

## Research Paper

# Reduction of oral liquid controlled drugs discrepancy in day-to-day practice

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Received September 10, 2020; Accepted May 5, 2021.

## Abstract

**Objectives** The storage, use and disposal of controlled drugs (CDs) in hospitals and other health-care centres are governed by a combination of government legislation and local policy. In the UK, a running balance must be kept for Schedule 2 CDs and when discrepancies arise, they must be investigated and reconciled. Policies on acceptable discrepancies are varied and based on anecdotal evidence. This study was designed to simulate dosing and stock check procedures for oxycodone oral solution, as a sample CD solution, and evaluate where the volume losses that cause discrepancies could arise from.

**Methods** Hypromellose solutions were formulated to simulate oxycodone commercial solutions. These were used to simulate dosing and stock check practices. Quantification of volume loss during simulated routine dosing and stock check of viscous oral CD formulations were performed in triplicate.

**Key findings** Dosing with enteral syringes *via* a fitted rubber bung never resulted in volume loss. Volume loss was always observed during stock checks with no statistical difference between methods used.

**Conclusions** The findings of this study support the following recommendations. Hospital pharmacy departments should provide oxycodone and other CD liquid formulation bottles pre-fitted with a bung and make sure personnel use enteral syringes that are compatible with the chosen adaptor and of the most appropriate size for the intended dose. Stock checks should be limited to the minimum required by law or local policy.

**Keywords:** controlled drugs; discrepancy; oxycodone; oral administration; enteral syringes

## Introduction

In the UK, drugs defined as controlled drugs (CDs) are listed in the Misuse of Drugs Act 1971. The Misuse of Drugs Regulations 2001 further classifies CDs into five different schedules depending on the level of control attributed to each. Schedule 2 contains the drugs for therapeutic use with the most stringent requirements in terms of prescription, supply, storage and destruction.<sup>[1]</sup> Similar classifications

are used in different countries with strict laws governing the manufacture, supply and possession of these drugs.<sup>[2]</sup> Hospitals and other healthcare settings must comply with a combination of legal requirements and local policy for the storage, prescribing, administration and destruction of these substances. In secondary care settings, these include keeping a running balance of stock for each clinical and non-clinical area. However, maintaining an accurate record of the quantity of liquid CDs kept is problematic, as loss of volume can

occur through repeat dose preparation and periodic stock checks that involve multiple individuals. This is further complicated due to variable, but allowable, overage of CD volumes during manufacture (confirmed by conversation with manufacturer). Anecdotally, healthcare organisations accept a 5% loss of the total volume, but this limit is arbitrarily determined.<sup>[1]</sup> Overall, there is uncertainty in clinical practice as to what constitutes loss through normal use and what loss may be due to the CD being misappropriated.<sup>[3–5]</sup> A 2013 Australian study<sup>[6]</sup> determined a 4% discrepancy to be acceptable in the case of four different CD liquids [morphine hydrochloride (Ordine), oxycodone (OxyNorm), hydromorphone (Dilaudid) and methadone]. The experiments found that the least natural wastage was achieved by dosing the liquid medicines via a bottle-fitted bung using an enteral syringe.<sup>[6]</sup> The major limitation of this study was that the volume of dose measured was limited to 2.5 ml throughout the experiment, which does not reflect clinical practice where a range of doses are administered on a ward. A 2016 American study<sup>[7]</sup> aimed at defining the characteristics of controlled medication discrepancies. The study identified 2468 discrepancies. The medicine found to have the highest discrepancy (15%) was the hydrocodone/paracetamol combination. However, this study included a variety of dosage forms such as tablets, liquids, solutions for injection and considered both I/V and oral administration so it was not specific to oral liquid formulation. Furthermore, being a specialist trauma hospital, the results are likely to be skewed, due to the limited cross-section of patients seen at this facility, and may not be generalisable.<sup>[7]</sup> Overall, both the Australian and American studies emphasise the need for more published evidence-based information on oral CD liquid loss in practice.<sup>[6,7]</sup> This study aimed to determine best practice in dose measurement and stock checking techniques to minimise loss of liquid medication, by simulating a range of methods in a laboratory setting using a hypromellose solution of viscosity equivalent to that of commercially available oxycodone oral solution 5 mg/5 ml (Shortec).

## Methods

### Materials

BD syringes (1.25, 10 and 60 ml) were supplied by Medisave and precision syringes (5 ml) were purchased from Valley Northern. Blaubrand Pycnometers (25 ml) and Poulten Selfe Ostwald Viscometer D (range 20–100 mm<sup>2</sup>/s) were obtained from Fisher Scientific. Hydroxypropyl methylcellulose (hypromellose; Mw 86,000 Da) and citric acid 99.6% were obtained from Acros Organics; sodium citrate dihydrate and Alfa Aesar indigo carmine (food blue colouring) were from Fisher Scientific.

### Preparation and characterisation of hypromellose stock solutions

Hypromellose solutions were used to simulate oxycodone oral formulations as conditions for the use, storage and disposal of CDs could not be abided by on our premises. Hypromellose is the suspending agent used in oxycodone formulations furthermore the manufacturer stated solutions had a pH of 3, we therefore tested the effect of hypromellose concentration and pH on the viscosity of the solution to best simulate the commercial formula. Hypromellose solutions were prepared by dispersing the polymer in either water or citrate buffer at 80°C and adding water to final weight after cooling the solution to room temperature. The sodium citrate buffer was prepared by dissolving sodium citrate (2.714 g) and citric

acid (17.437 g) in deionised water to a final volume of 1 L (pH 3). Solutions were stored at 4°C until further use and made fresh fortnightly. The density and viscosity of the hypromellose solutions prepared were determined experimentally using a pycnometer and an Ostwald viscometer. All measurements were carried out in triplicate.

### Simulations

A series of tests was designed to simulate the common practices seen in the UK ward environments when preparing and administering liquid doses and when undertaking stock checks (Figure 1). Through informal conversation with hospital nurses regarding the extraction of small doses (e.g. 1.25 or 2.5 ml), we identified a number of dosing practices that informed the different techniques as described below.

#### Simulated dosing: cup

It is common practice in some hospital wards to pour a small volume of oral solution into a cup (paper or plastic) to facilitate measuring via an enteral syringe, the remaining solution is then returned to the stock bottle. This test was carried out to determine the residual volume when using a measuring cup and to investigate the effect of time and volume on loss. Before testing, 1 ml of food blue colouring was added to a 250 ml batch of hypromellose solution. A paper or plastic medicine cup was weighed and tared on a top pan balance. Five grams of accurately weighed hypromellose solution were poured into the cup and left there for either 2 or 10 min before discarding and measuring the residual weight (Figure 2a). Colouring was used for visual inspection.

#### Simulated dosing: syringe

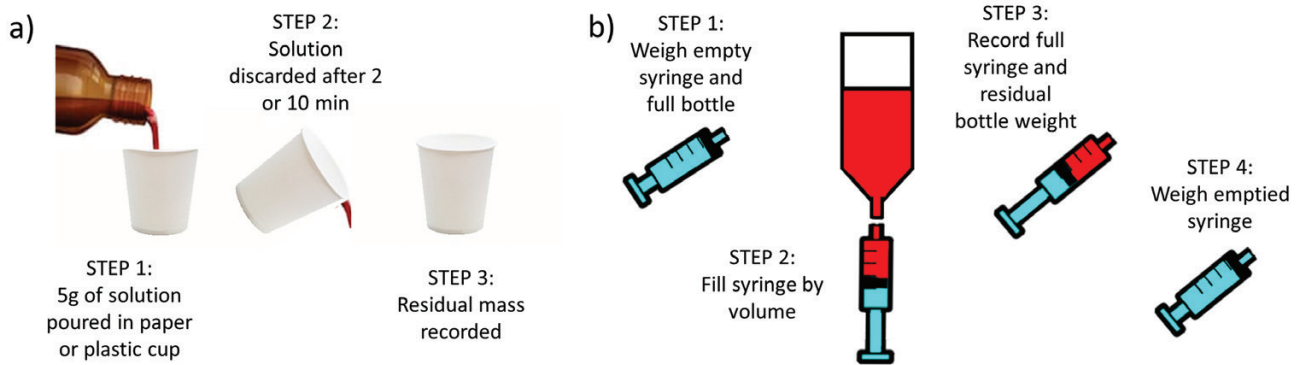
The stock solution (254 ml to include an overage) was poured into a tared, 250 ml amber bottle that was subsequently sealed with a permanent bung. Doses were taken from the bottle as illustrated in Table 1. Throughout the experiments, the weights of the empty syringe, the filled syringe, the stock bottle from which the dose was taken and the discarded solution were recorded (Figure 2b). To reduce measurement error bias, a second researcher carried out a set of dosage extractions. The second researcher was not informed of the purpose of the experiment and simply asked to extract the dose in whichever way they thought was acceptable. A control experiment was also carried out with water instead of the hypromellose solution.

#### Simulated stock checks

Simulated stock checks were carried out using a variety of techniques that are used at the University Hospital Southampton pharmacy department and wards using an identical stock bottle sealed with a bung. The methods used to take a balance check were: (1) removing



Figure 1 Oxycodone bottle fitted with a rubber bung for use with enteral syringes.



**Figure 2** Diagrams describing the procedure of simulated dosing: (a) cup and (b) syringe.

**Table 1** Experimental design for dosing with a syringe

Experiment name	Total volume to be dosed	Dose volume			
		1.25 ml	2.5 ml	5 ml	10 ml
		Number of doses (percentage of total volume)			
Fixed dose 2.5	250.00 ml	–	100	–	–
Fixed dose 5	250.00 ml	–	–	50	–
Fixed dose 10	250.00 ml	–	–	–	25
Mixed doses – low	247.50 ml	100 (50%)	25 (25%)	6 (12.5%)	3 (12.5%)
Mixed doses – high	258.75 ml	25 (12%)	13 (13%)	13 (25%)	13 (50%)

the bung and pouring the remaining stock into a 250 ml measuring cylinder, (2) withdrawing the remaining volume with 60 ml enteral syringes via the fitted bung, (3) removing the bung and pouring the remaining stock into a 60 ml enteral syringe fitted with a stopper, (4) removing the bung, pouring the remaining stock into a cup (paper or plastic) and measuring by drawing into 60 ml enteral syringes. All doses were measured by weight and converted into volume by using the experimental density value. Weights were recorded in three ways: (a) weight of the filled syringe (syringe), (b) weight difference in the stock bottle (from stock), (c) and weight difference in the discard beaker (administered). All tests were carried out in normal ambient conditions and in triplicate.

### Statistical analysis

Analysis of variance test was carried out followed by Tukey multicomparison test. Unpaired two-tailed *t*-test was carried out when comparing two samples. Details of the specific statistical methods used to analyse the different sets of data are reported in each figure caption. Data were plotted and analysed using GraphPad Prism 8.

## Results

### Characterisation of the stock solution

In order to simulate the measuring of clinically used formulations of oxycodone containing hypromellose as the suspending agent, a number of hypromellose solutions of different concentrations were prepared and their viscosity was measured (Table 2). Performing viscosity testing on hypromellose solutions in water narrowed down a suitable range of concentrations between 0.25 and 0.5% w/w for obtaining the desired viscosity of 15 mPa·s (corresponding to the

**Table 2** Density and viscosity values for experimental hypromellose solutions of different concentrations prepared to simulate the commercial oxycodone formulation that has a viscosity of 15 mPa·s and a pH = 3

Solvent	Hypromellose (% w/w)	Density (g/cm <sup>3</sup> )	Viscosity (mPa·s)
Water	0.2500	1.01 ± 0.00	4.33 ± 0.07
	0.5000	1.03 ± 0.00	18.64 ± 1.17
	0.7500	1.00 ± 0.00	46.49 ± 2.77
Citrate buffer pH 4	0.4375	1.02 ± 0.02	14.84 ± 0.92
	0.4500	1.02 ± 0.02	15.97 ± 0.37
	0.5000	1.01 ± 0.01	21.24 ± 1.83

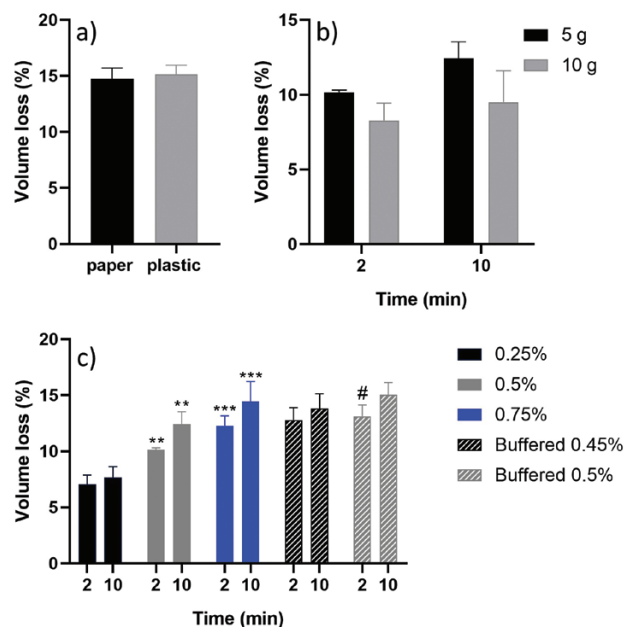
oxycodone commercially available solution). The addition of sodium citrate buffer to the formulation increased the viscosity. The target viscosity of 15 mPa·s was obtained using a 0.4375% w/w hypromellose buffered solution.

### Simulated dosing: cup

A similar loss ( $P > 0.05$ ) was found independent of the type of cup used in this method (Figure 3a). No statistical difference was found in the loss occurred when pouring 5 or 10 g of solution (Figure 3b). An increased concentration and therefore viscosity of hypromellose solution correlated with an increase in residual volume (Figure 3c). The highest residual volume ( $0.76 \pm 0.06$  ml) was found with buffered 0.5% w/w solution left for 10 min.

### Simulated dosing: syringe

Before simulating the extraction of doses, the most precise measuring method was evaluated. The highest precision was achieved by



**Figure 3** (a) Percentage liquid loss when 5 g of hypromellose 0.4375% w/w solution was poured into a paper or plastic cup and left for 2 min (*t*-test,  $P > 0.05$ ). (b) Percentage liquid loss when 5 or 10 g of hypromellose 0.5% w/w was poured into a paper cup and left for 2 or 10 min (*t*-test: 5 versus 10 g and 2 versus 10 min,  $P > 0.05$ ). (c) Percentage volume loss when 5 g of different hypromellose strengths (% w/w) were poured into a paper cup and left for 2 or 10 min. A one-way ANOVA was performed to compare volume loss percentage at 2 and 10 min between different concentrations and between buffered and non-buffered solutions. The symbol \* indicates difference from 0.25% solution (\*\* $P < 0.01$ , \*\*\* $P < 0.001$ ) and # indicates difference from the equivalent non-buffered solution (# $P < 0.05$ ) at the same time point. All data are reported as mean  $\pm$  SD ( $n = 3$ ).

weighing the filled syringe (Figure 4a) and this measurement method has been used hereafter. Accuracy was also evaluated and no difference was found between the different doses measured (Figure 4b). All doses measured were lower than the target dose. All syringes presented a residual volume as expected, with the 5 ml syringe having the smallest residual volume (Figure 4c). Measurement error bias was tested and no significant difference was observed ( $P > 0.05$ , Figure 4d). The maximum amount of doses was extracted from a stock bottle using a different set of dose combinations as outlined in Table 1 (Figure 5). In all cases but one, the volume withdrawn in the consecutive doses was lower than the overall expected volume, indicating that under-dosing can be a common problem. The smaller the volume of the doses withdrawn or the higher the proportion of low doses, the lower is the residual volume in the bottle (Figure 5). This suggests that fewer extractions of a higher volume lead to an excess of residual volume compared with a higher number of small doses. No wastage was associated with the dosing.

### Simulated stock checks

Different stock check techniques were used to evaluate the volume loss associated with each of them. No statistical difference was identified; on average, all stock checks caused the loss of  $2.5 \pm 1.3$  ml of solution (Figure 6).

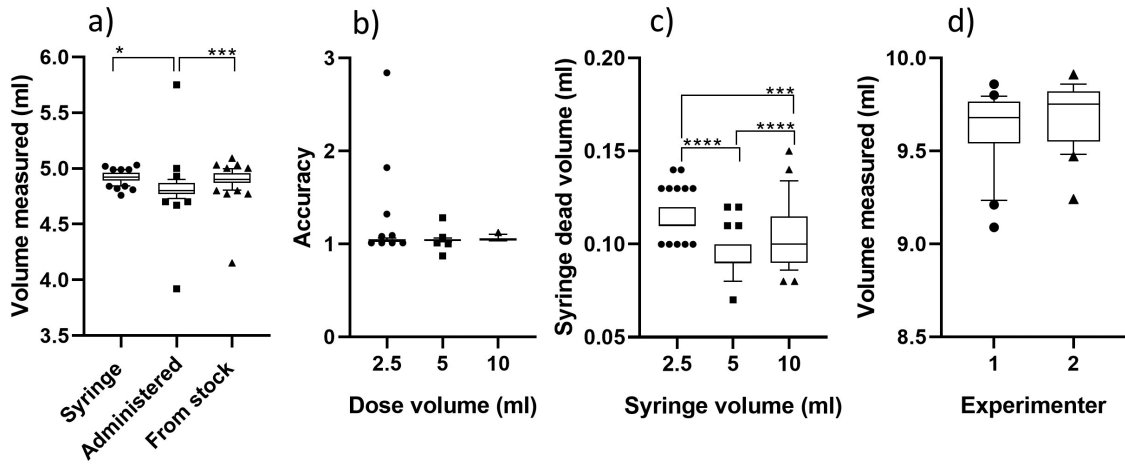
## Discussion

This study provides an insight into ways to improve current practice in the administration and record-keeping of oral CDs liquid

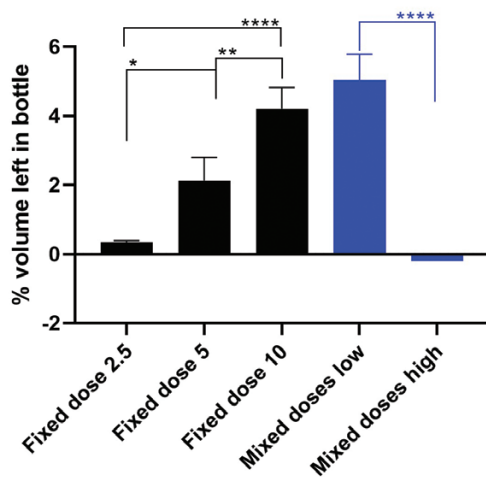
formulations. We demonstrated that dosing of these formulations with enteral syringes using a suitable bottle adaptor constitutes best practice and that local policy should dictate to keep stock checks to a minimum that allows to satisfy legal requirements. The study did not provide evidence to support a defined percentage discrepancy that should trigger further investigation. One of the limitations of the study was that a simulated drug solution was used and only oxycodone solution was simulated; more studies using the commercial formula and a variety of CD formulas would be beneficial. Furthermore, only one or two researchers, depending on the test performed, undertook the measurements, while in practice, multiple users could be withdrawing doses from the same bottle with a high probability of difference in dosing occurring. Therefore, there may still be some risk of bias in the data; however, it was not feasible for more individuals to undertake the experiment.

The storage, use and disposal of CDs in hospitals are governed by a combination of legal requirements and local policy. If unexplained or unacceptable discrepancies between recorded and actual volumes of CDs occur, this can trigger time-consuming investigations. There are no clear standards on the amount of acceptable loss during normal use of the product in a hospital setting. Overage included in manufacturer-supplied bottles and loss during each administration or balance check may contribute to discrepancies and overall loss. To determine actual losses rather than an arbitrary 'standard', a solution of hypromellose in citrate buffer with similar viscosity to oxycodone commercial solutions was formulated. We experimentally identified a concentration of 0.4375% w/w hypromellose in citrate buffer as the best formula to achieve the desired viscosity of 15 mPa·s. We demonstrated that the cup technique is associated, as expected, with high volume loss, using both paper and plastic cups, and that the percentage loss is dependent on the viscosity and the volume of the solution poured into the cup. Since the volume poured in the cup is generally not measured, this would lead to a very high and variable loss of liquid at every dose administered. Furthermore, the dependence on viscosity suggests that different results would be obtained if formulations of other CDs were used. Considering that the use of this open system is not in line with good infection control practice and results in residue being incorrectly discarded, we recommend this method be avoided.

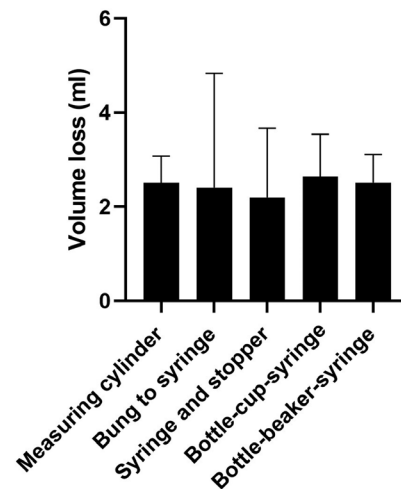
Previous studies<sup>[8,9]</sup> indicated that enteral syringes, when correctly used, provide the best dose accuracy, and for this reason, all subsequent experiments were performed using an enteral syringe and withdrawal of the solution *via* a rubber bung permanently fitted to the stock bottle. Our study showed that the use of the enteral syringes led to under-dosing, however, all measurements of volume contained in the syringe were within a 10% error, considered the maximum acceptable error.<sup>[10]</sup> The observed under-dosing is consistent with previous studies.<sup>[11]</sup> Measurement accuracy, with different volume doses, was also evaluated; accuracy was higher for larger volumes, but there was no statistical difference when comparing volumes in the range of 2.5–10 ml. We further evaluated the dead volume of the syringes used; this would not contribute to discrepancies but would contribute to the under-dosing observed. The difference in dead volume was observed to be correlated with the brand of enteral syringe used and the size of the syringe/dose measured. When using the same brand syringe a higher dead volume was observed for the smaller syringe. It is important to stress that the most appropriate size syringe should always be chosen according to the volume to be measured.<sup>[11,12]</sup> Finally, we evaluated the possible effect of measurement error bias by involving a second researcher; the latter was not provided with instructions on how to perform the measurements. Results showed no statistical difference between the measurements of the two researchers demonstrating that different individual techniques



**Figure 4** (a) Precision of syringe dose measuring methods using 5 ml of hypromellose 0.4375% (w/w) solution. One-way ANOVA ( $P < 0.001$ ): Tukey multicomparison test  $*P < 0.05$ ,  $***P < 0.001$ . (b) Volume-dependent accuracy of dose measurement. One-way ANOVA,  $P > 0.05$ . (c) Syringe dead volume after each administration. One-way ANOVA,  $P < 0.0001$ : Tukey multicomparison test  $***P < 0.001$ ,  $****P < 0.0001$ . (d) Volume of hypromellose 0.4375% w/w was measured by two different experiments with a 10 ml syringe. Data are represented as median (line within the box), 25th percentile (bottom of the box), 75th percentile (top of the box), 10th percentile (lower whisker), 90th percentile (upper whisker) plus outliers ( $n = 100$  for 2.5 ml,  $n = 50$  for 5 ml,  $n = 25$  for 10 ml).



**Figure 5** Percentage volume left in the stock bottle after extracting all doses as described in Table 1. Data are reported as mean  $\pm$  SD ( $n = 3$ ). A one-way ANOVA  $P < 0.0001$ ; Tukey multicomparison test  $*P < 0.05$ ,  $**P < 0.01$  and  $****P < 0.0001$ .



**Figure 6** Liquid loss caused by different methods of taking a stock level. Data are reported as mean  $\pm$  SD ( $n = 3$ ). One-way ANOVA,  $P < 0.05$ .

have little effect on possible volume loss. With the established methodology, we investigated if withdrawing a serial number of identical or varied doses would lead to a volume loss. Contrary to the findings of other researchers,<sup>16</sup> we always observed a residual volume in the bottle regardless of the dose-volume or combination of dose volumes withdrawn from the bottle. The residual volume was dependent on the type of doses taken from the stock bottle. These data confirm the observed under-dosing discussed above and suggest that discrepancies are very unlikely linked to the dosing when an enteral syringe is used with the correctly fitting rubber bung. This therefore implies that the regular stock checks are linked to discrepancies in residual volumes. Simulated stock checks were performed using different techniques as reportedly used in different hospital wards. The two measuring devices most commonly used on hospital wards for stock checks are 250 ml cylinders and 60 ml enteral syringes. In both cases, the liquid must be transferred

into the measuring device and back into the stock bottle. Fewer manipulation steps were expected to help eliminate contamination and potential volume loss when handling oral solutions. Pouring the solution into the cylinder was the procedure with the least manipulations, however, if the stock bottle is fitted with a permanent rubber bung this procedure would not be possible. Limitations in the use of the syringe have been identified. Firstly, in case of a volume higher than 60 ml more than one syringe must be used. Furthermore, the rubber bung that snugly fits the smaller syringes, used for dosing, is unlikely to fit correctly the 60 ml syringe. This can lead to spilling and introduction of air bubbles that can affect the measurements. In addition, equalising the pressure during this process could lead to spillage. Pouring into a syringe barrel also provided the possibility of errors as the scale would have to be read upside-down. Decanting the solution into a plastic cup or glass beaker could help with correct filling of the measuring syringe

but would add steps to the manipulation. In the absence of an ideal method, all methods were evaluated to quantify the volume loss they were associated with. Overall, each balance-taking method showed less than 5 ml loss in volume. It should be also considered that discrepancies are more likely to arise in wards with less frequent/smaller dosing because a higher number of stock checks must be performed before the stock is completely used.

## Conclusion

This paper identifies poor procedures that hospital ward staff should avoid in the dosing and administration of liquid oral CDs and best practice in dosing and stock checks of CDs is suggested to reduce discrepancies. Data demonstrated that dosing with enteral syringes was not associated with loss of volume from the stock bottle and it should be suggested as the best method for measuring and administering doses of liquid CD formulations. The evaluation of different methods to perform stock checks failed to identify a method without drawbacks. It is therefore suggested that local policy set stock checks to a minimum that allows to comply with the current law. This study provides healthcare staff with a greater understanding of the likely nature of possible losses based on the number of doses or volume checks that have been undertaken.

## Author Contributions

S.M. contributed to methodology, investigation, formal analysis, writing of original draft. P.R. contributed to conceptualisation, supervision, review and editing. A.F. and K.W. contributed to conceptualisation, review and editing. M.R. contributed to conceptualisation, supervision, methodology, formal analysis, writing of original draft, review and editing.

## Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors, but it was supported by the School of Pharmacy and Biomedical Sciences of the University of Portsmouth and the Pharmacy Department of the University Hospital Southampton NHS Foundation Trust.

## Conflict of Interest

The authors declare no conflicts of interest.

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