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Ethylene Vinyl Acetate (EVA) Copolymers and Their Current and Future Use in Parenteral Applications

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ABSTRACT

EVA has a long and successful history in parenteral applications. Currently, one type of administration route where EVA is used is for intravenous (IV) delivery of total parenteral nutrition. Biologics continue to demonstrate impressive growth as new and valuable agents for treating a number of diseases more effectively. Monoclonal antibodies are examples of biologics that use parenteral administration. EVA offers excellent properties for medical device performance and delivery requirements of these new advanced drugs. This paper will examine, using select case studies, the relationship of EVA in medical applications for parenteral delivery of therapeutics.

INTRODUCTION

Parenteral fluid administration is the delivery of a fluid not given through the digestive system but rather injected into veins or muscle (1). The first intravenous injection in a human is believed to have occurred in 1662 when Johann Major injected a compound of questionable quality into a man's vein. The result was a poor outcome (2). Table 1 illustrates some additional historical events in the evolution of parenteral administration. Of significance, are the following. First, development was spread across various countries and continents. Pioneers of parenteral administration were spread out over far and wide geographies. Second, early results often ended in death of the patient. Third, successful results occurred shortly after failed initial attempts. Last, after blood and water were successfully administered, pioneers moved on to create formulated fluids to improve patient health and safety. Today, it is estimated that approximately 80 percent of hospital patients receive some form of parenteral administration of fluids (3). Parenteral fluid administration has become very safe and standard practice.

Year	Event
1662	First IV injection into a human
1667	First published animal (sheep) to human transfusion (France)
1829	First documented blood transfusion – patient died (England)
1830	First successful transfusion of blood results to save a woman dying from postpartum hemorrhage (England)
1830	First IV use of water, patient died 2 days later (Russia)
1832	First parenteral administration of saline, patient dies (Scotland)
1833	First successful parenteral administration of saline (Scotland)
1876	Ringer's solution introduced by Sydney Ringer, later modification made by Alexis Hartman who added lactate to create lactated Ringer's solution – England / USA
1950	Harvard surgeon, Carl Walter, develops the plastic bag (USA)
1969	Total parenteral nutrition (TPN) developed by S. Dudrick at UPenn (USA)

Table 1 - Early history of Parenteral Administration (2)

EVA CHEMISTRY

Reyes provided an overview of EVA chemistry and its long use in medical applications (4). 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.

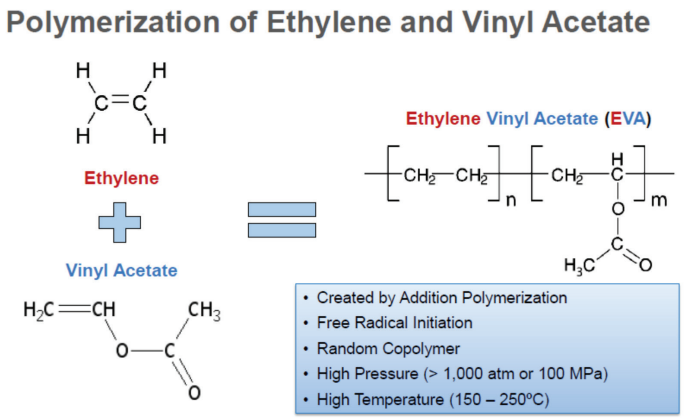

Figure 1. Polymerization of EVA

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.

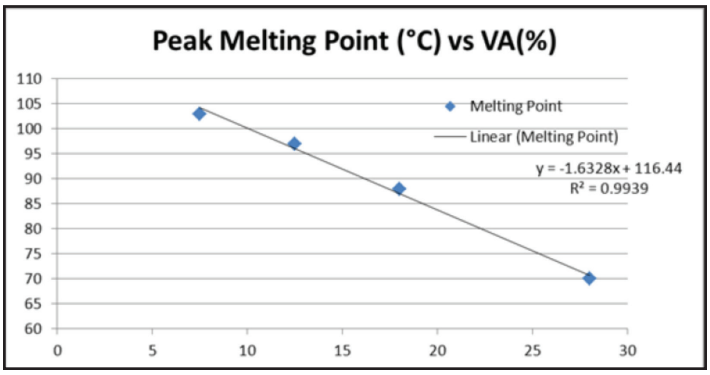

Figure 2. Melting point versus VA%

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.

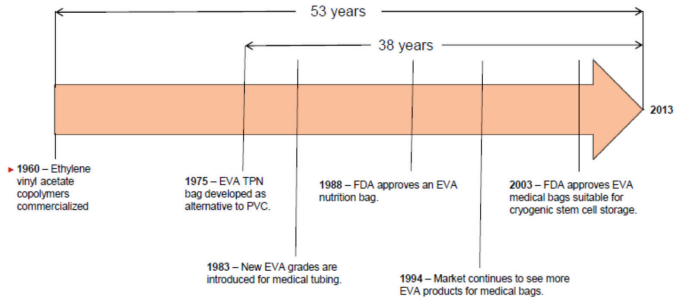

Figure 3. Timeline of EVA in Healthcare

CASE STUDY 1

EVA FOR USE IN PARENTERAL DELIVERY OF BLOOD

It was observed in Table 1, that blood was among the first fluids attempted for parenteral administration. Furthermore, it was observed that plastic bags were developed in 1950. PVC medical bags have been used in blood applications for over 50 years. To make PVC resin flexible for medical bag applications, approximately 30 to 40 weight percent of a plasticizer is required. The most common has been di (2-ethylhexyl) phthalate also known as DEHP. This plasticizer has the ability of stabilizing red blood cells but has issues of toxicity. Globally, there is growing interest in finding alternative materials to PVC. For example, from a regulatory perspective, in December 2012, the French senate passed a law which will ban use of DEHP in medical tubing used in pediatric, maternal, or neonatal wards beginning in 2015 (5). In

addition to regulatory reasons for PVC alternatives, there are also sustainability reasons. When PVC is incinerated chlorinated dioxins, furans and HCl can be created. This makes end of life waste even more expensive to dispose of for hospitals. It also creates toxic pollution to the environment.

Figure 3 showed that, EVA has demonstrated a long and successful role in a variety of medical applications. Therefore, it is reasonable to consider this resin as an alternative to PVC for blood bag applications. Blood bag applications require resin performance properties such as: processing for film production, weldability, and minimization of hemolysis. Table 2 summarizes some key performance properties including hemolysis. While DEHP has been known to help stabilize red blood cells, EVA has also demonstrated good hemolysis results. These data show that EVA can be an effective alternative to PVC for blood bag applications.

Property	Method	Result
Processing	Film Quality	EVA can be processed up to 210 C in both cast and blown film operations. Additionally, EVA is well suited for use in multilayer film construction. EVA film is manufactured globally for a number of industries including medical.
Weldability	RF	EVA is RF weldable for vinyl acetate contents of 18% or higher.
Hemolysis	Target < 5.0%	Celanese EVA medical grades have demonstrated less than 1.0%

Table 2 – EVA as Alternative to PVC in Parenteral Delivery of Blood

CASE STUDY 2
EVA FOR USE IN PARENTERAL DELIVERY OF COMPOUNDED FLUIDS

Often, various medications are mixed together using various drugs and or ingredients. The process of combining these is called compounding. Typically this can be done at a hospital pharmacy. Two examples of fluids resulting from compounding are parenteral nutrition and chemotherapy. Some refer to this as compounded sterile preparations, CSP, (6). Which situations exist that requires compounding? Table 3 provides some examples.

Need	Example
Alter a dose	To increase or reduce a drug concentration
Alter a dosage and delivery system	Change from oral to parenteral
Patient requires various drugs	Required drugs are compounded for one parenteral delivery
Specific dose	Prepare drug product from bulk substances

Table 3 – Compounding Examples

An important requirement of medical grade polymers used in compounding relates to (a) compatibility of polymer in relationship to the drugs and (b) leachables and extractables. The parenteral delivery of the fluids (e.g. nutrition or chemo) will have intimate contact between the bag's inner layer and on into the vein. In the previous case study, we saw that EVA has excellent hemolysis performance. It is important that resins not leach additives into fluids which go into the bloodstream. PVC medical bags may have plasticizer leaching into the parenteral fluids which can interact with lipids or drugs. EVA does not require the use of plasticizers for achieving flexibility required in compounding bags. Furthermore, EVA is used in chemo applications because, unlike PVC, it is compatible with chemo drugs (7).

CASE STUDY 3
EVA FOR USE IN PARENTERAL DELIVERY OF BIOLOGICS

Biologics are generally large molecules manufactured using living processes. Some biologic examples are proteins, monoclonal antibodies, peptides, etc. Consider that a monoclonal antibody has an approximate molecular weight of 150,000 Dalton versus aspirin having a molecular weight of 180 Dalton. Today, the routes of administration are parenteral (infusion or injection). Table 4 illustrates how biologics are dominating the list of top 10 selling drugs. Biologics are a class of drugs creating enormous therapeutic value.

Rank	Drug	Type
1	Humira	Biologic
2	Enbrel	Biologic
3	Remicade	Biologic
4	Advair	Small Molecule
5	Lantus	Biologic
6	Rituxan	Biologic
7	Avastin	Biologic
8	Herceptin	Biologic
9	Crestor	Small Molecule
10	Abilify	Small Molecule

Table 4 – Top 10 Selling Drugs 2013

Because these drugs are delivered parenterally, it is important to consider the medical polymers used to make the IV bags which contain the biologics during storage and administration. Similar to Case 2 above, leachables and extractables are very important properties. Biologics can be sensitive to various impurities. It is for this reason that polymers are carefully studied and characterized. In addition, the processes used to manufacture the polymers and their subsequent handling should have manufacturing controls over and above those used for standard industrial applications. For example, the plant should be free of additives derived from animal origin and genetically modified organisms. It is customary before infusion to inspect the contents in the bag for possible specks and or impurities. This implies that the polymer used for infusion bags are of sufficient clarity to enable inspection. Last, it is common to have multilayer film construction. EVA copolymers have excellent properties for meeting these demanding requirements. EVA offers, and will continue to offer, excellent performance to support parenteral delivery of biologics as this important field of biotechnology continues to evolve.

CONCLUSIONS

This paper has examined the successful role EVA has demonstrated in parenteral applications. From its use in blood bags as a PVC alternative, to its success in pharmacy compounding applications like nutrition and chemotherapy fluid delivery, to its growing future role in biotechnology, EVA copolymers will continue to offer excellent solutions and innovations going far into the future.

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