to compress.

2. Cooling, Grinding and Tabletting Method

This method has been developed with an attempt to lower the moisture content and alleviate the problems mentioned in conventional method[3,19].

Cooling and Grinding

The chewing gum 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 chewing gum and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperatures of the refrigerated mixture are around -15^{o}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 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 adding incorporating additional carbon dioxide and/or precipitated silica at each step.

Certain additives can be added to the chewing gum composition to facilitate cooling, grinding and to achieve desired properties of chewing gum. These include use of anti-caking agent and grinding agent.

Use of 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.

Use of grinding agents: To prevent the gum from sticking to the grinding apparatus, 2-8% by weight 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. They also tend to remain in the composition and final chewing gum tablet and thus may be problematic for therapeutic and safety point of view.

After the composition is ground to a powder, the coolant can be removed by allowing the coolant to evaporate. Alternatively it has been found that such a powdered mass when warmed to room temperature from the refrigerated state, they become 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.

Tabletting

Once the coolant has been removed from the powder, the powder can be mixed with other ingredients such as binders, lubricants, coating agents and 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 & staged for compression. Compression can be carried out by any conventional process like punching.

Limitation:

It requires equipment other than conventional tabletting equipment and requires careful monitoring of humidity during the tabletting process

3. Use of directly compressible chewing gum excipients

The manufacturing process can be accelerated if a directly compressible chewing gum excipient is available. The limitations of melting & freezing can be overcome by the use of these. PHARMAGUM® is one such compactable gum system developed by SPI Pharma. Pharmagum is a mixture of polyol(s) & or sugars with a chewing gum base. It is available as directly compressible powder, free flowing powder which can be compacted into a gum tablet using conventional tablet press thus enabling rapid and low cost development of a gum delivery system. It is manufactured under Chewing gum MP conditions and complies with Food Chemicals Codex specifications as well as with FDA, so they can be considered as "Generally regarded as safe" (GRAS).

Pharmagum® is available in three forms namely S, M and C. Pharmagum® M has 50% greater gum base compared to Pharmagum®S. Pharmagum®S consists primarily of gumbase and sorbitol. Pharmagum®M contains gumbase, mannitol & Isomalt. Release of nicotine from directly compressible nicotine gum formulations and from Nicorette® prepared by conventional methods has shown that use of Pharmagum in formulation showed a faster release rate. Formulations made with Pharmagum® M & S are similar to tablet in appearance. Gums formed using compressible formulation are 10 times harder and crumble when pressure is applied resulting in faster release than conventional methods [6,20].

FACTORS AFFECTING RELEASE OF ACTIVE INGREDIENT

1. Contact Time: The local or systemic effect is dependent on time of contact of chewing gum in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use.
2. Physicochemical properties of active ingredient: Physicochemical properties of active ingredient plays very important role in release of drug from CHEWING GUM. 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 chewing gum 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[21].

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[2].

SOME IMPORTANT FORMULATION ASPECT

1. Increased amount of softeners and emulsifiers in gum base fasten release whereas hard gum may retard[2,4].
2. Cyclodextrin complexation or solubilization technique increases aqueous solubility of drugs that are poorly water soluble [22,23].
3. A solid system of lipophilic active ingredients bound to the cation exchange resin permits a sustained drug delivery system.
4. Microencapsulation and agglomeration are the methods to modify and control the release of active ingredient [24,25].

EVALUATION OF CGDDs

Drug release studies

A number of devices to mimic the chewing action have been reported[26]. In 2000, the European Pharmacopoeia published a monograph describing a suitable apparatus for studying the in vitro release of drug substances from chewing gums.[27-29]

The most common in vitro method involves a using chamber in which excised buccal mucosa from either humans or animals are placed as a barrier between two chambers. The transport of active substances across the mucosa is measured by withdrawal of samples from each chamber. Buccal mucosa from domestic pigs is recommended, primarily because of the morphological similarity in mucosa from the human and porcine oral cavities.

Likewise, a human TR146 cell culture model has proven to be a good in vitro model for investigating permeability, permeability mechanisms, effects of chemical enhancers, and toxic effects[30]. The machines are driven by air, and are set to a specific number and frequency of chews inside a water bath at 37 °C, similar to the temperature of saliva in a person's mouth. Once the gum is "chewed," the fluid is tested to see how much of the drug has been released. The results are used to evaluate effectiveness and to develop new gum products[31,32].

STABILITY

The stability of chewing gum is comparable to that of most other solid delivery systems. Chewing gum normally contains little water (2–5%), and the water can be bound to other components in the product and is therefore not significantly reactive. The water activity in chewing gum is normally below 0.6 and typically 0.4– 0.5. If the water content is very critical for the stability of a drug, the chewing gum can be manufactured without water (less than 0.2%). This will, however, often make the product hygroscopic and affect the texture.

The low water content also inhibits microbial growth in the chewing gum during storage. Antioxidants are normally added with the gum base. Furthermore, the product can be protected against oxidation by a sealed coat and by an appropriate packaging[33]. For very temperature-labile components, e.g., enzymes, the process temperature of 50–60 °C during mixing may create a stability problem. It is, however, possible to operate the process at a lower temperature to avoid this issue[34].

USES

Oral Fungal Infection

Chewing gum has advantages as a drug delivery system for active substances where a local effect is the object of treatment. Several studies have been performed regarding the possibility of obtaining a constant, prolonged level of active substance locally for the treatment of oral fungal infections. The release of Metronidazole[35] from chewing gum was tested in an early study. It was possible to make a formulation that released 90% (+/- 16) of Metronidazole within 15 minutes of chewing. A similar study was carried out with Nystatin[36] and good release results were obtained one of the formulations tested had a release of 95%.

Miconazole has also been formulated as chewing gum[37,38] and these formulations have been used in clinical trials. The first study[39] proved that a good correlation existed between the in vivo and in-vitro release of Miconazole from different chewing gum formulations. In another study[40] different formulations of chewing gum containing Miconazole were used and, again, good correlation between in-vivo and in-vitro release was proven. A more interesting finding from the latter study is the result of a comparison between gel and chewing gum formulations: the same level of Miconazole concentration was found in the saliva whether oral gel or chewing gum were used despite the fact that a dosage of 100 mg of Miconazole was applied when using gel versus only 3.8 mg of Miconazole when using chewing gum. Inspired by these findings, a pilot study[41] was performed. The study included 32 patients with chronic oral candidosis, 11 of which were HIV infected.

Smoking Cessation

The use of chewing gum as a drug delivery system in smoking cessation is well established. It has become highly accepted by consumers. In 1983, nicotine chewing gum was first approved for smoking cessation, though the first clinical trials date back to the 1960s.[42] Prior to the launch of nicotine chewing gum, a chewing gum containing silver acetate was sold as a smoking cessation aid. The success of chewing gum in this treatment area may be explained by M J Peters and co-worker[43] "the process of their [the smokers'] use [of nicotine chewing gum] is a ritual that is in some ways analogous to smoking, and this may be an advantage."

The use of sugar free gum to counteract dental caries by stimulation of saliva secretion has led to a more widespread use and acceptance of gums. It has been proved that chewing non-medicated chewing gums increases plaque pH, stimulates saliva flow and decrease decay[44]. Chewing gums containing Chlorhexidine for treatment of gingivitis and plaque has been available. The use of chewing gum in the treatment of oral infections has also been reported[45]. The active ingredient is released from the chewing gum and sufficient concentration is achieved in the oral cavity to prevent or treat local conditions of oral cavity.

Chewing gum is also useful delivery system for agents intended for systemic delivery. Drug that is released from gum within oral cavity can be absorbed via buccal mucosa. The chewing gums can also be used as an alternative tool to buccal and sublingual 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 chewing gum. Chewing gums for systemic effect in conditions like vitamin C deficiency[46], pain & fever[47], alertness[48], motion sikness[49] as well as for local effect in the conditions like plaque acid neutralization[50], fresh breath[44], and antibacterial[51] are available.

CONCLUSION

For most drugs there are realistic possibilities of formulating them into a suitable chewing gum delivery system, although active agents with an extremely bitter taste would not be suitable candidates. Poorly water-soluble drugs require specialized formulation techniques to promote release, but these techniques are reasonably well developed. Dental health chewing gum for caries prevention has come to stay and the indications are that it will become more and more accepted. Chewing gum for smoking cessation will also remain despite the fact that nicotine patches have grown in popularity lately. This is because the very act of chewing gum also provides a physical substitute for the smoking habit and thereby increases the possibility of successfully quitting.

Finally, in the future, we may see drugs formulated into chewing gum in preference to other delivery systems to deliver drugs locally to the oral cavity. The reason is simple - that the chewing gum delivery system is convenient, easy to administer - anywhere, anytime - and is pleasantly tasting making it patient acceptable.

Marketed products

PRODUCT	DRUG	INDICATION (S)
Nicorette®	Nicotine	Smoking cessation
Nicotinell®	Nicotine	Smoking cessation
NiQuitin CQ®	Nicotine	Smoking cessation
Fluorette®	Fluoride	Prevention of dental caries
Vitaflo CHX®	Chlorhexidine	Antibacterial
Advanced+®	Chlorhexidine	Prevention of caries
HEXIT®	Chlorhexidine	Antibacterial
Stay Alert®	Caffeine	Motion sickness
Travvell®	Dimenhydrinate	

ACKNOWLEDGEMENT

The authors are thankful to Maratha Mandal's college of pharmacy for providing facilities and support.

REFERENCES

1. Wilkinson L, Scholey A, Wesnes K. Chewing gum selectively improves aspects of memory in healthy volunteers. Appetite; 2002; 38: 235-36.
2. http://www.fertin.com/fileadmin/pdf/Chewing_gum_as_a_DDS.pdf
3. Athanikar NK, Gubler SA. Process for manufacturing a pharmaceutical chewing gum. US Patent 6,322,828, 2001.
4. Jacobsen J, Christrup LL, Jensen NH. Medicated Chewing gum: Pros and Cons. Am J Drug Dev; 2004; 2 (2):75-88.
5. Conway B. Chewing gum as a Drug Delivery System. The Drug Delivery Companies Report 2003; Autumn/Winter: 33-5.
6. Naik H, Gupta S. Medicated chewing gums-updated review. Int. J Pharm Res Dev; 2010; 2(8): 66-76.
7. Imfeld T. Chewing gum-facts and friction: a review of gum chewing and oral health. Crit Rev Oral Biol Med 1999; 10: 405-19.
8. Mehta F, Keservani RK, Karthikeyan C, Trivedi P. Chewing gum as a drug delivery system. App Sci Res; 2010; 2(2): 79-99.
9. Rassing MR. Specialized oral mucosal drug delivery systems, chewing gum. In: MJ Rathbone: Oral Mucosal Drug Delivery. Marcel Dekker; 1996; 319-57.
10. Rassing MR; Jacobsen J; Nielsen HM. Chewing gum as a drug delivery system. 2nd ed, Ellermann Carecom International, Copenhagen, Denmark, 2003.
11. Barabolak R, Hoerman K, Kroll B, Record D. Gum chewing profiles in the US populations. Dent Oral Epidemiol; 1991; 19: 125- 26.
12. Morjaria Y, Irwin WJ, Barnett PX, Chan RS and Conway BR. In vitro release of nicotine from chewing gum formulations. Dissolution Technologies; 2004; 05: 12-15.
13. Goldberg LD, Ditchek NT. Chewing gum diarrhea. Am J Dig Dis; 1978; 23(6): 568.
14. Addy M, Roberts WR. Comparison of the bisbiguanide antiseptics alexidine and chlorhexidine. II. Clinical and in vitro staining properties. J Clin Periodontol; 1981; 8(3): 220-30.
15. Munksgaard EC, Nolte J, Kristensen K. Adherence of chewing gum to dental restorative materials. Am J Dent; 1995; 8(3):137-9.
16. Weil AT. Coca leaf as a therapeutic agent. Am J Drug Alcohol Abuse; 1978; 5(1): 75-86.
17. Zyck DJ, Greenberg; MJ., Barkalow DG, Marske SW, Schnell PG, Mazzone P. Method of making coated chewing gum products containing various antacids. US Patent 6,645,535, 2003.
18. Cherukuri SR, Bikkina ., Tabletted chewing gum composition and method of preparation. US Patent; 1988; 4,753,805.
19. Mochizuki K, Yokomichi F. Process for the preparation of chewing gum.US Patent;1976; 4,000,321.
20. http://www.spipharma.com/ProductsFolder/120ParmaGum/120Pharmagum.html
21. European Pharmacopoeia. Strasbourg: European Directorate for the Quality of Medicines. Chewing gums: Medicated. 5th ed; 2004; 260 & 601.
22. Barabolak R, Hoerman K, Kroll N. Chewing gum profiles in the US population. Community Dent Oral Epidemiol; 1991; 19: 125-6.
23. Jacobsen J, Bjerregaard S, Pedersen M. Cyclodextrin inclusion complexes of antimycotics intended to act in the oral cavity--drug supersaturation, toxicity on TR146 cells and release from a delivery system. Eur J Pharm Biopharm 1999; 48(3): 217-24.
24. Gudas VV, Reed MA, Schnell PG, Tyrpin HT, Russell MP, Witkewitz DL. Method of controlling release of caffeine in chewing gum. US Patent 6, 165.516: 1998.
25. Yang RK. Encapsulation composition for use with chewing gum and edible products. US Patent 4, 740, 376, 1988.
26. Kvist C, Andersson SB, Fors S, Wennergren B, Berglund J. Apparatus for studying in-vitro release from medicated chewing gums. Int J Pharm; 1999; 189: 57-65.
27. Biradar SS, Bhagavti ST, Hukkeri VI, Rao KP, Gadad AP. C.V.P. pharmaceutics journal; 2005. Available at: http://www.scientific-journal-articles.com
28. Rider JN, Brunson EL, Chambliss WG, Cleary RW, Hikal AH, Rider PH, Walker LA, Wyandt CM, Jones AB. Development and evaluation of a novel dissolution apparatus for medicated chewing gum products. Pharm. Res; 1992; 9: 255-60.
29. European Pharmacopoeia. Strasbourg: European Directorate for the Quality of Medicines. Chewing gums: Medicated. 4th ed., 227-28.
30. Nielsen HM. Buccal absorption of basic drugs and its application as an in vivo model of passive drug transfer through lipid membranes. Ph.D. Thesis, HCO Tryk, Copenha gen, DK; 2000.
31. McKay G. Pharmalytics chewing machines unique in North America. Regina research parks. 2004. Available at: http://www.innovationplace.com
32. Semwal R, Semwal DK, Badoni R. Chewing gum: A novel approach for drug delivery. J App Res; 2010; 10(3): 124-32.
33. Margrethe RR, Jacobsen J, Medicated Chewing gum. Marcel Dekker, Inc: New York; USA, 2003; 419-29.
34. Angel US, Chewing gum and process for manufacture thereof. EP 2078186, 1994.
35. Andersen T, Gram-Hansen M, Pedersen M, Rassing MR, Drug. Dev. Ind. Pharm; 1990; 16: 1985-1994.
36. Pedersen M, Rassing MR, Miconazole chewing gum as a drug delivery system test of release promoting additives. Drug Dev Ind Pharm; 1990; 16 (1): 55-74.
37. Jacobsen J, Bjerregaard S, Pedersen M. Cyclodextrin inclusion complexes of antimycotics intended to act in the oral cavity-- drug supersaturation, toxicity on TR146 cells and release from a delivery system. Eur J Pharm Biopharm 1999; 48: 217-24.
38. Pedersen M, Rassing MR. Miconazole chewing gum as a drug delivery system: application of solid dispersion technique and lecithin. Drug Dev Ind Pharm; 1990; 16: 2015-30.
39. Pedersen M, Rassing MR. Miconazole chewing gum as a drug delivery system. Drug Dev Ind Pharm; 1991; 17 (3): 411-20.
40. Rindum JL, Holmstrup P, Pedersen M, Rassing MR, Stoltze K. Miconazole chewing gum for treatment of chronic oral candidosis. Scand J Dent Res; 1993; 101: 386-90.
41. Bastian HL, Rindum J, Lindeberg H. A double-dummy, double-blind, placebo-controlled phase III study comparing the efficacy and efficiency of miconazole chewing gum with a known drug (Brentan gel) and a placebo in patients with oral candidosis. Oral Surg Oral Med Oral Pathol 2004; 98(4): 423-8.
42. Peters MJ, Morgan LC. The pharmacotherapy of smoking cessation. Med J Australia; 2002; 176: 486-490.
43. Malcolm R, Currey HS, Mitchell MA, Keil JE. Silver acetate gum as a deterrent to smoking. Chest 1986; 90: 107-11.
44. Imfeld T. Chewing gum-facts and friction: a review of gum chewing and oral health. Crit Rev Oral Biol Med; 1999; 10: 405-19.
45. Pedersen M, Rassing MR. Miconazole chewing gum as a drug delivery system. Drug Dev Ind Pharm; 1991; 17 (3): 411-20.
46. Christrup LL, Rasmussen SN, Rassing MR. Chewing gum as a drug delivery system. Farmaci Sci; 1988;16: 44-7.
47. Woodford DW, Lesko LJ. Relative bioavailability of aspirin gum. J Pharm Scie; 1981; 70(12): 1341-3.
48. Tyrpin HT, Russell MP, Witkewitz DL, Johnson SS, Ream RL, Corriveau CL.: Caffeine coated chewing gum product and process of making. US Patent: 6,444,241, 2002.
49. Seibel K, Schaffler K, Reitmeir P, Golly I. A randomised, placebo-controlled study comparing two formulations of Dimenhydrinate with respect to efficacy in motion sickness and sedation. Arzneimittelforschung 2002; 52(7): 529-36.
50. Finn SB, Jamison HC. The effect of a dicalcium phosphate chewing gum on caries incidence in children: 30-month results. J Am Dent Assoc1967; 74(5): 987-95.
51. Wertalik F, Bonorden R. salivary levels of antibiotics from use of neomycin-gramicidin chewing troches. J Pharm Sci 1968; 57(3): 530-1 .

Fig. Chewing machines for testing medicated chewing gum

Figure 1: A selection of some of the chewing gums currently sold in the Kingdom of Saudi Arabia.