

Insulin chewing gum: Need of the day for diabetic patients

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Abstract

Chewing gum is an excellent drug delivery system for self medication as it is convenient, can be administered discreetly without water and offers the removal of 'needle fear' for the patients. As it releases insulin orally, it helps in tackling of the deprivation of insulin by digestive enzyme without adding digestive enzyme inhibitor. This can be done by binding of vitamin B12 and insulin. The vitamin B12 is protected with haptocorrin which is a salivary protein. Another chemical pathway takes over to help vitamin B12 pass into the bloodstream as haptocorrin reaches the intestines. The binding of vitamin B12 and insulin molecules makes the insulin to be protected on this supply chain. The insulin could ride all the way into the bloodstream, where it is released to do its work. By stimulating the brain, chewing gum also increases the releases of insulin. Finding simpler ways to deliver insulin into the blood stream is one important avenue for tackling the diabetes epidemic that is sweeping the developed world. The conditions in gastrointestinal tract may damage the body's protecting and absorbing mechanisms for the valuable molecules. Chewing gum would be a better delivery method in humans.

Key words: Chewing gum, diabetes mellitus, drug delivery system, insulin

INTRODUCTION

Diabetic patients cannot produce sufficient insulin which is required to convert sugar, starches, and other food source into energy. Scientists have been looking for effective ways to deliver insulin into the blood stream. This problem can be solved by using insulin chewing gum. Chewing gum has been used worldwide. Since ancient times human being has been experiencing the pleasure of chewing a variety of substances. One thousand years ago, the Mayan Indians chewed tree resin from the sapodilla tree in order to clean their teeth and freshen the breath.^[1] In 1928, the first medical chewing gum containing aspirin was introduced but it was accepted after the approval of nicotine chewing gum in 1980.^[2] In the current world, the medical chewing gums are as acceptable as tablets and enables targeting

the distinct patient group.^[3] It allows systemic and local delivery of the drug and it can be taken without water. Today, chewing gum delivery systems are majorly manufactured by conventional gum process. The examples of worldwide available chewing gums and noninvasive insulin products and their status were explained in the Tables 1 and 2.

MECHANISM OF DRUG RELEASE THROUGH CHEWING GUM

The release of substances from chewing gum during the process of mastication can be studied by employing a panel of tasters and chew-out studies. In the process of mastication, the medication contains within the gum product releasing insulin into the saliva. It is either absorbed through the oral mucosa or swallowed and absorbed through the gastrointestinal tract (GIT). Pharmacokinetics can be determined from the blood samples only after chewing gum is removed and analyzed for the residual drug substance. Drug release from chewing gum can be explained through the mechanism of drug release in Figure 1. Disadvantages of chew-out studies include the requirement for human volunteers, lack of chew control, and variations in the flow and composition of subject's saliva. A number of devices to mimic the chewing action have been reported.^[4] In 2000, the European pharmacopeia published a monograph described a suitable apparatus for studying the *in vitro* release of drug substances from chewing gums.^[5]

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Table 1: Examples of worldwide available chewing gums

| Active substance | Category | Trade name | Commercially available |
|-------------------|-----------------------------|--------------------|---------------------------|
| Aspirin | Analgesic | Aspergum | North America |
| Caffeine | Attentiveness | Stay alert | USA |
| Caffeine | Attentiveness | Café coffee | Japan |
| Calcium carbonate | Antacid | Chooz | USA |
| Chlorhexidine | Prevention of dental caries | Hexit, Vitaflo CHX | USA |
| CR | Diet | Chroma slim | USA |
| DHA and CCE | Enhances of brain activity | Brain | Japan |
| Dimenhydrinate | Travel sickness | Trawell | Italy, Switzerland |
| Dimenhydrinate | Travel sickness | Superpep | Germany, Switzerland |
| Dimenhydrinate | Motion sickness | Travvel | USA, Australia |
| Fluoride | Cariostatic | Flourette | USA |
| Guarana | Alertness | Buzz Gum | United Kingdom |
| Guarana | Alertness | Go Gum | Australia |
| Nicotine | Smoking cessation | Nicorette | India and other countries |
| Nicotine | Smoking cessation | Nicotinelle | New Zealand |
| Vitamin C | Nutrition | Endekay Vitamin C | United Kingdom |
| Vitamin C | Nutrition | Stamil Vitamin C | Australia |
| Vitamin C | Nutrition | Source Vitamin C | Australia |
| Xylitol | Prevention of dental caries | V6 | United Kingdom |

Table 2: Examples of noninvasive insulin products and their status

| Trade name | Name of the company | Nature of the product | Adverse effect | Stage of development |
|-------------------|--|---|-------------------------------------|---|
| Generex oral-lyn™ | Generex | Oral spray | Not available | In market |
| Exubera | Pfizer | Inhaled insulin powder | Shortness of breath and sore throat | In market |
| Passport™ system | Alter therapeutics | Transdermal insulin patch | Not available | In FDA clinical trials |
| ORMD-0801 | Oramed | Oral insulin capsule | Not available | Phase 2b non FDA clinical trials completed. |
| AEERxldms | Aradigm and Novo Nordisk | Inhaled insulin solution | Not available | Clinical Phase III |
| IN-105 | Biocon | Oral insulin | Not available | Clinical Phase III |
| HIIP(Air) | Alkermes and Eli Lilly | Inhaled insulin powder | Not available | Clinical Phase III |
| NIN-058 | Nobex corporation and Glaxo smith line | Tablet | Not available | Clinical Phase I |
| VIAtab | Biodellnc | Oral sublingual prandial insulin | Not available | Clinical Phase I |
| Cobalamin™ | Access pharmaceutical Inc. | Nanoparticle for oral delivery of insulin | Not available | Preclinical studies |
| Technosphere | Aerogen | Inhaled insulin powder | Not available | Phase III trials FDA new drug application |

MECHANISM OF ACTION OF INSULIN CHEWING GUM

Post studies have shown that the digestive system breaks down an insulin pill taken orally, and that any surviving enzyme is not easily absorbed into the blood stream from the gut. Mammals have an active transport mechanism for the absorption and cellular uptake of the relatively large vitamin B12 molecule which relies upon complexing to a naturally occurring transport protein known as intrinsic factor such as heptocorrin. Release of insulin is triggered by production of saliva which can be produced by chewing anything. The saliva contains a protein named haptocorrin which is released during the mastication of the chewing gum. In the gut, haptocorrin acts as an intrinsic factor for the absorption of vitamin B12 which is coated on insulin. In addition, the active substances like guaran, caffeine and chromium are found to be efficient

for the treatment of obesity. Guaran and caffeine reduce the feeling of hunger and stimulate lipolysis and also have increased energy expenditure. Because of improved blood glucose balance Chromium observed to reduce the craving for food.^[6,7]

INSULIN CHEWING GUM AS A DRUG DELIVERY SYSTEM

Insulin chewing gum is considered as a sophistic drug delivery system that releases the active ingredient by chewing. Chewing gum has proven as a great delivery vehicle for nutrients and drugs. It is noninvasive, readily accepted and can be given at any time. It has local effect in the mouth and systemic effect after absorbing through the oral mucosa. It absorbs directly through the buccal membrane which avoids metabolism in GIT and first pass effect of the liver. Therefore, a reduced dose might be advised.^[8]

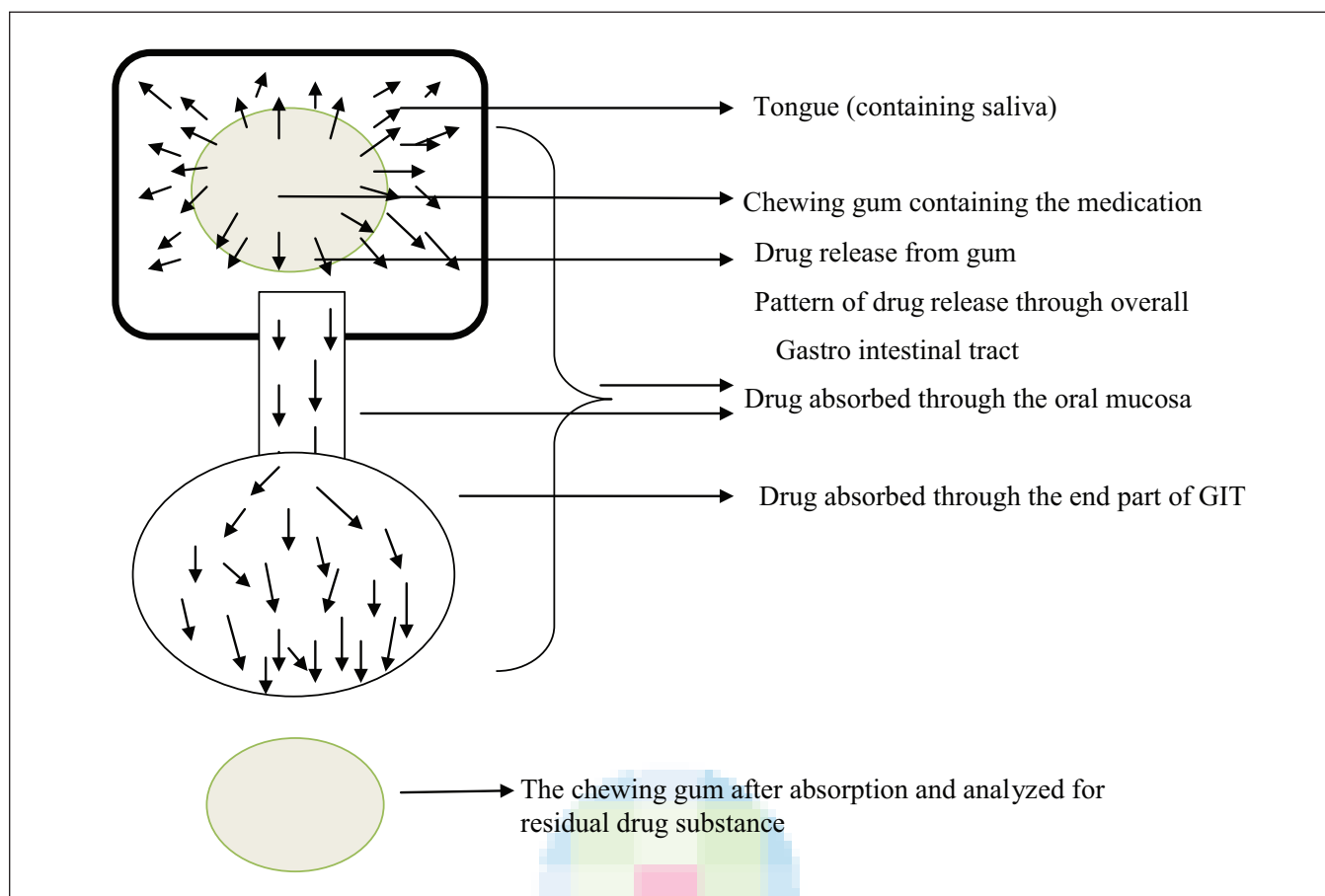


Figure 1: Mechanism of drug release

IN VIVO STUDIES OF INSULIN CHEWING GUM

Experiments are conducted in streptozotocin (STZ) – treated rats to determine the uptake kinetics and efficiency of the vitamin B12 – insulin systems which assess blood insulin and glucose concentration. Monitoring acute changes in blood glucose and insulin concentration is determined for biological efficiency. In some embodiments the STZ is administered through a cannula inserted in the jugular vein and a change in the blood glucose concentration is indicative that the oral-insulin deliveries was successful and provide a means of providing biological efficiency. To support the observed changes in blood, glucose assays are conducted for the quantification of insulin and C-peptide in plasma. To examine the *in vivo* efficiency of the B12 conjugate, blood from the STZ induced diabetic model was sampled by means of jugular catheter and subsequent to oral administration of the B12 conjugate are compared to the blood glucose response following administration of an equimolar solution of free insulin. Results identified that B12 insulin conjugate was associated with a 4.7 fold decrease in the area under the blood glucose curve ($P=0.056$) when compared to the blood glucose response to the administration of free insulin. Results obtained from the oral administration of the B12 insulin conjugate are more effective than free insulin in reducing blood glucose levels.^[9]

Advantages of chewing gum

- Easy of administration without water promotes better patient compliance.
- Children and for the patients who find swallowing tablets difficult are obvious.^[10]
- Fast onset of action.
- Less side effects.
- Effective on dry mouth.
- Local therapy.
- Diet and weight management.
- It may help to reduce the tension and anxiety and help improve mood.^[11]
- Avoids first pass metabolism and increases the bioavailability of drugs.^[12]

Disadvantages of chewing gum

- Sorbital present in this formulation may cause flatulence and diarrhea.
- Additives in gum like flavouring agent and cinnamon causes oral ulcers and liquorices causes hypertension.
- Prolong on chewing on gum may result in pain in facial muscles and earache in children.
- Chewing gum known to cause to enamel dentures and fillers.^[1]

Other health benefits of insulin chewing gum

- It helps in improving memory and enhances cognitive powers.
- It reduces symptoms of stress and increases alertness and concentration.^[10,13]
- It helps in the management of weight.
- It helps to improve intestinal motility, also helps to increase saliva flow which promotes more frequent swallowing.
- It is good for oral health and teeth specifically

NEED FOR NONINVASIVE ROUTES FOR DELIVERY OF INSULIN

- Rapid onset of action.
- Improved bioavailability.
- Good tolerability.
- Ease of administration.
- To avoid existing long-term dependence on multiple subcutaneous injections.^[14, 15]
- Improves pharmacodynamic properties of insulin.
- Improves patient compliance.

SAFETY ASPECTS OF CHEWING GUMS

Chewing gum has several drawbacks as the drug released into saliva disappears rapidly from the oral cavity because of involuntary swallowing. The concentration of the drug in the oral cavity always tends to decrease as a result of salivary dilution. Administration of such dosage form is restricted to short period of time because the presence of the delivery system in the oral cavity causes disturbance in drinking, eating, and speaking. Generally, it is perfectly safe to chew a gum. Previously, hard chewing gums have caused broken teeth and pain full jaw muscles, and extensive use of sugar-alcohol-containing chewing gum may cause diarrhea.^[16,17]

CONCLUSION

Chewing gum is need of the hour for better survival of the diabetic patients. It is considered as an excellent drug delivery system for self-medication, as it is convenient and can be administered discreetly without water. It offers removal of needles fear from the patient. Chewing gum helps to give insulin orally for diabetic patients and tackle the degradation of insulin by digestive enzyme without adding digestive enzyme inhibitor. It can help to reduce the cost of therapy and improve the brain boost power, concentration, and smoking cessation. The release of insulin leads to increased heart rate and also supplies glucose and oxygen to

the brain. The glucose and oxygen in the brain helps to improve concentration and learning. An insulin chewing gum can offers a significant solution to the breaking down of orally taken insulin by the digestive system.

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