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INNOVATIVE USES OF ETHYLENE VINYL ACETATE POLYMERS FOR ADVANCING HEALTHCARE

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ABSTRACT

Ethylene vinyl acetate (EVA) has a long and successful history of innovation in medical packaging, medical devices, and pharmaceutical applications. In fact, EVA has been an innovative force in those applications for over 35 years and continues its innovation legacy through enablement of solutions in areas of ever increasing challenges. New solutions are required for continually improving patient healthcare. This paper will examine the evolutionary role of EVA innovation in diverse applications ranging from its early use in parenteral applications for delivery of life saving medications to cryogenic storage bags for stem cells used in the emerging field of cell therapy to controlled release of small molecule active pharmaceutical ingredients (API) and finally as an innovative gastroretentive delivery vehicle for controlled release of large molecule therapeutics for the high growth field of biologics and personalized medicine. It is the simplicity of the molecular architecture of EVA which leads to its ability to create innovative solutions to some of healthcare's most challenging and complex problems. Case studies will provide an illustration of each of these applications.

INTRODUCTION

We are living at a time when healthcare is undergoing exciting new developments and innovations. The medical device industry and the pharmaceutical industry are developing innovative products which provide for better patient care and improved quality of life. Also, and of no surprise, the two industries have applications in common as well as areas of uniqueness. For example, an intravenous (IV) bag containing drugs illustrates where a medical device and pharmaceutical product work together in support of patient needs. For an application where a medical device and a pharma product work independent of one another, one may consider a sleep apnea device versus a tablet containing an API. Here, the sleep apnea device does not contain a pharma product

and the tablet (pharma product) is not part of a medical device.

Ethylene vinyl acetate (EVA) has been used for many years in both industries and has historically been an important enabler of innovation. Today and going into the future, EVA is enabling innovation in emerging fields like cell therapy and controlled release of biologics. In the following sections, this paper provides an overview of EVA polymers followed by three case studies demonstrating EVA's innovative use for advancing healthcare.

INTRODUCTION TO EVA POLYMERS

Ethylene vinyl acetate copolymers are made using two monomers: ethylene and vinyl acetate (VA). The polymerization may take place by either autoclave or tubular reactors. Figure 1 illustrates the polymerization (1).

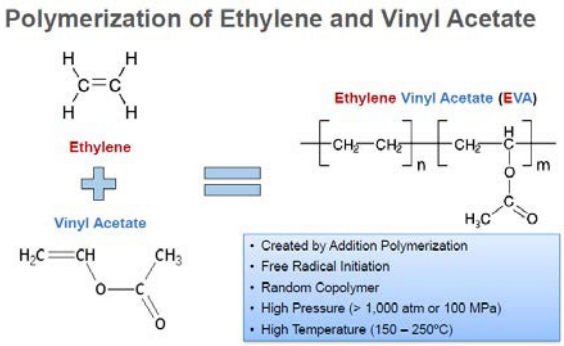

Figure 1. Polymerization of EVA

The percent of VA incorporated into the polymer backbone can vary from 0 to 40. At 0% the polymer is essentially low density polyethylene. As VA content is increased, the polymer becomes more flexible and transparent. EVA polymers with VA content higher than 40 percent tend to become a handling challenge from a commercial pelletized perspective. The melting point of the EVA is influenced by the vinyl acetate content. As VA content increases, melting point decreases. Figure 2 illustrates the linear relationship (2).

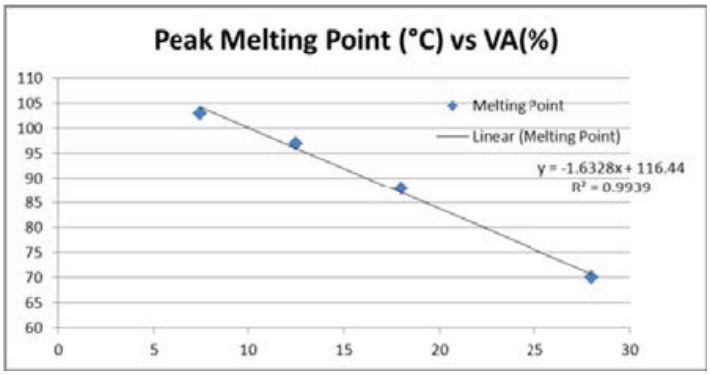

Figure 2. Melting point versus VA%

EVA has been commercially used for over 35 years in medical device applications. Figure 3 illustrates some examples following the commercial launch of EVA in 1960.

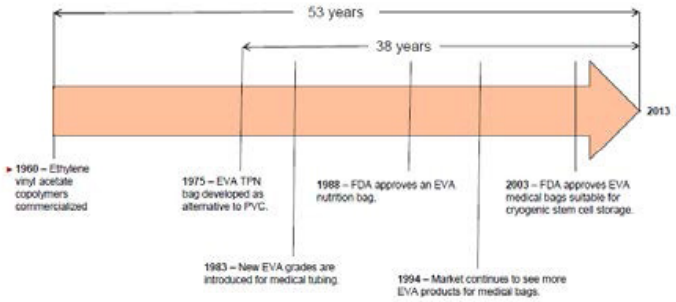

Figure 3. Timeline of EVA in Healthcare

CASE STUDY 1: IV THERAPY AND EVA

IV therapy is when medicine or fluids are infused directly into a vein. The majority of IV therapy is for delivery of nutrition, sodium chloride, potassium chloride or sucrose. Approximately 80% of hospitalized patients receive some form of IV therapy. In 1950 Dr. Carl Walter, a Harvard surgeon and pioneer in kidney transplants invented the plastic medical bag (3). This enabled plastic bags to replace glass bottles thereby reducing breakage, less weight during shipment and safer handling during dangerous but urgent situations such as a battlefield or natural disaster where patients need immediate attention and are often being carried away with IV lines in. It is difficult to estimate how many soldiers' lives have been saved through the use of rapidly available plastic IV bags and their contents. In 1969 Dr. Stanley Dudrick at the University of Pennsylvania (4) conducted work that ultimately led to the foundation for total parenteral nutrition (TPN).

In the 1970's and 1980's alternatives to PVC plastic IV bags were sought because the phthalate plasticizer, commonly used in PVC, was leaching into nutrition fluids including the lipid components.

Case Study 1 – EVA Innovation

EVA was found to be an excellent solution for TPN bags. EVA offered the ability to have high flexibility without having to incorporate plasticizers. The simplicity of the molecular architecture enabled said flexibility by increasing the content of vinyl acetate comonomer. The higher VA content, e.g. 18 to 28 percent, also provides excellent transparency. Film of high quality was possible due to EVA's excellent rheology. Of additional importance was EVA's ability to be welded for construction of the bags. For IV nutrition bags, EVA provides excellent biocompatibility as measured by USP Class VI testing.

Case Study 2 – Cell Therapy and EVA

This case study will be limited to the area of stem cell therapy. It is a very large and promising area for treating diseases such as: Parkinson's, diabetes, ALS, and heart disease. Successful therapies for these diseases enable treatment of between 100 million to 150 million Americans (5). Consider the untapped power of an embryonic stem cell. This is a cell that can differentiate into any type of body tissue. Researchers and medical professionals store stem cells at cryogenic conditions so that they are available when needed. Consider the lifesaving situation in a 2 year old toddler from the UK who received frozen stem cells. She was facing a rare life threatening form of acute myeloid leukemia having a 30% life expectancy. She was given a transplant of frozen stem cells which were originally located in Tokyo. She made a complete recovery. Which type of medical packaging is used for storage of these precious cells? EVA is used as a polymer for these storage containers.

Case Study 2 – EVA Innovation

Stem cells are stored at temperatures of -156C to -196C (6). Various materials have been used for storage bags. They include EVA and fluorinated ethylene propylene (FEP) or polytetrafluoroethylene (PTFE). In the USA, EVA is the material most commonly used for cryocontainers (7). FDA 510K clearances illustrate EVA's use. If one looks at the simple molecular structure of EVA it is observed that EVA can achieve remarkable diversity of properties due to its two monomer design, ethylene and vinyl acetate. The reactivity of each monomer is such that the overall composition of ethylene to VA content in the final copolymer is approximately the respective feed ratios . Therefore, one can vary flexibility and glass transition temperature, Tg by varying the vinyl acetate content. For high VA content grades, e.g. 28%, a glass transition temperature of -30C is achievable. This provides good low temperature performance with a high clarity of the container. Furthermore, because of the designable nature of properties by varying solely the VA content, one does not need to add additives such as plasticizers which can leach into the storage contents. EVA is easily sterilized by gamma radiation which is commonly used for sterilization of cryo storage bags. Gamma sterilization is not recommended for FEP due to its low tolerance level of 50 kYG. Polytetrafluoroethylene (PTFE) has a tolerance level of 5 kGY and may disintegrate into powder with gamma radiation. Also PTFE may liberate fluorine gas during gamma sterilization.

The innovative nature of EVA and its simplicity of molecular architecture have positioned it to be the leading material in the field of cryogenic stem cell storage materials.

Case Study 3 – Controlled Release of Low or High Molecular Weight Active Pharmaceutical Ingredients

Folkman and Long are believed to be the first to have reported the use of polymers for controlled release of APIs. They investigated the use of silicone tubing (7). The early work with silicone polymers demonstrated that certain drugs could release in a sustained manner but they had to be low molecular weight drugs,

e.g. less than 1000, and of non polar nature. Drugs higher than 1000 molecular weight and possessing polarity would not diffuse out. Molecular motion is possible through amorphous regions. Over time other polymers were introduced as excipients for drug delivery. Hydrophobic polymers include ethylcellulose and EVA. Ethylcellulose is combined with a solvent and plasticizer to create a film. Some solvents used include acetone, chloroform, ethanol, toluene and blends. Controlled release of APIs can be designed by the thickness of the ethylcellulose film which alters the diffusion path.

EVA is a hydrophobic polymer which does not require the use of solvents or plasticizers for drug delivery. EVA has been used in a wide variety of applications and administration routes. Anderson et.al. (8) conducted a study examining the release characteristics of two, but different, low molecular weight APIs. A hormone, etonogestrel MW = 324, was compared to cyclosporine A, MW = 1203 for release characteristics based on molecular considerations of the EVA and the APIs. Two EVA polymers were used in the study. One containing 18% VA and the other containing 28% VA. As the VA content increased, it created higher amorphous content which should offer greater release rates as amorphous content goes up. As expected, the higher amorphous content EVA released API faster. Another important finding was that as VA content increases, polarity increases which offers the drug delivery designer the capability of tailoring polarities between EVA and APIs to improve API solubility with the excipient. Recall in the early work of Folkman it was found that polar APIs would not diffuse from their silicone tubing excipient. Table 1 illustrates Anderson's results (9).

Polymer VA content (wt %)	Cyclosporine loading (mg)	% Released in 30 days
18	5	18
18	25	12
28	5	29
28	25	26

Table 1. Release rate as a function of VA Content for Cyclosporine A in EVA

In 2012, 8 of the top 15 selling drugs were biologics. These are high molecular weight molecules, e.g. 40,000 to 2 million Daltons. Some biologic examples are proteins, monoclonal antibodies, peptides, etc. Biologics are becoming a very promising filed of therapeutics. All of the top selling biologics are administered through injection. It would be of value to have an oral dosage administration route for improving patient compliance. Because biologics are large molecules (e.g. polymers), they require more space for diffusion than what an excipient can offer via traditional amorphous content. To that end, Reyes et.al. propose drug delivery vehicle technology to accomplish this (10) using microcellular foaming in combination with a rheologically engineered EVA copolymer. During microcellular foaming a supercritical fluid is injected. This process enables the design of highly symmetrical microstructure of closed or open cell foam delivery vehicles. The symmetry is used for engineering a uniform diffusion path. The biologics are then seeded into the EVA foam core. Tablets can be manufactured such that they have coatings for enabling passage of the biologics through the stomach for delivery to the lower intestine.

Case Study 3 – EVA Innovation

In Case Study 3 it was observed that various polymers have been used as excipients. Ethylcellulose polymers provide controlled release but can require harsh solvents like chloroform as part of the application process. Silicone was shown to offer controlled release. However those polymers require curing steps which can contain harsh curing agents and take long processing times for achieving proper cure state. Also, silicone is polarity limited as found by Folkman et.al.

EVA provides an excellent approach for engineering polarity and amorphous content owing to its simple two monomer structure. Furthermore, because EVA is a thermoplastic, it does not require curing steps like silicone. EVA has been used in various administration routes including, dermal patches, subcutaneous implants, and intravaginal rings. Going forward, as

healthcare enters into the growing area of biologics and individual medicine, EVA is innovating the field for controlled release drug delivery. EVA's ability to have engineered rheology in combination with supercritical fluid microcellular foaming for open or closed cell foam advances its value as an excipient for the multibillion dollar field of biologics.

CONCLUSION

This paper has examined the evolution of EVA's innovation in healthcare. EVA has experienced a long successful history in advancing healthcare. From its leading role in nutrition bags and expanding the field of IV therapy, to its importance in the storage of critical products like stem cells and into its emerging role as a controlled release excipient for biologics, EVA has been at the forefront of innovation in healthcare for decades.

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