



Private prescription:

A thought-provoking tonic on the lighter side

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By gum – a buccal delivery system

It is now 25 years since the first registration of a medicated chewing gum containing nicotine for tobacco dependence [1]. With its success has come the official acceptance of chewing gum as a pharmaceutical dosage form, and the inclusion of monographs for both the preparation itself and a chewing apparatus for the determination of drug release, in the European Pharmacopoeia – a rapid rise to acceptability for a preparation that has been around for centuries.

Origins

The history of chewing gum is as fascinating as it is long [2,3]. The ancient Greeks, chewed mastiche, a resin containing triterpinoid acids and triterpene alcohols with about 2% volatile oil, obtained from the mastic tree, *Pistacia lentiscus* var *chia*, which is found mainly in Greece and Turkey and cultivated on the Greek island of Chios. In 50 AD, the Greek physician Pedanius Dioscorides reported that it was used it to sweeten the breath and clean the teeth.

The Mayans chewed chicle, a resin containing a mixture of low molecular-weight polyisoprenes, obtained from

the sapodilla tree *Achras sapota* (found in the Yucatan, Guatemala and Central America) and the native Americans chewed the gum from the black spruce, *Picea mariana*, which is found throughout northern North America.

The first commercial gum was produced in 1848 by John Curtis and his brother in Maine, USA, and consisted of pure spruce resin, although they later modified the formulations to include paraffin wax and flavours. The first chewing gum patent was granted on 28 December 1869 to William Finley Semple (a dentist from Ohio, USA) [4], although there is no record of its commercial manufacture. The patent claimed the 'combination of rubber with any other articles, in any proportions adapted to the formation of chewing gum'.

At about the same time, Thomas Adams, a photographer and inventor from New York, began experimenting with chicle sold to him by the exiled former president of Mexico, Antonio Lopez de Santa Anna (infamous for his victory at the Alamo), in an attempt to create a cheap rubber combination for carriage tyres. He failed in his primary aim but was successful in formulating the first chicle-based chewing gum. In

1871, Adams patented the first gum-producing machines and continued to develop new formulations, including a liquorice-flavoured gum called 'Black Jack', launched in 1872 – a brand that was only discontinued in the 1970s.

Progress

The next two decades saw a dramatic rise in activity on the formulation front. In 1880 John Colgan, a pharmacist from Louisville, (KY, USA), was the first to add sugar to gum. Edward Beeman, a doctor from Ohio, developed a formulation containing pepsin to relieve indigestion. William White, a popcorn salesman from Cleveland, found that combining flavours with corn syrup before blending with chicle provided a gum with a longer-lasting flavour on chewing. He subsequently introduced the popular peppermint-flavoured formulation. Fruit and spearmint flavours were introduced by William Wrigley in 1893, and in 1899 the first dental gum, Dentyne, was invented by Franklin Canning, a pharmacy manager from New York.

The early twentieth century saw even further progress, with many of the leading gum manufacturers (excluding Wrigley) organizing themselves into the American Chicle Company (this company was eventually acquired in 1962 by the Warner Lambert Company, now part of Pfizer). Wrigley expanded to become the largest manufacturer in the world. In the 1920s and 1930s, during prohibition in the USA, a clove-flavoured formulation was released that was ideal for disguising the smell of alcohol on the breath. Supplies of chicle virtually dried up during the 1940s, forcing scientists to develop new resins that were as good as the natural extracts but purer. Sugar-free gums were introduced in the 1960s and the 1970s saw the introduction of the first nicotine-containing formulation.

There are now formulations containing acetylsalicylic acid, ascorbic

acid, chlorhexidine acetate, carbamide, dimenhydrinate, silver acetate, calcium carbonate and vitamins. In fact the list grows longer every year, as more applications are found for this versatile preparation.

Development issues

Between 15 and 40% of chewing gum consists of what is known as gum base [5], a formulation in its own right, comprised primarily of elastomers, resins, waxes, fats and emulsifiers. The elastomers are styrene-butadiene copolymers mixed with polyisobutene. The addition of rosin esters and polyvinyl acetate improves texture and reduces the tendency of the gum to stick to teeth. Agents such as glycerol monostearate and lecithin act as emulsifiers and promote the uptake of saliva during chewing. A similar amount of bulk sweeteners are then added (originally powdered sugar and corn syrup but more commonly in sugar free and medicinal products, a mixture of sorbitol, xylitol, mannitol and aspartame). Glycerol is often added to keep the gum soft and flexible and flavours are included as required. Nicotine gums contain a nicotine–resin complex buffered with sodium carbonate and bicarbonate to increase the percentage of the lipid-soluble base form of nicotine in the saliva [1].

During manufacture, the gum base is first softened to the consistency of thick

syrup by heating at 50–70°C in a steam-jacketed mixer. The sweeteners and other ingredients are added according to a specific time schedule, with flavours added last. The mixture is then cooled, rolled into sheets, scored and cut. Prior to packaging, the gum is conditioned at a carefully controlled temperature and humidity.

'A bright future for a preparation with a long history'

Medicated chewing gums are formulated to release the majority of their active ingredient after 20–30 minutes but factors such as intensity of chewing and quantity of saliva produced will influence this release and the absorption from the buccal cavity. *In vitro* dissolution testing can be carried out using a variety of equipment designed to mimic the human chewing action. Variables include chewing frequency, distance between, and twisting action of, the jaws, as well as chewing time, volume and temperature of the 'saliva'. It is claimed (5,6) that the large freedom of choice of the conditions provides a good basis for tuning the test to provide usable *in vitro/in vivo* correlations.

Future

Chewing gum is no longer seen simply as confectionary. Wrigley have recently

created a Healthcare Division to use chewing gum as a delivery system for active ingredients that provide health benefits [3]. Dental health chewing gum is here to stay, as is medicated gum for smoking cessation and travel sickness. A bright future for a preparation with a long history.

References

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