

Introduction of Four Collagen-Based Dental Membranes

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A. BACKGROUND

The use of a membrane for guided tissue and bone regeneration surgeries has become the standard care in dentistry in recent years. Even though a limited number of non-resorbable membranes (e.g., PTFE membrane) are still being used in these procedures, majority of the membranes are made of resorbable materials, particularly collagen-based materials. Accumulated experience over the past two decades has indicated that the key requirements for use of a membrane in these procedures include: 1) the membrane is cell occlusive; 2) the membrane is resorbable *in vivo* and the resorption time is sufficiently long for the membrane to function as a cell barrier during the period of new tissue regeneration and wound healing; 3) the membrane has sufficient biomechanical strength that can be stabilized via suturing or tacking; 4) the membrane can be exposed without losing its barrier function in cases where primary closure is not feasible; 5) the membrane possesses certain characteristics that can conform to the

wound site if needed and 6) the membrane is compression resistant preventing the underlying graft material from collapsing in certain procedures.

It can be seen that there is not a single membrane that can simultaneously satisfy all the requirements cited above. As a result, a number of dental membranes have been developed and commercialized with each membrane fulfilling some requirements for a particular type of procedure. Although degradable synthetic polymers (e.g., copolymer of DL-lactide and polycaprolactone) have been used to manufacture dental membranes, natural polymeric materials such as collagen-based materials are more commonly used for the design and engineering of the membranes. It is worth while mentioning that type I and type III based collagen materials are well accepted by the FDA for their biocompatibility properties. Table 1 summarizes the key membranes that are on the market today along with their characteristics.

Table 1. Key Dental Membranes Currently on the Market

Product Name	Composition	<i>In Vivo</i> Resorption Time** (weeks)	Suture Pull-out Strength (Kg ± S.D.)	Pore Size (µm)	Conformability
BioMend®	Short type I collagen fibers	8	0.074 ± 0.010	0.004***	Medium
BioMend® Extend™	Short type I collagen fibers	18	---	0.004***	Low
RCM6™	Reconstituted long type I collagen fibers	26-38	0.285 ± 0.075	< 0.01	Medium
Cytoplast®	Reconstituted long type I collagen fibers	26-38	0.281 ± 0.102	< 0.01	Medium
Memlok®	Reconstituted long type I collagen fibers	26-38	0.308 ± 0.081	< 0.01	Medium
BioGide®	Porcine peritoneum tissue	16-24	0.485 ± 0.030	---	High
OsseoGuard®	Reconstituted long type I collagen fibers	26-38	0.300 ± 0.058	< 0.01	Medium
Zimmer® Socket Repair Membrane	Reconstituted long type I collagen fibers	26-38	0.308 ± 0.085	< 0.01	Medium

*BioMend® is a registered trademark of Integra LifeSciences Corp, Plainsboro, NJ

BioMend® Extend™ is a trademark of Sulzer Calcitek Inc., Carlsbad, CA

RCM6™ is a registered trademark of Ace Surgical, Brockton, MA

Cytoplast® is a registered trademark of Osteogenics, Lubbock, TX

Memlok® is a registered trademark of BioHorizons, Birmingham, AL

BioGide® is a registered trademark of Geistlich, Switzerland

Osseoguard® is a registered trademark of Biomet 3i, Palm Beach Gardens, FL

Zimmer® Socket Repair Membrane is a registered trademark of Zimmer Dental, Carlsbad, CA

**Reported from product's package insert

***Reported from 510(k) no. K992216 and K924408

B. COLLAGEN MATRIX DENTAL, INC. COLLAGEN BASED DENTAL MEMBRANES

B1. COLLAGEN TECHNOLOGY

The technologies for engineering collagen-based dental membranes are briefly described here. Generally, collagen-rich tissues such as tendon or dermis (middle layer of skin) of an animal (e.g., bovine, porcine) are used as the source of collagen fibers. Detailed methods for obtaining highly purified intact collagen fibers from tendon tissue have been described elsewhere [1-3]. The following is a brief summary of how the purified intact tendon collagen fibers are prepared. The tendon is mechanically disintegrated into small pieces and the materials are chemically extracted to remove most, if not all, of the non-collagenous materials from the tissue. The purified collagen fibers are then dispersed in an acidic solution followed by reconstitution of the fibers and the engineering of the fibers into membranes or other forms for various applications including dental surgeries [1-3].

The engineered membranes are subsequently chemically crosslinked for controlling the *in vivo* stability and minimizing any potential immune response [4]. Since the shapes, forms, and other characteristics can be designed and the chemical crosslinking can be controlled for various medical and dental applications, the technology is highly versatile. This technology is referred to as “Fiber Reconstitution Technology.”

Another method for the preparation of collagen-based material is to remove non-collagenous moieties from collagen-rich tissues without going through mechanical disintegration in order to preserve the structural integrity of the material for mechanical strength. Similar extraction steps described above are involved to remove the non-collagenous materials from the tissue of interest. The purified, tissue-based materials are then crosslinked to control the *in vivo* stability. Generally, the material is in the form of a membrane. The common materials used in dental surgeries are derived from dermis, pericardium and peritoneum. This technology is referred to as the “Tissue-Based Technology”.

B2. DENTAL MEMBRANE PRODUCTS

Based on the technologies described above, Collagen Matrix, Inc. has designed and engineered four unique dental membranes for guided tissue and bone regeneration procedures. The membranes have recently obtained market clearance from the FDA. The physical, physico-chemical and biological characteristics of the membranes are summarized in Table 2.

As one can see from Table 2, these membranes cover a range of properties that can be applied to different dental surgeries. Each of these membranes is further discussed in sections below.

Table 2. Characteristics of Porcine Collagen Dental Membranes*

Product Name** Reconstituted long type I collagen fibers	Technology	Composition	Thickness (mm)	Hydration Time (min)	In Vivo Resorption Time*** (weeks)	Suture Pull-out Strength (kg)	Pore Size (µm)	Conformability
MatrixDerm™	Tissue Based	Porcine dermis type I and type III collagen	0.3-0.5	< 2	26-38	0.456 ± 0.092	< 0.01	Medium
MatrixDerm™ EXT	Tissue Based	Porcine dermis type I and type III collagen	0.4-0.7	< 1	36-52	0.667 ± 0.101	< 0.01	Low to Medium
MatrixDerm™ Cap	Tissue Based	Porcine dermis type I and type III collagen	0.4-0.7	< 1	36-52	0.509 ± 0.093	< 0.01	Low to Medium
MatrixMem™	Fiber Reconstitution	Porcine tendon type I collagen	0.25-0.45	< 4	16-28	0.284 ± 0.053	< 0.01	Medium to High

*Data on file

**MatrixDerm™, MatrixDerm™ EXT, MatrixDerm™ Cap, and MatrixMem™ are all trademarks of Collagen Matrix, Inc.

***Data obtained based on the *in vivo* evaluation using a rat subcutaneous implantation model

MatrixDerm™

MatrixDerm™ (Figures 1-3) is a purified dermis tissue from the corium layer of skin of a 12 months old pig. The tissue was harvested by a well controlled tissue procurement method that met the FDA requirements. A series of chemical treatments (enzyme, detergent, acid, base, alcohol, and salt) were performed to remove most of the extractable and enzyme degradable non-collagenous materials from the tissue, leaving a cohesive collagen-fiber matrix with intact intrinsic crosslinks for mechanical strength. The residual non-collagenous moieties were analyzed by a number of validated test methods developed internally. The lipid, total sugar, hexosamine, and hydroxyproline contents were determined to estimate the total non-collagenous materials in the purified matrix. SDS PAGE was performed to evaluate the final purified collagen matrix to detect any collagen denaturation during the chemical treatment procedure. The SDS PAGE also provided an estimate of the amount of type III collagen associated with the preparation. The material was then further chemically crosslinked to meet the *in vivo* stability requirement for a particular dental surgery. The dimensions (size, shape and thickness) were then determined and sized to meet the needs of various procedures.

The chemical analysis showed that the purified porcine dermis contained mostly collagen fibers with only trace amount of non-collagenous materials. SDS PAGE (Figure 11) showed that the purified dermis contained mostly type I collagen, with only a trace amount of type III collagen. The collagen fibers were mostly in the intact form, i.e., the collagen molecules and fibers maintained their native structure. The final crosslinked, sterilized dermis matrix (MatrixDerm™) had a hydrothermal transition temperature that is consistent with a total resorption time of the material *in vivo* of about 26-38 weeks (data on file). As anticipated, the MatrixDerm™ maintained high mechanical strength that could be stabilized via suturing or tacking with pins or tacks that are commonly used in dental surgeries. MatrixDerm™ is permeable to macromolecules the size of carbonic anhydrase with a molecular weight of 29,000 Daltons, the size of most nutrient molecules and growth factors, with a pore size of <math><0.01\mu\text{m}</math>. Therefore, the cell barrier function of the membrane is assured. It conforms well to surfaces that do not have sharp ridges. The final sterilized membrane passed all biocompatibility tests for human implantation according to the FDA guidelines and European ISO standards.

The characteristics of MatrixDerm™ make it suitable for most of the dental surgeries as a barrier membrane for guided tissue and bone regeneration where minimum or no membrane is exposed post-surgery.

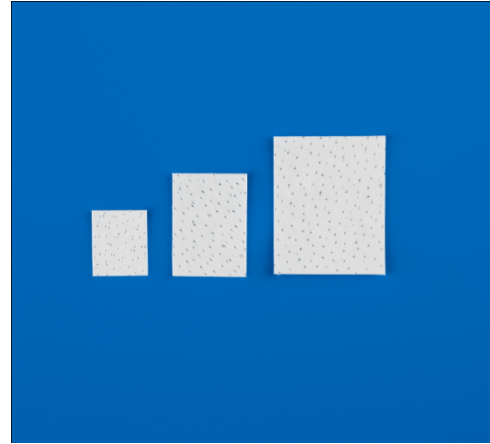


Figure 1. Three available sizes of MatrixDerm™ (15mm x 20mm; 20mm x 30mm; 30mm x 40mm)

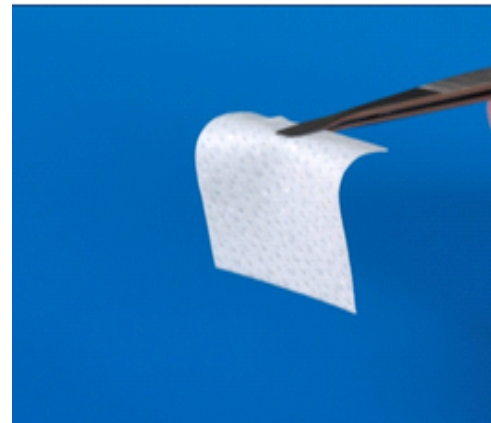


Figure 2. Hydrated MatrixDerm™

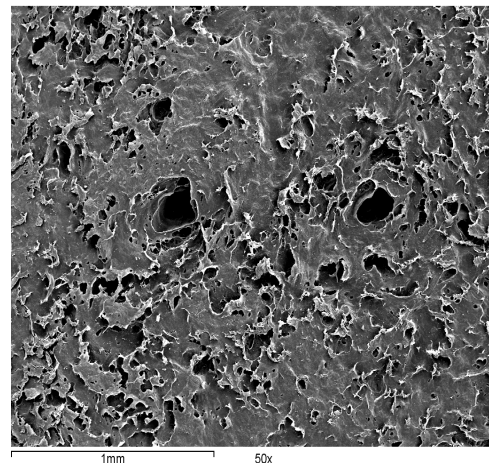


Figure 3. SEM Micrograph of the surface of MatrixDerm™

MatrixDerm™ EXT

MatrixDerm™ EXT (Figures 4 and 5) was developed to meet the needs when a surgery requires that the membrane is more firm in holding the underlying bone grafting material volume or when the membrane is exposed in the oral cavity where both mechanical stresses and enzymatic activities are high. One potential application is in sinus lift procedures where the membrane is likely to be exposed post-surgery.

MatrixDerm™ EXT is made from the same material as the MatrixDerm™, i.e., porcine dermis. The procedure for making MatrixDerm™ EXT is the same as the MatrixDerm™ except that the MatrixDerm™ EXT is a slightly thicker membrane with a higher hydrothermal transition temperature than the of MatrixDerm™ for longer *in vivo* stability.

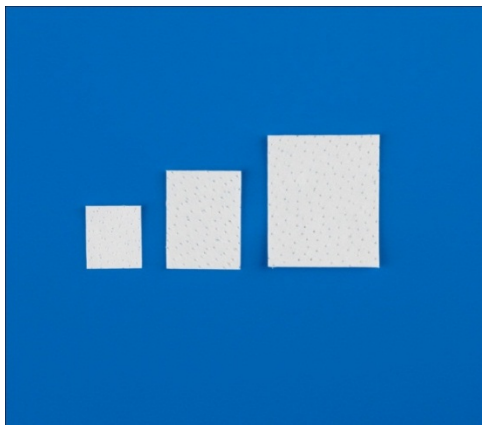


Figure 4. Three available sizes of MatrixDerm™ EXT (15mm x 20mm; 20mm x 30mm; 30mm x 40mm)

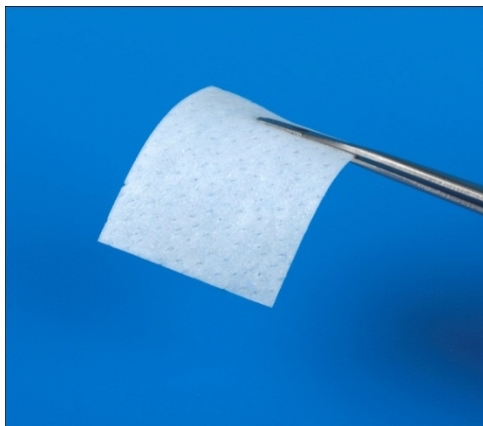


Figure 5. Hydrated MatrixDerm™ EXT

MatrixDerm™ Cap

Collagen-based dental membranes are often used in socket ridge augmentation procedures. In this procedure a dental membrane is used in combination with a bone grafting material in the form of granules. After a tooth is extracted, the socket is filled with bone grafting granules. A dental membrane is then placed over the bone graft to protect the wound site and to guide the new bone regeneration. Suture is generally applied to stabilize the membrane. Often the primary closure is not accomplished, leaving the membrane exposed to the oral cavity. The common clinical observation is that when the membrane is exposed, its residence time at the wound site is reduced. Therefore, the barrier function of the membrane may be minimized.

MatrixDerm™ Cap (Figures 6 and 7) was specifically designed to meet the needs for socket ridge preservation procedures. The method of manufacturing material and characteristics of MatrixDerm™ Cap are similar to that of MatrixDerm™ EXT. The size, shape, strength, *in vivo* stability and conformability of the membrane are particularly useful for guided socket ridge bone regeneration applications. The final membrane product passed all the requirements for human implantation.

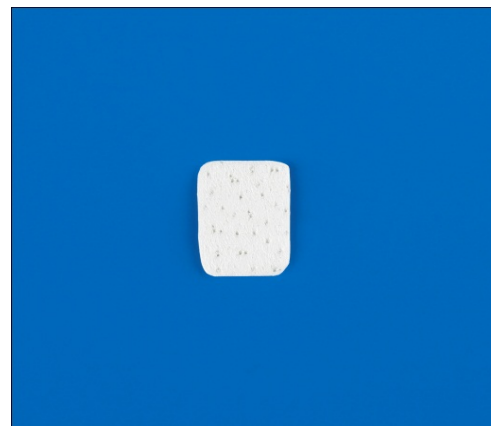


Figure 6. MatrixDerm™ Cap (12mm x 16mm)

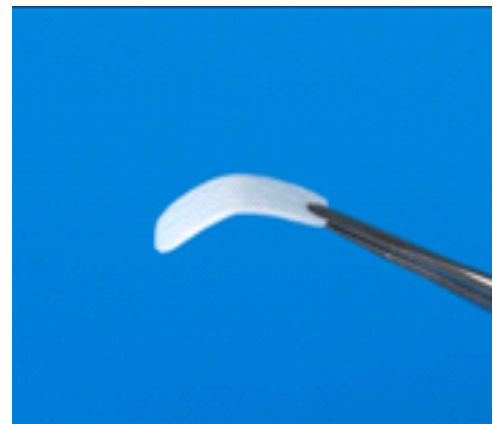


Figure 7. Hydrated MatrixDerm™ Cap

MatrixMem™

MatrixMem™ (Figures 8-10) is engineered following the Reconstitution Fiber Technology. Porcine tendon was the source of collagen fibers. The tendon was cut into thin slices and extensively extracted to remove the non-collagenous materials. The residual non-collagenous materials were estimated based on the methods similar to of MatrixDerm™. The purified fibers were then dispersed in an acid solution and reconstituted by adjusting the pH to a point where fibers precipitate out to form cohesive long fibers as described previously [1- 3]. The fibers were then engineered into membrane form, lyophilized and lightly crosslinked for *in vivo* stability. The thickness, density, permeability, mechanical strength and *in vivo* stability were properly balanced such that the membrane handling characteristics were suitable for guided tissue and bone regeneration applications where the membrane can conform to the surfaces of mild irregularities. Figure 11 shows that the reconstituted collagen fibers were mostly in the intact native collagen structure. The final membrane product passed all the requirements for human implantation.

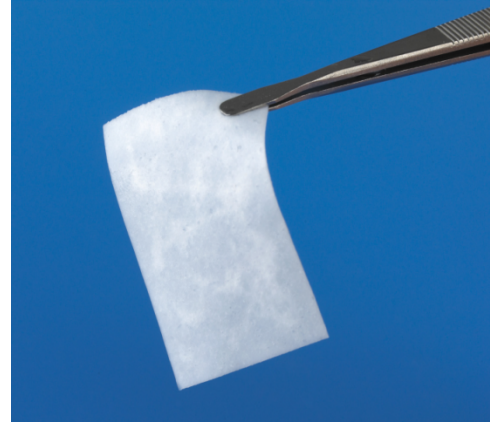


Figure 9. Hydrated MatrixMem™



Figure 8. Three available sized for MatrixMem™ (15mm x 20mm; 20 x 30mm; 30x 40mm)

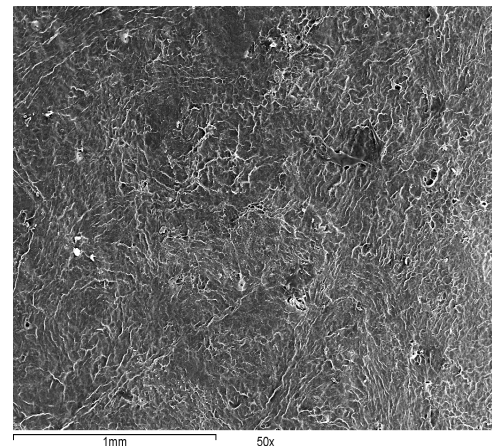


Figure 10. SEM micrograph of the surface of MatrixMem™

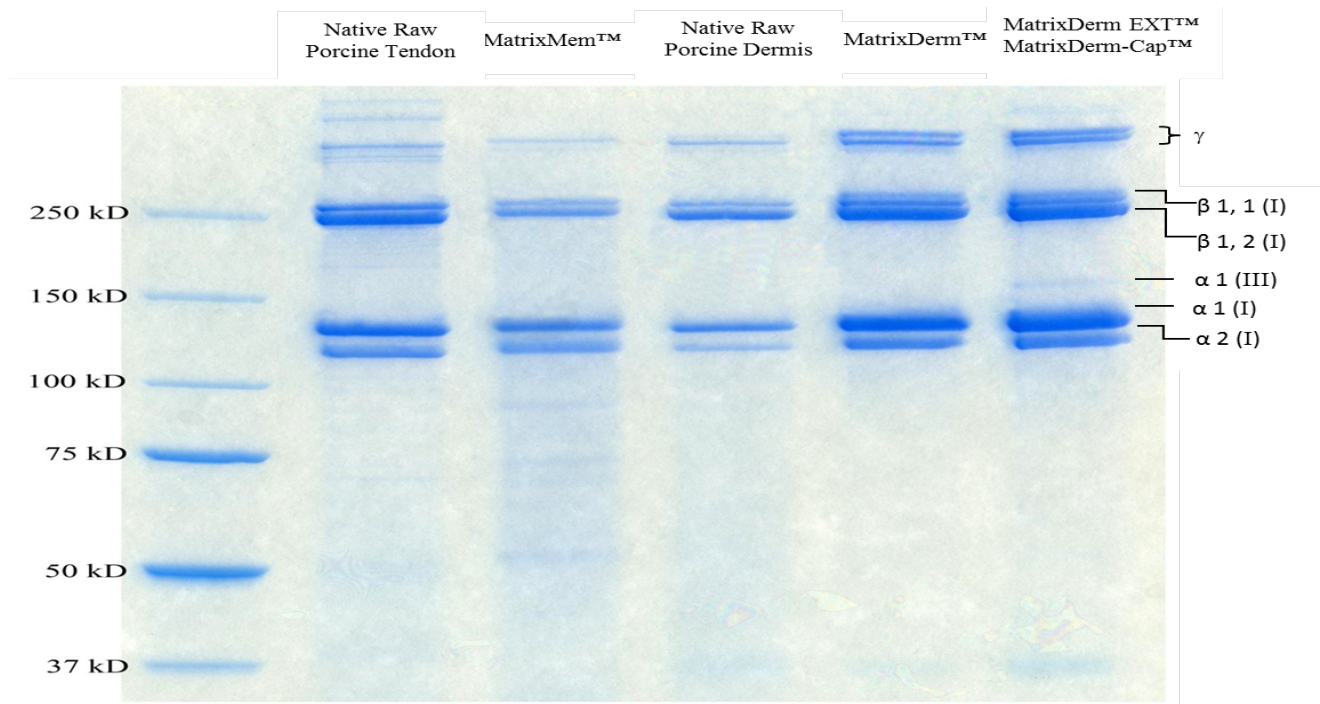


Figure 11. SDS PAGE Analysis of Porcine Based Collagen Dental Membranes

C. SUMMARY

There are many commercial dental membranes made of synthetic or biological materials with varying characteristics. These membranes have been used in a wide range of dental surgeries including periodontal, socket preservation, sinus lift and ridge augmentation procedures. The primary function of these membranes is to provide a cell barrier for guided tissue and bone regeneration such that subsequent dental implants can be implanted to replace the missing tooth or teeth in the oral cavity. However, with the lack of proper design characteristics, the benefit of these membranes cannot be maximized. The purpose of this article was not to exhaustively review the advantages and disadvantages of various commercial dental membranes. Our objective was to introduce several new dental membranes derived from porcine tissues having distinct characteristics that can be selected by the clinicians for a particular dental surgical procedure. Our rationale is to provide some basic information about each membrane and its associated characteristics such that the membrane received by a patient will have the maximum possibility of success in a given surgery.

REFERENCES

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4. Timpl, R. "Immunology of the Collagens". *Extracellular Matrix Biochemistry*. Piez, K. and Reddi, A.H. ed., New York: Elsevier, p. 159-190. 1984.