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POLYMERS IN DRUG DELIVERY SYSTEMS

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ABSTRACT The future of pharmaceutical industry is now shifting from new drug research to novel drug delivery systems. Biopharmaceuticals present challenges because of their unique nature and difficulty in delivery through conventional routes. These challenges inspire for the invention of new medical grade polymers for novel drug delivery systems. Polymeric drug delivery systems bring a true benefit over glass. Polymer provide improved robustness against breakability and better ergonomy, while delivering for many product an adequate stability performance level regarding water/gas permeability as well as extractible/leachable. Polycarbonate and Cyclic Olefin Copolymer are an excellent substitute of glass drug delivery systems because of its unique characteristics. Polycarbonate falls under the category of Amorphous polymers that is used as clear as glass but lighter and less prone to breakage. Polycarbonate and Cyclic Olefin Copolymer are also more resistant to water transmission than Polypropylene which was first time used for polymeric prefilled drug delivery systems. Due to this extra ordinary property it lengthen the shelf life of the drugs. Cyclic Olefin Copolymer provides an impressive array of physical and chemical properties that are attractive to drug makers, like high heat resistance: material is autoclvable, excellent low temperature characteristic, high break resistance, high transparency, low extractables, solvent resistance, wide range of pH stability, easy safe and environmentally friendly disposal. Because biocompatibility is essential for any material used in direct or indirect contact with patients, Polycarbonate and Cyclic Olefin Copolymer grades comply with biocompatibility testing standards such as ISO 10993-1 and USP Class VI. Due to this extra ordinary combination of physical-chemical properties and biocompatibility with drug formulations, Polycarbonate and Cyclic Olefin Copolymer can be used for pre-filled syringes, needleless injectors and other drug delivery systems.

Keywords—polymeric drug delivery systems, Polycarbonate, Cyclic Olefin Copolymer, Glass drug delivery systems, physical and chemical properties, biocompatibility with drug formulations

I INTRODUCTION:

INTRODUCTION TO POLYCARBONATE

Polycarbonates are a particular group of thermoplastic polymers. They are easily worked, moulded, and thermoformed. Because of these properties, these polymers find many applications.

Structure

Polycarbonate contain carbonate groups (–O–(C=O)–O–). Most polymers of commercial interest are derived from rigid monomers. A balance of useful features including temperature resistance, impact resistance and optical properties position these polymers between commodity plastics and engineering plastics.

Properties and Processing

Polycarbonate is a very durable material. Although it has high impact-resistance, it has low scratch-resistance and so a hard coating is applied to Polycarbonate eyewear lenses and Polycarbonate

exterior automotive components. The characteristics of Polycarbonate are quite like those of polymethyl methacrylate (PMMA, acrylic), but Polycarbonate is stronger, usable in a wider temperature range but more expensive. This polymer is highly transparent to visible light and has better light transmission characteristics than many kinds of glass.

Polycarbonate has a glass transition temperature of about 150 °C (302 °F), so it softens gradually above this point and flows above about 300 °C (572 °F). Tools must be held at high temperatures, generally above 80 °C (176 °F) to make strain- and stress-free products. Low molecular mass grades are easier to mould than higher grades, but their strength is lower as a result. The toughest grades have the highest molecular mass, but are much more difficult to process.

Unlike most thermoplastics, Polycarbonate can undergo large plastic deformations without cracking or breaking. As a result, it can be processed and formed at room temperature using sheet metal techniques, such as forming bends on a brake. Even for sharp angle bends with a tight radius, no heating is generally necessary. This makes it valuable in prototyping applications where transparent or electrically non-conductive parts are needed, which cannot be made from sheet metal. Note that PMMA/Plexiglas, which is similar in appearance to Polycarbonate, is brittle and cannot be bent at room temperature.

Main transformation techniques for Polycarbonate resins:

extrusion into tubes, rods and other profiles

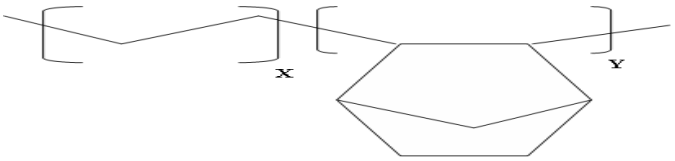
extrusion with cylinders into sheets (0.5–15 mm (0.020–0.59 in)) and films (below 1 mm (0.039 in)), which can be used directly or manufactured into other shapes using thermoforming or secondary fabrication techniques, such as bending, drilling, routing, laser cutting etc.

injection molding into ready articles

INTRODUCTION TO CYCLIC OLEFIN COPOLYMER

Cyclic olefin copolymers consist of amorphous transparent copolymers based on cyclic olefins and linear olefins.

Structure



Properties and Processing

Cyclic olefin copolymers are a new class of polymeric materials with property profiles which can be varied over a wide range during polymerization.

These new materials exhibit a unique combination of properties of which can be customized by varying the chemical structure of the copolymer. Performance benefits include: Low density, High transparency, Low birefringence, Extremely low water absorption, Excellent water vapour barrier properties, Variable heat deflection temperature up to 170 °C, High rigidity, strength and hardness, Very good blood compatibility, Excellent biocompatibility, Very good resistance to acids and alkalis, Very good electrical insulating properties, Very good melt processability/flowability.

2. STERILIZABILITY

The use of plastics in the pharma and diagnostics sector in many cases requires sterilizability of the plastic material. The effect of various sterilization methods, using high energy radiation (gamma and electron beam), ETO, hot air and hot steam, has been investigated for Polycarbonate and Cyclic olefin copolymer. Standard test specimens were subjected to conditions simulating one time exposure. Table 1 summarizes the results of this testing.

	Method of Sterilization				
Material	Hot steam	Hot air	ETO	High-energy radiation	
				gamma	electron
Polycarbonate	√	√	√	√	√
Cyclic Olefin Copolymer	√	√	√	√	√

Table 1: Sterilizability

3. ANNEALING POLYCARBONATE AND CYCLIC OLEFIN COPOLYMER

3.1 WHY TO ANNEAL?

If, during the machining process, significant material is removed, annealing is recommended to relieve machined-in-stress and minimize possibility of premature part failure.

All extruded stock shape plastics are compressed through a profile die when extruded. The compression that occurs in the material is not relieved because the plastic "sets up" as soon as it comes out of the die and it remains in this compressed or highly stressed state. This high state stress will cause four problems if not addressed:

1. Materials will tend to warp and distort

2. Physical properties will be different than published data (usually lower)

3. Material may crack

4. Finished part dimension may change.

In order to eliminate these problems extruded products are annealed. Annealing is a stress relief process, which occurs when the material is exposed to heat (air or fluid) above its glass transition point, which allows the material to "decompress" back to a relaxed state. Annealing is important if you want a quality, finished part out of your stock shape.

ANNEALING/STRESS RELEIVING PROCEDURES FOR POLYCARBONATE AND CYCLIC OLEFIN COPOLYMER

1. Place parts in air circulating oven such that air can circulate around them.

2. Heat oven to 250°F at a maximum heating rate of 20°F per hour.

3. Hold oven temperature at 250°F for 30 minutes plus 15 minute for every 1/8" of cross-section.

4. Cool oven to 150°F over 10 hours with a maximum cooling rate of 10°F per hour.

5. Turn off oven and allow to cool to room temperature before removing parts.

4. BIOCOMPATIBILITY

Criteria for the use of plastics in the pharma and diagnostics sector are specified in the national pharmacopoeias (US, EU and JP), and by the appropriate regulatory agencies. Material test program guidelines are given by the FDA, and the International Organization for Standardization (ISO 10993). The test program depends on the particular application and the duration of contact with the human body.

The initial biocompatibility tests of Polycarbonate and Cyclic olefin copolymer are carried out with WFI (Water For Injection). The test results are shown in table 2.

(Wash 5times with WFI and autoclaved at 121°C for 30 minutes)							
	At Room temperature						
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**
pH: **WFI + Cyclic Olefin Copolymer**	**5.90**	**5.91**	**5.91**	**5.92**	**5.89**	**5.93**	**5.88**

pH: **WFI + Polycarbonate**		**5.92**	**5.87**	**5.90**	**5.88**	**5.89**	**5.93**

5. MEDICAL APPLICATIONS OF POLYCARBONATE AND CYCLIC OLEFIN COPOLYMER

5.1 MEDICAL APPLICATION OF POLYCARBONATE AND CYCLIC OLEFIN COPOLYMERS

Polycarbonate plastic is a lightweight, highly versatile, durable, heat and shatter resistant, formable and transparent thermoplastic. It is the material of choice for a wide range of end-user applications as diverse as DVDs, computers and home appliances, spectacles and optical lenses, reusable water bottles, and medical devices or construction materials.

Applications in the medical devices sector are 100% unique:

Only Polycarbonate provides the required safety characteristics, combining biocompatibility, light weight, contact safety, ease of sterilisation, transparency and virtual

unbreakability. For example, more than 700,000 people suffer from chronic kidney failure. Their lives depend on dialysis machines. Almost all renal dialysis machines use Polycarbonate technology. The same applies to open heart surgery. Polycarbonate components in blood oxygenation equipment are critical to the functionality of this advanced technology. Without these devices, over 500,000 open heart operations in Europe could not be performed each year.

6. BENEFITS OF POLYMERS OVER GLASS DRUG DELIVERY SYSTEMS

Despite their limitations, glass prefilled syringe systems still dominate the market; with the development of novel polymer materials, however, manufacturers can now offer high-quality, transparent, break-resistant syringes that are less prone to contamination.

The advancement of regulatory science, innovation, safety and integrity of the global pharmaceutical environment is one of the FDA's strategic priorities for the 21st century. Pharmaceutical manufacturers are faced with increased scrutiny by the FDA, following concerns that the high cost of drugs has been related in part to low manufacturing efficiencies that result in rejected drug product. Prefilled syringe systems can enhance drug product integrity and delivery by providing convenient, premixed, sterile, fixed dosages to the patient. The use of high-quality components will help ensure efficient manufacturing processes, resulting in a reliable supply of drug products.

6.1 NEEDS FOR QUALITY ASSURANCE

The delivery of a safe and effective drug product depends on multiple factors. Many complex systems and components must come together to create a drug product with appropriate safety and quality controls. The drug development, scale-up, manufacturing, filling, packaging, storage and shipping processes require an in-depth understanding of factors affecting drug product safety and efficacy; the primary, secondary and ancillary packaging components, along with the raw materials for all processes, have an impact on drug product quality and are obtained from multiple sources. The appropriate knowledge is not always shared in advance, and unexpected issues may occur, leading to development through lessons learned, as opposed to understanding the science and potential hazards to enable appropriate risk assessments.

These multifaceted and numerous variables become even more challenging with the growing global supply chain. There will always be some degree of risk, but this risk should be reduced as much as possible to realise the greatest benefit for the patient. Balancing up-front investment with desired time to market must be a coordinated effort among the various stakeholders. By forming alliances early in the drug product lifecycle, manufacturers can help ensure a product's integrity within the delivery system, which is vital to the wellbeing of the patient.

6.2 PREFILLED SYRINGE SYSTEMS

The accurate dosing of a drug product, its reliable delivery and ease of use are major advantages to patient therapy and satisfaction. In addition the control of components is more easily qualified and tracked when managed from a single source. The mutual dependency between a drug and its administration system throughout the product lifecycle should be established early and monitored. The control of components as well as the opportunities for improvements can be recognised and quickly addressed to improve quality and meet the growing needs of delivery systems or devices. Drug product quality indicators are based on uniformity, purity, integrity and stability, and can be strongly influenced by the materials with which the drug may come into contact. The drug product formulation comprises multiple raw materials - as are the components of prefillable syringes – and it is ultimately the compatibility of these systems that will qualify a system for its intended use. Components of prefillable syringe systems typically include pistons, syringe barrels, needles and needle shields – all of which must be compatible both as a system and with the drug product. An understanding of the potential hazards to be mitigated can be explored and supported, based on the combined knowledge of drug manufacturers and components suppliers throughout the product lifecycle.

Prefilled Syringes with their premeasured dosage, have the potential to reduce dosing errors and increase patient compliance with potentially saving manufacturers money. Single or multi-dose vials mar require drug product overfill by as much as 30 per cent to ensure adequate withdrawal, whereas a prefillable syringe can virtually eliminate the need for excess overfill, thus conserving expensive drug product. This is important where manufacturing and product costs are high and bulk manufacturing capacity is limited.

Additionally, there is some degree of variability when removing drug product from a vial with a conventional disposable needle and syringe. With a prefilled syringe system, the very nature of its design eliminates the withdrawal step and delivers drug product directly to the patient, resulting in a more accurate dose of the drug and less exposure to needles.

6.2 Limitation of Glass

Glass is the most commonly used material for syringe barrels, but it has a number of limitations that can potentially contribute to delays in production, reduced supply or even recalls due to quality issues. When comparing Glass with Plastic syringe barrels, these limitations are easy to identify.

Dimensional Variability

Glass is a formed product and in order to create the component, the glass is heated and mandrels are used to form the syringe's overall length, nose or tip, and flanges. These actions create dimensional variability. When the syringe is used manually, such variability is overcome by the human user, but with delivery devices such as auto-injectors, the device itself must overcome this variability. Since the device cannot judge the pressure required to do so, failure – including incomplete injections or incorrect needle depth upon injection

– may occur. By contrast, Plastic components are moulded and this process creates dimensional tolerances that are consistent and tighter than with a glass product.

Siliconisation

The prefillable syringe component that has the highest contact area with the drug product is the syringe barrel, and this can have a major influence on drug product quality. The compatibility of a drug product with the barrel's contact surface is critical to product quality, while the break-loose and glide forces are key to successful administration. Prefillable syringe barrels are manufactured from either glass or plastic materials such as Modified bis-phenol A polymers. Glass requires lubrication to facilitate the break-loose and glide forces; this can be accomplished through a siliconisation process but not without a concern of quality. Silicone can have a negative impact on the drug product, especially in the biopharmaceutical arena where there is risk of protein aggregation.

Eliminating the need for silicone oil can be an important advantage. Problems with siliconisation can arise from uneven application, particularly towards the nose of the syringe, which is less accessible to the siliconisation process. Such issues can create a higher break-loose force or glide force variability – particularly at the end stroke of the piston – resulting in incomplete injection. This is especially of concern when the syringe is used in a delivery system such as an auto-injector. In extreme cases, the syringe may 'stall' before the end of the stroke and the full drug dose may not be delivered.

Glass Fragility and Delamination

Glass is fragile and broken glass syringe barrels can result in lost product, as well as compromise patient safety. In addition glass is not inert and is particularly susceptible to chemical reactions at the surface. The glass formulation and manufacturing processes can influence the potential for glass flakes (delamination); this is more pronounced as the temperature and alkalinity of the contacting solution increases. While basic solutions favour siliceous flakes, these flakes can also be observed in neutral or slightly acidic solutions that have been stored for some time, particularly if the containers have a low chemical durability. These flakes – which have been the subject of several drug product recalls – are elusive and may occur during storage of the drug product and/or shipping.

Other Contaminants

Tungsten is another potential hazard associated with glass prefilled syringes. The inner needle channel is formed in glass by the use of a tungsten pin, and the high temperature required for glass forming can oxidise tungsten in the presence of air and interact with the glass. The resulting residuals are not easily removed during washing and the potential to interact with the drug product. Low levels of tungsten in biological products can produce aggregation, resulting in rejected product batches.

Glues and adhesives are also used to hold the needle in place once it has been staked into the glass syringe. These are additional sources of potential leachables and can also contribute to the rejection of the contaminated drug products.

6.3 Polycarbonate and Cyclic olefin copolymer

Despite their limitations – drug product compatibility, performance issues and manufacturing operations – glass prefilled syringe systems still dominate the market. However, with the development of Novel materials – including Polycarbonate and Cyclic olefin copolymer – Manufacturers can now offer high-quality, transparent, break-resistant material that is more inert than glass and, unlike glass, dose not flake, thereby reducing particulate contamination from the syringe container. Also, these components can be stored and shipped at low temperatures – a requirement for many biological products.

Switching from a glass to a Polycarbonate and Cyclic olefin copolymer moulded prefillable syringe can reduce the variability and breakage issues associated with glass, as well as reduce the need for silicone oil. The injection moulding technology used to manufacture plastic syringe barrels maintains tight tolerances to ensure consistent functionality (for example, break-loose and extrusion) and minimise the risk of 'non-fit' with secondary systems such as auto-injectors.

A significant benefit of this plastic barrel is that it can be moulded around a needle – eliminating the need of tungsten pins, glues and adhesives. This in turn minimises exposure to leachables and offers manufacturers an option to provide additional protection for the drug product.

Ultra high quality Polycarbonate and Cyclic olefin copolymer syringe systems provide a compelling alternative to existing

glass systems, and provide better dosage precision and support for new classes of biopharmaceutical product. At the same time, plastic prefillable syringe solutions minimise the drug product wastage that can occur due to excessive overfills or loss due to breakage, and provide for silicone free-systems that reduce the risk of protein aggregation.

Plastic Prefillable components, together with fluoropolymer film coated pistons in a ready-to-use format, present benefits that are gaining strength industry-wide. Recognising an opportunity to improve drug product quality should not be burdensome, and efficiencies can be achieved with the appropriate regulatory support and cooperation between the drug manufacturer and component supplier resulting in an overall patient benefit. Plastic syringe systems, which have been extensively used in all major markets for some time, continue to gain strong acceptance from both pharmaceutical and biotech drug manufacturers thank to a member of benefits:

High break-resistance
Consistent break-loose and glide force
Silicone-oil free
Low exposure to extractables and leachables
Low particulate levels
Minimum adsorption and absorption
Improved drainability
Excellent low temperature characteristics
High transparency

As the industry trends towards the increased use of prefilled syringes, these same components can be used in devices or delivery systems to support the increased use of injections in the home setting. Because of the flexibility in moulding, these polymers can be used in a variety of drug delivery systems including custom auto-injectors and cartridges.

7. CONCLUSION

Polycarbonate and Cyclic olefin copolymers occupy a unique niche in the medical device market. Engineers have tapped its key characteristics of toughness, rigidity, and strength for critical device applications in which safety and performance are vital. The ease of sterilizability of Polycarbonate and Cyclic olefin copolymers give designers wide latitude in developing products that are not dependent on a single sterilization method. These features are further complemented by Polycarbonate and Cyclic olefin copolymer's high clarity, a key benefit when visual assessment of patients and their prescribed therapies is indispensable.

8. FUTURE SCOPE

Demands to ensure the global quality and safety of drug products are ever growing. By collaborating with component manufacturers early in the product lifecycle, manufacturers can develop new solutions for providing quality drug products with a manufacturing efficiency that can overcome administration challenges. Innovative drug products and prefilled syringe or auto-injector systems are mutually beneficial to achieving high standards of quality and patient safety. Multiple interactions are needed throughout the development process to identify and mitigate risks to the integrity of a drug product, and to ensure improvements throughout the

drug product lifecycle. The involvement of all stakeholders in the early development stages will lead to the successful design and evaluation of delivery systems to meet the needs of patient.

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