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In-vitro evaluation of the pharmacological and therapeutic equivalence of some acetaminophen trademarks

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Abstract

There are currently many laboratories throughout the world that sell acetaminophen with legal registration. However, the fact that it is a legal drug does not ensure its quality, as it may undergo changes during its manufacture or marketing, which can affect its efficacy and pharmaceutical safety. Therefore, this project was developed, in which 30% of the brands of acetaminophen 500 mg tablets marketed in Colombia were analysed with the aim of determining their pharmacological and therapeutic equivalence. Know the pharmaceutical characteristics and therapeutic similarity between the different brands of acetaminophen analysed a methodology was followed in accordance with the parameters and guidelines of the United States Pharmacopeia 42, National Form 37, and Resolution 1124 of the Ministry of Health and Social Protection of the Colombian government. The samples' dissolving profiles at different pH values were then compared, and tests were run to check for impurities, content, uniformity, and dissolution. The results of these analyses are all totally consistent with the pharmacological and therapeutic equivalents. These comply both with the physical-chemical quality control parameters required as well as with therapeutic equivalence. From the findings of this investigation, it was concluded that since there is no evidence of significant differences between the brands analysed, it is recommended that those who need to buy acetaminophen or Tylenol from the brands surveyed can purchase any of them with complete confidence that any of them will have the same pharmaceutical quality and the same therapeutic performance.

Keywords: Comparison of Acetaminophen and Tylenol, In Vitro Experiments, Pharmaceutical and Therapeutic Equivalence, Quality in Drugs.

1. Introduction

By 1970, Acetaminophen had become the world's most popular pain reliever, prescribed by doctors, and self-administered by consumers to treat pain, viral fevers, malaria, dengue, flu, migraine, osteoarthritis, and colds in children and adults of all ages, regardless of underlying disease, and even to treat postoperative pains (Bertolini et al., 2006). The molecular formula of acetaminophen is C8H9NO2, and its structural formula presents a benzene ring in which a hydrogen has been replaced by a hydroxyl group and a nitrogen atom by an amide group (Sankarraman, 2022). Acetaminophen in doses of 100 mg has also been used to reduce pain after laparoscopic tubal ligation (Siripruekpong et al., 2022). Acetaminophen can be used alone or in combination with opioids for the treatment of pain and as an antipyretic agent (Acetaminophen - DrugBank, n.d.). Acetaminophen has had a lot of impact on the world as it has been synthesized by many methods with the purpose of reducing its production costs and making it more accessible to humanity (Castellar-Buelvas et al., 2022).

Acetaminophen, also known as Tylenol, is the most used non-opioid analgesic and antipyretic around the world (Anderson, 2008). Currently, acetaminophen is involved in many cases of poisoning due to its free sale and easy access for adults and children (Mancipe et al., 2010). Acetaminophen poisoning is treated with activated charcoal in doses of 1 g/kg of weight, and in vitro studies have also demonstrated the use of cholestyramine (Castellar-Buelvas and Troncoso-Palacio, 2021). Acetaminophen as raw material is described as a fine crystalline powder of white colour with a slightly pungent flavour, freely soluble in alcohol, soluble in boiling water and in 1 N sodium hydroxide (Farmacopea de los Estados Unidos de America Formulario Nacional USP 40 NF 35, 2017). Acetaminophen is highly recognized by paediatricians for its safety and effectiveness in the paediatric population (Tan et al., 2022). In women of childbearing age and during pregnancy, acetaminophen has been shown to be safe since no proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus has been observed (Acetaminophen Dosage Guide with Precautions, n.d.). However, acetaminophen should be administered with great caution in lactating women because it is considered compatible between breast milk and this medication (Acetaminophen - ClinicalKey, n.d.).

Acetaminophen has been the drug most involved in poisoning cases in India and the United States with more than 56,000 cases reported between 1990 and 1998 (Ghaffar and Tadvi, 2014). Hepatotoxicity is the main adverse reaction to which patients are exposed during the consumption of acetaminophen (Walls et al., 2007). Hepatotoxicity is produced by the metabolism carried out in the liver of non-steroidal anti-inflammatory drugs to activate the form of their prodrugs or to facilitate their elimination in the body (Tolman, 1998). A well-known example of how the liver participates in the metabolism of acetaminophen is shown when it comes into contact with liver enzymes such as cytochrome P450, resulting in the formation of the more toxic metabolite called N-acetyl-p-benzoquinone imine (NAPQI) (Manyike et al., 2000). The initial symptoms of hepatotoxicity are nausea, vomiting, and abdominal pain (Paracetamol, n.d.). Yellow discoloration could also be observed in the eyes and skin (Vidhya Malar and Mettilda Bai, 2012). Alcohol consumption with acetaminophen should be avoided since this combination increases the risk of hepatoxicity for both (Prescott, 2000). However, moderate alcohol consumption with acetaminophen has not shown increased hepatoxicity (Graham et al., 2004). Another adverse reaction reported has been acute renal failure due to ingestion of acetaminophen, which must be controlled in time (Blakely and McDonald, 1995). However, despite the adverse reactions already described for the use of acetaminophen, it has been shown to have many benefits in children when compared to non-steroidal anti-inflammatory drugs (Litalien & Jacqz-Aigrain, 2001).

During 2018 in Colombia, the Acetaminophen is the most prescribed medication. (Acetaminofén, El Medicamento Más Prescrito En Colombia En 2018, n.d.). Even today, 2024 continues to be the most prescribed medication by Colombia's public health systems, either alone or combined with other active ingredients (Alertan Por Posible Escasez de Acetaminofén En Colombia - Infobae, n.d.). It is known that of the 165 current health

registrations in Colombia, 13 of them belong to different commercial brands of products in tablet pharmaceutical form with only Acetaminophen as the active ingredient and with a concentration of 500 mg per tablet (Sistema de Tramites En Linea - Consultas Publicas, n.d.). It also is known that in Colombia, obtaining a sanitary registration for pharmaceutical products and its validity does not guarantee the quality of the product, as demonstrated by one most recent case of contamination with diclofenac (Dololed: La Historia de La Caída de Un Medicamento Estrella - Salud - ELTIEMPO.COM, n.d.). Acetaminophen is classified as Class 3 Drugs with low permeability and high solubility according to the Biopharmaceutical Classification System (Inalbon et al., 2016). This classification allows one of the ways to determine therapeutic equivalence to be through biowaiver study, in vitro analysis of dissolution profile at pH 1.2, 4.5, and 6.8 (Resolution 1124, 2016).

Based on the 80/20 rule, proposed by the Pareto diagram (Diagrama de Pareto, n.d.). This study will be analysed 30% of the 13 registered brands that market Acetaminophen 500 mg in Colombia, so a sample of 4 brands must be analysed (Sistema de Tramites En Linea - Consultas Publicas, n.d.). The bioequivalence test will ensure bioavailability, and by ensuring therapeutic equivalence, the efficacy, and safety of the drug will be guaranteed (Perry, 2010).

2. Material and Methods

The materials, equipment, samples, and methods used are the following: 10 acetaminophen tablets were selected from each of the laboratories under study as samples and were crushed to carry out the respective analyses. Standard 4-aminophenol was used to determine impurities, and an Acetaminophen Standard USP, for the high-performance liquid chromatography assays (Figure 3). In addition, buffer solutions were used for the analysis of the different PH profiles.

The methodological steps of the United States Pharmacopeia USP 42 and NF 37 were followed, which was the one in force in Colombia at the time of this writing Resolution 1124 of 2016 was also applied, which is mandatory to demonstrate the quality, safety, and efficacy of drugs marketed in Colombia. The methodology was developed in the next two steps.

2.1 Stage 1

In accordance with USP 42, which contemplates made the analysis of the physicochemical quality control parameters, such as description, identification, weight variation, valuation, dissolution, and organic impurities.

2.2 Stage 2

In vitro profiles are determined at pH 1.2, 4.5, and 6.8. See details in Figure 1. Matrix methodological steps.

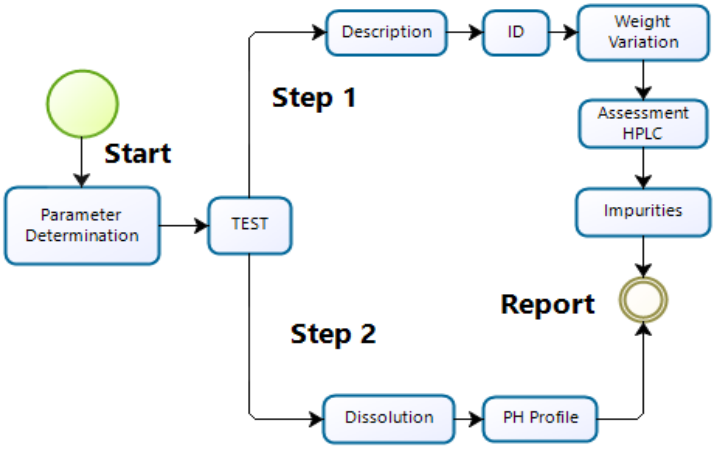

Figure 1. Methodological Matrix

3. Results and Discussions

Tylenol and the four analysed brands of Acetaminophen 500 mg tablets from Laboratories AG, Best, La Sante, and GSK met the description criteria because no foreign material or colour changes were detected in any of the samples tested. The fulfilment identification by all samples during the assay is also highlighted as the retention time of the main peak of the standard was identical to the samples that appeared in 1.707 minutes. All four brands tested, including Tylenol, passed the uniformity of weight test since they tested within the acceptability limits, which are 85.0 to 115.0% of the claimed value and the percentage of variance. Relative standard percentage (%RSD) is less than 6%. Likewise, the ten results for each brand analysed can be seen in Table 1. It should be noted that the samples from Best Laboratory presented the best precision, reflected in a %RSD of 0.5%, and the samples from AG Laboratory were the least accurate. It was showing a %RSD of 2.9%.

Table 1. Uniformity of Content %

Units	Tylenol	Ag	Best	La Sante	GSK
1	99.5	104	98	98.8	101
2	99.5	101	98.1	98.2	99.4
3	100.9	98.2	99	99.5	102
4	99.9	103	97.7	99.3	99
5	100.7	98.1	97.5	98.8	98.9
6	99.2	99.1	98.6	99.4	99.6
7	100.2	97.9	98.1	98	99.2
8	100.3	96.6	98.4	100.5	100
9	100.3	103	97.8	99.4	99.8
10	99.7	96.1	98	99.3	101
Average	100	99.7	98.1	99.1	99.9
%RSD	0.6	2.9	0.5	0.7	0.9

Table 2 shows the three replicates analysed by brands. It also shows the averages obtained and the %RSD. Acceptance criteria for the assay were met for Tylenol and all four brands of Acetaminophen as all samples provided results within specifications of 90.00 to 110.00% of the labelled value, and the %RSD was at 2.00%. The average of the three replicates of Tylenol revealed the highest percentage recovered of 100.03%, while AG Laboratory revealed the lowest result of 98.13%. The correct functioning of the chromatographic system was guaranteed since the aptitude of the system was met in the five injections of USP Standard Acetaminophen, both the tail factor and the %RSD both gave results lower than 2.

Table 2. Recovered HPLC Method

Units	Tylenol	Ag	Best	La Sante	GSK
1	100	99.6	98.1	99.1	99.9
2	100.03	99.7	98.1	99.01	99.8
3	100.02	99.6	98	99.15	99.9
Average	100.03	99.7	98.13	99.1	99.92
%RSD	0	0.05	0.08	0.08	0.07

In the dissolution test, Tylenol and the four brands of Acetaminophen met the acceptance criteria for dissolution since the percentage recovered was greater than 80% in all the dissolution containers. In Table 3, we can see the results of the six dissolution vessels analysed for each of the brands under study as well as their mean. However,

the average percentage recovered from the La Sante Laboratory samples was the highest at 101.1%. The lowest value revealed is that of Tylenol, with 95.1%.

Table 3. Recovered Dissolution Method

	Tylenol	GSK	AG	La Sante	Best
Acceptance 80%	97.4	97	97	101.8	99.1
	95.1	98.4	97	98.5	97.7
	95.8	95.6	98	101.1	99.5
	97.4	96.9	97	102	99.1
	95.1	98.4	97	98.7	97.7
	95.9	95.5	98	101.1	99.4
Average	96.1	97	97	100.5	98.7

Impurity testing resulted in meeting table 4. The acceptance criteria for 4-aminophenol, unspecified impurities, and total impurities in the Tylenol sample and all four brands of Acetaminophen, see Table 4. However, it is noted that Tylenol only presented the 4-aminophenol impurity with the lowest result of 0.0083%. Best Laboratories had the best results for the 4-aminophenol impurity and total impurities, with values of 0.0135 and 0.0176%, respectively. The performance of the chromatographic equipment utilized for the impurity test was satisfactory because the %RSD of the five injections did not exceed 5.0% for the 4-aminophenol and Acetaminophen Standard in the solution. The noise-signal ratio gave a result of 710, being not less than 10 for 4-aminophenol in the sensitivity solution, guaranteeing the correct functioning of the system.

Table 4. Organic Impurities

Item	Tylenol	AG	Best	La Sante	GSK
%	0.008	0.01	0.01	0.01	0.01
% I	0	0	0	0.001	0
% II	0	0	0	0.002	0
% III	0	0	0	0	0
% Total	0	0.02	0.01	0.01	0.01

Acceptance criteria are 0.15% maximum for 4-aminophenol, 0.15% maximum for unspecified impurities and 0,60% maximum for total impurities.

Below, from figures 4 to 8, the respective peaks of the chromatograms evaluated are observed.

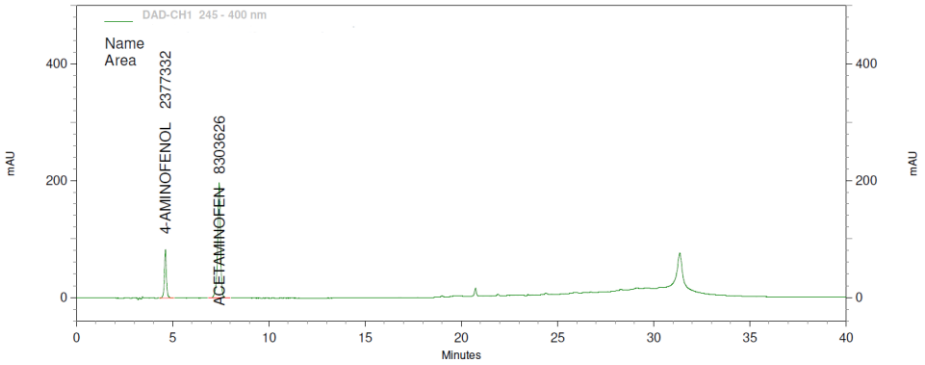

Figure 4. Tylenol Impurities

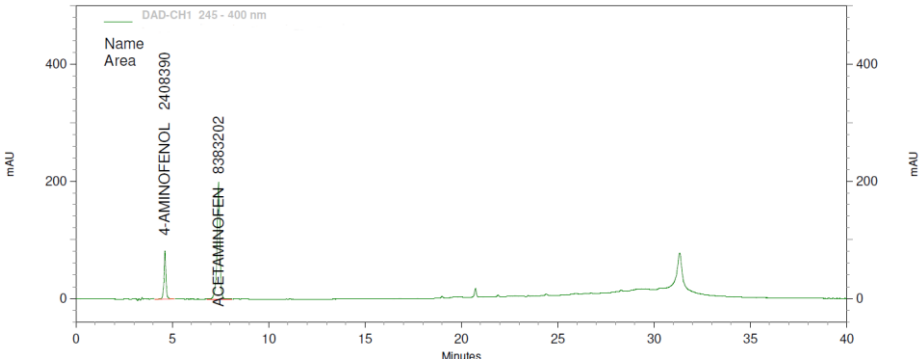

Figure 5. AG laboratory Impurities

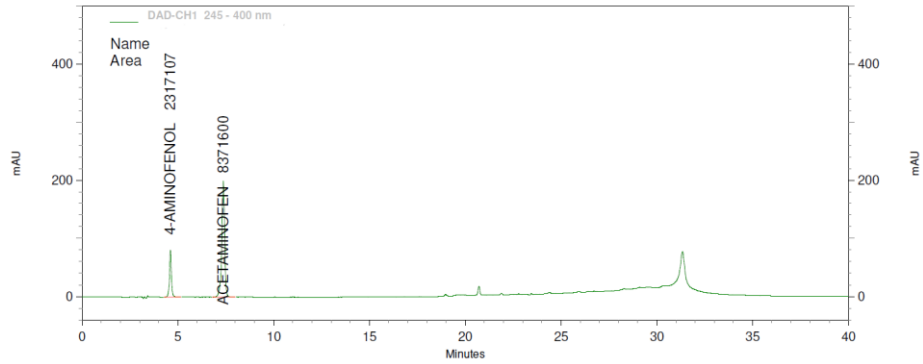

Figure 6. Best laboratory Impurities

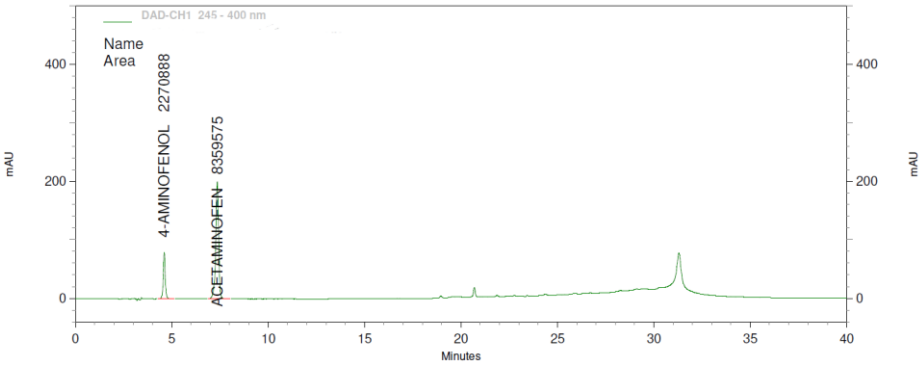

Figure 7. La Sante laboratory Impurities

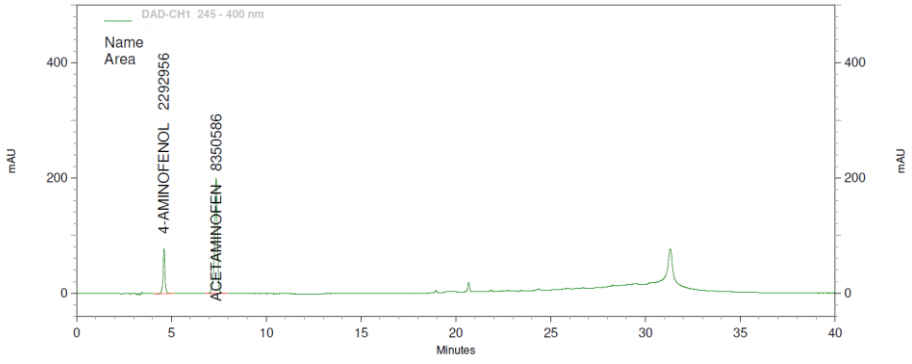

Figure 8. GSK laboratory Impurities

Tables 5, 6 and 7, show the results of the profile test at pH 1.2, 4.5 and 6.8, with times of 5, 10, 15, 30, 45, and 60 minutes in the Tylenol sample and the four brands of Acetaminophen. The good behaviour of the dissolution profiles was also demonstrated, revealing compliance with the F1 value, which was between 0 and 15, as well as the F2 criterion, which was between 50 and 100. GlaxoSmithKline turned out to be the most comparable laboratory compared to Tylenol in all the pH profiles analysed, and the findings show the following results: For a profile at pH 1.2, values of F1 = 3 and F2 = 70 were obtained. For a profile at pH 4.5, values of F1 = 2 and F2 = 77 were obtained. For a profile at pH 6.8, values of F1 = 1 and F2 = 85 were obtained. Best Laboratories had the least similarity to Tylenol. For a profile at pH 1.2, values of F1 = 5 and F2 = 57 were obtained. For a profile at pH 4.5, values of F1 = 4 and F2 = 61 were obtained. For a profile at pH 6.8, values of F1 = 4 and F2 = 64.

Table 5. PH 1.2 Profile

Minutes	Tylenol	AG	Best	La Sante	GSK
5	79.9	73.7	75	75	74
10	90.2	81	79.2	79.6	84.8
15	96.2	86.8	84	85.5	91.5
30	98.6	99.7	98.2	97.7	98.4
45	99	99.7	99.4	99.3	98.7
60	99	99.7	99.3	99.4	100.7
F1	-	4	5	5	3
F2	-	61	57	59	70

Table 6. PH 4.5 Profile

Minutes	Tylenol	AG	Best	La Sante	GSK
5	74.8	69.8	68.5	69.6	71.3
10	83.2	76.6	75.3	75	80.5
15	90.8	83.2	80.7	81	85.8
30	97.6	98.4	98.1	98.3	98.3
45	99.2	99.4	99.3	99.3	99.2
60	99.3	99.4	99.4	99.3	99.6
F1	-	3	4	4	2
F2	-	66	61	62	77

Table 7. PH 6.8 Profile

Minutes	Tylenol	AG	Best	La Sante	GSK
5	76.1	73.4	70	73.1	74.6
10	83.1	79	76.7	79.7	80.8
15	98.4	91.4	89.6	88.6	95.3
30	99.6	99.3	99.6	99.4	99.1
45	99.6	99.4	99.6	99.4	99.5
60	99.6	99.6	99.6	99.7	99.4
F1	-	3	4	3	1
F2	-	72	64	67	85

The four brands selected to compare Acetaminophen vs Tylenol were randomly chosen, with INVIMA health registration and current expiration date. There was no brand discrimination, nor were there any manufacturer laboratory preferences or a preferential site to acquire the samples. Obtaining results revealed that the physicochemical parameters required by USP 42, such as description, identification, weight variation, valuation,

dissolution, and organic impurities, were met by all the brands analysed, which is considered a complying with these parameters is a guarantee of quality.

During the analysis of the description of the tablets, it was observed that three brands had a round shape and one including Tylenol oblong. This is because currently, in Colombia, there is no law that regulates the physical shape and weight of the tablets, for which the Manufacturing laboratories choose and adjust these characteristics to what is most convenient for their process.

Regarding the results obtained from identification and assessment, all the brands complied with the identification despite presenting a slight difference in retention times due to the imbalance that the chromatographic system could present. All the brands analysed in the evaluation test showed results above 98% as a recovered percentage, which demonstrated excellent quality.

The dissolution test is a very important quality parameter because, by means of this in vitro method, it is possible to demonstrate the percentage of active ingredients released in relation to time. Within the results revealed in the dissolution test, we were able to observe that the average of the six glasses of Tylenol dissolution yielded a result of 96,1%, this result being surpassed by the results of the four samples analysed.

This indicates once again the quality of the 500 mg Acetaminophen tablets brands marketed in Colombia. On some occasions, the impurities generated in a pharmaceutical product are usually more toxic than the same active ingredient. Therefore, the control and regulation of impurities must be carried out, which should not exceed the permitted daily exposure limits.

The result of the impurities detected in the Tylenol sample and the four brands analysed was discussed, and it was stated that Tylenol and the four brands met the specifications. However, the quality of Tylenol is highlighted as only the 4-aminophenol impurity was detected. The result obtained from the GlaxoSmithKline brand is also praised because it only presented two impurities which were 4-aminophenol, and only one unspecified impurity.

On the other side, it is important to highlight that the samples from Laboratories La Sante and Laboratories Best also yielded good results, revealing the presence of the impurity 4-aminophenol and two unspecified impurities. Compliance with the specifications is very important because in this way the quality and safety of the product is guaranteed, and the case of the Laboratories AG sample was discussed, where the greatest number of impurities was detected, such as 4-aminophenol and three impurities. not specified. But all met the acceptance criteria, guaranteeing the safety of the product.

It was also discussed that the Best Laboratory sample presented a higher value of total impurities despite having fewer impurities present compared to the AG Laboratory sample. This is due to the individual values that the impurities can present. It was also discussed that in the dissolution profile study at pH 1.2, 4.5, and 6.8. All brands gave excellent results and met this test when compared to Tylenol.

However, it is highlighted that Tylenol at times 5, 10, and 15 minutes presented a higher percentage of active release compared to the brands analysed. Likewise, it was observed that the analysed brands equalled the percentage of active released against Tylenol only after 30 minutes. This could be due to the different excipients and quantities used in the manufacturing processes.

4. Conclusion

In this study, 30% of Acetaminophen 500 mg tablet brands manufactured in Colombia were examined, which are currently legally INVIMA registered. The analysis preliminarily demonstrated the pharmaceutical and therapeutic equivalence between them versus Tylenol. This demonstration could reinforce confidence and guarantee efficacy and safety in patients who will be given Acetaminophen in 500 mg tablets. Since the results show that they contain the same amount of drug, it can be concluded that they are bioequivalent by USP 42 NF 37.

Therapeutic equivalence was demonstrated by an in vitro method in which dissolution profiles at pH 1.2, 4.5, and 6.8 were compared. The display of results showed that they met the acceptance criteria for the difference factor F1 and the similarity factor F2.

These findings allow us to ensure that the pharmaceuticals tested here are identical to one another. Hence, there should be no brand discrimination between them at the time of medical prescription.

This research only applies to the results of the analysed brands, demonstrating the pharmaceutical and therapeutic equivalence between them. However, this study preliminarily revealed the brands that presented the lowest percentage difference and the greatest similarity versus Acetaminophen USP Standard, the first being GlaxoSmithKline Laboratories, the second AG Laboratories, the third La Sante Laboratories, and the fourth Best Laboratories.

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References

Acetaminofén, el medicamento más prescrito en colombia en 2018. (n.d.). https://consultorsalud.com/acetaminofen-el-medicamento-mas-prescrito-en-colombia-en-2018/. Accessed 24 January 2021.

Acetaminophen - ClinicalKey. (n.d.). https://clinicalkey.unicartagenaproxy.elogim.com/#!/content/drug_monograph/6-s2.0-4. Accessed 18 August 2021.

Acetaminophen - DrugBank. (n.d.). https://go.drugbank.com/drugs/DB00316. Accessed 30 September 2020.

Acetaminophen Dosage Guide with Precautions. Drugs.com. (n.d.). https://www.drugs.com/dosage/acetaminophen.html. Accessed 30 September 2020.

Alertan por posible escasez de acetaminofén en Colombia - Infobae. (n.d.). https://www.infobae.com/colombia/2024/03/16/alertan-por-posible-escasez-de-acetaminofen-en-colombia/. Accessed 30 September 2020.

Anderson, B. J. (2008). Paracetamol (Acetaminophen): Mechanisms of action. Paediatric Anaesthesia, 18(10), 915–921.

Bertolini, A., Ferrari, A., Ottani, A., Guerzoni, S., Tacchi, R., & Leone, S. (2006). Paracetamol: New Vistas of an Old Drug. CNS Drug Reviews, 12(3-4), 250–275.

Blakely, P., & McDonald, B. R. (1995). Acute renal failure due to acetaminophen ingestion: a case report and review of the literature. Journal of the American Society of Nephrology, 6(1), 48-53.

Castellar-Buelvas, J., & Troncoso-Palacio, A. (2021). Using in vitro cholestyramine as an instead of activated charcoal for the treatment of drug poisoning. International Journal of Research in Engineering and Science, 9(9), 47–54.

Castellar-Buelvas, J., Troncoso-Palacio, A., & Figueroa-Mercado, R. (2022). Acetaminophen Synthesis Reaction Performance Using Ultrasound, Microwave, and Conventional Methods. International Journal of Engineering Inventions, 11(10), 87–94.

Diagrama de Pareto (n.d.). https://www.jmp.com/es_co/statistics-knowledge-portal/exploratory-data-analysis/pareto-chart.html. Accessed 26 August 2021.

Dololed: la historia de la caída de un medicamento estrella - Salud - ELTIEMPO.COM. (n.d.). https://www.eltiempo.com/salud/dololed-la-historia-de-la-caida-de-un-medicamento-estrella-459262. Accessed 24 January 2021.

Ghaffar U.B., & Tadvi, N. A. (2014). Paracetamol Toxicity: A Review. Journal of Contemporary Medicine and Dentistry, 2(3), 12–15.

Graham, G. G., Scott, K. F., & Day, R. O. (2004). Alcohol and paracetamol. Australian Prescriber, 27(1), 14–15. https://doi.org/10.18773/austprescr.2004.009

Inalbon, M., Muñoz, R., & Sallietti, V. (2016). Estudio de bioequivalencia farmacéutica in vitro de comprimidos de Paracetamol 500 mg comercializados en Córdoba, Argentina. Córdoba: Facultad de Ciencias Químicas.

Litalien, C., & Jacqz-Aigrain, E. (2001). Risks and benefits of nonsteroidal anti-inflammatory drugs in children: A comparison with paracetamol. Pediatric Drugs, 3(11), 817–858.

Mancipe, L. C. Fernandez, A. D. C., & Fernandez, A. D. G. (2010). Intoxicación por Acetaminofén. Revista Med, 18(2), 221-227.

Manyike, P. T., Kharasch, E. D., Kalhorn, T. F., & Slattery, J. T. (2000). Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. Clinical Pharmacology and Therapeutics, 67(3), 275–282.

Paracetamol. (n.d.). https://www.vademecum.es/principios-activos-paracetamol-N02BE01. Accessed 30 September 2020.

Perry, R. (2010). Perspectives on the bioequivalence and therapeutic equivalence of generic formulations: An overview of the landscape. Clinical Therapeutics, 32(10), 1796–1797.

Prescott, L. F. (2000). Paracetamol, alcohol and the liver. British Journal of Clinical Pharmacology, 49(4), 291–301.

Resolution 1124. (2016). https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/resolucion-1124-de-2016.pdf. Accessed 20 September 2020.

Sankarraman, S. M. (2022). A computational approach on acetaminophen drug using degree-based topological indices and m-polynomials. Biointerface Research in Applied Chemistry, 12(6), 7249–7266.

Siripruekpong, S., Aphinyankul, J., Chanchayanon, T., Oofuvong, M., Pakpirom, J., Choksuchat, C., Packawatchai, P., & Klongdee, J. N. (2022). Minimal effective dose of ultrasound-guided rectus sheath block to reduce oral analgesic requirement after ambulatory laparoscopic tubal resection: a randomized controlled superiority trial. Trials, 23(1), 228.

Sistema de Tramites en Linea - Consultas Publicas. (n.d.). http://consultaregistro.invima.gov.co:8082/Consultas/consultas/consreg_encabcum.jsp. Accessed 21 January 2021

Tan, E., Hoare, K., Riley, J., Fernando, K., Haskell, L., McKinlay, C. J., Dalziel, S. R., & Braithwaite, I. (2022). Panic or peace – prioritising infant welfare when medicating feverish infants: a grounded theory study of adherence in a paediatric clinical trial. BMC Pediatrics, 22(1), 195.

Tolman, K. G. (1998). Hepatotoxicity of non-narcotic analgesics. American Journal of Medicine, 105(1B), 13S-19S.

Vidhya Malar, H. L., & Mettilda Bai, S. M. (2012). Beware of Paracetamol Toxicity. Journal of Clinical Toxicology, 2(7), 2–4.

Walls, L., Baker, C. F., & Sarkar, S. (2007). Acetaminophen-induced hepatic failure with encephalopathy in a newborn. Journal of Perinatology, 27(2), 133–135.

** (2017). Farmacopea de los Estados Unidos de America Formulario Nacional USP 40 NF 35 (p. 2784). 40th ed. Rockville (EEUU): U. S. Pharmacopeial Convention, Inc.