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Original Article

Evaluation of Dosage and Stability of Drugs Prepared by Modification of Commercial Drugs for Administration to Patients in Pediatrics Clinic

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ABSTRACT

Objective: The aim of this study was to assess whether nurses, when modifying commercial solid dosage forms (crushing and suspending), successfully provide targeted doses.

Methods: This solely in vitro study involved no pediatric patients. To examine the impact of drug modification techniques performed by 3 different nurses on the targeted dose administered, these nurses were instructed to prepare targeted drug doses from tablets and capsules, mimicking their routine practices in the pediatric clinic. Three commonly utilized commercial solid dosage forms (2 tablets and 1 capsule), containing levothyroxine sodium, spironolactone, or lansoprazole, were selected. In this study, we crushed the tablet, suspended the powder in isotonic saline solution (0.9% sodium chloride solution), mixed tablets directly with isotonic saline solution to allow dispersion, and opened the capsule to mix its content (the enteric-coated lansoprazole micropellets) with isotonic saline solution. Following drug modification, samples were extracted from the dispersions prepared by the nurses and analyzed using a high-performance liquid chromatography method.

Results: Crushing the tablet, immersing the tablet into the liquid to allow dispersion, and opening the capsule to dilute its content in isotonic saline solution resulted in under-dosing (in the range of relative error: −1.597% to −76.030%) or over-dosing (in the range of relative error: 0.893% to 43.041%) of the targeted drug doses. Furthermore, it was determined that the nurses incorrectly modified the capsule containing the enteric-coated-lansoprazole micropellets.

Conclusion: We observed that these nurses lack any electronic or printed resources for modifying solid dosage forms, and their knowledge on the subject is insufficient. Solutions may include developing age-appropriate doses or dosage forms, creating electronic and printed resources to guide solid dosage form modifications for pediatric clinic nurses, educating nurses on drug modification/resource use, and consulting a pharmacist about the safety of opening capsules or crushing tablets. If feasible, a pharmacist should perform these modifications to solid dosage forms.

Keywords: Crushing, drug modification, medical, pediatric clinic, HPLC, suspending

Introduction

Patient safety stands at the core of healthcare service systems. Inevitably, these services carry some risks to patient safety and health, including medication errors, a significant threat to healthcare systems.[1] Medication errors are defined as "any preventable event occurring in the medication ordering or delivery process, regardless of the occurrence or potential for injury."[2] These errors result from human mistakes or system flaws.[2] Hospitalized infants and children are particularly susceptible to medication-related errors due to factors such as organ maturity, body surface, and weight. Differences in the pharmacodynamic and pharmacokinetic properties and toxic profiles in the pediatric population further heighten the risk of medication errors in pediatric clinics. Thus, the dosage administered to pediatric patients must account for variables such as age, body weight, and body surface area.[3] The incidence of pediatric medication errors is challenging to determine, leading to a range of reported values. For example, some studies indicate an incidence of 1 in 20 medication orders,[3] while others report 1 in 6.4 medication orders.[2] Errors can occur at any stage of the medication process, including drug selection, ordering, transcription, modification, and administration. Among pediatric patients, the most common errors typically involve inaccurate dosing, dose calculation errors, and incorrect dosage intervals.[2] In pediatric hospital

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units, healthcare professionals often struggle to administer solid dosage forms like tablets due to the lack of commercially available, age-appropriate doses for pediatric patients, coupled with swallowing issues in younger children. Since dosage forms are generally designed for adults, existing forms need modification to obtain suitable pediatric doses. These modifications, such as splitting, breaking, or cutting the tablet, or dispersing the crushed tablet's powder in liquid/food, or opening capsules to disperse their contents in liquid/food, carry several risks potentially leading to adverse outcomes.[4-8] For instance, Van Riet-Nales et al[9] found that techniques for splitting tablets to achieve lower doses can result in inaccuracies. Moreover, some drugs' stability might be compromised during the tablet-crushing or capsule-opening processes, particularly for enteric- or film-coated solid dosage forms.[6] Besides, solid dosage forms may have a coating that masks the unpleasant taste of drugs or reduces the irritating effect of some drugs on the gastrointestinal mucosa. Modifying the dosage forms containing drugs with unpleasant taste makes it difficult for children to take these drugs. In this situation, to mask the unpleasant taste, crushed/opened medications are often dispersed in a food vehicle (juice, jam, yogurt, honey, applesauce, etc.) to facilitate medication administration. This administration can affect drug absorption and stability due to possible chemical incompatibilities with the pH of the vehicle or drug molecule chelation.[6,10,11]

Drug loss during the crushing process (e.g., due to powder remaining in the mortar/container) and contamination of drug particles remaining in unclean containers are also a concern. Therefore, patients may receive reduced and variable doses and experience adverse effects.[6]

This study aimed to evaluate whether nurses, through modification (crushing and suspending) of 3 commercial drugs (2 tablets and 1 capsule commonly used in a pediatric clinic) containing levothyroxine sodium (LS), spironolactone (SP), and lansoprazole (LP), could provide the targeted doses. Additionally, the study examined whether there were any changes in the drugs' stability under the clinic's storage conditions until administered to pediatric patients. The nurses were asked to perform the drug modifications as part of their routine practice, replicating all steps (such as storage conditions and duration if the drugs were not immediately administered post-preparation).

Methods

Materials

High-performance liquid chromatography (HPLC)-grade methanol was procured from Merck (Darmstadt, Germany), and trifluoroacetic acid was obtained from Sigma-Aldrich (Darmstadt, Germany). Ultrapure water was produced using the Thermo Scientific™, Barnstead™, and MicroPure™ water purification system (Waltham, Mass, USA). Two tablets that contained LS (Levotiron®, 100 mcg; Abdi İbrahim İlaç San. ve Tic. A.Ş.) and SP (Aldactone®, 100 mg; Ali Raif İlaç Sanayi A.Ş.) as active substances, and 1 capsule that contained LP as the active substance (Lansor®, 30 mg; SANOVEL İlaç San. ve Tic. A.Ş.), which are extensively used in pediatrics, were obtained commercially. All chemicals/solvents used were of analytical grade/HPLC grade.

Methods

This study is classified as an in vitro study.

The Analysis of Lansoprazole, Spironolactone, and Levothyroxine Sodium

The quantitative analysis of LP, SP, and LS in samples that were prepared by 3 nurses with modifications to the commercial tablets/capsules was performed using a Shimadzu Prominence CBM-20A series HPLC system (Shimadzu, Kyoto, Japan), which consisted of a degasser unit (DGU-20A5R), column oven (CTO-10ASVP), and diode array detector (SPD-M20A). The HPLC conditions employed for this study are described in Table 1. The standard stock solution of each active substance was prepared in methanol (for SP or LP) or a mixture of ultrapure water with 0.02 M NaOH and methanol (1:1 v/v) (for LS) at concentrations of 50 µg/mL of LS, 1000 µg/mL of SP, and 300 µg/mL of LP.

The HPLC analysis methods were validated for the following parameters: specificity, linearity, sensitivity [the limit of detection (LOD) and the limit of quantitation (LOQ)], accuracy, and precision, according to the International Conference on Harmonization Q2 (R1) guideline.[12] The specificity parameter of the analytical method, which is the ability to distinguish an analyte's response from the responses of other components in samples, was evaluated by examining the chromatograms obtained to confirm the absence of interfering peaks. For the linearity parameter, the stock solution of each active substance was diluted by using methanol (for SP or LP) or the mixture of ultrapure water with 0.02 M NaOH and methanol (1:1 v/v) (for LS) to prepare the working standard solutions in the concentration range of 1-100 µg/mL for SP and LP, and 0.5-20 µg/mL for LS. The working standard solutions at different concentrations were injected into HPLC in 3 individual replicates. For sensitivity parameters of the HPLC method, the LOD and LOQ values were calculated from the obtained calibration curves for LS, SP, and LP. Intra- and inter-day accuracy [expressed as percentage relative error (RE%)] and precision [expressed as percentage relative standard deviation (RSD%)] were determined by the assay of freshly prepared quality control solutions at 3 different concentrations [5, 25, and 75 µg/mL for LP and SP in methanol; 1, 5, and 10 µg/mL for LS in ultrapure water with 0.02 M NaOH:methanol (1:1 v/v)].

The Preparation of the Targeted Doses of Lansoprazole, Spironolactone, and Levothyroxine Sodium

To assess the impact of drug modification methods performed by 3 different nurses on the targeted dose administered to the patient, the nurses were asked to prepare the targeted doses of drugs from the tablets or capsules in the manner they routinely prepare in a pediatric clinic.

Table 1. Optimized Operating Conditions for HPLC analysis of LS, SP, and LP

Parameter	Conditions for LP	Conditions for SP	Conditions for LS
Column	ODS-3 C18 (5 µm, 4.6 × 250 mm)	ODS-3 C18 (5 µm, 4.6 × 250 mm)	ODS-3 C18 (5 µm, 4.6 × 150 mm)
Detector	DAD	DAD	DAD
Wavelength (nm)	285	239	225
Mobile phase	Water:methanol (30:70 v/v) with 0.05% TFA	Water:methanol (20:80 v/v) with 0.05% TFA	Water:methanol (35:65 v/v) with 0.05% TFA
Temperature of column	20ºC	20ºC	20ºC
Flow rate (mL/min)	1	1	1
Pump mode	Isocratic	Isocratic	Isocratic
Injection volume (µL)	10	10	20

HPLC, high-performance liquid chromatography; LP, lansoprazole; LS, levothyroxine sodium; SP, spironolactone.

For LP, each nurse carefully removed the capsule cap from the capsule body and directly transferred its contents (the micropellets containing LP) into a syringe barrel, to which isotonic saline solution (ISS) (the measured pH for ISS: 6) was added to obtain the target dose. After the addition, this dispersion was left at room temperature for 6 hours to dissolve the micropellets containing LP under fluorescent light. At the end of this period, the dispersion was shaken, and the samples (n = 3/nurse; total n = 9) were collected.

For SP, nurse 1 crushed a tablet of SP inside a plastic bag, and then carefully transferred the powder directly into a syringe barrel, to which ISS (pH 6) was added to obtain the target dose. The dispersion was shaken, and samples (n = 3) were collected. Conversely, the other 2 nurses put the tablet directly into the syringe barrel containing ISS (pH 6) and let it disperse to obtain the target dose, and then collected samples (n = 6/2 nurses) from the shaking dispersions.

For LS, all 3 nurses placed each tablet containing LS directly into the syringe barrel containing ISS (pH 6) and let it disperse to achieve the target dose, after which they collected samples (n = 3/nurse; total n = 9) from the shaking dispersions.

After preparation, these mixtures in the syringe were indicated to contain LS (the targeted dose: 40 µg), SP (the targeted dose: 30 mg), or LP (the targeted dose: 10 mg) prepared by different nurses and were then diluted to a concentration of 5 µg/mL (for LS) or 25 µg/mL (for SP and LP) in ultrapure water with 0.02 M NaOH and methanol (1:1 v/v) for LS or in methanol for SP or LP. The mixtures were degassed for 30 minutes, and after filtration on a Millipore filter, the resulting solutions were analyzed by the validated HPLC method.

Data Analysis

The statistical analyses were conducted using Statistical Package for the Social Sciences Version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). The results obtained were expressed as mean ± SD or RSD%, and the "Mann–Whitney *U*-test" was employed to evaluate the statistical significance of the difference between the targeted dose and the dose of the prepared drug (a *P*-value less than .05 was considered to indicate a significant difference).

Ethical Considerations

This research obtained ethics approval from the Ataturk University Ethics Committee of Medicine Faculty Clinical Research (date: December 17,2020, decision no: B.30.2.ATA.0.01.00/11) and board approval from the University Hospital (date: February 8,2021, decision no: E.2100038192). All nurses who participated in the research provided both written and oral consent prior to their admission. This study is purely in vitro, and no application has been made to pediatric patients.

Results

The literature contains numerous studies focused on the accurate and reliable analysis of LP[13-15], SP[16,17], and LS[18,19] using the HPLC method. These compounds are widely analyzed in various fields, such as pharmaceutical manufacturing for quality control purposes, stability studies, and bioavailability studies. In this study, we first developed and validated HPLC methods for analyzing LP, SP, and LS in samples prepared by nurses from commercial tablets/capsules. We determined the optimal chromatographic conditions to ensure the robust performance of the analytical method. An examination of the obtained chromatograms revealed that the retention times of LP, SP, and LS were 3.9 minutes, 5.27 minutes, and 5.97 minutes, respectively. The calibration curves for LP, SP, and LS were constructed by plotting the concentration of the active substance (µg/mL) versus the peak area (mAu), as shown in Figure 1A, Figure 2A, Figure3A and Table 2. The representative HPLC chromatograms for LP, SP, and LS in standard solutions are displayed in Figure 1B, Figure 2B, Figure-3B.

The results of intra- and inter-day accuracy, which signifies the proximity of the observed value in an experiment to the actual value[20], and precision, which signifies the level of agreement between measured

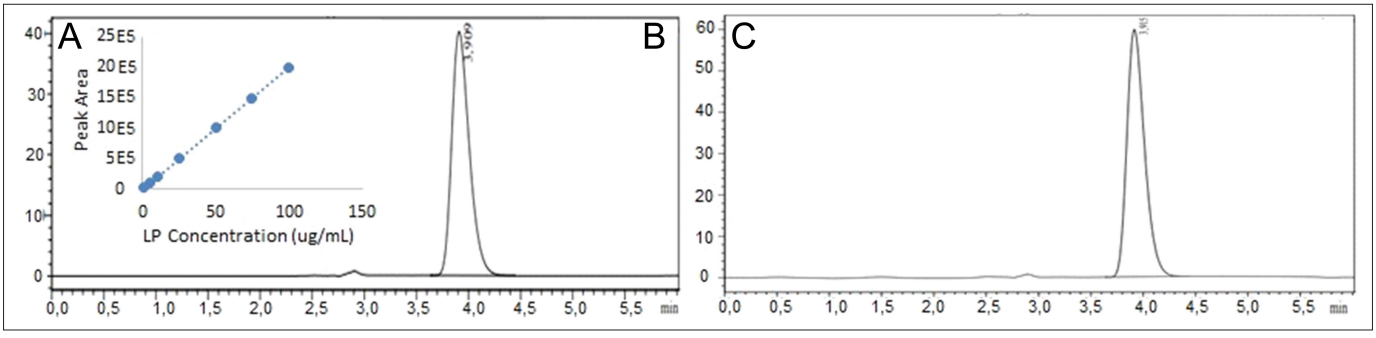

Figure 1. The calibration curve (A: 1, 5, 10, 25, 50, 75, and 100 µg/mL) and representative HPLC chromatograms for LP in standard solution (B: 25 µg/mL) and drug samples (C: 25 µg/mL). HPLC, high-performance liquid chromatography; LP, lansoprazole.

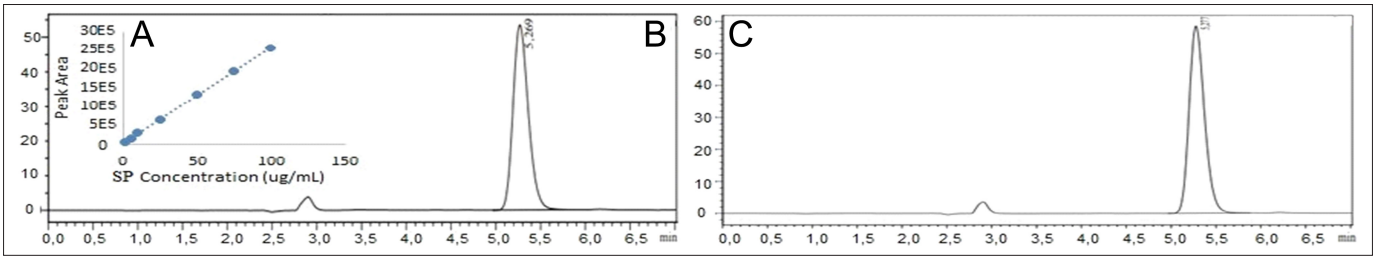

Figure 2. The calibration curve (A: 1, 5, 10, 25, 50, 75, and 100 µg/mL) and representative HPLC chromatograms for SP in standard solution (B: 25 µg/mL) and drug samples (C: 25 µg/mL). HPLC, high-performance liquid chromatography; SP, spironolactone.

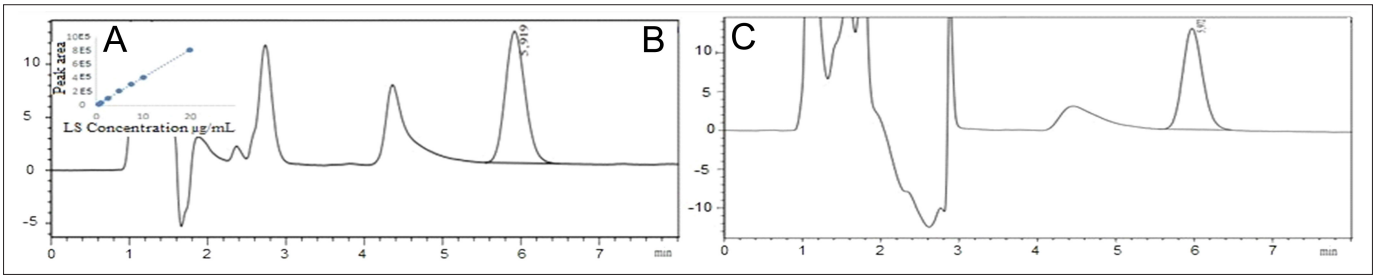

Figure 3. The calibration curve (A: 0.5,1, 2.5, 5, 7.5, 10, and 20 µg/mL) and representative HPLC chromatograms for LS in standard solution (B: 5 µg/mL) and drug samples (C: 5 µg/mL). HPLC, high-performance liquid chromatography; LS, levothyroxine sodium.

Table 2. Statistical Data of Calibration Curves of LP, SP, and LS (n = 3)

Parameters	For LP	For SP	For LS
Linearity range (µg/mL)	1-100	1-100	0.5-20
Regression equation	$y = 19881x + 3336.4$	$y = 25547x + 17763$	$y = 40729x + 5457.8$
S_a	1147.5	221.27	363.65
S_b	33.50	21.57	292.43
Correlation coefficient (R^2)	0.9998	0.9999	0.9998

LP, lansoprazole; LS, levothyroxine sodium; S_a, standard deviation of the intercept; S_b, SD of the slope; SP, spironolactone; x, concentration of active substance; y, peak area.

quantity values obtained by a series of measurements under specified conditions[21], of HPLC methods developed for active substances, are provided in Table 3.

The intra-day and inter-day accuracy and precision of the HPLC methods for LP, SP, and LS were appropriate (RE is <±2% and RSD% is <2% for the in vitro conditions).[22]

The lowest concentrations of the standard solutions of LP, SP, or LS under optimized chromatographic conditions were injected into the HPLC system, and the values for LOD and LOQ were found to be 0.021 µg/mL and 0.072 µg/mL for LP, 0.025 µg/mL and 0.086 µg/mL for SP, and 0.026 µg/mL and 0.089 µg/mL for LS, respectively.

The drug samples prepared by the nurses were analyzed using the validated HPLC methods, and the results, along with representative chromatograms, are presented in Table 4 and Figure 1C, Figure 2C, Figure-3C, respectively.

The stability of the drugs prepared by the nurses was also assessed. The nurses reported that they stored the drugs they prepared from commercial tablets/capsules in a refrigerator for a maximum of 24 hours until the drugs were administered to the patient. Therefore, the drug samples prepared by nurses (10 mg of dose for LP, n = 3; 30 mg of dose for SP, n = 3; 40 µg of dose for LS) were analyzed at 0 hour by HPLC (comparison samples). The drug samples were then stored at +4°C for 12 and 24 hours and analyzed by HPLC at the end of these periods. The percentage recoveries for 12 and 24 hours for the drug samples are provided in Table 5. The drug content in the samples must be within 95%-105% of the specification during the storage period.[23] The recovery values obtained for LP, SP, and LS in the samples were all within the content limits of 95%-105% (Table 5), thus demonstrating that the samples remained stable for 12 and 24 hours at +4°C.

Discussion

In pediatric clinics, the manipulation of dosage forms becomes necessary when suitable forms or doses for pediatric patients are not available, or when infants or children are unable to swallow.[5] In this

Table 3. The Results of Intra- and Inter-Day Accuracy (as RE%) and Precision (as RSD%)

		Added Concentration (µg/mL)	Found Concentration (Mean ± SD; n = 6) (µg/mL)	RE%	RSD%
LP	Intra-day	5	4.945 ± 0.058	−1.093	1.186
		25	24.045 ± 0.359	0.182	1.436
		75	75.056 ± 0.808	0.074	1.076
	Inter-day	5	4.935 ± 0.057	−1.284	1.166
		25	25.063 ± 0.176	0.253	0.706
		75	75.300 ± 0.553	0.401	0.735
SP	Intra-day	5	5.028 ± 0.041	0.566	0.808
		25	24.929 ± 0.202	−0.282	0.809
		75	75.050 ± 0.217	0.067	0.290
	Inter-day	5	5.097 ± 0.101	1.974	1.198
		25	24.884 ± 0.282	−0.462	1.133
		75	75.066 ± 0.319	0.088	0.426
LS	Intra-day	1	0.992 ± 0.016	−0.792	1.612
		5	5.022 ± 0.092	0.436	1.833
		10	10.010 ± 0.056	0.100	0.556
	Inter-day	1	0.994 ± 0.018	−0.563	1.811
		5	5.099 ± 0.082	1.987	1.608
		10	10.064 ± 0.105	0.639	1.045

LP, lansoprazole; LS, levothyroxine sodium; RE%, percentage relative error; RSD%, percentage relative standard deviation; SP, spironolactone.

Table 4. The Amount Assay of LP, SP, and LS in the Drug Samples Prepared from Commercial Tablets/a Capsule by 3 Nurses, Using the HPLC Method

Active Substances	The Targeted Dose	Nurses	Sample	Found Dose (mg or μg) Mean ± SD* (RSD%)	RE%
LP	**10 mg**	1	1	9.334 ± 0.461 (4.94)	−6.658
			2	8.059 ± 0.300 (3.73)	−19.401
			3	9.32 ± 0.216 (2.32)	−6.804
		2	1	8.123 ± 0.283 (3.49)	−18.768
			2	9.037 ± 0.266 (2.94)	−9.629
			3	8.288 ± 0.251 (3.03)	−17.113
		3	1	2.309 ± 0.07 (3.21)	−76.030
			2	8.468 ± 0.298 (3.52)	−15.313
			3	14.304 ± 0.009 (0.06%)	43.041
SP	**30 mg**	1	1	28.203 ± 0.141 (0.498%)	−5.989
			2	15.786 ± 0.037 (0.235%)	−47.381
			3	9.172 ± 0.043 (0.472%)	−69.428
		2	1	31.585 ± 0.017 (0.053%)	5.284
			2	14.961 ± 0.004 (0.025%)	−50.131
			3	30.378 ± 0.214 (0.703%)	1.261
		3	1	38.596 ± 0.134 (0.348%)	28.655
			2	21.330 ± 0.051 (0.239%)	−28.900
			3	19.594 ± 0.091 (0.494%)	−34.688
LS	**40 μg**	1	1	43.925 ± 1.243 (2.830%)	9.813
			2	40.357 ± 0.908 (2.249%)	0.893
			3	39.361 ± 0.507 (1.289%)	−1.597
		2	1	29.520 ± 0.153 (0.517%)	−26.200
			2	28.189 ± 0.289 (1.024%)	−29.527
			3	28.901 ± 0.428 (1.482%)	−27.747
		3	1	51.152 ± 1.018 (1.990%)	27.880
			2	45.179 ± 0.398 (0.882%)	12.947
			3	42.717 ± 0.759 (1.777%)	6.793

LP, lansoprazole; SP, spironolactone; LS, levothyroxine sodium; HPLC, high-performance liquid chromatography; RE, relative error; RSD, relative standard deviation; RSD%, percentage relative standard deviation.
*Each analysis was repeated 3 times.

Table 5. The Percentage of Recoveries and RSD Values to Evaluate the Stability of the Drug Samples Prepared by Nurses

Storage Temperature	Drug	Nurse	Sample	12 Hours (Recovery% ± SD)*	24 Hours (Recovery% ± SD)*
+4 ºC	LP	1	1	95.459 ± 0.196	95.874 ± 1.403
			2	95.385 ± 0.751	98.855 ± 0.467
			3	95.454 ± 2.436	95.113 ± 0.536
		2	1	104.679 ± 0.333	103.265 ± 2.130
			2	102.934 ± 1.326	99.858 ± 2.237
			3	100.330 ± 2.170	101.515 ± 2.148
		3	1	98.431 ± 1.855	101.948 ± 1.130
			2	97.497 ± 2.012	102.637 ± 2.223
			3	103.792 ± 2.002	101.216 ± 0.616
	SP	1	1	98.994 ± 2.202	99.955 ± 0.171
			2	102.020 ± 0.099	102.296 ± 0.052
			3	99.429 ± 0.435	97.758 ± 0.251
		2	1	99.946 ± 0.294	97.884 ± 0.144
			2	96.650 ± 0.406	98.607 ± 0.253
			3	99.247 ± 0.105	101.032 ± 0.162
		3	1	97.165 ± 0.532	98.959 ± 0.057
			2	101.033 ± 0.143	102.872 ± 1.740
			3	100.423 ± 1.257	102.944 ± 0.246
	LS	1	1	101.952 ± 1.325	98.082 ± 2.392
			2	99.220 ± 1.351	100.125 ± 1.884
			3	96.877 ± 1.553	97.904 ± 1.567
		2	1	98.040 ± 0.230	102.132 ± 2.397
			2	98.013 ± 2.822	98.547 ± 0.130
			3	99.262 ± 1.415	98.348 ± 1.436
		3	1	100.860 ± 1.399	100.537 ± 0.668
			2	101.743 ± 1.474	101.631 ± 0.670
			3	97.509 ± 1.016	99.413 ± 2.293

LP, lansoprazole; LS, levothyroxine sodium; SP, spironolactone.
*Each analysis was repeated 3 times.

study, 3 commercial drugs (2 tablets containing LS or SP and 1 capsule containing LP micropellets), frequently used in pediatric clinics, were selected to evaluate whether the targeted doses were achieved. The processes of crushing and diluting the tablets or powders, or opening the capsule and diluting its contents, were performed to attain the targeted doses.

Levothyroxine sodium, a synthetic T4 hormone akin to the endogenous hormone produced by the thyroid gland, is slightly soluble in water and dissolves in dilute alkali hydroxide solutions. It is shielded from light and stored at 2°C-8°C in an airtight container.[24] Levothyroxine sodium is a thyroid hormone used in the treatment of hypothyroidism[24] and other conditions such as euthyroid goiters, including subacute or chronic lymphocytic thyroiditis, thyroid nodules, and multinodular goiter.[25] Various formulations (tablet, soft gel capsule, and liquid formulations) containing levothyroxine are available for oral administration. The conventional tablet formulation contains LS. Soft gel and liquid formulations of levothyroxine are available in the USA and/or Europe. These formulations, containing lower doses of levothyroxine, are preferable because the disintegration of the tablets does not need to occur before the levothyroxine is available for absorption from the gastrointestinal system. The use of soft gel and liquid formulations is apt for patients with reduced levothyroxine intestinal absorption due to concurrent medications or gastrointestinal disorders.[26] Liquid formulations are particularly suitable in terms of administration to pediatric patients and dosage adjustment. Unfortunately, in Turkey, only tablet formulations containing LS (25 µg-0.1 mg) are available, necessitating drug modification to administer appropriate doses to pediatric patients. Levothyroxine's absorption from the gastrointestinal system increases in the fasted state following oral administration. For hypothyroidism, initial oral doses of LS are 50-100 µg daily for adults and children aged 12-18 years, 10-15 µg/kg once daily for neonates, and 5-10 µg/kg once daily for children aged 1 month-12 years.[24] The sodium salt enhances the absorption of levothyroxine from the gastrointestinal system.[27] The prepared drug should be administered immediately to pediatric patients after tablets containing LS are crushed and suspended in suitable mediums such as water or breast milk. The remaining portion should not be stored.

Lansoprazole is practically insoluble in water and is stored in airtight containers and protected from light. Lansoprazole is rapidly absorbed after oral doses, with its bioavailability being 80% or more, even with the first dose. Lansoprazole must be given in enteric-coated dosage forms as it is unstable at acidic pH. The absorption of LP is slow in the presence of food, and its bioavailability is reduced by about 50%.[24] Lansoprazole is a proton pump inhibitor used in treating peptic ulcer disease and in other conditions where inhibition of gastric acid secretion might be beneficial. It inactivates the final step in gastric acid secretion in a dose-dependent manner.[28] Lansoprazole is generally administered orally as dispersible tablets, capsules, or suspensions containing enteric-coated granules. In the short-term treatment of symptomatic gastroesophageal reflux disease and erosive esophagitis, LP may be given to children weighing 30 kg or less in doses of 15 mg once daily. Those weighing more than 30 kg are given 30 mg once daily, for up to 12 weeks.[24,29] The suspension formulation is not available. The capsule, which contains enteric-coated micropellets of LP, is opened, and its content can be mixed with a small amount of fruit juice (such as apple juice) and immediately swallowed because LP is acid labile. The enteric-coated micropellets of LP pass through the stomach, and the coating dissolves as LP is absorbed.[28]

Spironolactone is practically insoluble in water. It is well absorbed from the gastrointestinal tract, with a bioavailability of approximately 90%. Spironolactone, a steroid lactone with a structure resembling the natural adrenocortical hormone aldosterone, is used to treat high blood pressure, edema, and heart failure. Suggested doses of SP for children range from 1 to 3 mg/kg daily (in divided doses). There was no significant loss of SP from extemporaneously prepared suspensions of SP in a cherry syrup (2.5, 5, and 10 mg/mL) after storage for 2 weeks at 5°C or at room temperature under intense fluorescent light.[24] Degradation was less than 5% for samples stored for 4 weeks but was more noticeable in suspensions with a higher initial concentration.[24]

Levothyroxine sodium and LP should be protected from light.[24] However, in our study, it was observed that nurses overlooked this while preparing the medications. They performed the drug modifications under fluorescent light. Moreover, as previously mentioned, LP is unstable at acidic pH. In our study, the practice of keeping the enteric-coated micropellets of LP in ISS (pH 6) for 6 hours caused the enteric coating to dissolve. When the drug prepared in this way is administered orally to pediatric patients, the degradation of LP in the stomach will accelerate. Therefore, the enteric-coated micropellets of LP should be dispersed in a small amount of fruit juice (such as apple juice) and administered immediately to the pediatric patient to maintain the stability of LP in the stomach. The enteric coating should be preserved.

Crushing some solid dosage forms (especially controlled-release tablets, enteric-coated dosage forms, etc.) can alter the drug's efficacy and safety parameters, with clinically significant consequences. Crushing enteric-coated tablets or opening enteric-coated capsules eliminates the enteric coating that protects the drugs from stomach acid, thereby reducing the stability, absorption, and efficacy of the drug.[6]

A significant limitation of the practice of crushing tablets/opening capsules, diluting, and administering parts of the dose is the high variability in the dose administered to pediatric patients. In our study, this situation was observed, and it was determined that the doses of the drugs were detected below and above the targeted dose for administration to pediatric patients (Table 4). Crushing the tablet/placing the tablet directly into the liquid and waiting for dispersion/opening the capsule and diluting its content in ISS resulted in either less (in the range of RE: −1.597 to −76.030%) or more (in the range of RE: 0.893%-43.041%) drug doses than the targeted drug doses (Table 4). The RE% in the doses depended on the drug, the method of preparation used during drug modification, and the nurse who performed the drug modification.

In this study, HPLC methods were developed and validated for the assay of active substances in these 3 commercial drugs. In previous studies, the analyses of LP[13-15], SP[16,17] and LS[18,19] were performed using a C18 column with different mobile phases. The choice of the mobile phase is crucial in HPLC analysis as it directly affects the separation and elution of the target compounds. Different mobile phases, such as aqueous buffers, organic solvents or their combinations, have been studied to optimize the separation and achieve the desired results. In our research, a C18 column was also used for the HPLC analyses of LP, SP, and LS. However, it was decided to use different mobile phases (Table 1) than those used in previous studies.[13-19] The selection of the mobile phase was based on several considerations, including the solubility of the target compounds, chromatographic efficiency, and compatibility with the detection method. The nurses performed the modification of these commercial drugs, and then the obtained samples were analyzed using HPLC to determine the amount of active substances. As a result of the analysis, it was determined that the drug samples prepared by the nurses showed significant differences from the targeted doses [$P < .05$ for LS (except for LS prepared by nurses 1); $P < .05$ for SP (except for SP prepared by nurses 2 and 3); $P < .05$ for LP (except for LP prepared by nurse 3)]. During this study, it was observed

that these nurses did not follow any resources to guide solid dosage form modification when preparing these 3 drugs from commercial tablets/capsules. Therefore, they used different preparation methods to modify the same drug (especially LS and SP). Both printed and electronic resources should be prepared to guide dosage form modification for nursing staff to prevent this situation.

Similarly, Mercovich et al[6] observed the modification of solid dosage forms in aged care facilities. They evaluated the types of resources available to nurses to guide dosage form modification and whether the staff used the resources appropriately. They stated that both printed and electronic sources were available for nursing staff; however, none of the 6 different nurses' 6 different resources were used in practice for the observed drug modifications. It was also reported that all drug carts contained guidelines on the dosage forms that should not be crushed, but there was a lack of training for nurses on how to find and use these resources.[6]

Another study on drug modification was performed in a pediatric hospital by Nguyen et al.[5] The effect of crushing the tablets, which contain warfarin or hydrocortisone or amiodarone or captopril, and suspending the resulting powder in purified water in terms of the targeted dose was evaluated.[5] They found that due to suspending the powder obtained after crushing tablets in water, drug loss ranged from 5.6% to 19.7% for warfarin, 0.1% to 5.5% for captopril, 5.0% to 30.7% for hydrocortisone, and 18.9% to 30.5% for amiodarone. The results indicated that the tablet-crushing practice was insufficient to administer the drugs' correct doses to pediatric patients. Therefore, the authors recommended that the nurse first contact the hospital pharmacist to prepare an oral liquid dosage form suitable for the pediatric patient. However, if this option is not possible, it was stated that the nurse should first confirm whether the tablet is suitable for crushing from the related database before drug modification.[5]

A study was conducted to investigate the accuracy and precision of the method in which it was manipulated by splitting different types of aspirin tablets (dispersible, conventional, and chewing tablets) into half and quarter fragments and the dispersing of the fragments in a small volume of liquid in an oral syringe to obtain a fraction as a dose. It was observed that the recovered amount of the drug was more than 90% for the 4 manipulated tablet types in the presence of a rinsing step.[30]

In another study, it was shown that the cutting of nifedipine-containing modified-release tablets using the cutter did not produce quarters or half tablets, and the cutting of the tablets changed the dissolution profiles of nifedipine. It was also observed that nifedipine in the suspension in water of powder prepared by crushing these tablets started to degrade after 15 minutes under light, and the targeted dose could not be obtained due to the stability problem.[31]

Manipulation of solid dosage forms can cause potential medication errors in preparation or dose calculation, leading to an inaccurate dose, drug instability, etc. Crushing tablets may alter the absorption and stability of the active substance, impairing the efficacy and safety of the drug.[5]

While the use of manipulations in pediatric practice is accepted, there is little information about the extent to which this occurs, how accurately dosage forms can be manipulated, or the most commonly manipulated products. When calculating doses or modifying dosage forms, there is a risk that manipulation may reveal the potential for a medication error, cause an incorrect dose, and have unknown effects on the stability and bioavailability of the drug. For this reason, crushing solid dosage forms is not always a suitable solution to the challenges in oral drug administration to pediatric patients.[4,6] On the other hand, a healthcare professional who modified the dosage forms and administered the drug to the patient can be held fully responsible for any adverse consequences resulting from a modification in the original (licensed) dosage form without authorization from the prescriber.[6]

Conclusion and Recommendations

Solid dosage forms might be manipulated in various ways (cutting/splitting, crushing, suspending in a liquid, etc.) to obtain pediatric patients' targeted dose. However, as can be seen in this study, the manipulation/modification of commercially available drugs cause medication errors such as inaccurate doses and incorrect preparation methods for specially modified release dosage forms in practice.

Relevance to Clinical Practice

The development of age-appropriate dose/dosage forms, the preparation of electronic and printed resources to guide the modification of solid dosage forms for the use of nurses in the pediatric clinic, training of nurses on drug modification/resource use, or consulting a pharmacist about the safety of opening capsules or crushing tablets, if possible, and performing the modification of solid dosage forms by a pharmacist can help overcome these issues.

Data Availability Statement: Further information is available from the corresponding author upon reasonable request.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ataturk University (Approval no: B.30.2.ATA.0.01.00/11, Date: December 17, 2020).

Informed Consent: Written informed consent was obtained from the nurses who agreed to take part in the study.

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