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ASSESSMENT OF PRACTICES FOR SUSPENDED ORAL DRUGS BY TABLET CRUSHING IN PEDIATRIC UNITS

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ABSTRACT

The aim of this study was to assess the impact of suspended drug by tablet crushing in our pediatric hospital in term of targeted dose and to identify parameters involved in the potential variability. Four usually crushed pediatric drug substances were selected: amiodarone, warfarin, hydrocortisone and captopril. Each tablet was crushed in a bag using a crusher device. Once crushed, a pre-determined volume of water was added using oral syringes before taking the necessary volume to obtain the targeted drug amount. For each drug, operators among pharmacy technicians and nurses investigated 2 targeted doses (high and low). Each suspension was assayed 3 times using the corresponding validated HPLC procedure.

Statistical analysis was performed (GraphPad Prism®) to evaluate the impact of operators, the level of suction in bag, and actual drug doses. To investigate the impact of formulation change on syringe drug content, five generic drugs of amiodarone were selected. Syringes contents were compared using one-way ANOVA. Drug loss in syringe ranged from 8.1% to 54.1%. The drug loss represented 18.9% to 30.5% for amiodarone, 0.1% to 5.5% for captopril, 5.6% to 19.7% for warfarin and 5.0% to 30.7% for hydrocortisone. The comparison of level sampling of suspensions presented significant differences for amiodarone, hydrocortisone, and warfarin. Comparison of operators demonstrated significant difference between pharmacy technician and nurse ($p=0.0251$). Finally, comparison of 5 generic drugs for amiodarone showed some statistical difference between the syringes content obtained when using the original medicine as compared to the generics. The physicochemical properties of each drug substance and the formulation of the drug product may both factor that should be considered. As a result, crushing tablets in water for oral administration needs a case by case assessment.

Although appropriate pediatric formulations are lacking, suspend the crushed material in a given volume of water should be discouraged and not recommended because far from good practice.

Keywords: tablets, crushing, pediatrics, suspending, drug dosage

Introduction

In pediatric hospital units, the health professionals are challenged by several issues to administer solid dosage forms such as tablets because of swallowing problems in young children and limitation of adapted dosage forms. Acceptability factors for pediatric population to swallow tablets include the age of children, the palatability, size, shape, texture and hardness. Age at which it is safe for children to swallow tablets is contentious with intervals of 3 to 6 years old [1]. However, the age at which children are able to safely swallow solids is highly controversial between healthcare professionals, caregivers, and regulatory authorities [2]. As a consequence, to enable easier medication administration and adjust its dose according to the body weight or the body surface area, hospitals prepare oral liquids or crush tablets. If no alternative is available, tablet crushing is being considered following recommended guidelines [3,4,5]. Because no consensus is available, crushed tablets are administered to the patients by mixing them with various vehicles as food, water, juice, yoghurt, honey [6-8]. However, altering tablet formulation by reducing drug to powder and diluting the powder into a liquid is a practice associated with potential harmful consequences for a pediatric patient [5]. Indeed, crushing tablets can impair the efficacy and safety parameters of the drug by changing the absorption characteristics, the stability, and the palatability [6,7,9]. Such manipulation would present potential for medication errors in dose calculation or preparation, lead to an inaccurate dose and has undetermined effects on the stability of the drug [5]. Furthermore, the crushing process can affect the amount of drug administered with powder being spilled or mixed in food or liquid [7]. The MODRIC (Manipulation of Drugs Required in Children) has provided guidelines for manipulation of tablets and recommended that dispersion should only be performed if there is knowledge of the solubility of active ingredients [8]. To ensure an optimal standardization of the crushing practice, a range of advanced pill crushing devices is available. The pill crusher enables to

reduce the drug to powder with an integrated handle. By lifting a lever up and down, the handle exerts a pressure on the crushing pad [9]. Some studies reported the loss of tablet weight was correlated with loss of active drug with estimation ranging from 3-13% loss using a mortar and pestle, to 30% loss with an electric grinder [10-12]. However, these devices do not imply that the full dose is delivered to the patient, as a significant amount of the drug can be unsuspected and remain in the crushing container. A study investigated the drug loss of paracetamol while using tablet crushing devices by measuring the quantity delivered to a patient and the quantity remaining in the device [9]. When the powder from the crushed tablet was reclaimed from 24 crushers, an average loss of 5.8% was observed. From 18 crushers, once rinsing of the crushed powder with water resulted in average of 24.2% drug loss, and second rinsing reduced it to 4.2% [9]. A study showed that an extemporaneous suspension of nifedipine prepared by crushing tablets started to degrade after 15 minutes under light and was very unstable dispersed [13]. In a recent study, fractions from different dispersed aspirin tablet formulations varied from 99% to 3% [14]. The poor result was obtained from the conventional tablet whereas the most accurate dose was obtained from dispersible drug. These publications highlighted the potential risk of delivering a dose significantly less than prescribed to the patient during crushing whole tablet.

To our knowledge, there is no data in pediatrics on the administration for a prescribed dose when the crushed tablet is blended with a food or liquid. Our study was designed to investigate drug recovery after tablet crushing, mixing in water, and collecting the appropriate volume.

Materials and Methods

Drug investigation

Four commercially available drugs containing active pharmaceutical ingredient widely used in pediatrics amiodarone (Cordarone 200-mg tablet, lot 7R035, Sanofi Aventis, France),

captopril (Captopril EG 25-mg tablet, lot 61964, EG Labo, France), hydrocortisone (Hydrocortisone RSL 10-mg tablet, lot 6HD2E, Sanofi Aventis, France), and warfarin (Coumadine 2-mg tablet, lot 173488, Bristol-Myers-Squibb, France) were selected. To evaluate the impact of crushing on generic drugs, four commercially available generic of amiodarone were selected and compared such as amiodarone TEVA 200-mg (Téva Santé, La Défense, France), amiodarone ARROW 200-mg (Arrow Génériques, Lyon, France), amiodarone BIOGARAN 200-mg (Biogaran, Colombes, France), and amiodarone MYLAN 200-mg (Mylan, Saint Priest, France).

Crushing protocol

To best reflect the crushing tablet performed in clinical units, the local protocol validated by our hospital care management and used by nurses was exactly reproduced. The standardized protocol is detailed in Figures 1 and 2. Each tablet was transferred in a single-use plastic bag and crushed using a manual crusher (Tookan, Practicima, France) to obtain a powder. A pre-determined volume of purified water (Evian, Danone, Amiens, France) was then added with an oral syringe with sampling straw (Nutrisafe2, Vygon, France) into the bag to suspend the powder. To homogenize the suspension, three aspirations and push-backs of the syringe piston were done into the bag. For each drug, two targeted doses were investigated corresponding to dosages for a one-month year old infant and one year old infant (Table 1). For each dose, three repeatable sampling levels in the bag were performed with a high point, a middle point and a low point (Fig. 3). The three levels were determined with the volume of purified water added in the bag related to the dose to be administered (Table 1). For each determined volume, the same rules to sample were used. The bag was placed against a vertical wall. The high point corresponded to the high line between the sample and the empty bag. The middle point corresponded to the measure related to the half of the total volume. The low point corresponded to the bottom of the bag. Before sampling, the suspension was mixed and

reposed 5 seconds to mime the real preparation in clinical unit. Aliquots represented each of the three sampling levels and each of the two doses from independent bag. Samples were performed in triplicate. Six independent operators (3 pharmacy technicians, 3 nurses) completed the full procedure from start for each drug by replicating the actual use in the clinical service.

Drug sample analysis

The total volume of each oral syringe was diluted in the appropriate solvent to achieve full active pharmaceutical ingredient dissolution and to obtain a targeted concentration within the linearity range of drug. Samples were assayed in triplicate by a validated high-performance liquid chromatography using an Ultimate 3000 system (Dionex®, ThermoFisher Scientific, Courtaboeuf, France) (Table 2). The pH of each drug suspension was performed using calibrated digital pH meter (Mettler-Toledo, SevenEasy).

Data analysis

The drug measures were expressed in % recovery by dividing the quantity recovered by the theoretical quantity of drug in diluted volume for each syringe. All results are given as mean \pm standard deviation (SD). Comparison of level of suspension suction and operators was made using one-way analysis of variance (ANOVA) at a 95% confidence level ($\alpha = 0.05$) followed by Tukey multiple comparisons test. All statistical analyses were performed using GraphPad Prism version 6.01 (Graphpad software, La Jolla, CA), and $p < 0.05$ was considered statistically significant.

Results

The calibration curve for each drug was linear with correlation coefficient at least 0.997. For both standard and sample tests, %RSD for inter- and intra-day precision were under 3% and recovery was over 99%. For each dose and sampling level, three samples were assessed

independently. The data presented as the average for each drug covered samples from both groups of operators and all sampling levels.

Amiodarone recovery

For the 60-mg dosage, the mean recoveries of amiodarone ranged from 75.0 to 81.1% regarding the suction level into the bag, which represented a loss of 18.9 to 25.0% (Table 3). However, the data range was wide with a minimum at 57.6% and a maximum at 96.0% (Fig. 4). For the 150-mg dosage, the mean recoveries of amiodarone ranged from 69.6 to 72.5% regarding the suction level into the bag, which represented a loss of 27.5 to 30.4% (Table 3). The data range was wide with a minimum at 61.2% and a maximum at 82.6% (Fig. 4).

Captopril recovery

For the 1.2-mg dosage, the mean recoveries of captopril ranged from 96.1 to 99.9% regarding the suction level into the bag, which represented a loss of 0.1 to 3.9% (Table 3). However, the data range was wide with a minimum at 86.3% and a maximum at 110.8% (Fig. 4). For the 3-mg dosage, the mean recoveries of captopril ranged from 94.5 to 96.7% regarding the suction level into the bag, which represented a loss of 3.3 to 5.5% (Table 3). The data range was wide with a minimum at 71.6% and a maximum at 114.5% (Fig. 4).

Hydrocortisone recovery

For the 1-mg dosage, the mean recoveries of hydrocortisone ranged from 75.8 to 95.0% regarding the suction level into the bag, which represented a loss of 5.0 to 24.2% (Table 3). However, the data range was wide with a minimum at 52.8% and a maximum at 82.2% (Fig. 4). For the 3-mg dosage, the mean recoveries of hydrocortisone ranged from 69.3 to 80.3% regarding the suction level into the bag, which represented a loss of 19.7 to 30.7% (Table 3). The data range was wide with a minimum at 45.9% and a maximum at 87.8% (Fig. 4).

Warfarin recovery

For the 0.64-mg dosage, the mean recoveries of warfarin ranged from 93.6 to 99.1% regarding the suction level into the bag, which represented a loss of 0.9 to 6.4% (Table 3). However, the data range was wide with a minimum at 66.7% and a maximum at 114.4% (Fig. 4). For the 1.2-mg dosage, the mean recoveries of warfarin ranged from 80.3 to 84.8% regarding the suction level into the bag, which represented a loss of 15.2 to 19.7% (Table 3). The data range was wide with a minimum at 67.4% and a maximum at 97.4% (Fig. 4).

Comparison of level of suspension suction and operators

The results of statistical comparison of level sampling of suspension and operators are presented in Table 4. Significant differences were noted for amiodarone 150-mg (middle point vs. low point, $p=0.0177$), hydrocortisone 1-mg (high point vs. low point, $p<0.0001$; middle point vs. low point, $p=0.0475$), and warfarin 0.75-mg (high point vs. low point, $p=0.0087$).

Comparison of operator impact demonstrated significant difference between nurses and pharmacy technicians ($p=0.025$). The mean recoveries of samples performed from nurses and pharmacy technicians were 86.4% and 92.6%, respectively. The significant difference may be explained by specific professional training provided to the pharmacy technicians in the course of their studies.

Comparison between generics of amiodarone

The results of generic drug recoveries from available amiodarone tablet are presented in table 5. Significant differences of recoveries were obtained between Cordarone i.e. the brand drug, and that of the generic drugs (Fig. 5). The mean recovery obtained by crushing Coradarone tablets was less than other recoveries achieved with generics.

Discussion

In infants 1 year old or less, nurses usually crush tablets that the children are unable to swallow, or because the adult dosages are not suitable requiring dilution of the dose.

Therefore, for each drug, the choice was made to study a mean dose equivalent to a 1-month-

old infant as well as a mean dose equivalent to a 1-year old child. Large dilutions of crushed tablets were required to achieve target doses, which may explain variations in drug recoveries.

Crushing tablet and diluting it in purified water part of which administered to infant resulted in the overall range from 8.1% to 54.1% of drug loss, depending on the drug. According to the French legislation and the British Pharmacopeia, drug tablet content should fall within the limits of 95 to 105% of the labelled amount [9,15]. The US Food and Drug Administration recommend less than 3.0% loss of mass of tablet upon subdivision [16]. Because the drug recovery from suspension after crushing tablets was highly variable, it is likely that infants do not receive the corrected dose of drug in many cases. Aqueous solubility is one of the key factors that determine the solubilization of the drug substance in the bag. Thus, the low recovery may be explained by the variable water solubility of the active drug. Hydrocortisone, amiodarone and warfarin are sparingly soluble in water (320 mg/L for hydrocortisone, 700 mg/L for amiodarone, 17 mg/L for warfarin). Captopril is freely soluble in water (160 mg/ml). At pH of the diluted crushed tablet suspension, the calculated aqueous solubility of each compound provided the capacity of drug to be partially or fully dissolved in water (Table 6). When the concentration of the suspension exceeds the maximal solubility value of the drug at the given pH, the drug substance is not entirely dissolved in water. As a result, undissolved drug substance particles may be formed and settle down in the bag. For example, if we consider the maximal solubility of the amiodarone and captopril drug substances (2.53 mg/mL and 5.89 mg/mL, respectively) compared to the theoretical diluted concentration (100 mg/mL and 5 mg/mL, respectively), the mean drug recoveries were at 71.8% for amiodarone and at 96.8% for captopril. These data showed the impact of pH of the drug suspension related to its diluted concentration. This may explain lower recoveries for drugs that are not widely soluble in water.

Syringes made with Cordarone, the brand name drug of amiodarone, and generics of amiodarone may differ in recovery because of the higher difficulty in crushing Cordarone as compared to generic drugs. Indeed, the hardness of a tablet has a major influence on the dissolution of the drug; consequently, it may be assumed that this hardness has an impact on the amount dissolved in water [20]. This hypothesis should explain in part the significant difference between Cordarone and generic recoveries (Fig. 5). Therefore, the variability in recoveries between marketed amiodarone drugs indicates that the formulation properties of the tablets do not match. In practice, crushing a tablet for a drug is not applicable to all laboratories that commercialize this drug.

Undertaking tablet crushing action according to the information support is required to ensure good practice by nurses. In our hospital, a crushing tablet practice workshop for nurses provides adequate and specific educational resources related to pediatrics. Although nurses are trained, our study results revealed that tablet crushing practice was inadequate to administer an accurate dose of drug. The primary recommendation for nurses is to contact the hospital pharmacist to formulate if possible an oral liquid form suitable to infant. If the pharmacy is unavailable to prepare the oral liquid product or split the tablet dose, the nurse first verifies that crushing tablet is safe by consulting our accessible intranet database. The database provides information on oral dosage forms that should or not be crushed, the solubility in water, the possible enteral administration, and the possible use of injectable form. The data of this specific approach for crushing and taking parts of the dose could be generalized in this context. A major limitation of this practice is the wide variability of the dose administered to infants. The protocol could be optimized by substituting water by a suspension vehicle when the powder is diluted. Data on the physicochemical properties of molecules (notably water solubility) might enable a dilution table to be made for each drug. However, in the absence of drugs suitable for pediatrics, tablet crushing by the nurses is

largely performed in French hospital, permitting nevertheless the administration of the drugs to infants.

Conclusion

If the potential consequences of manipulating drugs on occupational health and safety issues are recognized, our study demonstrates that infants may not receive the prescribed dose after crushing tablet and dilution in water. The overall lack of active pharmaceutical ingredient in the prepared syringes implies that preparing medication by crushing tablets should only be considered if no other alternative is available; further, even though a protocol was designed to avoid drug loss, the pharmaceutical formulation and generics change should be considered as it may have some impact on the drug content in the syringe intended to be administered.

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Figure legends

Fig. 1. Devices for crushing tablet.

Fig. 2. Tablet crushing protocol.

Fig. 3. Sampling of suspension for drug analysis **after tablet crushing**.

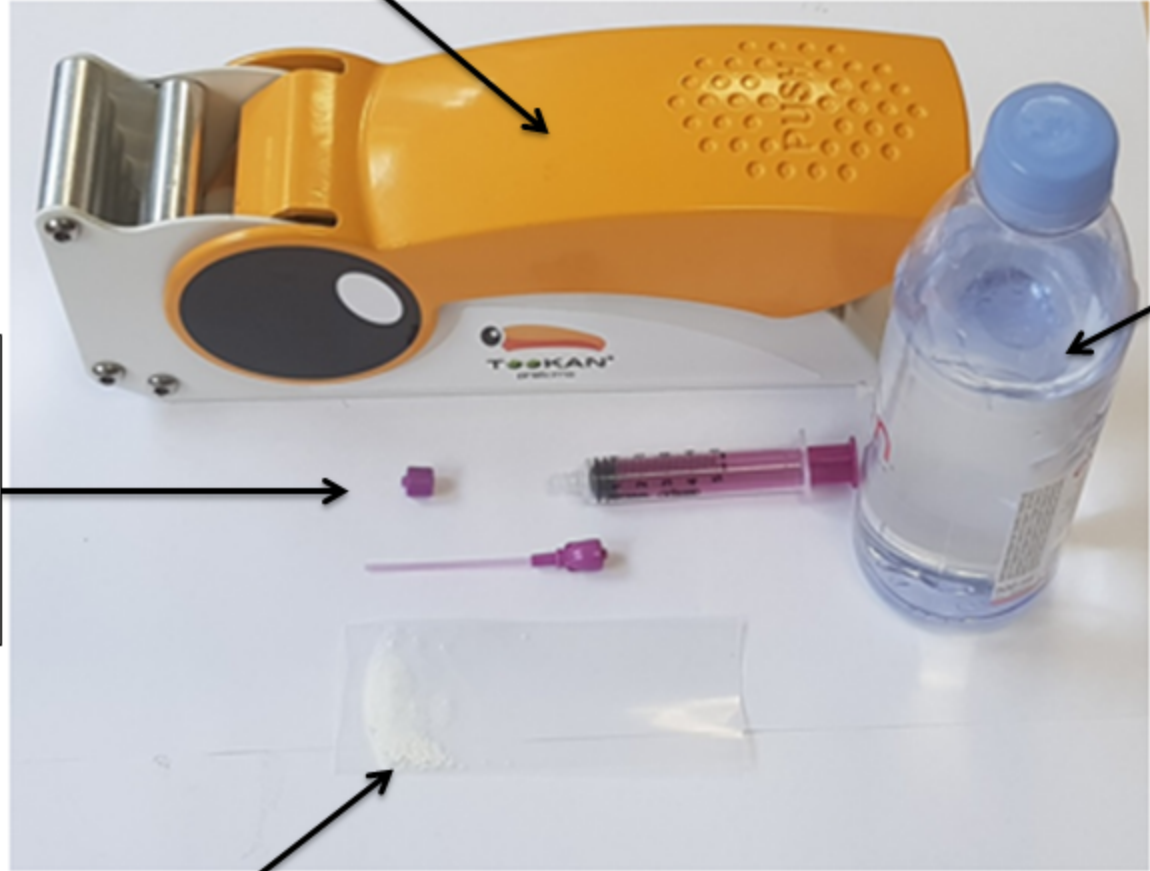
Fig. 4. Recoveries of amiodarone, captopril, hydrocortisone, and warfarin at different points of sampling. **Values show low, medium and high recoveries**.

Fig. 5. Recoveries of the brand (**Sanofi**) and four generics amiodarone tablets (** $p < 0.0001$; **NS: non significant**).

Manual crusher

Purified water for dilution

Oral syringe, cap, and sampling straw



Single-use bag with crushed tablet powder

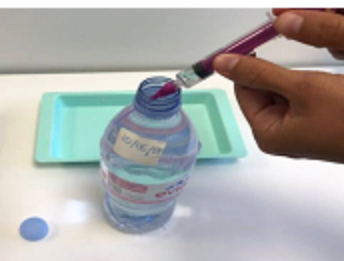
1. Prepare materials for the crushing



3. Press the handle to crush the tablet



5. Take the purified water



7. Take the right volume of dose



2. Transfer the tablet in bag

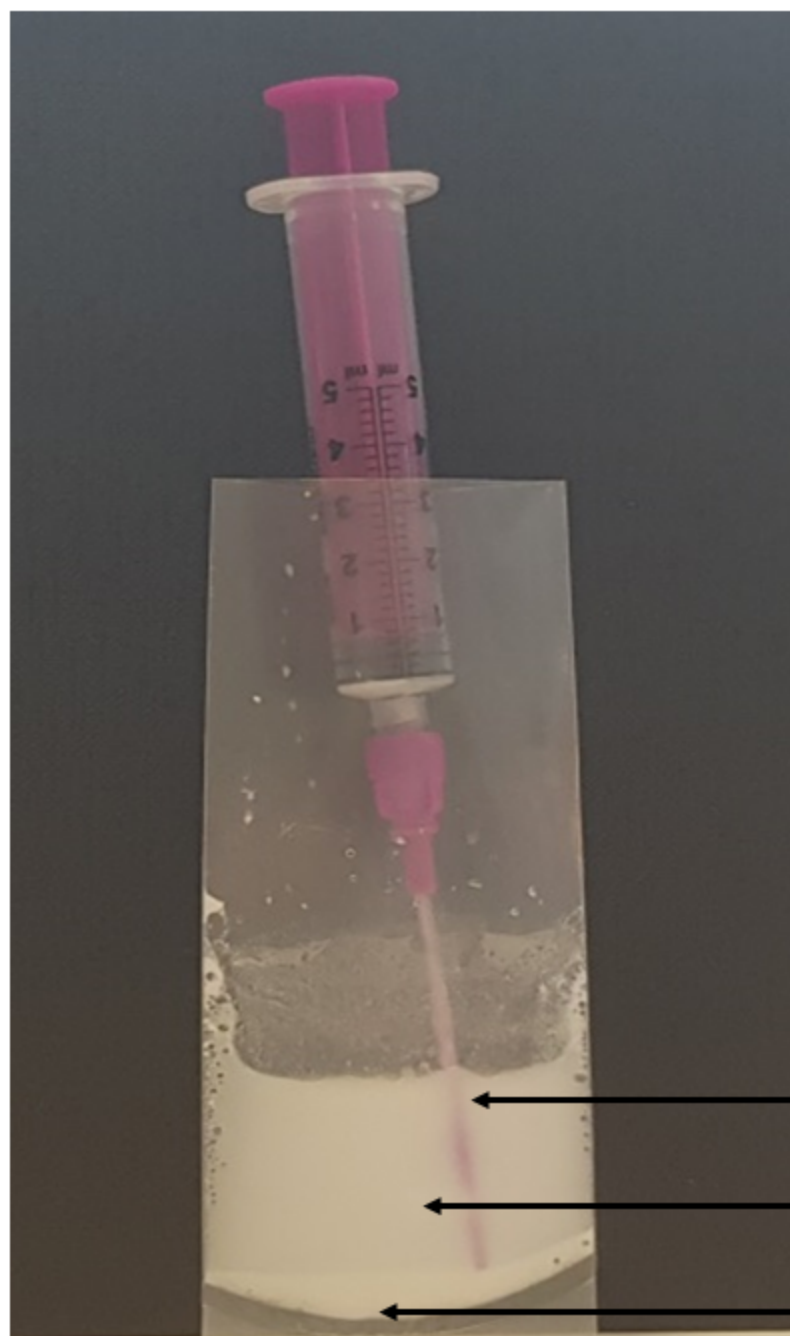


4. Tablet is crushed as a fine powder



6. Add the water and homogenize



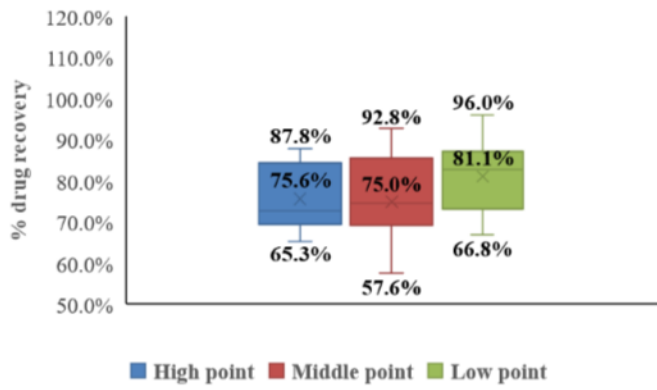


High point

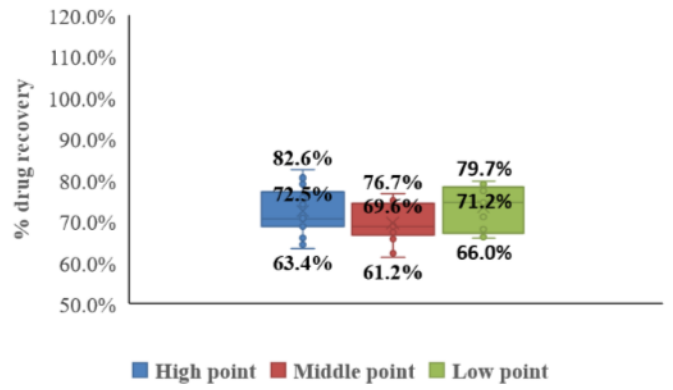
Middle point

Low point

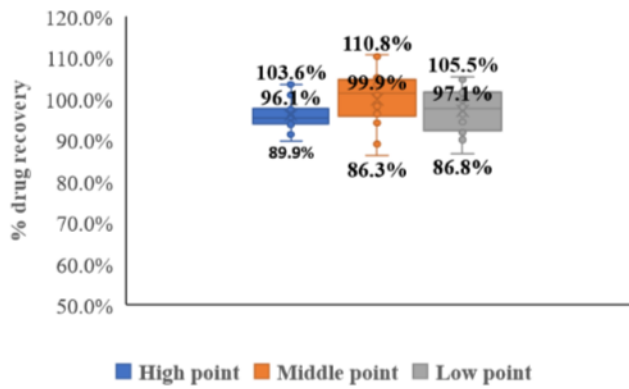
Amiodarone 60-mg



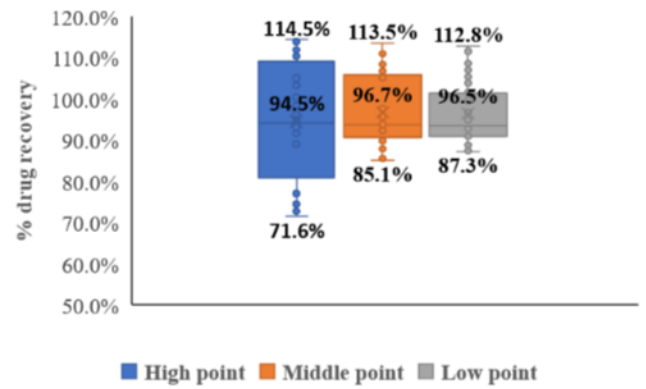
Amiodarone 150-mg



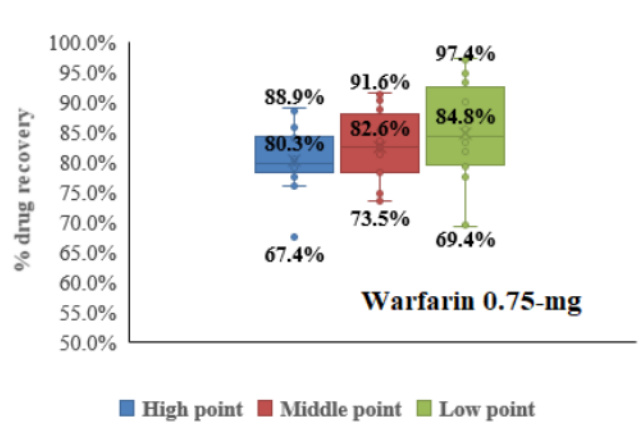
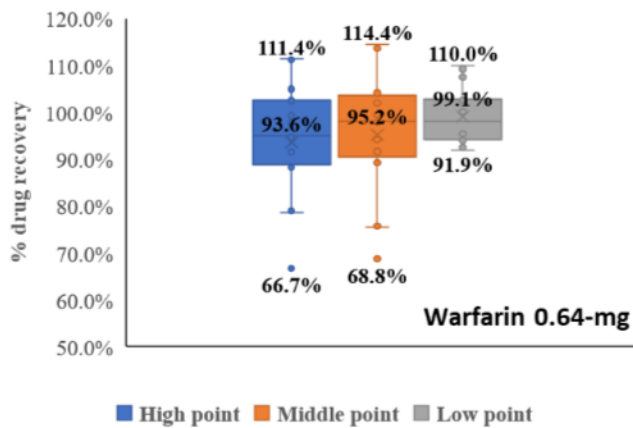
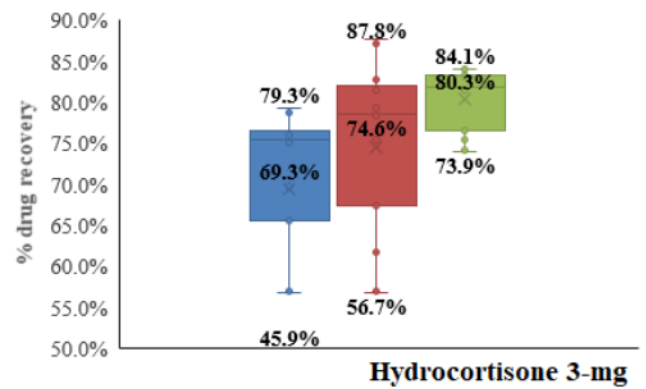
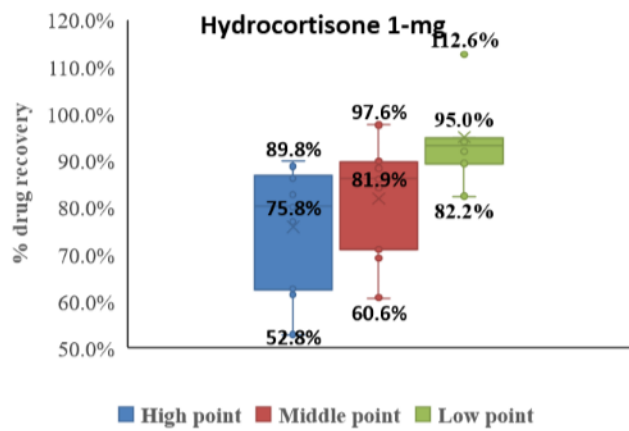
Captopril 1.2-mg



Captopril 3-mg



Hydrocortisone 1-mg



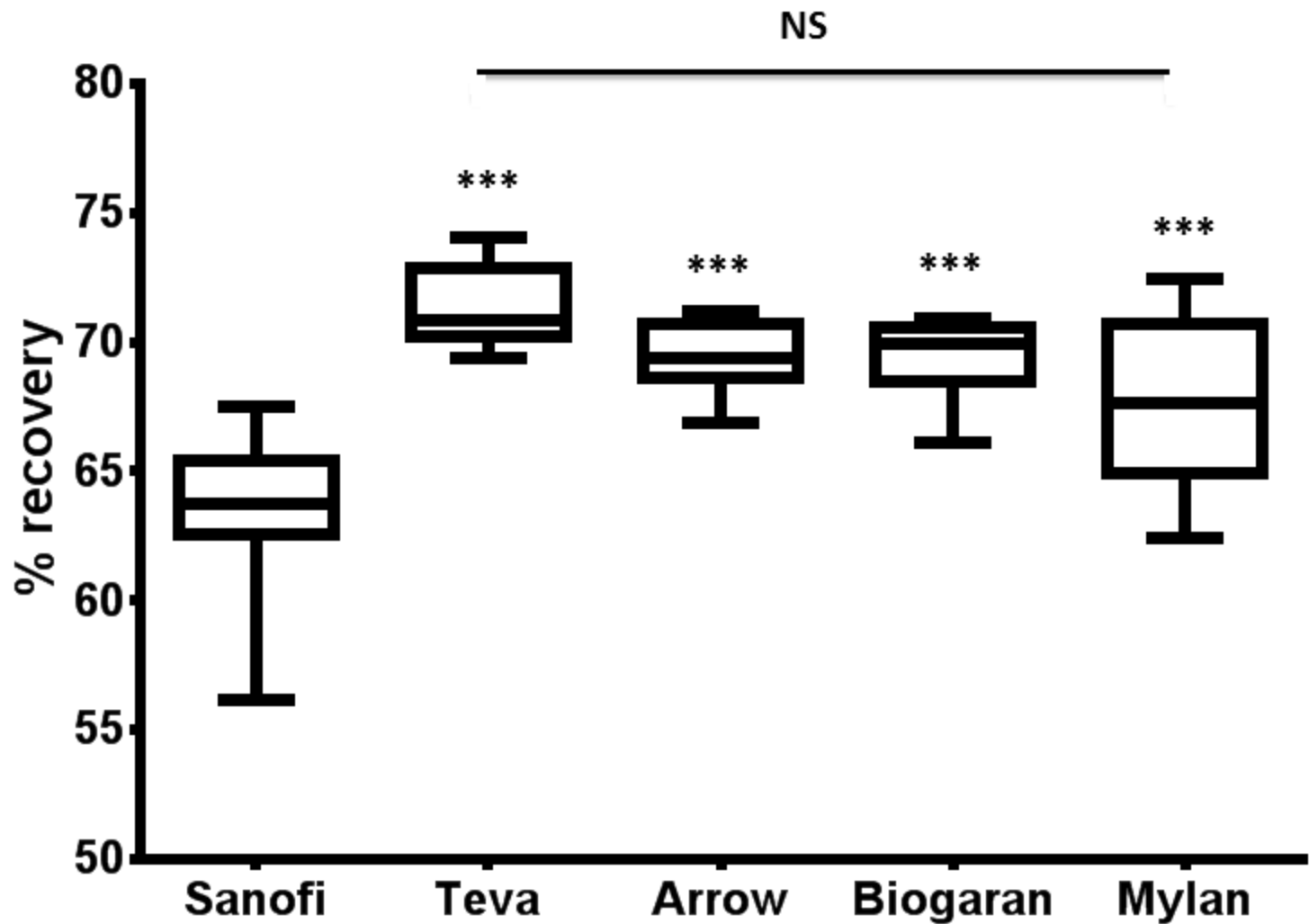


Table 1. Choice of dosage for each drug and protocol.

Drug	Dosage	Prescribed dosage	Added water (mL)	Volume to administer (mL)
Amiodarone	10 to 20 mg/kg/d	Infant = 60 mg	4	1.2
		One year old = 150 mg	2	1.5
Captopril	0.1 to 0.4 mg/kg/d	Infant = 1.2 mg	5	0.24
		One year old = 3 mg	5	0.60
Hydrocortisone	12 to 20 mg/m ² /d	Infant = 1 mg	5	0.5
		One year old = 3 mg	5	1.5
Warfarin	< 1 year = 0.32 mg/kg/d	Infant = 0.64 mg	2	0.64
	> 1 year = 0.15 mg/kg/d	One year old = 1.2 mg	2	1.2

Table 2. High-performance liquid chromatography method parameters and validation for each drug [17-20].

Drug	Column	Wavelength (nm)	Mobile phase	Flow rate (mL/min)	Injection volume (μL)	Analytical range (μg/mL)	Linearity (r ²)	Accuracy (% recovery)	Precision (% RSD)
Amiodarone	Polaris 5 C18 250*4.8mm	240	Acetonitrile 70% Phosphate buffer pH 3 30%	1.5	10	0 - 250	0.998	98.4	2.8
Captopril	Lichrospher 100 RP8 250*4mm (5 μm)	210	Methanol 65% Water 35% Phosphoric acid to pH 2.5	0.6	50	5 - 100	0.998	97.0	3.1
Hydrocortisone	Lichrospher 100 RP8 250*4mm (5 μm)	254	Methanol 80% Water 20%	1	50	0 - 40	0.997	99.8	1.8
Warfarin	Lichrospher 100 RP8 250*4mm (5 μm)	282	Methanol 60% Acetic acid 0.1% 30% ACN 10%	1	50	5 - 20	0.998	99.6	1.9

Table 3. Percentage of drug recoveries, and loss for tablet crushed following by suspending the powder with purified water in oral syringe. Comparison of level of suspension suction using one-way ANOVA at a 95% confidence level ($\alpha=0.05$) (Low point vs middle point or high point).

Drug/dosage	Level of suspension suction	Recovery (%)	
		Mean ^a	S.D.
Amiodarone (Sanofi) 60 mg	High point (NS)	75.6	7.8
	Middle point (NS)	75.0	11.4
	Low point	81.1	8.6
	Overall (n=9)	77.4	9.8
Amiodarone (Sanofi) 150 mg	High point (NS)	72.5	5.7
	Middle point (*)	69.6	4.5
	Low point	73.5	5.2
	Overall (n=9)	71.8	5.4
Captopril (EG Labo) 1.2 mg	High point (NS)	96.1	3.8
	Middle point (NS)	99.9	6.8
	Low point	97.1	5.3
	Overall (n=9)	97.7	5.6
Captopril (EG Labo) 3 mg	High point (NS)	94.5	13.9
	Middle point (NS)	96.7	8.6
	Low point	96.5	7.4
	Overall (n=9)	95.9	10.3
Hydrocortisone (Sanofi) 1 mg	High point (***)	75.8	13.0
	Middle point (**)	81.9	11.6
	Low point	95.0	10.6
	Overall (n=9)	84.2	14.1
Hydrocortisone (Sanofi) 3 mg	High point (***)	69.3	10.9
	Middle point (*)	74.6	9.9
	Low point	80.3	3.6
	Overall (n=9)	74.7	9.8
Warfarin (Bristol-Myers-Squibb) 0.64 mg	High point (NS)	93.6	11.9
	Middle point (NS)	95.2	12.1
	Low point	99.1	5.6
	Overall (n=9)	96.0	10.5
Warfarin (Bristol-Myers-Squibb) 1.2 mg	High point (**)	80.3	5.3
	Middle point (NS)	82.6	5.6
	Low point	84.8	7.8
	Overall (n=9)	82.6	6.5

NS: not significant

* p value < 0.05

** p Value < 0.01

*** p value < 0.001

^a The mean recoveries for each dose and sampling level were obtained from 3 independent bags

Table 4. Comparison of level of suspension suction and operators using one-way ANOVA at a 95% confidence level (alpha=0.05) followed by Tukey multiple comparisons test.

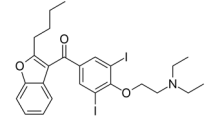
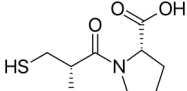
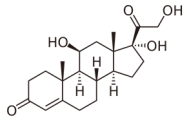
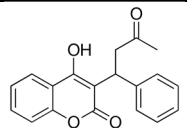
Drug	ANOVA Summary			Tukey's multiple test				
	F	p value	R square		Mean Difference	95% CI of difference	P Value	Significant
Amiodarone 60-mg	3.349	0.0407	0.0851	High point vs. Middle Point	0.6005	-6.018 to 7.219	0.9744	No
				High point vs. Low point	-5.559	-12.18 to 1.060	0.1171	No
				Middle Point vs. Low point	-6.159	-12.35 to 0.03169	0.0515	No
Amiodarone 150-mg	4.196	0.0186	0.09715	High point vs. Middle Point	2.893	-0.4665 to 6.252	0.1055	No
				High point vs. Low point	-1.037	-4.396 to 2.322	0.7419	No
				Middle Point vs. Low point	-3.93	-7.289 to -0.5705	0.0177	Yes
Captopril 1.2-mg	2.341	0.1065	0.08408	High point vs. Middle Point	-3.778	-8.151 to 0.5954	0.103	No
				High point vs. Low point	-0.9833	-5.357 to 3.390	0.8506	No
				Middle Point vs. Low point	2.794	-1.579 to 7.168	0.2799	No
Captopril 3-mg	0.5059	0.6044	0.009545	High point vs. Middle Point	-2.233	-8.042 to 3.576	0.6327	No
				High point vs. Low point	-2.006	-7.815 to 3.803	0.691	No
				Middle Point vs. Low point	0.2278	-5.581 to 6.037	0.9952	No

Hydrocortisone 1-mg	18.92	<0.0001	0.3267	High point vs. Middle Point	-6.111	-13.74 to 1.521	0.1418	No
				High point vs. Low point	-19.23	-26.86 to -11.60	<0.0001	Yes
				Middle Point vs. Low point	-13.12	-20.75 to -5.486	0.0003	Yes
Hydrocortisone 3-mg	10.59	<0.0001	0.2136	High point vs. Middle Point	-5.226	-10.93 to 0.4749	0.0792	No
				High point vs. Low point	-10.98	-16.68 to -5.277	<0.0001	Yes
				Middle Point vs. Low point	-5.752	-11.45 to -0.05106	0.0475	Yes
Warfarin 0.64-mg	2.693	0.0725	0.05016	High point vs. Middle Point	-1.572	-7.467 to 4.324	0.8017	No
				High point vs. Low point	-5.541	-11.44 to 0.3541	0.0701	No
				Middle Point vs. Low point	-3.969	-9.735 to 1.796	0.2347	No
Warfarin 0.75-mg	4.582	0.0124	0.08028	High point vs. Middle Point	-2.325	-5.877 to 1.227	0.2693	No
				High point vs. Low point	-4.522	-8.074 to -0.9704	0.0087	Yes
				Middle Point vs. Low point	-2.197	-5.749 to 1.355	0.3091	No
Operator	ANOVA Summary			Tukey's multiple test				
	F	p value	R square		Mean Difference	95% CI of difference	P Value	Significant
	11.87	<0.0001	0.04646	Pharmacy technician vs. Nurse	6.234	0.5497 to 11.92	0.0251	Yes

Table 5. Characteristics and drug recoveries from generic and brand amiodarone tablet crushed and suspended with purified water in oral syringe.

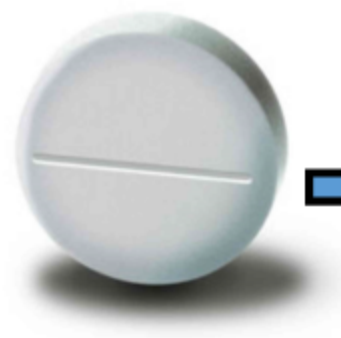
Drug/dosage	Tablet weight (mg)	Ingredients	Recovery (%)	pH of suspension
	Mean (n=20) ± S.D.		Mean (n=6) ± S.D.	Mean (n=6) ± S.D.
Cordarone 200-mg SANOFI	347.8 ± 0.004	Maize starch Lactose Povidone Magnesium stearate Colloidal silica	63.4 ± 3.2	4.00 ± 0.04
Amiodarone 200-mg TEVA	335.7 ± 0.003	Maize starch Lactose 50-mg Povidone k90 Magnesium stearate Colloidal silica Pregelatinised starch	71.4 ± 1.6	3.95 ± 0.09
Amiodarone 200-mg ARROW	352.3 ± 0.003	Maize starch Lactose 50-mg Povidone k90 Magnesium stearate Colloidal silica Pregelatinised starch	69.4 ± 1.4	4.05 ± 0.10
Amiodarone 200-mg BIOGARAN	354.3 ± 0.003	Maize starch Lactose 50-mg Povidone k90 Magnesium stearate Colloidal silica Pregelatinised starch	69.4 ± 1.5	4.03 ± 0.13
Amiodarone 200-mg MYLAN	380.4 ± 0.002	Talcum Lactose 100-mg Povidone Magnesium stearate Colloidal silica Crospovidone	67.6 ± 3.2	3.97 ± 0.04

Table 6. Physicochemical properties of amiodarone, captopril, hydrocortisone, and warfarin in water dilution.^a

Drug	Chemical structure	Suspension pH	LogD at suspension pH	LogS (mg/mL)	Theoretical drug concentration	% overall recovery
Amiodarone hydrochloride (CASRN:19774-82-4)	 <chem>C25H29I2NO3</chem> , HCl	3.92 ± 0.07	4.14	2.53	50 mg/mL 100 mg/mL	77.4 71.8
Captopril (CASRN:62571-86-2)	 <chem>C9H15NO3S</chem>	2.78 ± 0.04	0.70	5.89	5 mg/mL	96.8
Hydrocortisone (CASRN:50-23-7)	 <chem>C21H30O5</chem>	6.90 ± 0.05	1.28	0.41	2 mg/mL	79.5
Warfarin (CASRN:81-81-2)	 <chem>C19H16O4</chem>	6.90 ± 0.03	1.40	1.30	1 mg/mL	89.3

^aToxicology Data Network (Toxnet) from U.S. National Library of Medicine, Chemicalize software (ChemAxon, Cambridge, USA)

Tablet



Crushing Tablet



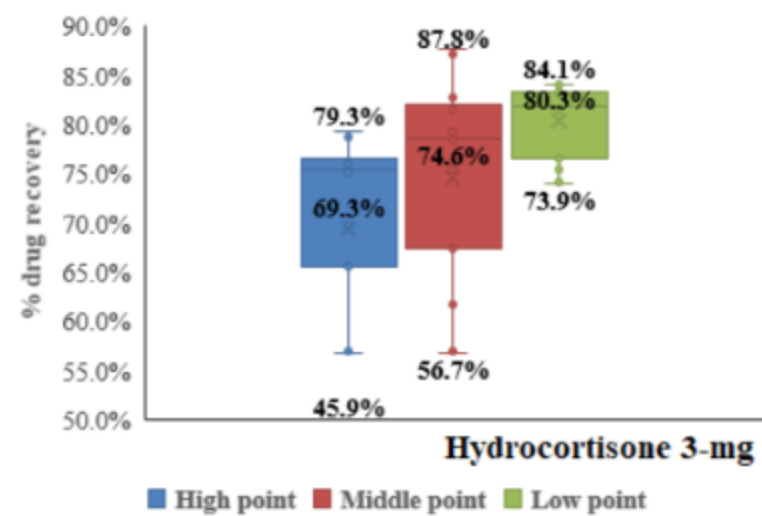
Suspended powder in oral syringe



Suspended drug administration



Sampling



Wrong dosage

