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A REVIEW ON MEDICATED CHEWING GUMS

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ABSTRACT

Now a day's these Medicated chewing gum is considered as a potential and convenient modified drug pattern of release system which can be used in pain relief medication, smoking cessation, travel illness, freshening of breath, prevention of dental caries, vitamin or mineral supplementation etc. Medicated chewing gums are prepared by using suitable excipients like water insoluble gum base and water soluble bulk portions. Medicated chewing gum is a Masticatory gum base containing active ingredient. It can offer various advantages over the conventional drug delivery system. Not like chewable tablets medicated chewing gums are not supposed to be swallowed and will be removed from the site of application without device to enveloping means of medicated chewing gum is nothing but gum base containing an active substance either in its core or coating. The medicated chewing gums include one or more active components which are released by chewing and are intended to be used for local treatment of mouth diseases or systemic delivery after absorption through the buccal mucosa it will follows diffusion mechanisms.

INTRODUCTION[1, 3]

The medicated chewing gums are defined according to European pharmacopeia for pharmaceutical dosage forms issued in 1991 by the CPMP as the solid single dose preparations with a base consisting mainly of gums that are intended to be chewed but not to be swallowed, providing a progressively release of the API. The first MCG was introduced in United Stated of America in 1924 with the brand name of Aspergum. Oral route is most commonly used for the administration of drugs; the oral route contains the various advantages because of easy of administration. One of the reasons that the oral route achieved such popularity may be in part attributed to its ease of administration. The active pharmaceutical ingredients are incorporated in medicated chewing.

Now days the MCG are one of the most accepted dosage form. The pharmacological active ingredients are formulated into various dosage forms by considering physicochemical properties, pharmacodynamic and pharmacokinetic parameters of API. During this Chewing gums are also has conformed values as a delivery vehicle for pharmaceutical and nutraceutical ingredients or materials. Most of the chewing gums were used for smoking cessations and also used for oral and dental hygiene, motion sickness and freshening of breath. The medicated chewing gums are nothing but the gum base is containing an API either in core or coating of gum base. The medicated chewing gums are contains powdered sugar whose among and grain size determine the brittleness of the resulting gum, corn syrup or glucose which serve as humectants and coat the sugar particles their suspensions and keep the gum flexible, various softening agents, colorants and preservatives flavoring agents etc.

Types of chewing gums [10]

Chewing gums is gaining its market because of its lot of applications, so the manufacturer is making it in many shapes, size (cube shape, ball shape, oval shape and also in strips) flavor (mint flavor, strawberry, orange, mango etc.) And there is no standard size and shape for Chewing gum basically containing water-insoluble phase i.e., Gum base with a water-soluble phase of sweeteners, coloring agent and active pharmaceutical ingredient.

Figure 1 Types of chewing gums.

Advantages of medicated chewing gums [5.7,9,10]

- Does not require water to swallow the dosage form.
- Advantageous for patient having difficulty in swallowing.
- It's avoids the first pass metabolism, thus increases the bioavailability of drugs.
- Highly acceptable by children.
- Dosage form shows the fast onset of action due to rapid release of drug in buccal cavity and subsequent absorption in systemic circulation.
- The medicaments like aspirin, Dimenhydrinate and caffeine shows faster absorption through medicated chewing gum than tablets.

Disadvantages: [5, 7]

- ✓ The action of prolong chewing of MCGs may causes in pain in facial muscles and earache in children
- ✓ The medicated chewing gums have been shown to adhere to different degrees fillers and dentures.
- ✓ The sweetening agent like sorbitol is presents in the base of MCG formulation its causes the diarrhea.
- ✓ The formulation containing the flavoring agent its causes the ulcers in oral cavity and licorice causes hypertension.

Formulation of medicated chewing gums

1. **Gum base** [1,5]

The Gum base in MCGs considered as an inert and insoluble nonnutritive material. The raw ingredients are generally grouped in following classes

a. **Water insoluble portion**

2. **Elastomers** [3,8]

The Elastomers are considered as natural and synthetic rubbers. The gum base of MCG consisting of the conventional elastomer agent to help in softening the gum base. The elastomers solvents include terpinene resins such as polymers of alpha-pinene or beta-pinene, methyl glycerol or pentaerythritol. The esters of resins or modified resins and gums, such as hydrogenated, the elastomer solvents may be employed in medicated chewing gums ranges from 5.0% to 75.0%, by weight of the gum base. The 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. In naturally the gum base of medicated chewing gum contains the synthetic elastomer ranges from 5% to 94%, by weight of the final chewing gum composition.

3. Plasticizer [11,16]

It is used to regulate cohesiveness of medicated chewing gum base. These plasticizers are following types. Natural plasticizers are consisting of natural rosin esters like glycerol esters or partially hydrogenated rosin, glycerol esters of partially demonized.

Synthetic plasticizers are consisting of terpene resins.

4. Adjuvants [4]

Adjuvant materials like Calcium carbonate, talc, Mineral adjuvant such as calcium carbonate, magnesium carbonate, dicalcium phosphate serve as fillers and textural agents.

b. Water soluble portion

5. Antioxidants [2]

An anti- oxidant materials are used in MCG formulation those materials such as butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate and mixtures.

6. Sweeteners [10]

Table: 1 Sweeteners are following types

Water soluble sweeteners	Water soluble artificial sweeteners	Dipeptide based sweeteners
Xylose, glucose, mannose, maltose, mannitol, glycyrrhizin, sorbitol.	Sodium saccharin Calcium saccharin Cyclamate salts.	Aspartame, Alitame, methyl esters

7. Coloring agents [11]

In the US, FD & C numbers (which generally indicate that the Food And Drug Administration has approved the artificial coal tar dye colorant for use in foods, drugs and cosmetics) are given to approved synthetic food dyes that don't exist in nature, whereas in the European Union, E numbers are used for all additives, both synthetic and natural, that are approved in food applications.

8. Flavoring agents

The various Flavoring agents appropriate to be use are essential oils and synthetic flavors such as citrus oils, fruit essences, peppermint oil, spearmint oil, clove oil and anise oil.

Preparation of medicated chewing gums [4, 8,9,14]

The medicated chewing gums are successively prepared by adding the excipients to a mixer. 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 following methods are used to prepare the MCG such as

a. Conventional/ traditional Method (Melting).
b. Freezing, grinding and tabletting Method.
c. Direct Compression Method.

A. conventional/ traditional method

The ingredients of medicated chewing gum base are melted or softened in a kettle mixer to which add the active ingredients, sweeteners, and other excipients at a definite period of time. The gum is sent through a series of rollers that forms into a thin, wide ribbon form. during of this process, coating is done by using the finely powdered sugar materials is added this coating material is kept aside from sticking and these added to enhance the flavor of chewing gums. Whole gum base is carefully controlled room temperature; the chewing gums are cooled for upto 48 hrs. This allows the gum to set properly. Then finally the gums are cut to the desired size and cooled at controlled temperature and humidity.

Limitation

I. This method is restricted to thermo labile materials(drugs)
II. Lack of exact form, shape or weight of dosage form.
III. Technology not so easily adjustable to incorporate the severe developed conditions essential for production of pharmaceutical products.
IV. Melting and mixing of highly viscous gum mass that makes controlling of accuracy and uniformity of drug dose difficult.

B. Cooling, grinding and tabletting method

This method has been developed with an effort to lower the moisture content and improve the evils mentioned in conventional method

Cooling and grinding

The medicated chewing gum composition is cooled to a temperature at that the composition is satisfactorily delicate and would stay brittle throughout the consecutive grinding step without adhesion to the grinding equipment. The temperature needed for cooling is determined partly by the composition of the medicated chewing gum and is definitely determined through empirical observation by observe the properties of the cooled chewing gum composition. Typically the temperatures of the refrigerated mixture are around -15^{o}C or lower. Amongst the assorted coolants like nitrogen, organic compound slush use of solid carbon dioxide is favored because it will offer temperatures as low as -78.5^{o}C; it sublimes promptly on warming the mixture, isn't absorbed by the chewing gum composition, doesn't

act adversely with the process equipment and doesn't leave behind any residue which can be undesirable or potentially dangerous. The cold composition is then crushed to get minute fragments of finely ground pieces of the composition. Alternatively, the steps of cooling the chewing gum composition will be combined into one step. As associate example, cooling the grinding equipment itself which might be done by contacting the grinding equipment with a agent or by inserting the grinding placing in a cooling jacket of nitrogen or alternative cold liquid. For more economical cooling, the chewing gum composition can be pre cooled before cooling to the refrigeration temperature.

Tabletting

Once the coolant has been removed from the powder, the powder is mixed with alternative materials like binders, lubricants, coating agents and sweeteners etc, all of that are compatible with the components of the chewing gum base during a appropriate blender like sigma mill or a high shear mixer. Instead a fluidized bed reactor (FBR) can be used. The use of FBR is advantageous because it partially reconstruct the powder into granules, as well as coats the powder particles or granules with a coating agent thereby minimizing undesirable particles agglomeration. The granules therefore obtained are mixed with Antiadherents like talc. The mixture is homogenized in a V type blender, screened and staged for compression. Compression is carried out by any conventional method like punching

Direct compression method

The method of preparation can be accelerated if directly compressible chewing gum excipients are available. By using the direct compression method, overcome the limitations in melting and freezing methods. The Pharmagum is a one such material is developed by the SPI pharma, the Pharmagum is a mixture of polyls or sugars with the chewing gum base. These Pharmagum is a available in directly compression powder form. This Pharmagum is free flowing form and which can be compacted into a MCG tablet by using the tablet compression machine. The medicated chewing gums are prepared under chewing gum MP conditions and fulfill with FDA. Generally these Pharmagum is available in three forms namely S, M and C. Pharmagum M has 50% greated gum base compared to Pharmagum S. the Pharmagum S is mixture of gum base and sorbitol and Pharmagum M is mixture of gum base, mannitol and isomalt. The release of drug (nicotine) from this directly compressible nicotine gum formulations and from the nicorrete by conventional method has shows that the by the using of directly compressible Pharmagum in formulation shows the faster drug release.

Factors affecting release of drug [3, 11, 15]

Membrane factors

The regional difference in both permeability and thickness of mucous membrane affect both the rate and the extent of drug reaching the systemic circulation. Keratinization and composition also affect systemic mucosal delivery. Additional factors such as absorptive membrane thickness, blood supply, blood/ lymph drainage, cell renewal rate, and enzyme content will also govern the rate and extent of drug absorption.

Environmental factors

Saliva: Saliva is composed of 99% water and its pH varies between 6.5 to 7.5 depending on the flow rate and location. Increase in the salivary flow leads to the secretion of watery saliva. Stimulated salivary secretion affects the film thickness and aids in the easy migration of the test compounds. Salivary pH is also important for the passive diffusion of the unionized drug.

Salivary glands: The medicated chewing gum should be placed over or adjacent to the salivary duct because it may result in excessive washout of drug or rapid dissolution of the system making it difficult to achieve high local drug concentration.

Chewing time and chewing rate: The chewing time should be around 20 to 30 minutes. The rate of chewing also affects the drug release. Average chewing rate is about 60 chews/ min.

Contact time: The local or systemic impact depends on time of contact of medicated chewing gum within the oral cavity. In clinical test chewing time of half-hour is taken into account near normal use physicochemical properties.

Physicochemical properties of active ingredient: This property of API plays necessary role in release of drug from medicated change of state gum. The saliva soluble ingredients are immediately released at intervals from minutes whereas lipid soluble medicine is released 1st into the gumbase then released slowly.

Formulation factor: The composition and concentration of gum base affects the rate of release of API. If lipophilic part of gum is higher, the release is lower.

EVALUATION PARAMETERS

Uniformity of mass [6]

Uncoated medicated chewing gum and except otherwise even and authorized coated medicated chewing gum go with the test for uniformity of mass of single dose preparation.

Test for uniformity content [9]

Unless or else prescribed or justified and approved medicated chewing gum with content of 2mg or less than 2% of the total mass of gum fulfill with the test.

Drug release from Medicated Chewing Gum [15]

Drug release has been reported commercially that the drug release from medicated chewing gum as per the condition given in European Pharmacopoeia and is determined by applying a mechanical manipulation procedure to a chunk of medicate chewing gum placed in a small chewing chamber containing a known volume of buffer solution.

Product performance test [8]

Two different types of tests are carrying out to evaluate the drug product characteristics product quality and performance tests. Currently USP contains individual monographs with product quality tests for Nicotine Polacrilex and Nicotine Polacrilex Gum. Ph. Eur. has adopted a general monograph on medicated chewing gums and a monograph describing the apparatus for dissolution testing of medicated chewing gums.

***In vitro* drug release of medicated chewing gum** [7, 3]

Ph. Eur. has adopted an instrumentation to determine the release rate from medicated chewing gum formulations. The essential principle could be a simple chewing movement used to simulate the chewing action on a section of gum positioned in a small chewing chamber containing a known volume of buffer solution at a particular temperature. The drug release rate is influenced by the chewing rate and angle, that provides the required shear force to reveal new gum surfaces and could be a requisite for more drug release. The mechanism and kinetics of drug release from medicated chewing gums haven't nonetheless been completely understood due to the quality of the formulation itself. The transition from the inactive gum to the active dose kind is influenced by mechanical forces, temperature, wet ability and water permeation. As a general rule underneath sink conditions, the speed at that the drug is released is directly proportional to the chewing frequency and liquid solubility of drug substance and is indirectly proportional to the mass of the gum base.

Apparatus I- chewing gum apparatus, compendia

The chewing gum equipment for the MCG was adopted by Ph. Eur. In 2000. Fig shows the constructions of the equipment. The medicated chewing gum equipment consist of chewing chamber , two horizontal pistons, and a 3rd vertical piston tongue, this vertical piston tongue operates as an alternative with the 2 horizontal pistons and makes certain the gum stays within the right place between chew. If necessary, it's potential to construct the machine so at the tip of the chew the horizontal pistons rotate around their own axes in opposite direction to every alternative to obtain most maximum.

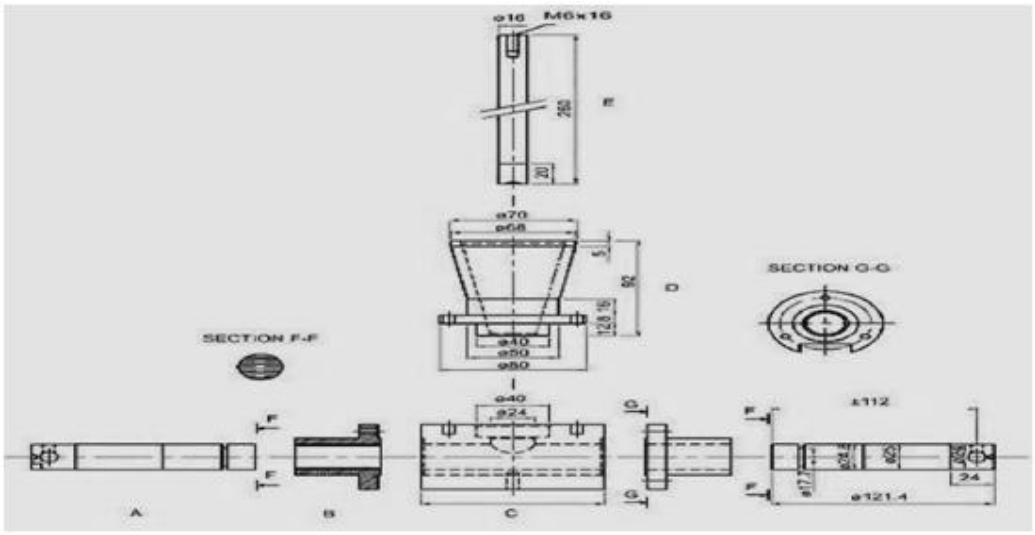

Figure 2 Apparatus of chewing gum apparatus compendia-Ph-Eur

Apparatus II- alternative chewing gum apparatus, non compendia, Wennergren.

The non compendia equipment commercially available was designed by the Wennergren. Schematic representation of the equipment is shown in below.

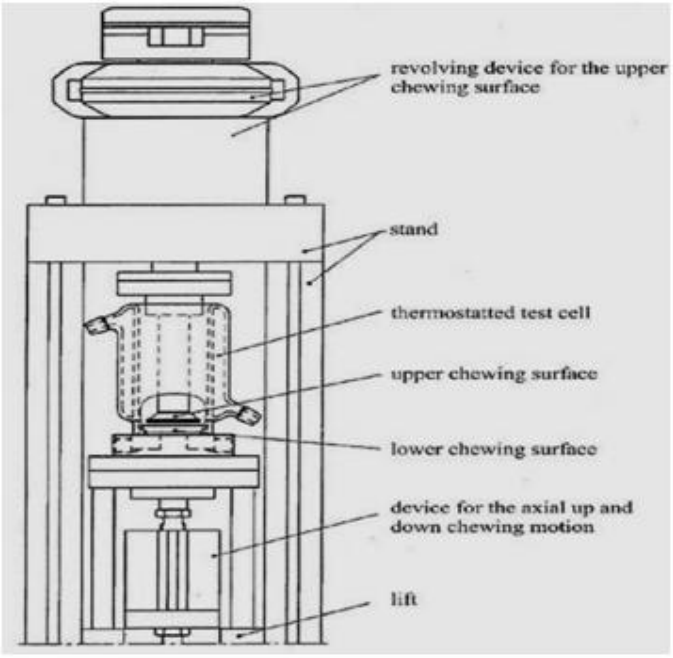

Figure: 3 Apparatus of chewing gum apparatus non-compendial wennergren

The mastication procedure consists of reciprocations of the lower surface together with a twisting movement of the upper surface that gives mastication of the mastication gum and at the same time adequate agitation of the test medium. The upper jaw includes a flat surface that's parallel to central a part of the lower surface. The little brim of the lower surface is

angled upward so the lower surface functions as a small bowl with a flat bottom. This bowl prevents the mastication gum from during throughout mastication. Investigations of the performance of the mastication instrumentation with multiple drug products. The influence of distinction operational parameters of the mastication gum equipment on drug release is carefully investigated.

***In vivo* chew out studies [1, 4]**

The *in vivo* release of drug from medicated chewing gum during mastication can be studied by employ a panel of adequate numbers of volunteers and scheduled chew-out studies. For the period of the chewing process the drug contained within the MCG is released in the saliva and then it is either absorbed through oral mucosa, if swallowed dosage form, it is absorbed through the gastrointestinal tract.

I. Release of drug in saliva

Panel of volunteers is asked to chew the drug delivery device for a definite a period of time and to assess the remaining amount of active substance within the residual gum. during this means, the gums are extremely chewed and the formulation is subjected not solely to the mechanical stresses of an artificial machine however also it undergoes all the phenomena involved during this method (increase of secretion, saliva ph variation, swallowing and absorption by the oral mucosa, etc.) which might powerfully influence the performance of the dosage form still because the quantity and rate of drug release. Optimized formulation with good consistency is often designated for their lease of drug within the saliva. Minimum four human volunteers are often designated (two male and 2 female). Volunteers are instructed to rinse their mouth with H2O and allowed to chewing the medicated chewing gum for 15 minutes, in order that its most release must be taken. Sample of saliva are taken once 2, 4, 6, 8, 10, 12, 14 and 15. The spit samples are created diluted in needed solvent and absorbance is measured using appropriate analytical methodology.

II. Dissolution test of residual medicated chewing gum

In this experiment, gums are tested by a panel of volunteers to verify the drug release process from the drug delivery system. Everyone chews one sample of the tableted gum for various time periods (1, 5, 10 and 15 minutes). The residual gums are withdrawing little pieces, frozen then ground until getting a fine powder. The residual drug content is determined by exploitation appropriate analytical technique. The quantity of free drug released during mastication is calculated by subtracting the quantity of residual active ingredient present within the gum from the whole content, wherever as pharmacokinetics may be determined

from withdrawn blood samples at specific time intervals. The conditions of human volunteers, person-to-person variability within the chewing pattern, chewing frequencies, composition of individual salivary fluid and rate of saliva are a number of limitations of chew-out studies.

III. Urinary excretion profile of medicated chewing gum

This method is applicable only to those drugs that are excreted via urine. In this minimum four healthy human volunteer are selected for the study of formulations. Volunteers are strictly instructed that they shouldn't take any medication within the last 48 hours. They fasted long, and empty their bladder within the volumetric flask. The collection of samples starts from blank of zero hour urine. Then sample collection is done on 15 minutes, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12 and 24 hour intervals once administration of medicated are gum. The volunteer's area unit asked to drink water at regular intervals of half-hour and urine samples is analyzed by appropriate analytical strategies.

Buccal absorption test

Human volunteer swirled mounted volume of drug solution of known concentration at completely different ph values of 1.2, 5, 6, 6.5, 7, 7.5, 7.8, 8.0, within the oral cavity for 15minutes so expelled out. The expelled saliva is analyzed for drug content and back calculated for buccal absorption.

Applications [4, 7, 9.16]

i. Medicated chewing gums are used for the systemic effecting conditions like vit. C deficiency, relief pain and fever, alertness, motion sickness, smoking cessions
ii. Medicated chewing gums are used for the local effect in conditions like dental plaque acid neutralization, freshening of breath, antiplaque, antibacterial infections
iii. These are used for the cure the oral disease.
iv. Fluoride containing gums have been useful in preventing of dental carries in children and adults with dry mouth.
v. Chlorhexidine medicated chewing gums can be used to treat the gingivitis, periodontitis and oral infections
vi. The bitter taste of chlorhexidine can be masked quite well in chewing gum formulation.
vii. These medicated chewing gums are also used for the inhibition of plaque growth on teeth.

CONCLUSION

The Medicated chewing gums could be a great way of delivering drug to the body either for local effects. The preparation procedure is easy to develop for convenient to use, has got great patient compliance. The mouth freshening effect also adds some advantages. The USP does not have any official method of *in vitro* drug release.

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