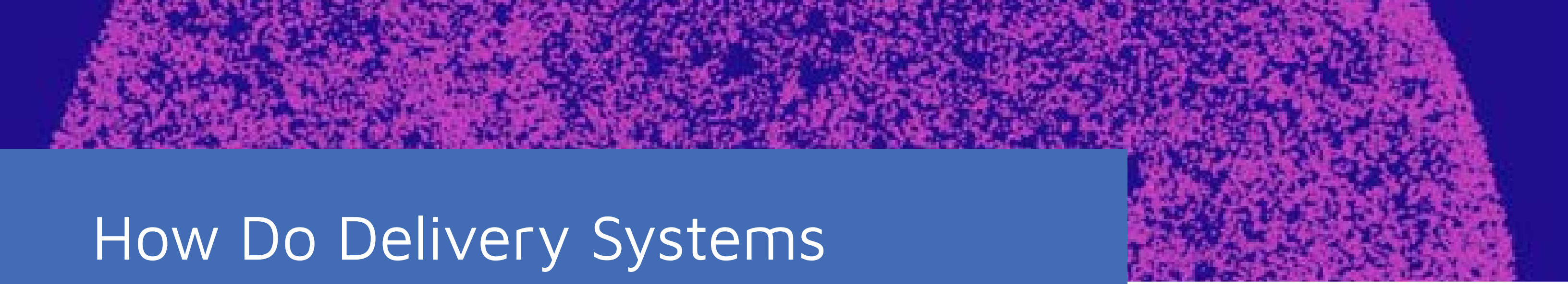

How Do Delivery Systems Impact Cell Therapy

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As medical innovations advance, cells can be used to repair sites of injury or reverse the effects of disease. However, one of the major challenges for the cell therapy field is the lack of a defined delivery system. Although a delivery system can solve numerous problems for cell therapies, the predominant one is the ability to maintain the cells at the target site long enough to have an effect. By comparison, when taking a chemical drug, the patient does not swallow the active ingredient alone. Rather, it is packaged with inactive ingredients that help to stabilize the drug, assist with absorption, and optimize the drug's function. The same type of delivery system (inactive ingredients) is needed for cell therapies.

The goal of any cell therapy delivery system is three-fold:

1. To hold the cells in the target location (organ or tissue)
2. To optimize the therapeutic function
3. Improve safety by blocking migration of the cells to other sites in the body

There is a plethora of materials that can be used for cell delivery, but few can meet all three of those criteria. One category of materials that has been studied extensively for the delivery of cell therapies is hydrogels.

Hydrogels are hydrated, crosslinked polymer networks composed largely of water, as the name implies, often above 95% by weight. Despite their high water content, hydrogels can still possess properties of traditional solid elastic materials such as rubber, meaning they retain a specific physical shape, and will return to that shape even after being deformed by external forces.

However, unlike rubber, the hydrated, porous structure of a hydrogel provides a pathway for nutrients and oxygen to reach living cells contained within, which is critical to their survival and function. The table below provides a few examples of hydrogels used to encapsulate cell therapies.

Examples of Hydrogels to Encapsulate Cell Therapies

Natural	Synthetic
Alginate	Polyglycolic acid
Agarose	Polyethylene glycol
Cellulose	Poly-L-lysine (PLL)
Chitosan	Poly-L-ornithine (PLO)
Collagen	Poly methyl methacrylates
Gelatin	Polyvinylamine
Hyaluronic acid	Polyacrylic acid
Fibrin	Polyvinyl alcohol
	Polyglycolide

Unfortunately, not all of these compounds are suitable as a delivery system for cells. For example, when one of the hydrogels, polyamino acid, breaks down in vivo, it activates the immune system leading to fibrotic overgrowth[1]. In fact, poor interactions between some of these molecules and the surrounding tissue has led to several failed clinical trials[2].

Natural Hydrogels

Hydrogels can be characterized in numerous ways. One of the most common is to group them by the sources of the starting material – natural, synthetic and hybrid. Natural hydrogels include alginate, collagen, and chitosan. Amongst natural

How Do Delivery Systems Impact Cell Therapy (Cont.)

hydrogels, alginate is the most widely used encapsulation material. In fact, it is the most widely studied hydrogel in any category, because it can be produced under physiological conditions and is non-toxic to the encapsulated cells[3]. Due to its extremely rapid crosslinking (also referred to as gelation) rate, manufacturing injectable microspheres with alginate is simple and relatively inexpensive.

Alginate hydrogel microbeads have been used in research and clinically to encapsulate proteins, microbes, vaccines, and cells[4]. It has been commonly used in food and cosmetics in particulate form as a method to increase viscosity[5] and as an excipient in drug delivery[6]. Alginate works well in these orally ingested or topical applications, however, when implanted within the body it evokes a strong immune response, given that it's originally derived from brown seaweed[7]. Improving the purity or otherwise modifying alginate has certainly improved the biocompatibility profile, yet recent attempts to encapsulate a cell therapy in modified-alginate failed because of the continued poor biocompatibility profile[8].

Other natural hydrogels, such as hyaluronic acid (HA) and fibrin, are endogenous to the human body. For example, HA is an essential component of the extracellular matrix and is found throughout the body including in the eye[9]. Fibrin, HA, and a myriad of other hydrogels have slow gelation properties. This complicates their utilization when manufacturing microspheres compared to alginate. However, because many of the slow gelation hydrogels are already endogenous to the body, they tend to have better biocompatibility profiles[10].

Synthetic Hydrogels

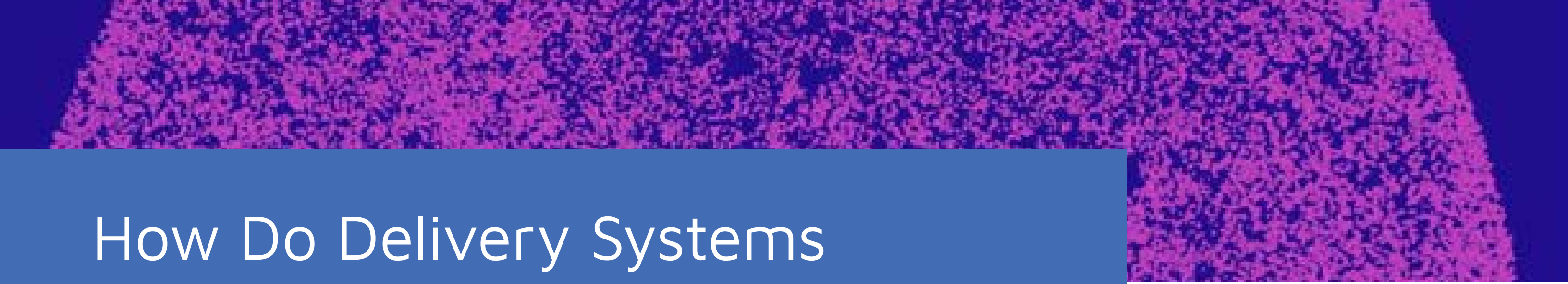
The synthetic category of hydrogels is quite interesting because the polymers are highly controllable from their chemistries and crosslinking modalities. The numerous combinations of crosslinkers and synthetic hydrogels increases the possibility of customization to fit the exact needs of the user. Synthetic polymers can also be manufactured in a more reproducible and controlled manner. Polyethylene glycol (PEG) is one of the most commonly used materials in tissue engineering and is already approved by the FDA for human clinical use in some formats. For example, PEG has been used for decades as a delivery method for drugs[11]. It is easily modified, often by the addition of the Arg-Gly-Asp motif (RGD), which improves cell attachment and improves cell function[12]. PEG is conducive to cell growth and proliferation, and it is tunable allowing control over the stiffness, durability and porosity of the end product[13].

Traditionally, crosslinked synthetic polymers are not generally degraded by enzymes, so they can be formulated to last longer in the body. This is why PEG has recently been targeted as a hydrogel for long-term cell encapsulation strategies for use in chronic diseases such as diabetes[14]. However, degradable synthetic hydrogels are important for bioengineering, especially polyglycolic acid (PGA), which is commonly used to produce tissue scaffolds that can be seeded with stem cells[15].

Hybrid Hydrogels

The polymers used to create hydrogels can be mixed to create unique combinations that collectively are referred to as hybrid hydrogels. There are several definitions for hybrid hydrogels – from a hydrogel consisting of hundreds of physically separate and unique crosslinked nanogels, to a hydrogel made of at least two different groups connected either physically or chemically[16].

In general, hybrid hydrogels are heterogeneous in their chemistry. For example, chitosan (a natural hydrogel) is often added to other hydrogels creating hybrid mixtures, as is polylactic acid (PLA), PEG and polyvinyl alcohol (PVA)[17]. The combination of hydrogels can provide new benefits that working with a single hydrogel entity may not[18]. Specific hybrids such as the combination of PEG, HA and gelatin have been shown to enhance cell attachment, survival and function[19].



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Hybrid hydrogels are important in the maturation of the tissue engineering field including:

- Supporting cell growth and differentiation, including in cell culture[20]
- Serving as the structural components for 3D organ printing
- Creating biodegradable forms that can enhance tissue repair such as growing new skin[21]

Conclusion

While hydrogels are utilized in numerous implantable medical products and are being studied extensively for tissue engineering applications, their use in cell delivery and microencapsulation efforts continues to face barriers. Many of these hydrogels work well for small scale applications such as individual 3D printed scaffolds for cell growth or organs. However, scaling of manufacturing has remained a challenge, as microfluidics and 3D printing are not well suited for large scale manufacturing of "off the shelf" treatments.

Biocompatibility issues and cytotoxic manufacturing processes continue to hinder therapeutic cell function, efficacy, and long-term survival. However, not all hydrogels are created alike, and with the large number of hydrogel chemistries available, along with unique crosslinking approaches and novel manufacturing processes to enable scaled up production of advanced hydrogel products, these challenges can be overcome.

If you are developing a new cell therapy and want to discuss improving its function, safety, or efficacy, contact us today.

Have a Delivery System Issue?

If you believe you have a delivery system issue with a cell therapy currently in development, or you're planning on developing a new cell therapy and want to avoid delivery system issues, learn more about how Likarda's targeted delivery system can help you: **https://likarda.com/biologic-and-cell-solutions/**

Or book a call today with the Likarda team at **816.605.6440.**

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