Application of poly(trimethylene carbonate) and calcium phosphate composite biomaterials in oral and maxillofacial surgery
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chapter 1

GENERAL INTRODUCTION AND AIM OF THE THESIS
Tissues and organs in human bodies constantly renew themselves during their life time. Our hair and nails keep growing and need to be cut regularly. We shed off dead skin every day. Although not seen, epithelium lining our stomach and intestines is renewed and replaced by new cells within a week(1). Despite the constant renewing of a human body, only a few organs, including skin, liver and bone, are capable of self-regeneration when damaged, and even such a regenerative capacity is within limitations. A simple bone fracture can heal by rigid fixation of the fracture, but a large missing piece of skull or a severely resorbed alveolar ridge, due to progressive periodontitis, do not come back to normal without augmentation. Other needs for bone regeneration include reconstruction of bone defects caused by trauma, tumors, infections, harvesting of bone grafts, and congenital abnormalities. Facing diverse clinical challenges, a transition of bone substitute materials from space holders to biologically active, custom-made biomaterials has been actively witted in oral maxillofacial surgery(2).

Calcium phosphate bioceramics in forms of granules, scaffolds, coatings and injectable cements have become increasingly popular bone substitutes for autologous bone grafts in oral and maxillofacial surgery and orthopedics, because they chemically resemble the inorganic components in natural bone and should possess osteoconductive capacities to support bone ingrowth in the scaffolds(3). Hydroxyapatite (HA) has become a reference material in the field of calcium phosphates for biomedical applications and other important members of calcium phosphate bioceramics include beta-tricalcium phosphate(β-TCP) and biphasic calcium phosphate (BCP), a mixture of HA and TCP. β-TCP is more commonly used than α-TCP in biomedical applications because β-TCP has a lower solubility and thus lower resorption kinetics(4). Various factors determine bioactivities of calcium phosphate bioceramics, including sintering temperature, porosity and pore sizes, and these factors are connected to each other. HA powders can withstand sintering temperatures of 1000 - 1200 °C and start becoming unstable at temperatures around 1250 - 1300 °C. Porous HA bioceramics can be colonized by bone tissues, so interconnecting porous structures with pore sizes larger than 100 μm is intentionally introduced in solid bioceramics(5). It takes years for HA bioceramic scaffolds to get fully degraded in vivo and new bone formation is seen occupying peripheral parts of the scaffolds(6). BCP bioceramic particles sintered at a relatively low temperature (1150 °C) show a porous structure with interconnected pores under the electron microscope (microporous), while BCP bioceramic particles sintered at 1300 °C do not show such a microporous structure(7). When implanted in a goat dorsal muscle, BCP bioceramic particles sintered at 1150 °C induce new bone formation which appears to be initiated at the surface of the particles. Such ectopic new bone formation is not induced by BCP bioceramic granules sintered at 1300 °C. When implanted in defects in goat iliac wings, the BCP bioceramic scaffolds with osteoinductive capacity lead to new bone formation that is of significant large amount and deeper inside the scaffolds than the BCP bioceramic scaffolds with only osteoconductive ability(7), stressing the importance of osteoinductivity in regeneration of critical-sized bone defects. Although calcium phosphate bioceramics have gained wide biomedical applications as fillers, coatings(8) or
drug delivery carriers(9), their applications as scaffolds in load-bearing sites are still limited by their inherent brittleness with a poor fatigue resistance(8).

One feasible solution to overcome the brittleness of calcium phosphate bioceramics is to combine calcium phosphate bioceramics with polymers(10), since natural bone tissue is a composite of HA and collagen fibers and mechanical properties of bone mainly depend on the strength of the collagen fibers(11). A variety of polymers, of natural origin or synthetic, have the potential to become part of composite biomaterials with calcium phosphate bioceramics for bone regeneration. The most renowned choices include collagen, poly(lactic acid), poly(glycolic acid), poly(ε-caprolactone) and copolymers of lactic acid/glycolic acid/ε-caprolactone(12). In our studies, we have used poly(trimethylene carbonate) to incorporate calcium phosphate bioceramic particles because of its unique physical and biocompatible properties.

Poly(trimethylene carbonate) (PTMC), an aliphatic polycarbonate, can be synthesized by ring opening polymerization of 1,3-trimethylene carbonate (TMC) in different conditions and using different catalysts, resulting in PTMC batches with different molecular weight(13-15). Different molecular weights determine mechanical properties of PTMC biomaterials and subsequently their biomedical applications. PTMC biomaterials undergo degradation in a surface erosion process mediated by enzymes(16) both in vitro(17) and in vivo(18) and the metabolites are not acidic in nature(19). Thanks to the degradation behavior of surface erosion, PTMC of low molecular weight and TMC-based copolymers can be used as carriers for controlled release of hydrophilic drugs(20, 21), growth factors(22, 23), anti-tumor drugs(24, 25), and antibiotics(26). PTMC with a number average molecular weight above 200,000 (very high molecular weight) is synthesized under 130°C in vacuum for 3 days with stannous octoate as a catalyst(27) and shows a Young’s modulus of 6 MPa, an elongation at yield of 130%, and an elongation at break of 830%(28). With a glass transition temperature of around -17°C, the amorphous PTMC polymer is in its rubbery state at room temperature and is flexible(13, 27). Therefore, PTMC biomaterials with very high molecular weight display favorable properties, combining high flexibility with high tensile strength, which are suitable for tissue engineering purposes but not in load bearing situations. Besides, TMC monomers are commonly used to form copolymers with lactic acid, glycolic acid, ε-caprolactone, or other monomers, imparting elasticity to these copolymers and tuning their degradation behaviors. Copolymers made of glycolic acid and TMC have been successfully used as synthetic degradable monofilament sutures with high tensile strength (Maxon™)(29). In soft tissue engineering, PTMC and copolymers of TMC with lactic acid, glycolic acid, ε-caprolactone, or other monomers have been applied for regeneration of damaged nerve tissue(30, 31), myocardial tissue(32, 33) or blood vessels(34-37). The application of TMC-based polymers in hard tissue regeneration is less well investigated. PTMC microspheres with high molecular weight are used to formulate calcium phosphate cements (CPC) with an initial setting time of around two to three minutes and a compression strength of 15-24 MPa(38). In repairing defects in jawbones, membranes made of very-high-molecular-weight PTMC have been shown suitable to be used as barrier membranes for guided bone regeneration(39). Besides,
such PTMC membranes have also been shown feasible to be used in bone augmentation procedures with bone grafts (40).

**AIM OF THE THESIS**

Aim of the present research is to evaluate applications of composite biomaterials composed of poly(trimethylene carbonate) (PTMC) and calcium phosphate bioceramic particles in the forms of membranes and porous scaffolds for indications in the field of oral and maxillofacial surgery. The clinical circumstances to which the composite biomaterials should be applied include guided bone regeneration, bone augmentation with block autologous bone grafts for a proper placement of dental implants and reconstruction of critical sized cranial bone defects.
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