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The Application of Degradable/Bioactive Glasses in Dentistry: An Overview

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Abstract

The UK spends an estimated £5.8 billion a year on dental treatment. A large percentage of this treatment is due to dental caries, a preventable disease where the tooth structure is broken down due to demineralisation of its surface layers. The demineralisation of the tooth tissue, for example during orthodontic treatment where adhesive brackets are attached to the teeth, is due to the bacteria such as Strep mutans in the oral cavity causing a drop in the pH below 5.5. There have been numerous methods to try and prevent demineralisation, mainly through the application of a fluoride varnish or tooth mousse, but this can only be applied by a dentist and as such a large proportion of the population who do not attend a dental practice do not receiving this treatment. Some countries (e.g. USA) also classify fluoride as a drug due to its ability to cause adverse effects, such as fluorosis of the teeth. Providing or delivering fluoride alone to the tooth surface may, however, be ineffectual as both calcium and phosphate are also required in the process. This has led to development of materials such as Amorphus Calcium Phosphate (ACP), CPP-ACP formula (Casein Phosphopeptide - Amorphus Calcium Phosphate) and bioactive glass for the treatment of the early carious lesion to prevent or delay the onset of cavitation. Research has also shown that by incorporating different ions into a bioactive material (e.g. bioglass) may lead to apatite formation as demonstrated in several in vitro studies. Ions such as fluoride and chloride have also been incorporated into the apatite structure via a bioglass formulation. There is a subgroup of patients who however do not want to use a fluoride toothpaste, and therefore,

researchers at Queen Mary University London (QMUL) have developed a bioglass toothpaste containing the chloride ion instead of a fluoride ion, an element in the same column of the periodic table as fluoride exhibiting similar properties. The aim of this overview is to review the different types of apatite and its formation in the in vitro environment as well as discussing the rationale for incorporating chloride into a bioactive toothpaste formulation for the remineralisation of tooth tissue.

Introduction

There is global concern about the amount of sugar in the form of fermentable carbohydrates being consumed by the world's growing population. According to several researchers (Marcenes et al. 2013, Kassebaum et al. 2015, Wen et al 2022) untreated caries in permanent teeth was the most prevalent condition evaluated during these studies and as such the burden of dental caries remains a global public health challenge.

Dental caries is the scientific term to denote tooth decay or cavities (a cavitated lesion), and the process is initiated by oral bacteria that are attached to the teeth forming acids in the presence of sugars, mainly sucrose, and refined starches (Dental caries. Dictionary.com). The early white spot lesion (affecting the surface of the tooth with no cavitation) on the tooth structure is indicative of the first stages of demineralisation, which if left untreated, can progress to a carious lesion as observed following orthodontic treatment where the brackets are cemented (using an adhesive material) to the buccal (facial) surfaces of the teeth. Once these brackets are removed, the presence of demineralisation (in the form of a white spot) may be observed. Bacteria can create a biofilm on the tooth surface, also known as plaque, that accumulates on the teeth and initiates a process that may move from an early-stage lesion to cavitation of the tooth surface. This process is called demineralisation and is due to a drop-in the pH in the oral cavity initiated by bacteria producing acid. If this decrease in pH drops below the critical level, this may result in a net loss of mineral in the enamel and dentine. This is commonly illustrated by the Stephen Curve shown below with the orange section demonstrating when demineralisation occurs (Fig. 1).

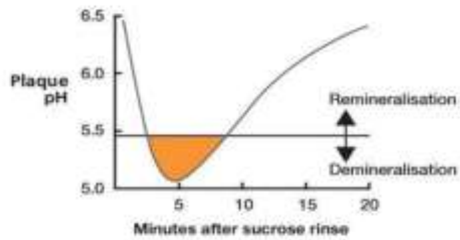

Figure 1: The Stephen curve to illustrate demineralization and remineralization of a tooth after eating (Wrigley healthcare programme, 2016)

How quickly demineralization and dental caries occurs is dependent on numerous factors and will differ between individuals. For example, it can be influenced by pathological factors such as cariogenic bacteria, frequency of fermentable carbohydrates and rate of salivary flow and function, e.g. sub optimal rates and function). According to Featherstone (2008) dental caries is a continual balance between these pathological factors and so-called protective factors such as: 1) components of the saliva (buffering capacity), 2) salivary flow, 3) remineralisation with fluoride, calcium and phosphates and) 4) adjunctive anti-bacterial agents (e.g., mouthrinses and toothpastes). It is also important to acknowledge the individual's general health, education and day to day (behavioural) habits (e.g., frequency of brushing etc).

The caries process is initiated within the surface/sub surface layer of enamel. The process of remineralisation and demineralisation is in equilibrium and is dependent on the calcium and phosphate from the saliva to remineralise any mineral loss because of demineralisation from the acids initiated by bacteria. Once the early lesion or white spot cavitates then the process is more likely to become irreversible and, if left untreated, the process will spread to the pulp, causing infection and necrosis. As indicated above remineralization of the tooth tissue occurs when phosphate and calcium, present in saliva, diffuse into the tooth tissue, as shown in Figure 2. These ions strengthen the apatite crystals within the enamel structure. Although both phosphate and calcium are present in saliva, there have been interventions to try and increase these ions in the body and introduce the levels of other ions, such as fluoride and chloride. One of these interventions is to introduce the ions in the form of bioglass within a toothpaste formulation.

$$Ca_{10}(PO_4)_6\ (OH)_2 \leftrightarrow Ca_2+ + PO_4{}^{3}- \leftrightarrow HPO_4{}^{2}-H_2PO_4-H_3PO_4$$

Figure 2: Remineralisation and demineralisation of apatite.

For simplicity, the ions on the right of the equation (Fig. 2) are when the oral cavity is under acidic conditions. The calcium and phosphate ions are present in the saliva. When acidic conditions are present within the oral cavity the phosphate within the tooth structure is removed to restore the levels in the salvia and so enamel demineralisation occurs. Remineralization occurs when there is an excess of calcium and phosphate in the salvia.

The aim of the literature review, therefore, was to explore the different types of apatite and its formation in the in vitro environment as well as discussing the rationale for incorporating chloride into a bioactive toothpaste formulation for the remineralisation of tooth tissue.

Bioactive Materials

There have been numerous dental products developed for the treatment of the early carious lesion to prevent or delay the onset of cavitation such as Amorphus Calcium Phosphate (ACP), CPP-ACP formula (Casein Phosphopeptide - Amorphus Calcium Phosphate) and bioactive glass (De Caluwe et al 2016, Al-eesa et al. 2017, Tiskaya et al. 2021a, b, Salah et al 2022). Some of these products and their resultant remineralising properties will be discussed further in the following paragraphs.

A bioactive material is defined as "a material that stimulates a beneficial response from the body, particularly bonding to the host tissue' (De Caluwe et al., 2016). These bioactive materials have become very popular in the dental setting, with the bioglass bonding to the teeth and creating a layer of apatite. Bioglass products have become increasingly popular in dentistry mainly due to an increase in dentine hypersensitivity, with 4-74% of the population affected, and a move towards a more preventive approach rather than restorative one (Ananthakrishna et al., 2012). Dentine hypersensitivity (DH) is characterized by a reaction to stimuli such as thermal, evaporative, chemical, osmotic or tactile. The reaction is often a short sharp pain. Anyone can be affected by dentine hypersensitivity (DH) but the condition often peaks during the third and fourth decades of life (Majji et al., 2016). The prevalence and the debilitating pain that is associated with DH and the potential impact on the quality of life (QoL) perhaps is one reason why the consumer (over-the-counter product) market is developing new formulations, as of December 2022, the market for toothpaste products in the UK was worth approximately 563.8 million British pounds (Petruzzi 2023).

Bioglass

A bioglass is a material that degrades and dissolves upon contact with a physiological fluid to allow controlled release of therapeutic ions and formation of an apatite-like surface layer (Al-eesa et al., 2017). Bioglass particles react with saliva tin the mouth to release sodium, calcium and potassium which creates the ideal conditions for tooth remineralization (Ananthakrishna et al., 2012). The original bioglass composition consisted of 45% silica, 24.5% calcium oxide, 24.5% sodium oxide and 6%

phosphorous pentoxide in weight percentage (Krishnan et al., 2013). Several patent applications based on the original 45S5 formulation have been granted in the past. The aim of incorporating bioglass into dental materials is to form a substance known as apatite or fluorapatite which is more resistant to an acid challenge. Apatite is an important material in the body, with a large percentage of our teeth and bones consisting of apatite, with bone comprising of 70% of inorganic substances such as apatite. (Kamitakahara et al., 2008).

The first bioglass was developed by Hench and colleagues in 1969 with several subsequent papers (Hench et al., 2015). Bioglass works by the hydrated silica that forms on the glass surface, undergoing rearrangement by polycondensation of the neighbouring silanols resulting in a silica rich gel layer. Precipitation of the calcium and phosphate ions, released from the glass, then form a calcium-phosphate rich layer on the surface (Elgayar et al., 2005). Bioglass can create a form of apatite known as hydroxyapatite.

The development of a bioactive bioglass in dentistry resulted in series of in vivo studies over a four-year period using an implant in the anterior region on the mandible of a baboon which remained stable after four years of function (Hench et al., 2015). It was a ground-breaking discovery and paved the way for more in-depth research. Subsequently researchers have been trying to create a bioglass that converts directly to apatite and if successful may result in the long-term survival rates of implants and bone grafts. Although the development of bioglass was originally formulated to be used in bone grafting procedures such as in medicine and dentistry it has subsequently been formulated to be used as an over the counter (OTC) toothpaste (Patel et al 2019, Prasad et al. 2024).

Types of Apatite

Numerous types of apatite have been formed over the years, but a synthetically produced apatite like natural apatite appears to be illusive.

Apatite Mullite

One of the most common apatite’s created by bioglass is apatite mullite. Apatite mullite is created when there is a lack of fluoride, calcium and phosphate. It is often created as a side product once fluorapatite has been made and offers favourable conditions for apatite formation due to the similarity in their compositions. Apatite mullite can be easily cast to shape and has little or no crystallisation upon casting (Stanton et al., 2010). It is also inexpensive, an advantage in the ever-increasing medical budget cuts, and is resistant to chemical degradation, another advantage with our acidic diets (Fathi et al., 2004). It is biocompatible, so the body should not reject it, but only after it has been produced by a ceraming process (Freeman et al., 2003). Although it has advantages it is not like the biological apatite and therefore does not have the ideal properties for the dental setting.

Apatite wollastonite

Another type of apatite is apatite wollastonite It is one of the “most common calcium silicate biomaterials used for bone tissue regeneration” (Magallanes-Perdomo et al., 2011). It is used in bone tissue regeneration as it is mechanically strong and bioactive in comparison to other glass ceramics (Magallanes-Perdomo et al., 2011). Although it is very bioactive it can dissolve at a quick rate which can be a disadvantage in a toothpaste as it would not remain in the oral cavity long enough to occlude the dentine tubules or remineralise the tooth surface.

Fluoroapatite

Fluoride has been a successful ion when added to the bioglass formula. Its ability to produce fluoroapatite makes it ideal for a toothpaste as it is extremely resistant to acid. It can inhibit both dentine and enamel demineralisation, enhance remineralisation and inhibit bacterial enzymes which can help to prevent dental caries (Brauer et al., 2010). The OH ion at the centre of the apatite molecule is replaced with the larger fluoride ion. Although this has its advantages it is also a disadvantage. By replacing the CaO with CaF_2, and lowering the phosphate, it can weaken the glass network due to a larger crystal lattice, which lowers the chemical durability leading to the formation of fluorite and calcite rather than fluorapatite (Lusvard et al., 2009). It cannot convert to hydroxyapatite, the ideal apatite formed (Rafferty et al., 2000) and when in vivo it increases the pH which can affect the surrounding tissues (Brauer et al., 2010).

Fluoride is also classified as a drug by the Federal Drug Administration (FDA) in the United States which means that there are restrictions on the amount of fluoride that can be incorporated into a toothpaste. Fluoride ions are not naturally present in the body, whereas chloride ions are and therefore may be more relevant. Chloride can be added to toothpastes above 5% and as it does not cause fluorosis, it will not be classed as a drug. (Chen et al., 2015). Chloride is therefore a good alternative to research to replace fluoride, especially for the American toothpaste market.

Strontium Chloride

Strontium chloride has been used in toothpastes for over four decades, (Ananthakrishna et al., 2016). It has been proven to help relieve the symptoms of dentine hypersensitivity by occluding the tubules, but also by acting as a protein precipitant (Majji et al., 2012). According to the published literature, the amount added to a toothpaste is 10% to obtain the desired effect (Anathakrishna et al. 2016, Majji et al., 2012,). Strontium has also been used in a bioglass due to its bone seeking ability and has been demonstrated to enhance the metabolic activity of bone cells, encouraging the regrowth of bone (Gentleman et al., 2010). If it can enhance the activity of bone cells, then there may be a possibility it can help enhance cells within the teeth. Another advantage of strontium is that is has an increased x-ray radio-opacity, an important aspect for dentistry (Hill et al., 2004).

Adding a high salt concentration to a toothpaste can affect its viscosity and therefore a binder is added to provide a stable viscosity over an extended period (Zeng et al., 2013). It is important to decide which binders are safe to incorporate to avoid any adverse reactions.

The formulation of how much strontium is required needs to be closely monitored as well. Strontium is often substituted for calcium; however, calcium and phosphate are important in the formation of hydroxyapatite. Supersaturation drives the precipitation of hydroxyapatite, so it is not ideal to substitute all the calcium for strontium (O'Donnell et al., 2009).

Topbas et al, (1998) reported that the participants using a toothpaste containing strontium chloride had decreased levels of dentine hypersensitivity but in most cases (93%) the results were short-lived and as such the toothpaste needs to be applied daily to be successful (Topbasi et al, 1998).

Researchers have also questioned whether the results were achieved by the abrasive fillers rather than strontium chloride, however, Gillam et al., (1992) disputed this finding in a double-blind parallel study where two strontium chloride containing dentifrices with different abrasive systems were compared. At the end of the two-month trial there were no significant differences, thus supporting the conclusion that changing the abrasive component does not necessarily affect the results of the toothpaste's ability to decrease sensitivity (Gillam et al., 1992).

The success of strontium chloride in toothpastes for dentine hypersensitivity however is somewhat controversial since several investigators have questioned it ability to reduce sensitivity (Cummins 2010, Karim & Gillam 2013).

Chloroapatite

Chloride comes from the same group in the periodic table as fluoride and therefore exhibits similar properties. The chloride ion is slightly larger than the fluoride ion and is displaced further above the plane in the Ca triangle (Chen et al., 2014). Due to the presence of water, the chloroapatite will completely convert to hydroxyapatite, a preferred apatite which is something the fluoride ion cannot form (Chen et al., 2014). Chen et al. also discovered that the glasses containing chloride bulk nucleate which is more suitable for the glasses forming apatite (Chen et al., 2014). By bulk nucleating this also allows the glasses to be cast to shape, although this may not be required when making a toothpaste, it does however, offer other alternatives within the dental environment. This will reduce costs as a diamond tip will not be required to create the desired shape. Compared with fluoride, the glass transition temperature is also lower with chloride, saving more money by requiring less heat (Sandland et al., 2004). The hardness of a glass is also expected to correlate to the glass transition temperature; therefore, a chloride containing glass should have a lower hardness. This is attractive for a desensitizing toothpaste since dentine hypersensitivity is often due to loss of enamel, and the abrasive in a toothpaste may be responsible for this hard tissue loss. If this glass is less abrasive and can remineralise the teeth this will be an attractive alternative for treating dentine hypersensitivity (Chen et al., 2015). Chen et al (2017) also reported that a chlorine toothpaste (BioMin C® - A Smart Fluoride-free Remineralising and Desensitising Toothpaste) had been formulated as an over-the-counter toothpaste.

In an increasingly demanding world for cosmetic dentistry, chloride containing toothpaste could be the answer for safer teeth whitening. Chloride containing glass ceramics have been used in solar cells due to their ability to keep the crystal phase dimensions lower than the wavelength of light. This is used in up conversion applications, such as solar cells, but this up conversion also makes natural teeth appear whiter in natural light containing these shorter wavelengths. This could be a safer solution to teeth brightening compared to the bleaching products currently being used in cosmetic dentistry. Not only could this chloride containing toothpastes be whitening teeth and remineralizing them, but they would be also replacing harmful bleaching products that can destroy the protein component in teeth (Chen et al., 2015).

These toothpastes, however, do have their disadvantages. Due to the large chloride ion, when this is introduced into a glass it can cause the glass to expand, causing the glass structure to be less compacted. This makes it less abrasive, which is an advantage, but it also causes the glass to be softer and can be dissolved at a quicker rate (Chen et al., 2015). The glass needs to remain on the teeth for a sufficient period to remineralise the tooth surface. The size of the chloride ion may also disrupt the crystallization phase during synthesis (Chen et al., 2015).

Another issue with creating the chloride containing glass is how volatile chloride can be. For example, during the synthesis of the glass, it is common for the loss of chloride via three routes. The first is via direct volatilisation as $CaCl_2$, reacts with the sodium to create NaCl and the other is via HCl by reacting with the water vapour in the furnace (Chen et al., 2015). Therefore, it is extremely important to prevent the loss of chloride via these routes. One possible solution would be to remove sodium in the composition to minimise the loss of chloride via the NaCl route.

Discussion and Conclusion

Apatite formation is required to 1) remineralise lost mineral in the tooth surface and 2) occlude the tubules to prevent dentine hypersensitivity. The apatite created must be similar to the natural hydroxyapatite to minimise rejection, sufficiently resilient to withstand forces in the oral cavity, acid resistant and rapid in action to enable deposition before any residual toothpaste is removed from the oral cavity. One method of achieving this goal is to develop a chloride containing bioglass. The evidence from the in vitro studies using bioglass formulations have demonstrated that apatite can be formed in Tris buffer solution. Tris buffer mimics human saliva and as such provides an indication of how these materials would act under normal clinical conditions. Based on these studies, chloride bioglasses may form apatite which would be beneficial in treating demineralisation of lost mineral and in occluding dentinal tubule to prevent hypersensitivity. Currently there have not been any published papers on the results of chloride bioglass toothpastes in vivo. From the results of the in vitro studies, however, a chloride containing bioglass may have superior remineralisation properties than that of a fluoride containing bioglass although this would have to be substantiated in clinical studies. Currently bioactive glasses appear to be gaining in popularity for the treatment of 1) Dentine hypersensitivity, 2) the early carious lesion (remineralisation of the white spot lesion) and 3) in the restoration of the cavitated lesion using bioactive glass composite materials.

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