Bioadhesives and the effects of Nanoparticle Incorporation:

By:

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Abstract:

This paper reviews bioadhesives, the adhesives used for medical applications. Specifically, it focuses on the use of hydrogels as they are a class of polymers commonly used for many medical applications such as wound dressings, bioelectrodes, and targeted drug delivery systems. With such wide spread uses of bioadhesives, much research is being done on ways to both improve the adhesives' mechanical properties while also investigating ways to make the adhesive more effective for the medical device. With these goals in mind, the incorporation of nanoparticles into adhesives is an area that has recently received a lot of attention, and is another area that the review focuses on.

Introduction:

From envelopes, furniture and everyday tape to aircrafts and automobiles, adhesives are all around us and have become increasingly important as technology has continued to develop. Their versatility and ease of use make them valuable and of great interest. One use of adhesives that is a little less obvious than others is their use for medical purposes. However, this has recently become the subject of increasing research as the demand for improved and more efficient medical and surgical devices continues to grow. In terms of medical applications, adhesives have been used in a variety of applications, from the basic bandages and wound care to ostomy appliances and medical diagnostics. In fact, these adhesives have been classified as their own group known as bioadhesives. A bioadhesive is a polymer that serves to adhere two materials together for an extended period of time, one of which being biological in nature and often has mucus as a substrate (Lee and Tsao 2006).

While the term bioadhesive encompasses many different types of polymers, hydrogels are the polymer that this review will focus on. The review will start off with a brief discussion of hydrogels and how their physical and chemical properties make them favorable for biomedical applications. The review will then move on to discuss three uses of hydrogels for biomedical purposes; wound care, biomedical electrode applications, and a new and developing field, targeted drug delivery systems. With such wide spread uses of adhesives, it isn't a surprise that much of the recent research focuses on ways to improve their mechanical properties and overall effectiveness. One such method that has gained significant attention is the incorporation of nanoparticles into the adhesives. This review will focus much of its attention on how the addition of nanoparticles affects the adhesive. It will show that the addition of nanoparticles not only increases the mechanical strength of the adhesive but also has the ability to add properties and characteristics to the adhesives that can serve to make the overall medical device more effective. Throughout, the review will highlight and focus around the general theme of the importance that surface chemistry has in determining the properties and function of bioadhesives.

1. Characterizing Hydrogels:

In order for a polymer to be an effective bioadhesive, certain properties are necessary such as strong hydrogen bonding groups, high molecular weight, flexible chains, and surface characteristics that allow for the spread onto biological surfaces such as mucus. (Lee and Tsao 2006) Hydrogels are thus a class of polymers that have proven to be a valuable bioadhesive as they exhibit the properties above along with many others. A hydrogel is a 3-D polymer network that contains water. Because of this, it has the unique property of swelling in water while maintaining the structure of the polymer and not dissolving. Furthermore, the amount of water that the hydrogel takes up is something that can be controlled by changing properties of the hydrogel such as the cross-link density, pore size, and molecular weight. The ability to easily regulate these properties, and thus change the nature of the polymer, makes hydrogels very valuable as bioadhesives because of how versatile they can be. For example, the equilibrium water content, ECW, is defined as the amount of water that the hydrogel has taken up after immersion in an aqueous solution and equilibrium is reached. In applications such as wound dressings, where we want the dressing to adhere to the skin, it is desirable to have water content in the hydrogel below the ECW. In contrast, for an application like contact lenses, the water content is usually kept at the same level as the ECW (Skelhorne and Munro 2002). Furthermore, hydrogels are favorable for medical applications because based on their surface chemistry and adding different functional groups, such as carboxylic or amine groups, to the polymer, they develop the ability to quickly respond to environmental stimuli, such as changes in temperature, light, pH etc. This allows for changes in the amount of swelling and other physical parameters to be at the control of researchers, as shown in Figure 1. Along with the easy control of adhesive parameters and response to stimuli, many hydrogels are biodegradable considering they are primarily held together by secondary molecular forces and hydrophobic interactions (Jagur-Grodzinski 2009). An important property for any medical system that is going into the human body, because you want to make sure the substance will not be traveling through the body indefinitely. Therefore, the ability to know and control the bio-degradability of adhesives makes hydrogels especially favorable for targeted drug delivery. Lastly, and perhaps most importantly, hydrogels are biocompatible because of how similar their matrix structure is to that of the extracellular matrix. (Datta 2007) Examples of hydrogels that are often used in bioadhesives include polymers such as polyethylene glycol, polyethylene oxide, and polyAMPS hydrogels.

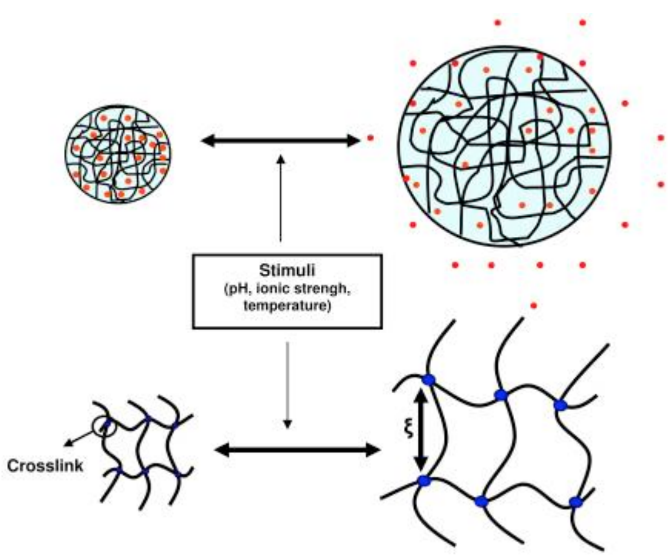

Fig 1- image depicting the effect of environmental stimuli on hydrogels. – taken from Serra et al. 2009

1.2 Mechanisms of Adhesion

It is important to note that in essence bioadhesives do not differ significantly from conventional adhesives and in fact utilize the same basic mechanisms of adhesion as the conventional adhesives. Therefore, before discussing specific applications of bioadhesives, it is important to first understand the mechanisms of adhesion, and the different ways that polymers adhere to biological structures. The mechanisms of adhesion can be broken down into four mechanisms: electronic, adsorption, diffusion, and mechanical (Roy and Prabhkar 2010). While the primary mechanisms are thought to be adsorption and diffusion, more often than not, multiple mechanisms work together to create adhesion, as some mechanisms are not possible without others.

The adsorption mechanism explains the adhesion as a result of a combination of covalent bonds and secondary forces such as Van der Waals, dispersion forces, and hydrogen bonding, as depicted in Figure 2. Thus the surface chemistry of the adhesive becomes very important in determining what the adhesive will bind to and how well. This surface bonding is thought to be a primary mechanism because anytime two materials are in close proximity, secondary bonds will form to some extent, and considering that close proximity is necessary for all of the mechanisms, these secondary bonds end up occurring in almost every mechanism, at least to some extent.(Palacio and Bhushan 2012 & Peppas and Sahlin 1996) Diffusion is when there is interpenetration of the polymer chains as a result of the concentration gradient across the interface, resulting in adhesion. This mechanism primarily occurs when the polymer has long, lose, flexible chains that are capable of movement and have the ability to diffuse into gaps and pores of the material it is adhering to. Furthermore the two phases have to be compatible, having somewhat similar surface chemistry. This can be determined by looking at the solubility parameter and the Flory interaction parameter; two parameters that can be used to determine the compatibility of polymer blends. In this situation, the difference in the solubility parameter should be approaching zero or the materials should have a Flory interaction parameter that is less than half. While many of the other mechanisms are thought to primarily just initiate adhesion, the diffusion mechanism is thought to be the mechanism that upholds the adhesion between the materials. In the case of bioadhesives, it can be explained as the polymer chains of the adhesive diffusing into the mucus layers, and the chains of the glycoproteins diffusing into the polymer matrix because of the concentration gradient. This mechanism can be affected by many factors, such as the swelling capacity, for example. A polymer with a high swelling capacity will experience a stronger bond because it will have greater chain mobility, thus increasing the penetration. (Palacio and Bhushan 2012 & Peppas and Sahlin 1996)

The electronic mechanism is explained as being a result of the attractive electrostatic forces between the two materials such as the biological layer and the bioadhesive material due to electrons transferring between the two, creating a double layer of electrical charge at the interface. The electron transfer is a result of trying to achieve a balance in the Fermi levels, or the potential energy of the electrons in the highest occupied orbital. This can be important in bioadhesives because under most physiological conditions, the polymer (adhesive) and biological surface, such as the mucin layer will typically have opposite charges. (Kharenko, Larionova, and Demina 2009) Lastly, the mechanical mechanism states that the adhesion comes about because of the interlocking of the adhesive to a rough surface. The interlocking can be due to the fact that rough surfaces result in an increased surface area and thus increased interaction area or points of contact. (Roy and Prabhkar 2010) Another explanation of the adhesion can be that a rough surface allows for a liquid adhesive to fill in the nooks of the polymer but upon solidification of the polymer, it resists removal. This concept becomes important later when looking at the effect nanoparticles have on adhesives because nanoparticles have a tendency to increase the roughness of the surface.

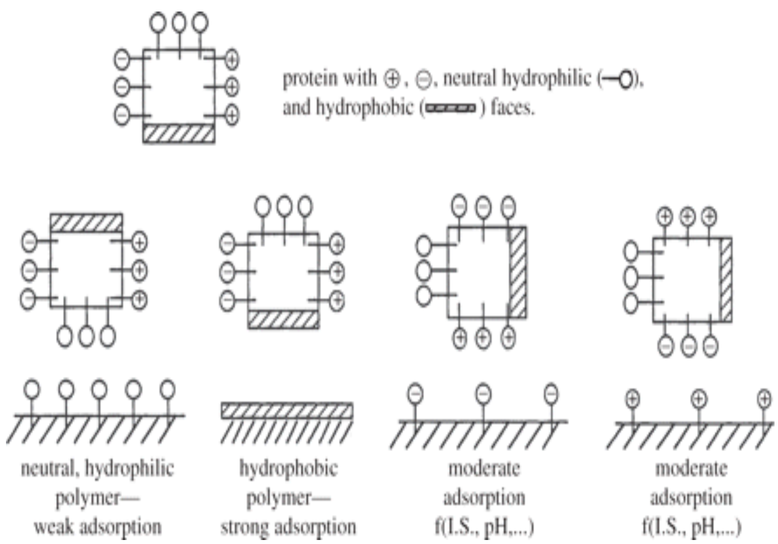

Figure 2—taken from (Palacio and Bhushan 2012) Shows the effects different surface chemistries can have on adhesion

Another important concept in terms of adhesion is known as wetting. Wetting is the ability of an adhesive to spread and thus develop close contact with the substrate, such as a biological layer. Wetting is not really a mechanism; rather a measure of the interfacial energy that results from creating the new interface between the adhesive and biological surface, the thermodynamic work of adhesion. Certain parameters can be used to determine if adequate spreading will occur such as the contact angle and the spreading coefficient. Adequate spreading occurs in cases were the contact angle is zero and the spreading coefficient is positive. The thermodynamic work of adhesion is determined by taking the surface energy of the new interface that is formed (between the polymer and body layer) and subtracting the sum of the surface energies of the two original interfaces (the polymer and liquid; and the liquid and layer of body) (Roy and Prabhkar 2010) The surface energy of the new interface between the polymer and body layer is often a result of the mechanisms described above.

When discussing bioadhesives and their adhesion mechanisms, it is important to mention the specific process of adhesion to cells. This is particularly important to understand targeted drug-delivery, which is explained later in the paper. When the bioadhesive material is introduced into a living organism, the cells do not automatically attach to the adhesive. Instead, the adhesive is first covered by a layer of proteins that will then be displaced by various extracellular matrix proteins such as fibronectin, fibrinogen, and albumin. Furthermore, the surface charge of the gel, whether it is hydrophilic or hydrophobic, plays a big role in cell adhesion. Terminating groups such as CH_3, which are hydrophobic in nature, will have poor cell adhesion characteristics and can denature, or structurally change the conformation of proteins, such as fibronectin, a ECM protein that plays a key role in cell adhesion. Alternatively, hydrophilic functional groups such as (-OH) exhibit high cell adhesion as they do not cause denaturing of ECM proteins in the cell. Because hydrophilic groups can better adhere to the cell membrane, they have the ability to form focal adhesions, or assemblies and clusters of different cell structures that come together due to certain stimuli and that are necessary for cell signaling, or cell communication, to occur. (Palacio and Bhushan 2012) This becomes important in targeted drug delivery systems because creating these focal adhesion points for cell signaling and thus creating a pathway for communication with the cell is vital for controlling cell behavior.

2. Applications of Bioadhesives:

2.1 Wound dressings

The most common use of adhesives for medical applications is their use in wound healing, most notably the common bandage. This is also an application where the properties and benefits of hydrogels can really be seen. One of the major issues that originally came up with wound treatments was that the high levels of moisture would collect under a wound dressing, causing skin maceration. Acrylate-based adhesives originally seemed to be a solution to this problem. However, the acrylate-based adhesives posed certain problems; first, many people were allergic to them, and second, these adhesives would cause discomfort on removal, especially from sensitive skin. A better solution therefore was found in hydrogels. The properties of hydrogels, namely the combination of a polymer network, water and plasticizers, as well as having the ability to absorb excess water because of the hydrophilic nature of the adhesive, allow for effective adhesion for wound dressings. Furthermore, the above problems are avoided, for example the highly plasticized matrix of the hydrogel allows for easy removal from the skin with little pain, even from sensitive skin. (Skelhorne and Munro 2002) These favorable properties have allowed for hydrogel wound dressings to enter into the commercial market, including products such as Smith and Nephew's *FlexiGel Strands* and 3M's *Tegagel*. This example not only shows the use of adhesives in medical applications but also highlights some of the key properties of hydrogels that we will see throughout the rest of this paper as being reasons for why hydrogels are often chosen as the class of polymers for bioadhesives.

2.2 Bioelectrodes:

Another important use of adhesives in the medical field is their use in biomedical-electrode applications, or bioelectrodes. Bioelectrodes play a huge role in the medical field and are extremely important for delivering charge to the body and keeping track of neural activity. An example is appliances that monitor heart signals. Hydrogels are important for these medical tools as they serve a dual function of providing an electrical pathway to the body while also attaching the electrode to the skin. (Skelhorne and Munro 2002) Bioelectrodes typically use conducting polymers as these have proven to be a softer interface as compared to metal electrodes. However, conducting polymers typically have poor mechanical properties. Therefore, the incorporation of hydrogels into the conducting polymers has become a recent interest as it can increase the mechanical properties while still maintaining the conducting property. Many patents have recently been released on these hydrogel blends that can be used for bioelectrode applications such as patent 5087242 for a *hydratable iontophoretic bioelectrode.*

2.3 Targeted Drug Delivery:

Lastly, one of the most interesting uses of bioadhesives is their use in targeted drug delivery. Currently, one of the major issues facing targeted drug delivery is the difficulty that the drugs have in adhering to the mucus layers of the body. Mucosal tissues have moist surfaces and line the walls of many organs such as the gastrointestinal (GI) tract. They serve the purpose of acting as barriers against foreign substances while regulating the entry of substances such as nutrients and antigens into the body. However, the moist surfaces and constant movement of the mucosal tissues make retention of the drugs at a specific site difficult. (Kharenko, Larionova, and Demina 2009) The difficulty in retention causes a low flux of drug absorption. This particularly becomes a problem for orally digested drugs because of the mucus barrier in the intestinal tract. However bioadhesives, which attach a drug carrier system to a specific biological location, namely the GI tract, allow for the possibility of enhancing drug absorption by the mucosal cells through the process described above of cell adhesion. The effect is not small. In fact it was found that with microsphere targeted drug delivery systems, the incorporation of bioadhesive polymers actually increased the microsphere uptake from 5.8% to 66.9%. (Laulicht 2005) While the release of drugs from the delivery system can be controlled by different mechanisms such as diffusion controlled delivery systems, chemically controlled delivery systems or swelling controlled delivery systems, (Serra, Doménech, and Peppas 2009) the better retention at the site of absorption due to adhesives allows for the possibility of the drug being released at the site for an extended period of time and would serve to enhance all three of the mechanisms (Roy and Prabhkar 2010)

When bioadhesives are incorporated, the association of the drug and the mucus is strongly increased (Behrens et al. 2002). Targeted drug delivery systems using adhesives therefore have the unique property of having a higher absorption rate of the drug due to the tight and close contact of the drug delivery system to the mucus layer. Many researchers hope that this will allow for increased bioavailability of molecules such as peptides that currently have a very shallow concentration gradient. Drugs that have narrow absorption windows, meaning that there is a very limited time in which the body can absorb the drugs, would be improved by this system where the drugs will closely adhere to the mucosal cells for an extended period of time.

Furthermore, because so many properties of hydrogels can be controlled such as the pore size, the nature of the matrix, the level of environmental stimuli necessary to cause structural changes to the gel, etc, hydrogels offer the unique ability for a controlled drug delivery. This would mean that pharmaceutical scientists would have the ability to control at what rate the drugs should be delivered to the specific site (Datta 2007). For example, hydrogels such as poly(ethylene glycol) or PEG hydrogels are normally used in drug delivery systems because of how they can be controlled by changes in pH values. At low pH values, specifically, at pH values below that of the pKa of acrylic acid, 4.35, the PEG chain forms a hydrogen bond with carboxylic groups of the acrylic acid molecule. The additional hydrogen bonds make the drug diffusion through the polymer more difficult. Alternatively, at higher pH levels, the carboxylic groups get ionized, breaking hydrogen bonds, and causing swelling because of the electrostatic repulsion of the ions. The swelling can ease the process of diffusion of a drug out of the polymer matrix. Therefore, the specific location of delivery of drugs and at what rates can be controlled based on pH levels as depicted in Figure 3. Thus hydrogels prove to be an effective choice for drug delivery system because they allow for two important characteristics, controlled release rates as a result of certain environmental stimuli, and a localized drug delivery for an extended period of time. (Serra, Doménech, and Peppas 2009) This has significant medical implications because instead of taking drugs with high concentration frequently, a lower concentration would suffice and one would need less frequent dosages. Thus bioadhesives have opened the door to optimizing the usefulness of the drugs while reducing the negative side effects associated with over dosage.

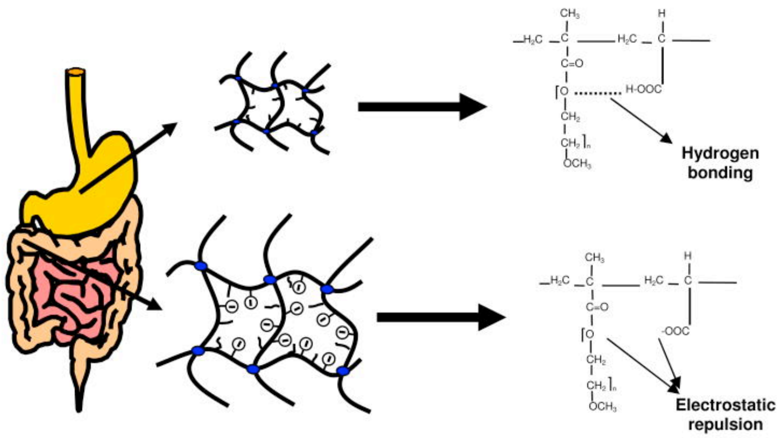

Figure 3: depicts how pH can control where the drug will be released by effecting the surface chemistry of the hydrogel. Figure received from Serra et al. 2009

3. Effects of Nanoparticle incorporation on adhesives

As adhesives continue to show an increasing importance in the development and enhancement of technology both inside and outside the body, continued research is being done on ways of making adhesives more effective. Especially for situations that vary from standard conditions such as high humidity, moisture, or higher temperatures, conditions which in the past have proven to decrease the strength of adhesives. However, many traditional methods for improving the strength of epoxies and other adhesives such as certain treatments and chromating can be expensive. (L. L. Zhai, Ling, and Wang 2008) One area where increased research is being done is in nanotechnology. It has been known for some time that in most general adhesives, the addition of nanoparticles have proven to greatly increase the strength of the adhesives.

Nanoparticles serve to be cheap and simple way to modify the physical and chemical composition of adhesives, making them stronger and more durable. (L. L. Zhai, Ling, and Wang 2008). For example, in a series of pull of tests conducted with varying amounts of nanoparticles, it was found that 2% nano- aluminum oxide increased the strength of the epoxide 5 times. (L. Zhai et al. 2006) Therefore it was not surprising that the addition of nanoparticles to bioadhesives showed similar results and was extremely beneficial due to the unique properties of nanoparticles. This paper will highlight the role nanoparticles can play, particularly in, first increasing the strength of an adhesive; second, adding characteristics to the adhesive which allow the nanoparticles to optimize the function of the medical device being used; and lastly, the paper touches upon some of the negative effects that nanoparticles can have.

3.1 Increasing Mechanical Strength

First, much like how researchers found that nanoparticles can increase the strength of epoxy adhesives on steel, nanoparticles have the ability to increase the strength of bioadhesives. The ability of nanoparticles to increase the mechanical strength of a bioadhesive can be broken down into the physical changes that the nanoparticles cause in the adhesives as well as chemical changes. One of the most unique properties of nanoparticles is their large surface area per unit gram or surface area to bulk ratio. (Meguid and Sun 2004). The increased interaction area that thus results from this property of nanoparticles along with the fact that nanoparticles can fill in any microscopic gaps that are present in the adhesive ((Meguid and Sun 2004) allows for more points of adhesion, thus increasing the strength. (L. Zhai et al. 2006). As briefly discussed above, one of the main ways hydrogels adhere is through the mechanical factor, (Roy and Prabhkar 2010) thus increasing the roughness by adding nanoparticles would serve to increase the strength of the bioadhesive. Similarly, another physical change that nanoparticles can causes is increasing the crosslink density, which can also serve to increase the strength of adhesion. This was found to be the case in a study were nanoparticles were added to bandages. In that study, clay nanoparticles were added to create what is known as a “snake and cage” structure where the linear polymers, or bioadhesive (snakes) are ‘caged’ in by a nanocomposite structure. This increase in the cross-link density proved to increase the adhesive nature of the bandages (Extance 2011). See Figure 4.

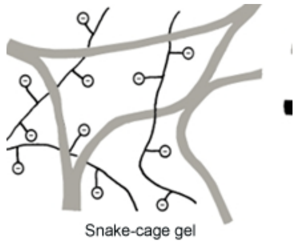

Figure 4: Snake and Cage configuration that results with addition of nanoparticles. Taken from (Extance 2011)

However, both of these physical characteristics play somewhat of a minor role in increasing the strength, as the surface area of the adhesive is not changed sufficiently to be the only impacting factor; meaning that chemical factors also play a significant role. Mainly, nanoparticles have the ability to give rise to polar functional groups such as carboxyl group because of the properties of the nanoparticles (L. L. Zhai, Ling, and Wang 2008). This chemical modification plays a significant role especially in bioadhesives used for targeted drug delivery. It has been found that hydrogels with a high degree of carboxylation have an enhanced ability to bind to mucus lined tissues due to increased hydrogen bonds (Laulicht 2005) as explained by the absorption mechanism of hydrogel bioadhesives (Roy and Prabhkar 2010).

3.2 Enhances certain properties of adhesives

Along with being a more economic and environmentally friendly way of strengthening adhesives, the addition of nanoparticles have proven to be a more favorable route for increasing the mechanical strength of adhesives, because the nanoparticles can also serve to add different properties to the adhesives which can play a significant role in improving the mechanical device. Specific nanoparticles are known for having unique properties, and by selecting the correct nanoparticle, such as silver nanoparticles, for example, one can add certain properties to the adhesives.

One of the biggest examples of adding necessary properties to bioadhesives is the role nanoparticles can play in bacteria inactivation, particularly through the addition of silver nanoparticles. A common problem with the use of adhesives for medical applications is that they can serve to be a hot bed for bacterial growth. This is referred to as a biofilm, the aggregation of micro-organisms that may form on the adhesive. The accumulation of bacteria can be extremely dangerous as they have the potential to cause diseases such as cystic fibrosis and endocarditis. (Palacio and Bhushan 2012) Therefore, silver nanoparticles are often used because of their own effectiveness in bacterial inactivation (Oldenburg 2012). Silver nanoparticles are often chosen because of their low toxicity to mammal cells, higher toxicity towards microorganisms and for having the unique ability to destroy bacteria by suppressing the activity of membranous enzymes and destroying the permeability of the bacterial membranes. The silver cations have the ability to displace native metal cations from the enzymes, thus altering the function of the membrane enzymes. Furthermore, the silver ions have the ability to inhibit oxidation of molecules like glucose and glycerol in the bacteria. (Li et al. 2010) In a recent study conducted by Lee and Tsao it was found that the addition of nanoparticles could lead to significant E.coli inactivation. (Lee and Tsao 2006). Therefore, the addition of nanoparticles can play a major role in adhesives being used for the body because, without the nanoparticles, adhesives have the ability to cause more damage than good when introduced to the body. Bacterial inactivation is an important property for all three of the bioadhesive applications that this paper discusses, but particularly for wound dressings.

Another key property that nanoparticles can add to adhesives is increasing the electrical conductivity of the adhesive. This again is due to the particular properties of the nanoparticle that is chosen. One of the main properties of silver nanoparticles is their electrical and thermal conductivity. Thus they are often added to composites as they make adhesives more conductive. (Oldenburg 2012) Particularly with hydrogels, the addition of silver nanoparticles can in fact decrease the electrical resistance of the gels by 2 orders of magnitude. An increase in nanoparticles could therefore improve the electrical conductivity of the adhesives; a property that becomes especially important in applications such as the biomedical-electrode applications where the adhesives are not only necessary to adhere the electrode to the skin, but also need to be able to provide the electrical pathway between the two. This example shows how nanoparticles can play a role in making the adhesives more useful and in doing so, make the medical equipment more effective overall. (Lee and Tsao 2006).

The last property that this paper touches upon, and perhaps the most important for adhesives used in targeted drug delivery, is that nanoparticles can offer protection to molecules such as peptides and other sensitive molecules, against degradation from the intestinal tract and lumen. This example highlights a different use of nanoparticles. Rather than the incorporation of nanoparticles into adhesives, polymer nanoparticles are used to encapsulate the drugs as shown in Figure 5. The encapsulation by adhesive nanocapsules serves as a form of protection while still offering all the benefits of adhesives previously described. Currently, while peptides are extremely useful for drugs because of their high specificity and biological activity, they are often unable to be used because of their low stability, hydro-philicity, low solubility, and rapid clearance from the body. In fact, one of the major problems that many orally administered drugs currently face is that many molecules experience enzymatic and hydrolytic degradation in the tract ,and furthermore, are limited in their ability to be effective in a targeted drug delivery because of their poor transport properties across mucosal barriers. This is an area where the use of nanoparticles can be of great benefit, as they can provide a level of protection to the sensitive molecules. (Behrens et al. 2002) The use of bioadhesives solve some of the problems associated with the poor absorption of peptides by creating extremely close contact with the mucosal barrier, (Roy and Prabhkar 2010) however, utilizing nanotechnology and having these polymers encapsulate the drugs in a nanocapsule can further enhance the uptake by surrounding the peptides with nanoparticles that can counter the unfavorable properties of peptides. The nanocapsules serve the duel purpose of first having the ability to offer a more favorable surface chemistry to the drug, allowing better absorption, and second, the smaller size allows for better diffusion and entry into small areas and junctions. An increase in size correlates with a decrease in diffusion across the mucin layer, capping off at 500 nm. Thus nanoparticles prove to be incredibly valuable for targeted drug delivery systems to be effective. (Yang et al. 2006) For example, incorporating a *Cyclosporine A* peptide, known to have poor absorption due its surface chemistry, in a polymeric nanoparticle formulation can cause the blood circulation time of the peptide based drug to be improved significantly. (Yang et al. 2006)

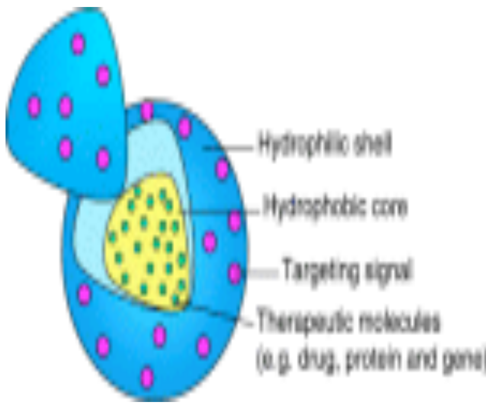

Figure 5- depiction of nanocapsule used to protect drugs such as proteins cause of favorable surface chemistry. Taken from Yang et al. 2006

3.3 Negative Effects

While nanoparticles add many capabilities to adhesives and to the medical devices in general, it is important to realize that there is a limit to what percent should be added to the adhesive before they begin to have the opposite effect and decrease the mechanical strength of the adhesives. This is caused by a couple of factors, first as explained above, nanoparticles increase the cohesive strength of adhesives by adding more points of contact by filling in the gaps in the matrix. Once all the gaps are filled, the additional particles are no longer serving a purpose. However, the additional particles can in fact decrease the strength of the adhesive by causing a strain in the polymer matrix and thus debonding the hydrogen bonds and other secondary bonds by changing the conformation of the polymer. It has been found that for most adhesives any percentage filling above a 10% by weight amount of nanoparticles can lead to a decrease in the mechanical strength of the adhesive. (Meguid and Sun 2004). Another issue that nanoparticles can cause when added to the adhesive has to do with the wetting mechanism of adhesion described earlier in the paper which states that closer the adhesive can get to the structure the better its adhesion will be. For this reason, especially in hydrogels, increased swelling is preferable because it causes more points of contact between the two materials and allows for a more intimate bond. (Peppas and Sahlin 1996) However, in a recent study, it was found that the addition of nanoparticles could in fact reduce the amount of swelling in composite hydrogels. This is thought to be due to the fact that the nanoparticles can block the pores that play a vital role in the swelling. (Lee and Tsao 2006). Therefore, it is important to realize that a balance needs to be maintained in terms of figuring out what amount of nanoparticles is necessary to perform functions such as increasing the electrical conductivity and inactivating bacteria, while still keeping in mind that there is a limit to the amount that can be added before the mechanical strength of the adhesive is sacrificed.

Increasing the Mechanical Strength	Additional Properties to the adhesive	Negative Effects
Physical: -Enhances the cross-linking (Snake and Cage structure) -Increased points of adhesion by filling in the gaps in the gel. (Mechanical Theory) Chemical: - Gives rise to more polar groups such as carboxyl groups. (adsoprtion theory)	-Increased electrical conductivity - Bacterial inactivation -Protection of molecules such as peptides from degradation in the gut.	-After a certain point nanoparticles can in fact have the opposite effect. -- once all the pores are filled in the nanoparticles aren't adding anything. -Specifically with hydrogels the nanoparticles can reduce the swelling. (diffusion theory)

Table 1: Summary of effects of nanoparticles on adhesives.

Conclusions:

While the use of adhesives for medical applications is not as obvious as their use in many other well-known applications, the use and importance of bioadhesives is anything but small. This review took a look at the functions and properties of a specific type of bioadhesive, hydrogels, and how the surface chemistry and the ability to alter the surface chemistry can play a major role in the function and properties of the hydrogel. The paper focused on the use of hydrogels in wound care, bioelectrodes, and targeted drug delivery in order to show the broad range of applications of hydrogels. The paper then focused on a new area of research, adding nanoparticles into adhesives to see how the properties of the adhesive can be enhanced or changed. While many far-reaching advancements have been made in this area, especially in the area of targeted drug delivery, it is clear that there is still a lot of work to be done. Future directions could include studies that perhaps worked to use bioadhesives for cancer-treatment. The incorporation of nanoparticles would allow for increased control and imaging from outside the body. These properties could be of great importance because targeting and imaging the tumor without negatively affecting the rest of the body, the way chemotherapy does, is the direction researchers hope to go in cancer treatment.

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