Effect of solvent polarity on the extraction of components of pharmaceutical plastic containers

Iqbal Ahmad[1], Arif Sabah[2]*, Zubair Anwar[1], Aysha Arif[2], Adeel Arsalan[1] and Kiran Qadeer[1]
[1]Baqai Institute of Pharmaceutical Sciences, Baqai Medical University, Toll Plaza, Super Highway, Gadap Road, Karachi, Pakistan
[2]Faculty of Pharmacy, Ziauddin Medical University, 4/B, Shahrah-e-Ghalib, Block 6, Clifton, Karachi, Pakistan

Abstract:A study of the extraction of polymeric material and dyes from the pharmaceutical plastic containers using various organic solvents was conducted to evaluate the effect of polarity on the extraction process. The plastic containers used included semi-opaque, opaque, transparent and amber colored and the solvent used were acetonitrile, methanol, ethanol, acetone, dichloroethane, chloroform and water. The determination of extractable material was carried out by gravimetric and spectrometric methods. The yield of extractable materials from containers in 60 h was 0.10-1.29% (w/w) and the first-order rate constant (k_{obs}) for the extraction of polymeric material ranged from 0.52-1.50 × 10^{-3} min^{-1} and for the dyes 6.43- 6.74 x$10^{-3}$$min^{-1}$. The values of ($k_{obs}$) were found to be an inverse function of solvent dielectric constant and decreased linearly with the solvent acceptor number. The extractable polymeric materials exhibited absorption in the 200-400 nm region and the dyes in the 300-500nm region. The rates of extraction of polymeric material and dyes from plastic containers were dependent on the solvent dielectric constant. The solvents of low polarity were more effective in the extraction of material indicating that the extracted material were of low polarity or have non-polar character. The dyes were soluble in acetone and chloroform. No plastic material was found to be extracted from the containers in aqueous solution.

Keywords: Plastic containers, extractives, dyes, polarity, kinetics.

INTRODUCTION

Plastic containers are among the most widely used containers for the storage of solid and liquid pharmaceutical products. These containers are manufactured to possess the prescribed performance characteristics of chemical inertness; air, moisture and light protection and minimum interaction between the plastic material and the pharmaceutical products (British Pharmacopoeia, 2016; Unites States Pharmacopeia, 2016). The interaction may result in the release of the polymeric material and dyes from the plastic containers into the pharmaceutical product affecting its quality, safety and efficacy. Two factors are important to consider in connection with the polymeric material used to manufacture the plastic containers (Jenke, 2007).

Extractables

Substances that can be extracted from a plastic material/system using extraction solvents and/or extraction conditions are expected to be more aggressive than the condition of contact between the material/ system and a finished drug product.

Leachables

Substances that are present in the finished drug product because of its interaction with a plastic material or system during its intended use. In view of the importance of these phenomena several workers have conducted studies on the leaching, extraction and determination of components of the plastic material from the containers and tubing to evaluate the contents (Bennan*et al*2002; Berg *et al* 1993; Green, 2005; Jenke,1997, 2002, 2004, 2005; Jenke, 2001, 2005, 2006; Kim *et al* 1990; Nicholas, 2006; Reif*et al* 1996; Sarbach*et al* 1996; Snell, 1993; Weitzmann, 1997; Wang, 2005) and their harmful effects on the products (Jenke, 2007; Kauffman, 2006; Northup, 2005; Osterberg, 2005). An important consideration in the study of the extractable from the plastic material is the nature of the solvent and its polar character. Organic solvents affect the rates of chemical reactions such as the degradation of drugs including riboflavin and analogs (Ahmed *et al.,* 2006), flouroquinolones (Ahmad *et al* 2013, 2014; Bilski*et al.*, 1998), steroids (Khatak*et al.*, 2013) and polymerization reactions (Ahmad *et al.,* 2013) on the basis of their polar character.

The kinetics of extraction and extraction efficiency depends on the nature of the extractable components and the polarity of the solvent employed (Spiro and Siddiqui, 1981).

Material/water equilibrium interaction constants have been determined for several organic models solutes and the material used in pharmaceutical plastic containers (non-PVC polyolefin). The interaction constants have been related to the polarity of the aqueous/organic solvent mixtures used (Jenke, 2006). The rate of a reaction between dipolar molecules depends on the dielectric constant, ϵ, (a measure of solvent polarity) of the medium (Sinko, 2011).

**Corresponding author:* e-mail: drarif_bips1@yahoo.com

$\ln k = \ln k_{\epsilon=\infty} - K\,(1/\epsilon)$ (1)

Where $k_{\epsilon=\infty}$ is the rate constant in a medium of infinite dielectric constant.

The ϵ of the medium is approximately equal to the ϵ of the solvent in dilute solutions. An increase in ϵ tends to increase the rate and a decrease in ϵ to a decrease in the rate. The rate constant of a reaction can be related to the ϵ of the solvent.

The aim of this work is to study the kinetics of extraction of polymeric material and dyes from different pharmaceutical plastic containers using a number of organic solvents and to develop a correlation between the rate constants and the polarity of the organic solvents used. It is also intended to determine the spectral characteristics of the extractable material and the dyes present.

MATERIALS AND METHODS

Materials

The following plastic containers of pharmaceutical grade were used in this study (white semi-opaque and white opaque, high density poly ethylene (HDPE); transparent and amber colored, low density polyethylene (LDPE). The containers were obtained from Friends Plastic Containers and Closures Manufacturer, Karachi. All the organic solvents used were of the purest form available from Merck & Co (Germany): Methanol (99.9%), ethanol (99.9%), acetonitrile (99.8%), acetone (99.5%), dichloroethane (99.8%) and chloroform (99.8%). The water used was freshly glass distilled water.

Extraction procedure and determination

Six samples each of the plastic containers were filled with 100 ml of the solvent and placed in a thermostat bath maintained at 25± 1°C for a period of 60 h. The samples of containers with different solvents were withdrawn at 10 h intervals. The solvent were evaporated to dryness under reduced pressure at room temperature (25°C). The residues of the semi-opaque, opaque and transparent containers appeared as a whitish mass and those of the amber containers as a reddish yellow mass. All the residues were carefully weighed and the percentage contents (w/w) calculated. Each experiment was performed in triplicate and the results were determined in averages.

Absorption spectra

The absorption spectra of the polymeric material and dyes extracted from the containers were determined on Shimadzu UV- visible recording spectrophotometer (model UV-160, Japan) using quartz cells of 10-mm path length.

RESULTS

Extractable material

The amount of chemical extractable polymeric material and dyes from the plastic containers was determined at different time intervals during the extraction with various solvents. The overall amount of the extractable material from the containers ranged from 0.10-1.29% (w/w). The results of atypical experiment for the extractable material obtained from the opaque containers using different solvents are given in table 1. The concentration values in different solvents vary, with time, and change with the solvent indicating the effect of the solvent characteristics on the extent of extraction of the chemical components of the containers. The LDPE containers (transparent and amber color) showed a greater amount of extractable materials than the HDPE containers (semi-opaque and opaque) probably due to ease of extraction with the organic solvents as indicated by the rates of extraction described under the kinetics section.

The UV absorption spectra of the material extracted from the containers in different solvents have been determined and the absorption maxima recorded (Table 2). These absorption maxima are in the range of 200-400 nm and represent a mixture of polymeric components present in different plastic containers. The polymeric material may include compounds with phenyl rings and conjugated double bond residue (Klevens, 1953) being extracted in various organic solvents with broad absorption in the UV region.

Extractable dyes

Two reddish pink dyes were also extracted from the amber colored containers using chloroform and acetone. The absorption spectra of the dyes were determined and are shown in fig. 1. The dyes extracted in chloroform exhibited absorption maxima at 420 and 444 nm and that in acetone at 369 and 442 nm in the visible region. The removal of the dyes showed a little change in the color of the containers. These dyes could be extracted into the product during the storage. Pigment orange and chromophthal brown absorbing in the 400-500 nm region have been used to give light-protecting properties to the plastic containers (Beyrich and Tibussek, 1981).

Kinetics of extraction

The various techniques used for the extraction of active components of plant materials have been reviewed (Azmir et al 2013). The extraction of drugs from the plant material has been shown to follow afirst-order kinetics process (Spiro and Siddiqui, 1981).

$\ln [C] - \ln [C^o] = -k_1 t$ (2)

or

$\ln [C] = 2.303 \log_{10} [C^o] - k_1 t$ (3)

or

$k_1 = 2.303/t \times \log_{10} [C^o/C]$ (4)

Table 1:Concentrations of extractable material from opaque plastic containers

Time (h)	Concentration (mg %, w/w) ± s.d.[a]					
	Acetonitrile	Methanol	Ethanol	Acetone	Dichloroethane	Chloroform
0	0.0	0.0	0.0	0.0	0.0	0.0
10	1.31±0.07	1.4±0.07	1.5±0.08	1.6±0.08	1.6±0.08	2.0±0.10
20	2.0±0.11	2.2±0.12	2.3±0.12	2.4±0.11	2.5±0.13	4.2±0.21
30	3.1±0.17	3.1±0.15	3.5±0.21	3.8±0.18	4.1±0.21	7.9±0.38
40	4.2±0.23	4.8±0.26	5.0±0.26	5.7±0.28	6.0±0.31	15.1±0.76
50	6.3±0.30	7.0±0.34	7.6±0.38	8.9±0.45	9.9±0.48	30.9±1.55
60	9.3±0.48	10.4±0.53	11.6±0.56	13.4±0.23	15.4±0.86	56.3±2.52
% yield	0.058%	0.065%	0.072%	0.084%	0.096%	0.35%

[a]n=3

Table 2:Absorption maxima (nm) of extractable material in organic solvents from plastic containers

Container	Acetonitrile	Methanol	Ethanol	Acetone	Dichloroethane	Chloroform
Amber	240, 287, 405	291, 358	374	369, 442[a]	289	420, 444[a]
Transparent	229	275, 291	302, 374	325	385	249,289, 386
Opaque	218	205, 275	273	255, 325	282, 372	275, 310, 373
Semi-opaque	239, 285	272, 292, 368	301, 366	330	265, 288	374

[a] dyes

Table 3:Apparent first-order rate constants (k_{obs}) for the extraction of polymeric material from plastic containers withorganic solvents

Solvent	Acceptor number (AN)	Dielectric Constant (ϵ) (25°C)	Inverse of dielectric Constant (1/ϵ)	$k_{obs}\times10^3$ (min^{-1})± s.d. for containers[a]			
				Semi-opaque	Opaque	Transparent	Amber
Acetonitrile	18.9	37.5	0.0266	0.52±0.020	0.62±0.0322	0.72±0.040	0.93±0.050
Methanol	41.3	32.5	0.0307	0.54±0.028	0.66±0.030	0.77±0.042	0.95±0.051
Ethanol	37.1	24.5	0.0408	0.56±0.031	0.68±0.035	0.79±0.038	0.98±0.048
Acetone	12.5	20.7	0.0483	0.59±0.034	0.72±0.036	0.85±0.046	1.02±0.055
Dichloroethane	16.7	10.4	0.0962	0.62±0.032	0.76±0.038	0.90±0.049	1.12±1.051
Chloroform	23.1	4.7	0.2128	0.91±0.047	1.12±0.051	1.32±0.065	1.50±1.058
Extractable material (%)				0.03-0.10%	0.04-0.18%	0.06-0.33%	0.17-1.29%

[a]n=3

In a first-order kinetic process a plot of log concentration versus time will be linear with a slope equal to $k_1/2.303$ where $k1$ is the first- order rate constant.

The concentrations of extractable material obtained from different containers have been used to determine the rate constants for extraction by the organic solvents. The analytical data have been found to comply with first-order kinetics and the values of first-order rate constants (k_{obs}) determined from the slopes of log c versus time plots for different containers are given in table 3. These values vary with the containers and are in the range of 0.52-1.50×10^{-3} min^{-1}indicating the effect of solvent characteristics (e.g., polarity) on the extraction efficiency. As an example, the concentrations of extractable material from the opaque containers using different solvents (table 1) were used to construct the first-order plots shown in fig. 2 that vary with the solvent used. The overall amount of the extractable material from all the containers ranged from 0.10 -1.29% w/w.No plastic material was found to be extracted from the containers in aqueous solution.

Since two dyes have also been extracted from the amber colored containers in chloroform and acetone, their rates have been determined. The extraction of these dyes has been found to follow first-order kinetics. In order to determine the values of k_{obs} for these dyes the absorbance values (log A) have been plotted against time (fig. 3) and the values of k_{obs}determined as 6.74 and 6.43×10^{-3}min^{-1}for the extraction in chloroform and acetone, respectively.

DISCUSSION

Effect of solvent polarity

The solvent dielectric constant (ϵ) is an important parameter that affects the rates of chemical reactions (Ahmad and Tollin, 1981, Ahmad *et al;* 2015; Reichardt, 1988; Spiro and Jago, 1982) and extraction processes. It may influence the extraction efficiency of a solvent depending upon the nature of the extractable material from the plastic container. To develop a correlation between the rate constants for the extraction of material from different containers by the organic solvents, the values of k_{obs} have been plotted against the inverse of solvent dielectric constant (1/ϵ) and a linear relation has been obtained (fig. 4). However, the effect of solvent is not very large as a big change in dielectric constant produces a relatively small change in the values of $k_{obs.}$ This may probably be due to the nature of the extractable material. The plots presented indicate that the polarity of a solvent plays a considerable role in the extraction of material from the containers. It is evident from the plots that a decrease in solvent polarity leads to an increase in the amount of extractable material from the containers. It suggests that the extractable material has a weakly polar or non-polar character and is, therefore, increasingly being extracted in solvents of low polarity such as chloroform. This could affect the products in aqueous-organic solvent mixtures stored in plastic containers.

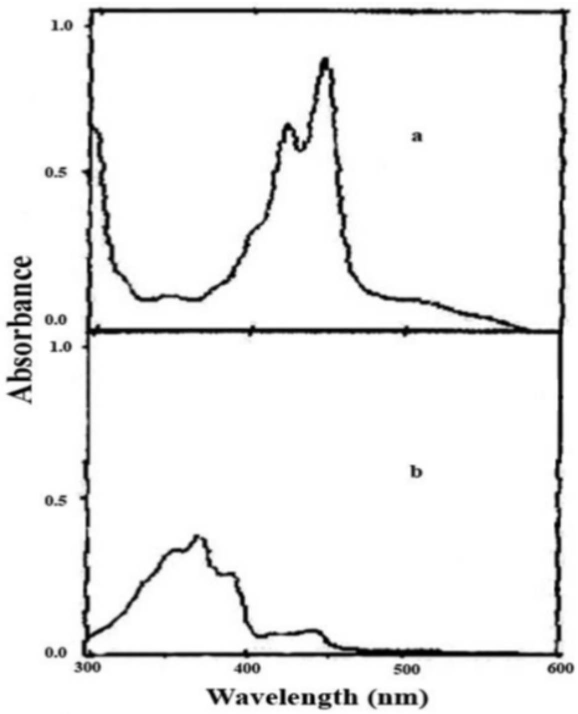

Fig. 1: Absorption spectra of the extracted dyes from amber container in: (a) chloroform: (b) acetone.

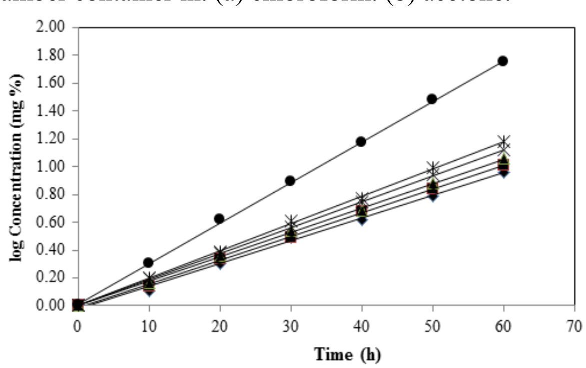

Fig. 2:First–order plots for extractable material from opaque containers: chloroform: -●-methanol: - ◙- ethanol: -▲- acetonitrile: - ♦- dichloroethane: -■- acetone: -×-.

Solvent- Container components interaction

It has been considered necessary in this study to observe the effect of any electronic interaction between a particular solvent and the components of the containers being extracted. The effect of solvent on the rate of a chemical reaction may also be expressed by its donor number (DN) and acceptor number (AN) on the basis of the donor-acceptor approach (Guttman, 1978). The DN and the AN measure the ability of the solvent to give shares in electron pairs to suitable acceptors and to take shares in electron pairs from suitable donors, respectively. In order to develop a correlation between the rate-constants for extraction and the solvent AN value (table. 3), log k versus AN of the solvent has been plotted (fig. 5) and a linear relation has been observed. It shows that an increase in AN value of the solvents results in a decrease in the values of k_{obs}. Therefore, AN of the solvent also plays a role in the extraction process. However, it is evident from the plots that AN does not significantly affect the extraction of polymeric material from the containers. The rate constants or extraction in chloroform from all the containers did not follow the relation probably due to the predominant solubility factor in that solvent. Any relation between the rate constants and DN values of the solvents has not been found.

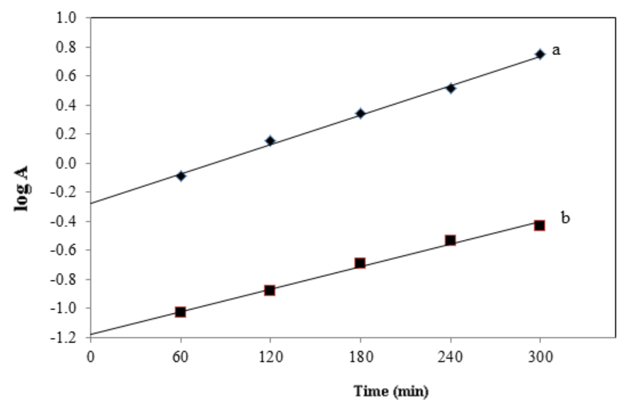

Fig. 3: First-order plots for the extracted dyes from amber container in: (a) chloroform (444nm) and: (b) in acetone (369 nm).

Nature of extractable material

Plastic containers are mainly manufactured from different polymers or their combinations, like polyethylene, polyethylene terephthalate, polyamide, polymethylmethacrylate, polytrifloroethylene and amino-formaldehyde. Certain additives consisting of antioxidants, antistatic agents, coloring agents, impact modifiers, lubricants, plasticizers and stabilizers are also added to impart the desired characteristics. The light stabilizers such as Tinuvin, the derivatives of 2-hydroxybenzophenone, absorbing UV and visible light (320- 450 nm) are used to prevent photooxidation of drug substances. The chemical composition of different plastic containers has been reported (Robertson, 1996; Shivsharan*et al*2014; Sunil, 2013). These materials may be extracted from the containers into the product during storage.The isolation and identification of potential migrants in gamma-irradiated plastic laminates by using GC/MS and GC/IR techniques have been reported (King-Kang and Gilbert, 1991). All these materials are generally of a weakly polar or non-polar character and would be easily extracted in the solvents of low polarity. It is, therefore, advisable to study the extraction /leaching of polymeric material from the containers into the product to ensure the safety of consumer (Jenke, 2007).

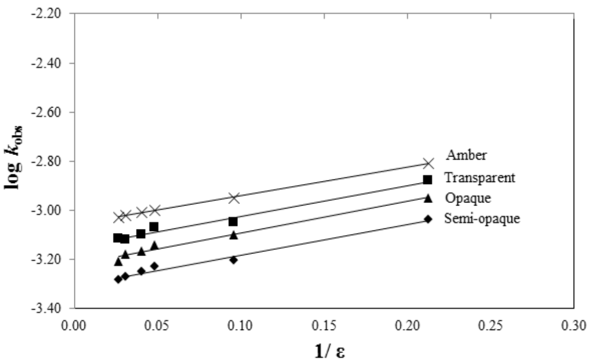

Fig. 4: Plots of *k*obs for extractable material versus the inverse of dielectric constant (1/є) of solvents.

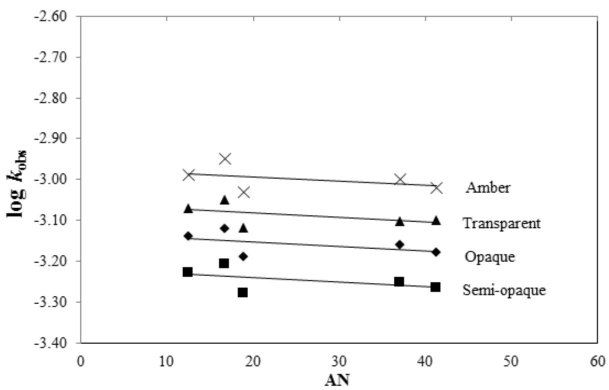

Fig. 5:Relationship between log *k* for extractable material and solvent acceptor number (AN).

CONCLUSION

The liquid pharmaceutical products in aqueous-organic solvent mixtures stored in plastic containers may be affected by extraction of the polymeric constituents and other additives of the plastic containers. These constituents have been found to be extracted in organic solvents depending on the polarity of the solvent. The lower the polarity of solvent, the greater the extractable from the containers. This is probably due to the weakly polar or non-polar nature of the extractable constituents from the containers. The organic dyes present in colored containers have also been found to be extracted in some solvents and may affect the product. This requires a careful evaluation before using the storage of containers for a particular product to ensure the safety of the end-user.

ACKNOWLEDGEMENT

We are thankful to Dr. Waqas Bin Aftab for providing the pharmaceutical plastic containers to conduct this study.

REFERENCES

Ahmad I and Tollin G (1981). Solvent effect on flavin electron transfer reactions. *Biochemistry*, **20**: 5925-5928.

Ahmad I, Fassihullah Q and Vaid FHM (2006). Photolysis of formylmethylflavin in aqueous and organic solvents. *Photochem. Photobiol. Sci*., **5**: 680-685.

Ahmad I, Bano R, Sheraz MA, Ahmed S and Ansari SA (2013). Photodegradation oflevofloxacin in aqueous and organic solvents: A kinetic study. *Acta Pharm*., **63**: 221-227.

Ahmad I, Iqbal Q, Sheraz MA, Ahmed S, Ali SA and Qazi SH (2013). Solvent effects on photoinitiator reactivity in the polymerization of 2-hydroxyethyl methacrylate. *Adv. Phys. Chem*., ID: 838402.

Ahmad I, Bano R, Musharraf SG, Ahmed S, Sheraz MA and Arfeen Q (2014). Photodegradation of moxifloxacin in aqueous and organic solvents: A kinetic study. *AAPS Pharm SciTech*., **15**: 1588-1597.

Ahmad I, Anwar Z, Ahmed S, Sheraz MA, Bano R and Hafeez A (2015). Solvent effect onthe photolysis of riboflavin. *AAPS PharmSciTech*., **16**: 1122-1128.

Azmir, J, Ziadul ISM, Rehman MM, Sharif A, Ghafoor K and Nourlaini NAN (2013).Techniques for extraction of bioactive compounds from plant materials: A review. *J. Food Eng*., **117**: 426-136.

Bennan J, Bing F, Boone H, Fernandez J, Seely B and Van Denise H (2002). Evaluation ofextractables from product-contact surface. *Biopharm. Int*., **15**: 22-34.

Berg BE, Hegna N, Orlien N and Greibrokk T (1993). Determination of low levels of polymer additives migrating from polypropylene to food simulated liquid by capillary SFC and solvent venting injection. *Chromatographia*., **37**: 271-276.

Beyrich T and Tibussek P (1981). Studies on the light transmittance of coloured plastic bottles for liquid pharmaceutical preparations. Part 43: Contributions to problems concerning the use of plastic containers for liquid pharmaceutical preparations. *DiePharmazie*., **36**: 337-341.

Bilski P, Martinez LJ, Koker EB and Chignell CF (1998). Influence of solvent polarity and proticity on the photochemical properties of norfloxacin. *Photochem. Photobiol*., **68**: 20-24.

British Pharmacopeia (2016).The Stationary office, British Pharmacopeia Commission Office, London, UK, Electronic version.

Castner J, William N and Bresnick M (2004). Leachables found in parentral drug products. *Am. Pharm. Rev*., **7**: 70-75.

Green S (2005). Extractables and leachables: A biopharmaceutical perspective. *Am. Pharm. Rev*., 8: 24-29.

Gutmann V (1978). The donar-acceptor approach to molecular interactions, Plenum Press, New York and London, p.279.

Jenke D (1997). Utilization of extraction profile to estimate the accumulation of extractables from polymeric materials. *J. Appl. Polym. Sci*., **63**:843-848.

Jenke D (2002). Extractable / leachable substances from plastic containers / devices. *PDA J. Pharm. Sci. Tech*., **56**: 332-371.

Jenke D, Zietlow D and Sadain S (2004). Leaching of organic acids from irradiated EVA Plastics as a function of solution pH and polarity. *PDA J. Pharm. Sci. Tech*., **58**: 24-31.

Jenke D, Swanson S, Edgcomb E, Couch T, Chacko M and Garber MJ (2005). Strategy for assessing the leachables impact of material change made to a container / closure system. *PDA J. Pharm. Sci. Tech*., **59**: 360- 380.

Jenke D, Odufu A and Poss M (2006). The effect of solvent polarity on the accumulation of leachables from pharmaceutical product containers. *Eur. J. Pharm. Sci*., **27**: 133-142.

Jenke D (2007). Evaluation of the chemical compatibility of plastic contact material and pharmaceutical product; safety consideration related to extractables and leachables. *JPS*., **96**: 2566-2581.

Jenke DR (2001). Evaluation of model solvent system for assessing the accumulation of container extractables in formulation. *Int. J. Pharm*., **224**: 51-60.

Jenke DR (2005). Linking extractables and leachables in container/ closure applications. *PDAJ. Pharm. Sci. Tech*., **59**: 265-281.

Jenke DR, Story J and Rukhsana L (2006). Extractables / leachables from plastic tubing used in product manufacturing. *Int. J. Pharm*., **315**: 75-92.

Kauffman JS (2006). Identification and risk assessment of extractables and leachables. *Pharm. Technol*., **1**: 14-22.

Khatak SR, Sheikh D, Ahmad I, Ghani KU, Sheraz MA and Ahmed S (2013). Photodegradation and stabilization of betamethasone-17 valerate in aqueous / organic solvents and topical formulations. *AAPS PharmSciTech*., **14**: 177-182.

Kim H, Gilbert SG and Johnson JB (1990). Determination of potential migrants from commercial amber polyethylene terephtahalate bottle wall. *Pharm. Res*., **7**: 176-179.

King-Kang H and Gilbert SG (1991). Isolation and identification of potential migrant'sin Gamma irradiated plastic laminates by using GC/MS and GC/IR. *Appl. Spectrosc*., **45**: 572-580.

Klevens HB (1953). Extreme ultraviolet absorption spectra of various polymers. *Polym. Chem*., **10**: 97-107.

Nicholas K (2006). Extractables and leachables determination: A systematic approach to select and quantify a container closure system for a pharmaceutical product. *Am. Pharm. Rev*., **9**: 21-27.

Northup SJ (2005). Assessing the biological safety of extractable and leachable chemicals in pharmaceutical and medical products. *Am. Pharm. Rev*., **20**: 38-42.

Osterberg RE (2005). Potential toxicity of extractables and leachables in drug products. *Am. Pharm. Rev*., **8**: 64-70.

Reichardt C (1988). Solvent and Solvent Effects in Organic Chemistry, 2nd Ed. VCH Publishers, New York., pp.1-46.

Reif AW, Sockner P and Rupp J (1996). Analysis and evaluation of filter cartridge extractable for validation in pharmaceutical downstream processing. *PDA J. Pharm. Sci. Tech*., **50**: 399-410.

Robertson MJ (1996). Licensing consideration regarding the immediate packaging of the pharmaceuticals for human use, In: Lockhart H and Paine FA (eds.) Packaging of Pharmaceuticals and Healthcare Products. Chap 5;Chapman & Hall, London, pp.68-97.

Sarbach C, Yagoubi N, Sanzieres J, Renaux C, Ferrier D and Postaire E (1996). Migration of impurities from a multi-layer plastic container into a parenteral infusion solution. *Int.J. Pharm*., **140**: 169-174.

Shivsharan US, Rault ES and Shaikh ZM (2014). Packaging of cosmetics: A review. *JPSI*., **3**: 286-292.

Sinko PJ (2011). Chemical kinetics and stability. In: Martin's Physical Pharmacy and Pharmaceutical Sciences, Lippincott Williams & Williams, New York. Chap. **14**: 318-354.

Snell RP (1993). Solid phase extraction and liquid chromatographic determination of monophthalates and phthalide extracted from solution administration sets. *J. AOAC*., **76**: 531-534.

Spiro M and Jago DS (1982). Kinetics and equilibria of tea infusion Part 3 Rotating-disc experiments interpreted by a steady state model. *J. Chem. Soc., Farady Trans*., **78**: 295-305.

Spiro M and Siddique S (1981). Kinetics and equilibria of tea infusion: Analysis and Partition constants of thea-flavins, thearubigins and caffeine in Koonsong Broken Pekoe. *J. Sci. Food Agric*., **32**: 1027-1032.

Sunil K (2013). Pharmaceutical packaging technology: A review. *IJRPBS*., **4**:1400-1414.

United States Pharmacopeia (2016). United States Pharmacopeia Convention, Rockville, MD, USA, Electronic version.

Wang Q (2005). Selection of analytical techniques for pharmaceutical leachable studies. *Am. Pharm. Rev*., **8**: 38-44.

Weitzmann C (1997). The use of model solvents for evaluating extractables from fillers used to process pharmaceutical products. *Pharm. Technol*., **75**: 72-89.