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Drug Discoveries and Challenges for Polymeric Medical Packaging Devices

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1. 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.

2. 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. Incase 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 (Figures 1-6) and (Tables 1-13).

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.

Figure 1: Solid Dose Drug Products Devices
Fig1a and Fig1b: PET Transparent and HDPE opaque Bottle

Figure 2: Liquid oral Drug Products Devices
Fig 2a and 2b: PET bottles for Padeatric product

Fig 2c and 2d: Oral drop products in Amber Glass bottle & Doses application process

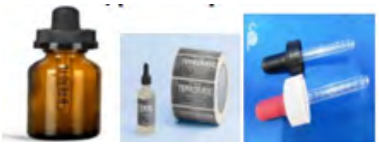

Fig 2e and 2f: Amber dropper bottle for oral Drugs, poplymeric droppers with marking and Bottle Label.

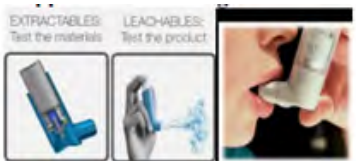

Fig 2g and 2h: Oral Inhaler Devises and Leachability problems in product showing blue colour in spray.

Figure 3: Ophthalmic Drug Products Devices
Fig 3a and 3b: Eye drop application system and bottle design

Fig 3c: Single doses eye drop devise design

Figure 4: Nasal Drug Products Devices
Fig 4a and 4b: Nasal drop and spray application

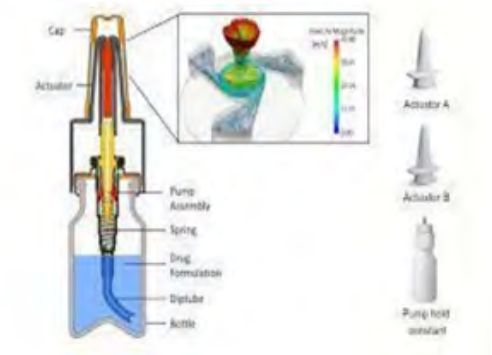

Fig 4c: Different parts of the Dispensing devise shown here

Fig 4d: Nasal spray application system and devise position

Figure 5: Injectable Drug Products Devices
Fig 5a: HIP Tray for Prefilled syringes

Fig 5b: Auto injector

Figure 6: I.V Drug Products
Fig 6a: Catheter made by PVC or Polycarbonate

Fig 6b: PVC bag for I.V; Mostly PVC is using for manufacturing of IV Bags. Ethylene vinyl Acetate also using.

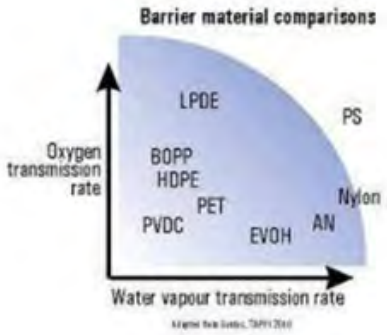

Fig 6c: WVTR Polymeric comparisons

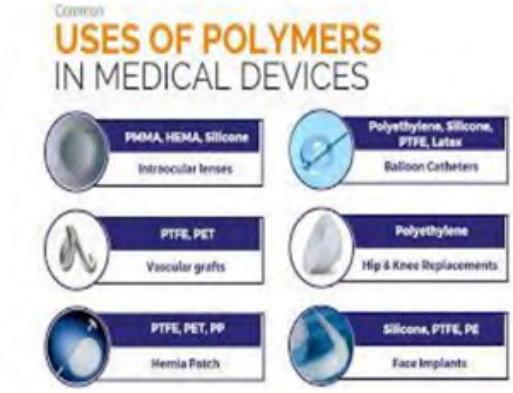

Fig 6d: Uses of Polymers in Medical Devices

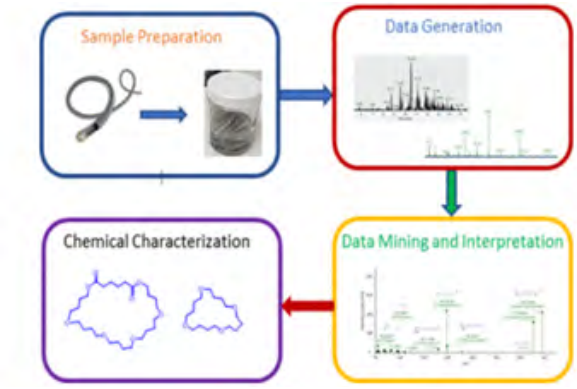

Fig 6e: Testing of Polymers

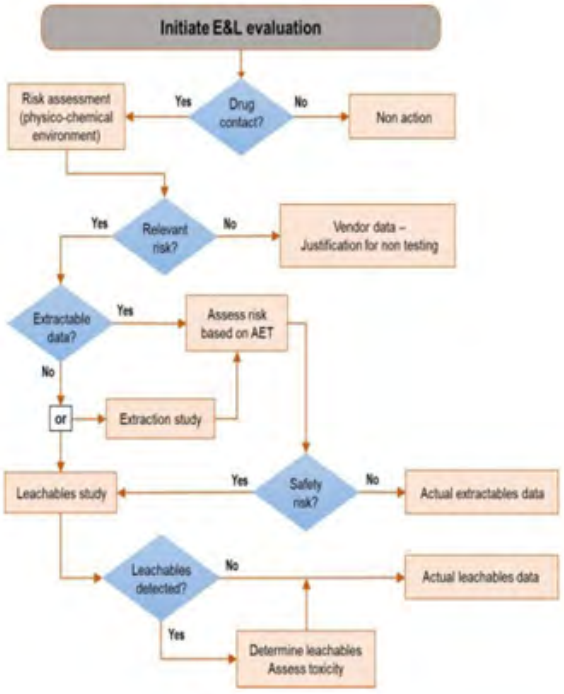

Fig 6f: Leachables from Polymeric materials in contact with drugs. Analytical approaches

Table 1: Acceptance criteria for E/L study in different media (one specific example)

Compounds	Analytes	Quantification limit (ppb)
Elements	Mg	50
	Al	10
	Cr	10
	Mn	10
	Fe	10
	Ni	10
	Cu	10
	Zn	50
	Cd	2
	Sd	2
	Pb	2

Table 2:

Compounds	Analytes	Quantification limit (ppb)
Antioxidants and UV absorbers	2, 2- methylene-bis(4-methyl-6-tert butyl-phenol)	10
	2,6-di-tert-butyl-4-sec-butylphenol	5
	2,6-di-tert-butyl-N, N-dimethylamino-p-cresol.	10
	2,4-dihydroxy benzophenone.	5
	2-hydroxy-4-octyloxy benzophenone	5
	2-hydroxy-4-methoxy benzophenone	5
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 3: 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

Table 4: 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	--

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 - 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 - 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 - Aminoalkylsilanes - 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)

Table 6: 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

Table 7: 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

Table 8: 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

Table 9: Polymers and it's standard extractable(metal) value

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

Table 10: 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

Table 11: Do and Not to do Leachables and Extractables Testinyg for Inhalers

Product Type		Control led extracti on study	Leacha bles study	Routine Extracta bles testing	Routine Leacha bles testing
MDI	Valve compone nts(poly meric – 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
	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

Table 12:

Product Type		Controlled extraction study	Leachables study	Routine Extracta bles testing	Routine Leach able 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

Table 13: 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, polyamides, polystyrene, thermoplastic elastomers, silicones, polyesters, epoxides, cellophane, fluoropolymers, styrenics, paper / paperboard, metals, glass
Ophthalmic Transdermal	bottles, droppers, screw caps, liners, tips, tubes/liners, labels/ink adhesives, membranes, barrier films, reservoir, coatings, blister packs, preformed trays, overwraps, substrates, topical aerosol components	polyolefins, acrylics, vinyls, epoxies, polyamides, thermoplastic elastomers, polyesters, cellophane, glass, paper / paperboard, metals
Associated Components	nebulizers, dosing spoons, dropper, dosing cups	polyolefins, glass, rubber, thermoplastics, polyesters

2.1. Practical Problems

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

2.2. Solutions

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

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. Sometimes leachable issues observed for oral spray.

2.3. Practical Problems

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

2.4. Solutions

a) Need to change the polymer. Leachability test need to carryout.

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.

2.5. Practical Problems

a) Discoloration of the product.
b) Inaccurate dispense of the product.
c) Bottle wall is very hard to squeeze.
d) Product Leakage.

2.6. Solutions

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

2.7. Practical Problems

a) Discoloration of the product.
b) Inaccurate dispense of the product.
c) Product Leakage.

2.8. Solutions

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

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.

2.9. Practical Problems

a) Discoloration of the product.
b) Inaccurate dispense of the product
c) Gliding force is not uniform.
d) Plunger movement is not smooth inside the syringe.

2.10. Solutions

a) Advisable to use Check the "Extractable and Leachable test report" and take the necessary changes.
b) Advisable to use Polymeric Needles.
c) Advisable to use "Fluro coated" rubber stoppers. or plungers.
d) 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.
e) Use"Blow back vials and Blow back Rubber stoppers to avoid product leakage and perfect crimping as well.
f) For "Double chamber PFS" Accurate doses of the product depends on the smooth movements of the Plunger Rod and "inner Plunger".

Mostly PVC is using for manufacturing of IV Bags. Ethylene vinyl Acetate also using.

2.11. Practical Problems

a) Discoloration and lumps observed.
b) Inaccurate dispense of the product
c) Improper fitment of the pipe with the cap.
d) Leakage observed in the pouch. Ink leachability into the product.

2.12. Solutions

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

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

3. Typical Plastic Additives

a) Lubricants, antistatic agents, initiators, stabilizers, impact modifiers, antioxidants, bactericides catalysts., blowing agents, processing aids, plasticizers, colourants, brighteners, release agents, vulcanizing agents

References

1. Book- Packaging Technology an advance Practical Approach, By Anupam Chanda.
2. COMPARISON OF POLYMER MATERIALS FOR BOTTLES