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Drug Discoveries and Challenges for Polymeric Medical Packaging Devices

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Abstract

Background of this study is to analyze different kind of challenges are facing during stability studies of the product. Significance of this study is whether the primary Medical Packaging devices are compatible with the product or not. Basic methodology is used wide ranges of Analytical testing required to avoid market complaint and financial loss of the company. Major findings of the studies are to provide solutions for the respective problems in different options. Inshort this Article is going to impact hugely those are working in R&D and production line as well.

Keywords: Extractable, Leachable, Water and Leakages.

Introduction

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. In case of "I.V infusion bottles Poly carbonates and Poystyrene are using. Need to be very much careful leachability problems especially leachables are additives, colourantsanti oxidants, 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.

Solid Dose Drug Products Devices

Pic#1

Pic#2

PET Transparent and HDPE opaque Bottle

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. WVTR test is the most important test for polymeric bottle with product to ensure products shelf life. for children. Very few cases PVC bottles being used. Sometimes leachable issues observed for oral spray.

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.

Liquid oral Drug Products Devices

Pic#3

Pic#4

PET bottles for Padeatric product


Pic#5 Pic#6

Oral drop products in Amber Glass bottle & Doses application process


Pic#7 Pic#8 Pic#9

Amber dropper bottle for oral Drugs, poplymeric droppers with marking and Bottle Label

Pic#10 Pic#11

Oral Inhaler Devises and Leachability problems in product showing blue colour in spray.

PET bottles,PP and Aluminium ROPP cap are widely using for packaging of liquid oral products for children. Very few cases PVC bottles being used. Some times leachable issues observed for oral spray.

Practical Problems:

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

Solutions

- Need to change the polymer..Leachability test need to carryout.

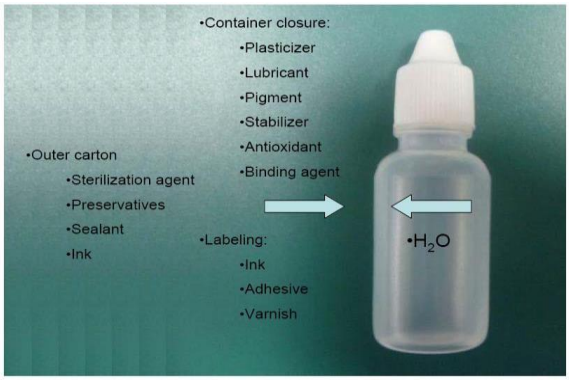
C) Ophthalmic Drug Products Devices


Pic# 12 **Pic#13**

Eye drop application system and bottle design

Pic# 14 (Single doses eye drop devise design)

Mostly LDPE and few cases PP bottles are using for packaging for ophthalmic products. PP cap with tamper evident locking is must.Inside PVC plug is using. Leakage is the most common issue need to take. LLDPE is using for single dose eye drops.



Pic#15

Essential Leachable of polymeric Bottle

Practical Problems

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

Perfect CAP design plays an important role for accurate product dispensing doses. LDPE and HDPE bottle and PP cap are using. All parts are shown in the drawings.

Practical Problems:

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

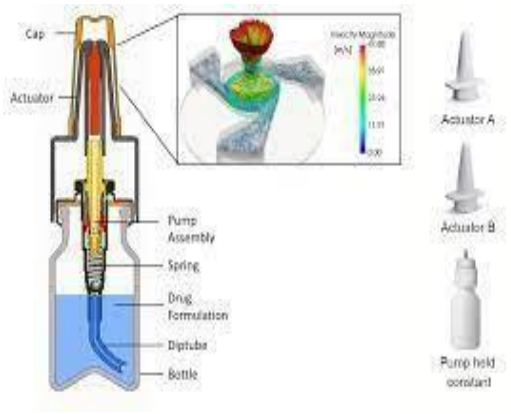
Solutions

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

D) Nasal Drug Products Devices


Pic #16 **Pic#17**

Nasal drop and spray application



Pic#18(Different parts of the Dispensing devise shown here)

Pic#19 **(Nasal spray application system and devise position)**

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) Injectable Drug Products Devices

Pic# 20 (HIP Tray for Prefilled syringes)

Pic # 21 (Auto injector)

COC and COP are mostly using for vials, syringes and cartridges. Protein adsorptions is the one most serious issue. Autoinjector is using for muti dosing and accurate dosing purposes

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

F) I.V Drug Products

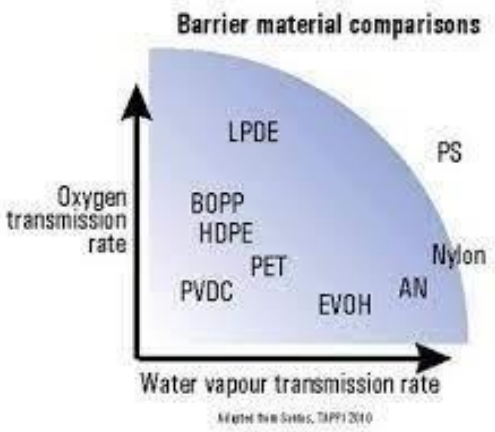
Pic#22 (Catheter made by PVC or Polycarbonate

Pic # 23 (PVC bag for I.V)

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

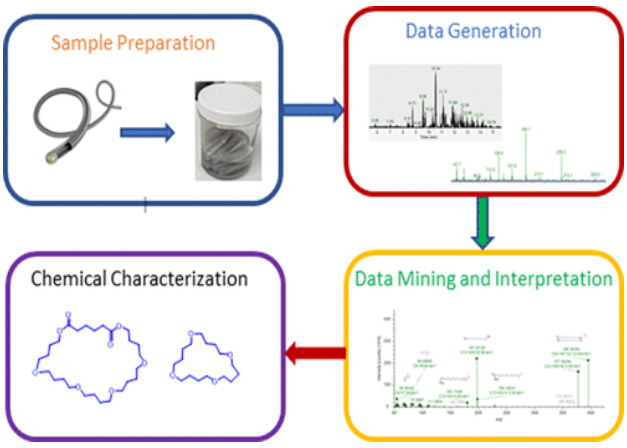
Solutions

- 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

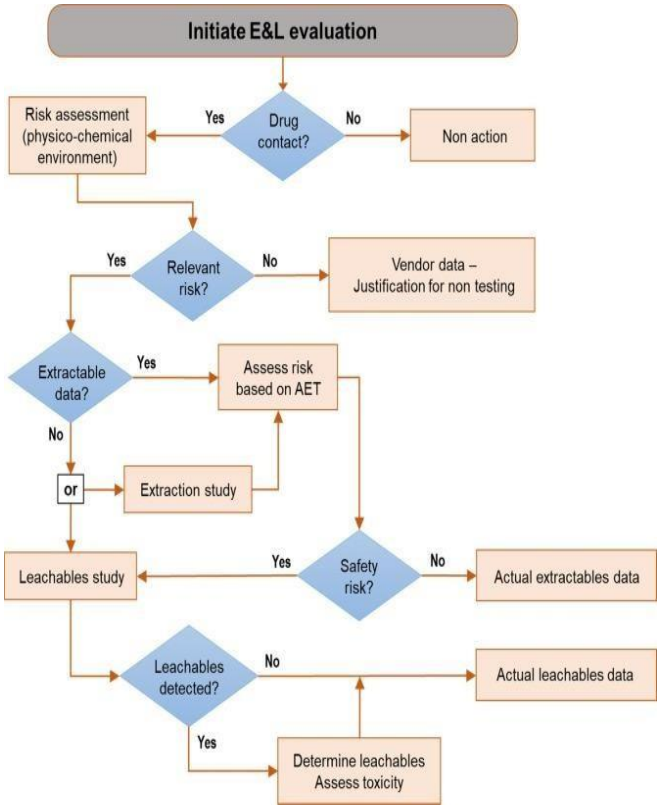


Pic#24(WVTR Polymeric comparisons)

Pic#25 (uses of Polymers in Medical Devices)



Pic#26 (Testing of Polymers)



Pic# 26 (Leachables from Polymeric materials in contact with drugs. Analytical approaches

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, anti-fogging, 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

Table 1

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

Table 2

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

Polymers are typically classified by different Criteria Table#3

Additives –Advantages / Disadvantages of Plastic materials Table# 4

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	-

Table#5

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 - Thiobisphenolsandothers
Plasticizers	-Gives the plastics flexibility anddurability - Low extractabilityby water andsolvent - Stability to heat and light - Low odor,taste and toxicity	-Phthalates (esters) - Fatty acids (Stearic acid, Palmitinixc acid) - Oils such as epoxidizedlinseed oil, tall-oil - Adipates, azelates,sebacates - Derivates of glycols and aliphatic dicarboxylic acids
Antidegradants	-Stops the degradation ofthe finished plastic product -	Antiozonants (ozoneprotection, barrier) - Alkylphenylamines UV-Stabilizers (UV protection against discoration) - Benzophenones - Benzotriazoles - Salicylate eters - Cyanoacrylates - Malonates - Benzilidenes - Polimericsterically 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 - Aminoalkylsilane s - Alkyl-alkoxysilyl -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)

Extractables from LDPE and HDPE
Table#6

Sl#	Component	Source
a	Aliphatic	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 fromLDPE / HDPE (Widely using in prefilled syringe Table#7

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
Table#8

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 Table# 9

Sl#	Polymer	Analytics /Extract	Component /Level [ppm]
a	PE	ICPMS, ICP-OESmicrowavedigestion	Mg / 0,5 Si / 16,0 Ca / 32 Zn / 1,8
b	LDPE	ICPMSmicrowavedigestion	Mg / 2,3 Al / 8,9 Mn / 0,01
c	PVC	ICP-OES, Al / 0,2/Extraction with5% acetic acid 2h122°C	Al / 0,2 Ca / 0,4 Si / 0,9 Zn / 0,4
d	Perfluoro elastomer	ICP-MS, IC /water 4 weeks80°C	F / 1,1 Metals < 0,1 TOC 1,54

Risk AssessmentTable#10

Solvent	Possible Migrants	Risk
Aqueous	Mostly	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 Table#11

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)	yes	Not applicable
	Canister	Yes(if coated)	Not applicable	Yes(if coated)	Not applicable
	Drug product	Not applicable	yes	Not applicable	no

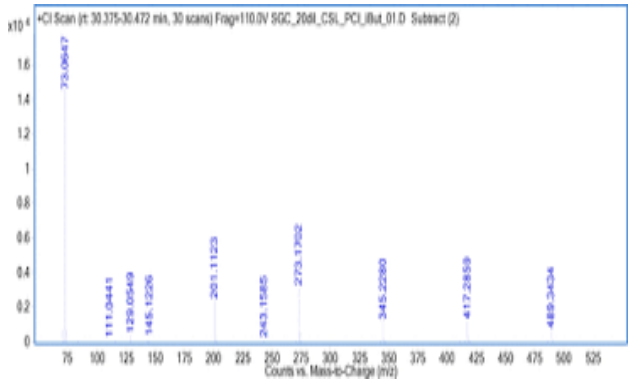
DPI	Protective secondary packaging(critical to the performance of the drug product)	Yes	Not applicable	yes	Not applicable
	Mouthpiece	Case by case	No(one time in-use study)	yes	Not applicable
	Canister	Yes(if coated)	Not applicable	Yes(if coated)	Not applicable

Table#12

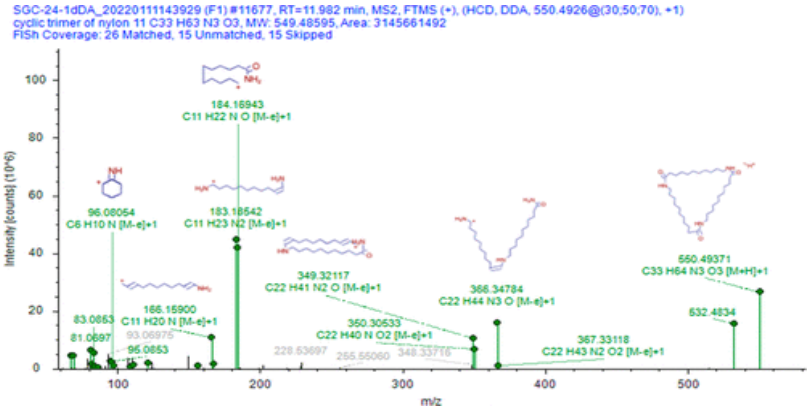
Product Type		**Controlled extraction study**	**Leachables study**	**Routine Extractables testing**	**Routine Leachable testing**
Inhalation solution/ suspension	Primary packaging material(polymeric)	yes	Not applicable	yes	Not applicable
	Protective secondary packaging(critical to the performance of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

Packaging Materials Associated with Parenteral Products Table#13

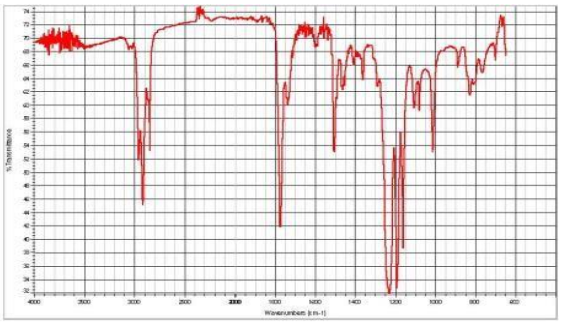
Dosage Form	Components	Example Material
Inhalation	MDI/DPI components, canisters, valves, gaskets, blister packs, bottles, actuators, mouthpiece, pumps, closures, liners, label/inks	polyolefins, styrene butadiene rubber, ethylene propylene diene monomer, rubber, thermoplastic elastomers, polyacetal, 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, polyamides, 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	
Associated Components	nebulizers, dosing spoons, dropper, dosing cups	polyolefins, glass, rubber, thermoplastics, polyesters



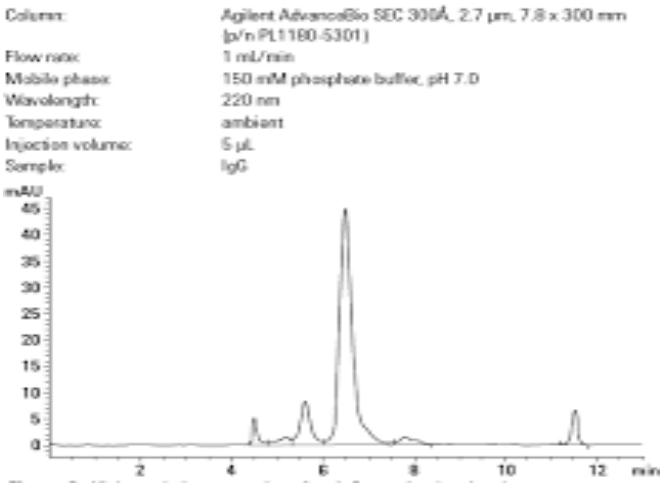
Graph #1
Chemical Characterization of Leachables in Catheter Device



Graph #2
Different polymers toxicology testing results



Graph# 3
Infrared Spectrum of a Heptane Extract of aPolycarbonate Component



Graph#4
Mass Spectrum of Irganox 168

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