FABAD J. Pharm. Sci., 41, 27-37, 2016

REVIEW ARTICLES

Syringes As Medical Devices

Merve KARPUZ[*,**], A. Yekta ÖZER[*°]

Syringes As Medical Devices

SUMMARY

Plastic syringes are Class IA medical devices which are used frequently for the administration of drugs parenterally. Syringes and their materials have to fulfil the tests like transparency, water vapor permeability, leakage and cytotoxicity. These tests are indicated in pharmacopoeias and they are applied for the understanding whether is suitable to standard. Also they obey to some requirements such as electrical properties, sterility, chemical resistance and extractables/ leachables. These requirements are indicated in standards. In this article, firstly the requirements and tests are mentioned. Afterwards, sterilization of plastic syringes with ethylene oxide or radiation and the effects of radiation sterilization on the plastic syringe materials are explained. Finally, several studies done on the possible interaction between plastic materials of syringes and some chemical solutions have been summarized.

Key Words: *Syringes, Sterilization, Radiation sterilization, Radiation effects on plastic material, Chemical interaction in plastic syringes.*

Tıbbi Cihaz Olarak Enjektörler

ÖZET

Plastik şırıngalar sıklıkla ilaçları parenteral yoldan uygulamak için kullanılan Sınıf IA tıbbi cihazlardır. Şırıngalar ve şırıngaların yapıldıkları malzemeler şeffaflık, su buharı geçirgenliği, sızdırma ve sitotoksisite gibi testleri geçmek zorundadır. Bu testler şırıngaların ve malzemelerin standartlara uyup uymadığını saptamak için yapılır ve farmakopelerde belirtilmiştir. Ayrıca şırıngalar elektriksel özellikler, sterilite, kimyasal direnç ve ekstre edilebilir maddeler/ ağartıcılar bakımından bazı gerekliliklere uymak zorundadırlar. Bu gereklilikler standartlarda belirtilmiştir. Bu makalede, ilk olarak bu gereklilikler ve testlerden bahsedilmiştir. Ardından plastik şırıngaların etilen oksit veya radyasyon ile sterilizasyonu ve plastik şırınga malzemeleri üzerinde radyasyonla sterilizasyonun etkileri açıklanmıştır. Son olarak plastik şırınga materyali ve bazı kimyasal çözeltiler arasında oluşabilecek etkileşimle ilgili yapılan çalışmalar özetlenmiştir.

Anahtar kelimeler: *Şırıngalar, Sterilizasyon, Radyasyonla Sterilizasyon, Plastik materyaller üzerine radyasyonun etkisi, Plastik şırınga materyalindeki kimyasal etkileşmeler.*

Received: 12.12.2016
Revised: 20.01.2017
Accepted: 23.01.2017

[*] Hacettepe University, Faculty of Pharmacy, Department of Radiopharmacy, 06100, Sıhhiye, Ankara-Turkey.
[**] İzmir Katip Çelebi University, Faculty of Pharmacy, Department of Radiopharmacy, 35620, Çiğli, İzmir-Turkey.

°Corresponding Author:
Phone: +90 312 305 21 96
Fax: +90 312 311 47 77
E-mail : yktzer@yahoo.com

INTRODUCTION

There are four major systemic routes for the administration of drugs to the body: enteral, parenteral, transdermal and inhalation. Parenteral routes have some advantages such as quick drug effect, 100 % bioavailability, protecting drugs from the effect of gastrointestinal system and preventing the formation of inactive drugs before drug effects occur (Oktay & Kayaalp, 2012). Plastic syringes are the most commonly used instruments for the administration of drugs parenterally and they are medical devices designated as Class IA.

The first study, which is about administration of drugs into the body through the skin, was made by Magendie in 1809. For this purpose, he administered strychnine into a dog by using a wood coated thorn. After that, Lafargue introduced morphine by using a lancet. Rynd invented a dripping needle in 1844. Finally in 1853 by Wood, first real syringe was invented for the purpose of treating birthmarks and a few years later after this date, he added a barrel and a better needle to this invention (How Products Are Made Volume 3 Syringe).

TYPES and CLASSIFICATION of SYRINGES

Syringes are named according to the volume and the usage purpose and they are classified into disposable syringes and non-disposable syringes. In Table 1, types of syringes and the commercial samples are summarized. Disposable syringes are sterile, packed, ready for use, non-toxic, non-pyrogenic and have lower risk in transmitting the diseases such as AIDS or Hepatitis B than non-disposable syringes. So they are preferred mostly. Non-disposable syringes are generally made of heat-resistant glass such as borosilicate and they are not used very often (Pharmacology chapter).

There are 2 type of syringes according to intended use; oral and hypodermic.

Oral syringes are used efficiently in the administration of drugs by oral or enteral route and the preparation of drugs which have very small volume (Grissinger, 2013).

Hypodermic syringes are calibrated by cubic centimeter (cc), mililitre (ml) or unit. Small volume syringes, which have 1, 2, 2.5, 3 ml volumes, are used in the administration of the intramuscular (i.m.) or subcutan (s.c.) injections. Syringes which have larger volumes such as 5, 6, 10, 12 ml, are used in the blood draw from patients or in the preparation of the drugs for intravenous (i.v.) injections and syringes, which have larger volume than 20 ml, are used in the injections of larger volume sterile solutions (Chapter 7 Syringes).

In accordance with the special intented use, there are 3 types of syringes: Insulin, Tuberculin and Pre-filled Syringes.

Insulin syringes are used in the injection of insulin hormone, which takes place in the treatment of Insulin Dependent Diabetes Mellitus and they are calibrated by unit (Chapter 7 Syringes).

Other syringe type is **Tuberculin syringes** which are used in the diagnosis of tuberculosis. Their volumes are 1 ml and on the syringe barrel there are 100 lines which show 0.01 ml each. This type of syringes are used for intradermal (i.d.) injection of very small volume drugs which are used in tubeculosis and allergy tests. Also, they are preferred for i.m. injection of the drugs which have small volumes lower than 1 ml (Chapter 7 Syringes).

When types of syringes are mentioned, pre-filled syringes mustn't be forgotten. **Pre-filled syringes**, which are used for the administration of the various liquid drugs (such as insulin or vaccines), are single dose cartridges that have fixed needles on it (Dunne & Whitaker, 2016). There are a lot of advantages of pre-filled syringes over traditional vials and ampoules for the patients and health workers (Yoshino *et al.*,2014; Makwana *et al.*,2011):

- ✓ Minimizing of the drug waste,
- ✓ Extra time for the drug shelf life,
- ✓ Being effective, safe and useful,
- ✓ Providing of the precise dose drug administration rapidly,
- ✓ Minimizing of dose mistakes and risk of biological contamination,
- ✓ Allowing the patients administration of drugs by themselves out of the hospital.

Pre-filled insulin syringes especially are recommended for the patients, who use insulin in diabetes treatment, because of adsorption effect of plastic syringes (Dunne & Whitaker, 2016). In the production of this type of syringes, Class I borosilicate glass for syringe barrel; stainless steel or elastomer for needle; elastomer for plunger and cap and plastic materials for the other pieces of the syringe are used, respectively. The plastic materials used in the production are cyclo olefin polymers (COP) or cyclic olefin copolymers (COC). In the sterilization of these types of syringes, autoclave or ionized radiation can be used but the main sterilization method is gamma radiation sterilization (Makwana *et al.*, 2011).

Table: 1. Types of Syringes

According to Material	1. Plastic Syringes 1.1. Polypropylene (Hayat®, Sigma-Aldrich®) 1.2. Polyethylene (Sigma-Aldrich®, Norm-Ject ®) 2. Glass Syringes (Sanitex ®)
According to Administration Route	1. Hypodermic Syringes (Hayat®) 2. Oral syringes (BD UniVia™)
According to Special Intended Use	1. Tuberculin Syringes (Monoject™) 2. Insulin Syringes (GNP®) 3. Pre-filled Syringes (Mırcera®)

MATERIALS of SYRINGES

Although a lot of syringes have been designed until now, all of the syringe types basically have the same pieces like plunger, barrel, needle and cap as shown in Figure 1 (How Products Are Made Volume 3 Syringe).

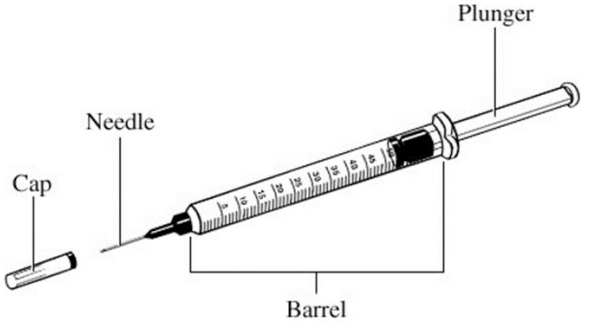

Figure: 1. Syringe and Pieces (Syringes).

If the syringe needle is made of stainless steel, it is hypodermic type needle. There are some methods for measuring the diameter of the syringe needle such as French Catheter Gauge, Metric Sizes in Milimeters, Stubs Wire Gauge. Among them Stubs Wire Gauge method is the most frequently used for medical catheters and equipment in worldwide. In accordance with this system, if the aperture of pinhole is 0.134 inch it is called 10 gauge and is 0.035 inch for the 20 gauge (Kucklick, 2006).

Syringe plunger, barrel and cap are made of polypropylene (PP) or polyethylene (PE) plastic materials. These materials must be at medical grade because of their medical use. For this purpose, some essential tests are applied to the plastic materials and the materials are characterized by their composition, mechanical- thermal and electrical properties, sterility, chemical resistance and extractables/ leachables, biocompatibility, hemocompatibility and stability. Among them mechanical thermal and electrical properties, sterility, chemical resistance and extractables/ leachables are the most important properties of the produced syringes. Biocompatibility and hemocompatibility are not very important because of no contact in between the syringe barrels and skin or blood (Sastri, 2014).

Some test methods, like combustion, extractable substances, fine particles, transparency, water vapor permeability, leakage and cytotoxicity, take place in pharmacopeias. Depending on the results of these test methods, the requirements for PP and PE containers, which are used for aqueous injection, are indicated.

According to Japanese Pharmacopeia (2011a):

- **Transparency**: When it is tested as defined at pharmacopoeia, material transmittance is not less than 55%. At sensory test, turbidity is not more than 20% in the water loaded container and also being turbid is not more than 80% in the suspension loaded container.
- **Appearance:** Materials must not include cracks or bubbles.
- **Water Vapor Permeability:** Depending on the results of tests which are defined pharmacopoeial test methods, the loss of mass is not more than 0.2%.
- **Heavy Metals:** The turbidity of the test solution must not greater than that of the control solution.
- **Cadmium:** According to the results of applied test, the absorbance of the test solution must not be different from control's absorbance.
- **Residue on Ignition:** This must not be more than 0.1% in 5 gram.
- **Foaming Test:** The foam must disappear in 3 minutes.
- **pH:** The pH difference in between the blank and test solution is not more than 1.5.
- **UV Spectrum**: In 220-240 nm it must not be more than 0.08 and in 241-350 nm it must not be more than 0.05.
- **Residue on Evaporation:** It must not be more than 1.0 mg.
- **Half Maximal Inhibitory Concentration (IC_{50}):** It must not be more than 90%.

According to European Pharmacopeia (2008a):

- **Appearance of S Solution:** S solution, which is prepared with sufficient number of syringes, must be clear and colourless.
- **Acidity or alkalinity:** When 0.1 ml

bromothymol blue added to 20 ml S solution is titrated with 0.01 M HCl or NaOH, the amount of acid or alcali must not be used more than 0.3 ml.

- **Absorbance:** In between 230-306 nm, it must not be more than 0.2.
- **Reducing Agents:** When the S solution and blank solution (fitting to pharmacopeial requirements) are titrated with 0.01 M sodium thiosulfate solution, the difference between the volumes should not be more than 1.5 ml.

PRODUCTION of SYRINGES

Along the process of syringe production, some tests are applied to syringes in order to understand whether the requirements were provided or not. This tests and requirements are indicated in national and international standards which are summarized in Table: 2.

Table: 2. National and International Standards for Syringes

TS EN ISO 8537 Sterile single-use syringes, with or without needle, for insulin
TS EN ISO 21533/AC Dentistry - Reusable cartridge syringes intended for intraligamentary injections
TS EN ISO 7886-1 Syringes-Hypodermic-Single use, sterile Part1: Syringes-Manual
TS EN ISO 7886-2 Sterile hypodermic syringes for single use - Part 2: Syringes for use with power-driven syringe pump
TS EN ISO 7886-3 Sterile hypodermic syringes for single use - Part 3: Auto-disable syringes for fixed-dose immunization
TS EN ISO 7886-4 Sterile hypodermic syringes for single use - Part 4: Syringes with re-use prevention feature
TS ISO 11040-3 Prefilled syringes - Part 3: Seals for dental local anesthetic cartridges
TS 3592 Needles for Syringes
TS 4021 Ear Syringe- Metal
TS 5031 Insulin Syringes-Reusable
TS 5462 Tuberculin Syringes
TS EN ISO 9997 Dental Cartridge Syringes

According to TS EN ISO 7886-1 (1998), TS EN ISO 7886-2 (2006), TS EN ISO 7886-4 (2007):

✓ When the syringe pieces (plunger, barrel, needle and cap) are investigated in between 300 and 700 lux-light without magnifying glass, the syringe surfaces which are directly contact with injection liquids, must not include particles or impurities.

✓ For the evaluation of pH value and amount of extractable metals, at least 3 syringes are filled to nominal capacity line with distilled water which is suitable for the third degree in TS ISO 3696 and they are kept throughout 8 hours (0/+15 min.) at 37 (0/+3) ^{o}C. In order to evaluate the needle of the syringe pH, 25 needles are immersed in distilled water and kept throughout 60±2 minutes. The content was decanted to a borosilicate glass and is compared with control solutions which are prepared from freshly distilled water. When the pH values of the content are compared, it must not be higher 1 unit than control solution. Total amount of lead, tin, zinc and iron must not be higher than 5 mg.L^{-1} and also amount of cadmium must be less than 0.1 mg.L^{-1}.

✓ If any lubricant is used for the inner surfaces of syringe barrels and needles, particle of lubricant, which is in droplet form, must not be seen at visual inspection. For three pieces syringes, polydimethylsiloxane must be used as lubricant and its amount must not be higher than 0.25 mg. Also, in two pieces syringes amide of erucic and oleic acids must be used as lubricant and the amount of lubricant must not exceed 6% (m.m^{-1}) the mass of the cylinder.

✓ The pinpoint of syringe must be sharp and smooth.

✓ Syringe has to have identical scale which is calibrated in one or more interval and volume of syringe must be shown at syringe barrel.

✓ The length of syringe barrel is suitable to provide maximum usable capacity which must be at least 10 % more than the nominal capacity.

✓ Syringes must have finger grips which prevent rotation more than 180 degrees when syringes are placed horizontally at flat which is angled 10 degree with horizontal plane. In addition, finger grips must be in appropriate shape, measure and resistance and they must not have sharp edge or bulge.

✓ When the barrel of syringe is held in one hand, the plunger can be pushed by the same hand. For this purpose, syringe nozzle is connected to reference steel cone and syringe fills with water. While negative pressure is applied from nozzle, possible disconnection between piston and the body of piston is checked.

✓ When the syringe filled with water and hold vertically, body of piston must not move because of its weight. The force for the movement of piston body and to fill water to the syringe or to discharge the water from the syringe is determined by mechanical experiment machine.

✓ Fiducial line must be contacted with the inner surface of barrel.

✓ According to TS 3521-1 EN20594-1, syringe nozzle must be compatible with conical connection and nozzle lumen must not be less than 1.2 mm.

✓ In order to understand the void volume in syringe, the dry syringe is weighted and filled with water, discharged, syringe's outer surface is dried and it is reweighted. The void volume is calculated from the weight of the residual water. This finding is in accordance with the value mentioned in the standards.

✓ To test the air and liquid leakage, the syringe is filled with water, syringe nozzle is closed, a force is applied to piston and possible amount of leakage is checked.

✓ Flow properties of syringe is determined by using reference syringe driver. Depending on the results of this method, the time which is necessary for reaching at least 95% level, fixed flow speed is set by the movement of piston rod's push button must not exceed 10 minutes. Total percentage of error of flow/ set distribution speed, must not be higher than ±2%.

✓ The force which is necessary for the drainage of water is determined by a mechanical machine. At the end of these experiments, the determined force must appropriate to the designated values in standards.

✓ Packaging and labeling which are the last steps of the syringe production, should be appropriate to the designated values in standards.

STERILIZATION of SYRINGES

According to the old definition, sterilization is the elimination of all the alive organism, bacteria and fungi spores and saving the contents of products from microorganisms, absolutely.

Recently, sterilization is defined as the presence probability of viable microorganism in one million product.

Theoretically, in order to designate a medical device as sterile, the probability level should be lower than one to a million (Perçin, 2014). Sterility Assurance Level (SAL) is the term used for expression of reaching of the sterility to the desired level. In other words, SAL is a term which can be defined as probability of presence non-sterile products or survival of microorganisms in the samples. For medical devices SAL level is very low like 10^{-6} (Turker, 2009a.; Sterility Assurance Level).

Among the main sterilization methods, there are several sterilization methods like sterilization with dry air at oven, sterilization with pressurized steam in autoclave at 121°C, UV radiation sterilization, ethylene oxide (EO) sterilization, ionized radiation sterilization which uses gamma rays or electron beam (e-beam) and sterilization in aseptic conditions by using membrane filters which have pores in 0.22 μm diameter (Silindir & Ozer, 2009; Moraes *et al.*, 2014).

Syringes have to be sterile because of their use in the administration of sterile and apyrogenic drugs by parenteral route. Sterilization of products is possible in the terminal packages. Microbial death/ bioburden control are evaluated by this method and has the lowest risk. Because of these reasons, terminal sterilization method is recommended (Japenese Pharmacopoeia, 2011b).

Among the sterilization methods, there are two methods used for the sterilization of syringes. One of them is EO sterilization which has been used since the 1950s. This method is especially suitable for heat-sensitive and moisture-sensitive materials. Pure EO gas is flammable and explosive, also according to Environmental Protection Agency (EPA) toxic and carcinogenic gas. So EO gas is diluted with some agents like hydrochlorofluorocarbon (HCFC) and carbon dioxide. There are some disadvantages of this method; for instance it is complex because of depending on some critical parameters such as temperature (30-65°C), amount of relative humidity present (30-99%), EO concentration (250-1500 $mg.ml^{-1}$), overall exposure time (1-30 hours), type of microorganisms, product and load density, and gas permeability factors. In addition, due to the formation of EO decomposition products after sterilization process it requires aeration (Sastri, 2014; Silindir & Ozer, 2009; United States Pharmacopeia, 2009).

Other sterilization method is ionized radiation sterilization which uses gamma rays or e-beam. In order to apply this sterilization method in pratice, the first national draft law has been published in 1965. Nowadays, there are Food and Drug Administration (FDA) in USA and Department of Health and Social Services (DHSS) in UK for checking the suitability of facilities with laws and regulations. In addition, Occupational Safety and Health Administration (OSHA) and Environmental Protection Agency (EPA), which was established in 1997 within the framework US Clean Air Act, specify sine qua non about the safety of personnel and the protection of environment. Before mentioned authorities and International Atomic Energy Agency (IAEA) determine the high standards on international basis; among these:

providing the safety running of radiation sources and application of appropriate radiation doses to the products steadily, providing radiation sterilization use in industry (Fairand, 2002).

The radiation energy is supplied by accelerators, which provides 10 MeV power of e-beam or ^{60}Co radionuclide which emits 1.33 MeV power of gamma rays. Sterilization with e-beam has some advantages (Silindir & Ozer, 2009; Fintzou *et al.*, 2007a, 2007b; Haji-Saeida, 2007):

(a) Safe and reliable method,

(b) Ease of control,

(c) High dose rate,

(d) Insignificant increasing of temperature.

On the other hand, penetration of gamma rays is higher than e-beam, so this makes that gamma rays is more popular than e-beam. In addition, in the e-beam irradiation the applied dose rate is higher but the time is shorter than at gamma irradiation. For instance, there is an equality between 15 kW e-beam and 1 MCi gamma sources. The radiation dose for sterilization is changing in between 25 and 40 kGy. The application dose must be identified before the sterilization of syringes in order to show relationship between dose range and remaining of non-sterile items. Also, by the identification of dose rate, application of unsuitable radiation dose which is lower than effective sterilization dose, is prevented (Fintzou *et al.*, 2007a, 2007b; Haji-Saeida *et al.*, 2007; Ley *et al.*, 1972). In order to reach the desired SAL level, suitable radiation dose is determined by using Bacillus Pumilus spores which are the most resistant microorganism to irradiation. For this purpose, the samples obtained from products produced properly according to Good Manufacturing Practice (GMP) conditions, are contaminated by Bacillus Pumilus spores and in this way microbial bioburden is created. Microbal bioburden is the number of alive microorganisms on the products which will be sterilized, and is determined in fours steps (Berk, 2002a, 2002b):

I. Removal of microorganisms from the products,

II. Incubating of these microorganisms in the suitable medium,

III. End of the incubation period, counting of the microorganisms colony growth,

IV. Application of microbial bioburden correction factor.

The product, it's microbial bioburden which is known, is irradiated by specific radiation dose (such as 5, 10, 25, 50 kGy). The remaining microorganisms on the samples, after irradiation is counted and plotted to show the relation between radiation dose and microbial death rate. According to the graphs, the optimal irradiation dose is obtained showing this dose appropriate to SAL 10^{-6} (Berk, 2002a).

In the radiation sterilization method, 25 kGy irradiation dose is accepted for providing SAL at 10^{-6}. If there is no information about the number and resistance of the microbial bioburden, the product has to be irradiated with 25 kGy it means (Berk, 2002b).

After the sterilization of the syringes, some tests are performed on solutions which are prepared from the sterilized syringes, in order to check the sterility.

One of these tests is in vitro Limulus Amebosite Lysate (LAL) method, which is applied for the control of the existing pyrogens by using amebosite lysate, which is obtained from Limulus Polyphemus. In this method, endotoxins of gram negative bacteria and amebosite lysate react under in vitro conditions. By the results of this method, only endotoxins of gram-negative bacteria are identified then other toxins, which cause fever, can not be determined (Japenese Pharmacopoeia, 2011c).

Other method is Growth Promotion Test. The presence of microorganisms is checked in samples, which are taken from the sterilized syringes with this test. The samples are incubated in Soy Bean Casein Digest Medium (SCDM) and Fluid Thioglycolate Medium (FTM) and kept throughout at least 14 days at 30-35°C. At the end of the incubation period, media are checked whether there is any growth of micro-organisms or not. If there is no growth at media, it can be concluded that the sterilization process is successful and the syringes are sterile (Özer, 2005).

During the control of sterility, If the manufacturers validate the sterilization process as indicated and keep rules in the methodology of radiation dose selection, it is possible that syringes are released without these tests or quarantine period. These rules are indicated in *ANSI/AAMI/ISO 11137-1994 "Sterilization of health care products–Requirements for validation and routine control–Radiation sterilization"* by American National Committee, that have been chosen from Association for the Advancement of Medical Instrumentation (AAMI) (Berk, 2002a).

For the validation of terminal sterilization method, three processes are used (United States Pharmacopeia, 2006).

- Bioburden-based process
- Biological indicator/bioburden combined process
- Overkill process

The bioburden-based process depends on the

bioburden information of the product. Checking critical control points, obtaining of the relation between several radiation doses, bioburden counts and radiation resistance are the crucial knowledge of this method, especially, when the tight sterilization is needed.

Biological indicator / bioburden combined process shows the inactivation of microorganisms, which are resistant to the sterilization process. Also, this method is used when overkill process causes possible loss at product's properties and in the EO sterilization of syringes.

In order to benefit from **overkill process** product, bioburden count and prevalence of spore forms in the product should be known. This method can be used when sterilizing agent and sterilization cycle conditions don't affect the quality of product (United States Pharmacopeia, 2006).

RADIATION EFFECTS on PLASTIC SYRINGES

Between 25-40 kGy radiation doses, some changes can occur on the plastic syringe materials such as decomposition, discoloration, formation of more amorphous structure, chain scission, formation of cross-linking bond in polymeric chains, increasing of gas permeability. In these changes, the most important one is the formation of radiolytic products.

These changes are dependent on dose rate, dose type, the type and crystallinity level of polymer, the presence of additives and the method used (Fintzou *et al.*, 2007a, 2007b; Haji-Saeida *et al.*, 2007). For example, while cross-linking occurs in PE plastic material, PP is sensitive to discoloration (Sastri, 2014). Also, dose rate and the distance to the out surface cause the changes of packaging material. The oxidative degradation in plastic materials with e-beam is less than with gamma radiation. Because, the exposure time to irradiation is shorther than gamma sterilization (Fintzou *et al.*, 2007a, 2007b; Haji-Saeida *et al.*, 2007).

In order to obtain information about differences between non-irradiated and irradiated plastic materials, several tests were performed as follows (Fintzou *et al.*, 2006):

- Mechanical testing (tensile strength, percentage of elongation at break, compression testing, tear strength, puncture resistance)
- Physicochemical testing (thermal testing)
- Colorimetry (the measurement of discoloration degree)
- Fourier Transformation Infrared Spectroscopy (FTIR) (the measurement of structural changes)
- Gas Chromatography- Mass Spectroscopy (GC/MS) (the identification of radiolysis products)
- Electron Spin Resonance (ESR) (the identification of radiolytic products)
- Rheological testing (the measurement of molecular weight changes)

Fintzou *et al.*, (2007b) compared the effects of e-beam and gamma rays on PP syringes. For this purpose, they studied on non-irradiated and irradiated at 30, 60, 120 kGy PP syringes. Gamma rays are obtained from a source of ^{60}Co and e-beam obtained from a linear accelerator. After sterilization, they exhibited some changes on PP syringes. Firstly, they observed a decrease in the load at break and elongation at break while increase in irradiation dose and also the decrease at the gamma radiation sterilization which was higher than e-beam sterilization. According to the differential scanning calorimetry test results, melting enthalpy has decreased while irradiation dose has increased for two methods which shows the polymers had turned into more amorphous form due to the effect of irradiation. Furthermore, they demonstrated that the discoloration has been higher in the samples which were irradiated with gamma rays and color of these samples had turned into more yellow.

Fintzou *et al.*, (2007a) exhibited the effect of e-beam on PP syringes at different radiation doses. Depending on the results of mechanical tests, the decrease was found in the load break while increase in irradiation dose from 30 kGy to 120 kGy. In accordance with differential scanning calorimetry, melting and fusion enthalpy decreased as increasing irradiation dose. In order to understand alteration on PP material's color, they measured color before and after irradiation at various doses and reported that the color difference increased with the increasing of irradiation dose. In accordance with the results of FTIR analysis, they showed that there have been formation of aldehydes and ketones because of reaction between oxygen molecules and free radicals. In order to define radiolysis products which occurred at different radiation doses, they applied GC-MS chromatography and obtained some compounds such as 1,3-dichloro 2-propanone, 3,3,3-trichloro-2-methyl 1-propene, 3,4 dimethyl-phenol, 1,3 di-tert-butyl benzene, 4-tert-butyl-2-chlorophenol at 30 kGy; outside of above compounds 1,1,3 trichloro-2-pentanone, diisobutyl phthalate and heptacosane at 60 and 120 kGy. Also they indicated that at higher irradiation doses amount of these radiolysis have been more.

Another study about gamma-irradiated physicochemical and mechanical properties of PP syringes was made by Fintzou *et al.* (2005). They used ^{60}Co sources for irradiation PP syringes at 30, 60 and

120 kGy doses. After irradiation they tested mechanical properties of syringes, they observed that load at break and elongation at break of syringes material have decreased at higher irradiation doses. In order to obtain information about the changes of melting and crystallization behavior of PP syringes, they applied DSC and obtained the melting temperature and fusion enthalpy, which are connected with crystallinity, have decreased as increasing irradiation dose. From the results of color measurements, they also showed that total differences of color have increased at higher radiation doses. According to FTIR analysis, they observed that there have been a serious change at 1720 cm^{-1} in carbonyl band related to the formation of free radicals. The radiolysis products were described with GC-MS analysis and thirteen compounds were identified for non-irradiated syringes, fifteen compounds for irradiated syringes at 30 kGy and sixteen compounds for irradiated syringes at 60 and 120 kGy.

Abraham *et al.* (2010) made some studies for showing the effects of e-beam radiation on physical and chemical properties of PP syringe materials. They irradiated samples at 20,40,60 and 80 kGy doses for 4 min individually. They showed that strength, elongation at break and viscosity had decreased with the increase in radiation dose. Also, they indicated melting point decreased at higher irradiation doses depending on the results of DSC. In accordance with ESR, they indicated that the radicals in PP syringes had turned into another species and the short term changes had occurred in the radicals type and concentration in the first-two hours. In addition, depending on the results of ESR, it was indicated that the amount of radicals have increased during seven days, but after seven months any radicals have not been found in the samples.

In the sterilization process, gamma radiation effects on 3 types of PP syringes, which are commercially available, were investigated. After the sterilization, the properties of syringes (acidity or alkalinity, absorbance, reducing agents, silicone oil) have been found appropriate to the standards as indicated in pharmacopeias. In addition, suitable SAL doses for sterilization have been determined and the samples, which have been prepared from sterilized syringes with this dose, have been used on the sterility and pyrogenicity tests. At the end of these tests, growth and gelation have not occurred so, these results showed that syringes could be sterilized properly (Turker, 2009b).

In another study, effects of EO and gamma radiation sterilization on 2 PP and 2 PE commercial syringes, have been carried out. Sterility and gelation tests were applied on the EO and gamma irradiation sterilized samples, both. According to the results of these tests, growth and gelation have not occurred. At the end of the sterilization, syringes have been found suitable in terms of appearance, acidity or alkalinity, absorbance, reducing agents, silicone oil for the physicochemical standards available in the pharmacopeias. In addition; according to the results of mechanical tests, after the EO and gamma radiation sterilization maximum strength, elastic modulus, elongation, molecular structure have not changed in PP and PE syringes. However, melting flow rate (MFR) values of syringes, which are sterilized with EO, have not changed, MFR values of 2 PP and 1 PE syringes, which are sterilized with gamma radiation, have increased because of the breaks in the polymer chains (Berk, 2002c).

POSSIBLE INTERACTION of SYRINGES and CHEMICALS

Syringes are used at the administration, transportation or storage of different types of solvents and chemicals. As long as solvents and plastic syringe materials contact with each other, the stability of solutions can decay depending on plastic type, solvent type, the manufacturing process. For instance solvents may diffuse to the plastic, the plastic may extract to the solvent, undesirable products can occur. Possible interaction between syringe materials and solvents is very important. Because of the results of these interactions, the integrity of plastic materials may be lost, unwanted precipitate may occur. For the aim of the evaluation of the chemical resistance of plastic materials, ASTM D543 and ISO 4599 tests are used. In accordance with these test procedures, at least 5 samples, for each strain condition, chemicals, materials and time, are prepared and they exposed to the different solutions with suitable methods like immersion, wipe, spray. At the end of this period, changes in weight, possible hazing or cracks in appearance, physical properties (such as tensile strength and elongation) are evaluated and compared with the control group (Sastri, 2014; Intertek Plastic Technology Laboratories).

STABILITY STUDIES in the PLASTIC SYRINGES

In the literature, in order to show possible interaction between some solvents or solutions and plastic syringe materials some studies have been made.

Lewis *et al.* have investigated the possible adsorption of atropine and ephedrine to plastic syringe material. For this purpose, they kept atropine and ephedrine solution in 3 plastic syringes and for control group in 1 glass syringes during 4 days. Afterwards, they have analyzed the samples with HPLC and have

showed that there had been only 1.4 % reduction at ephedrine sulfate concentration between the first and the last day. On the other hand, they found that the decrease in atropine sulfate concentration had been 52 % at the end of fourth day. So according to these results, they said that there have been possible adsorption of atropine to plastic syringe (Lewis *et al.* 1994).

In order to understand the stability of heparin sodium in plastic syringe materials, Tunbridge *et al.* have diluted and stored heparin solution in PP syringes and glass containers. According to partial thromboplastin time (APTT) method, they found that heparin activity had decreased considerably in glass containers within 2 hours because of the absorption of heparin to the glass surface. Also, they kept PP syringes at 0-4°C and room temperature in the dark in order to obtain information about the effect of storage temperature. At the end of this study, they reached that the storage time was more than three weeks and there was an important decrease at heparin activity (Tunbridge *et al.*, 1981).

Stewart *et al.* (1992) investigated ceftazidime's stability in plastic syringes and glass vials under different storage conditions. They have kept PP plastic syringes or glass vials containing ceftazidime solutions at different storage conditions. They used HPLC for the evaluation of ceftazidime solution's concentration and reached that ceftazidime solution had been stable in plastic syringes and glass material during 8 hour at room temperature, 96 hour at 4°C and after 28 and 91 days at -20°C. Also, they indicated that the number of particulate matter is fitting to spesifications of USP for small volume injections and the number of particulate matter has not been changed during freezing and thawing.

Hung *et al.* (1988) to check the stability of morphine solution, they stored it at 3 and 22°C, with and without antioxidant and preservative, in ligth and dark in 2 types of plastic syringes at longer than 12 weeks. During the storage period, they investigated the contaminants which is extracted to the solution from syringe material and indicated that in 2 types of syringes degradation of morphine have been less than 3% in light at 22°C. Also, this value have been found less in dark at 3°C. The results of reversed-phase ion-pair HPLC with and without antioxidant or preservative showed the morphine solution's shelf-life is respectively 33 and 20 weeks in one type of plastic syringe. In the other type of plastic syringe they found that the shelf-life had been longer than 1 year.

Degradation of atracurium besylate injections in plastic syringes have been investigated by Pramar *et al.* They have reached that there had been positive effect of refrigeration on stability and also at room temperature the atracurium besylate injections could be stored up to 6 weeks (Pramar *et al.* 1996).

Nahata *et al.* (1992) have stored the plastic syringes containing ceftazidime (with arginine) in sterile water at three different temperatures (22, 4, -20°C) at certain time intervals. The solutions contacted with the inner surface syringes were analyzed with HPLC to obtain information about concentration of ceftazidime, pH, color changes and formation of any precipitate. When the results were evaluated, the concentration has remained the same, any precipitate has not occurred but pH has decreased and the color of the solution has changed from light straw to dark yellow.

Swanson *et al.* (2013) have studied adsorption of ^{99m}Tc-sestamibi radiopharmaceutical, which is used common in cardiac imaging at nuclear medicine, to 6 different brands of plastic syringes, which are used in hospital practice. They indicated that the main reason of adsorption was lubricant, used in the inside of the syringe barrel. In addition, they showed that the residual activity in syringes have been 22±8% and 11±4% in barrel of syringe, 9±5% of the residual activity have been in syringe plunger, 1% of the residual activity in the needle and the cap of syringe and 1% of the residual activity in the scalp vein set. Also, any relation between volume of injection and the residual activity could not be found.

Keskintepe *et al.* (2005) have studied residual radioactivity with various ^{99m}Tc kits, which are used in nuclear medicine, in 2 different commercial plastic syringes. They reached that the residual radioactivity had been less in rubber ending syringe because of little void volume. In addition, when the volume of solution has increased 2 times, amount of radioactivity has decreased significantly in 2 types of syringes. In ^{99m}Tc-Mikroagregat Albumin (^{99m}Tc-MAA) radiopharmaceutical used in pulmonary imaging, the residual radioactivity have been found higher than other kits because of the colloidal dispersion structure.

CONCLUSION

Plastic syringes, which are classified as Class IA medical devices, are one of the most important medical devices for the purpose of administration drugs into the body by parenteral route. Because of widespread use of them some requirements are designated on the national and international basis and resulting several standards are obligatory from quality point of view and therefore the materials used in the production of plastic syringes must be at medical grade.

To be sterile is one of these requirements. Sterilization can be applied by radiation (gamma

or e-beam), EO or heat (autoclave, oven). Owing to superiority of irradiation, this method is preferred commonly. But, while gamma or e-beam rays use for sterilization, possible changes in plastic material has to be considered.

On the other hand, possible interaction between plastic syringe materials and administered drugs with syringe is another important issue and this interaction is depending on the solvent type, plastic type and manufacturing process.

As a result, hypodermic syringes which are the most frequent used ones and made of PP or PE, take place under the umbrella of Class IA medical devices. They have to own several properties indicated in pharmacopeias, suitable process of production indicated in standards (TS EN ISO 7886-1, TS EN ISO 7886-2, TS EN ISO 7886-4) and pass the tests (Mechanical test, Physicochemical test, Colorimeter, Fourier Transformation Infrared Spectroscopy (FTIR), Gas Chromatography/ Mass Spectroscopy (GC/MS), Electron Spin Resonance (ESR), Rheological test) which are applied to plastic material after the radiation sterilization.

REFERENCES

Abrahama, A.C., Czayka, M.A., Fisch, M.R., 2010. Electron Beam Irradiations of Polypropylene Syringe Barrels and the Resulting Physical and Chemical Property Changes. *Radiation Physics and Chemistry*, 79, 83–92.

Berk, F., 2002a. Tek Kullanımlık Tıbbi Malzemelerin Gama Radyasyon ile Sterilizasyonu ve Diğer Yöntemlerle Karşılaştırılması (Master Thesis). Ankara: Hacettepe Üniversitesi, 52.

Berk, F., 2002b. Tek Kullanımlık Tıbbi Malzemelerin Gama Radyasyon ile Sterilizasyonu ve Diğer Yöntemlerle Karşılaştırılması (Master Thesis). Ankara: Hacettepe Üniversitesi, 54.

Berk, F. 2002c. Tek Kullanımlık Tıbbi Malzemelerin Gama Radyasyon ile Sterilizasyonu ve diğer Yöntemlerle Karşılaştırılması (Master Thesis). Ankara: Hacettepe Üniversitesi, 89-95.

Chapter 7 Syringes. http://health.prenhall.com/olsen/pdf/Olsen_ch7.pdf (accessed 20.07.2016).

Dunne, T., Whitaker, D., 2016. Prefilled Insulin Syringes. *Anaesthesia*, 71, 349-350.

European Pharmacopoeia, 2008a. Council of Europe, Strausbourg Cedex, 379.

Fairand, B.P., 2002. *Radiation Sterilization for Health Care Products: X-Ray, Gamma, and Electron Beam.* USA: CRC Press, 5-6.

Fintzou, A.T., Badekaa, A.V., Kontominasa, M.G., Stahlb, M.R., Riganakosa, K.A., 2007a. Changes in Physicochemical and Mechanical Properties of Electron-Beam Irradiated Polypropylene Syringes as a Function of Irradiation Dose. *Radiation Physics and Chemistry*, 76, 97–107.

Fintzou, A.T., Kontominasa, M.G., Badekaa, A.V., Stahlb, M.R., Riganakosa, K.A., 2007b. Effect of Electron-beam and Gamma-irradiation on Physicochemical and Mechanical Properties of Polypropylene Syringes as a Function of Irradiation Dose: Study under Vacuum. *Radiation Physics and Chemistry*, 76, 1147–1155.

Fintzou, A.T., Badeka, A.V., Kontominas, M.G., Riganakos, K.A.,2006. Changes in Physicochemical and Mechanical Properties of G-irradiated Polypropylene Syringes as a Function of Irradiation Dose. *Radiation Physics and Chemistry*, 75, 87–97.

Grissinger, M., 2013. Oral Syringes: Making Better Use of a Crucial And Economical Risk-Reduction Strategy. *Medication Errors*, 38, 5-6.

Haji-Saeida, M., Sampa M.H.O., Chmielewski A.G., 2007. Radiation Treatment for Sterilization of Packaging Materials. *Radiation Physics and Chemistry*, 76, 1535–1541.

How Products Are Made Volume 3 Syringe. http://www.madehow.com/Volume-3/Syringe.html#ixzz3tpvbPcEM (accessed 20.07.2016).

Hung, C.T., Young, M., Gupt, P.K., 1988. Stability of Morphine Solutions in Plastic Syringes Determined by Reversed-phase ion-pair Liquid Chromatography. *Journal of Pharmaceutical Sciences*, 77, 719–723.

Intertek Plastic Technology Laboratories. http://www.ptli.com/testlopedia/tests/Compat-d543.asp (accessed 20.07.2016).

Japenese Pharmacopoeia (JP16), 2011a. Ministry of Health, Labour and Welfare, Tokyo, Japan 147.

Japenese Pharmacopoeia (JP16), 2011b. Ministry of Health, Labour and Welfare, Tokyo, Japan 2221.

Japenese Pharmacopoeia (JP16), 2011c. Ministry of Health, Labour and Welfare, Tokyo, Japan 104.

Keskintepe, D., Ozer, A.Y., 2005. Residual Radioactivity in the Syringes used in Injection of Radiopharmaceuticals and Factors Affecting the Amount of Residual Radioactivity. *Journal of Pharmaceutical Sciences*, 30, 176-180.

Kucklick, T., 2006. Introduction to Needles and Cannulae In: Kucklick TR, ed. *The Medical Device R&D Handbook*. Florida: CRC Press, 91-112.

Lewis, B., Jarvi, E., Cady, P., 1994. Atropine and Ephedrine Adsorption to Syringe Plastic. *Journal of the American Association of Nurse Anesthetists*, 62, 257-60.

Ley, F.J., Winsley, B., Harbord, P., Keall, A., Summers, T., 1972. Radiation Sterilization: Microbiological Findings from Subprocess Dose Treatment of Disposable Plastic Syringes. *Journal of Applied Bacteriology*, 35, 53-61.

Makwana, S., Basu, B., Makasana, Y., Dharamsi, A., 2011. Prefilled syringes: An Innovation in Parenteral Packaging. *International Journal of Pharmaceutical Investigation*, 1, 200-206.

Moraes, M.A., Weska, R.F., Beppu, M.M., 2014. Effects of Sterilization Methods on the Physical, Chemical and Biological Properties of Silk Fibroin Membranes. *Journal of Biomedical Materials Research* Part B, 102B, 869-876.

Nahata, M.C.,, Morosco, R.S., Fox, J.L., 1992. Stability of Ceftazidime (with arginine) Stored in Plastic Syringes at Three Temperatures. *American Journal of Hospital Pharmacy* 49, 2954-2956.

Oktay, Ş., Kayaalp, O., 2012. Genel Farmakoloji, Farmakokinetik ve Toksikoloji. In: Oğuz Kayaalp, ed. *Akılcıl Tedavi Yönünden Tıbbi Farmakoloji*. Ankara: Ertem Basım, 27-29.

Ozer, A.Y., 2005. Gama Radyasyonla Sterilizasyon ve Tıbbi Malzemeler. 4. Ulusal Sterilizasyon Dezenfeksiyon Kongresi, 220-229.

Perçin, D., 2014. Sterilizasyon Uygulamaları ve Hastane İnfeksiyonları. *Antibiyotik ve Kemoterapi Derneği Dergisi*, 28, 63-66.

Pharmacology chapter 12. https://quizlet.com/40628451/pharmacology-chapter-12-flash-cards/ (accessed 20.07.2016).

Pramar, Y.V., Loucas, V.A, Word, D., 1996. Chemical Stability and Adsorption of Atracurium Besylate Injections in Disposable Plastic Syringes. *Journal of Clinical Pharmacy and Therapeutics*, 21, 173–175.

Sastri, V.R., 2014. Material Requirements for Plastics used in Medical Devices. In: Sastri VR, ed. *Plastics in Medical Devices: Properties, Requirementes and Applications*. Pennsylvania: William Andrew, 33-54.

Silindir, M., Ozer, A.Y., 2009. Sterilization Methods and the Comparison of E-Beam Sterilization with Gamma Radiation Sterilization. *Journal of Pharmaceutical Sciences*, 34, 43–53.

Sterility Assurance Level. https://en.wikipedia.org/wiki/Sterility_assurance_level (accessed 20.07.2016).

Stewart, J.T., Warren, F.W., Johnson, S.M., Fox, J.L., Mullaney, J., 1992. Stability of Ceftazidime in Plastic Syringes and Glass Vials under Various Storage Conditions. *American Journal of Hospital Pharmacy*, 49, 2765-2768.

Swanson, T.N., Troung, D.T., Paulsen, A., Hruska, C.B., O'Connor, M.K., 2013. Adsorption of 99mTc-Sestamibi onto Plastic Syringes: Evaluation of Factors Affecting the Degree of Adsorption and Their Impact on Clinical Studies. *Journal of Nuclear Medicine Technology*, 41, 247–252.

Syringes. http://www.syringes.cn/img/insulin-syringes.jpg (accessed 20.07.2016).

Tunbridge, L.J., Lloyd, J.V., Penhall, R.K., Wise, A.L., Maloney, T., 1981. Stability of Diluted Heparin Sodium Stored in Plastic Syringes. *American Journal of Hospital Pharmacy*, 38, 1001-1004.

Türk Standardı TS EN ISO 7886-1, 1998. Şırıngalar-Hipodermik- Bir Kullanımlık Steril Bölüm 1: Şırıngalar-Elle Kullanım İçin. Ankara: Türk Standartlar Enstitüsü.

Türk Standardı TS EN ISO 7886-2, 2006. Şırıngalar-Hipodermik- Bir Kullanımlık Steril Bölüm 2: Güç Tahrikli Şırınga Pompasıyla Kullanım İçin. Ankara: Türk Standartlar Enstitüsü.

Türk Standardı TS EN ISO 7886-4, 2007. Şırıngalar-Hipodermik- Bir Kullanımlık Steril Bölüm 4: Tekrar kullanımı önleme özelliğine sahip şırıngalar. Ankara: Türk Standartlar Enstitüsü.

Turker S., 2009a. Diş Hekimliğinde (Periodontolojide) Kullanılan Madde ve Materyallerin Gama Radyasyonuyla Sterilizasyonu (PhD Thesis). Ankara: Hacettepe Üniversitesi, 5.

Turker, S., 2009b. Diş Hekimliğinde (Periodontolojide) Kullanılan Madde ve Materyallerin Gama Radyasyonuyla Sterilizasyonu (PhD Thesis). Ankara: Hacettepe Üniversitesi, 168-170, 147-152.

United States Pharmacopeia–National Formulary (USP30–NF25), 2006. Rockville MD: United States Pharmacopeial Co., 1741.

United States Pharmacopeia–National Formulary (USP32–NF27), 2009. Rockville MD: United States Pharmacopeial Co., 728.

Yoshino, K., Nakamura, K., Yamashita, A., Abe, Y., Iwasaki, K., Kanazawa, Y., Funatsu, K., Yoshimoto, T., Suzuki, S., 2014. Functional Evaluation and Characterization of a Newly Developed Silicone Oil-Free Prefillable Syringe System. *Pharmaceutics, Drug Delivery and Pharmaceutical Technolog*, 103, 520–1528.