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***ARTICLE***

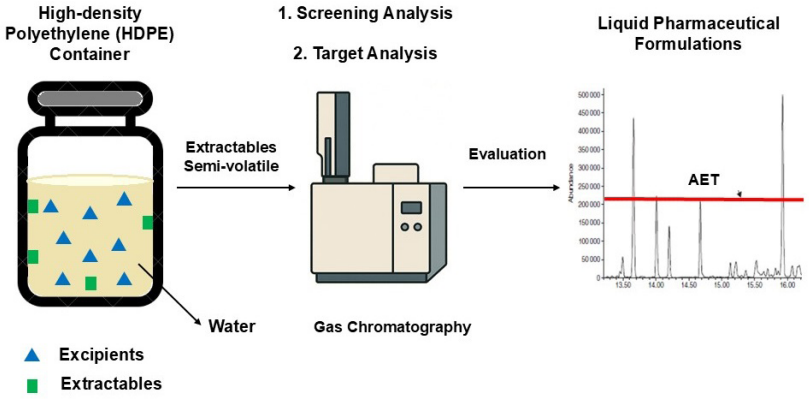
# Study of Extractables in High-Density Polyethylene Packaging: Evaluation of the Impact of Excipients Propylene Glycol, Mint Flavor, and Benzalkonium Chloride on the Leaching Process of Semi-volatile Additives

**Vanessa Mucedola Gonçalves da Cunha[1], Leonardo Duarte de Medeiros[1], Fernando Pugliesi[1], Bruna de Oliveira[2], Alessandra Sussulini[3]***

[1]*Cosmed e Brainfarma Indústria de Cosméticos e Medicamentos S/A, Av. Fernando Cerqueira César Coimbra, 1000, 06465-090, Barueri, SP, Brazil*

[2]*Universidade Evangélica de Goiás, Av. Universitária, km 3.5, Cidade Universitária, 75083-515, Anápolis, GO, Brazil*

[3]*Instituto de Química, Universidade Estadual de Campinas (UNICAMP), Rua Monteiro Lobato, 270, 13083-862, Campinas, SP, Brazil*




The study of extractables and leachables has become increasingly important in the pharmaceutical industry, with growing concerns about minimizing impurity risks in final products. Polymeric materials are widely used in pharmaceutical packaging due to their many advantages, but they can also introduce impurities. These materials often contain low molecular mass additives that may migrate into the product during storage and shelf life. This issue is particularly critical in liquid pharmaceutical formulations, which are more prone to interactions with packaging materials. In this context, the present work evaluates the extractive potential of selected excipients - benzalkonium chloride, propylene glycol, and mint flavor - in aqueous formulations stored in high-density polyethylene (HDPE) containers. The main goal is to compare the physicochemical properties of these excipients in the formulation with the additives extracted from the packaging. In summary, benzalkonium chloride (the excipient with the highest log P value) demonstrated the greatest extraction power, through the extraction of 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione, palmitic acid, and stearic acid. The mint aroma and propylene glycol contributed only to the extraction of 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione (the additive

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with the lowest log P value). Therefore, the novelty of this study lies in its empirical approach to correlating the physicochemical parameters of excipients with leachables, providing a predictive framework for leaching behavior in the pharmaceutical industry.

**Keywords:** extractables, leachables, excipients, polymer, liquid pharmaceutical forms, partition coefficient, mass spectrometry

## INTRODUCTION

Leachable compounds can be defined as “organic and inorganic chemical entities that migrate from the packaging/delivery system, packaging component, or packaging material of construction into the drug under normal storage and use conditions or during accelerated stability studies of the drug”.[1] Extractable compounds, on the other hand, can be defined as “organic and inorganic chemical entities released from a packaging system and/or packaging component through extraction under laboratory conditions”.[2] These compounds can be found in various products, including pharmaceuticals,[3-7] cosmetics,[8] and food,[9] and may pose health risks due to their continuous ingestion. For example, additives such as Irganox® 1010 have been detected in ophthalmic drug products stored in plastic packaging.[5] This process occurs due to the interaction between the plastic and the formulation, which can cause the migration of low molecular mass additives to the product. This phenomenon is dependent on the pharmaceutical form, being more relevant in liquid/aerosol formulations and lower in solid formulations.[1,10]

Pharmaceutical products are formulated with excipients to provide a specific and definitive therapeutic benefit to the user. The function of these compounds is to protect and enhance the stability of the formulation (since some active pharmaceutical ingredients - API - do not maintain stability when isolated, either denaturing or adhering to the walls of the container), increase the volume of the formulation, aid in solving formulation problems such as dissolution and improve the consumer acceptance. Furthermore, they aid in the bioavailability of the API, as in many cases, these compounds are not easily absorbed by the human body. Thus, the mixture with an excipient can act as a solvent in this process.[11] In this context, the choice of excipients during formulation development can be crucial to the product success, potentially impacting the leaching of packaging components. The same properties of excipients that facilitate an increase in the solubility of the active ingredient may also facilitate the leaching of compounds in contact with various polymeric materials.[12]

Plastics are widely used in packaging and the production process within the pharmaceutical industry due to their excellent cost-effectiveness compared to other available materials, as well as their unique characteristics. The versatility of plastic can be attributed to the different types of monomers and additives added during the process to enhance the polymer performance and durability. Additives can be categorized into various classes, such as: plasticizers, flame retardants, antioxidants, acid removers, light and heat stabilizers, lubricants, pigments, antistatic agents, slip compounds, and thermal stabilizers.[10,13]

In this article, the focus was on evaluating the extraction potential of different excipients present in liquid formulations stored in high-density polyethylene bottles in order to infer which excipients and concentrations might be critical for the product. This information can support the choice of excipients during formulation development and, subsequently, the risk analysis of extractables and leachables in the product. For this purpose, analytical methods were developed to evaluate the semi-volatile additives from the plastic bottle using gas chromatography coupled to mass spectrometry (GC-MS). In order to obtain realistic results, an accelerated study was conducted to simulate the interaction between the drug and the packaging material under storage conditions. The results were used to correlate the physicochemical characteristics of the excipients with the concentration of additives extracted from the packaging material.

## MATERIALS AND METHODS

### *Extractables study*

Potassium chloride, monosodium phosphate, disodium phosphate, sodium hydroxide, dichloromethane and sodium chloride were purchased from Merck (New Jersey, USA), isopropanol and acetonitrile were

purchased from J.T. Baker (Pennsylvania, USA), and hexane and hydrochloric acid were purchased from Biograde (North Carolina, USA). The high-density polyethylene packaging material purchased from Plastic Industrial Bacic (São Paulo, Brazil).

A pH 2.0 solution (0.01 mol $L^{-1}$ KCl and 0.003 mol $L^{-1}$ HCl), a pH 10.0 buffer solution (0.0045 mol $L^{-1}$ $NaH_2PO_4$ and 0.066 mol $L^{-1}$ $Na_2HPO_4$), and a water:isopropanol (1:1) solution were prepared. Isopropanol and hexane were used in their pure form. Both were used as extraction media. The packaging material was cut into pieces and submerged in the aqueous extraction media in an oven (at 70 °C for 7 days) and ultrasound treatment (at 10 °C for 2 h), and the organic extraction media were subjected to Soxhlet extraction for 24 h. The sample extracts were prepared as detailed in Figure 1.

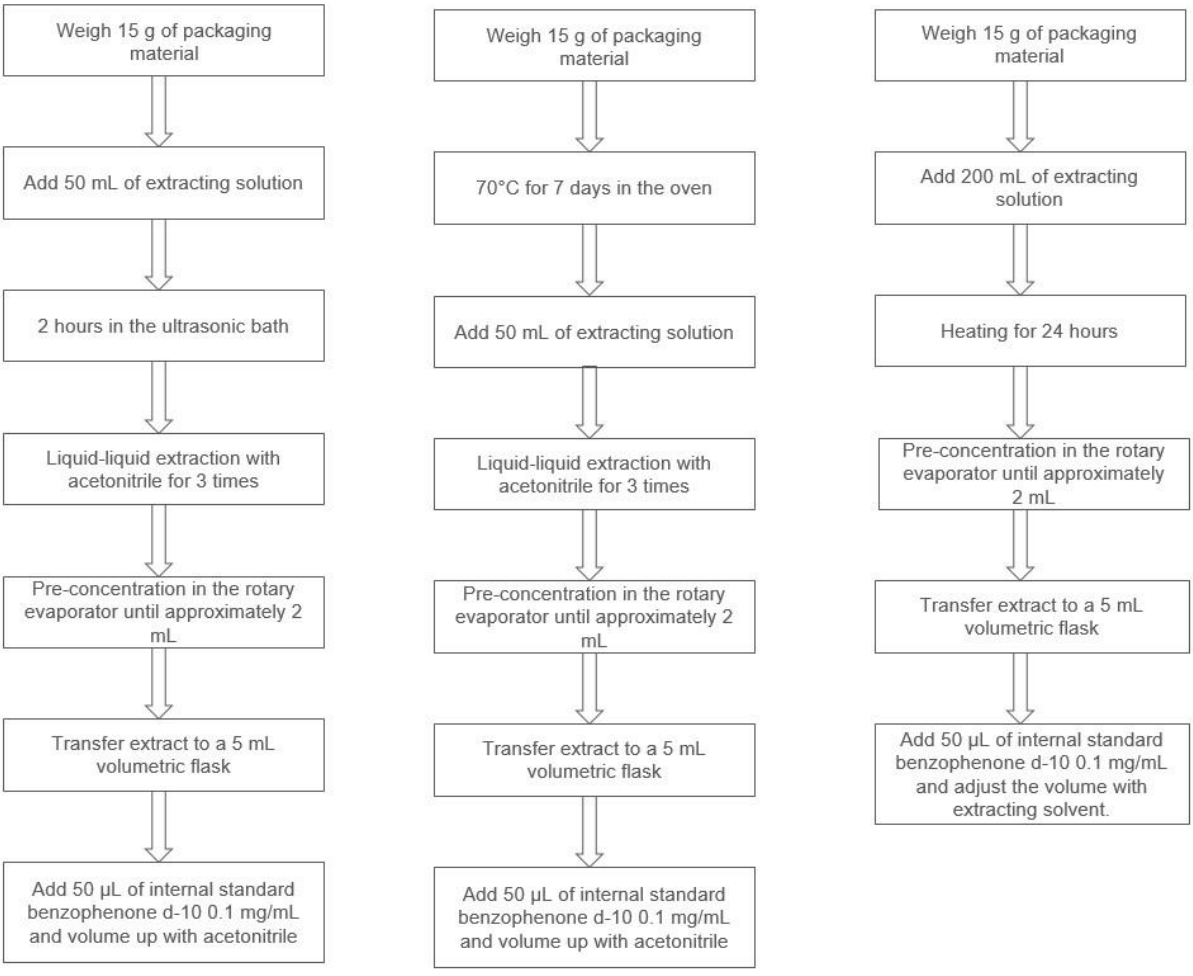


**Figure 1.** Flowchart of extract preparation using different extraction apparatuses in the extractables study.

### *Accelerated study*

Propylene glycol was purchased from Dow Brasil Indústria e Comércio (São Paulo, Brazil), benzalkonium chloride from Novo Nordisk Pharmatech (Copenhagen, Denmark), and mint flavor powder from International Flavors & Fragrances (New York, USA) – composition: 90.8% d-carvone, 6.0% terpinen-4-ol, and 2-cyclopenten-1-one, and 3.2% 3-methyl-2-(2-pentenyl)-, (Z)-. Aqueous extraction media in concentration of 5% (m/v) mint flavor excipient, 30% (v/v) propylene glycol, and 0.02% (m/v) benzalkonium chloride were prepared. 50 mL of the solution were added to 15 g of the cut packaging material in a Teflon jar, and the set was exposed to the oven at 70 °C for 7 days. Due to the large amount of packaging material required

and the limited availability of Teflon containers, the accelerated extraction experiments were performed in single replicate. A parallel study under more aggressive conditions was conducted to assess reproducibility, and the results confirmed the overall trends observed.

***Analytical curves and sample preparation***

Palmitic acid and stearic acid were purchased from Sigma Aldrich (Massachusetts, USA), linoleic acid was purchased from Pharmaffiliates (Haryana, India). For quantification of organic acids, an analytical curve was prepared at concentrations of 0.5, 1, 2.5, 5, and 7.5 μg $mL^{-1}$ palmitic and stearic acids, and 5 μg $mL^{-1}$ linoleic acid used as surrogate standard in dichloromethane. Both stock solutions were prepared at a concentration of 20 μg $mL^{-1}$. For the samples, 5 mL of the extract was pipetted, 1 spatula of sodium chloride was added, along with 2 drops of hydrochloric acid and 1.25 mL of the surrogate standard stock. Liquid-liquid extraction was performed using 10 mL of dichloromethane three times, with agitation for 1 min. After allowing the solution to rest and phase separation, the organic phase was isolated and the extract was concentrated to a final volume of 5 mL.

7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione was purchased from Simson Pharma Limited (Haryana, India) and benzophenone d-10 was purchased from Sigma Aldrich (Massachusetts, USA). For the quantification of 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione, an analytical curve was prepared at concentrations of 5, 15, and 20 μg $mL^{-1}$ for and 5 μg $mL^{-1}$ for benzophenone d-10 as internal standard in dichloromethane. The 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione stock was prepared at a concentration of 80 μg $mL^{-1}$, and the benzophenone stock was prepared at 20 μg $mL^{-1}$. For the samples, 5 mL of the extract was pipetted, 1 spatula of sodium chloride was added, along with 2 drops of hydrochloric acid. Liquid-liquid extraction was performed using 10 mL of dichloromethane three times, with agitation for 1 min. After allowing the solution to rest and phase separation, the organic phase was isolated, and the extract was concentrated to a final volume of 5 mL. The sample was quantitatively transferred to a 5 mL volumetric flask, and 1.25 mL of the benzophenone d-10 stock standard was added. The flask was then filled to the mark with dichloromethane.

***Instrumental analysis***

The screening analyses were performed on a 7890B gas chromatograph coupled to a 5977B MSD single quadrupole mass spectrometer (Agilent, Santa Clara, CA). The column used was DB-XLB (60 m x 0.250 mm, and 0.25 μm) (Agilent, Santa Clara, CA). The temperature ramp was held at 40 °C for 4 min and then increased to 100 °C at a rate of 20 °C $min^{-1}$. The temperature was then raised to 340 °C at a rate of 4 °C $min^{-1}$ and held for 5 min, and further increased to 350 °C at a rate of 5 °C $min^{-1}$. The injected volume was 0.5 μL. Helium was used as the carrier gas at a flow rate of 1.2 mL $min^{-1}$. The injector temperature was 340 °C in splitless mode. The solvent cut in the detector was at 9 min. Data acquisition was performed in scan mode from *m/z* 19 to 670, with ionization energy of 70 eV. The interface temperature was 350 °C, and the ionization source temperature was 320 °C. Total run time was 74 min. A mix of extractables and leachables GC 50 μg $mL^{-1}$, containing: 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate of octadecyl, ε-caprolactam, 2-mercaptobenzothiazole, bisphenol A, butylated hydroxytoluene (BHT), 1,3-di-tert-butylbenzene, oleamide, bis(2-ethylhexyl) phthalate, stearic acid, cis-13-docosenoamide, tris(2,4-di-tert-butylphenyl)phosphate, 2,4-di-tert-butylphenol, and 2,6-di-tert-butylphenol, purchased from Supelco (Pennsylvania, USA), was used as system suitability standard.

The quantification of organic acids was performed on a gas chromatograph (model 8890) coupled to a triple quadrupole mass spectrometer (model 7000E) (Agilent, Santa Clara, CA). The column used was HP 5-UI (30 m x 0.250 mm, and 0.25 μm) (Agilent, Santa Clara, CA). The temperature ramp started at 60 °C and was increased to 160 °C at a rate of 15 °C $min^{-1}$. The temperature was then raised to 215 °C at a rate of 3 °C $min^{-1}$, and finally, the temperature was increased to 340 °C at a rate of 10 °C $min^{-1}$ and held for 5 min. The injected volume was 3 μL. The injector temperature was 320 °C in split mode (1:3). Helium was used as the carrier gas at a flow rate of 1.2 mL $min^{-1}$. The solvent cut in the detector was at 14 min.

Data acquisition was performed in selected ion monitoring (SIM) mode, monitoring *m/z* 256, 213, and 129 (palmitic acid), 241, 185, and 129 (stearic acid), and 280, 124, and 110 (linoleic acid), ionized with 70 eV energy. The interface temperature was 350 °C, and the ionization source temperature was 320 °C. Total run time was 42.5 min.

The quantification of 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione analyses was performed on a gas chromatograph (model 8890) coupled to a triple quadrupole mass spectrometer (model 7000E) (Agilent, Santa Clara, CA). The column used was DB-XLB (60 m x 0.250 mm, and 0.25 µm) (Agilent, Santa Clara, CA). The temperature ramp was held at 40 °C for 4 min and then increased to 100 °C at a rate of 20 °C $min^{-1}$. The temperature was then raised to 340 °C at a rate of 4 °C $min^{-1}$ and held for 5 min, followed by a temperature increase to 350 °C at a rate of 30 °C $min^{-1}$. The injected volume was 0.5 µL. Helium was used as the carrier gas at a flow rate of 1.2 mL $min^{-1}$. The injector temperature was 340 °C in splitless mode. The solvent cut in the detector was at 9 min. Data acquisition was performed in SIM mode, monitoring *m/z* 192, 110 (benzophenone d-10), and 191, 206 (7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione), ionized with 70 eV energy. The interface temperature was 350 °C, and the ionization source temperature was 320 °C. Total run time was 74 min.

## RESULTS AND DISCUSSION

### *Controlled extractables study*

The controlled extraction study is characterized by employing aggressive extraction conditions, such as extended times, high temperatures, and a wide range of polarity and pH, aiming to prevent the decomposition of the material.[14] The Product Quality Research Institute (PQRI) has defined a controlled extractables study protocol at parenteral and ophthalmic formulations, in which the study design depends on the composition of the product being evaluated, guiding the experimental procedure. For example, in products containing organic solvents as vehicles with continuous direct contact with the packaging material, the use of organic solvents with different polarities, such as isopropanol and n-hexane, is recommended.[15-17] In this case, a simplified study was conducted to evaluate the extracts with different extraction techniques and extracting solutions, aiming to identify additives present in the packaging material at relevant concentrations that are likely to migrate into the aqueous formulation under the product storage conditions. The obtained data were compared with the National Institute of Standards and Technology (NIST) library, a database that contains various reference standard information, including mass spectra of these compounds. Based on this, the target compounds described in Table I were selected.

**Table I.** Selected extractables as targets and information related to identification

| Extractables | Chemical Formula | CAS | Match Factor NIST | Reliability of Identification |
|---|---|---|---|---|
| 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione | $C_{17}H_{24}O_3$ | 82304-66-3 | 923 | Confirmed |
| Palmitic acid | $C_{16}H_{26}O_2$ | 57-10-3 | 856 | Confirmed |
| Stearic acid | $C_{18}H_{36}O_2$ | 57-11-4 | 889 | Confirmed |

The described compounds are of confirmed identification, meaning they are based on the comparison of the mass spectrum and retention time with the reference standard.[2] 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione is a associated compound of the Irganox® 1076.[18]

### *Accelerated extractables study*

An accelerated extractables study produces an extractables profile similar to that of the leachables profile, but with a shorter extraction time, without affecting the extractable compounds. The leaching process

involves the diffusion of the additive through the polymer; thus, it is dependent on the diffusion coefficient and the thickness of the packaging material. To assess this effect, the factor of 10 rule is used, which is based on the energy range for compound migration from polymers, typically between 80 and 100 kJ $mol^{-1}$. In practice, this causes the diffusion coefficient to increase by one order of magnitude for every 20 °C rise in temperature, according to the accelerated aging factor, as described in Equation 1.[18]

$$AAF = Q_d^{\frac{TAA-TREF}{20}} \qquad \text{Equation 1}$$

where:
AAF = Accelerated aging factor
$Q_d$ = Aging factor, with the conventionally accepted value of 10.0
TAA = Accelerated contact temperature
TREF = Typical reference use temperature

The extraction time and temperature for the accelerated study were defined based on the factor of 10 rule, according to Equation 1, in order to simulate long-term stability conditions. Therefore, considering the accelerated contact temperature of 70 °C and the typical reference use temperature of 30 °C, the calculated accelerated aging factor is 100. This value is divided by the usual shelf life of a product (2 years, equivalent to 730 days), resulting in 7.3 days, which explains the proposed condition for the accelerated study. The concentrations of the target extractable compounds were determined in the excipient samples subjected to the accelerated study. The results are presented in Table II and Figure 2.

**Table II.** Concentration (μg $g^{-1}$) of the target compounds in the accelerated extractables study in the experiment conducted at unicata

| Excipients | Palmitic Acid | Stearic Acid | 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione |
|---|---|---|---|
| Propylene Glycol 30% | < 1 | < 1 | 5 |
| Mint Flavor 5% | < 1 | < 1 | 4 |
| Benzalkonium Chloride 0.02% | 8 | 12 | 25 |

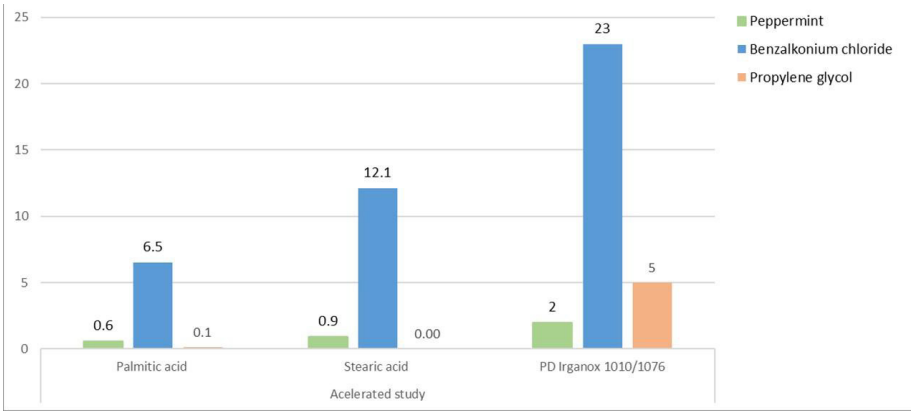


**Figure 2.** Comparison of the extraction power of different types of excipients in the experiment conducted at unicata.

In a quantitative assessment, the recovery of these compounds was evaluated across the different excipient matrices used, ensuring that the matrix effect was not significant and that no losses occurred during the liquid-liquid extraction. To this end, an accuracy test was conducted with all the excipients evaluated within the evaluated work range. Polyethylene glycol and benzalkonium chloride showed recoveries ranging from 75% to 113%. The mint flavoring exhibited recovery values between 36% and 87%. As a result, concentration values were corrected to enable a valid comparison.

A parallel study performed under more aggressive conditions revealed a variation of approximately 25% at higher concentrations and up to 100% at lower concentrations. Although such conditions do not represent realistic pharmaceutical scenarios, the results mirrored the trends of the accelerated extraction experiments, supporting the reliability of the conclusions despite the experimental limitations.

Based on these results, the influence of the physicochemical parameters on the leaching process of additives from the plastic material will be discussed in the topics of partition coefficient and pH.

***Partition coefficient***

There is an empirical approach that correlates the concept of partition coefficient within the scope of leachables. In this context, the solute is the leachable, the receiving phase is the simulant/product, and the donor phase is the packaging material. Based on this analogy, a mathematical relationship is established between the partition coefficient and log $P_{o/w}$, as the polymer behaves like octanol and the liquid behaves like water, according to Equation 2.[18]

$$log\ K_{\frac{P}{L}} = slope\ x\ log\ P_{\frac{o}{w}} + intercept \qquad \text{Equation 2}$$

where:

$log\ K_{\frac{P}{L}}$ = Partition coefficient between plastic and liquid

$log\ P_{\frac{o}{w}}$ = Partition coefficient between octanol and water

The intercept and slope vary depending on the material, but the linear relationship remains consistent across all materials. The advantage of using this relationship is that log $P_{o/w}$ is a well-established parameter with easily accessible values, relating characteristics such as solubility and bioavailability.[18] The excipients propylene glycol, mint flavor, and benzalkonium chloride have partition coefficient values of -0.81, 2.27, and 9.98 - 82.5, respectively. The target compounds palmitic acid, stearic acid, and 7,9-di-terc-butyl-1-oxaspiro(4,5)dec-6,9-dieno-2,8-dione have partition coefficient values of 7.15, 8.22, and 3.08, respectively.[19]

The colloidal suspension of benzalkonium chloride presented the highest extraction potential, preferentially extracting compounds with lower log $P_{o/w}$, i.e., compounds with greater solubility in aqueous media, in this case, 7,9-di-terc-butyl-1-oxaspiro(4,5)dec-6,9-dieno-2,8-dione. Benzalkonium chloride is a type of cationic surfactant,[20] composed of a mixture of benzyl dimethyl ammonium alkyl chlorides, which have various even alkyl chain lengths, totaling 24 structurally similar quaternary ammonium compounds characterized by a positively charged nitrogen covalently bonded to three alkyl group substituents and one benzyl substituent.[21] This excipient stands out due to its surfactant nature, meaning that, in aqueous solution, at the critical micelle concentration (CMC), surfactant molecules aggregate around organic molecules in the medium, with the polar part facing the aqueous solution and the non-polar part facing the organic molecule, forming micelles, as illustrated in Figure 3 (the reverse procedure is also possible). This layer created is responsible for reducing surface tension, consequently increasing the solubility of organic molecules in aqueous media.[22] In the context of extractables, this behavior causes the release of the packaging additive, typically organic, into the aqueous pharmaceutical product.

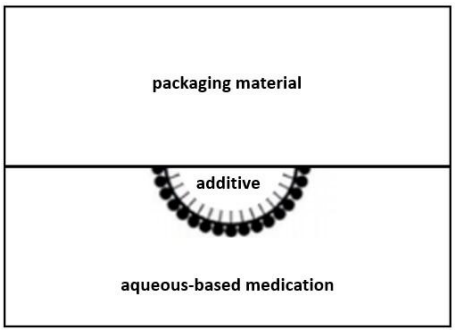


**Figure 3.** Interaction scheme between packaging material additives and surfactant excipients present in the formulation.

On the other hand, excipients with a low log $P_{o/w}$ value and no surfactant properties, such as propylene glycol, have low extraction potential, as observed in previous studies that evaluated the impact of the formulation on the extraction of additives.[23] Despite this, these excipients contribute to the migration of compounds with low log $P_{o/w}$, such as 7,9-di-terc-butyl-1-oxaspiro(4,5)dec-6,9-dieno-2,8-dione, which migrated in relevant concentrations.

Organic acids are in higher concentration in the packaging material, but due to their high log $P_{o/w}$ value, which reflects their hydrophobic nature, only the excipient benzalkonium chloride was able to extract it in relevant amounts (higher than 1 μg $g^{-1}$).

Conversely, 7,9-di-terc-butyl-1-oxaspiro(4,5)dec-6,9-dieno-2,8-dione is in lower concentration in the packaging, but due to its low log $P_{o/w}$, i.e., hydrophilic nature, it migrated in all excipients. For this reason, an accelerated study was conducted with the packaging material in water to segregate the impact of the excipient's extraction power and its solubility in water. The experiment resulted in the extraction of only 1 μg $g^{-1}$ of the additive; therefore, it can be concluded that the increase in additive concentration is due to the excipient present in the solution.

Thus, although the concept of "like dissolves like" is well-established, when it comes to excipients in aqueous formulations stored in plastic packaging, it can be inferred that the effect caused by the surfactant is dominant in the solubilization and extraction of additives from the packaging material. Although log $P_{o/w}$ provides general insight into compound polarity, it does not quantitatively predict extractive behavior in this study. This is due in part to surfactants, which have a range of log $P_{o/w}$ values, and because small variations in log $P_{o/w}$ did not significantly influence leaching, preventing a linear correlation from being established.

### *pH*

In aqueous formulations/simulants, the pH of the solution in contact with the packaging can directly alter the extractables profile of the study, as it modifies the partition coefficient, which is directly related to the solubility of an additive. This behavior is due to the fact that the solubility of the dissociated form of an acid or base is higher than the solubility of the undissociated molecules, so the solubility of an acidic or basic substance is pH-dependent.[24] Therefore, solutions with high pH values tend to favor the migration of acidic molecules, since under these conditions, these molecules are in their ionized form and consequently dissolve well in aqueous media. On the other hand, acidic solutions favor the migration of basic additives. Because of this, a correlation was made between the pH of aqueous excipient solutions and the pKa of the additives to investigate a possible link between the results. The pH of the propylene glycol, mint flavor, and benzalkonium chloride solutions are 5.6, 4.6, and 3.8, respectively. In practice, the behavior predicted by theoretical concepts was not observed in the results for palmitic acid (pKa: 4.75)[19] and stearic acid (pKa: 5.50),[19] which were extracted in higher proportions precisely in the more acidic medium (benzalkonium chloride surfactant mixture).

Although no pKa is available, the compound 7,9-di-terc-butyl-1-oxaspiro(4,5)dec-6,9-dieno-2,8-dione does not have acidic or basic groups. However, there is a chemical reaction occurring at high pH due to basic hydrolysis,[25] as demonstrated in Figure 4. Since both solutions are at slightly acidic pH, there is no significant impact from this variable. However, it is crucial to highlight that this compound was semi-quantified exclusively by gas chromatography coupled to mass spectrometry, a method that may have underestimated the results, thereby increasing the degree of criticality, given the finding of high concentrations.

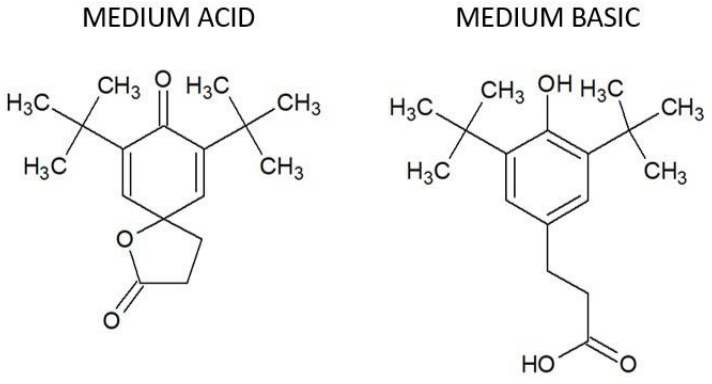


**Figure 4.** Comparison between the molecular structures of the two species of 7,9-di-terc-butyl-1-oxaspiro(4,5)dec-6,9-dieno-2,8-dione existing in aqueous medium at different pH values.[19]

Therefore, these findings confirmed a lesser impact of extreme pH on the leaching of target compounds in relation to the partition coefficient of the excipient present in the aqueous solution.

***Toxicity***

In the toxicological context, organic acids are not carcinogenic, mutagenic, or genotoxic, and are classified as class I in the Cramer rule. Therefore, their maximum daily dose is 1,800 µg person$^{-1}$ day$^{-1}$, which is a relatively high limit. On the other hand, 7,9-di-terc-butyl-1-oxaspiro(4,5)dec-6,9-dieno-2,8-dione, although not carcinogenic, mutagenic, or genotoxic, is classified as class III in the Cramer rule, with a maximum daily dose of 90 µg person$^{-1}$ day$^{-1}$.[26] Available data indicate that both additives can be irritating to the skin, eyes, and respiratory tract. Therefore, depending on the concentration, this compound could be critical for eye drops, dermal solutions, and inhalation products.[27] Due to these warnings and the personalized assessment based on the route of administration and the maximum daily dose of the medication, a toxicological evaluation by a specialist is required, as the Cramer rule only covers general toxicity aspects, and a broader approach is essential for the safety of the medication.

The toxicological assessment presented herein is intended as a general framework, since patient exposure and safety thresholds (AET) depend on factors such as the maximum daily dose of the active pharmaceutical ingredient and the volume of the packaging material. Therefore, a product-specific evaluation is required for precise risk assessment.

## CONCLUSIONS

Liquid pharmaceutical medications stored in plastic packaging are critical in terms of product safety due to the high interaction between the packaging material and the formulation, which increases the likelihood of additive migration from the polymer. This behavior can be exacerbated depending on the excipients used in the formulation, which can have a significant influence on the leaching process. In this context, the extraction potential of different excipients present in this type of pharmaceutical form in contact with high-density polyethylene was evaluated for some additives, aiming to establish correlations between the physicochemical properties of excipients and leachables during the leaching process.

Benzalkonium chloride, an excipient with the highest log $P_{o/w}$ value, proved to be an effective extractor, even at concentrations typically used in formulations (0.02%), demonstrating the high extraction capacity of additives from surfactant compounds. On the other hand, overall, mint flavor and propylene glycol exhibited low extraction potential under the different conditions evaluated, which can be attributed to the lower log $P_{o/w}$ values of these excipients. Therefore, the leaching process demonstrated a greater impact from the physicochemical properties of the excipients. Hence, this study demonstrates that it is possible to predict the leaching of compounds from the packaging into the aqueous product by correlating the log $P_{o/w}$ data of the additives identified in the polymer extractables study and the excipients of the aqueous formulation.

**Conflicts of interest**

The authors declare that they have no conflicts of interest.

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