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Off-label use of hydrochlorothiazide in neonatology: impact of tablet adaptation techniques on dose accuracy

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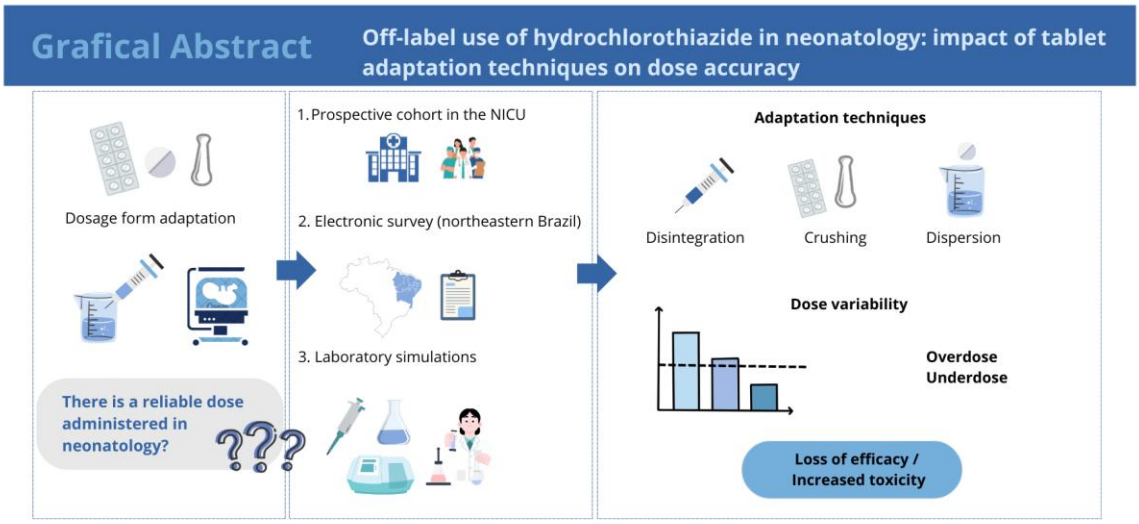
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Abstract

Purpose: To investigate the occurrence, preparation practices, and physicochemical characteristics of hydrochlorothiazide tablet adaptations performed in neonatal intensive care units (NICUs) in northeastern Brazil, aiming to characterize clinical manipulation practices and assess their potential implications for the quality, dose accuracy, stability, and safety of compounded preparations intended for neonatal use. **Methods:** A three-phase study was conducted comprising: (i) a prospective cohort in a NICU to determine the frequency of hydrochlorothiazide tablet adaptations among hospitalized neonates; (ii) a survey with NICU healthcare professionals to characterize routine manipulation practices and preparation techniques; and (iii) laboratory simulations reproducing the reported methods, followed by physicochemical characterization to evaluate preparation homogeneity and dose accuracy. **Results:** Among 300 hospitalized neonates, frequent hydrochlorothiazide tablet adaptations were identified, highlighting the widespread use of manipulated formulations in neonatal care. Three primary preparation techniques were reported: tablet dispersion, crushing, and disintegration. Experimental analyses demonstrated substantial variability among techniques, resulting in inconsistent drug distribution and clinically relevant differences in delivered doses. **Conclusion:** Hydrochlorothiazide tablet adaptations demonstrated poor homogeneity and considerable dose variability, potentially compromising therapeutic effectiveness and medication safety. These findings reinforce the need for standardized preparation protocols and the development of age-appropriate neonatal formulations.



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Keywords: Hydrochlorothiazide; Neonatal intensive care; Dosage form adaptations; Tablet manipulation; Dose accuracy.

Abbreviations

NICU Neonatal Intensive Care Units

HCTZ Hydrochlorothiazide

URFN Federal University of Rio Grande do Norte

Introduction

In neonatology, the off-label use of medicines is frequent, because most drugs do not have appropriate pediatric formulations. The scarcity of clinical studies in newborns limits the development of safe dosage forms, given that more than 90% of hospitalized neonates receive at least one drug prescribed off-label or unlicensed [1,2]. In this context, tablet manipulation is common practice for dose adjustments and alternative routes of administration, although it presents potential risks related to therapeutic efficacy and safety [3,4].

The development of specific formulations for neonatology is limited by the pharmaceutical industry's lack of interest, due to limited financial return and ethical and methodological barriers to conducting pediatric clinical trials [4]. Thus, many therapeutic needs remain without adequate alternatives, as in the case of hydrochlorothiazide (HCTZ), widely used in bronchopulmonary dysplasia and hypervolemia but without an available liquid pediatric formulation [5]. This gap leads to tablet adaptation, a procedure subject to significant dose variation and risk of adverse events [6,7].

Dosage form adaptations, also known internationally as compounding or customized compounding, are technical processes in which a commercially available dosage form is modified, combined, or recreated to alter dose, route of administration, flavor, excipients, or physical form, using techniques such as crushing, dilution, pulverization, disintegration, or tablet division. These adaptations are applied when no commercial product meets individual therapeutic needs due to dose, solubility, form, or formulation requirements [1,2,5].

The physiological characteristics of neonates—such as erratic oral absorption, immature hepatic metabolism, and reduced renal clearance—make pharmacokinetics and pharmacodynamics unpredictable [8,11]. Therefore, achieving exact doses is crucial, and obtaining them through tablet manipulation is a considerable pharmaceutical challenge [12]. Despite the extensive use of adapted medicines in neonatology, few studies describe and systematically evaluate the techniques employed; available literature focuses on clinical practice reports without methodological standardization or rigorous assessment of the impact of such adaptations on dose accuracy [13,14]. This gap is particularly relevant for HCTZ, whose oral use in neonates is frequent but without available liquid formulations [15].

Given this context, the present study aims to investigate the occurrence of HCTZ tablet adaptations in neonatal units, characterize the techniques used, and evaluate their accuracy under experimental conditions simulating real-world practice techniques.

Methodology

Study design, population, and sample

The study combined observational and experimental approaches in three complementary stages. First, a prospective cohort was conducted in the NICU of a teaching maternity hospital in Natal, northeastern Brazil (stage 1). Between May 2023 and February 2024, all neonates hospitalized for at least 24 hours who received any medication were included, excluding those readmitted or admitted only for diagnostic procedures. In parallel, nurses, nursing technicians, and pharmacists were interviewed regarding procedures, materials, and techniques used for adapting HCTZ tablets for neonatal administration.

The second stage consisted of a cross-sectional survey conducted between August 2024 and July 2025 with NICU professionals in all capitals of northeastern Brazil. An electronic questionnaire, based on techniques identified in stage 1, was applied to map methodological variations and document additional techniques.

The third stage, experimental in nature, was conducted in the Galenic Pharmacy Laboratory of the Pharmacy Department at the Federal University of Rio Grande do Norte (UFRN), Brazil. Tablets adaptation techniques identified in the previous stages were reproduced in the laboratory and preparations were evaluated for final hydrochlorothiazide concentration.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Maternidade Escola Januário Cicco (Opinion No. 7.029.609), in accordance with Brazilian Resolution 466/12. Informed consent was obtained from neonates' guardians and interviewed professionals.

Cohort with neonates and on-site interviews with professionals (Stage 01)

Neonatal admission characteristics included sex, gestational age, birth weight (g), admission diagnosis, NICU length of stay, Apgar score at 5 minutes, and prescribed medications.

The identification of adaptations was performed through analysis of electronic medical records, observing prescriptions of hydrochlorothiazide, whose only approved dosage form in Brazil is tablet. Professionals responsible for the adaptation were interviewed regarding materials and procedures. Demonstrations of described techniques were then requested.

Electronic survey with professionals in northeastern Brazil (Stage 02)

A questionnaire was developed from stage 01 findings to characterize tablets adaptation techniques used in NICUs. It targeted neonatal intensive care professionals in hospitals across northeastern Brazil. At least one institution with a NICU per capital was identified through a public database [16].

Professionals could participate after accessing the electronic form and consenting. The questionnaire collected sociodemographic data (age, sex), professional information (role, years of experience), and which techniques described in stage 01 they routinely used, with space for additional methods.

Laboratory simulation and evaluation of adaptation techniques (Stage 03)

HCTZ tables adaptation techniques identified in the previous stages were simulated in a laboratory setting, using the same hospital materials and diluents (Figure 1). The brand of HCTZ tablets used corresponded to the one most commonly employed in the institution from stage 01. Tablets of 25 mg were used, consistent with routine practice.

Preparations followed usual NICU doses (1–2 mg/kg/day; NeoFax® 2024). A theoretical concentration of 2.5 mg/mL was established by diluting one 25 mg tablet in 10 mL of double distilled water. Aliquots of 0.2 mL and 1.4 mL were withdrawn, representing neonates with 1,000 g and 3,500 g, respectively (10th and 90th percentiles) and administered through nasogastric tube.

Physicochemical characteristics analyzed included macroscopic appearance, and drug content. Drug content was quantified by ultraviolet spectrophotometry at 273 nm following pharmacopeia methodology (Anvisa, 2019) [17].

Statistical analysis

Descriptive statistics were applied in stages 01 and 02. Continuous variables were expressed as mean ± SD or median (IQR), and categorical variables as frequencies. The proportion of neonates requiring HCTZ tablet adaptation was calculated with a 95% CI.

For stage 03, inferential statistics assessed whether measured concentrations differed from the theoretical 2.5 mg/mL using Student's t test. Comparisons among techniques used ANOVA or Kruskal-Wallis depending on data normality. Significance was set at $p < 0.05$.

Results

During the study period of the first phase, between May 2023 and February 2024 a total of 533 newborns were admitted to the NICU of the teaching maternity hospital. After excluding 233 neonates who remained hospitalized for less than 24 hours, were readmitted during the study period, or did not receive any medication, the final sample consisted of 300 patients. The characteristics of the neonatal population at the reference institution are summarized in Table 1. The neonates had a mean gestational age of 33.8 ± 4.0 weeks and a mean birth weight of 2,142.1 ± 953.0 grams. The most common reason for admission was unspecified respiratory distress (67.5%; n = 197), and the NICU mortality rate was 7.9% (n = 23). Hydrochlorothiazide (HCTZ) was the medication most frequently requiring dose adjustment in the neonatal intensive care unit (NICU), accounting for 19.15% of cases, followed by Ursodeoxycholic acid (14.95%) and Methadone (13.06%).

Analysis of the interviews conducted with the NICU staff identified frequent adaptation of hydrochlorothiazide tablets due to the absence of a commercially available liquid formulation. Three distinct techniques for tablet adaptation were also identified (Table 2). The first technique, referred to as negative-pressure disintegration, involved fragmenting the tablet inside a 10-mL syringe using repeated aspiration and release movements in 10 mL of double distilled water. The second technique consisted of spontaneous dispersion of the tablet in double distilled water (10 mL) without any mechanical intervention. The third technique used crushing of the tablet by applying external compression directly onto the sealed blister, followed by transferring the resulting powder to a container with 10 mL of double distilled water. The resulting preparations were administered via enteral or nasogastric tube in volumes adjusted according to the prescribed dose. Descriptions of the techniques were obtained from interviews with the NICU's multidisciplinary team (neonatologist doctor, clinical pharmacist, nurse, and nursing technicians) during stage 1.

In the second phase, which included NICU professionals from all state capitals in northeastern Brazil, 23 professionals responded to the electronic questionnaire, with pharmacists representing the majority (60.6%) and an average of 8.9 years of professional experience in the field (Figure 1). Hydrochlorothiazide was reported as the second most frequently adapted drug (60.8%), second only to furosemide (65.2%), and followed by spironolactone (52.1%). Among the techniques used, disintegration was the most frequently mentioned (34.8%), followed by crushing (30.4%) and dispersion (21.7%); only 8.7% of professionals reported using unspecified alternative methods (Table 3). Notably, 86.9% of respondents used one or more of the three techniques, with minor variations in methodology and materials employed.

The third phase experimentally evaluated the adaptation techniques. In the laboratory simulations, doses were prepared considering a theoretical concentration of 2.5 mg/mL. When collecting the 0.2-mL volume—representative of the lowest neonatal weight range (very low birth weight)—it was observed that the disintegration technique resulted in overdosing at 3.6 ± 0.2 mg/mL (+43.3%), whereas spontaneous dispersion and crushing generated underdosing with concentrations 44% and 60.5% below the theoretical 2.5 mg/mL, respectively. For the 1.4-mL volume—representative of larger doses (appropriate birth weight)—all techniques produced concentrations below the expected value: 1.6 ± 0.4 mg/mL for disintegration (−37.9%), 1.5 ± 0.4 mg/mL for spontaneous dispersion (−39.5%), and 1.6 ± 0.3 mg/mL for crushing (−36.0%) (Figure 2).

Regarding organoleptic characteristics (Supplementary Figures 1, 2 and 3), the resulting adaptations exhibited a turbid appearance, white to slightly yellowish coloration, and visible particles, with a tendency to sediment during resting and adhere to the container surface.

Discussion

In this study with an observational and experimental approach, we identified that the adaptation of HCTZ tablets is commonly used in NICUs. However, the techniques are not standardized and usually utilize everyday hospital materials, such as plastic containers and syringes, for their execution. We identified three predominant techniques that result in concentrations significantly different from the expected value, with a significant risk of therapeutic ineffectiveness and toxicity.

Hydrochlorothiazide is known to be poorly soluble in water [18], a characteristic that justifies the inaccuracy of the obtained dose compared to the intended one across the evaluated techniques. In syringe disintegration, smaller volumes resulted in concentrations above the expected value because rapid sedimentation causes the particles to accumulate at the tip of the device; thus, when the first volume is aspirated, it contains the solid fraction richer in drug. Larger volumes encompass part of the diluted supernatant and also experience losses due to adhesion to the syringe walls and dead space, resulting in underdosing.

In crushing, although contamination risk is reduced because the tablet is crushed inside the blister, uniform underdosing was observed due to the rapid sedimentation of the reconstituted powder and adhesion to the container surfaces. In spontaneous dispersion, even with agitation before dosing, consistent underdosing was observed in both volumes, reflecting the low solubility of the molecule and rapid sedimentation that prevents complete homogenization, in addition to the increased contamination risk during preparation. These findings demonstrate that regardless of technique, hydrochlorothiazide's poor solubility compromises dose accuracy and reinforces the need for standardization and development of formulations appropriate for neonatal use.

In neonatology, HCTZ is commonly prescribed for the treatment of bronchopulmonary dysplasia [4]. However, incorrect doses can worsen clinical conditions. Underdosing—potentially resulting from manipulation losses or imprecise preparation—may lead to therapeutic failure, manifested by persistence of conditions that increase respiratory risk and compromise hemodynamic stability in this vulnerable population. Conversely, overdosing may cause serious complications, including electrolyte disturbances (hypokalemia, hyponatremia, hypochloremia, metabolic alkalosis, hypomagnesemia), dehydration, hypotension, and acute kidney injury due to hypovolemia [19].

In this context, validated and precise manipulation techniques must be adopted, with attention to excipient and vehicle selection, and continuous monitoring of clinical and laboratory parameters. Due to the unavailability of certain dosage forms, tablet adaptation for oral use is common in NICUs [20]. As observed in our findings, hydrochlorothiazide may be used for extended periods [21]. Despite this, pharmaceutical form adaptation for neonates and children remains a poorly explored topic in the literature. Brustugun et al. [22] evaluated the concentration of warfarin solutions prepared from tablet fragmentation and found that children may receive doses ranging from 69% to 134% of the recommended dose. Nguyen et al. [23] evaluated tablet crushing in NICUs and noted wide inter- and intra-operator variability in technique performance, in addition to final doses lower than intended. Regarding pediatric diuretic use, adaptations of spironolactone and hydrochlorothiazide tablets, capsules, and suspensions resulted in marked differences in intended concentration [24]. Recently, Desquines et al. [25] evaluated dose precision of spironolactone suspensions in pediatric intensive care environments and found that underdosing and variability persisted even after educational interventions.

Previous studies have evaluated drug content from different manipulation methods; however, we did not find investigations on the prevalence of tablet adaptation techniques in neonatology nor predominant techniques across a large region of a developing country. Another important aspect of the present study was replicating conditions similar to routine NICU practices using comparable devices and volumes. An exception was the study by Desquines et al. [25], in which drug quantification was performed using samples collected directly from the administration site.

To the best of our knowledge, this is the first study to investigate the frequency of HCTZ tablet adaptation, characterize techniques used across various northeastern Brazilian cities, and evaluate whether intended concentrations are achievable in conditions similar to actual clinical practice. Despite methodological differences and the different drugs evaluated in previous studies, there is consensus that tablet adaptation in NICUs frequently results in concentrations different from the intended dose.

Neonates present physiological characteristics that make pharmacokinetics unpredictable [26]. Enteral absorption is erratic due to higher gastric pH and reduced intestinal motility; distribution is affected by higher total body water, lower body fat, and hypoalbuminemia, increasing free drug fraction; and immature hepatic metabolism with broad interindividual variability prolongs half-life unpredictably [27]. In preterm infants, renal clearance is even more limited, and increased permeability of the blood–brain barrier favors neurotoxicity [28].

Additionally, low tolerance to excipients such as propylene glycol and the need for very small doses—often requiring manipulation or fractioning—further increase the risk of error and dose variability [29].

This study has limitations. The cohort was conducted in a single reference center, which may limit generalizability. The identification of techniques in other northeastern institutions relied on an electronic survey with a modest response rate, subject to selection and non-response bias. The experimental phase evaluated only HCTZ under specific conditions (tablet brand, double distilled water, volumes of 0.2 and 1.4 mL), without assessing additional vehicles, stability, or dose uniformity.

On the other hand, the study has important strengths: integrated methodologies (prospective cohort, multicenter survey, laboratory simulation), reproduction of real techniques using hospital materials, standardized volumes based on real NICU practice, and pharmacopeial methods. Mapping practices across all capitals in northeastern Brazil and reproducing techniques under controlled conditions confer pragmatic relevance and clinical applicability, contributing uniquely to understanding the impact of HCTZ tablet adaptation in neonatology.

Future clinical studies should systematically investigate the impact of dose variability on neonatal outcomes. It is also necessary to validate manipulation techniques for HCTZ and other neonatal-use drugs and promote development of standardized liquid formulations and neonatal-specific vehicles that ensure greater precision, stability, and safety.

The findings highlight the need to strengthen pharmacovigilance practices and standardize HCTZ tablet adaptation techniques. Public policies and regulations should encourage availability of pediatric formulations and validation of new manipulation methodologies. Establishing or expanding hospital compounding units is essential for safe manipulations, especially in developing countries.

Conclusion

Pharmaceutical adaptations of hydrochlorothiazide in neonatology are routine practices but result in significant variability in the administered dose. Hydrochlorothiazide has low water solubility, compromising dose accuracy in all evaluated techniques. Syringe disintegration showed variability due to heterogeneous sedimentation, while crushing and spontaneous dispersion consistently resulted in underdosing due to drug-poor supernatant and adsorption to surfaces.

Our findings demonstrate that none of the techniques guarantees adequate homogeneity, reinforcing the need for rigorous standardization and development of neonatal-specific formulations. The study also underscores the importance of future research aimed at validating adaptation techniques, creating innovative vehicles and standardized liquid formulations, and evaluating the clinical impact of dose variability on therapeutic efficacy and safety.

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Table 1 Characteristics of cohort population of the stage 01 of study (n=300)

Features	Values	
Gestational age, weeks (mean, SD)	33.8 ± 4.0	
Birth weight in grams (mean, SD)	2142.1 ± 953.0	
Female (n, %)	140	47.0 %
5-minute Apgar score < 7 (n, %)	16	5.3 %
Neonatal admission diagnosis - ICD-11 (n, %)		
Newborn respiratory distress, unspecified (P22.9)	230	76.6 %
Neonatal respiratory distress syndrome (P22.0)	11	3.8 %
Other respiratory discomforts in newborns (P22.8)	9	3.1 %
Cardiovascular disorder, unspecified (P29.9)	7	2.4 %
Days of hospitalization (median, IQR)	11.5	14.0
Mortality (n, %)	23	7.9 %
HCTZ tablets adaptation (n, %)	174	19.15%

SD: standard deviation; n, %: Absolute and relative frequency; IQR: interquartile range.

Table 02 Description of the techniques and materials usually used in the dosage form adaptation of hydrochlorothiazide tablets by neonatologists.

Technique	Materials used	Description
Disintegration by negative pressure in a syringe	1 HCTZ 25 mg tablet 20 mL syringe 1 AMP of double distilled water 10 mL 1 mL syringe Nasogastric tube No. 6	The intact tablet is placed inside a 20 mL syringe. The air is removed with the plunger and 5 mL of double distilled water is drawn up. The aspirating end is closed and the draw-and-release motion is performed, pulling the plunger to the other end of the syringe until the tablet is completely fragmented.
Spontaneous dispersion in solution	1 HCTZ 25 mg tablet Disposable plastic container 1 AMP of double distilled water 10 mL 1 mL syringe Nasogastric tube No. 6	The intact tablet is placed in a plastic container, then 10 mL of double distilled water is added, and it is left to stand for 5 minutes, until spontaneous dissolution occurs without mechanical intervention.
Crushing by compression in the blister pack	1 HCTZ 25 mg tablet Syringe plunger Disposable plastic container 1 AMP of double distilled water 10 mL 1 mL syringe Nasogastric tube No. 6	With the blister sealed, an external vertical mechanical force is applied, using a syringe plunger or pestle, so that the tablet is completely crushed. Then, the seal is broken and the crushed tablet is transferred to a plastic container and 10 mL of double distilled water is added.

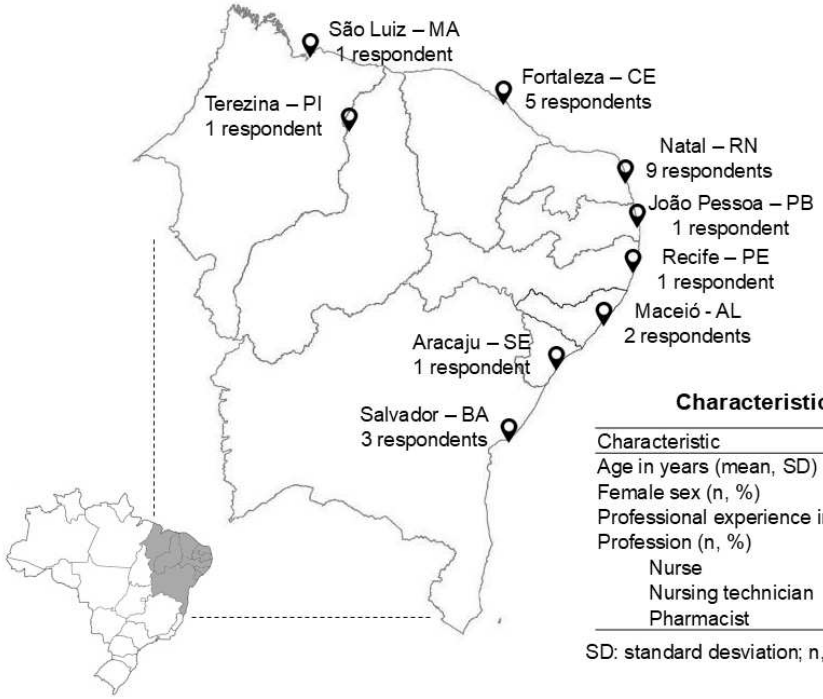
HCTZ: Hydrochlorothiazide; AMP: Ampoule.

Table 3 Profile of dosage form commonly adapted by respondents from hospitals in northeastern Brazil and the adaptation techniques used.

Adapted dosage form	n	%
Furosemide	15	65.2
Hydrochlorothiazide	14	60.8
Spironolactone	12	52.1
Captopril	11	47.8
Ursodeoxycholic acid	9	39.1
Methadone	9	39.1
Propranolol	6	26.0
Acetylsalicylic acid	4	17.3
Atenolol	3	13.0
Omeprazole	2	8.7
Lorazepam	2	8.7
Caffeine	1	4.3
Gabapentin	1	4.3
Levothyroxine	1	4.3
Clonidine	1	4.3
Sildenafil	1	4.3
Fluconazole	1	4.3
Pantoprazole	1	4.3
Adaptation techniques performed	**n**	**%**
Disintegration	8	34.8
Crushing	7	30.4
Dispersion	5	21.7
Others	2	8.7

n, %: Absolute and relative frequency

Fig. 1 Characteristics of intensivist professionals who adapt dosage forms in the different capitals of the Brazilian Northeast.

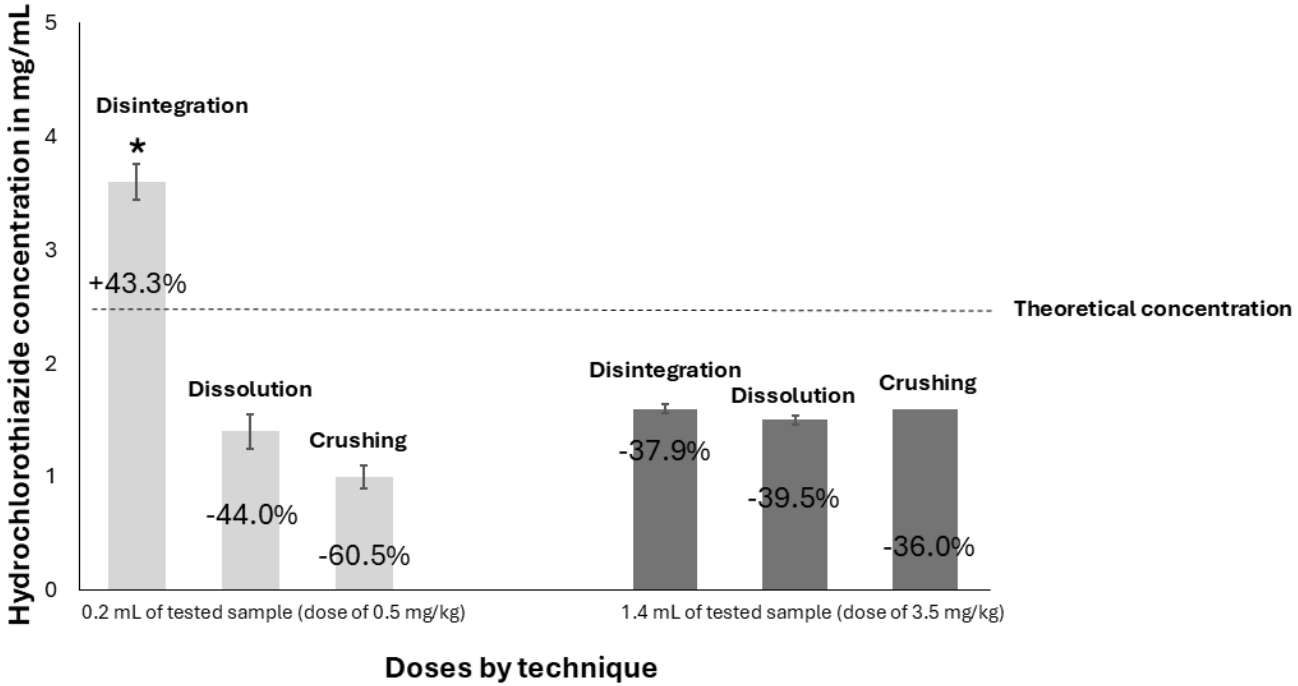


Characteristics of the respondents

Characteristic	Values
Age in years (mean, SD)	41.1 ± 12.0
Female sex (n, %)	11 (84.6%)
Professional experience in years (mean, SD)	8.5 ± 6.8
Profession (n, %)	
Nurse	11 (84.6%)
Nursing technician	11 (84.6%)
Pharmacist	11 (84.6%)

SD: standard desviation; n, %: Absolute and relative frequency

Fig. 2 Techniques for adapting of the hydrochlorothiazide tablets



HCTZ tablet adaptation techniques. The percentages represent the overdose (+) and underdose (-) relative to the theorical HCTZ concentration.

*$p<0.05$ compared to the other groups. The concentrations of all groups were statistically different from the target concentrations of 0.5 and 3.5 mg/kg (one-sample t-test, $p<0.05$)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.tiff
- SupplementaryFigure2.tiff
- SupplementaryFigure3.tiff