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DRUG DISCOVERIES AND CHALLENGES FOR POLYMERIC MEDICAL PACKAGING DEVICES

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ABSTRACT

Mostly this has been observed polymeric packaging materials are most suitable to prevent product protein adsorption, prevent delamination and those products are highly acidic in nature. Incase of "I.V infusion bottles Poly carbonates and Poystyrene are using. Need to be very much careful leachability problems especially leachables are additives, colourants antioxidants, heavy metals as extractable those are harmful for product contamination and product stability. To avoid breakage of glass better to use polymeric materials for catheters it's made from latex, silicone, Teflon.

Keywords: Polymeric packaging materials, Drug discoveries

INTRODUCTION

a) Solid Dose Drug Products Devices

Mostly HDPE bottles and PP caps are using for packaging of solid doses products. Very few cases PET is using. PVC, PVC/PVDC, PVC/PE/PVDC and many combinations are using in blister packaging.

Practical Problems:

- Leachability is the issue rarely found and discolorations observed in products.

Solutions

- Need to change the polymer in blister pack or switch to HDPE bottle pack.

There are many Extractables in Polymeric materials and those are Additives, anti oxidents, stabilizers, plasticezers, emulsifiers, colourants, monomars, oligomers residual catalists, impurities UV absorvers fillers, antifogging, anticrobialsetc.

Typical Plastic additives:

- Lubricants, antistatic agents, initiators, stabilizers, impact modifiers, antioxidants, bactericides catalysts., blowing agents,

processing aids, plasticizers, colourants, brighteners, release agents, vulcanizing agents.

Acceptance criteria for E/L study in different media (one specific example)

Compounds	Analytes	Quantification limit (ppb)
Elements	Mg	50.0
	Al	10.0
	Cr	10.0
	Mn	10.0
	Fe	10.0
	Ni	10.0
	Cu	10.0
	Zn	50.0
	Cd	2.0
	Sd	2.0
	Pb	2.0

Compounds	Analytes	Quantification limit (ppb)
Antioxidants and UV absorbers	2, 2- methylene- bis(4-methyl-6-tert butyl-phenol)	10.0
	2,6-di-tert-butyl-4-sec-butylphenol	5.0
	2,6-di-tert-butyl-N, N-dimethylamino-p-cresol.	10.0
	2,4-dihydroxy benzophenone.	5.0
	2-hydroxy-4-octyloxy benzophenone	5.0
	2-hydroxy-4-methoxy benzophenone	5.0
Ethylene oxide and propylene oxide	Ethylene oxide	0.5
	Propylene oxide	0.5
plasticizers	Butylated hydroxyl toluene	0.2
	2- Butanone peroxide	0.2
	Di Butyl Phthalate	0.2
	4,4- Isoprpyledene di phenol	0.2
	Benzyl Butyl Phthalate	0.2
	Di(Ethylene Glycol) Dibenzoate	0.2
	Bis(ethyl hexyl) phthalate	0.2

Polymers are typically classified by different Criteria

Origin	Natural Polymers, Synthetic Polymers
Chemical composition	Organic Polymers, Inorganic Polymers
Thermoelastic properties	Elastomers, Thermoplastics, Thermosets
Route of synthesis	Chain-growth and step-growth polymers
Number of monomers	Homo-Polymer, Co-Polymer

Additives –Advantages / Disadvantages of Plastic materials

Advantage	Disadvantage
Light materials	Ageing by UV or Oxygen impact
Rigid or flexible	Tread grove cracking
Mouldable	Damage to the environment
Reasonable inert	Migration of plastic components
Printable	-
Transparent or colored	-
Combinable with other materials	---

Additives	Advantage	Chemical Classes
Antioxidants	**Assure protection against thermal and oxidative degradation during processing and during environmental exposure.**	**-Sterical Hindered phenols BHT (radical scavengers) - Organic phosphites / phosphonates (peroxides decomposers -Thioethers - Thiocarbamates - Mercaptobenzimidazoles - Thiobisphenolsand others**
Plasticizers	**-Gives the plastics flexibility and durability - Low extractability by water and solvent - Stability to heat and light - Low odor, taste and toxicity**	**-Phthalates (esters) - Fatty acids (Stearic acid, Palmitinixc acid) - Oils such as epoxidized linseed oil, tall-oil - Adipates, azelates, sebacates - Derivates of glycols and aliphatic dicarboxylic acids**
Antidegradants	**-Stops the degradation of the finished plastic product -**	**Antiozonants (ozone protection, barrier) - Alkylphenylamines UV-Stabilizers (UV protection against discoration) - Benzophenones - Benzotriazoles - Salicylate eters - Cyanoacrylates - Malonates - Benzilidenes - Polimeric sterically hindered phenols**
Coupling agents	**Are substances that are capable of bonding organic polymer systems to inorganic substrates such as glass, mineral fillers and metals**	**Silanes - Aminoalkylsilanes - Alkyl-alkoxy silyl-sufides - Epoxy-alkyl-silanes - Vinyl-alkoxy-silanes**
Flame retardants	**Added to inhibit ignition or flammability of the end-use product and used in thermoplastics like - Polystyrene, polyesters, polyolefins**	**Inorganic - Aluminiumtrihydrate - Antimony oxide - Boron compounds Organic - Brominated and chlorinated compounds - Brominated diphenyl ethers (PBDE)**

b) Ophthalmic Drug Products Devices

Practical Problems:

- Discoloration of the product.
- Inaccurate dispense of the product.
- Bottle wall is very hard to squeeze.
- Product Leakage.

Solutions

- Extractable and Leachable for bottle need to check thoroughly.
- It's advisable to use "Meter dose dropper "
- "Bottle wall squeeze ability" need to check.
- "Cap fitment" checking is must.
- Need to revalidate the " Cap design" with product.

c) Nasal Drug Products Devicese

Practical Problems:

- Discoloration of the product.
- Inaccurate dispense of the product.
- Product Leakage.

Solutions

- Extractable and Leachable for bottle need to check thoroughly.
- It's advisable to use "Meter dose dropper "
- "Bottle wall squeezeability" need to check.

d) Injectable Drug Products Devices

Practical Problems:

- Discoloration of the product.
- Inaccurate dispense of the product
- Gliding force is not uniform.
- Plunger movement is not smooth inside the syringe.

Solutions

- Advisable to use Check the "Extractable and Leachable test report" and take the necessary changes.
- Advisable to use Polymeric Needles.
- Advisable to use "Fluro coated" rubber stoppers. or plungers.
- In case of "Auto injectors" we need to revalidate the design with product or replace the old Auto injector with New one, if we not get the right dispensing doses.
- Use " Blow back vials and Blow back Rubber stoppers to avoid product leakage and perfect crimping as well.
- For "**Double chamber PFS**" Accurate doses of the product depends on the smooth movements of the Plunger Rod and " inner Plunger".

e) I.V Drug Products

Practical Problems:

- Discoloration and lumps observed.
- Inaccurate dispense of the product
- Improper fitment of the pipe with the cap.
- Leakage observed in the pouch.

Solutions

- Advisable to Check the "Extractable and Leachable test report" and take the necessary changes.
  - Change the cap and pipe.
  - Replace the pouch and need to take care during "Leak test" of the pouch.

Extractables from LDPE and HDPE

Sl#	Component	Source
a	Aliphatic hydrocarbons	Not polymerized monomers
b	Branched aliphatic hydrocarbons	Mould release agents
c	Irganox 1010, 1076, Irgafos 168	Antioxidants
d	Tetra-methyl succinonitrile	Catalyst
e	Alcohols	Hydrolyze product of DEHP

Polyolefines– Extractables / Extractables from LDPE / HDPE (Widely using in prefilled syringe)

Sl#	Extractables
a	Carbonic acids: C1, C2, C3 etc.
b	C2 – C5 -Aldehydes
c	Ketones
d	BHT derived from Irganox1010, 1076(BHT: 3,5-di-tert-butyl-4-hydroxytoluol)
e	2,5-di-tert-butyl benzene and2,5-di-tert- butyl phenol from Irgafos 168

Extractables from PVC

Sl#	Component	Source
a	Ethylenoxide	Sterilization residue
b	Di-(2-Ethylhexyl)phtalat (DEHP)	Plasticizer
c	Phthalic acid	Hydrolysis of DEHP
d	Mono-(ethylhexyl)phtalat (MEHP)	Hydrolysis of DEHP
e	Dibutylphtalate	Impurity of DEHP
f	2-Ethyl-1-hexanol	Hydrolysis of DEHP
g	Vinyl chloride monomer	PVC
h	Acetic acid	Oxidation of PVC
i	Formic acid	Oxidation of PVC
j	Cyclohexanone	Residue solvent
k	9,10-Epoxy stearic ester	Impurity
l	Ethanol	Residue solvent
m	Toluene	Residue solvent
n	1,1 –Dimethylethyl-4-methoxyphenol (BHA)	Antioxidant
o	Bisphenol A	Antioxidant
q	3,5-di-tert-butyl-4-hydroxytoluene (BHT)	Antioxidant
r	t-Butyl cyclohexanol	Inks

Polymers and it's standard extractable(metal) values

Sl#	Polymer	Analytics /Extract	Component / Level [ppm]
a	PE	ICPMS, ICP-OESmicrowave digestion	Mg / 0,5 Si / 16,0 Ca / 32 Zn / 1,8
b	LDPE	ICPMSmicrowave digestion	Mg / 2,3 Al / 8,9 Mn / 0,01
c	PVC	ICP-OES, Al / 0,2/Extraction with 5% acetic acid 2h 122°C	Al / 0,2 Ca / 0,4 Si / 0,9 Zn / 0,4
d	Perfluoro elastomer	ICP-MS, IC /water 4 weeks 80°C	F / 1,1 Metals < 0,1 TOC 1,54

Risk Assessment

Solvent	Possible Migrants	Risk
Aqueous	Mostly Inorganics	low
Aqueous Buffer w/ 20% Tween 80	Inorganics, Siloxanes, Monomers	Moderate
Oil Based or High Organic	Monomers, Siloxanes	high

Do and Not to do Leachables and Extractables Testing for Inhalers

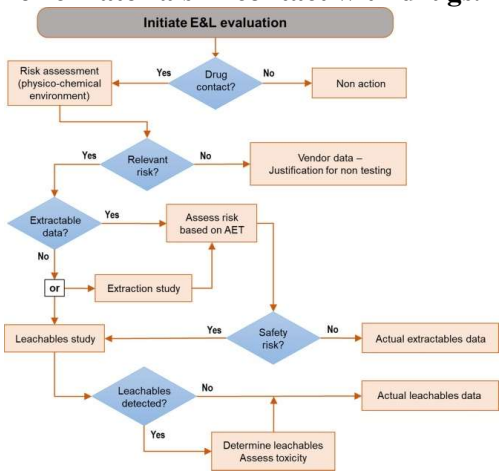
Product Type		Controlled extraction study	Leachables study	Routine Extractables testing	Routine Leachable testing
MDI	Valve components(polymeric – contact with drug)	yes	Not applicable	yes	Not applicable
	Mouthpiece(including spacer)	yes	No(one time in-use study)	ye	Not applicable
	Canister	Yes(if coated)	Not applicable	Yes(if coated)	Not applicable
	Drug product	Not applicable	yes	Not applicable	no
DPI	Protective s econdary packaging(critical to the performance of the drug product)	Yes	Not applicable	yes	Not applicable
	M outhpiece	Case by case	No(one time in-use study)	yes	Not applicable
	Canister	Yes (if coated)	Not applicable	Yes(if coated)	Not applicable
	Drug product	Not applicable	yes	Not applicable	no
Nasal spray	Pump components(polymeric contact with product)	yes	No(one time in-use study)	yes	Not applicable
	container	yes	Not applicable	yes	Not applicable
	Canister	yes	No(one time in use study)	yes	Not applicable
	Drug product	Not applicable	yes	Not applicable	No

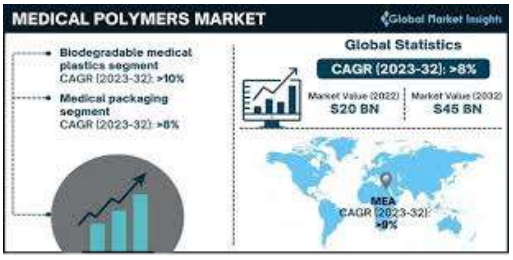
P Product Type		Controlled extraction study	Leachables study	Routine Extractables testing	Routine Leachable testing
Inhalatio n solution/ suspension	Primary packaging material(polymeric)	yes	Not applicable	yes	Not applicable
	Protective secondary packaging(critical to the performance of the drug product)	yes	Not applicable	yes	Not applicable
	Drug product	Not applicable	yes	Not applicable	no

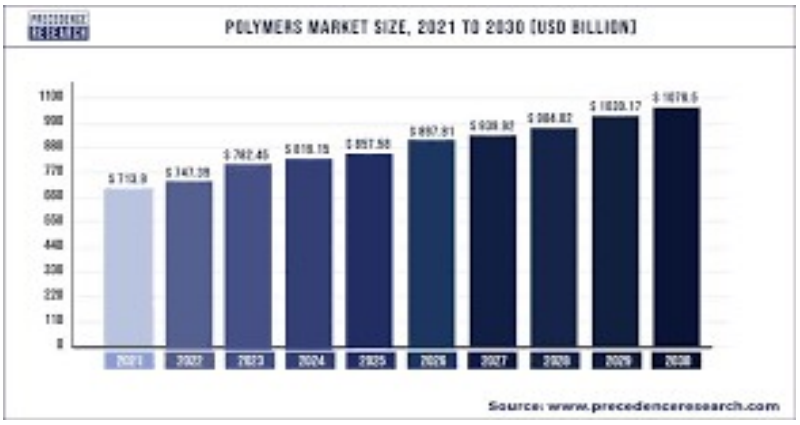
Packaging Materials Associated with Parenteral Products

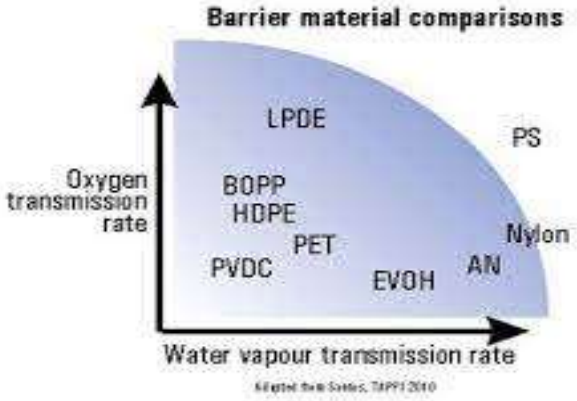
Dosage Form	Components	Example Material
Inhalation	MDI/DPI components, canisters, valves, gaskets, blister packs, bottles, actuators, mouthpiece, pumps, closures, liners, label/inks	polyolefins, styrene butadiene rubber, ethylene propylene diene monomer, rubber, thermoplastic elastomers, polyacetal, polyesters, polyamides, acrylics, epoxies, paper / paperboard, metals, glass
Injectable	SVP <100 ml/LVP >100ml cartridge, syringe, vial, ampoules, flexible bag, closures / plungers, injection ports, needles, adhesives, inks, overwraps	polyolefins, butyl rubber, ethylene propylene diene monomer rubber, polyvinyl chloride, polyurethanes, polycarbonate, acrylics, poly-amides, polystyrene, thermoplastic elastomers, silicones, polyesters, epoxides, cellophane, fluoropolymers, styrenics, paper / paperboard, metals, glass
Ophthalmic	bottles, droppers, screw caps, liners, tips, tubes/liners, labels/ink	polyolefins, acrylics, vinyls, epoxies, polyamides, thermoplastic elastomers, polyesters, cellophane, glass, paper / paperboard, metals
Transdermal	adhesives, membranes, barrier films, reservoir, coatings, blister packs, preformed trays, overwraps, substrates, topical aerosol components	polyolefins, acrylics, vinyls, polyamides, polyesters, styrenics, rubber material thermoplastics, metal
Associated Components	nebulizers, dosing spoons, dropper, dosing cups	polyolefins, glass, rubber, thermoplastics, polyesters

Leachables from Polymeric materials in contact with drugs. Analytical approaches









Solid Dose Drug Products Devices

Liquid oral Drug Products Devices

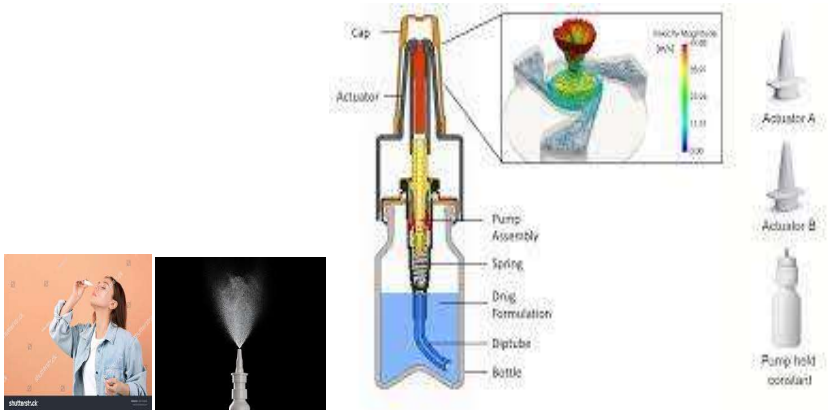



Ophthalmic Drug Products Devices

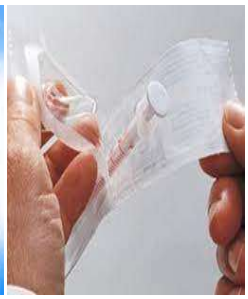



Essential Leachables

Nasal drug Product Devises



Injectable Drug Products Devices

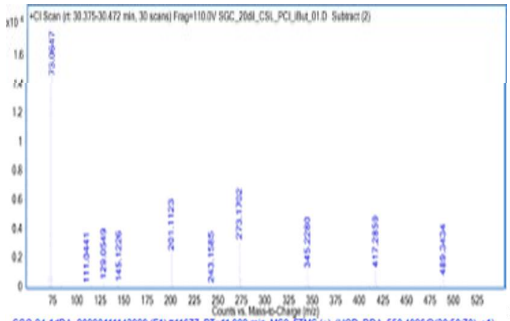


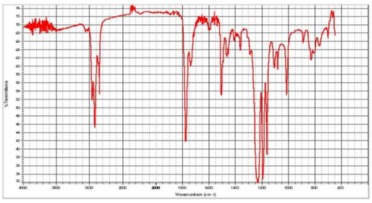

I.V Drug Products Devices






Chemical Characterization of Leachables in Catheter Device





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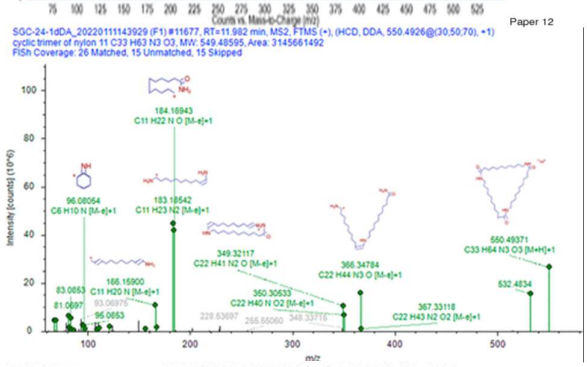
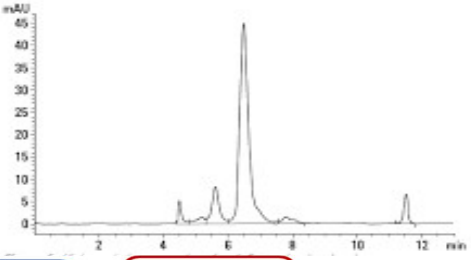
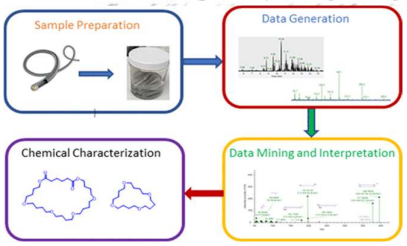


Column:	Agilent AdvanceBio SEC 300Å, 2.7 µm, 7.8 x 300 mm (p/n PL1180-5301)
Flow rate:	1 mL/min
Mobile phase:	150 mM phosphate buffer, pH 7.0
Wavelength:	220 nm
Temperature:	ambient
Injection volume:	5 µL
Sample:	IgG





Recent Publications:

[1] Double chamber Devices and their Advantages.

[2] Challenges for Alternate Packaging materials for Injectable Devices.

[3] Nasal Spray is the Most Suitable Options to Replace Injectables for Microgravity and Packaging Challenges.

[4] Packaging Challenges for "Multi-planets"

[5] Mining on MARS and MOON for Primary Packaging materials.

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New studies on leachables in commercial scale protein drug filling lines using stir bar sorptive extraction coupled with TD-GC–MS and UPLC/QTOF-MS/MS analytic **https://www.sciencedirect.com/science/article/abs/pii/S0378517318308512**

Infrared Spectrum of a Heptane Extract of a Polycarbonate Component

Biography

Anupam completed his Post Graduate in Packaging and Polymer Science (PG) and worked for 30 years in different Pharmaceutical companies in Packaging Development department in India and abroad. Widely travelled throughout the world. Gain and share his thoughts with scientist from various institution and industry professionals. Author's Technical book **" Packaging Technology An advance Practical approach ", Packaging Innovation for Microgravity and Regulatory Audit observations and style of Responses. Published from Germany and Amazon is distributing** to 77 countries. Book is available in www.amazon.de, www.amazon.com and www.morebooks.de. He has more than 15 publications in national and International Journals. He currently works mainly in packaging device innovation for oncology and non-oncology and Biosimilar products. Doing consultancy for " bioxytran Inc, MA,Boston, USA and First Person Solutions, PA, USA for last four years as a Principal Consultant.

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