

# Localised Drug Delivery via Collagen-Based Biodegradable Matrices

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## Introduction

Collagen is the most abundant protein in the human body and accounts for approximately 30% of all proteins. It is the essential structural building block, comprising about 95% of bone and 75% of skin, and is the main component of other connective tissues (cartilage, tendon and ligament). Collagen surrounds the cells and forms the 3-D cellular matrix of all tissue, giving each its characteristic structure, texture and shape. Twenty-one different types of collagen are known and these have been classified according to molecular composition and tissue distribution (Gelse *et al.*, 2003). Bone, dermis, tendon and ligament are predominantly type-I collagen.

The structure, function and biosynthesis of collagens have been thoroughly investigated (Nimmi and Harkness, 1988; Gelse *et al.*, 2003). The type-I molecule is made up of three peptide subunits, all having similar amino acid composition and conformed as a triple helix. In addition to the helical portion, the terminal amino acid sequence at each end of the molecule is comprised of short (less than 5% of the total), non-helical domains called telopeptides, which are involved in non-covalent polymerisation with adjacent helices. Subsequent formation of intra- and inter-molecular cross-links aid in the formation of collagen fibres, fibrils and macroscopic bundles that combine to form tissue.

The main sources of type-1 collagen for biomedical applications are either animal skin (predominantly bovine or porcine) or Achilles tendon, which is usually of bovine or equine origin. After extraction and purification, the primary to tertiary structure of the collagen may either be preserved (commonly referred to as “insoluble”, “fibrillar” or “native” collagen) or else the collagen may be further digested and degraded by enzymes and/or extreme pH leading to partial or complete removal of higher order fibril structures (so-called “soluble” collagen).

## Collagen-Derived Medical Products

Collagen is well established as a safe and effective biomaterial and was one of the first to be used in medical products. It combines the properties of high tensile strength, biocompatibility and absorbability in living tissue. Before the era of synthetic polymers, collagen sutures

were used as a standard material in surgical procedures, a practice which can be traced back to the Ancient Egyptians. In more recent times, sophisticated collagen-based medical devices such as blood vessel prostheses, heart valves and urinary sphincter implants have been introduced.

The physiological properties of the soluble and insoluble collagens are different, which has led to a wide variety of medical applications. Soluble collagen can be used to produce biodegradable or non-biodegradable materials with excellent mechanical properties and biocompatibility, whereas insoluble collagen additionally retains the haemostatic and wound healing properties of native collagen.

## Tissue augmentation

Products for tissue augmentation are essentially biocompatible dermal fillers, whereby soluble collagen is cross-linked to produce a semi-permanent, non-absorbable implant deliverable by intradermal injection. Probably the most familiar of all collagen-based products are those used for facial aesthetics. First approved by the US FDA back in the early 1980s, these products are manufactured from bovine dermal collagen. Interestingly with respect to drug delivery, they may also contain lidocaine to provide local anaesthesia as a secondary action at the time of injection.

## Surgical haemostats

During the healthy process of blood clotting, platelets become activated by thrombin and aggregate at the site of injury. Stimulated by the protein fibrinogen, the platelets then clump by binding to the collagen that becomes exposed following rupture of the endothelial lining of blood vessels. Collagen is therefore a natural haemostat and a wide variety of collagen-based products are used in surgery and dentistry to control excessive bleeding or haemorrhage.

## Wound healing

Collagen plays an integral role in the repair and replacement of both hard and soft tissue. The histological and biochemical fate of implanted insoluble collagen has been well studied. Collagen implants first become populated with a number of cell types, primarily those cells

responsible for production of fibrous tissue (fibroblasts) (Anselme *et al.*, 1990). It has been found that new collagen production by fibroblasts is increased when the cells are bound to an extracellular matrix, such as a collagen implant (Postlethwaite *et al.*, 1978). Macrophage collagenases then slowly degrade the implant into amino acids and peptides, such that it is gradually remodelled and replaced by host type-I collagen (Burke and Naughton, 1983). This sequence of cellular response, absorption and remodelling of a collagen implant is classic to the normal wound healing mechanism (Cooper, 1997) and studies have demonstrated that such implants accelerate this natural process (Lepiziger *et al.*, 1985).

The natural healing properties have led to a number of collagen-based dressings and related wound management products for the treatment of chronic and acute wounds, including ulcers (pressure, venous, arterial and diabetic), burns, skin graft/donor sites, traumatic and surgical wounds. Several companies have taken this concept a stage further and developed more sophisticated artificial skin substitutes. Other bioengineered products even contain living human fibroblasts and/or keratinocytes. These and related collagen-containing products for dermal wound healing have recently been subject to comprehensive review by Ruszczak (2003), and Ruszczak and Schwartz (1999, 2000).

## Collagen-Based Localised Drug Delivery Systems

The concept of delivering a drug directly to a specific tissue, organ or region of intended action is receiving increasing attention in the medical and investment community (Patterson and Numerof, 2003; Marcus, 2004). The key benefit of localised drug delivery over systemic therapy is that high concentrations of drug can be maintained at the target site, while avoiding risk of systemic toxicity and associated side-effects.

Many of today's products aimed at localised delivery are device-drug combinations. Examples include pumps for continuous infusion of local anaesthetic (e.g. ON-Q® Painbuster®, **I-Flow Corporation**), medicated stents (e.g. Taxus™ Express™ paclitaxel-eluting coronary stent, **Boston Scientific**) and bone cements containing an antibiotic (e.g. Simplex™ P with Tobramycin, **Stryker Orthopaedics**).

Biodegradable polymers make ideal vehicles for localised drug delivery. Systems based upon synthetic polymers are currently under development and include the SABER™ (**Durect Corporation**) and Biochronomer™ (**A.P. Pharma, Inc.**) technologies. However, collagen offers the advantages of a natural and well established biocompatible material, together with its complimentary wound healing and haemostatic properties. **Innocoll, Inc.** pioneered the use of collagen for localised drug delivery with the breakthrough therapeutic product Collatamp® G, based upon its CollaRx® platform technology.

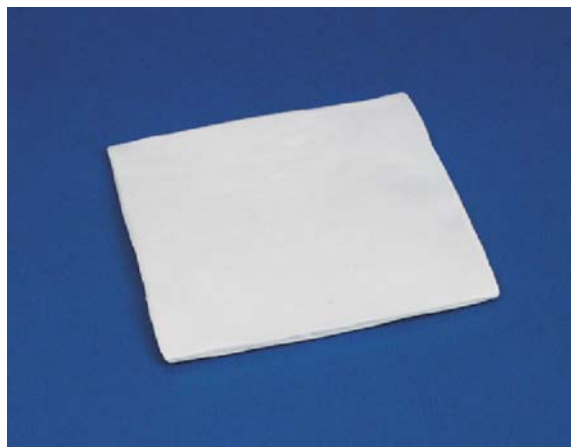


Figure 1 – CollaRx® Sponge (Innocoll, Inc.).



Figure 2 – CollaRx® Membrane (Innocoll, Inc.).

### CollaRx technology

CollaRx is a localised drug delivery system based upon a type-1 collagen matrix derived from bovine or equine Achilles tendon. Products may be formatted either as a lyophilised porous sponge (Figure 1) or as a transparent/translucent sheet (or “membrane”) about 50 µm in thickness (Figure 2). *In vivo*, drug is released by a combination of diffusion and natural enzymatic breakdown of the collagen matrix. This provides both rapid and prolonged release, which has been mathematically modelled (Radu *et al.*, 2002). The matrix itself is fully resorbed within one to seven weeks according to implant location (i.e. well vascularised areas versus bone cavities).

The drug release profile can be further controlled with process modifications to affect porosity, structural/geometric modifications (including the use of laminated systems), formulation additives and/or collagen cross-linking (Radu *et al.*, 2002), some of which are subject to recent patent application (Ruszczak *et al.*, 2003). In addition, classical techniques such as the use of alternative or mixed drug salts with different intrinsic solubility, or incorporation of drug microparticulate systems (Schlapp and Friess, 2003) can be utilised in combination with CollaRx.

Both CollaRx formats can be implanted or applied topically and can accommodate high drug loadings (40-60% w/w) with no known drug limitations or incompatibilities. A wide variety of drugs are known to act locally, including antibacterials, anaesthetics, analgesics, anti-inflammatories, growth modulators, wound healing and anti-scarring compounds, all providing great potential for utilisation of the technology (either as single active or combination products). Collagen implants for relief of post-operative pain and medicated collagen dressings for treatment of infected, slow-healing wounds are of particular interest and already under development.

### Collatamp G

Collatamp G is an implantable type-I collagen sponge impregnated with 2.0 mg/cm<sup>2</sup> of gentamicin sulfate. It is approved as a medicinal drug product in many European countries and is currently marketed under various brand names by **Schering Plough Corporation**. The product is indicated for the surgical treatment and post-surgical prevention of infection in bone and soft tissue and has been clinically proven to reduce rates of infection/re-infection and substantially reduce the average duration of a hospital stay. Pharmacokinetic studies have demonstrated that high local concentrations of gentamicin (up to 9000 µg/ml) are maintained at the wound site for at least 72 hours, while serum levels remain well below the established toxicity threshold of 10-12 µg/ml (Stemberger *et al.*, 1997; Ruszczak and Friess, 2003). *In vitro* experiments have also suggested that such high local concentrations are not only well above the minimum inhibitory concentration (MIC) of gentamicin-susceptible bacteria (MIC ≤4 µg/ml), but also exceed MIC concentrations of bacteria normally considered as gentamicin resistant (Stemberger *et al.*, 1997). Furthermore, the high local concentrations may actually reduce the likelihood of organisms developing resistance.

Following the commercial success of Collatamp G in Europe, competing collagen-gentamicin products such as Septocoll® E (**Biomet Europe**) have since been introduced. However, these are not licensed as medicinal products and make no therapeutic claims, but instead are classified as haemostat medical devices with secondary antibacterial activity.

### INFUSE™ Bone Graft and InductOs™

Recombinant human Bone Morphogenic Protein-2 (rhBMP-2 or dibotermis alpha) has been shown to induce bone formation and is an alternative to bone graft or bone graft substitutes (Geiger *et al.*, 2003). Collagen sponges have been selected as the preferred matrix for local delivery of rhBMP-2 directly to the bone defect, serving to prolong the residence time of the protein and, in some instances, as support for invading host osteoprogenitor cells (Geiger *et al.*, 2003). Two such products have been commercialised: INFUSE™ Bone Graft (**Medtronic, Inc.**) is approved by the **FDA** for treatment of spinal degenerative disc disease; and InductOs™ (co-developed by **Wyeth**, and **Yamanouchi Europe B.V.**) is marketed in Europe for acute fractures of the tibia.

Before implantation, surgeons must first reconstitute the rhBMP-2 powder with sterile water and then apply the sterile solution to a plain type-I purified and cross-linked bovine collagen sponge. Such systems may therefore lack the convenience, homogeneity and dose reproducibility of an impregnated sponge, such as afforded by the CollaRx technology.

### Localised delivery to blood vessels and nerves

**Ark Therapeutics Ltd** has developed a biodegradable collagen collar, which is intended for local delivery of drugs to tubular structures, such as blood vessels and nerves. The lead product (Trinam®) uses the device to deliver a vascular endothelial growth factor (VEGF) gene and is currently undergoing clinical trials to prevent the blocking of veins and arteries that frequently occur after vascular surgery.

**Collagen Matrix, Inc.** has patented (Li *et al.*, 2003) and is developing collagen devices for peripheral nerve regeneration, including the localised delivery of bioactive molecules (such as growth factors) to bridge long nerve defects.

### Conclusion

Localised drug delivery technologies are emerging as a way of targeting the optimum dose of a bioactive substance to precisely where it is needed, rather than distributing excessive and unnecessary drug throughout the body via the systemic circulation. Such products can be significantly more effective and safer than their IV or orally administered counterparts, particularly with respect to unwanted side-effects. Collagen is well established as an excellent biomaterial for medical applications, and offers great potential as a matrix for localised drug delivery. Collagen implants and dressings are not only fully biodegradable and resorbable via natural pathways, but can also provide haemostatic and wound healing advantages over synthetic biomaterials.

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