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Packaging of Non-Injectable Liquid Pharmaceuticals: A Review

Harshita Raina, Anil Jindal*

Department of Pharmacy, Birla Institute of Technology and Science Pilani, Pilani Campus, Rajasthan-333031, India.

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ABSTRACT

Stability of the pharmaceutical product is strongly influenced by the type and material of packaging, thereby it is gaining substantial attention during the formulation development. Selection of suitable packaging material depends upon several factors which include type of dosage form, route of administration, chemical nature of the active pharmaceutical ingredients and excipient used in the formulations. Non-injectable liquid formulations such as elixirs, suspensions, syrups etc are less susceptible to interaction with packaging material when compared to that of the injectable formulations, probably due to the difference in processing conditions used during the formulation development. In the present review, we focus on the packaging aspects of non-injectable liquid formulations. Different packaging materials, which can be used for packaging of non-injectable liquid formulation are discussed. Regulatory aspects of Unlisted State Food and Drug Administration [USFDA] and European Medicines Agency [EMA] are also highlighted. Additionally, packaging of non-injectable liquid formulation for pediatric use is discussed.

INTRODUCTION

Pharmaceutical packaging is considered an integral part of the formulation development in the industry and exerts profound impact on the stability of drug product throughout product shelf life. Therefore, pharmaceutical packaging material should have following desirable characteristics. 1) It should `protect the drug product from the environmental conditions such as light, reactive gases e.g. oxygen and moisture, 2) It should be compatible with the dosage form and should not interact with any of its components to produce undesirable changes, 3) It should be non-toxic and 4) It should be FDA approved (Croce *et al.*, 1987). Selection of packaging material is based upon the type of dosage form, route of administration, chemical nature of the active pharmaceutical ingredients and excipient used in the formulations. Among the factors enlisted, type of dosage form and route of administration significantly affect the selection of container closure system and packaging material as well. For instance, liquid dosage forms are more likely to interact with the packaging materials as compared to solid dosage forms. Moreover, among the liquid dosage forms, non-injectable formulations are less susceptible to interaction with packaging material as compared to the injectable formulations due to significant difference in the preparation techniques.

Table 1: Non-injectable liquid formulations.

Route of administration	Typical liquid formulations
Oral	Elixirs, emulsions, extracts, fluid extracts, solutions, gels, syrups, spirits, tinctures, aromatic waters, and suspensions.
Topical	Aerosols, solution and suspension
Ophthalmic	Solution and suspensions

Typical non-injectable liquid formulations with the possible route of administration are summarized in table 1. In the present review, we focus on the packaging aspects of non-injectable liquid formulations.

* *Corresponding Author*
Anil Jindal, Department of Pharmacy, Birla Institute of Technology and Science Pilani, Pilani Campus, Rajasthan-333031, India.
Email: anil_jndl @ yahoo.co.in

Different packaging materials, which can be used for the packaging of non-injectable liquid formulation are discussed. Regulatory aspects of Unlisted State Food and Drug Administration [USFDA] and European Medicines Agency [EMA] are also highlighted. Additionally, packaging of non-injectable liquid formulation for pediatric use is discussed.

PACKAGING MATERIAL

Glass

Glass is the most commonly used material in pharmaceutical industries for the packaging of non-injectable liquid formulations. It is used for the fabrication of vials, ampoules, storage bottles, solvent reservoirs etc. Glass contains certain properties, which make it suitable for its use in the packaging of pharmaceutical products. These properties include FDA approval, high strength, ability to modify in different shapes, its crystal clear appearance, shape and size accessibilities, resistivity towards various chemicals and gases. It can also be flint or colored based upon their use. Flint glasses or crystal glass is transparent in nature, which enables visual observation of the product. They are rigid, clear, can absorb light of 300 nm wavelength and above and consist of preferably lead and potassium silicates while colored glass are used to protect the light sensitive pharmaceutical products from photo degradation and hence play a significant role in the stability of such products. Colored glass is usually consists of metal oxides of iron, magnesium etc from which amber or red color are the choice of containers for pharmaceutical purposes. The major issue with glass containers is the challenge of manufacturing high weight containers and fragile nature of glass (Croce *et al.*, 1987).

Composition of Glass

Glass is composed of mainly silica which is added in the form of sand and two or more substances such as soda ash i.e. sodium carbonate, limestone i.e. carbonates of calcium and cullets. Cullets are the broken or melted glass which is added during the manufacturing and act as fusion agents in the containers. Glass also consists of cations such as sodium, potassium, zinc, calcium, barium, and silicon or anion like oxygen. By varying the elemental composition, various properties of the glass can be adjusted according to the use (Croce *et al.*, 1987, Carter, 2008). Effect of elements on various properties of glass is summarized in table 2.

Table 2: Effect of elements on the properties of glass.

Element	Property of glass
Sodium	Decrease chemical resistance
Boron	Aid in melting process
Lead	Impart clarity and brilliance, softness
Aluminum	Increases hardness, durability and chemical resistance

The natural glass usually consists of silicon and oxygen tetrahedron wherein each silicon cation is covalently bonded by four oxygen anions and each oxygen anion is bonded with two silicon cations. Introduction of any cation in the glass to improve various properties results in breaking of silicon - oxygen linkage and formation of new electrostatic bonds. These new bonds are weak in nature and hence glass becomes chemically reactive. For instance, addition of more than 12-14% of boric oxide reduces the chemical resistance of glass (Carter, 2008)

Manufacturing of Glass

Manufacturing of glass is based on its use and type of the container. There are various processes by which glass can be made. Generally, the raw glass materials consisting of sand, soda ash, cullets, limestone etc are melted in hot furnaces at high temperatures i.e. 1500 ºC for 24 hours. The molten glass is then cooled up to 1000-1200 ºC. The temperature plays an important role in strength and quality of the container. The cooled glass is then allowed to cast into various shapes by various methods such as blowing, tubing, pressing, drawing etc (Croce *et al.*, 1987; Dimbleby, 2011).

Types of Glasses

Based on surface properties, glass can be classified as Type I, II, III and NP. Type 1 and type II glass are highly resistant and generally considered suitable for the packaging of parenteral pharmaceutical products whereas type III and NP glass are used for the packaging of non-injectable liquids such as oral and topical formulations[3]. Keeping scope of the chapter in mind, we will describe type III and NP glass in detail.

Type III

These are simple type of soda lime glass without treatment of the surface with sulphur. It is therefore also known as untreated/regular soda lime glass. Type III glass is generally used for dry powders and the solutions which are not sensitive to alkali i.e. unbuffered solutions or non aqueous and liquid formulations. Such type of glass is not used for the solutions which are to be sterilized in final containers (Croce *et al.*, 1987, Carter, 2008, Ambrosio, 2002).

Non-parentral glass

These are general purpose soda lime glass which is used for oral and topical formulations. They are not preferred for the parentral preparations as most of the alkali release occur from such types of glass (Croce *et al.*, 1987, Carter, 2008, Ambrosio, 2002).

General Considerations

While selecting glass as a packaging material for the non-injectable liquid formulations following factors should be considered.

Delamination

Separation of glass sheets from the product contact surface is termed as delamination of glass containers. It results in the appearance of visible flakes in the drug product. Delamination

of glass is a major concern in the quality of parenteral drug products.

However, delamination can occur whenever aqueous solution of drugs comes in contact with glass surface. It has also been observed that lack of glass surface integrity produces significant effect on the stability of drugs which is formulated in the form of aqueous solutions. In one study, Watkins MA *et al.* showed that glass containers negatively influence the stability of drug in solution (Watkins, *et al.*, 2014). They have shown that drug degradation occur due to the interaction of drug with delaminated glass surfaces within glass container. In another study, Iacocca *et al.* (2007) demonstrated that temperature, terminal sterilization and chemical structure of the drug in solution were the key factors which affects glass durability. They have shown that vials coated with silicon oxide revealed less dissolution of glass as compared to uncoated vials containing glutaric acid, stored at 40°C (4 h at 350°C, two terminal sterilization cycles).

Leaching of alkali

A Glass container mainly constitutes sodium, calcium etc alkali metals. Such alkali metals have a tendency to get leached out from the glass surface.

This process is known as dealkalization and mainly occurs due to attack of water which further leads to removal of alkali from the glass surface or depletion of alkali content from the surface. Dealkalization leads to loss of brilliance and this phenomenon is called as weathering (Mithal, 1997). In case of weathering, the glass surface comes in contact with water. Water has tendency to extract the alkali atoms from the surface which further leads to weakening of bonds leading to loss of brilliance.

This layer can be easily washed by water or weak acid leading to removal or depletion of the alkali atoms. The depleted alkali zone is mainly replaced by the protons and hence an ion exchange phenomenon occurs due to dealkalization process. Dealkalization can also sometimes lead to flaking (Carter, 2008). The silicon atoms present on the glass surface gets entangled with the water molecules and form silicic acid which further ionizes and hence is responsible for weakening of structure and formation of flakes. It is therefore become important to consider the delamination potential of glass containers for the non-injectable aqueous based liquid formulations (Dimbleby, 2011; Mithal, 1997).

Photodegradation of drugs

Some drugs like indomethacin, imipramine, and thyroxine, nifedipine, riboflavin, nitroprussides fluoroquinolones such as ofloxacin (in ointments) undergo degradation on exposure to sunlight (Asker, 2006, Welankiwar *et al.*, 2013). Such types of drugs, if kept in glass containers undergo discoloration, degradation during its shelf life. Glass containers have tendency to absorb visible as well as ultraviolet light (Asker, 2006). In such cases the container should have property to prevent the light to pass through the surface. Amber colored glass is preferred over simple glass containers in order to avoid the photo degradation (Mithal, 1997).

Drugs such as doxorubicin undergo photo degradation in clear glass containers but can be prevented using amber colored glass. Amber color glass not always prevents the photo degradation. Drugs such as adrenaline can get easily degraded in amber colored glasses. In such cases plastic containers are more preferred over the colored glass containers (Asker, 2006).

Container size

Container size plays an important role in the stability of pharmaceutical formulation. Container size is inversely proportional to the amount of alkali leached from the containers. This is because of low surface to volume ratio of the container and the solution present in it. If the container is small in size, the area under the contact of alkali increases, thus leaching occurs to a great extent. However, in case of large containers, the surface area with respect to the solution present in the container, so less leaching takes place (Ambrosio, 2002).

Mechanical properties

Design of the container is also to be taken into consideration. Glass container should be such that it can overcome the heat, hydrolytic degradation. For this purpose appropriate amount of various metal oxides is to be kept in order to prevent such types of degradation (Carter 2008).

Quality of the container

Container should be such that it retains its quality even after long exposure to sunlight and other environment conditions such as moisture. Cerium oxide is incorporated in glass which prevents the discoloration of the glass, thus maintaining its quality. The surface of glass is treated in order to avoid abrasion and weathering (Ambrosio, 2002).

Tests for Glass Containers

There are several quality control tests for glass which are performed in order to check its property such as hydrolytic resistance, surface quality etc.

Test for Hydrolytic Resistance: Inner Surface Test (Test A)

This test is performed to evaluate the quality of outer surface of the glass container. The test is performed under controlled conditions with the help of thermocouples, pressure gauge, and autoclave. Quantity of glass containers to be taken for the test is based upon the capacity of the container. Briefly, Wash the glass container with distilled water for the prevention of the entry of air bubbles and dry it properly. Fill the containers with carbon dioxide free water and wrap properly with aluminum foils. Place the containers in autoclave within the temperature range of 100-120°C for 20 minutes followed by 120°C for 60 minutes and then 120°C for 40 minutes. Remove the containers out of the autoclave after the equalization of the inside pressure with the atmospheric pressure.

Use methyl red solution as an indicator. Perform the titration using hydrochloric acid [HCl] in burette and compare the end point with the carbon dioxide free water taken as a blank. The volume of HCl required to get the end point is noted and subtracted from the final reading of the blank. The result should not exceed the limits mentioned in table 3 (Welfare, 2007, European Pharmacopoeia 5.0, 2005).

Table 3: Limits for Hydrolytic test (test A).*

Container capacity	No. of containers	Test solution volume (ml)	Volume of 0.020N HCl for Type I or II glass(ml)	Volume of 0.020N HCl for Type III glass(ml)
NMT 1	At least 30	10	2.0	20.0
1-2	At least 20	25	1.8	17.6
2-5	At least 10	50	1.3	13.2
5-10	At least 5	50	1.0	10.2
10-20	At least 5	50	0.80	8.1
20-50	At least 5	60	0.60	6.1
50-100	At least 3	100	0.50	4.8
100-200	At least 3	100	0.40	3.8
200-500	At least 3	100	0.30	2.9
>500	At least 3	100	0.20	2.2

*(Welfare, 2007; European Pharmacopoeia, 2005).

Powdered Glass Test: Glass Grain Test (Test B):

Take three out of all the containers, rinse and dry them .Crush the containers into coarse fragments and transfer them to the mortar. Pass the crushed fragments through sieves 710(mu) m and 425(mu) m and sift properly. Separate the fragments retained by sieve 710(mu) m. Glass fragments obtained on sieve 425(mu) m are taken for further procedure. Magnets can be used for removal of metals such as iron. These glass fragments can also be suspended in acetone to remove metal impurities. Immerse the glass fragments completely in acetone, wash and dry.

Take the fragments out of the dried glass fragments, in conical flask with of carbon dioxide free water and titrate with HCl. Compare with the blank containing only carbon dioxide free water. Perform the hydrolytic tests. The limit is same as test A with same limits (European Pharmacopoeia 5.0, 2005).

Etching Test: Surface Treatment Test (Test C):

This test is performed to check whether the surface of container is treated or not i.e. to differentiate between Type II and III. Select and rinse the containers with distilled water, hydrofluoric acid and hydrochloric acid in ratio 1:9.Wash the containers several times with water and perform test A. If the values exceed the limits of test A, then it is concluded that glass containers are surface treated (European Pharmacopoeia 5.0, 2005).

Water Attack Test

This test is performed for the treated glass containers, i.e., type-II glass. The treated glass container loses its resistivity to chemicals, solvents if they are repeatedly subjected to autoclaving. Water attack test is generally performed in order to check the alkali limits in the treated glass containers. Rinse and dry the glass containers with purified water. Fill the container with the purified water free from carbon dioxide and seal them properly with aluminum foils. Subject these containers to autoclave for temperature 121 degrees Celsius for 60 minutes. Take the containers out of the autoclave on the equalization of the pressure. Take 100 ml of this content in 250 ml conical flask and add methyl red solution as an indicator. Titrate the solution with 0.02 N sulphuric acid and observe the end point. Compare the end point of the test solution with that of blank and subtract the blank reading from it. The volume limits of 0.02 N sulphuric acid for type-2 glass with capacity of 100 ml or less should not exceed 0.7 and 0.2 for more than 100 ml (United States Pharmacopoeia USP 38 and National Formulary NF 33).

Spectral Transmission: Spectral Transmission Is Done Using Uv-VIS Spectrophotometer

Cut the Glass with uniform wall thickness and place into a holder. Carefully rinse and dry the pieces. Cover the holder properly with an opaque paper. The glass pieces (specimen) should have more length than the slit. Mount the specimen carefully and kept in the UV-VIS Spectrophotometer. Pass the beam of light in such a manner that it is perpendicular to the surface of specimen. Measure the transmission in region of 290-450 nm. The containers for the parentral purposes should not exceed the limits mentioned in the table 4 (European Pharmacopoeia 5.0, 2005, United States Pharmacopoeia USP 38 and National Formulary NF 33).

Table 4: Limits for the Spectral transmission test.*

Maximum percentage of spectral transmission at any wavelength between 250-450 nm		
	Flame-sealed containers	Containers with closures
1	50	25
2	45	20
3-5	40	15
6-10	35	13
11-20	30	12
More than 20	25	10

*(European Pharmacopoeia, 2005). General Tests and Assays. In United States Pharmacopoeia and National Formulary.

Plastic

Plastic is also widely used for the construction of whole body of the container or a part of the containers. Bottles, bags and tubes are the most commonly used plastic based containers. Moreover, inner side of the metal tubes sometime is also coated with plastic to prevent the interaction between the content of the container and the metal. Plastic based closures are also used for the packaging of pharmaceutical products.

Plastic as a packaging material offer several advantages including unbreakable nature light weight, ability to form different shaped containers, flexibility and durability. Plastic is made from cross linking of synthetic or semi synthetic long chain polymers[2]. High durability and flexibility of the material are due to the cross linked polymeric structures. Certain additives are also added with the building block polymers to improve the various physicochemical properties of the material. In general, different additives include antioxidants, antistatic agents, colors, impact modifiers, lubricants, plasticizers and stabilizer (Croce *et al.*, 1987;

Ambrosio, 2002).

Plastic has a tendency to develop a static charge on the surface because of its insulating nature which further is responsible for the attraction of dust particles on the surface of plastic making it dull in appearance and contaminate. Additives such as long chain aliphatic amines, phosphate esters act as antistatic agents which prevents this charge to develop on plastic surface. Fillers are used to add to the strength of the plastic and to increase the bulk quantity of the whole plastic material. Plastics have a tendency to permeate oxygen through its surface hence oxygen reacts with the plastic surface, breaks its polymerized long chain structure and react with them which leads to oxidation of the material, hence additives such as antioxidants like phenolic compounds are used to prevent oxidation. Antimicrobials such as silver ion based Microblok are added for prevention from the microbial attack. Increasing the shear stress, plastic may get deformed and cracked.

To prevent this damage, impact modifiers such as acrylic impact modifiers, paraloid are added to increase its strength. Reinforcing agents such as glass fibers and metal powders are added to plastics in order to improve the tensile strength of plastic material.

Plastics melt while processing for smooth flow ability and to mould plastic in various forms. Thus, processing aids like flouoropolymers is used to increase the flow ability of plastic for easy conversion of plastics in variety of forms. Plastics made from simple long chain polymerization are less flexible, thus it is the role of plasticizers such as di-Ethylhexyl phthalate to increase its flexibility. Light stabilizers such as HALS (hindered amine light stabilizers) are available which prevents the photo degradation of the product. Lubricants are added to improve the process of manufacturing of plastic by increasing the flow ability (Deanin, 1975).

Integrity of the plastic depends on the chemical structure of the copolymers bonded together, molecular weight of the plastic, orientation of the molecules, linkage pattern of the copolymers as well as additives present in the plastic.

Plastic Material

Polyethylene

Polyethylene is the most widely used material in fabrication of plastic containers for pharmaceutical purpose. Excellent barrier for moisture and resistance to the attack of strong acids and alkali are the two major advantages of polyethylene while lack of transparency and highly permeable to oxygen, odors and flavors are major limitation of this class of material with respect to their use in pharmaceutical packaging (Croce *et al.*, 1987). Based upon density, polyethylene can be classified in two type's namely high density and low density polyethylene. As the density increases, material become less permeable to reactive gases and hence high density polyethylene is generally preferred over low density material for the packaging of oxygen sensitive drugs (Carter, 2008). Antioxidants are generally added to these polymers to prevent oxidation during processing. Generally used antioxidants are butylated hydroxy toluene or dilauryl thiodipropionate. Antistatic agents such as polyethylene glycol and long chain fatty amides are added to bottle grade polyethylene to minimize the accumulation of dust at the surface of bottles during packaging and storage (Croce *et al.*, 1987).

Polypropylene

Polypropylene is resistant to various chemicals/solvents and heat hence suitable for the packaging of the products which need to be sterilized. However, it is sensitive to hot aromatic solvents and become soften when come in contact with these chemicals. Unlike low density polyethylene, polypropylene is less permeable to reactive gases like oxygen or vapor (Croce *et al.*, 1987). The only disadvantage of the material is that polypropylene become brittle at low temperature and need to be mixed with polyethylene to overcome this problem (Carter, 2008).

Nylon

Nylon is a polyamide based material and generally used in the fabrication of thin walled containers. Nylon based containers can be sterilized by autoclave (Croce *et al.*, 1987). Nylon is also resistant to strong acids and alkali as well as various organic and inorganic chemicals. It provide strong barrier to oxygen while it is highly permeable to moisture (Carter, 2008). It also has a high potential of interaction with the drugs and hence not preferred when the long term storage of drug products is required.

Polyvinylchloride

Polyvinylchloride is used to construct plastic bottles and lamination of inner side of the glass bottles for the packaging of liquid formulations. PVC offers several advantages including rigid, transparent, and stiff in nature. Incorporation of plasticizer in the PVC reduces the rigidity. It is also sensitive to heat and ultraviolent light. To improve the stability of PVC towards temperature and radiations, stabilizers need to be incorporated. Generally used stabilizers to improve the stability of PVC are dioctyl-tin-marcaptoacetate, sulfur, calcium and zinc salts and calcium-zinc stabilization materials[1]. PVC is impermeable to fixed and volatile alcohols, oxygen and moisture. PVC is resistant to acids and alkali but sensitive to oxidizing agents (Carter, 2008).

Acrylic multipolymers

It has several advantages like rigid, transparent, resistant to wide range of chemicals, impermeable to oxygen and cost effective. It is found to be suitable for the packaging of wide range of products including sterile and non-sterile liquid formulations (Croce *et al.*, 1987).

Other Plastic Materials

Other materials like polystyrene, polyterpthalate [PET] and polycarbonates are also used in the packaging of pharmaceutical products however; these materials are not used for the packaging of non-injectable liquid formulations. For instance,

polystyrene is used for the packaging of solid oral dosage form and dry formulations, PET is used to prepare of packaging films and plastic bottles for the carbonated beverages and polycarbonate is used for the packaging of sterile products (Croce *et al.*, 1987).

General Considerations

Sorption

Sorption is characterized as the loss of formulation constituents due to the interaction with packaging materials (Yahya *et al.*, 1988). A sorption phenomenon is more prominent in liquid formulations as compared to the solid dosage forms. Sorption of drugs from the liquid formulations leads to significance decrease in drug content of the formulations and subsequently affects the therapeutic efficacy of the drug. Martens HJ *et al.* (1990) demonstrated that Diazepam, isosorbide dinitrate, nitroglycerin, and warfarin sodium showed significant sorption of drugs when stored in the dark at room temperature for 24 h in PVC bags while there was no loss of drug content observed when the same formulations were stored in glass bottles and clear flex bags (Martens *et al.*, 1990). In another study, decrease in concentration of diazepam and nitroglycerin was observed within 4 h at room temperature in PVC containers whereas no change in concentration of drugs was observed in glass bottles and polyethylene containers (Yliruusi *et al.*, 1982). Sorption influxes not only the drug content of the formulation but also responsible for the loss of preservatives and pigments from the liquid formulation which subsequently affects the stability as well as performance of the formulation. Significant loss of propyl and butylparaben in oral solutions packaged in PET bottles has been observed. Preservative concentration and temperature influenced the sorption of parabens by the PET (Bergquist *et al.*, 2006). Sorption of pigments by low density polyethylene containers has been reported (Grünert *et al.*, 1983). Factors which affect the sorption by packaging material are pH of the formulation, chemical structure and concentration of the drug, type of packaging material, temperature and contact duration.

Photo degradation

Many active pharmaceutical ingredients degrade when exposed to the ultra-violet [UV] light. This phenomenon is termed as photodegradation of the drugs. Presence of specific functional groups in most polymers like carbonyl and aromatic rings are prone to absorb UV radiations and increase the transmittance of the plastic container towards UV radiations. Moreover, absorption of UV radiation also results in the change in physical and chemical properties of the plastic containers which subsequently affect the stability of the drugs in formulations. Opacifying agents are generally added to the plastic containers to prevent the photodegradation of the light sensitive drugs. Lamination of plastic containers by aluminum foils and use of light resistant secondary packaging materials are the other options to prevent the photodegradation (Mithal, 1997).

Desorption

One or more additives are added in the plastic materials to impart specific properties to the plastic. This additive provides possibility of leaching or migration from the containers to the formulations. Migration of the coloring agents from the plastic containers to the liquid formulations is an example of leaching or desorption of additives. Factors which generally affect the desorption are pH, temperature, solvent type and type of plastic material and additive present in the plastic materials (Croce et.al, 1987; Mithl, 1997).

Permeation

Plastic materials may provide passage to the gases and water vapor and leads to the instability of the packaged formulations. Permeation of oxygen and water vapors through packaging material can be a serious concern for the stability of oxidation and hydrolysis sensitive drugs respectively. Storage conditions like temperature and humidity significantly affect the permeation of gases and vapor and permeation increases with increase in temperature. Type of materials also affects the permeation For instance, nylon provides poor barrier to water vapors as compared to polyethylene (Carter, 2008). Method of manufacturing and type of additives also affects the permeation of plastic based packaging containers. Permeation of volatile oils from the formulations packaged in the plastic containers affect the aroma of the formulation.

Physical stability of the formulation is also affected by the permeation. Certain oil in water type emulsions have shown the permeation of oils from the formulation to the package in hydrophobic plastic containers (Mithal, 1997).

Tests for Plastic

Leak Test

The test is performed to check for any leakage from the container. Invert 10 filled closed containers of water at room temperature for 24 hours. No leakage observed from the container indicates the container is fit for use (Welfare, 2007, United States Pharmacopoeia USP 38 and National Formulary NF 33).

Collapsibility Test

Collapsibility test is performed in order to check the squeezing property of the container. Take container with the required contents. Squeeze the contents with optimum force. 90% of the content extruded indicates at optimum force and temperature indicated the container is fit for use (Welfare, 2007, United States Pharmacopoeia USP 38 and National Formulary NF 33).

Clarity of Aqueous Extract Test

Cut several strips of 20cm sq area from both the sides from the container to be tested. The strips should be taken from the area of the container that is unlabelled, unmarked, and non-laminated. Wash the strips twice with distilled water. Select about

60-65 strips from the washed strips and transfer them in cleaned conical flask of 250ml. Add water to the conical flask and keep for autoclave for 120 ºC for 30 minutes. Carry out the same procedure for the blank containing water. Cool the strips and compare the test with the blank for the clarity (Welfare, 2007, United States Pharmacopoeia USP 38 and National Formulary NF 33).

Non Volatile Residue Test

Take 100ml of extract from the clarity extract solution and heat it to dryness till the constant weight is obtained. The residue obtained should not be more than 12.5 mg (Welfare, 2007, United States Pharmacopoeia USP 38 and National Formulary NF 33).

Biological Test

Biological test is performed to check the compatibility of the container with the humans. The plastic should not react with the solution to cause toxic problems. Prepare the extract and the blank and dilute with PEG 400 and 4.1 volumes of sodium chloride injections respectively. Keep the solutions the type 2 glass container. Agitate the solution properly before withdrawing it with the help of injection.

Table 5: General Considerations of Biological test.*

Blank	Animal	Route	Dose/Kg As per IP	Dose/Kg As per USP
NaCl Injection	Mice	IV	50 ml	50 ml
NaCl + 5% v/v ethanol	Mice	IV	50ml	50ml
PEG 400	Mice	IP	10g	10g
Vegetable oil	Mice	IP	50ml	50ml

*(Welfare, 2007; General Tests and Assays. In United States Pharmacopoeia and National Formulary).

Take healthy albino mice weighing 17-23g and group them in test and blank. Inject the extracted sample in the test group and blank in the blank group. Observe the mice for 0, 4, and so on till 72 hours. Compare the test group with the blank for any reactivity. If two or more mice die, continue the test with 10 more mice. The fitness of plastic is indicated if no single mice undergo reactivity. General considerations for the biological tests including route of administration dose and blank is summarized in table 5 (Welfare, 2007, United States Pharmacopoeia USP 38 and National Formulary NF 33).

Intracutaneous Test

It is done in order to find any local toxicity if occurred due to the reactivity of the container with the product. Take three rabbits for each sample to be tested. Remove the hairs from the surface to be examined and clean it with dilute ethanol. Inject or use an implant to be tested of test and blank on same animal at two different sites. Observe and compare the local area for the edema, erythema and necrosis of test with that of blank. Compare the limits by calculating the score for the local toxicities according to the table 6 and 7 (Welfare, 2007, United States Pharmacopoeia USP 38 and National Formulary NF 33).

Table 6: Score for erythema and eschar formation.*

Erythema and eschar Formation	Score	
	As per IP	As per USP
No erythema	0	0
Very slight erythema	1	1
Well-defined erythema	2	2
Moderate to severe erythema	3	3
Severe erythema to slight	4	4

* (Welfare, 2007; General Tests and Assays. In United States Pharmacopoeia and National Formulary)

Table 7: Score for edema formation.*

Edema formation	Score	
	As per IP	As per USP
No edema	0	0
Very slight edema	1	1
Slight edema	2	2
Moderate edema	3	3
Severe edema	4	4

*(Welfare, 2007; General Tests and Assays. In United States Pharmacopoeia and National Formulary)

Eye Irritation Test

Select healthy rabbits for the test and examine it properly. Restrain the animal and instill 100µl of sterile water for injection as blank in one eye and the sample extract to be tested in other eye. Observe the animal for 24, 48 and 72 hours. Compare the test for irritation with respect to blank.

Metal

Among the non-injectable liquid formulations, aerosols for topical applications are generally packaged in the metal containers. Metal containers offer several advantages including good strength, light weight, low cost of production, good heat conductivity, impermeability towards gases and solvents[6]. Aluminum. Tin, lead, stainless steel with some other elements such as zinc, nickel, chromium can be used in manufacturing collapsible tubes, sachets, containers, foils, cook wares, hardware surgical etc. Aluminum, tin and stainless steel are generally used for the fabrication of containers for the aerosols (Sciarra *et al.*, 1991).

Tin

In topical aerosol containers, tin is generally electroplated on the stainless steel containers. Tin is obtained from casseriate in the form of its oxide. Purity, ductility, malleability, resistance to various gases and water make it suitable for the packaging of pressurized dosage form. High cost and non-resistance to organic solvents are two major drawbacks of tin as pharmaceutical packaging material. According to the need, tin is also used with various other metals to form alloy with different properties. For instance, copper is usually added to tin in order to maintain its rigidity. Tinplated steel, which is used for the packaging of topical aerosols, is usually coated with organic layer, lacquer, resin in order to prevent corrosion as well as to provide a finish to the container (Sciarra *et al.*, 1991). Inside organic layer coating to tinplated steel containers helps to avoid the contact of tin with the product while outer coating is important to avoid

corrosion. Tin free steel is generally used for low cost production and is coated with chromic acid. Tin plated containers are most widely used for the packaging of non-aqueous, non-injectable formulations.

Aluminum

Aluminum is also used for the packaging of topical aerosol. It is the most preferred metal due to its non-corrosive highly compatible nature. Aluminum is susceptible to water and organic solvent such as pure ethanol. It has been found that combination of ethanol and propellant 11 reacts with aluminum based containers and produces many corrosive products. It is used in manufacturing of ferrules which helps in attachment of valve to the container in case of aerosols. These are generally coated with epoxy resins to avoid corrosion (Sciarra *et al.*, 1991).

Stainless Steel

Stainless steel also known as inox steel has high strength, resistant to corrosion, may or may not require coating. They are most widely used in inhalational aerosols and specifically in manufacturing spring used in aerosols (Sciarra *et al.*, 1991).

REGULATORY ASPECTS FOR THE PACKAGING OF NON-INJECTABLE LIQUID PHARMACEUTICALS

Packaging materials come in direct contact with drug formulation for entire period of shelf life and hence exert significant effect on product stability. It is therefore packaging of pharmaceutical product is an important aspect in the process of formulation development in industry. Faulty packaging sometime can be the reason of recall of product from the market. Therefore, different regulatory agencies provide guidelines on the packaging of pharmaceutical products and description of the method of packaging of drug product with details of facilities and control used in the packaging should be included in the product development report. We will provide specific regulatory requirements of USFDA and EMA with reference to non-injectable liquid formulations such as solution and suspension for oral, topical and ophthalmic use (USFDA guidelines, 1999, EMA, 2005).

USFDA guidelines

According to the USFDA, regulatory requirements of the packaging of pharmaceutical product depend upon the dosage form as well as route of administration. Liquid based formulation show high potential of interaction with packaging components. Non injectable liquid formulations are generally packaged in the glass or plastic container and sometime metal containers is used for the packaging of topical aerosols. According to the USFDA, general regulatory requirements of the packaging materials are summered in the table 8.

EMA guidelines

EMA provides the guidelines on the plastic immediate packaging material. These guidelines includes specific requirements for general information, specifications, extraction, interaction and toxicological information of the packaging materials [table 9].

Table 8: General requirements of the packaging materials.

Route of administration	Packaging material	
	Glass	**Plastic**
Oral and topical	Protection from solvent loss, microbial contamination and from light and reactive gasses like oxygen	Protection from solvent loss, microbial contamination and from light and reactive gasses like oxygen
	Container should meets the requirements of USP containers	For LDPE components, USP containers test for the proof of compatibility
		For the proof of safety, patient's exposure to the extracted substances from the HDPE, LDPE and PP should be comparable to the exposure from the same packaging material used to pack foods For chronic regimens, toxicological information of extracted substances need to be provided for the proof of safety
Ophthalmic	Protection from solvent loss, microbial contamination and from light and reactive gasses like oxygen	Protection from solvent loss, microbial contamination and from light and reactive gasses like oxygen
	Data of sterility testing leak testing	Data of sterility testing and leak testing
		Chemical composition
	Container should meets the requirements of chemical resistance of USP containers	Containers should meets the requirements of USP biological tests
		If total weight of the extract is greater than the weight obtained after water extraction, complete extraction profiling is required
	Particulate matters and eye irritants	Particulate matters and eye irritants
		USP containers physicochemical testing

PACKAGING OF NON-INJECTABLE LIQUID PHARMACEUTICALS FOR PEDITRICS USE

Packaging protects the product from chemical and physical instability and from environmental conditions such as light, oxygen and moisture. One more important function of packaging which is to be taken into consideration is to avoid the access of drug product to the child. Such special type of packaging is termed as child resistant packaging. The major objective of the child resistant packaging is to prevent the child from accessing and taking the products which can be harmful to the children. In earlier times the children were at risk of toxicities and poisoning. Severe cases happened in which a large percentage of children underwent paracetamol, aspirin poisoning (Chambers, 1981).

Another case happened in which 5 children died due to high intake of dietary supplements between 1992-93. Consumer product safety commission approved poison prevention packaging act for child resistant packaging in order to prevent harm to children (Mrvos and Krenzelok, 2007). By the year 1880-1966, 63 patents came out with the designs of child resistant packaging which were tested by the children of different ages in order to make them approved.

Till now child resistant package has been designed for solid dosage forms, liquid orals etc. Taking non parental liquid dosage form into consideration an ideal child resistant package should have following characteristics:

1. The closure/cap should not be easily opened by children especially from age 5-11 yrs.
2. The packaging or the closure should be easily accessible to adult i.e. adult friendly.
3. The closure, container should have a good strength
4. Containers should not be fragile in nature.

Glass and plastic bottles are mostly used for the packaging of non-injectable liquid formulations for children. Glass has ideal characters for the child resistant packaging as well as standard containers because of the less reactivity but still some drawbacks make it unfit form some cases. Glass due to its higher weight is not selected for high dose containers and they are difficult to handle because of their high weight, fragile nature, and large storage space requirement as well as handling during transportation Plastic on the other hand are more preferable containers in comparison to glass as they are light in weight, modified with various modifiers and unbreakable and inexpensive. Polymers such as low and high density polyethylene, Polycarbonates, polypropylene are most commonly used in case of liquid orals. The basic disadvantage and problem of choosing plastic is temperature elevation, leaching, sorption which can be cured completely but avoided to some extent. Films containing layer of aluminum and plastics can also be used. Such films are generally selected to form pouches, sachets etc. These can be used because of their inaccessible opening by children and protection against outer environment. Sachets provide an excellent protection from infestation, contamination and are generally used for single dose formulations. Sachets, pouches are generally used for solid oral dosage forms, dry powders. These are out of the scope of this chapter as liquid packaging is avoided in such sachets, pouches (Campbell and Vallejo, 2015).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Glass, plastic and metal are the most widely used materials for the packaging of non-injectable liquid formulations.

Table 9: General requirements of the packaging materials.

Route of administration	Data to be submitted		
	Data	**Material described in Ph.Eur. or in the pharmacopoeia of a Member State**	**Material is not described in Ph.Eur. or in the pharmacopoeia of a Member State**
Oral and topical	General information	Chemical name of the material or any monomer used	Chemical name of the material used or any monomer used, qualitative composition of the material used
	Specifications	As per monograph	Description and identification of the material, characteristic properties like mechanical or physical parameters
	Extraction studies	YES	YES
	Interaction studies	NO	YES
	Toxicological information	NO	YES
Ophthalmic	General information	Chemical name of the material or any monomer used, name of the material supplier	Chemical name of the material or any monomer used, name of the material supplier, qualitative composition of the material used
	Specifications	As per monograph	Description and identification of the material, characteristic properties like mechanical or physical parameters, identification of the main additives, in particular those which are likely to migrate into the contents (such as antioxidants, plasticizers, catalysts, initiators, etc.)
	Extraction studies	YES	YES
	Interaction studies	NO	YES
	Toxicological information	NO	YES

Selection of packaging material is product specific and one material cannot be suitable for packaging of all the products. However, metal containers are used for the packaging of topical aerosols while glass and plastic containers are used for the packaging of oral and ophthalmic liquid formulations.

Choice of packaging material depends upon the number of factors including product stability during processing and storage conditions, type of dosage form, route of administration, chemical nature of the drug.

Now days, apart from the general considerations of packaging, environment friendliness is also in main lead and development of eco-friendly materials for the packaging of pharmaceuticals are of great use with respect to pollution free environment, biodegradability, reusability and quality. Eco friendly materials such as bio-plastics like oxo-biodegradable plastic, hydrobiodegaradable plastic are safe and obtained from agricultural sources. It is therefore a target for generic pharmaceutical industries to focus on the eco friendly packaging materials as well as to achieve the goal. Eco-friendly materials can be the next generation packaging materials for the pharmaceutical products.

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REFERENCES

Croce CP, Fischur A, Thomas RH. Packaging Material Science. In: L. H. Lachmann L, The theory and Practice of Industrial Pharmacy, Lachman L, Lieberman HA, Kanig JL (Eds) Third edition, Varghese Publishing House, Bombay1987:711-732.

Carter, SJ. Cooper and Gunn's Dispensing for Pharmaceutical Students, twelth ed, CBS publishers 2008:357- 391.

Dimbleby V. Glass for pharmaceuticl purpose. J. Pharmacy. Pharmcology 2011;5(1): 969-989.

Ambrosio TJ. Packaging of Pharmaceutical Dosage Form. In: RT Banker SG, Rhodes CT. (Eds) Modern Pharmaceutics, Marcel Dekker Inc. NewYork 2002:588-606.

Watkins MA, Iacocca RG, Shelbourn, TL, Dong, X, Stobba-Wiley C. Impact of Glass Corrosion on drug Substance Stability. J Pharm Sci. 2014;103(8):2456-63.

Iacoccca RG, Allgeier M. Corrosive attack of Glass by a Pharmaceutical compound. Journal of Materials Sciences 2007: 42(3):801- 811.

Mithal BM. A texttbook of Pharmaceutical Formulation. sixth edition, Vallabh Prakashan 1997:355- 377.

Asker AF. Photostability Studies of Solutions and Methods of Preventing Photodegradation. In Pharmaceutical Photostability and Stablization Technology, Piechocki, TJ, Thoma, K, (Eds), Informa Healthcare 2006: 345-378.

Welankiwar A, Saudagar S, Kumar J, Barabde A. Photostability Testing of Pharmaceutical Products. International Research Journal of Pharmacy 2013;4(9): 11-15.

Welfare GO. Containers. In Indian Pharmacopoeia 2007:361-77.

European Pharmacopoeia 5.0. Strasburg, France 2005:303-8.

General Tests and Assays. In United States Pharmacopoeia and National Formulary[USP 38, NF 33], Rockville MD: 88: 661.

Deanin RD. Additives in Plastic, Environ Health Perspect 1975;11: 35–39.

Yahya AM, McElnay JC, D'Arcy PF. Drug Sorption to Glass and Plastics 1988; 6(1):1-45.

Martens HJ, De Goede PN, Van Loenen AC.Sorption of various drugs in Polyvinyl chloride,glass and polyethylenelined infusion containers. Am J Hosp Pharm 1990;47(2):369-73.

Yliruusi JK, Sothmann AG, Laine RH, Rajasilta RA, Kristoffersson ER. Sorptive loss of Diazepam and Nitroglycerin from Solutions to three types of Containers. Am J Hosp Pharm 1982;39(6):1018-21.

Bergquist PA, Kemp EA, Seburg RA, Zhu LM. Acceleration of Paraben Sorption to polyethylene terephthalate: a freeze thaw phenomenon. PDA J Pharm Sci Technology 2006;60(4):240-7.

Grünert R, Wollmann H. Light Transmittance and Light-Protective action of containersfor phenylalkylaminesolutions. Pharmazie 1983;38(1):30-3

Sciarra JJ, Cutie AJ. Pharmaceutical Aerosols. In: L. H. Lachmann L, The theory and Practice of Industrial Pharmacy, Lachman L., Lieberman HA, Kanig JL. (Eds) Third edition, Varghese Publishing House, Bombay 1991:711-732.

United States Food and Drug Administration (USDFA) guidlines, Guidance for Industry. Containers Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing and Controls Document 1999.

European Medical Agency (EMA) guidlines. Guideline on Plastic Immediate Packaging Materials. London 2005.

Chambers TL. Child-resistant containers for drugs. Arch Dis Child. 1981; 56(10): 739–740.

Mrvos R., Krenzelok E.P. Child-Resistant Closure for Mouthwash:do they make diffrence. Pediatr Emerg Care 2007;23(10):713-5.

Organisation WH. Guidelines on Packaging for Pharmaceutical Products 2002.

Campbell GA, Vallejo E. Primary Packaging Considerations in Developing Medicines for children: Oral Liquid and Powder for Constitution. Journal of Pharmaceutical Sciences 2015;104(1):52-62.

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