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Review Article

Medicated Chewing Gum – A Review.

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ABSTRACT

Chewing gum has been used worldwide. Also Approval of medicated chewing gum has been enlarged through years. The merits and therapeutic benefits of chewing gum support its progress as we can see new formulations with new drugs contained have been formed from past and are going to find a place in market by formulation of new medicated chewing gums. The advantages for children and for patients who find swallowing tablets difficult are noticeable. Chewing gum supported by statements that chewing sugar free gum can help reduce the risk of dental caries. Thus, study recommended that good quality elasticity and chew capacity and high trend of chewing gum can act as a prospective for medicated chewing gum.

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INTRODUCTION

Chewing gum is a pleasure that everyone enjoys. Although medicated chewing gum has important potential to develop into a suitable alternative approach to patient compliance. Chewing gum is being used worldwide since earliest times after man experienced the pleasure of chewing a variety of substance.

One thousand years ago the Mayan Indians chewed tree resin from the Sapodilla tree in order to clean their teeth and freshen their breath. Shortage of natural gum bases during

World War II enhanced development of the synthetic gum bases that are used today. Chewing gum can be used as a convenient modified release drug delivery system. Medicated chewing gums are currently available for pain relief, smoking cessation, travel illness, and freshening of breath. Chewing gum is intended to use for local treatment of mouth diseases through oral mucosa. Such as: Motion sickness, Smoking cessation, Nowadays, Chewing gums must meet the high quality standards as

tablets. Particularly, for children this is very convenient method of administration when compared to tablets, liquids,

Improved technology and extended know how have made it possible to develop and manufacture convenient drug delivery system which is appropriate for a wide range of active substances. Medicated chewing gum offers advantages in comparison to conventional oral mucosal and oral dosage forms both for;

(a) Local treatment

(b) Systemic effect

After absorption through the buccal and sublingual mucosal and from the gastrointestinal tract .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 pass metabolism of susceptible drugs. Generally, medicated chewing gum has a good stability, the medicine can be taken potential for avoidance of gastrointestinal and hepatic first – easily and directly without the prerequisite of water, and if required, prompt Discontinuation of medicament is possible.

Dosage forms such as mouthwashes, erodible/chewable buccal tablets, and chewing gums allow release of drugs for only a short period and thus the reproducibility of drugs absorption is comparatively poor. Application of bioadhesive semisolid gels creates considerable technical problems in the buccal absorption. Although medicated chewing gums pose difficulties in regulating the dose administered, they still have some advantages as drug delivery devices, particularly in the treatment of diseases the oral cavity and in nicotine replacement therapy. Some commercially available chewing gums are Caffeine chewing gum, and Nicotine chewing gums (e.g. Nicorette ® and Nicotine®). The permeability of nicotine across the buccal mucosa is faster than across the skin. (B. D. Ingole, et al)

Advantages of Medicated chewing gum (Imfeld, T. *et al*, 1999)

- Chewing gum is Healthy treat after a meal.
- It helps to Increase rate of efficiency rather than other oral delivery systems

- Elimination of gum at any time as termination of drug delivery.

- Helps to reduce risk of overdosing while it is swallowed.

- It does not Require water to drink

- It protect the susceptible drugs consist of chemical or enzymatic attack in gastrointestinal (GI) tract.

- It has systemic and local drug delivery.

- Chewing gum is highly trendy by children and teenagers

- It has Low first-pass effect so reduced dose is formulated in chewing gum compared to other oral delivery systems

- Chewing gum is good for speedy delivery

- Chewing rarely have side effects

- Reduced risk of intolerance to gastric mucosa

- Chewing gum has excellent stability against light, oxygen, and moisture

- Rapid bowel healing after GI surgery.

Disadvantages of medicated chewing gums (Surana, A.S., 2010)

- Chewing gum causes problems like jaw pain and headaches if used continuously.

- This drug delivery leads to disappearing of drug in oral cavity followed by dilution in saliva.

- It has Different releasing profiles as of chewing style differences

- There is Short time of administration due to eating, speaking, and drinking.

- Simultaneous stress on jaws that may cause temporomandibular joint disorder

- It causes Teeth decay because coated by sugar.

- Chewing gum can cause Stomach irritations, aches, gastric ulcer through continuous swallowing of saliva and even flatulence as it include presence of sorbitol in some formulations

- As it is not suitable for under-aged child will causes choking by swallowing gum in under-aged children.

Problems Occurred During Manufacturing of Chewing Gums

- As chewing gum contains adhesive ingredients that will jam the grinding machine, sticking to blades, screens and other surfaces if the moisture level is not controlled.

- Another problem associated with the above methods is that the gum base is heated to a fluid

mass to facilitate mixing of other ingredients. Such elevated Temperatures can cause degradation of heat sensitive compounds, including active agents and flavors.

– In manufacturing of chewing gum, for gum bases or gum core organic solvents are used to dissolve the active agents. It is difficult to eliminate these organic solvents from the final product and may present certain health risks if even trace amounts remain in the final dosage forms.

– It is hard to provide sanitary condition while manufacturing medicated chewing gum. (Patel, V.P. 2011).

Composition

The composition of chewing gum consists of gum base which are composed of an insoluble resins, humectants, elastomers, fillers, waxes, antioxidants and softeners. 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 main ingredients in modern chewing gum are Gum Base. 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 polyvinyl acetate and similar polymers can be used as gum base. For years gum base was made from chicle which was the ingredient in chewing gum. (Kumar, R. et al).

MANUFACTURING (Gadhavi, G. et al, 2011)

Following Are the Constituents used in Manufacturing Process

Gum Base

Gum base is an static and insoluble non nutritive product used as a support for the edible Department of Pharmaceutical Sciences and Technology, near Arvind Baug, Shri Sarvajani Pharmacy College, Mehsana 384001, Gujarat, India and easily soluble of the chewing gum (sugar, glucose, polyoils and flavours) Other raw materials are generally Grouped in following Classes.

Elastomers

The gum base composition may include conventional elastomeric solvents to aid in

softening the elastomers base constituent. Such elastomers solvents may contain terpinene resins such as polymers of alpha-pinene or beta-pinene, methyl, glycerol or pentaerythritol esters of resins or modified resins and gums, such as hydrogenated, dimerized or polymerized resins or mixtures. The elastomers solvents are employed in amounts from 5.0% to 75.0%, by weight of the gum base, and preferably from 45.0% to 70.0%, by weight of the gum base Synthetic elastomers such as butadiene; styrene copolymers, polyisobutylene, isobutylene isoprene copolymers, polyethylene mixtures, and non-toxic vinyl polymer, such as polyvinyl alcohol are widely used bases. The molecular weight of the vinyl polymer may range from 3,000 to 94,000. The amount of gum base employed varies greatly depending upon various factors such as the type of base used, the consistency of the gum desired and the other components used in the composition to make the final chewing gum product. In general, the gum base will be present in amount from 5% to 94%, by weight of the final chewing gum composition. Preferably, the gum base is used in amounts from 15% to 45% and more preferably in amounts from 15% to 35% weight of the final chewing gum composition.

Plasticizers

Waxes, vegetable oils, glycerines, Plasticizers or softeners such as lanolin, palmitic acid, oleic acid, stearic acid, sodium stearate, potassium stearate, acetylated monoglyceride, glycerine, natural and synthetic waxes, hydrogenated vegetable oils, polyurethane waxes, paraffin waxes, microcrystalline waxes, fatty waxes, propylene glycol may be included into the gum base to gain a variety of advantageous textures and consistency properties.

Adjuvants

Calcium carbonate, talc, or other charging agents are used. Mineral adjuvant such as calcium carbonate, magnesium carbonate, aluminium hydroxide, aluminum silicate, talc, tricalcium phosphate, dicalcium phosphate serves up as fillers and textural agents.

Antioxidants

An anti- oxidant such as butylated hydroxytoluene, butylated hydroxyanisole,

propyl gallate and mixtures thereof, may be incorporated as antioxidants.

Compression adjuncts

Appropriate compression adjuvant such as silicon dioxide, magnesium stearate, calcium stearate and talc can be used in medicated chewing gum for ease of compression. The alkali metal phosphates prevent caking and balling of "High". Additionally, it has been discovered that malt dextrin enhances the grinding of "high" moisture-containing chewing gum compositions by absorbing moisture to allow lubrication in the gum as it separates into granules. If oil lubricants are used, it is preferred to be 0.4% to 1% by weight of the tableted chewing gum composition. The amount of glidants present in the tableted chewing gum composition is from 0.5% to 5% by weight of the tableted chewing gum composition. Those glidants useful are selected from the group consisting of alkali metal salts, talc, starch, polyhydric alcohols and mixtures. Anti-adherents function to prevent tablet granulations from sticking to the faces of the punches and the die walls, but most importantly, prevent adherence of chewing gum granules from adhering to one another, a phenomenon known as blocking. Anti-adherents may be added to the chewing gum composition while the composition is in the hoppers, or subsequent to grinding and are selected from the group consisting of silicates, silicon dioxide, talc and mixtures thereof present in amount of 0.2% to 1% by weight of the tableted chewing gum composition and preferably about 0.3 to about 0.6% by weight. Generally anti-adherent is a finely divided low bulk density powder, which is preferably water insoluble. The preferred anti-adherents are fumed silica and talc. The term-fumed silica is meant to include pyrogenic silica's; micron sized silica's and hydrated silica's.

Sweeteners

a. Water-soluble sweetening agents: xylose, ribulose, glucose, mannose, galactose, fructose, sucrose, maltose, invert sugar partially hydrolyzed starch, dihydrochalcones, monellin, steviosides, glycyrrhizin, and sugar alcohols such as sorbitol, mannitol, hydrogenated starch hydrolysates.

- b. Water-soluble artificial sweeteners: soluble saccharin salts, i.e. sodium or calcium saccharin salts, cyclamate salts.
- c. Dipeptide based sweeteners: L- aspartic acid derived sweeteners such as Aspartame, Alitame, methyl esters of L-aspartyl-L-phenyl-glycerine and L-aspartyl-L 2,5-dihydrophenylglycine, L-aspartyl 2,5-dihydro-L phenylalanine – L aspartyl – L (1-cyclohexen) alanine.
- d. Water-soluble sweeteners: derived from naturally occurring water soluble sweeteners, chlorinated derivatives of ordinary sugar (sucrose, known as Sucralose)
- e. Protein based sweeteners: such as thaumaococcusdanielli (Thaumatococcus) In general an effective amount of sweetener is utilized to provide the level of sweetness desired, and this amount will vary with the sweetener selected and are present in amounts from 0.0025% to 90% by weight of the gum composition.

Coloring agents

The colouring agents comprise pigments, which may be incorporated in amounts up to about 6% by weight of the gum composition, titanium dioxide may be incorporated in amounts up to about 2%. The colorants may also include natural food colors and dyes suitable for food drug and cosmetic applications.

Flavouring agents

Flavouring agents suitable for use are essential oils and synthetic flavours such as citrus oils, fruit essences, peppermint oil, spearmint oil, clove oil wintergreen oil, and anise oil.

Bulking agents

If low calorie gum is desired then they are used. Examples of low down calorie bulking agents include Polydextrose, Oligofructose, Inulin, Guar gum hydrolysate, heavy Dextrin.

Manufacturing Process

Fusion method

Most chewing gum are made using the conventional gum process (i.e fusion method). The first step of this method for manufacturing chewing gum is to melt and soften the gum base at about 60°C and place it in a kettle mixer or Z-blade mixer in which blades soften the base, then other ingredients such as

sugar, glycerin, sweeteners, taste-masking agent are added to the softened base, After this the flavoring agent is added in the mixing procedure at 40°C, then cooling and rolling steps would be done, and finally the rolled chewing gum would then be cut into pieces of required shapes and sizes and packaged as unit doses. To make a coated gum tablet, a coating agent should be sprayed to form a uniform surface. Second type of this method is somehow different: The primary step of preparation is to set up a mixer (the mixer could be sigma blade or other types of mixers), if a sugar-containing gum is needed, the first step is to add corn syrup to the mixer, and then finely powdered sugar is added gradually. Sugar, used in this step, could be powdered sucrose, dextrose, fructose, corn syrup solids or combination of them.

After adding these sweeteners, plasticizers are added to modify the texture and regulate the cohesiveness. Glycerine is the most preferably plasticizer used. The mechanical forces of mixer, that is, compressive and shear and heat can ease the softening process. When no heat is applied, a higher power is demanded. The mixing process continues until a homogenous mass is formed. (Rassing MR et al 1994)

Cooling, grinding, and tableting method

This method has been developed with an attempt to lower the moisture content. In manufacturing of medicated chewing it is used to Provide a chewing gum with desired taste, color, and flavour is to mix gum base with favourable and suitable sweeteners, corn syrups, starches, flavouring agents, and colorants, and then refrigerate and cool it by a freezer apparatus or by contacting with a coolant like carbon dioxide to a temperature below -15°C which is therefore crushed and pulverized with a cutter or grinding apparatus to obtain minute particles then these finely ground particles are heated to a temperature which makes them adhere to each other and form a slick and uniform bulk with consistent texture and low specific gravity. If the fragments are such that they do not self-adhere, low pressure would be applied manually or mechanically before they are warmed to the normal room temperature to thereby promote self-adhesion. The cooling and grinding steps can be combined by cooling the grinding apparatus.

After the grinding step, we can let the coolant (if used) evaporate and disappear from our desired composition. The minute particles may be coated by edible substances or premixed with powdery materials. For stabilization, compressing punches may be needed but anti-adherent agent should be added to prevent sticking. (Athaniar, N.K. et al 2001.)

Direct compression

New technology to make a chewing gum tablet is direct compression and tableting. This cost-effective method involves compression of gum bases mixed with active ingredients. At high-speed standard machine, but as explained in a patent, this way of forming chewing gum tablets provides a quickly dissociable chewing gum, but after a few seconds of chewing, particles adhere together to form a uniform and homogenous mass. In this method; we need a granulating agent, most preferably that is sorbitol which can also act as a sweetener. A lubricant such as magnesium stearate, talc, stearic acid, hydrogenated vegetable oils, and sodium stearyl fumarate is added to formulation before tableting. First step of this method is dry mixing of gum base, granulating agent and at least one processing material then adding active ingredient, sweeteners, and other needed ingredients to the formulation in free flowing form of materials then directly compressing the chewing gum into tablets. In the first step, the temperature should not raise higher than the melting point of the gum base. After obtaining a uniform and slick mass, the temperature would lower to add other ingredients.

Other significant benefits of this method are as follows- fast release, fast absorption and high content uniformity.

Medicated chewing gums by direct compression method are 10 times harder and crumble when pressure is applied resulting in faster release than medicated chewing gum formed by fusion method (Heema, N. et al 2010).

Packaging

The advantages of chewing gum packaging are clear to the world since it extends shelf-life of the product by preventing aroma and flavour to disappear. It also provides moisture retention and gum stability. There are too many packaging methods with a wide range of options. In almost

all of packaging types, we need a wrapping machine that receives and wraps the sticks of gums; in some cases, the wrapper machine seals the end of the package. In the following, a formed blister pack may be used then a foil will be heat-sealed at the back or a traditional packaging may be applied by lining the pellets up in a row and wrapping then sealing the both ends. The manufacturing and packing steps should be performed at about 20-25°C and relative humidity of 57%. Packaging has a substantial portion in the whole process both in terms of cost and time. Undoubtedly, packaging influences attraction of product among consumers, thus a well-flavoured and stylish design can attract more consumers to buy the specific product. Therefore, besides protecting the content, avoiding impurity, expediting transport and improving storage, packaging can influence consumers' willingness to buy the product and capture his attention during purchase competition. (Bahoshy BJ, et al US Patent No. 4,000, 320.)

Limitations (Ritesh Kumar et al, 2014)

- High temperature used in melting restricts the utilize of this method for thermo labile drugs.
- Melting and mixing of extremely viscous gum mass makes controlling of accuracy and uniformity of drug dose complicated.
- Lack of accurate form, shape or weight of dosage form.
- Technology not so easily adaptable to integrate the stringent manufacturing conditions essential for production of pharmaceutical products

QUALITY CONTROL

As per specifications given in European Pharmacopoeia.

Test for Uniformity of Content

If not or else prescribed or justified and authorized medicated chewing gum with content of 2 mg or less than 2 percent of the total mass of gum comply with test.

Uniformity of mass

Uncoated medicated chewing gum and if not or else justified and authorized coated medicated chewing gum comply with the test for uniformity of mass of single- dose preparations.

Drug release from medicated chewing gum

It has been observed 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. (Asija, R., et al, 2012)

SAFETY ASPECTS

Different commercial chewing gums have been shown to stick on to dissimilar degree to dentures, fillers and crowns. Over chewing causes painful jaw muscles. Chewing gum appears to offer a slighter risk of overdosing by inaccuracy or misuse than flavored chewable tablets. Medicated chewing gums should, like other medicaments, be kept out of reach of children and it would be wise to advice people prone to allergic response to confirm the flavoring and sweetening agents incorporated in the chewing gum formulations.

FUTURE TRENDS

Future of chewing gum will reveal all the scientists efforts for the development of chewing gum as a modern drug delivery system and progress of chewing gum as it not only offers clinical benefits but also convenient easy to administer. 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. The potential of MCG for buccal delivery, fast onset of action and the opportunity for product line extension makes it an attractive delivery form. Reformulation of an existing product is required for patent protection, additional patient benefits and conservation of revenues. The potential of medicated chewing gum for buccal delivery, fast onset of action and the

opportunity for product line extension makes it attractive delivery form.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

CONCLUSION

According to the advantages of chewing gum as a novel drug delivery ,like simultaneously supporting both local and systemic delivery ,protection against acids and enzymes ,low first pass metabolism ,uplifting alertness and cognitive function , excellent stability, taste masking of certain drug and a lot more; we can conclude that chewing gum will be much more familiar to patient, and market in next few years . Chewing gum can be used, as a carrier for vast categories of drugs where extended release and the local action are desired. Chewing gum can be used without water, at any time. Medicated Chewing gums can produce both local effects as well as systemic effects in the oral cavity. They can be used for the purpose of taste masking of certain drugs too.

Scientist and researchers should also consider new formulations for chewing gums for increasing variations of chewing gum due to patient's different styles and providing appropriate release pattern for chewing gum containing drugs.

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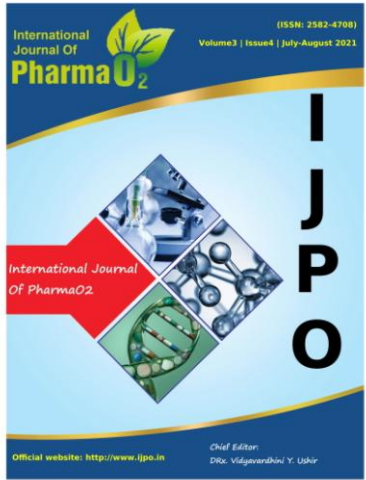
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