MEDICATED CHEWING GUM AS A NOVEL DRUG DELIVERY SYSTEM - A REVIEW

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Summary

Chewing gum is an excellent drug delivery system for self-medication, as it is convenient and can be administered discreetly with out water. It offers several advantages compared to chewable tablets, lozenges and other related formulations hence in the coming years it is very likely that chewing gum will become a common drug delivery system.

Key Words: Novel drug delivery system, Chewing gum, Chicle, Oral mucosa, Bioavailability.

Introduction

It is a well-known fact that the right drug delivery system is critical to the success of a pharmaceutical product. A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug and, thus, conserve or increase revenue. Man has a habit of chewing the chewing gum since ancient times. Today it is one of the most popular dosage form, used for delivering the many active components. People of all cultures chew gum, and a variety of gums and gum-like substances have been enjoyed for thousands of years[2].

The first medical chewing gum was introduced in market in 1928 consisting of aspirin an analgesic drug. However, chewing gum did not gain acceptance as a reliable drug delivery system until 1978, when nicotine chewing gum became available in 1980. Most of the chewing gum were used for smoking cessation (containing the nicotine) and also used for oral and dental hygiene (consisting of fluoride and carbamide etc).

Chewing gum can be used as drug delivery for many active components. With the inclusion of medical chewing gum in the *European Pharmacopoeia* in 1998, have further contributed to the acceptance of this method of drug delivery[3].

Today, medical chewing gum meets 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. As many active substances are buccally absorbed, efficacy can be greatly enhanced due to the associated fast onset of action and high bioavailability. Medical chewing gum also provides a topical effect in the oral cavity and in the throat.

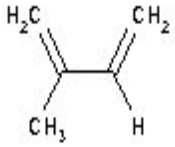
What are the ingredients in chewing gum?

Active substances and additives sweeteners like sorbitol mannitol and suitable fruity flavours and nonsticky Gum Base The gum base is the insoluble part left in the mouth while chewing and it is a polymer. The gum base is made of resins from trees, latexs or the milky juices from plants, and manmade polymers. If the gum base is chicle from the sapodilla tree, this product is being harvested in Belize, Mexico and Guatemala. Chicle is harvested from July to February which is during the rainy season. Slashes are cut into the bark of the tree so that the sap runs down the tree into a collection bucket[4,5].

Cuts on the sapodilla tree let the sap run into a collection bucket.

Chicle is boiled over an open fire in the rainforest to evaporate some of the excess water. Once it is thick and taffy-looking, it is packed into wooded forms to make blocks. These blocks are shipped to some American chewing gum manufacturers. Chicle is a rubbery latex or polyterpene. Polyterpenes are composed of thousands of C_5H_8 isoprene subunits.

Natural rubber is a polymer consisting of isoprene (2-methyl-1,3-butadiene) units.



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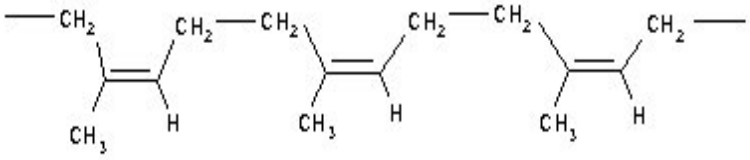

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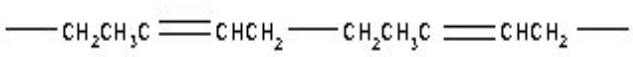


Today, the gum base could also be made from styrene butadiene, poly (vinyl acetate) or polyethylene. The sugar is for sweetening the product[9]. The corn syrup keeps the gum fresh and flexible. Softeners or fillers such as vegetable oils help to blend the ingredients and retain moisture. Sugar free gum has sorbitol, mannitol, aspartame or saccharin instead of sugar. The gum base determines the basic characteristics of the product example texture whether it is soft? Does it crumble? Does it stick to the teeth?

Chocolate

Wintergreen mint

Grapefruit

Why we use chewing gum as a drug delivery system? [10,11,12]

There are many reasons for selecting the chewing as a drug delivery system, the following are the some reasons highlighted.

1) Easy for administration without water promotes higher patient compliance.
2) Children and for patients who find swallowing tablets difficult are obvious.
3) Local effect
4) Systemic Effect
5) Fast onset of action
6) Less side effects

7) Less risk of overdosing
8) Effective on Dry mouth
9) Fast onset of action and high bioavailability
10) Pleasant taste
11) Higher compliance (easy and discreet administration without water)
12) Ready for use
13) High acceptance by children

High acceptance in children

Many children find it difficult to swallow tablets. To overcome this problem, liquid formulations have been developed, however, administering liquid formulations may be difficult and circumstantial as well. A chewing gum formulation is an obvious alternative. In a chewing gum formulation, it is most often possible to disguise the bitter/bad taste of the active substance, making it a pleasant experience for the child. However, it is important that the child chews the chewing gum for the prescribed period of time. Compared to a liquid formulation, chewing gum also provides easier Storage as there is no risk of microbial contamination.

Local therapy

Prevention and cure of oral diseases are obvious targets for chewing gum formulations. Chewing gum can release an active substance at a controlled. Sugar-free chewing gum is known to be beneficial to dental health. It has been shown that use of sugar-free chewing gum after meals re-elevates plaque pH [1]

Indications for fluoride chewing gum are prevention of dental carries in Children in fluoride-deficient areas, in adults with a high incidence of carries, and in patients with xerostomia. The carries-preventive effect of fluoride chewing gum has been compared with the effect of placebo chewing gum in oral infections caused by bacteria or fungi are often seen, especially in patients with impaired immune system. Chlorhexidine Chewing gum can be used for treatment of gingivitis, peridontitis and other oral and pharyngeal infections[4] it can also be used for inhibition of plaque growth and has shown Successful treatment of minor pains, headaches, pains of cold, muscular aches, etc. requires rapid absorption of therapeutic doses of the active substance. Chewing gum as a drug delivery system could be beneficial in minor pain treatment, when buccal absorption results in fast onset of action and reduces the risk of gastrointestinal side effects. The bioavailability of acetylsalicylic acid in a chewing gum formulation relative to an unbuffered tablet formulation has been determined[8].

A chewing gum formulation may also be useful in the treatment of acute, strong pain. Bioavailability of methadione from a chewing gum formulation has been compared to a tablet formulation. There was no significant difference in the bioavailability of the two formulations[9].

Patient compliance

As no water is required, taking medication in chewing gum is very convenient and therefore suitable for acute treatment[13]. The medication may be taken without regard to time and place, thus promoting compliance. Chewing gum does not draw attention to the medication, it is discrete and does not Stigmatize the patient.

Today, there is a trend towards higher patient involvement in drug administration and handling. Chewing gum is in line with this trend as it allows easy self-administration and does not prevent patients from living an active life. Further Clinical trials involving patients with oral candidosis have shown that miconazole chewing gum is at least as efficient as miconazole oral gel in the treatment of fungal infections in the mouth[6,7].

Fewer side effects
Active substances absorbed buccally bypass the hepatic first pass metabolism, which may result in a higher bioavailability of the active substance. Thus, the equivalent efficacy may be obtained with a lower dosage, and consequently less side effects are expected. Further, a lower dosage may reduce the risks of interactions with other active substances. The controlled release rate also reduces the risk of side effects, as high plasma peak concentrations are avoided.

Systemic effect
Active substances can be absorbed through the buccal mucosa and/or through the GI tract when saliva is swallowed. Once the active substance is present in the blood, systemic affect can be obtained.

Fast onset of action:
Fast onset of systemic effect is seen for active substances absorbed through the buccal mucosa, as the active substances pass by the jugular veins directly to the systemic circulation.

Local effect :
Chewing gum is an obvious drug delivery system for local treatment of diseases in the oral cavity and in the throat, as sustaining the release of active substances may deliberately prolong exposure.

Effect on dry mouth:
Dry mouth is a side effect of many types of medication (e.g. antidepressants), and it is also part of the symptomatology of several diseases (e.g. Sjögren's syndrome). It is well known that chewing gum stimulates salivary secretion[1], and a chewing gum formulation therefore partly alleviates this condition. Furthermore, as dry mouth increases the incidence of dental caries, chewing gum may also be beneficial to dental health[14]. It has been shown that long-term activation of the salivary glands by chewing gum several It has been shown that long-term activation of the salivary glands by chewing gum several times per day for two months enhanced resting salivary flow, especially in individuals with low salivary flow[1].

Less risk of overdosing:
Chewing is required to release the active substance from chewing gum. If the chewing gum is swallowed accidentally, only limited amounts of the active substance will be released over a relatively long period of time, thus reducing the risk of high plasma peak concentrations and overdosing[15].

CONCEPT OF FORMULATION DEVELOPMENT:

A piece of chewing gum usually consists of gum core, which may or may not be coated. The core is composed of an insoluble gum base resin, elastomers, emulsifiers, fillers, waxes, antioxidants and softeners, sweetners, flavoring agents, and in case of medical chewing gum, active substances. The water content of chewing gum is very low and no preservative is needed. The gum base determines the basic characterstics of the product, e.g. the texture: is soft or hard to chew? Does it crumble? Does it stick to the teeth? The gum base also determines the release profile of active substances and changing the gum base compostion may therefore change the release profile[16].

As many active substances are lipophillic, they will adhere to the gum base and may therefore be released slowly and incompletely. Methods to increase rate and extent of the release include the addition of buffering agents or solubilizing agents and coating/encapsulating the active substances. In contrast, hydrophillic active substances are rapidly released and it may therefore be necessary to slow down the release rate by means of various methods, like encapsulating the active substances or by increasing the amount of gum base. The water content of gum base is very low and the gum binds lipophillic substances very firmly. In order to obtain the optimal formulation it is possible to decrease the release rate go highly lipophilic substances and increase the release rate of lipophillic substances.

Changing the water solubility of the active substances will increase or delay the release. A similar effect may be obtained by changing the hydrophilic/lipophillic balance of the chewing gum formulation[17]. {/josquote}The simplest way of achieving this is to increase or decrease the amount of gum base. An increase in the gum base will make the formulation more lipophillic and thus reduce the release rate of a given active substance. To obtain a viable formulation, it is far more effective to change the release properties by adding solubilizers to the formulation.

To succeed in the market, a chewing gum formulation must have a pleasant taste and texture. Most active substances have an unpleasant, bitter, or metallic taste. Since the active substance will be released in the oral cavity and remain there for a longer period of time than is the case with oridinary delivery forms, unique expertise in taste definition, taste masking and taste modification are essential to the success of a medical chewing gum product.

One of the major challenges for the product developer is that any small adjustment in the amount of active ingredient, flavor, sweetener, or gum base component may lead to changes in several parameters. Therefore every active ingredient requires a custom-made gum base.

The gum base determines the basic characteristics of the product like the texture, its softness, hardness, elasticity, crumbleness, stickiness, mouthfeel etc. It also determines the release profile of active ingredients and flavors.

Formulation[19]

The main components of medicated chewing gum are:

Active substances-

vitamins, oral contraceptives, nicotine, minerals, analgesics, antacids, muscle relaxants, antihistamines, decongestants, anesthetics, antitussives, antibiotics, etc.

Flavors-

essential oils like citrus, peppermint, spearmint, anise and wintergreen oil are employed as flavors. Synthetic flavors are also used.

Sweetners-

Sugar free chewing gums contain sweetening agents like sorbitol, mannitol, aspartane, saccharin etc

Gum base-
Natural or synthetic gum base is used. Example of synthetic gum base includes styrene butadiene rubber, polyethylene and polyvinyl acetate. Smoked rubber is natural source. In addition to above ingredients various additives are also used to improve properties of chewing gum, like plasticizers, elastomers, lipids (soyabil), emulsifiers (lecithin), softners and fillers, texture agents (talc), coating and binding agents, film formers, coloring agents etc. Corn syrup keeps the gum flexible and fresh. Xylitol has been investigated to play a significant role in dental caries.

MANUFACTURING PROCESS

In general, chewing gum is manufactured by sequentially adding the ingredients to a commercially available mixer known in the art. After the ingredients have been thoroughly mixed, the gum mass is discharged from the mixer and shaped into the desired form such as extruding in to chunks or casting into pellets which are then coated or panned. The ingredients are mixed by first melting the gum base and adding to it the running mixer. The base may be melted in the mixer itself and other additives added at this time. The entire procedure takes from 5-15 min, but longer mixing time may be manufactured depending on the texture and function of gum base.

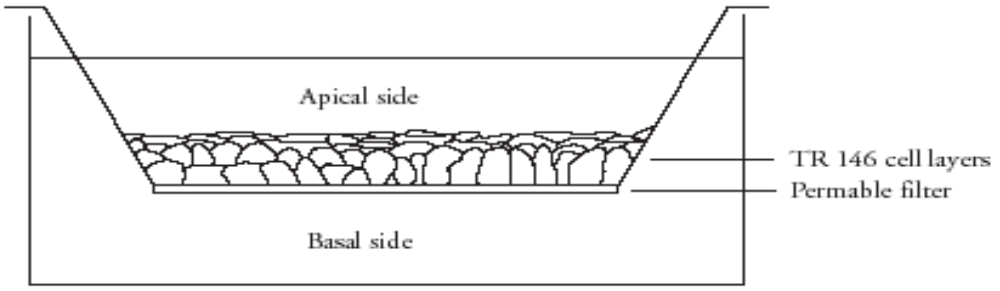
Oral Mucosa
The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. Epithelium has a mitotically active basal cell layer, advancing through a no. of differentiating intermediated layers to the superficial layers, when cells are shed from the surface of the epithelium. The epithelium cells increases in size and becomes flatter as they travel from the basal layer to the superficial layers. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin[20]. In general the permeabilities of the oral mucosa decreases in order of sublingual greater than buccal and buccal greater than palatal. The main target mucosa for drug absorption from chewing gum formulation is sublingual mucosa. However, drug is released into saliva and its subsequent spreading may cause the drug to be absorbed across other mucosa of oral cavity.
Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirement with infrequent dosing regimen. Buccal mucosa on the other hand is more suited for sustained delivery applications as it is less permeable and has immobile mucosa.
The buccal mucosa consists of 20-40 layers of cells with a total thickness of 450-600mm. The main barrier of the buccal mucosa is situated in the outer one third of the epithelium. The submucosa is highly vascularized and rapidly removes any permeated active substances to the systemic circulation thus avoiding first pass metabolism.

EVALUATION OF CHEWING GUM:

The absorption of active substances through the buccal mucosa can be examined by both in vitro and in vivo methods. The most common in vitro method involves an Using chamber, in which excised buccal mucosa from either humans or animals is placed as a barrier between two

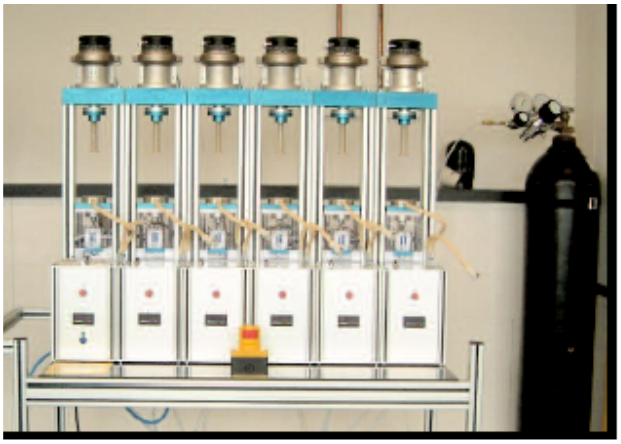
chambers[21].The transport of active substances across the mucosa is measured by withdrawal of samples from each chamber. Buccal mucosa from domestic pigs is recommended, mainly because of the morphological similarity in mucosa from the human and porcine oral cavities.

Likewise, a human TR146 cell culture model has proven a good in vitro model for investigating permeability, permeability mechanisms, effects of chemical enhancers, and toxic effects[18].
The machines are driven by air and are set to a specific number and frequency of chews inside a



The TR146 cells form a stratified epithelium of 4-8 cell layers after culturing for 3-4 weeks on a permeable filter[21]. Apical side = mucosal side, basal side = serosal side. With permission[18].

water bath at 37 degrees Celsius, similar 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[25]



Chewing machines at Pharmalytics used for testing medicated chewing gum.

Buccal absorption of active substances can also be tested by various in vivo methods. Beckett and Triggs introduced a mouth wash procedure in 1967, in which a buffered solution of the active substance is swirled in the oral cavity for a known period of time[23].
Subsequently, the solution is expelled and the oral cavity is rinsed with buffer. The difference between the amount of active substance contained in the original solution and the amount recovered is assumed to be the amount of active substance absorbed from the oral cavity. Since the introduction of this method, it has been improved by various modifications, however, the

main limitation lies in the fact that the method cannot account for storage of active substances in the mucosa.
Another in vivo method involves a perfusion chamber, which is adhered to the buccal mucosa of the test person. The absorbed amount of active substance perfused through the chamber is calculated as the decrease in active substance[24].

THERAPEUTIC USES:

The Chewing gum can be used for therapeutic purposes by incorporating the various medicaments especially antiasthamatic and Nonsteroidal anti-inflammatory and antiobsedrugs[22].
1.**Dental caries**- Prevention and cure of oral disease are obvious targets for chewing gum formulations. It 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. Chlorhexidine chewing gum
2.***S*ystemic therapy**- chewing gum as a drug delivery system is beneficial to a number of indications, some of which are discussed below:
a)**Pain**- Treatment of minor pains, headache, muscular aches can be successfully accomplished
b)**Smoking cessation**- Chewing gum formulation containing nicotine, lobeline and silver acetate have been clinically tested as aids to smoking cessation. Nicotine is a natural alkaloid occurring in the leaves of tobacco plant. It is a therapeutic agent intended to help smokers break the psychological habit of smoking by reducing the nicotine withdrawal symptoms normally experienced when smoking is stopped. The formulation nicoretteÒ available as mint and classic with different flavor and dosage, is developed with ion- exchange resin, released 90% of drug after 30 min chewing (Russel et.al 1980). The release rate was controlled by the rate and vigour of chewing. Thus the patient can control the drug intake to match his needs. Increasing the pH of the medium in which it is dissolved can enhance nicotine absorption.
c)**Obesity**- Active substances like chromium, guaran and caffeine are proved to be efficient in treating obesity. Chromium is claimed to reduce craving for food due to an improved blood-glucose balance. Caffeine and guaran stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger.
d)**Other indications**- xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety etc are all indications for which chewing gum as drug delivery system could be beneficial

FUTURE TRENDS

Chewing gum not only offers clinical benefits but also is an attractive, discrete and efficient drug delivery system. A few decades ago, the only treatment for some disease was surgical procedure but now more and more disease can be treated with Novel Drug Delivery Systems. Generally, it

takes time for a new drug delivery system to establish itself in the market and gain acceptance by patients, however chewing gum is 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

Conclusion

A chewing gum formulation must have a pleasant taste and texture. Most active substances have an unpleasant, bitter, or metallic taste. Since the active substance will be released in the oral cavity and remain there for a longer period of time than is the case with ordinary delivery forms (usual chewing time is 10 to 20 minutes), unique expertise in taste definition, taste masking, and taste modification are essential to the success of a medical chewing gum product.Though chewing gum as a drug delivery system has currently gained wide acceptance only within smoking cessation and oral healthcare, vast interest in this mode of drug delivery for a wide variety of other indications exists and continues to grow. Clinical trials have confirmed the advantages to be gained by exploiting the effects of chewing gum, *per se*, the convenience of the delivery and the possibilities of buccal absorption and local effect. Furthermore, one trial has indicated that chewing gum is possibly a safer drug delivery system for active substances that are susceptible to abuse. As chewing gum as a drug delivery system is to be expanded into additional therapeutic areas, it is important that the delivery form is acceptable to the end-users. Clinical trials and market research have proven this to be the case. In the coming years, new formulations will enter the market and chewing gum will become a much more common drug delivery system.

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