IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

TYPES OF FORMULATION OF MEDICATED CHEWING GUM

Modhave Abhaya P .[1]

Department of Pharmaceutics, Konkan Gyanpeeth Rahul Dharkar college of pharmacy and Research institute, Karjat, Maharashtra, India. [1,]

Abstract: Medicated chewing gum represents an advanced dosage form that merges the therapeutic advantages of medications with the practicality and adherence-enhancing features of chewing gum. This innovative drug delivery system consists of a chewing gum base infused with pharmacologically active substances. This review paper examines the different types of medicated chewing gum formulations, emphasizing their composition, advantages, disadvantages, and applications. We classify these formulations into several categories: traditional medicated gums, which depend on straightforward dissolution and absorption mechanisms; sustained-release gums, which use specialized matrices to regulate the release of the drug over extended periods; and bioadhesive gums, which improve drug retention and localized effects. The goal is to enhance both the efficacy of these formulations and their acceptability among patients.

Keywords : Medicated Chewing Gum , Drug Delivery System , Sustained-Release , Bioadhesive .

I. INTRODUCTION

A. Dosage forms that significantly improve buccal absorption, like chewing gum, chewable pills, and lozenges, provide for a more rapid beginning of therapeutic impact than oral dosage forms.
Medicated chewing gum can be used to treat oral disorders locally as well as systemic issues. Apart from that, suspension doesn't have an unpleasant taste or a precise dosage.
Modified release dosage forms are far more palatable than traditional dosage forms since they have undergone advancements in product design and formulation development.
The active ingredients are released from the gum base during the chewing process, combine with saliva, and absorb in the oral mucosa before being swallowed and transferred to the stomach for gastrointestinal absorption

B. The recommended method of administering medication is orally due to patient acceptability and self-administration.

C. Method of preparation: Different method are used for the manufacturing of medicated chewing gum further classified into parts:

1) Conventional method
2) Fusion method
3) Cooling, grinding and tableting
4) Direct compression method
5) Spray drying process
6) Hot melt technique
7) Molding Method
8) Wet granulation method

1) Conventional method

Each component that was used in making the chewing gum was carefully measured and added one at a time at scheduled intervals [1]

In the production process, heat is introduced at the first melting stage. The solid gum base and synthetic polymer are either dissolved or softened in hot water or steamed kettles at a mixing temperature between 50° C and 90° C to produce a homogeneous solution with the appropriate viscoelastic properties [2]

In the second phase, sweeteners and syrups are incorporated and mixed for 4 minutes. Next, the third phase ingredients are blended using the kettle's mixing blades for 8 to 10 minutes. The resulting gum mixture is then processed through rollers to create a smooth, thin ribbon sheet. During this rolling stage, fine sugar or sugar substitutes are added to enhance flavor and prevent the gum from sticking to the machinery. The gum is then cooled gently for 48 hours in a controlled environment. Finally, the gum is cut into the desired shape and size, and coating agents are sprayed on to produce coated chewing gums. .(Athanikar and Gubler, 2001).[3]

The conventional manufacturing method has the following limitations:
1) It is not possible to accurately control the weight, texture, or shape of the MCG.
2) The high temperatures required to melt the gum prevent the inclusion of thermosensitive medications.
3) Ensuring uniformity in the mixture is challenging due to the extreme viscosity of the gum mass during melting and combining [4]
However, these techniques also come with some limitations, including:
- They are not suitable for all drugs and are particularly limited in their use of thermostable medications.
- Achieving precise control is challenging.
- Maintaining consistent drug quantities is difficult.
- High moisture content and lack of accuracy are also issues [5]

table no. i. merits and demerits of conventional method

Method of chewing gum production	Merits	Demerits
Conventional Method	1) Convenient and cost-effective. 2) Requires no specialized expertise or knowledge to operate. 3) Does not need specific equipment. 4) Utilizes standard instruments for the production of mediated chewing gum.	1) High melting temperatures of the gum base make it unsuitable for heat-sensitive materials. 2) Produces highly viscous gums, making it difficult to maintain uniformity of bioactive ingredients. 3) Challenges in achieving precise form, weight, and shape of the dosage. 4) Issues with producing chewing gum tablets. 5) Problems such as equipment jamming, sticking to punches, and adherence to blades during the compression process.

2) Fusion method

Solid Dispersion Technique

Polyethylene glycol 6000 is employed to prepare a solid dispersion of domperidone in different ratios (1:0.5, 1:1) using the fusion method, which improves the medication's solubility. The thoroughly mixed dispersion is then screened through a 100# mesh to achieve uniformly sized particles of domperidone. Aerosol, flavor, color, and specific amounts of Health in Gum®, butylated hydroxytoluene, glyceryl monostearate, magnesium stearate, titanium dioxide, talc, acesulfame potassium, and aspartame are also sifted through a mesh screen. The sifted flavoring is then combined with the sifted domperidone maleate dispersion. After this, the flavored solid dispersion is mixed with the gum base and stirred for 10 minutes.
Separately, after preparing the gum base with the solid dispersion, Glyceryl Monostearate, Titanium Dioxide, Talc, Acesulfame Potassium, Aspartame, Butylated Hydroxytoluene, Aerosil, and Erythrosine are added to the mixture and stirred for another 10 minutes. Finally, the mixture is combined with sieved magnesium stearate and stirred for three minutes. The resulting powder blend is then compressed into domperidone-infused chewing gum using a 13.5mm round punch.

Limitations

I. High temperatures used in the melting process can damage heat-sensitive medications.
II. The very viscous nature of the material may lead to inconsistencies in the distribution of bioactive ingredients.
III. The 2-8% moisture content in medicated chewing gum can create production issues, such as machine jamming, blade sticking, and adhesion to punches during compression.
IV. The dosage form may be imprecise regarding weight and shape.

3) Cooling, grinding, and tableting

This approach aims to address the moisture content and resolve issues from previous processes. It consists of three stages:

I) Cooling: In the first stage, the mixture is cooled to -15°C or lower using coolants like liquid nitrogen, hydrocarbon slush, or solid CO_2. These coolants do not react with the chewing gum components or the machinery, and they leave no residue in the final product. Another method involves cooling the grinding machine with a jacket or coolant filled with liquid nitrogen or another cold liquid. To enhance cooling efficiency, the gum base materials are pre-cooled before grinding.

II) Grinding: During the second stage, solid CO_2 and precipitated silica anti-caking agents are added to aid grinding efficiency. The gum base, kept at a very low temperature, is mixed with additional ingredients. After cooling and grinding, the gum is further processed using a grinding device or cutter to produce fine particles. Grinding agents (2-8%), such asmaltodextrin or alkaline earth metal phosphates, are added to prevent the gum from sticking to the equipment. However, these substances are not suitable for use with acidic ionizable therapeutic agents due to their high alkalinity. The finely powdered gum is then heated to evaporate the coolant or allowed to reach room temperature. This process helps the gum base become cross-linked, creating a light and soft texture with tiny air bubbles inside.

III) Tableting: In the final stage, the powdered gum particles are compressed into tablets using a punch and then packed into appropriate packaging materials. The gum can be combined with binders, lubricants, coating agents, and sweeteners in a fluidized bed reactor, sigma mill, or high shear mixer. Low pressure can be applied if adhesion issues arise.

table no. ii .merits and demerits of cooling, grinding, and tableting

Method of chewing gum production	Merits	Demerits
Cooling, grinding, and tableting method	1) Reduce the gum composition's tendency to stick to the grinding equipment and improve grinding efficiency. 2) Utilize cooling, grinding, and tableting processes to achieve the desired flavor, colour, and texture of the chewing gum.	1) Specialized equipment is needed for producing chewing gum tablets. 2) Controlling humidity is crucial for the tableting process. 3) Problems with gum clumping and balling can hinder tablet formation. 4) The process is complex and more expensive compared to other methods.

4) Direct compression method

This method involves combining granulating agents like sorbitol and xylitol with the gum base at a low temperature, below its melting point. Afterward, lubricants, sweeteners, and active ingredients are added at low temperatures (Amin and Norman, 2007). Lubricants such as stearic acid, magnesium stearate, talc, sodium stearate fumarate, and hydrogenated vegetable oils are included. The mixture is then compressed into tablets and packaged using suitable materials (Gadhavi et al., 2011).

Chewing gum is typically processed at temperatures between 70°C for melting and 120°C for heating to ensure the accuracy and consistency of the drug. The optimal moisture content of the product ranges from 2% to 8%, which helps control clogging during production. Key factors to consider for maintaining the uniformity of active ingredients include mixing for 2-8 minutes and kneading for 1-4 minutes.
If directly compressible chewing gum excipients are available, this technique can overcome the challenges of melting and freezing. Pharma gum, a type of immediately compressible, free-flowing powder made from polyols or sugars, can be compressed into gum tablets using a standard tablet press. This approach enables the rapid and cost-effective creation of a gum delivery system but requires specialized machinery and equipment for producing medicated chewing gum .

The full potential of medicated chewing gums remains untapped, despite their noted benefits. This is largely due to the differences between the technology used for gum production and that required for pharmaceuticals. Traditional gum manufacturing involves hot-melt processes and specific machinery that are not typically used in the pharmaceutical industry. However, recent innovations include free-flowing, compressible co-processed gum materials such as Pharma gum by SPI Pharma and Health in gum by CAFOSA. These new materials are chemically composed of a mix of sugar, gum, plasticizers, anti-caking agents, and polyols like sorbitol, xylitol, and mannitol.

These gums are classified as "generally regarded as safe" (GRAS) according to FDA Title 21 C.F.R. Section 172.615 and are manufactured following food chemical standards and current Good Manufacturing Practice (cGMP) guidelines. The gum made from this material can be directly compressed using a pharmaceutical tablet compression machine, which facilitates the rapid and cost-effective production of medicated chewing gum (MCG). This method also accommodates thermosensitive APIs, as it does not require high temperatures, and is suitable for water-sensitive APIs. Additionally, the compressible formulation results in a crumblier and tougher gum compared to traditional methods, enabling a quicker release of the medication under pressure.[3] ,[1].

Table No. III. Merits and demerits of Direct compression method

Method of chewing gum production	Merits	Demerits
Direct compression method	1) Rapid release of the active ingredients 2) Swift absorption 3) Consistency in the distribution of active material 4) A leading method in the chewing gum industry 5) The most efficient method for producing disintegrable chewing gum before achieving a homogeneous and uniform mixture.	1) Challenges in extracting the finished product from the mixers. 2) Gum adhering to various parts of the machinery.

5) Spray drying process

The components were uniformly distributed in a solvent by agitating at 2000 rotations per minute for 60 seconds. Granules were then formed by feeding the solution into a spray dryer using a standard 0.5mm nozzle. A peristaltic pump delivered the solution to the nozzle, where it was atomized by compressed air. The atomized droplets, along with heated air, were introduced into a chamber, where the solvent evaporated. The resulting dehydrated granules were collected from the equipment's receptacle and stored in a desiccator until required.

The spray drying process was conducted with operational parameters including an inlet temperature between 70°C and 80°C, an outlet temperature ranging from 50°C to 55°C, a spray pressure of around 2 atm, and a feed spray rate of 3 to 4 ml/min.

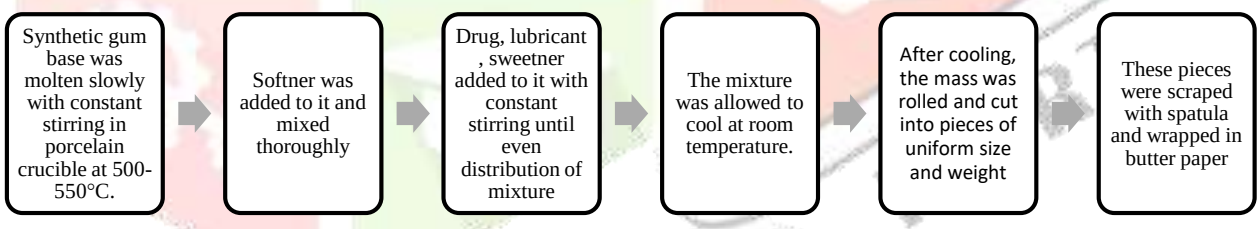
A blend of flavor and colorants was mixed and then filtered through a #60 ASTM sieve.

Finally, talc, also filtered through a #60 ASTM sieve, was added to the granules. Compression was performed using round, flat-faced punches and dies with a diameter of 12.00 mm. [6]

6) Hot melt technique

The synthetic gum base was carefully weighed and melted in a porcelain dish on a steam bath, maintaining a temperature of approximately 50-60°C. Once melted, a plasticizer was added and mixed thoroughly. Afterward, the mixture was allowed to cool to 15-20°C. For the medicated chewing gum formulation, different proportions of gum base (10%, 20%, 30%, 40%, and 50%) were tested to find the optimal percentage. The required amount of gum base was melted at 50-60°C, and sorbitol was incorporated and mixed well. A uniform blend of chlorhexidine gluconate, talc, and sucrose was then added while continuously stirring to ensure even distribution of the drug. Flavor and colour were added last. The mixture was allowed to cool at room temperature on a steel plate, then rolled out evenly and cut into uniformly sized pieces. The pieces were individually wrapped in aluminium foil [7]

8) Molding Method



Each component was carefully weighed. The synthetic gum base was slowly melted at 500–550°C in a porcelain crucible while being stirred continuously. Weighed glycerine was then added and thoroughly blended into the melted base. Following this, a physical mixture of sorbitol, sucrose, and domperidone maleate was introduced, with continuous stirring to ensure even distribution. The mixture was then allowed to cool to room temperature. Once cooled, the mass was rolled out and cut into pieces of uniform size and weight. After cutting, the pieces were scraped with a spatula and wrapped in butter paper. [8]

9) WET GRANULATION METHOD

Health in Gum®, butylated hydroxytoluene, microcrystalline cellulose, lactose, glyceryl monostearate, talc, magnesium stearate, titanium dioxide, acesulfame potassium, aspartame, aerosol, flavor, and colour were combined with a precisely measured amount of domperidone maleate, equivalent to the amount of domperidone. After that, this mixture was sieved. Sieved domperidone maleate was granulated with lactose and microcrystalline cellulose. By dissolving povidone, butylated hydroxytoluene, and erythrosine supra in water, a binder solution was created. To create a homogenous mass, the binder solution was added to the dry mix and well blended.

The granules were then dried in an oven. The granules were sieved and collected in poly bags once they had dried. The above-mentioned dried granules were mixed for five minutes after the sifting flavor was added. The sieving gum base was mixed with the flavor-infused granules and swirled for ten minutes. The previously mentioned mixture was combined with Glyceryl Monostearate, Titanium dioxide, Talc, Acesulfame potassium, Aspartame, and Aerosil, and mixed well. Then, the granules were added to the sifted magnesium stearate, and they were combined for three minutes. Using a 13.5mm round punch, the resulting granule mixes were then pressed into Domperidone Medicated Chewing Gum. [9]

IV. CONCLUSION

Chewing gum with medication is an entirely novel and important delivery method for pharmaceutical and medical purposes. The many varieties of medicated chewing gums have been examined in this review, with an emphasis on their varied formulations, therapeutic advantages, and the ways in which they improve patient compliance and drug administration. To overcome current obstacles and realize the full potential of this delivery system for improving patient care and treatment results, more research and development in this area is required.

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