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Evaluation of the Quality Parameters of Anti-flu Combinations Containing Phenylephrine Hydrochloride Available in the Brazilian Market

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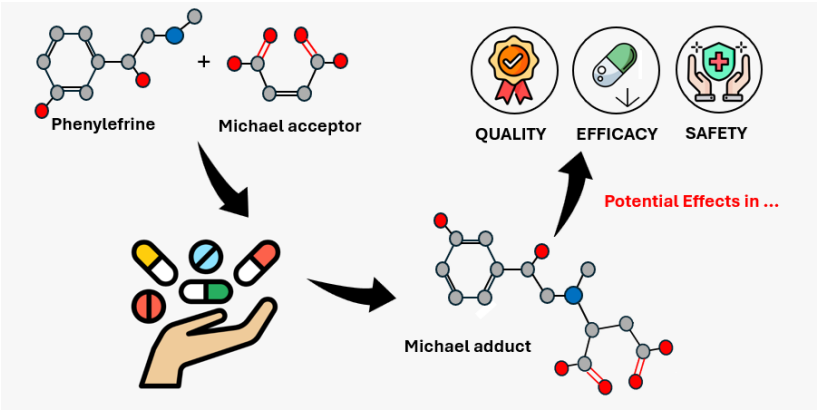
The combination of different active substances in drug products is responsible for optimizing therapies and improving patient adherence. However, the development process of these formulations is highly challenging due to differences in the physicochemical properties of the active ingredients, which can impact formulation stability. Thus, the present study evaluated the incompatibility profile in five different combinations/formulations containing phenylephrine hydrochloride and the maleate compound as a counter-ion by measuring the active pharmaceutical ingredient (API) content and the degradation products (succinyl phenylephrine adducts). This incompatibility occurs due to reactions via Michael addition. The quantification of the API and degradation products was performed using an HPLC-DAD system. The analyses revealed that in all formulations where there is no physical separation between phenylephrine and the maleate counter-ion, a decrease in phenylephrine content and appearance of impurities were observed. Furthermore, the physical separation between the active ingredients was effective, and no markers of the respective reaction were identified. Based on these findings, it is evident that the pharmaceutical form impacts formulation stability, and the reduction in API content along with the increase in impurities may negatively affect product efficacy, quality and safety parameters. This reinforces the need for additional information regarding regulatory registration aspects.

Graphical abstract



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1. Introduction

Paracetamol or acetaminophen (N-(*4- hydroxyphenyl)acetamide*) is an analgesic and antipyretic

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agent with inhibitory action on prostaglandin synthesis in the Central Nervous System [1]. The analgesic action is also attributed to the blocking of peripheral nerve impulses that are associated with pain. Chlorpheniramine (3-(*4-chlorophenyl*)-*N,N-dimethyl-3-(pyridin-2-yl)-propan-1-amine*) is an antihistamine agent with action on the smooth muscles of the respiratory tract, reducing bronchiospasms and the permeability of small blood vessels [2]. Phenylephrine (*3-[(1R)-1-hydroxy-2-(methylamino)ethyl]phenol*) has direct vasoconstrictor action due to agonist action on alpha-1 adrenergic receptors [3]. Another antiallergic is carbinoxamine, which acts as a competitive histamine antagonist (H1 receptor antihistamine) and interferes with the capillaries that irrigate the mucous membranes and sensory nerves of the nasal cavity and adjacent regions. The drug also has antimuscarinic action, partially inhibits the secretion of acetylcholine from the nose, mouth and pharynx and is associated with depression of the Central Nervous System, in addition to inducing sedative effects and acting as a serotonergic antagonist agent [4]. Therefore, the combination of these active ingredients (Figure 1) is widely justified and has been used in drug products to fight flu and cold symptoms, such as nasal congestion, runny nose, fever, headache, muscle pain and other symptoms present in flu-like conditions, with these combinations being classified as over the counter (OTC).

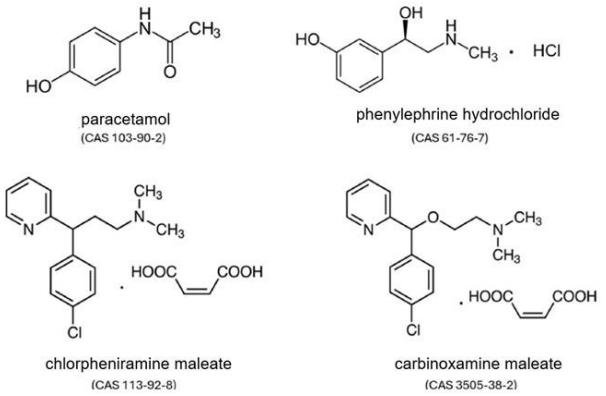

Fig. 1. Chemical structure of paracetamol, phenylephrine hydrochloride, chlorpheniramine maleate and carbinoxamine maleate.

In general, during the development of a pharmaceutical form with active pharmaceutical ingredients (APIs) individually or in combination, it is necessary to know the interactions and predict any incompatibility reactions that may occur between the APIs and excipients, or even between the APIs themselves in the formulation. These interactions can occur in different ways and lead to the degradation of the active ingredient, which reduces the amount available and consequently impacts therapeutic efficacy [5]. In addition, these interactions can give rise to related compounds (degradation products), which can compromise the safety of the pharmaceutical product depending on their levels and toxicity profile. It is also known that the formation of degradation products can lead to other physical interactions that can affect the dissolution, bioavailability and ease of administration of the product [5]. In fact, a rigorous process of designing studies for pharmaceutical combinations and possible physicochemical interactions involves a theoretical evaluation of the reactivity of the components of the formulation, considering their chemical structures and possible impurities, as well as comprehensive literature search that can provide relevant information on the reactivity/incompatibilities of the APIs and excipients. This information guides pharmaceutical development more effectively and supports the selection of the appropriate formulation technology to be employed during pharmacotechnical development.

In this context, the research and development sector of several pharmaceutical industries has developed pharmaceutical forms (reference or generic drugs products) using different technologies. Both pharmaceutical combinations containing paracetamol, chlorpheniramine maleate and phenylephrine hydrochloride (combination 1), or paracetamol, carbinoxamine maleate and phenylephrine hydrochloride (combination 2), are currently available on the pharmaceutical market in presentations that include: oral solution, drops, dragees, capsules, triple-layer tablets and tablets (in which the dose is composed of the joint administration of two tablets of different colors). It is noteworthy that these types of combinations containing two or more active ingredients are marketed with the promise of excellent patient adherence, improved disease management and lower cost. However, the development of this type of product must involve adequate process control, where, for example, an adequate understanding of the physical and chemical properties of the active pharmaceutical ingredients (APIs) is required, as well as all other components of the formulation, such as excipients, packaging materials and manufacturing auxiliaries.

From the point of view of the chemical reactivity of the active compounds of the anti-flu combinations considered here, the reactivity of the secondary amine present in the phenylephrine molecule stands out. This functional group has the ability to react with reducing sugars and aldehydes (Maillard reaction), carboxylic acids (amidation) and can also act as a nucleophile and react with α,β-unsaturated carbonyl compounds (called Michael acceptors), via Michael addition [7]. An example of a Michael acceptor is maleic acid, which is present in both combinations 1 and 2, as a counterion of chlorpheniramine and carbinoxamine, respectively. The mechanism involved in the reaction of phenylephrine and maleic acid is shown in Figure 2. Since double bond carbons have sp^2 hybridization with trigonal planar geometry, in the Michael addition the nitrogen of phenylephrine can attack the double bond of maleic acid from both sides. A new chiral center is generated with *R* and *S* configurations. Given that phenylephrine already has a chiral center, the reaction results in a pair of diastereoisomers, as can be seen in Figure 2.

The incompatibility of phenylephrine with maleic acid is well known and has been previously described in scientific literature [8,9] and patents [10,11].

Considering the information presented, this study aimed to perform a comparative evaluation of six different fixed-dose combinations products (FDCs) available on the Brazilian market, containing APIs from combination 1 or 2, but differ in their pharmaceutical form. In this scenario, the phenylephrine content and the amount of impurities resulting from its incompatibility with the maleate ion (Michael adducts) were used as parameters to assess the quality of the different products. It is noteworthy that this is the first study conducted in Brazil to evaluate the effects of incompatibility in drug products containing phenylephrine and other APIs in combination, which can lead to the formation of degradation products by Michael addition mechanisms in parallel with the reduction in content, which impacts quality parameters and can affect the efficacy and possibly the safety of the product.

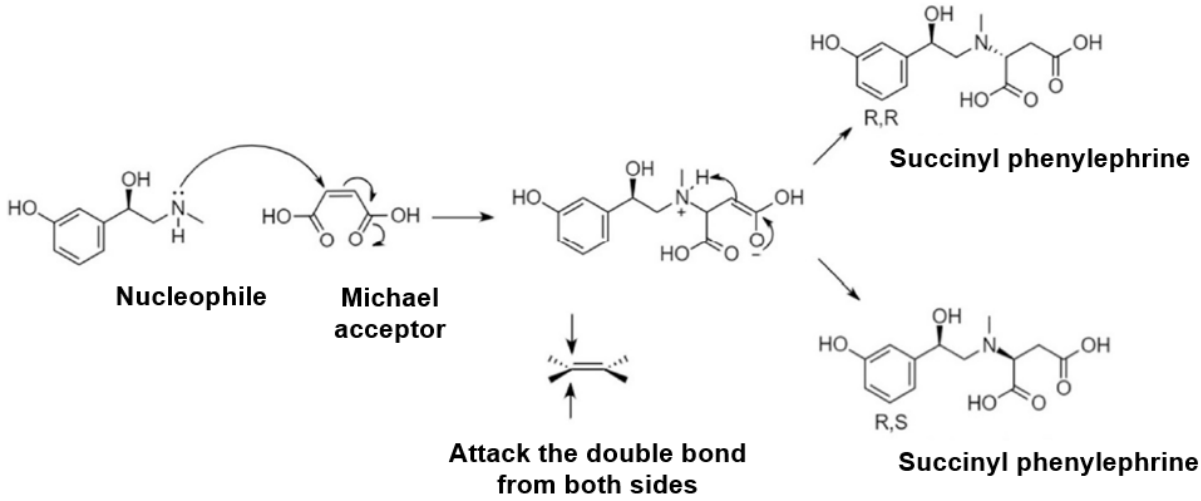

Fig. 2. Reaction scheme for the formation of the diastereoisomer pair (Michael adducts) by the reaction of phenylephrine with maleic acid.

2. Material and Methods

2.1 Chemicals

Sodium octanesulfonate and sodium decanesulfate were purchased from Sigma-Aldrich® (St Louis, Missouri, United States), phosphoric acid, acetonitrile and methanol were purchased from J.T. Baker® (Radnor, Pennsylvania, United States), potassium phosphate dibasic was purchased from Supelco Ascentis (Bellefonte, Pennsylvania, United States) and ultrapure water was purchased from Millipore®.

Phenylephrine hydrochloride was purchased from Nortec Química (Duque de Caxias, Rio de Janeiro, Brazil), paracetamol was purchased from Anqiu Lu'an Pharmaceutical Co., Ltd. (Anqiu, Weifang, Shandong, China), chlorpheniramine maleate was purchased from Supriya Lifescience Ltd. (Mumbai, Maharashtra, India) and carbinoxamine maleate was purchased from MSN Pharmachem Pvt Ltd (Sangareddy, Telangana, India) Reference standard of the Michael Adducts (N-(Succinyl)phenylephrine, CAS number: 915278-80-7, mixture of isomers) were purchased from TLC Pharmaceutical Standards Ltd (Newmarket, Ontario, Canada). Six products sold in Brazil were selected, five containing the combination of paracetamol (400 mg), phenylephrine hydrochloride (4 mg) and chlorpheniramine maleate (4 mg), referred to here as combination 1 (PA, PB, PC, PD and PE) and one product containing the combination of paracetamol (800 mg), phenylephrine hydrochloride (20 mg) and carbinoxamine maleate (4 mg), combination 2 (PF). For each product, three different batches with different manufacturing dates were purchased.

2.2 Compatibility analysis between APIs

Binary mixtures of API:API (phenylephrine hydrochloride:chlorpheniramine maleate; phenylephrine hydrochloride:carbinoxamine maleate and phenylephrine hydrochloride:paracetamol) in a 1:1 ratio (w/w) were incubated for 25 days at 50°C. After this period, the content of phenylephrine hydrochloride was determined by an adequate assay method (internal data).

2.3 Drug product analysis

To quantify the impurities of phenylephrine and maleic acid, a reference solution of *N*-(succinyl)phenylephrine adduct isomers, at 1.0 µg.mL^{-1} in a mixture of 0.1% aqueous phosphoric acid and methanol (95:5, v/v), was used. Ten tablets were macerated and an adequate amount was transferred to a volumetric flask, which was filled with the same solvent mixture, so that the final concentration was equivalent to 0.2 mg.mL^{-1} of phenylephrine. For the analysis of phenylephrine hydrochloride content in combination 1, a reference solution of the API at 0.02 mg.mL^{-1} was prepared in a mixture of 5 mM sodium octanesulfonate pH 2 and methanol (90:10, v/v). Ten tablets were macerated and an adequate amount was transferred to a volumetric flask, which was filled with the same mixture of solvents, so that the final concentration was equivalent to 0.02 mg.mL^{-1} of phenylephrine; the analysis was performed in duplicate. For combination 2 (also performed in duplicate), the reference solution was prepared at 0.01 mg.mL^{-1} in a mixture of water and methanol (90:10) pH 2 and the tablets, after maceration, were dissolved in the same mixture, so that the final concentration of phenylephrine was 0.01 mg.mL^{-1}.

2.4 Apparatus

The analyses were conducted on an Infinity II 1260 chromatographic system (Agilent®, Santa Clara, California, United States) and the data was processed with the OpenLab CDS 3.5 software (Agilent®, Santa Clara, California, United States). Minitab version 21 software was used for statistical analysis.

2.5 Chromatographic conditions

Three chromatographic methods were used: method 1 determination of phenylephrine content in combination 1; method 2: determination of phenylephrine content in combination 2 and method 3: determination of succinyl phenylephrine adduct isomers 1 and 2, in both combinations. All methods were subjected to evaluation of linear working range, precision, accuracy and selectivity.

Method 1, assay of phenylephrine hydrochloride in combination 1, was performed in HPLC-DAD (220 nm), with an Acquity BEH Shield 100 x 2.1 mm, 1.7 µm column (Waters® Milford, Massachusetts, United States) maintained at 40°C, in which a flow rate of 0.5 mL.min^{-1} was maintained. A 5 mM sodium octanesulfonate solution at pH 2 was used as mobile

phase A (MPA) and acetonitrile as mobile phase B (MPB). For each injection of 3 µL of sample, the initial solvent ratio was 95% MPA, which was decreased over three minutes until reaching 80%, followed by another decrease over one minute to 70%, a ratio that was maintained isocratic for one and a half minutes, then increased again to 95% in half a minute, and maintained thus for the final two minutes.

Method 2, assay of phenylephrine hydrochloride in combination 2, was carried out in HPLC-DAD 268 nm, with an X-Bridge C18 column 150 x 4.6 mm, 5 µm (Waters® Milford, Massachusetts, United States) maintained at 45°C, in which a flow rate of 0.8 mL.min^{-1} was maintained. A mixture of 5 mM sodium decanesulfonate pH 6 and methanol (95:5, v/v) was used as mobile phase A (MPA) and a mixture of acetonitrile, methanol and aqueous 5 mM sodium decanesulfonate (72:8:20, v/v), as mobile phase B (MPB). For each injection of 10 µL of sample, the initial proportion of 100% MPA was maintained for seven minutes, then decreased to 70% for nine minutes, a condition that was maintained for another three minutes, and then decreased again until reaching 55%, which was maintained for 13 minutes, after which the proportion was increased again for six minutes to 100%, a condition maintained for the final five minutes.

Finally, the succinyl phenylephrine adduct impurities – method 3 – were quantified by HPLC-DAD at 274 nm, with a Kinetex Polar 150 x 4.6 mm, 2.6 µm column (Waters® Milford, Massachusetts, United States) maintained at 25°C. The MPA was composed of a mixture of 5 mM aqueous sodium octanesulfonate solution and 0.1% phosphoric acid with methanol (95:5, v/v) and the MPB was composed of a mixture of 5 mM aqueous sodium octanesulfonate solution and 0.1% phosphoric acid with methanol and tetrahydrofuran (20:75:5, v/v). For each injection of 5 µL of sample, the initial proportion of 88% MPA, with a flow of 0.35 mL.min^{-1}, was maintained for five minutes, being gradually decreased for 13 minutes until reaching 65%, followed by a new decrease, for one minute, to 20%, followed by an increase in flow to 0.5 mL min^{-1}, a condition maintained for six minutes, with the initial conditions being reestablished later and maintained for 14 minutes.

3. Results and Discussion

3.1 Compatibility analysis between APIs

The results of phenylephrine hydrochloride content in binary mixtures, after the incubation period (25 days at 50°C), are presented in Table 1. The sharp drop in phenylephrine content in binary mixtures with chlorpheniramine maleate (F2) and carbinoxamine maleate (F3) proves the high reactivity between phenylephrine and the maleate ion. This information confirms the incompatibility reported by Marín and Wong [8,9]. On the other hand, no changes in content were observed in the binary mixture of phenylephrine hydrochloride + paracetamol (F4).

Table 1. Results of phenylephrine hydrochloride content in control samples and binary mixtures with chlorpheniramine maleate or paracetamol.

Mixture nomenclature	Evaluated mixture	Content (%)
F1	phenylephrine hydrochloride control	99.2
F2	phenylephrine hydrochloride + chlorpheniramine maleate	89.5
F3	phenylephrine hydrochloride + carbinoxamine maleate	86.2
F4	phenylephrine hydrochloride + paracetamol	100.0

API-excipient or API-API compatibility studies in pharmaceutical combinations are important to understand the possible chemical and physical interactions between the components of the formulation and thus direct the development of the drug. Knowledge of these interactions guides the choice of formulation excipients and the best pharmacotechnical development strategy. The quantitative results of these studies may vary depending on factors such as humidity, hygroscopicity, microenvironmental pH, particle size and degree of crystallinity of the API, among others. Thus, these studies can be predictive of possible degradation reactions that may occur during the stability of a drug, but there is no way to quantitatively predict the degree of degradation of the API in the finished product based solely on compatibility studies.

3.2 Drug product analysis

The quality assessment of the analyzed batches consisted of determining the phenylephrine content and the formation of its adducts with maleic acid (succinyl phenylephrine), with the chemical structures shown in Figure 2. A comparison of the results obtained is presented in Table 2.

According to the package inserts for all medications in combination 1 (PA, PB, PC, PD and PE), the therapeutic regimen consists of administering one dose every 4 hours, with a maximum limit of 5 doses per day. For combination 2, the treatment in the package insert is described as the administration of one dose every 8 hours, without exceeding 120 mg of phenylephrine per day. Thus, considering the Maximum Daily Dose (MDD) of phenylephrine for each of the combinations, the impurity limits according to ICH Q3B (R2) [12] were determined, being: reporting threshold (RT), identification threshold (IT) and qualification threshold (QT). These limits are described in Table 3 and are considered critical parameters in the evaluation of the quality of the finished product and can have negative impacts on efficacy (loss of content) and safety (impurity profile). Table 3 also contains the specification of the phenylephrine content in tablets (value taken from the US Pharmacopeia monograph for the phenylephrine tablets, since there is no monograph for any of the combinations studied in this work).

The data on capsule medications, presented in Table 2, was evaluated using a correlation graph between the shelf-life variables of each batch and the content result and the sum of isomers 1 and 2. Graphical analysis shows that impurities increase as time passes (Figure 4). This data supports that the absence of a physical barrier is indeed a critical parameter for the stability of formulations in combination and consequent maintenance of the content at acceptable levels (greater than 90%).

Table 2. Results of phenylephrine content and succinyl phenylephrine impurities in market formulations (combinations 1 and 2).

Product	Combination/ pharmaceutical form	Batch	Shelf life (months)[a]	Phenylephrine content (%)[b]	*N*-(Succinyl)phenylephrine	
					Isomer 1 (%)	Isomer 2 (%)
	Combination 1	PA-L1	20	102.0	0.1	0.1
PA		PA-L2	15	100.6	0.1	0.1
	Triple layer tablet	PA-L3	10	95.4	< LOQ	< LOQ
	Combination 1	PB-L1	8	89.7	5.7	5.1
PB		PB-L2	14	91.8	7.0	6.2
	Capsule	PB-L3	12	87.2	7.5	6.7
	Combination 1	PC-L1	8	87.5	4.3	4.0
PC		PC-L2	13	85.7	6.8	6.4
	Capsule	PC-L3	8	96.5	4.7	4.6
	Combination 1	PD-L1	12	94.8	2.4	2.2
PD		PD-L2	12	92.9	4.4	4.0
	Capsule	PD-L3	21	83.3	8.6	8.2
	Combination 1	PE-L1	12	88.0	5.7	5.1
PE		PE-L2	16	87.5	8.2	7.3
	Capsule	PE-L3	11	95.4	5.5	5.2
	Combination 2	PF-L1	7	98.4	< LOQ	< LOQ
PF		PF-L2	13	96.7	< LOQ	< LOQ
	Two separate tablets	PF-L3	22	103.3	< LOQ	< LOQ

[a] Time elapsed after the manufacture of the medication, in relation to the date of analysis. [b] Percentage of declared dose. LOQ = limit of quantification of the method (0.1%).

Table 3. Critical quality parameters applicable to phenylephrine hydrochloride with specification of content and LN, LI and LQ according to ICH Q3B (R2), in each combination studied.

Product	Content Specification (%)	MDD (mg)	Specification limits (%)		
			NL	IL	QL
combination 1	90- 110%	20	0.1	0.2% or 2 mg TDD, whichever is less	0.5% or 200 µg TDD, whichever is less
combination 2	90- 110%	120	0.1	0.2% or 2 mg TDD, whichever is less	0.2% or 3 mg TDD, whichever is less

TDD: Total Daily Dose

Comparing the formation of the succinyl phenylephrine adduct in the different products analyzed (Table 2) with the specification values described in Table 3, it is clear that these impurities are within the specification in all analyzed batches only for PA and PF, while for the other products (PB, PC, PD and PE) the degradation adducts exceed the qualification limits recommended in ICH Q3B (R2) [12]. These results are in line with expectations, considering the chemical incompatibility between APIs widely discussed in the literature, since PA and PF are the only drugs that effectively separate phenylephrine hydrochloride from APIs that contain maleate as a counterion, either in different layers like PA (containing chlorpheniramine maleate) or in two distinct tablets like PF (with carbinoxamine maleate). Thus, it is confirmed that the drop in phenylephrine content is due to the formation of succinyl phenylephrine adducts.

As observed in Figure 3, the content results of at least one batch of the PB, PC, PD and PE products indicate that the phenylephrine result is outside the recommended limits (90-110%), with all batches of the PA and PF products meeting these specifications.

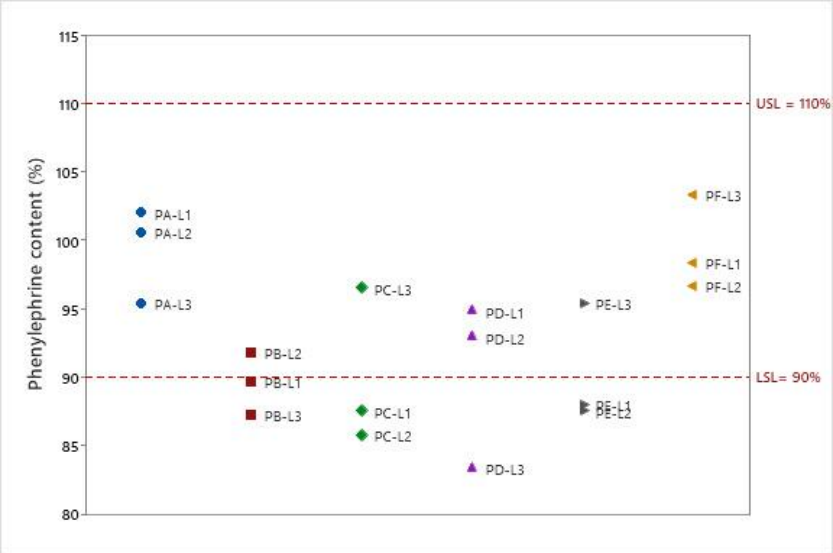

Fig. 3. Representation of the results of content (average values) of phenylephrine hydrochloride of the different products analyzed in relation to the Lower Specification Limit (LSL) of 90% and Upper Specification Limit (USL) of 110%.

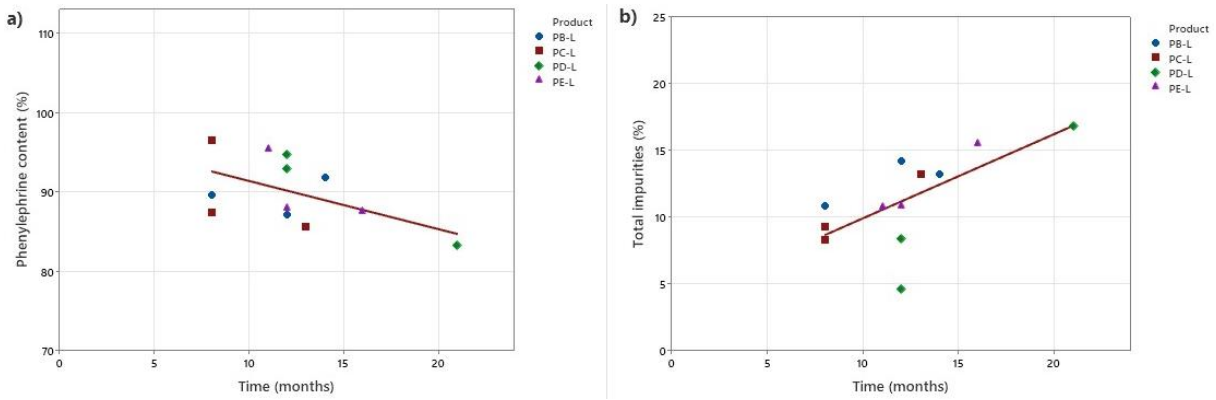

Fig. 4. Graphic correlation between the time after the manufacturing date of products available on the market that do not adopt the separation of APIs and the content (a) and percentage of total impurities (b).

In the review by Johnston and Holt [13] on the impacts of poor-quality medicines on public health, it is shown that there are reports of medicines that underwent regulatory registration procedures and yet presented inferior quality due to poor manufacturing practices or failures in quality control processes. Such changes have also been associated with risks of undesirable adverse effects. This data highlights the importance of compatibility and process control studies, in addition to accelerated stability studies during drug development.

In addition to this discussion, degradation pathways by Michael addition reaction mechanisms may involve several other APIs. Pan and collaborators conducted a review study evaluating the formation mechanisms of products from this type of reaction [14]. As observed in this study, the authors reported that amlodipine reacts with maleic acid via Michael addition, with the presence of two potential impurities being reported and highlighting the need for a comprehensive evaluation of compatibility in general, including potential products containing maleate or other chemical compounds (APIs and excipients) that may participate in some type of chemical reaction.

Furthermore, since the levels of degradation products exceed the requirements recommended in ICH Q3B (R2), it is necessary to present the biological safety assessment data for the succinyl adducts, since these impurities are found at levels above the QT for phenylephrine hydrochloride (QT: 0.5% of each impurity for combination 1, as per Table 3).

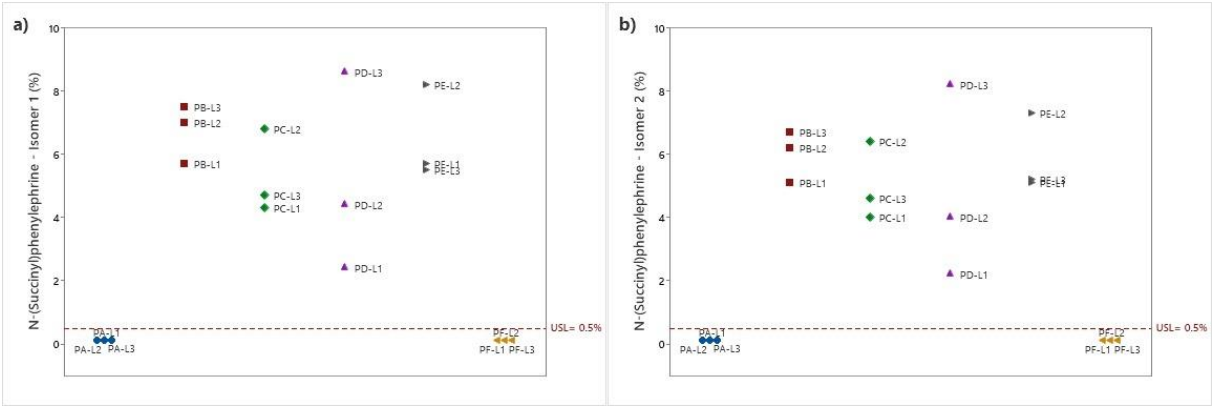

Fig. 5. Graphical representation of the results for impurity N-(Succinyl) phenylephrine isomer 1(a) and 2 (b) in relation to the qualification and specification limits for the different brands of the products evaluated.

Safety parameters of degradation products

In absolute dose levels, the concentrations of degradation products found were converted into daily intake values or total daily exposure (TDE) compared to the MDD described in the package insert for combination 1 (Table 4). For this evaluation only the batches that presented the highest levels of degradation products were presented, that is, the worst case of exposure under therapeutic conditions (for this reason, PF was not included).

The data in Table 4 demonstrates that the absolute quantity of degradation products present in the drugs evaluated exceeds what is considered safe according to the ICH Q3B (R2) guideline [12]. Therefore, it is essential that each drug manufacturer presents a complementary safety assessment with *in silico* data, structure-activity relationship (SAR) analysis and/or *in vivo* toxicity studies to demonstrate that the levels found are considered safe. On the other hand, although the use of a pharmaceutical product involves a risk *versus* benefits assessment, this relationship generally does not apply to impurities in pharmaceutical products, as these compounds may represent toxicological risks of high concern [15]. These substances must be reduced to the lowest possible levels, even if they cannot always be eliminated completely, specifications must be established following the recommendations of safety and quality guidelines [15]. Therefore, it becomes evident that the quantities found of both succinyl phenylephrine adducts are relatively high (mg/day). For isomer 1, the major degradation product found in all products analyzed, if the TDE of the impurity in MDD of phenylephrine hydrochloride is calculated, these values are

approximately 15, 13.6, 17.2 and 16.4 times higher than the QT of ICH Q3B in batches PB-L3, PC-L2, PD-L3 and PE-L2, respectively. For isomer 2, the impurity levels in TDE values are approximately 13.4, 12.8, 16.4 and 14.2 times higher than the concentration of 0.5% (equivalent to 100 µg/day) in batches PB-L3, PC-L2, PD-L3 and PE-L2, respectively.

Table 4. Analysis of the batches with the highest impurity levels in the five products Analyzed and comparative analysis with the TDE considering the MDD of phenylephrine.

Product	Batch Number	Shelf life (months)	Isomer 1		Isomer 2	
			Product concentration (%)	TDE Equivalent (µg/day)	Product concentration (%)	TDE Equivalent (µg/day)
PA	PA-L1/ PA-L2	20 and 15	0.1	20	0.1	20
PB	PB-L3	12	7.5	1500	6.7	1340
PC	PC-L2	13	6.8	1360	6.4	1280
PD	PD-L3	21	8.6	1720	8.2	1640
PE	PE-L2	16	8.2	1640	7.3	1420
Limit considering the ICH Q3B			**0.5**	**100**	**0.5**	**100**

In this context, the safety profile of the drugs PB, PC, PD, and PE is considered inconclusive, highlighting the need of further data to ensure a comprehensive evaluation of biological safety. This additional information is essential to confirm that, under therapeutic use, toxicological risks remain minimal. The importance of supplementing this information is evidenced in case studies and literature reviews that point to the occurrence of adverse events and moderate to severe toxicity, which are intrinsically associated with the presence of impurities in medications [14,16].

There are reports that the presence of impurities in the final pharmaceutical formulation was the root cause of adverse events, such as the case of tetracycline associated with Fanconi syndrome due to the presence of degradation products, the recall of clopidogrel in India and Europe due to the presence of methyl chloride (hepatotoxic substance), and ramipril, whose main metabolite was at levels above the reference specifications (5%) the recall of clopidogrel in India and Europe, and ramipril [14]. These deviations reinforce the need to control impurities in active ingredients and finished products.

4. Conclusions

The present study demonstrated in an innovative way that the type of pharmaceutical form can affect the stability of pharmaceutical combinations products containing phenylephrine hydrochloride and maleate as a counterion. Based on the results of phenylephrine hydrochloride content and the formation of succinyl phenylephrine degradation products (isomers 1 and 2), it is confirmed that the physical separation of phenylephrine hydrochloride and maleate, whether in different layers or different tablets, is effective in mitigating the formation of the degradation product due to the incompatibility of these active ingredients, in addition to maintaining the content within the range considered acceptable. It is also concluded that the presentation of capsules does not adequately isolate the APIs, leading to the formation of degradation products at levels above the qualification threshold, in addition to a sharp drop in content that can compromise the efficacy of the drug.

Therefore, several batches of these drugs, even within the expiration dates, do not comply with the critical quality parameters, which can interfere with efficacy and safety. Finally, it is worth noting that additional biological safety data for biological/health risk assessment must be presented to ensure that degradation products formed during stability do not pose toxicological risks to the finished product, in addition to the fact that these batches are outside the specifications for API content and impurity levels.

Author Contributions

CERC, RCS and RR were responsible for the conceptualization of the study. DVB, VRAC and CRMV were responsible for formal analysis of purchased drug products. DLLBC and RCS contributed with data interpretation, curation and statistics analysis. EWFC conducted toxicological evaluations. DLLBC and EWFC drafted the manuscript. All authors commented on drafts on the paper. All authors have approved the final draft of the manuscript.

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