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CHEMICAL CONTAMINATION IN PACKAGING MATERIAL OF PHARMACEUTICAL USE

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Abstract: *The use of packaging materials is important in the pharmaceutical industry. The pharmaceutical industry uses, as primary packaging materials, glass bottles, blister packs, caps and closures, glass vials, sealed tubes. The aim of this study is to perform global component migration analyses on these types of packaging, to see if there is a possibility of migration of components from the pharmaceutical package into the drug, so as not to alter in any way its therapeutic properties. The results obtained from the processing of the extracts obtained were below the maximum limits allowed for each category of packaging, respectively, plastic, paper and cardboard, glass.*

Key words: *plastic material, packaging materials, chemical migration.*

1. Introduction

The use of packaging is one of the most important part in the pharmaceutical industry. Packaging material's role is to protect the product, to inform the consumer about the product, to provide enough data about the production and expiry date, to be resistant during carriage, storage and against climatic conditions. Packaging materials contain chemical substances which should not migrate in the products [1]. There are three types of packaging for a pharmaceutical product, which are classified as primary, secondary and tertiary. These packaging are made from a wide range of materials available which are cost effective for the producers and consumers [2]. Primary packaging is the one which is in touch with the product. This package should be inert, should not interact with the product and should not cause alteration in the chemical composition of the dosage (ex. blister packs, glass bottles and vials, caps, closures etc.). Some chemicals are not allowed to be used in packaging materials [3]. Secondary packaging is the one that covers the first package (ex. cardboard boxes). Tertiary package is used to provide an easy handling and shipping of the products (ex. containers, edge protector etc.).

Small amounts of chemical compounds of a pack can migrate during the process of manufacturing, distribution and storage before the product is consumed [4-6].

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In general, different packaging materials can be used in pharmaceutical industry like glass bottles, glass vials, blister packs, caps and closures, sealed tubes and cardboard packaging. The most packaging materials is recycled [3].

Glass bottles are transparent, durable, resistant through decades and inert. There are three types of glass:

- Type I: ultra-resistant borosilicate glass which is a highly resistant and chemically inert glass. Alkali's and earth cations of glass are replaced by Boron and/or Aluminum and Zinc. These are used to contain strong acids and alkalis.
- Type II: surface treated soda lime glass is more chemically inert than Type I glass. The glass surface is de-alkalized by "Sulfur treatment" which prevents blooming/ weathering from bottles.
- Type III: soda lime glass has average chemical resistance.

Glass vials are used to hold liquids, solids or powders. They have a larger capacity than ampoules. The closure options of glass vials are a screw cap or a rubber stopper and a metal cap [4].

Blister packs are often used for solid unit doses. These packs are made from pre-formed plastic, foil or paper. The blister pack contain a cavity which is made from a thermoformed plastic and a lid. This lid is sealed to the base layer by heat and pressure.

Caps and closures are used to close or seal a container. Closures are made of flexible material such as cork, rubber, or plastic foam. Screw top bottle caps are used for glass or plastic bottles.

Sealed tubes are made from metal, plastic or lamination of foil, plastic and paper. The only way to access the product is to destroy the seal. Metal tubes are used for the products which need a high degree of barrier protection. Most tubes are made of aluminum. Extruded plastic tubes are used for products that are compactable and limited protection of plastic.

Cardboard packaging is made of recycling paper sandwiched between two liners. Typically, cardboard boxes have a test paper inner liner, and a Kraft paper outer because of its property of being resistant at water penetration.

The gravimetry analysis is the newest techniques used for determination of migration of components from the pharmaceutical package into the drug composition [13]. This technique is also quick and it is used in a lot of studies [14-18].

The aim of this study is to present the possibility of migration of components from the pharmaceutical package into the drug composition and the safe limit of migration for plastic, paper, cardboard and glass packages.

2. Materials and Methods

2.1. Sample Collection

In this study were tested 34 samples of primary or secondary packaging, from different types of materials (plastic, glass, paper, cardboard), used in the pharmaceutical industry. These packages were purchased from different manufacturers of packaging materials in Romania and kept in laboratory conditions until the time of analysis. The tested materials were Transparent PET bottle, PET bottle with cap/drop, Brown PET bottle, White HDPE

bottle, White HDPE container, White PET bottle, with cap and sealing ring, White HDPE sealed bottle, PE white tube, EVOH white tube, PP nasal atomizer spray pump, White PP aerosol spray, White HDPE cap, White PP cap, White PP box, Yellow PP box, Orange PP box, Green PP box, Red PP box, Blue PP box, White HDPE drop cap, White PP drop counter, Clear PS blister, Paper/PE blister, Paper/aluminium/PE blister, Aluminium tube with cap, Sealed Aluminium tube, Aluminium/paper/PE strip, PET/Aluminium/PE sachet, Paper / Aluminium / PE tea bag, Cardboard box (secondary packaging), Natural paper pharmaceutical bag, Clear glass vial and Brown glass bottle.

2.2. Reagents

Acetic acid (CH_3-COOH) and ethyl alcohol (C_2H_5OH) were purchased from Merck. All solutions obtained from these reagents were made with ultrapure water (18.2 MΩ.cm). All glassware was cleaned and decontaminated with 10 HNO_3 solution.

2.3. Sample preparation

To determine whether the package can chemically contaminate the packaged product, a gravimetric method was used that measures all the compounds that can migrate from the package to the product.

For plastic materials, testing was performed according to EU regulation no. 10/2011, namely OM2 conditions, 10 days at 40 degrees Celsius. As food simulants, simulant A (10% ethyl alcohol solution), simulant D1 (50% ethyl alcohol solution) and simulant B (3% acetic acid solution) were used. After the end of the extraction period, the extraction liquid is analysed to determine whether it complies with the provisions of the legislation in force.

The overall migration, expressed as milligrams of residue per square decimetre of the surface of the sample, was calculated for each test specimen using the following formula [12]:

$$M = \frac{(m_a - m_b) x\ 1000}{S}, \quad (1)$$

where:

M - global migration in simulant, in milligrams of residue per square decimetre of the surface of the sample;

m_a - mass of sample's residue, after evaporation of the simulant in which it was immersed, expressed in grams;

m_b - the mass of the residue which comes only from the simulant, expressed in grams;

S - the surface of the sample intended to come into contact with the product, in square decimetres.

For paper and board packaging a cold aqueous extract was prepared, according to SR EN 645:1996 standard, in order to analyse the total amount of substances that can migrate from the material to the simulant (distilled water).

For the glass packaging, a determination of the migration of lead and cadmium in a 4% acetic acid solution was performed, according to ISO 7086-1:2019.

3. Results and Discussions

According to the basic principle of Regulation (EC) no. 1935/2004 [11], any material or article intended to come into contact directly or indirectly with food must be sufficiently inert to preclude substances from being transferred to food in quantities large enough to endanger human health or to bring about an unacceptable change in the composition of the food or a deterioration in its organoleptic properties. Considering this issue, overall and specific migration tests were performed depending on the type of material. The results of overall migration tests for plastic materials are presented in Table 1.

Overall migration results for plastic materials Table 1

Code	Type	Description	Overall migration in food simulants (mg/dm^2)		
			A	B	D_1
P1	Bottle	Transparent PET bottle	1.08	1.17	-
P2	Bottle	PET bottle with cap/drop	1.08	1.25	1.33
P3	Bottle	Brown PET bottle	1.04	1.21	-
P4	Bottle	White HDPE bottle	1.17	2.0	-
P5	Bottle	White HDPE container	1.75	2.0	-
P6	Bottle	White PET bottle, with cap and sealing ring	1.0	1.08	1.25
P7	Bottle	White HDPE sealed bottle	0.92	1.08	-
P8	Tube	PE white tube	1.0	1.33	-
P9	Tube	EVOH white tube	1.17	1.58	
P10	Atomizer	PP nasal atomizer spray pump	1.13	8.42	-
P11	Spray	White PP aerosol spray	1.08	1.5	-
P12	Cap	White HDPE cap	1.13	1.88	2.38
P13	Cap	White PP cap	1.75	2.0	-
P14	Box	White PP box	1.04	1.46	-
P15	Box	Yellow PP box	1.0	1.42	-
P16	Box	Orange PP box	1.08	1.25	-
P17	Box	Green PP box	0.92	1.0	-
P18	Box	Red PP box	1.0	1.25	-
P19	Box	Blue PP box	1.08	1.5	-
P20	Drop cap	White HDPE drop cap	1.25	2.0	-
P21	Drop counter	White PP drop counter	1.08	2.25	-
P22	Blister	Clear PS blister	1.33	1.0	-
P23	Blister	Paper/PE blister	1.0	1.21	-
P24	Blister	Paper/aluminum/PE blister	1.0	1.25	-
P25	Tube	Aluminum tube with cap	1.04	1.21	-
P26	Tube	Sealed Aluminum tube	1.38	1.63	-
P27	Strip	Aluminum/paper/PE strip	1.0	1.33	-
P28	Sachet	PET/Aluminum/PE sachet	1.13	1.42	-
P29	Bag	Paper / Aluminum / PE tea bag	1.08	1.17	-

The maximum allowed limit for each simulant, provided in the (EU) Regulation 10/2011 is 10 mg / dm^2 [7]. As can be seen from the Table 1 and Figure 1, all values are below this limit, and can be used safely for pharmaceuticals, because they do not produce any chemical contamination and do not alter their properties.

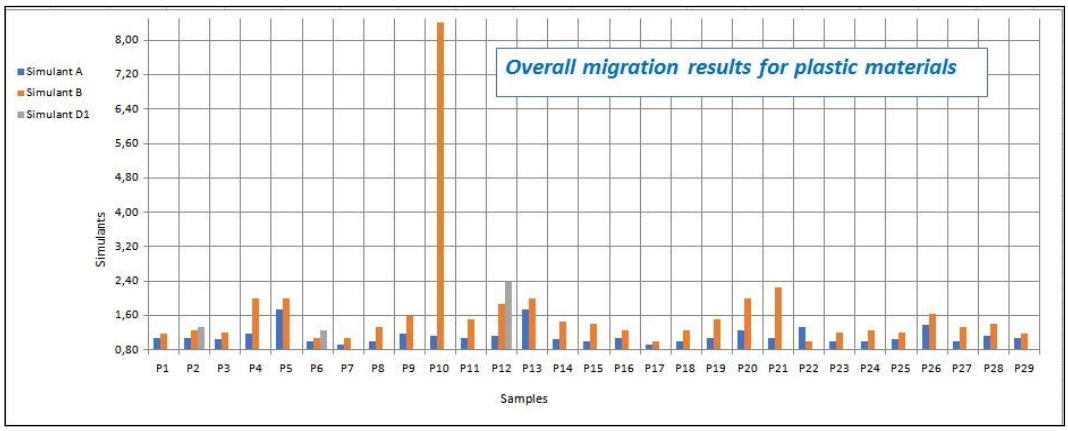

Fig. 1. *Overall migration results for plastic materials*

The results obtained for overall migration tests for paper and board materials are presented in Table 2 and Figure 2. All the results are below the limit of 10 mg/dm^2 stated by GD no. 1197/2002 with subsequent changes [8].

Overall migration results for paper and cardboard materials Table 2

Code	Type	Description	Overall migration in distilled water (mg/dm^2)
P30	Box	Cardboard box (secondary packaging)	4.38
P31	Box	Cardboard box (secondary packaging)	8.80
P32	Bag	Natural paper pharmaceutical bag	2.21

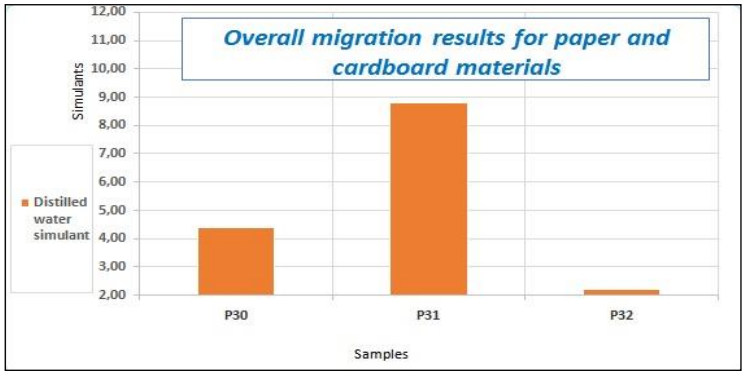

Fig. 2. *Overall migration results for paper and cardboard materials*

For glass materials were performed tests for heavy metals (Pb and Cd) specific migration. The results are presented in Table 3 and Figure 3, and are below the limit of detection of the equipment. According to ISO 7086-2:2019, the maximum allowed limits are: 5.0 mg/L for Pb and 0.5 mg/L for Cd [9], [10].

Overall migration results for glass materials Table 3

Code	Type	Description	Heavy metals migration (µg/L)	
			Pb	Cd
P33	Vial	Clear glass vial	< LOD	< LOD
P34	Bottle	Brown glass bottle	< LOD	< LOD

Note: LOD = Limit of detection (for Pb is 2.0 µg/L and for Cd is 0.2 µg/L)

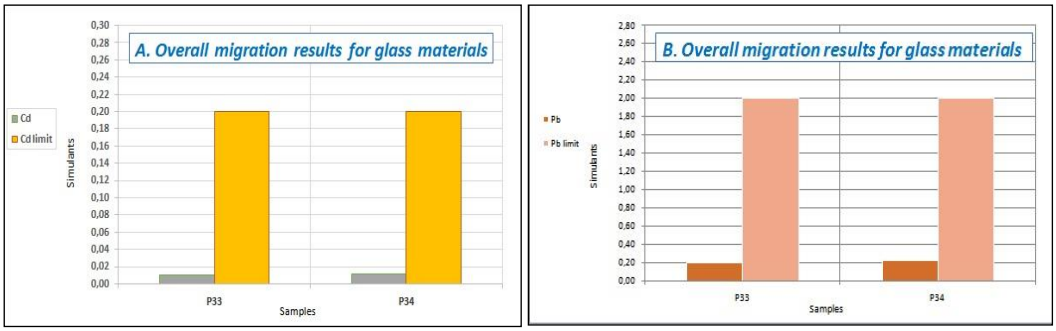

Fig. 3. *Overall migration results for glass materials (A - Cd, B - Pb)*

4. Conclusions

In this study, a gravimetric method was used that can determine all the compounds that can migrate from a packaging material into a packaged product. For both plastic and paper/cardboard packaging, the results were below the limits imposed by (EU) Regulation no. 10/2011, with subsequent changes, respectively GD no. 1197/2002 with subsequent changes. The results of the specific migration analyses of metals (Pb and Cd), performed by a GF-AAS spectrophotometric analysis, were below the limits imposed by the ISO 7086-2: 2019 standard.

From the point of view of the performed analyses and of the obtained results, the tested packaging materials can be used in contact with the pharmaceutical products.

All supplement manufacturers should ensure the quality of the packages because the safety of these packages is very important. It is also very important that the package should be inert and should not interact with the product. Package safety is very important in order not to transfer substances that chemically contaminate the pharmaceutical products so that they do not have the expected effect.

In order to determine exactly whether they are chemically inert, additional tests are needed to prove this.

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