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Moisture and oxygen barrier properties of glass, PET and HDPE bottles for pharmaceutical products

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ABSTRACT

The purpose of this study was to evaluate the influence of the material and volume/different finish diameters in the moisture and oxygen barrier properties for bottles for pharmaceutical products. Samples of glass, polyethylene terephthalate (PET) and high-density polyethylene (HDPE) bottles with different volumes (30, 60 and 120 cm^3) and finish diameters (18, 24 and 28 mm) were studied. It was previously verified that the integrity of the closure was not dependent on the torque applied to the polypropylene (PP) cap and not influence the barrier properties of the bottles. Provided integrity of the cap for all analyzed samples, water vapor transmission rate (WVTR) of glass increased with increase in finish diameter for the same bottle size, due to a large area exposed for moisture permeation through the PP cap. WVTR of PET and HDPE are dependent by the bottle size and its surface area since moisture permeability occurs preferentially by the bottle. The influence of the material in the moisture barrier properties have been confirmed by the WVTR results obtained for the same bottle volume ($30cm^3$/24 mm) with average values of 0.07, 9.9 and 0.8 $mg.day^{-1}.bottle^{-1}$ at 40 °C/75%RH for glass, PET and HDPE, respectively. Glass represents the greatest oxygen barrier, followed by PET and HDPE for the same bottle size.

1. Introduction

Packaging must ensure adequate stability of the product throughout its shelf life and so it is very important to consider the container and cover (cap) as a single and integrated material, that is, as a packaging system. Stability for all medical products is associated with the availability of the active ingredient during the entire shelf life, without the occurrence of any reaction of degradation [1]. Therefore, a package system must be chemically inert to avoid interactions between the product and packaging and closure material (avoid leachable or extractable materials) and ensure an effective barrier against moisture and gases to protect the product and thus guarantee the medicine efficacy [1,2].

Moisture or gas permeability, especially oxygen, can significantly affect the product quality and its shelf life and so alter the product safety and the efficacy of the active pharmaceutical ingredient (API) [3]. Moisture ingression in the packaging and the possibility of water absorption by dried products can lead to chemical or physical instability of the product and further its degradation [4,5]. Loss of moisture for liquid products by permeation during storage may also lead to a viscosity enhancement and as consequence an increase of the API concentration, and, thus, affect its quality [5,6]. For pharmaceutical products that contain components sensitive to oxygen and susceptible to oxidation such as vitamins, the oxygen permeability of the packaging is an important factor that can affect the drug stability and limit its shelf life (expiration date) [7].

Generally, the sorption of moisture by a solid pharmaceutical product can be used as a parameter to assess its quality during a long-term storage. It is also important to analyze the effect of moisture on the product quality separately, once the degradation of the API increases exponentially with increasing moisture [1,8]. Nokhodchi and Javadzadeh [9] reviewed the effect of the amount of moisture absorbed by drugs or excipients in tablet form, which can influence significantly the physical stability of the product (increase or decrease in mechanical strength, disintegration time and bioavailability problems, as well as the dissolution rate of the drug).

Glass bottles are one of the traditional materials used for packaging of pharmaceutical products and it is defined as an inert, solid and nonporous material and, therefore, glass packaging has good barrier properties against external agents, especially moisture and oxygen [10].

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Table 1
Total volumetric capacity and other characteristics for the analyzed bottles and closure system type.

Bottle volume/ finish diameter[1]	Packaging Material	Total volumetric capacity[2] (cm^3)	Minimum body thickness (cm)	Surface area[3] (cm^2)	PP continuous thread caps[4]
30/18	Glass	35.0 ± 0.2	0.14 ± 0.01	97.1	GL 18 DIN 168
	PET	37.5 ± 0.2	0.056 ± 0.006	88.8	
30/24	Glass	36.0 ± 0.2	0.12 ± 0.02	93.3	Pilfer Proof Standard (GPP 24 BR)
	PET	40.2 ± 0.2	0.053 ± 0.004	87.2	
	HDPE	37.2 ± 0.5	0.092 ± 0.005	82.1	
60/24	Glass	71.3 ± 0.4	0.12 ± 0.02	141.2	
	PET	71.2 ± 0.4	0.030 ± 0.004	127.4	
	HDPE	74.4 ± 0.3	0.085 ± 0.006	107.9	
120/28	Glass	139.2 ± 0.6	0.12 ± 0.01	213.4	MCA2-P special
	PET	136.3 ± 0.3	0.038 ± 0.003	193.9	
	HDPE	141.2 ± 0.4	0.068 ± 0.005	190.1	

PET = Polyethylene terephthalate/HDPE = High-density polyethylene/PP = Polypropylene.
[1] Bottle volume in cm^3 and finish diameter in mm, for example, 30/18 = 30 cm^3/18 mm.
[2] Average ± S.D. – standard deviation results of 20 bottles.
[3] External surface area for permeation estimated from the area of a cylinder body plus two times the bottom area (bottom and top).
[4] Polypropylene caps and its terminology adopted by national standard ABNT NBR 11819 [21]: GL 18 168 DIN = Deutsches Institut für Normung/GPP = Finish Pilfer Proof/MCA2-P = Metal Closure Adapted Plastic.

Table 2
Closure integrity with two applied torques.

Bottle volume/ finish diameter[1]	Packaging material	Torque (lbf. in) [2]	Helium flow rate (mbar.L. s^{-1}) [3]		
30/18	Glass	7.2 ± 0.1	$7.2E^{-10}$	to	$9.1E^{-10}$
		10.1 ± 0.2	$6.4E^{-10}$	to	$8.7E^{-10}$
	PET	7.1 ± 0.1	$5.2E^{-10}$	to	$8.9E^{-10}$
		10.2 ± 0.1	$5.5E^{-10}$	to	$9.9E^{-10}$
30/24	Glass	10.1 ± 0.1	$6.0E^{-10}$	To	$8.9E^{-10}$
		13.3 ± 0.7	$5.3E^{-10}$	To	$9.2E^{-10}$
	PET	10.2 ± 0.1	$6.2E^{-10}$	To	$9.3E^{-10}$
		12.7 ± 0.9	$5.4E^{-10}$	To	$9.3E^{-10}$
	HDPE	9.6 ± 0.8	$5.4E^{-10}$	To	$9.4E^{-10}$
60/24	Glass	10.2 ± 0.1	$1.9E^{-10}$	To	$8.7E^{-10}$
		13.3 ± 0.7	$6.6E^{-10}$	To	$9.1E^{-10}$
	PET	10.2 ± 0.2	$2.9E^{-10}$	To	$9.1E^{-10}$
		12.9 ± 0.4	$3.3E^{-10}$	To	$9.5E^{-10}$
	HDPE	10.1 ± 0.1	$6.3E^{-10}$	To	$9.3E^{-10}$
120/28	Glass	12.2 ± 0.1	$3.6E^{-10}$	To	$9.7E^{-10}$
		15.0 ± 0.5	$6.8E^{-10}$	To	$9.7E^{-10}$
	PET	12.2 ± 0.2	$4.1E^{-10}$	To	$9.8E^{-10}$
		15.4 ± 0.5	$4.5E^{-10}$	To	$9.5E^{-10}$
	HDPE	12.2 ± 0.3	$6.9E^{-10}$	To	$9.9E^{-10}$

PET = Polyethylene terephthalate/HDPE = High-density polyethylene.
[1] Bottle volume in cm^3 and finish diameter in mm, for example, 30/18 = 30 cm^3/18 mm.
[2] Average ± S.D. results of 10 bottles.
[3] 1 mbar L s^{-1} = 0.1 Pa $m^3.s^{-1}$.

Plastic materials such as polyethylene terephthalate (PET) and high-density polyethylene (HDPE) have made their way in the pharmaceutical industry and can used as a bottles for solid or liquid oral dosage forms products. Polymers are not able to crystallize completely and it has some permeation to moisture and gases, depending on the molecular structure of the material and its thickness [3,11,12]. PET, for example, has a high mechanical strength and good gas barrier properties, but it is not an effective barrier against moisture. HDPE has higher percentage of crystalline structure and less moisture permeability compared to low-density polyethylene (LDPE) and slightly lower than polypropylene (PP). Regarding to oxygen barrier properties, PET has lower oxygen permeability if compared to HDPE and PP [3,11].

According to Hernandez et al. [3] permeation is defined as the movement of gases, water vapors or liquids (called permeants) through a homogeneous packaging material and excludes the displacement of these permeants through perforations, cracks or other defects. Thus, for a plastic package without defect, the mechanism of ingress of moisture inside the package occurs mainly by the diffusion of water molecules through the wall of the package, mostly through the amorphous regions [5,12].

Allinson et al. [13] obtained the moisture barrier of some materials used for blister as polyvinyl chloride (PVC), polychlorotrifluoroethylene (Aclar), aluminum foil and cyclic olefin copolymer (COC) and their effect on the stability of a moisture-sensitive compound under different storage conditions. The values of moisture permeation obtained for these thermoformed materials in 13.3 mm × 7.5 mm x 4.4 mm cavities (length x width x height) were 0.259, 0.040, 0.008 and 0.001 $mg.day^{-1}$. $blister^{-1}$ for PVC, COC, Aclar and aluminum, respectively, under the storage condition of 23 °C/75%RH established in the American Pharmacopoeia.

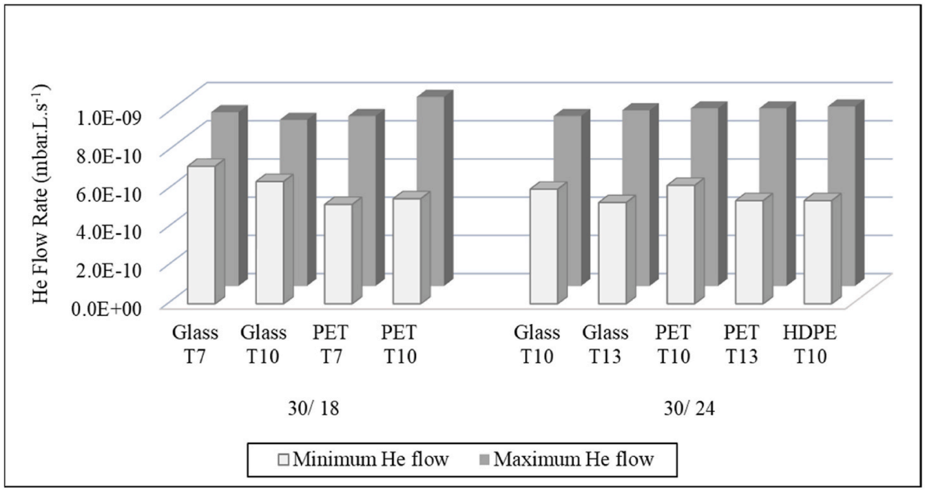
Another research obtained by Chen and Li [5] demonstrated that the water vapor transmission rate (WVTR) of HDPE bottles for pharmaceutical products increases according to the size/surface area of the package under similar conditions of temperature and relative humidity.

Polypropylene (PP) is the traditional material used for closure system mainly as screw caps that comply with the market expectations for convenience, consumer security with a tamper evident band, relative easy opening and re-closing if it is necessary. Regarding to a packaging system integrity, the dimensional compatibility between the closure and bottle finish, associated with the force to apply the cap, that is, the application torque, can affect the integrity and, consequently, the barrier packaging properties.

Torque is the rotational force (expressed at in.lbf) required for screw caps application (or removal) into the packaging and a wide range of application torque values can be suggested by some companies and also in the chapter <671> of the American Pharmacopoeia for diameters that range from 8 to 132 mm [14–16]. Previous study assessed by Bócoli and Jaime [17] observed that PP caps with 24 and 28 mm diameters could not be applied with the maximum torque values suggested in such references regardless the bottles material (glass, PET or HDPE). It was observed that high torque values caused a false rotation of the cap and favored the closure integrity loss. According to SKS [16] high application torque values can increase the chances of product leakage, as over-torque may pressure some points on the cap more than others which result in an inadequate sealing.

The importance to ensure a closure system integrity prior to the packaging use were demonstrated in a study performed by Kossinna and Meyer [18] since samples of 18 mm caps with expanded polyethylene (PE) liners provided from different suppliers showed distinct results of integrity. Caps from one supplier indicated low helium flow rates measured by helium leak testing independent of the applied torque, whereas for the other supplier an integrity linear dependence of application torque in the glass bottle was observed. According to these results, the author comments that this closure type will only have an efficient sealing on the package if it is properly compressed at the finish.

It is essential to use a product that simulates the characteristics of the pharmaceutical product to determine the packaging moisture barrier property and the storage condition under a temperature and relative humidity controlled by special chambers with adequate control of these



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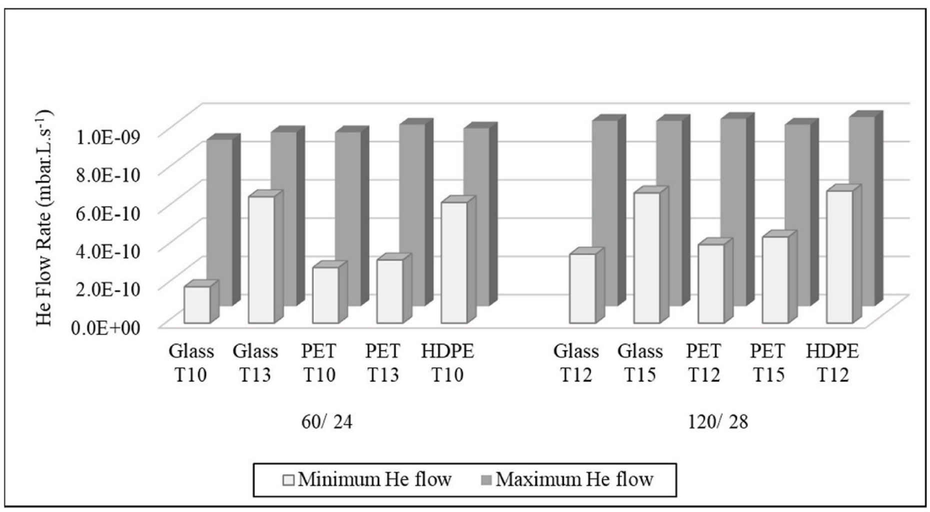

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Fig. 1. Helium flow rate with the minimum and maximum torques applied to the glass, PET and HDPE bottles of 30cm^3/18 mm and 30cm^3/24 mm (a) and 60cm^3/24 mm and 120cm^3/28 mm (b).

parameters. The American Pharmacopoeia, chapter <671> [14], establishes the storage conditions of 40±2 °C/75 ± 5%RH and 23 ±2 °C/75 ± 3%RH for studies for moisture ingress or weight gain (solid drugs) using calcium chloride as a desiccant. The storage condition of 25 ±2 °C/40 ± 2%RH using water as product simulant is established for weight loss studies (aqueous solution) [14]. Guidelines for conducting accelerated aging of stability studies for pharmaceuticals products in Brazil are defined by Resolution RDC nº 318, in accordance with the requirements established at the International Conference of Harmonization - ICH [14,19,20]. The storage conditions of 40±2 °C/75 ± 5%RH for weight gain and 40±2 °C/25 ± 5%RH for weight loss in accelerated studies are defined by Resolution RDC nº 318 [19].

To assure adequate product stability, some authors emphasize the importance of providing in advance the barrier properties of the packaging for pharmaceutical products [1]. An adequate choice of packaging prior to the accelerated drug stability studies can help the laboratories to reduce costs and usually relative extensive time of analysis.

Therefore, the present study aimed to determine the water vapor transmission rate (WVTR) and the oxygen transmission rate (O_2TR) of glass, PET and HDPE bottles with different size/finish diameter in order to predict the effect of packaging material on drug stability. The influence of the application torque on the integrity of the closure was also previous evaluated to cover this study as a packaging system.

The results obtained in this study will be very helpful for several pharmaceutical companies to distinguish which packaging system to be used for solid or liquid forms that will provide adequate stability for the drug regarding to moisture or oxygen barrier properties.

2. Materiais and methods

2.1. Materials

Glass, PET and HDPE bottles with nominal volumes of 30, 60 and 120 cm^3 and different PP cap's diameter (18, 24 and 28 mm) were analyzed according to description in Table 1.

Brazilian companies produced all analyzed samples: glass bottles by Industrial Glass Company (CIV, Recife/PE); plastic bottles by Gerresheimer Plastics São Paulo Ltd. (Cotia/SP) and PP caps by Closure Systems International (CSI, Barueri/SP).

Polypropylene (PP) caps, brand named All Pharma Lok, had a 360°

Table 3
Effects of the closure torque, successive opening/closing and heat-induction seal on the WVTR values for the glass, PET and HDPE bottles at 40 °C/75%RH.(1).

Bottle volume/ finish diameter(1)	Torque	Water Vapor Transmission Rate (WVTR) ($mg.day^{-1}.bottle^{-1}$, mean ± S.D., n = 10) (2)							
		Glass		PET			HDPE		
		PP cap	Successive opening/closing	PP cap	Successive opening/closing	Heat-induction seal	PP cap	Successive opening/closing	Heat-Induction Seal
30/18	T7	0.03 ± 0.003 (0.03–0.04)	*n.a.*	9.9 ± 0.4 (9.5–10.9)	*n.a.*	9.9 ± 0.3 (9.3–10.2)	*n.a.*	*n.a.*	*n.a.*
	T10	0.03 ± 0.004 (0.03–0.04)		9.4 ± 0.4 (8.9–10.0)					
30/24	T10	0.07 ± 0.008 (0.06–0.104)	0.2 ± 0.1 (0.1–0.5)	9.9 ± 0.2 (9.6–10.0)	9.8 ± 0.2 (9.3–10.0)	9.7 ± 0.2 (9.4–10.0)	0.8 ± 0.1 (0.7–1.0)	0.8 ± 0.1 (0.5–0.9)	0.8 ± 0.05 (0.7–0.8)
	T13	0.06 ± 0.005 (0.06–0.07)	*n.a.*	9.9 ± 0.2 (9.7–10.2)	*n.a.*		*n.a.*	*n.a.*	*n.a.*
60/24	T10	0.07 ± 0.006 (0.06–0.07)	*n.a.*	15.6 ± 0.3 (15.0–15.9)	*n.a.*	15,2 ± 0.3 (14.7–15.7)	1.2 ± 0.1 (1.2–1.3)	*n.a.*	*n.a.*
	T13	0.06 ± 0.005 (0.05–0.07)		15.4 ± 0.3 (14.6–15.8)					
120/28	T12	0.09 ± 0.005 (0.09–0.10)	*n.a.*	21.2 ± 0.2 (20.9–21.5)	*n.a.*	21.3 ± 0.2 (21.1– 21.6)	2.2 ± 0.2 (1.9–2.5)	*n.a.*	*n.a.*
	T15	0.09 ± 0.005 (0.08–0.10)		21.2 ± 0.2 (21.0–21.6)			*n.a.*		

PET = Polyethylene terephthalate/HDPE = High-density polyethylene/PP = Polypropylene/T = Torque/RH = Relative humidity.
n.a. = not available.
3– Average ± S.D. – Standard Deviation, n = results of 10 bottles, (minimum – maximum values).
1 Bottle volume in cm^3 and finish diameter in mm, for example, 30/18 = 30 cm^3/18 mm.
2 0% RH inside the package and 75% RH in the test chamber.

tamper-evidence ring integrated with the cap and can be used for glass or plastic bottles. GL DIN 168–18 mm cap diameter had an internal top plug (no liner or gasket) and just top seal to ensure integrity. GPP 24 mm and MCA2-P 28 mm caps containing a LDPE and ethylene-based vinyl acetate copolymer (EVA) liner, respectively, and therefore both caps had top and side seal.

2.2. Methods

2.2.1. Application torque and closure integrity test

In general, the influence of two intensities of application torque in the closure system integrity were previously evaluated for the analyzed samples.

It was applied the minimum and maximum values of application torque of 7 and 10 lbf.in, respectively, for 18 mm caps diameter in glass and PET bottles, according to suggested by the references [14–16].

For 24 and 28 mm cap diameters, it was also possible to apply the minimum torque values of 10 and 12 lbf.in, respectively, in glass and PET bottles. However, it was not possible to apply the maximum torque (18 and 21 lbf.in for 24 and 28 mm cap diameters, respectively) for neither of these cap diameters, according to previous study assessed by Bócoli and Jaime [17]. In this case, an alternative was the application of an intermediate torque of 13 and 15 lbf.in for 24 and 28 mm diameters, respectively. For HDPE bottles, it was only possible to evaluate the integrity with cap applied with the minimum torque values of 10 and 12 lbf.in, for 24 and 28 mm cap diameters, respectively.

A digital torque tester (Vortex MK, Mecmesin) with load capacity until 10 Nm (88 lbf.in and 0.01 lbf.in readability) was used to apply the cap into the analyzed bottles. A constant rotation at 5 rpm (revolutions per minute) for the torque application was set up [22].

The closure system integrity was assessed by helium leak testing with a mass spectrometer detector probe based in the ASTM F2391-05 [23], using an equipment produced by BOC *Edwards* (Crawley, UK), model *Spectron* 5000, with a detection limit of $1x10^{-10}$ $mbar.L.s^{-1}$. The unit mbar.L describes the amount of gas independently of the pressure. Then, 1 $mbar.L.s^{-1}$ corresponds to a flow of 1 mL per second at 1 bar, which is equivalent to 0.1 $Pa.m^3.s^{-1}$ [18].

Containers with the applied closure system were pierced in the bottom and after that, the hole was sealed with a silicon septum, which was checked for sufficient tightness. Each sample was filled manually with industrial helium gas up to partial internal pressure (≤2 bar) in a hood to avoid air contamination.

The same 10 units for each packaging material (glass, PET or HDPE) were evaluated in order to eliminate the influence of any dimensional finish variation on the integrity results.

2.2.2. Water Vapor Transmission Rate (WVTR)

The moisture ingression was measured via determination of the Water Vapor Transmission Rate (WVTR), using a dry calcium chloride with particle size from 4 to 8 mesh (4.76–2.38 mm) as hygroscopic material. Before applying the closure system, the containers were filled with the desiccant to a level of not less than two thirds of the bottle volume (0% RH internally) [14,24]. An analytical balance with 0.01 mg readability (model AT 201, Mettler) was used to determine the weight gain of the containers.

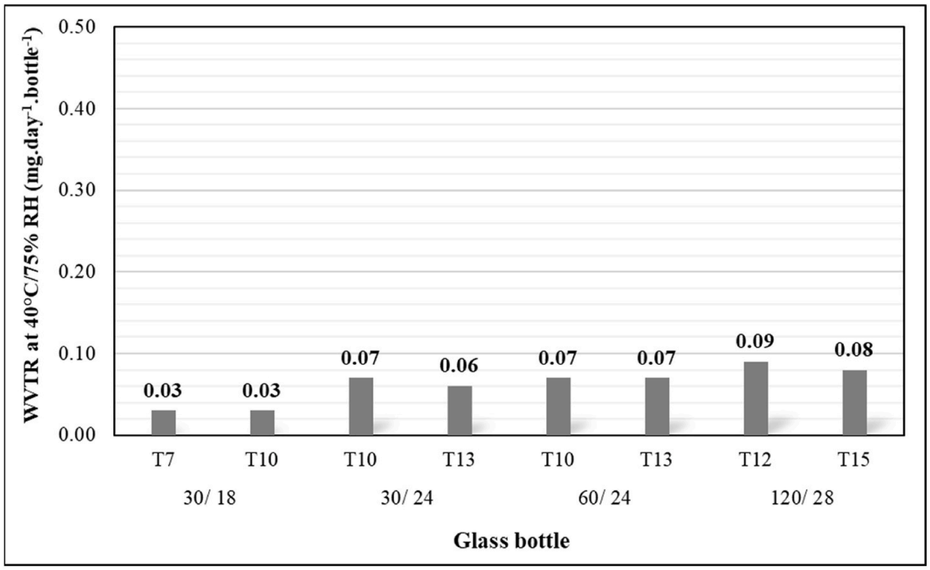
Bottles were evaluated under two storage conditions for moisture ingression (weight gain): at 40 ± 2 °C/75 ± 5% RH (gradient 75% RH), as established by national and international resolutions [14,19,24] and at 23 ± 2 °C/75 ± 5% RH (gradient 25%RH), as established by USP [14]. All bottles were stored in a test chamber (Model Pharma 1300, Weiss).

The WVTR of glass, PET and HDPE bottles were determined with their closures and evaluated with two applied torque values for each cap diameter, except for HDPE bottles.

The 30cm^3/24 mm glass, PET and HDPE bottles were also evaluated considering the methodology for assigning the classification for multiple-unit containers established by USP with successive opening/closing in 30 times within the range of minimum closing torque at 40 ± 2 °C/75 ± 5%RH (gradient 75% RH) [14]. To eliminate the influence of the cap material or moisture ingress through the bottle cap, the WVTR for 30cm^3/24 mm PET and HDPE bottles, were analyzed after heat-induction seal using an aluminum foil (45 μm) on the finish/sealing surface.

Glass and PET bottles were also analyzed at the storage condition of 23 ± 2 °C/75 ± 3%RH (gradient of 25% RH) for assigning the classification for multiple-unit containers (in $mg.day^{-1}.L^{-1}$) as "tight" or "well closed" packaging system, according to established by USP [14].

Moisture loss was determined by the bi-distilled water weight loss



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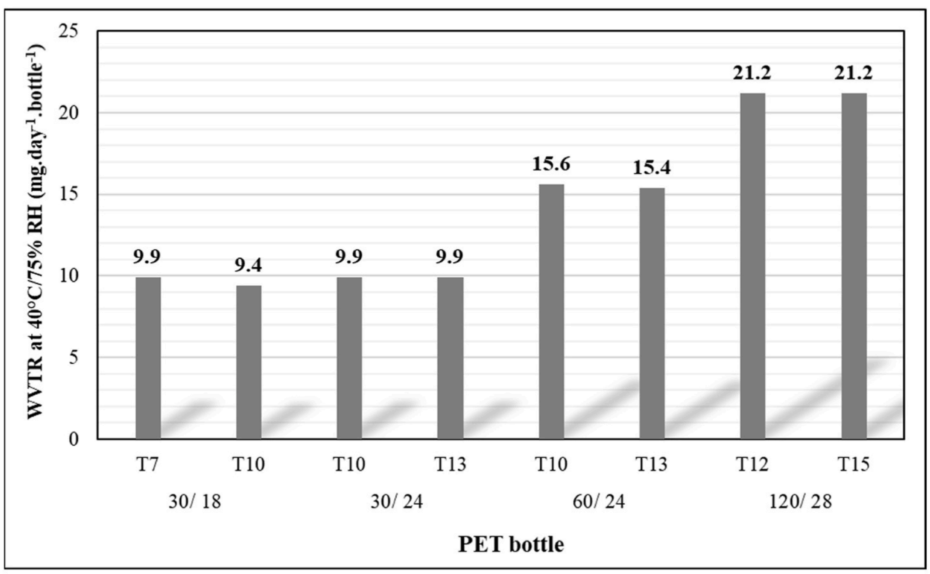

b)

Fig. 2. Results obtained for the WVTR of the glass (a) and PET (b) bottles at 40 °C/75%RH.

filled in the bottles up to the nominal capacity (100% RH internally). The individual weight for the 30 and 60 cm^3 containers were recorded using a analytical balance with resolution of 0.01 mg (model AT201, Mettler). A balance with resolution of 0.1 mg (model AT400, Mettler) was used for the 120 cm^3 bottle.

Loss of moisture (weight loss) was evaluated at 40 ± 2 °C/75 ± 5% RH, according to the Resolution RDC nº 318 [19] and the sample of $30cm^3$/18 mm PET bottle was also analyzed at 25 ± 2 °C/40 ± 2%RH as established by USP [14]. The test method was performed at 75% RH and the final result was multiplied by the factor 3.0 to express the weight loss at 40 °C/25% RH as established by Resolution RDC nº 318 [19].

Resolution RDC nº 318 also establishes if the percentage of weight loss exceeds 5.0% in relation to the initial weight in 3 months at 40 °C/25%RH, the package must be considered as having presented changes in the stability studies [19]. In this way, according to the weight loss results, it is possible to estimate the weight loss in 3 months of storage at 40 °C/25%RH.

2.2.3. Oxygen transmission rate (O_2TR)

The oxygen transmission rate (O_2TR) was determined by coulometric method, using the OX-TRAN, model 2/60, Oxygen Permeability Tester Mocon (Minneapolis, USA) at a temperature of 23 °C, according to the standard ASTM F 1307–14 [25].

The entire packaging system including body and cap was considered as the effective area for oxygen permeation and the results were expressed as mL.package^{-1}.day^{-1} for 0.21 atm of oxygen partial pressure.

To eliminate the influence of the cap material or oxygen ingress through the cap, the O_2TR properties for PET and HDPE bottles were also analyzed after heat-induction seal using an aluminum foil (45 μm) on the finish/sealing surface.

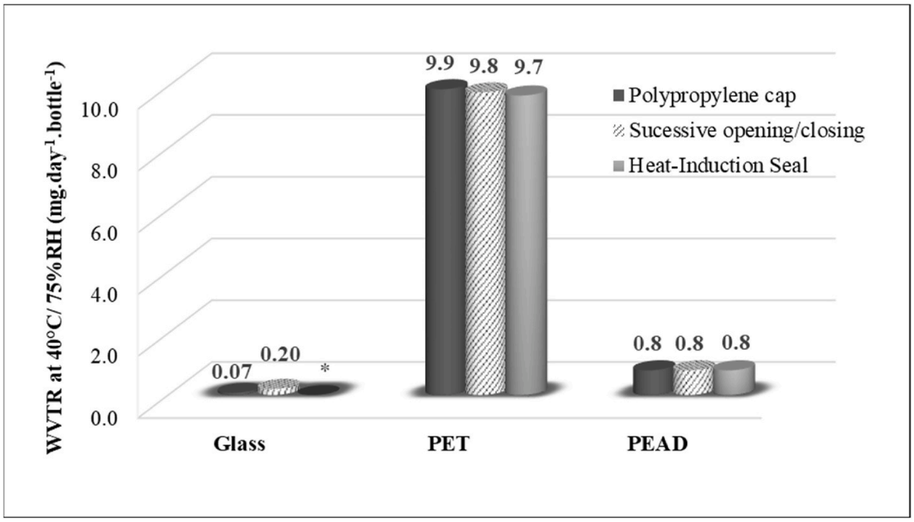

Fig. 3. WVTR results for 30cm^3/24 mm glass, PET and HDPE bottles with different closure conditions at 40 °C/75%RH (**not avaliable).*

Table 4
Water Vapor Transmission Rate (WVTR) of glass and PET bottles at 23 °C/75% RH[(2)].

Bottle volume/ finish diameter[(1)]	Torque	Values[(3)]	Water Vapor Transmission Rate (WVTR) (mg.day^{-1}.bottle^{-1})		Average rate of moisture vapor transmission (in mg.day^{-1}. L^{-1})	
			Glass	PET	Glass	PET
30/24	T10	Mean ± S.D. (Min. – Max.)	*n.a.*	3.3 ± 0.07 (3.2–3.4)	*n.a.*	82.1
60/24	T10	Mean ± S.D. (Min. – Max.)	≤0.01[(4)]	5.3 ± 0.1 (5.0–5.4)	≤0.14	74.4
120/28	T12	Mean ± S.D. (Min. – Max.)	*n.a.*	7.4 ± 0.07 (7.2–7.5)	*n.a.*	54.3

PET = Polyethylene terephthalate/T = Torque/RH = Relative humidity.
n.a. = Not available.
[1] Bottle volume in cm^3 and finish diameter in mm, for example, 30/24 = 30 cm^3/24 mm.
[2] 0% RH inside the package and 75% RH in the test chamber (gradient 75% RH), as established by USP.
[3] Average ± S.D. results of 10 determinations.
[4] Limit of quantification of the analytical method under the test condition

3. Results and discussion

3.1. Closure integrity as a function of the torque

As shown in Table 2, a slight variation in the torque values applied to the caps can be seen between the three packaging materials evaluated. The results indicated good homogeneity for the application torque onto the packages.

The values obtained for the helium flow rate varied from 1.9 x10^{-10} mbar.L.s^{-1} to 9.9 x 10^{-10} mbar.L.s^{-1}, corresponding to the smallest and the largest leakage values, respectively, independent of the torque applied and packaging material (glass, PET or HDPE), as shown in Table 2 and Fig. 1. All the results are in the same order of magnitude and indicate a very small variation in the helium flow rates as a function of the application torque regardless of the cap diameter and packaging material.

These results indicate a good integrity provided by the analyzed closure system independently of the range of applied torque, similar to the results obtained by Kossinna and Meyer [18] in one of their studies.

3.2. WVTR of the bottles – moisture gain permeability

The results obtained for the WVTR at 40 °C/75%RH for glass and PET bottles with the same volumetric capacity and cap diameter showed no statistically significant difference at the 95% confidence level with respect to the intensity of the applied torque, independent of the closure torque applied (Table 3 and Fig. 2).

This performance confirmed with the results of the closure integrity trial, which also found no evidence of changes as a function of the torque intensity applied (Fig. 2).

For the glass bottles, the WVTR increased from 0.03 to 0.09 mg. day^{-1}.bottle^{-1} with an increase in the cap diameter from 18 to 28 mm, independent of the bottle size (Fig. 2-a). This result shows that any gain in moisture content inside the glass bottle occurred mainly due to the closure system, considering that a greater cap diameter tends to favor a larger area exposed for moisture permeation through the PP cap material. Glass is non-porous, and thus this result confirmed that the moisture did not permeate through the body of the glass bottle. Thus, one can say that, so long as the closure system is intact and has no leakage holes, the moisture barrier of the glass bottles is inversely proportional to the cap size diameter.

For the 30 cm^3 PET bottles with 18 and 24 mm cap diameters (Table 3 and Fig. 2-b), a mean WVTR to the order of 9.8 mg.day^{-1}. bottle^{-1} was obtained, so it can be seen that the cap diameter and closure torque did not interfere significantly in the moisture barrier property. In this case, one can also observe that both PET bottles had similar wall thicknesses and surface areas exposed, which were to the same order of magnitude (Table 1). Thus for the 30 cm^3 PET bottle, the cap diameter and closure torque intensity did not significantly alter the moisture barrier of the bottle.

When the volume of the PET bottle was increased from 30 to 60 cm^3, the mean WVTR increased from 9.8 to 15.5 mg.day^{-1}.bottle^{-1}, independent of the cap diameter or closure torque. In sequence, with an increase in volume from 60 to 120 cm^3, the WVTR increased to 21.2 mg. day^{-1}.bottle^{-1}, and in all these evaluations, the performance was independent of the cap diameter and torque applied to the cap (Table 3 and Fig. 2-b). Thus for PET bottles of the same volume, one can say that the cap diameter and intensity of the closure torque did not significantly influence the change in moisture barrier of the bottle, since permeation occurs throughout the body of the bottle which is influenced by the

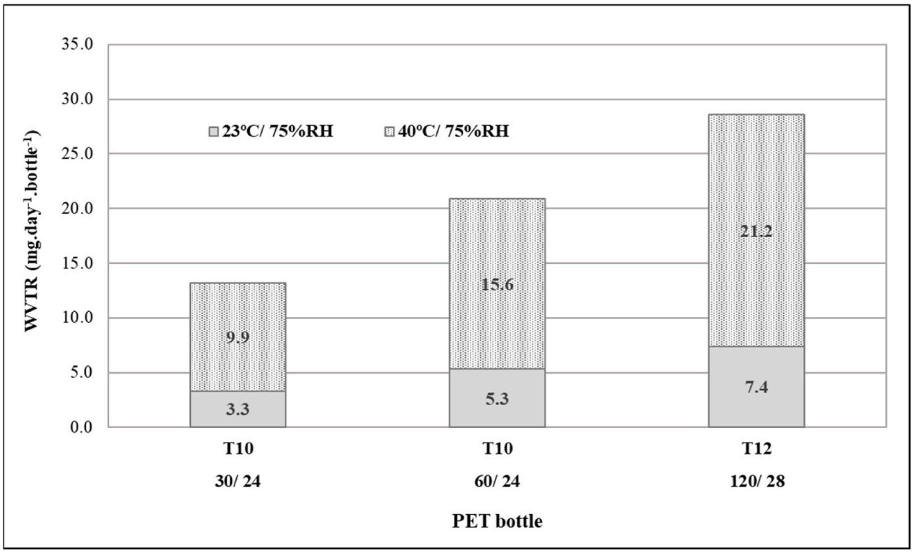

Fig. 4. Fig. 4. WVTR results for the PET bottles under two different storage conditions (23 °C/75% RH and 40 °C/75%RH).

Table 5
WVTR for moisture loss from glass, PET and HDPE bottles at 40 °C/25%RH[(2)] and 25 °C/40%RH.[(3)].

Bottle volume/ finish diameter[(1)]	Torque	Water Vapor Transmission Rate (WVTR) (mg.day^{-1}.bottle^{-1}, mean[(4)] ± S.D., n = 10)			
		40 °C/25%RH			25 °C/ 40%RH
		Glass	PET	HDPE	PET
30/18	T7	≤0.03[(5)]	10.8 ± 0.1 (10.2–11.7)	*n.a.*	3.6 ± 0.4 (3.4–4.3)
30/24	T10	0.09 ± 0.003 (0.09–0.12)	11.1 ± 0.04 (10.8–11.1)	0.81 ± 0.01 (0.78–0.84)	*n.a.*
60/24	T10	0.12 ± 0.007 (0.09–0.18)	17.4 ± 0.2 (16.5–17.7)	*n.a.*	*n.a.*
120/28	T12	0.15 ± 0.005 (0.15–0.18)	24.9 ± 0.09 (24.6–25.5)	*n.a.*	*n.a.*

PET = Polyethylene terephthalate/HDPE = High-density polyethylene/T = Torque/RH = Relative humidity.
n.a. = not available.
[1] Bottle volume in cm^3 and finish diameter in mm, for example, 30/18 = 30 cm^3/18 mm.
[2] Results obtained at 40 °C/75% RH and multiplied by a correction factor of 3.0 to express the weight loss at 40 °C/25% RH, that is, 100% RH inside the package and 75% RH in the test chamber (gradient 25%RH).
[3] According to USP storage condition.
[4] Average ± S.D. – Standard Deviation, n = results of 10 bottles (minimum – maximum values).
[5] Limit of quantification of the analytical method under the test condition.

Table 6
Weight loss after 90 days (3 months) at 40 °C/25%RH.

Bottle volume/finish diameter[(1)]	Percentage of weight loss after 90 days (%)		
	Glass	PET	HDPE
30/18	≤0.09	3.2	*n.a.*
30/24	0.03	3.3	0.2
60/24	0.02	2.6	*n.a.*
120/28	0.01	1.9	*n.a.*

PET = Polyethylene terephthalate/HDPE = High-density polyethylene.
n.a. = not available.
[1] Bottle volume in cm^3 and finish diameter in mm, for example, 30/18 = 30 cm^3/18 mm.

surface area and wall thickness. Large PET bottles are generally less thick than small ones and with a larger surface area have less moisture barrier properties.

Comparing the WVTR results obtained for the 30cm^3/24 mm PET and HDPE bottles, of 9.8 and 0.8 mg.day^{-1}.bottle^{-1}, respectively, one can say that since they have the same volume and similar surface areas, even with a slightly increase in thickness for HDPE bottle, the permeability obtained may be associated with the type of polymeric material. The structural characteristic of the HDPE polymer molecule, with a greater percentage of the crystalline phase, favored less permeability, and consequently a greater moisture barrier property as compared to PET. These results confirming reports in the literature that PET is not an efficient moisture barrier [3,11] and for products sensitive to moisture ingress, HDPE bottles should be preferable.

The moisture barrier results obtained for the HDPE bottles in the present study were similar to those reported by Badawy et al. [4] for bottles made of the same material with a volume of 30 cm^3, corresponding to 0.88 mg.day^{-1}.bottle^{-1}, and close to the value found by Chen and Li [8] for a 1 oz (~30 cm^3) HDPE bottle, corresponding to 0.92 mg.day^{-1}.bottle^{-1}, both determined at 40 °C/75%RH. Waterman and Macdonald [1] obtained WVTR values corresponding to 0.70 and 1.352 mg.day^{-1}.bottle^{-1} for HDPE bottles with volumes of 40 and 60 cm^3, respectively, also determined at 40 °C/75%RH.

According to the results obtained, it is possible to affirm that if the closure system has no defects, the cap diameter has no significant influence on the moisture permeability of PET and HDPE bottles. The WVTR of PET and HDPE bottles is proportional to the surface area exposed for permeation (that is influenced by wall thickness), which is directly proportional to its volume, since permeation occurs preferentially through the body of the bottle. This observation agrees with the comment of Chen and Li [5] that for plastic bottles with no gross defects, the moisture ingression mechanism into the bottle occurs mainly by diffusion of water molecules through the container wall.

It can also be seen that the WVTR results obtained for 30cm^3/24 mm PET and HDPE at 40 °C/75%RH with successive opening/closing operations, or when evaluated with an aluminum heat-inducted on the closure, did not indicate any statistically significant difference at a 95% confidence level, as compared to the same bottle with the PP cap, independent of the torque applied (Table 3 and Fig. 3).

This confirms that the closure system of PET and HDPE bottles does not significantly influence the WVTR results, since the barrier property

Table 7
O_2TR at 23 °C and 21 atm partial pressure gradient.

Bottle volume/finish diameter[1]	Oxygen Transmission Rate (O_2TR) (mL.day^{-1}.bottle^{-1}), mean ± S.D., n = 3) [2]				
	With PP cap			With heat-induction seal	
	Glass	PET	HDPE	PET	HDPE
30/24	≤0.005[3]	0.012 ± 0.00 (0.012–0.012)	0.084 ± 0.003 (0.081–0.088)	0.006 ± 0.0005 (0.006–0.007)	0.077 ± 0.007 (0.073–0.084)
60/24	*n.a.*	0.015 ± 0.001 (0.014–0.016)	0.137 ± 0.031 (0.115–0.160)	0.007 ± 0.005 (0.007–0.008)	*n.a.*
120/28	≤0.005[3]	0.020 ± 0.002 (0.018–0.021)	0.313 ± 0.058 (0.275–0.380)	0.013 ± 0.001 (0.012–0.014)	*n.a.*

PET = Polyethylene terephthalate/HDPE = High-density polyethylene/PP = Polypropylene.
n.a. = not available.
[1] Bottle volume in cm^3 and finish diameter in mm, for example, 30/24 = 30 cm^3/24 mm.
[2] Average ± S.D. – Standard Deviation, n = results of 3 bottles (minimum – maximum values).
[3] Limit of quantification of the analytical method under the test condition.

is strongly associated with the bottle size or volume, and, consequently, the surface area exposed for permeation and its thickness.

Glass bottles demonstrated that successive opening/closing affected its integrity due to a slight increase in the WVTR of the 30cm^3/24 mm bottle from 0.07 to 0.2 mg.day^{-1}.bottle^{-1} (Table 3 and Fig. 3).

When storage was carried out at 23 °C/75%RH (Table 4), there was a decrease in the WVTR results when compared to storage at 40 °C/75% RH (Table 3) for all the bottles analyzed, independent of the material and closure diameter. Fig. 4 shows the performance of the PET bottles, evaluated under both storage conditions.

A higher storage temperature (40 °C as against 23 °C) with the same relative humidity (75%RH) produced an increase in the results for WVTR for the same recipient, due to the increase in water vapor diffusion velocity through the plastic materials. At this condition, increase in temperature can also augment the micro-brownian motion of polymeric segmental units, which can result in an increase in free volume and affect the permeation rate of the material [12]. The same performance was shown by Chen and Li [5] and confirms other results reported in the literature, that the storage conditions of 40 °C/75%RH being the most adequate conditions to determine the WVTR of high barrier recipients destined to hold moisture sensitive products.

The average rate of moisture vapor transmission (mg.day^{-1}.L^{-1}) determined at 23 °C/75%RH, as established by USP methodology [14] (Table 4) showed that the glass and PET bottles could be classified as "tight" since none of the units evaluated exceeded the specification of 100 mg.day^{-1}.L^{-1} for moisture permeability.

It is possible to observe that the small bottle had a higher transmission of water vapor when associated with its volume (mg.day^{-1}.L^{-1}) (Table 4) and, therefore, the protection of pharmaceutical products against moisture ingress is more critical for small bottles size (small quantity of the product).

3.3. *WVTR of the bottle – moisture loss permeability*

The results for weight loss (Table 5) confirmed the elevated moisture barrier property of glass bottles, with WVTR values below 1 mg.day^{-1}.bottle^{-1}, but with a slight increase as a function of a larger cap diameter.

Under storage conditions of 40 °C/25%RH, the WVTR results were also of the same magnitude for 30 mL PET bottles, independent of the cap diameter (18 or 24 mm) (Table 5), again providing evidence that, if hermetic, the closure system does not exert a significant influence on the moisture permeability of the bottle.

For weight loss also, a better moisture barrier property was observed for the HDPE bottles as compared to PET (Table 5).

When the results for the 30cm^3/18 mm PET bottles were evaluated under both storage conditions of 40 °C/25%RH and 25 °C/40%RH (Table 5), the mean result for WVTR was higher at 40 °C/25%RH. This scenario indicates that storage at higher temperatures significantly affects the results for WVTR as compared to storage at lower temperatures, but with a higher relative humidity.

Thus considering the same bottle volume, glass represents the greatest moisture barrier, followed by HDPE and, in sequence, by PET.

Based on the results obtained for WVTR and the nominal volume of each bottle analyzed, one can estimate the loss of weight after 90 days (3 months) of storage at 40 °C/25%RH, as shown in Table 6.

Since all the bottles analyzed indicated a loss of water content less than 5% in relation to the initial weight, one can say that all the glass and PET bottles conformed to the requirements of Resolution RDC nº 318 [19] for the weight loss parameter, independent of the volume or cap diameter.

3.4. *Oxygen permeability – gas barrier properties*

The glass bottles were excellent oxygen barriers, showing an O_2TR value below the detection limit of the analytical technique employed (Table 7).

For the PET bottles, it can be seen that the greater the surface area (or volume) of the bottle, the greater the oxygen permeation (Table 7). Comparing the results for the same PET bottles, an increase in the O_2TR of about 1.5 to 2.0 times were observed with the use of the PP cap, as compared to the condition of an aluminum heat-induction sealed, independent of the volume. For the HDPE bottles, an increase in the O_2TR with the use of the PP cap was also observed, although smaller. This increase is due to oxygen permeation through the PP cap, even with hermetic closure. PP is more permeable to O_2 than PET, so even with a smaller surface area (caps with a smaller diameter) and thicker caps (as compared to the thickness of the PET bottle wall) it is not an efficient oxygen barrier as compared to an aluminum heat-induction seal. On the other hand, PP and HDPE show oxygen permeability to the same order of magnitude [3].

The 30cm^3/24 mm PET bottle showed a mean O_2TR value about 7 times lower than the equivalent HDPE bottle, and this characteristic should be considered when choosing bottles for oxygen-sensitive products.

Thus considering the same packaging volume, glass bottle represents the greatest oxygen barrier, followed by PET and, in sequence, by HDPE.

4. Conclusion

Based on the study, a small variation in the torque intensity for application PP caps in glass or PET bottles, did not alter significant the closure system integrity and the moisture barrier property of the packages.

Provided integrity of the closure system, the moisture barrier property of the glass bottle is independent of its volume, but increases with increase of the cap diameter. Glass is a non-porous material and, therefore, larger cap diameters allow an increase of the exposed area for moisture permeation by the PP cap. However, the cap diameter did not show significant influence onto the oxygen barrier property of the analyzed glass bottles.

PET and HDPE showed moisture barrier properties depending on their volumes, since the permeation occurred preferentially through the bottles wall, which is influenced by the polymeric molecular structure and its thickness. Regardless of the cap diameter with good closure integrity, large PET and HDPE bottles have a higher permeation surface area than a small one, resulting in low protection for a moisture sensitive compound that can result in significant degradation of the drug product. The same dependence on the bottle size and surface area was observed for the oxygen barrier property, being the results slightly influenced by the closure system provided by the PP cap oxygen permeation.

Independent of their volumes, all analyzed glass and PET bottles met the requirements set out in Brazilian Resolution RDC nº 318 for weight loss.

Author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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