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MEDICATED SOLUBLE CHEWING GUM; DOSAGE FORM WITH HIGH PAEDIATRIC ACCEPTABILITY: A REVIEW

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ABSTRACT

Owing to new social and behavioral trends in the past modern age, such as the growing consumer health awareness and increasing attention to safety products, chewing gum has been known for a new image and potential. Chewing gum is a solid, single-dose preparation with a base consisting mainly of gums that are intended to be chewed but not swallowed. They can be used therapeutically for the local or systemic treatment after the drug absorption. These formulations provide additional patient benefit; meet competitive challenges and conserves revenues. The drugs intended to act in oral cavity often have low water/saliva solubility and chewing gum constitute a valuable delivery system for such drugs. The research on NDDS is gaining importance now a day; Medicated Chewing Gum is one of them. It represents the newest system with potential uses in pharmaceuticals, over the counter medicines and neutraceuticals.

INTRODUCTION

Despite phenomenal advances in the inhalable, injectable, transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred delivery route.[1]The oral route of administration is the most popular and successful route used for conventional drug delivery because of convenience, ease of administration, greater flexibility in dosage form design, ease of production low cost of such a system and hence adopted wherever possible.[2] 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.[3]

The first medicated chewing gum was introduced in market in 1928 consisting of aspirin (aspergum) 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.[4]Chewing gum is

considered as a convenient "vehicle" or a "delivery system" to administer the drug that can improve health and nutrition, it has potential as an "alternative drug delivery system".

The European Pharmacopoeia defines medicated chewing gum as ''solid, single-dose preparations with a base consisting mainly of gum that are intended to be chewed but not swallowed''. They can be used as therapeutically for the local treatment of diseases related to buccal mucosa or for systemic treatment after the drug absorption. Moreover there is need of reformulation of existing drug into New Drug Delivery Systems (NDDS) to extend or protect product patents thereby delaying, reducing or avoiding generic erosion at patent expiry. To provide additional patient benefit, meet competitive challenges and to conserves revenues, the research on NDDS is gaining importance now a day. MCG is one of them. Owing to new social and behavioural trends in the past modern age, such as the growing consumer health awareness and increasing attention to safety products, chewing gum has been known for a new image and potential. Chewing gum today is gaining consideration as a vehicle or a delivery system to administer active principles that can improve health and nutrition. MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and neutraceuticals. The drugs intended to act in oral cavity often have low water/saliva solubility and chewing gum constitute a valuable delivery system for such drugs.[5]

Method of drug release

A medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose. During the chewing process, the drug contained in the gum product is released from the mass into the saliva and it could be absorbed through the oral mucosa or swallowed reaching the stomach for gastro-intestinal absorption. Thus, two absorption pathways are possible to introduce the active into the systemic circulation, giving rise to a systemic effect. Drug absorbed directly, via the buccal membrane, avoids metabolism in the gastrointestinal tract and the first-pass effect of the liver it might therefore be possible to administer a reduced dose in chewing gum compared to other oral delivery systems[6].

Why use chewing gum as drug delivery system?[7]

Chewing gum provides new competitive advantages over conventional drug delivery system:

1. Fast onset of action and high bioavailability[7]
2. Pleasant taste
3. Higher compliance (easy and discreet administration without water)
4. Ready for use
5. High acceptances by Children and for patients who find swallowing tablets difficult are obvious.
6. Local effect
7. Systemic Effect
8. Fast onset of action
9. Less side effects
10. Less risk of overdosing
11. Effective on Dry mouth

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.[7]

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.[7]

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.[7]

Effect on dry mouth (xerostomia):

Dry mouth is a side effect of many types of medicament (e.g. antidepressants) and it is also part of the symptomatology of several diseases disorder characterized by lymphocytic infiltration of the salivary and lachrymal glands). Chewing gum stimulates salivary secretion thereby decreasing dryness in the mouth.[7]

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.

Patient compliance as no water is required; taking medication in chewing gum is very convenient and therefore suitable for acute treatment. 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 candidiasis have shown that miconazole chewing gum is at least as efficient as miconazole oral gel in the treatment of fungal infections in the mouth.

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 fewer 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.

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.

Merits of chewing gum[8, 9].

- ✓ Avoids first pass metabolism -A drug released from medicated chewing gum has the potential of being absorbed through the epithelium of the oral cavity due to the rich Vascularise of the mucosa. The drug thereby gains direct access to the systemic circulation via the jugular veins and avoids drug transporters and first-pass metabolism in the gastrointestinal tract (GI) and in the liver. Thus, the bioavailability may increase.

- ✓ The therapeutic system need not be swallowed -This increases patient compliance especially for children or patient with swallowing disorders. Dysphasic population constitutes 35% of the general population, since this disorder is associated with a number of medical conditions such as stroke, Parkinsonism disease, AIDS, head and neck radiation therapy and other neurological disorders.

- ✓ No water needed -Chewing gums do not require water unlike conventional dosage forms, this is a very convenient for patients who are travelling or do not have immediate access to water. The medication may be taken without regard to time and place, thus enhancing patient compliance. Chewing gums do not draw attention to the medication; it is discrete and does not stigmatize the patient.

- ✓ Superior taste -Chewing gums contain various flavors and sweetening agent or a taste masked drug which will be readily acceptable particularly in case of children. It is often possible to disguise the bitter/bad taste of the active substance, making it a pleasant experience for the children. However, it is important that the child chews the chewing gum for the prescribed period of time.

- ✓ Accurate dose-Chewing gums have the advantage of convenience and accurate dosing as compared to liquids.

- ✓ More rapid drug absorption-Due to absorption from mouth pharynx and oesophagus mucosal layer. Increases

bioavailability in case of drugs which undergo extensive first pass Metabolism[8].

- ✓ Rapid drug therapy intervention is possible.

- ✓ Medicated chewing gums can also be used for local treatment of mouth diseases, Gingivitis, dry mouth, tooth hygiene and caries prevention are some of the conditions in which the use of chewing gum as drug delivery system has found practical application. There are various therapeutic areas in which the chewing gum as dosage form is most applicable.
- ✓ 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.Plaque pH plays an important role in the development of dental caries prevention. Sugar-free chewing gum is recommended after meals and snacks as a supplement to tooth brushing.
- ✓ Indications for fluoride chewing gum are prevention of dental caries, in children in fluoride- deficient areas, in adults with a high incidence of caries, and in patients with xerostomia. The caries-preventive effect of fluoride chewing gum has been compared with the effect of placebo chewing gum in experiments with artificial enamel lesions on teeth mounted in to removable mandibular appliances worn in situ in volunteers for several days. The re-mineralization has process proved to be faster when using fluoride chewing gum.

Characteristics of ideal Medicated chewing gums[9]

- ➢ They should not require water for administration and should not
- ➢ Disintegrate with in the mouth.
- ➢ They should be compatible with taste masking.
- ➢ They should have a pleasing mouth feel.
- ➢ They should allow high drug loading.
- ➢ They should exhibit low sensitivity to environmental conditions such as humidity and temperature.
- ➢ They should be manufactured and processed easily.

Components required for medicated chewing gum formulation.[10]

Component	Function	Example
Water insoluble gum base		
Elastomers	Provides elasticity and controls gummy texture	Natural (chicle gum, nispero, rosadinha, jelutong, periollo, lechicapsi, sorva etc.) and synthetic rubbers (butadiene, styrene copolymers, polyisobutylene, polyethylene mixtures,polyvinyl pyrrolidone, polyvinyl alcohol etc.)
Elastomer solvents	Softening the elastomer base component	Terpinene resins (polymers of alpha-pinene or beta-pinene), modified resins or gums (hydrogenated, dimerized or polymerized resins)
Plastisizers	To obtain a variety of desirabletextures and consistency proper-ties	Lanolin, palmitic acid, oleic acid,stearic acid, glyceryl triacetate,propylene glycol monostearate,glycerine, natural and synthetic waxes, hydrogenated vegetableoils, paraffin waxes, fatty waxes,sorbital monostearate.
Fillers or texturizers or mineral adjuvant	Provide texture, improve chewability, provide reasonable size of the gum lump with low dose drug	Calcium carbonate, magnesium carbonate, aluminium hydroxide, talc, aluminium silicate
Water soluble portions		
Softeners and emulsifiers	These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum	Glycerin, lecithin, tallow, hydrogenated tallow, mono/ di/ tri glycerides
Colorants and whiteners	Gives the formulation soothing colour and	Titanium dioxide, natural food colours and dyes suitable for food, drug and cosmetic applications

	improves acceptability of the formulation	
Sweeteners	To provide the desired sweetness of the product	Water soluble sweetening agents (xylose, ribulose, glucose, mannose, galactose, sucrose, fructose, maltose, monellin, sugar alcohols like sorbitol, mannitol etc.), water soluble artificial sweeteners (sodium or calcium saccharin salts, cyclamate salts etc.), di-peptide based sweeteners (aspartame, alitame etc.), naturally occurring water soluble sweeteners, chlorinated derivatives of ordinary sugar (sucralose), protein based sweeteners (thaumatin I and II)
Antioxidants	Prevents any possible microbial growth	Butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate
Flavouring agents	Toenhance consumer acceptability	Essential oils (citrus oil, fruitessences, peppermint oil, spearmint oil, mint oil, clove oil and oil of wintergreen) and synthetic or artificial flavours
Bulking agents	Used if low calorie gum is desired	Polydextrose, oligofructose, inulin, fructooligosaccharides, guargum hydrolysate, indigestible dextrin
Compression adjuvant	To ease the compression process	Silicon dioxide, magnesium stearate, calcium stearate, talc

The Manufacturing Process [11,12,13,14]

a) FIRST METHOD

Melting Method or Conventional Production Process

Today the majority of chewing gum delivery systems are manufactured using the conventional confectionary production process that begins with the melting of the gum base in a steam jacketed mixer. The active Medicament, the sweeteners and other ingredients are added to the melted phase according to specific time schedule, with flavours added at the last. The mixture is then cooled, rolled into sheets, scored and cut into pieces to produce sticks. Of course all the requirements for pharmaceutical formulations and good manufacturingpractice, established by the government authorities, must be fulfilled duringthe manufacture of medicated chewing gum.

b) SECOND METHOD

Direct Compression Process

Directly compressible free flowing powdered gums have been developed containing mixtures of polyols and/or sugars with gum base. These can becompacted in to a tablet form using a conventional tablet press. The products are harder than their counter parts and texture analysis shoes that they crumble under applied pressure. These chewing gums can include higher levels of active ingredients than traditional extruded gums; low temperature protects sensitive bioactivity and phytochemical components, moreover lower moisture content also improves shelf life of active molecules. Release is faster than from the conventional gums.

c) THIRD METHOD[12]

Step 1:
The gum base ingredients are melted together and filtered.
Step 2:
Powdered sugar, glucose syrup, flavoring and the other ingredients are slowly added to the gum base until the warm mix thickens like dough.
Step 3:
Machines called extruders are used to blend, smooth and form the gum.
Step 4:

It's time for the gum to be shaped. Gum can be flattened and cut into sticks, or squeezed into a rope shape and cut into chunks, or moulded into shapes and candy coated.
Step 5:
After the gum is cut or moulded into the appropriate shape, it is lightly sprinkled with powdered sweetener to keep it from sticking to machinery or packaging.
Step 6:
In a carefully temperature controlled room, the gum is cooled for up to 48 hours. This allows the gum to properly set.
Step 7:
If the gum is candy coated, like most gum balls or pellet gum, it is sprayed with liquid sweetener, allowed to dry and then sprayed again. This process is repeated several times until the candy shell reaches the proper thickness.
Step 8:
High speed machines carefully wrap and package the gum in air tight wrappers. This ensures the gum is fresh and soft when you open the pack. Then the gum is shipped to marketplaces and stores for people of all ages to enjoy.

d) FOURTH METHOD

1. The making gum begins by preparing gum base. If gum base is natural, it must first be harvested and processed. The process begins by melting and purifying the gum base. Gum base is placed in a warm room to dry for a day or two (hot air continually passes over the mixture). Gum base is then sterilized and melted in a steam cooker.
2. The substance is then pumped to a high-powered centrifuge to rid the gum base of undesirable dirt and bark.
3. The gum base is cooked and mixed with softeners and sweeteners (and all others additives).
4. The next step is kneading. Extruders (machines) are used to blend, smooth and form the gum.
5. A cutting machine cut the sheets into sticks or small pellets which are later candy coated.
6. Other machines then carefully wrap and package the gum in air tight wrappers[13]

e) FIFTH METHOD[14]:-

Hot melt extrusion-In this method synthetic elastomer along with, drug, filler and sweetener agent is firstly mixed properly and then plasticizer, flavour and a softer is heated until a liquid form is produced then with continuous stirring heated liquid is poured in the mixed powder to form a gummy substance .and allowed to cool

Evaluation parameter for chewing gum:-

Physical evaluation of MCG: The properties of synthetic gum base and formulations were reported on the basis of their colour, softening characters, sweetness, chewability, solubility etc.

Hardness/Plasticity: The Monsanto type hardness tester was used for determination of hardness of all MCG formulations.

Stickiness: MCG was placed on a plane surface; 250gm cylindrical hammer was collided on to it for a period of ten minutes. The frequency of hammering was about 30 strokes per minute. After 10 minutes, sticking of mass to hammered surface was observed and reported.

Flexibility: It referred to a test to check the tensile properties of moulded chewing gum. The sample thus produced was held at the ends and twisted to 180° quickly and smoothly avoiding jerking motion. A good piece did not crack or break into two or more pieces.

Flavour Impact: It measured the freshness feelings produced by the prepared sample. The "fast" rating was designated if the flavour was detected as soon as the gum wasput into the mouth.

Texture: This was an evaluation of smoothness or coarseness of the gum normally caused by the granulation of the bulk sweeteners used. The gum was held on the roof of the mouth and stroke with tongue. The abrasiveness felt was the texture measurement.
Stability studies of medicated chewing gum: 10 gm of chewing gum was stored in a bottle at 50°C for 30 days. After 30 days the gum was examined for natural ageing and physical nature.[15]

Ex- vivo 'chew-out' studies:

Release of drug in saliva:

With given instructions volunteers were instructed to rinse their mouth with distilled water and allowed to chew the medicated chewing gum for maximum 8 minutes. They were also instructed not to swallow the chewing gum and saliva, after complete solubilization they were said to rinse their mouth with 10ml of water which was collected & diluted to 50ml with 50% methanol and filtered with 0.02 micron nylon filter so that its maximum release had to be taken and absorbance was determined spectrophotometrically.

In-vitro release study in 'simulated salivary fluid':

It was analysed by adding the sample of produced chewing gum in beaker of dissolution apparatus containing 200ml of simulated salivary fluid so as to solubilise completely. The absorbance was recorded after the 5, 10, 15, 20, 25 min time intervals. Accordingly concentration of released amount of drug was determined with respect to the different samples withdrawn at given period of time.[16]

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