Paediatric and Perinatal Drug Therapy, 2007; 8 (2)

Dosing accuracy of measuring devices provided with antibiotic oral suspensions

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Background: **Liquid preparations are often used in order to meet the challenge of providing appropriate formulations for a wide range of differently aged paediatric groups. Dosing accuracy of pharmaceutical suspensions depends mainly on the homogeneity of the dispersion and the dosing aid supplied. However, previous studies mainly focussed on the effect of redispersibility of pharmaceutical suspensions on content uniformity.**

Methods: **Being aware that exact dosing is essential, the present study investigated the dosing accuracy of measuring devices provided with antibiotic oral formulations. All commercially available amoxicillin and erythromycin preparations as well as all clarithromycin suspensions (dosage 125 mg/ 5 ml) on the German market were included in this study.**

Results: **Dosing of suspensions using the measuring devices provided with the product may constitute a significant source for the lack of dosing accuracy. While whole spoonful dosing was relatively accurate, the median drug content determined for the ¼ and ½ marks on the measuring spoons provided with amoxicillin suspensions was 148% and 132% respectively. In comparison with amoxicillin preparations the measuring spoons supplied with erythromycin suspensions performed better, although overdosing, in the worst case 219%, was also observed when the ¼ graduations at the dosing spoon were used. In general, the magnitude of the dosing error correlated with an increase in the base area of the measuring spoons, revealing very flat measuring spoons to be unsuitable for accurate dose administration. Best results for dose uniformity were obtained using the syringes provided with clarithromycin suspensions, showing no significant deviation from the labelled content.**

Conclusion: **There is a clear need for action underlining the importance of standardising the measuring devices. A demand has also been incorporated recently in the EMEA guideline, on the suitability of the graduation of delivery devices for liquid dosage forms, pointing out the importance of this subject to the regulatory authorities.**

Paed Perinat Drug Ther 2007; 8: 61–70

Keywords: oral suspension – oral syringes – dosing accuracy – measuring devices – amoxicillin – erythromycin – clarithromycin

Introduction

Liquid preparations are often used in order to meet the challenge of providing appropriate formulations for a wide range of differently aged paediatric groups. In most therapy regimens, they are regarded as the golden standard and the most convenient method because the volume to deliver is easily adaptable to the patient's requirements using a simple and accurate dose delivery device. However, not all drugs can be formulated or made palatable in the form of a solution and must therefore be administered as tablets, capsules or suspensions. Because of their liquid character and the advantages in relation to other dosage forms, suspensions are an ideal alternative for children having difficulties in swallowing tablets or capsules. Unpleasant taste may be partly masked by a suspension and some drugs are chemically more stable in suspensions than in solutions.

Most newborns, infants and preschool children receive antibiotics in the form of a suspension. In order to increase the shelf-life, antibiotics are usually formulated as dry powders, which have to be reconstituted to a suspension prior to administration. The primary disadvantage of suspensions is their physical instability, as they may form sediments resulting in a lack of dose uniformity. Therefore, suspensions should usually be redispersed by shaking. This may lead to dosing errors if the preparation is not completely resuspended before measuring the dose[1].

Previous studies mainly focused on the effect of the redispersibility of pharmaceutical suspensions on content uniformity[2,3]. They reported that one out of three commercial erythromycin ethyl succinate oral suspensions did not perform satisfactorily, resulting in an increase in drug content of the measured volumes prior to emptying, indicating segregation of solid constituents upon standing and incomplete redispersion[2,3].

However, dosing accuracy of pharmaceutical suspensions does not only depend on the homogeneity of the dispersion but also on the properties of the dosing aid supplied. Thus the devices used for dose dispensing play a crucial role in assuring accurate dose measurement and controlled administration. In the past physicians prescribed antibiotics using teaspoons as the measuring unit. Several studies have documented the inaccuracy of this method, especially when parents use household teaspoons, since the volume of teaspoons may range from 2 to 9 ml[4-7]. Today a variety of dosing devices are marketed with liquid preparations including syringes, measuring spoons, cups or beakers.

In general, the dosing accuracy in the European pharmacopoeia 5.0 (2.9.5. and 2.9.6.) for single dose preparations like tablets, capsules etc is covered by the determination of the content and weight of a representative number of individual units but this is mostly not the case for liquid dosage forms in multidose containers[8]. In the case of liquid multidose containers, where the recommended dose needs to be administered with a measuring device, the European Pharmacopoeia 5.0 (2.9.27.) rules the determination of dosing accuracy, by just determining the uniformity of mass by weighing a representative number of single doses. In a previous study devoted to the content uniformity of 5 ml doses of oral amoxicillin suspensions, taken by a syringe, it was shown that the variability in the amoxicillin content measured in the individual doses was much higher than the variability in the weight of the individual doses, indicating that an assessment of dosing accuracy and homogeneity of suspensions based upon the determination of the weight of doses alone may be misleading. Therefore it was suggested to complement the pharmacopoeial requirements, with demands for the determination of the drug content in doses taken from multiple dose-containers[9].

Being aware that exact dosing is essential, the present study was intended to investigate the dosing accuracy of measuring devices provided with antibiotic oral formulations over a wide range of dosing volumes. The investigation focuses on commonly prescribed antibiotics in paediatrics and includes all commercially available liquid amoxicillin, erythromycin and clarithromycin liquid preparations on the German market. Moreover, the consequences of not exactly adhering to the shaking instructions by the parent/patient are discussed considering amoxicillin oral suspensions as an example.

Materials and methods

Reconstitution and sampling of suspensions

All commercially available amoxicillin preparations in Germany (April 2004), all clarithromycin preparations (dosage 125 mg/5 ml, September 2005) and all erythromycin containing oral suspensions (March 2006) were included in the study.

The suspensions were usually prepared by the same person with fresh tap water according to the instructions in the leaflets. Initially the bottle was filled up to 1 cm below the graduation and was vigorously shaken. After the foam had settled, tap water was added up to the marked limit.

After constituting the oral suspension as labelled, the active component concentration was determined by sampling with a calibrated pipette. Afterwards the freshly shaken suspension was dispensed on the enclosed dosing aid, considering each partitioning such as ¼, ½ and 1 spoon or 1, 2, 3, 4, 5 and 6 ml in the case of cups. While withdrawing the dose, great importance was attached to the simulation of the dispensing behaviour in every day life, thus measuring was intentionally not carried out at eye level. Each sample was analysed in triplicate using validated precise analytical methods.

For all investigations an isocratic high performance liquid chromatography (HPLC) system was used consisting of an injector, HPLC pump, ultraviolet detector, autosampler (Jasco, Groß-Umstadt, Germany) and a printer (Panasonic). Analytical reagents, chemicals, distilled water, methanol, tertiary butyl alcohol and acetonitrile in HPLC grade were purchased from Merck (Darmstadt, Germany).

Amoxicillin sample and standard preparation

After withdrawing the respective dose with the dosing device, the sample was quantitatively transferred into a 500 ml volumetric flask which was then filled to the mark with distilled water. The solution was shaken for 10 minutes and filtered through a 0.45µm PVDF filter. Afterwards each sample was placed in a vial and stored immediately in the cooled autosampler.

The standard aqueous solutions (stock solutions) were prepared by weighing appropriate amounts of amoxicillin trihydrate and lithium clavulanate, which were then dissolved in distilled water to yield a concentration of 2500 µg/ml (amoxicillin trihydrate) and 200 µg/ml (lithium clavulanate). Whereas lithium clavulanate dissolved quickly, frequent shaking and sonicating with ultrasound were necessary to bring the sparingly soluble amoxicillin trihydrate in solution. After preparation, the solutions were stored immediately in the cooled autosampler.

Amoxicillin assay

Lithium clavulanate CRS and Amoxicillin trihydrate CRS were used as standards. The HPLC conditions were specified according to USP monograph 'Amoxicillin and Clavulanate Potassium for Oral suspension' and validated according to the ICH guideline Q2A.

Thus liquid chromatography was carried out on a nucleodur 100-5 C18 gravity 4.0 mm × 25.0 cm column in conjunction with a guard column using a mobile phase consisting of methanol-sodium phosphate buffer (pH 4.4 adjusted to with phosphoric acid) (5 : 95, v/v) at a flow rate of 1.2 ml/min with an injection volume of 10 µl. The detection was carried out at a wavelength of 220 nm. The running time did not exceed 8 minutes.

Clarithromycin sample and standard preparation

An accurately measured volume of 5 ml of the constituted oral suspension were transferred into a 100 ml volumetric flask and diluted with the aid of about 33 ml of 0.067 M dibasic potassium phosphate. After shaking for 30 minutes, the samples were diluted with methanol, mixed and sonicated for 30 minutes. After cooling down, the samples were diluted to volume with the aid of a stirring bar stirring for 60 minutes. Finally 20 ml of the sample stock solution was diluted with mobile phase to 50 ml and filtered for analysis.

For preparing the standard solution, 20 mg clarithromycin CRS was quantitatively dissolved in methanol in a 10 ml volumetric flask. After shaking, 5 ml of the standard stock solution were diluted with mobile phase to a volume of 20 ml. A portion of this solution was passed through a filter of 0.45 µm porosity and was analysed afterwards.

Clarithromycin assay

The HPLC conditions were chosen according to USP monograph 'Clarithromycin for Oral suspension' and validated according to the ICH guideline Q2A. Thus liquid chromatography was carried out on a Thermo Hypersil HyPurity C18 column, 4.6 mm x 15.0 cm at a constant temperature of 50°C using a mobile phase consisting of methanol-monobasic potassium phosphate buffer (0.067 M, pH 3.5 adjusted phosphoric acid) (600 : 400, v/v) at a flow rate of 1.0 ml/min with an injection volume of 50 µl. The detection was carried out at a wavelength of 210 nm. The running time did not exceed 12 minutes.

Erythromycin sample and standard preparation

In general, erythromycin in drug products is determined by microbiological assay measuring the growth inhibition of *Staphylococcus Aureus* (United States and European Pharmacopoeia monographs). Although used very often, microbiological assays are known for their lack of sensitivity because of interference with related substances also contributing to biological activity.

Therefore, a sensitive and selective HPLC with ultraviolet (UV) detection at 215 nm was developed for the identification and quantification

of erythromycin and related substances in drug products. The method was validated according to the ICH guideline Q2A.

Erythromycin ethylsuccinate was determined as erythromycin after hydrolysis. The hydrolysis reagent was prepared by dissolving dibasic potassium phosphate in water (2 in 100) and adjusting the pH with phosphoric acid to 8.0. An exactly measured volume of 5 ml constituted oral suspension was placed in a 100 ml volumetric flask. After adding 50 ml methanol, the samples were diluted with 40 ml buffer of pH 8 and were vigorously shaken. The samples were left at room temperature overnight to allow hydrolysis of the succinic acid. On the next day, the solutions were mechanically shaken and diluted with buffer (pH 8) to volume. The samples were filtered through a 0.45 µm filter.

Erythromycin standard was prepared by weighing 22.5 mg of erythromycin A base CRS, dissolving it in 5 ml methanol and then diluting with buffer (pH 8) to 10 ml. Standards were allowed to cool to room temperature before making final volumetric adjustments.

Erythromycin assay

Erythromycin A CRS was used as standard. The buffer of pH 8 was prepared by dissolving dibasic potassium phosphate (3.5 in 100) and adjusting the pH with phosphoric acid to 8.0. 50 ml of buffer (pH 8.0) was then mixed with 400 ml water, 165 ml tertiary butyl alcohol, 30 ml acetonitrile and was finally diluted with water to 1000 ml.

The isocratic chromatographic separation was carried out on a polymerX 7 µm column, 4.6 mm × 25.0 cm at a constant temperature of 75°C with a flow rate of 0.8 ml/min and an injection volume of 50 µl. Detection was carried out at a wavelength of 215 nm. The running time did not exceed 12 minutes. During the whole analysis the autosampler was cooled.

Methods for the characterisation of sedimentation profiles

Sedimentation profiles were assessed for 6 different amoxicillin oral suspensions. Two bottles of each brand were prepared with fresh tap water according to the package inserts instructions. Following the manufacturer's instructions, one bottle was reconstituted by shaking before each dosing. The second one was not shaken at all through the whole investigation period. According to the usual dosing frequency samples, 5 ml samples (= 1 volume of measuring spoon) were taken from both bottles three times a day for one week. The oral suspension was spilt out carefully and samples were analysed as prescribed before.

Results

A total of 50 oral amoxicillin suspensions (including 32 amoxicillin preparations and 18 amoxicillin/clavulanic acid preparations), 14 erythromycin and 8 clarithroymcin suspensions were included in this study, aimed to investigate dosage errors associated with the measuring devices provided with the product. In order to obtain informative results, dosing uniformity has been evaluated by determining the content and not the mass of individual doses, as recommended. The results of dosing accuracy for the three different antibiotics are summarised in Tables 1–3. The outcomes obtained reveal huge variability in dosing as a result of the measuring device used and the total volume measured. Whereas amoxicillin and erythromycin oral suspensions are primarily provided with measuring spoons for dose administration, syringes are usually supplied with clarithromycin suspensions.

Amoxicillin

The highest dosing variability was observed with amoxicillin oral suspensions, showing the largest diversity in measuring spoons with regard to size and depth. Manifest overdosing (in the worst case 212%) was noticed when the ¼ and ½ graduation marks on the dosing spoon were used. While total spoonful dosing with a median of 105.5% was relatively accurate, the median using the ½ and the ¼ graduations on the dosing spoon was 132% and 148%, respectively. The drug contents ranged between 84.3% and 176.1 % using the ½ graduation and with the ¼ graduation the lowest content determined was 83.1 % and the highest 212.1%. The reproducibility within measurements (calculated as the variation coefficient of three repetitive measurements with the same measuring spoon) using the ¼ and ½ graduations ranged between 1.4% and 24%, indicating how difficult it is when using some measuring spoons to ensure dispensing the same amount of drug even upon repetitive measuring by the same person with the same spoon. The reproducibility between all measurements (expressed as variation coefficient of all measurements) averaged 8% when using the ¼ or ½ graduation of the spoons, confirming the overdosing observed in this study. Only one amoxicillin product was provided with a measuring cup. In this case the deviation of the determined dose contents ranging between 90.3% and 98.4% using different volumes (1, 2, 3, 4, 5 and 6 ml) was smaller than 10% from the labelled value.

Table 1 Dosing accuracy of commercially available amoxicillin (n =49) showing the actual doses (mg) and the drug content expressed as percentage in reference to the declared amount (%) upon administration with ¼, ½ and full spoon

Declared amoxicillin conc / full spoon	**Dosing accuracy of measuring devices provided with amoxicillin (measuring spoon)**					
	¼ spoon (%)	**¼ spoon (mg)**	**½ spoon (%)**	**½ spoon (mg)**	**full spoon (%)**	**full spoon (mg)**
125 mg	147.1	46.2	136.8	85.5	174.1	217.6
	130.1	40.7	125.3	78.3	100.5	125.6
	174.3	54.5	127.8	79.9	103.9	129.9
	150.2	46.9	140.9	88.1	102.6	128.3
	165.0	51.6	148.7	92.3	109.6	137.0
	128.8	40.3	107.8	67.4	96.0	120.0
200 mg	175.5	109.7	164.1	205.1	125.6	314.0
	*	*	129.3	129.3	143.7	287.4
	*	*	120.8	120.8	131.4	262.8
	*	*	138.8	138.8	143.1	286.2
	212.1	106.1	154.6	154.6	132.3	264.6
	191.4	95.7	118.2	118.2	94.7	198.4
	*	*	135.4	135.4	134.2	268.4
	*	*	120.3	120.0	121.7	243.4
	*	*	136.0	136.0	133.6	267.3
250 mg	143.1	89.6	147.6	184.5	109.2	273.0
	190.1	118.8	176.1	220.1	127.4	318.5
	161.8	101.1	147.0	183.3	116.1	290.3
	145.9	91.2	144.3	180.4	116.0	290.0
	159.8	99.9	129.4	161.8	97.9	244.8
	145.9	91.1	144.3	180.4	116.1	290.0
	90.7	56.7	96.6	120.8	94.5	236.3
	131.4	82.1	141.3	176.6	107.5	268.8
	132.7	82.9	127.1	158.9	106.1	265.3
	176.5	110.3	154.0	192.5	111.0	277.5
	172.0	107.5	156.1	195.1	133.1	332.8
	139.2	87.0	121.9	152.9	105.0	262.5
	*	*	*	*	93.1	232.8
	165.2	103.3	111.6	139.5	90.6	226.5
	152.3	95.2	135.2	169.0	100.3	250.8
	137.5	85.9	115.4	144.3	106.0	265.0
	152.0	95.0	131.8	164.8	102.2	255.5
	114.3	71.4	109.7	137.1	91.2	228.0
	145.5	90.9	122.9	153.6	101.6	254.0
	110.3	68.9	99.0	123.8	79.1	197.8
	*	*	*	*	94.4	236.0
400 mg	*	*	132.2	264.4	133.9	535.6
	*	*	102.4	204.8	101.1	404.4
	*	*	90.8	181.6	102.7	410.8
	*	*	84.7	169.4	91.5	366.0
500 mg	154.6	193.3	136.7	341.8	112.2	561.0
	137.7	172.1	151.4	378.5	110.8	554.0
	117.6	146.3	147.1	367.8	103.4	517.0
	169.0	211.3	132.0	330.0	108.8	544.0
	83.1	103.9	84.3	210.8	95.5	475.0
	168.7	210.9	140.9	352.3	98.9	494.5
	210.8	263.5	160.8	402.0	139.3	696.5
750 mg	129.3	242.4	119.6	448.5	99.3	744.8
	148.3	278.1	131.5	493.1	97.1	728.3
Median (%)	**148.3**		**132**		**105.5**	
Dosing range (%)	**83.1–212.1**		**84.3–176.1**		**79.1–174.1**	

* Indicates the absence of the respective graduation on the measuring spoon

The table does not include the results of the dosing accuracy of the only measuring cup provided with one of the amoxicillin suspensions (results are mentioned in the text).

Table 2 Dosing accuracy of commercially available erythromycin (*n*=14) showing the actual doses (mg) and the drug content expressed as percentage in reference to the declared amount (%) upon administration with ¼, ½ and full spoon

Declared erythromycin conc / full spoon	Dosing accuracy of measuring devices provided with erythromycin (measuring spoon)					
	¼ spoon (%)	¼ spoon (mg)	½ spoon (%)	½ spoon (mg)	full spoon (%)	full spoon (mg)
100 mg	110.3	27.7	119.6	59.8	100.8	100.8
200 mg	119.0	59.5	102.5	102.5	104.1	208.2
	114.5	57.3	120.6	120.6	105.6	211.2
	219.2	109.6	134.6	134.6	120.8	241.6
	88.8	44.4	83.7	83.7	82.0	164.0
	*	*	120.5	120.5	118.6	237.2
	93.9	47.0	103.9	103.9	114.7	229.4
	148.6	74.3	133.5	133.5	125.5	251.0
	*	*	92.4	92.4	84.3	168.6
400 mg	94.2	94.2	104.5	209.0	105.6	422.4
	87.9	87.9	98.8	197.6	93.1	372.4
	126.7	126.7	94.6	189.2	96.0	384.0
	*	*	92.2	184.4	98.0	392.0
600 mg	104.2	156.3	92.7	278.1	91.3	547.8
Median (%)	**110.3**		**103.2**		**102.45**	
Dosing range (%)	**87.9–219.2**		**83.7–134.6**		**82–125.5**	

* Indicates the absence of the respective graduation on the measuring spoon

Erythromycin

In comparison to amoxicillin preparations, the measuring spoons supplied with erythromycin suspensions performed better. Although overdosing was also observed, the median drug content determined for the ¼ and ½ marks was 110.3% and 103.2%, respectively, compared to a median content of 148.3% and 132% for amoxicillin. Nevertheless, extreme overdosing was also observed with certain dosing devices supplied with erythromycin suspensions reaching up to 134.6% when using the ½ graduation and 219.2%, when using the ¼ mark of broad measuring spoons. Again whole spoonful dosing with a median of 102.5% was relatively accurate. The median dosing accuracy of amoxicillin and erythromycin preparations using spoonful dosing as well as ¼ and ½ marks of the measuring spoon is presented in Figure 1.

Clarithromycin

The best results for dose administration were obtained using the syringes provided with clarithromycin suspensions, where no significant

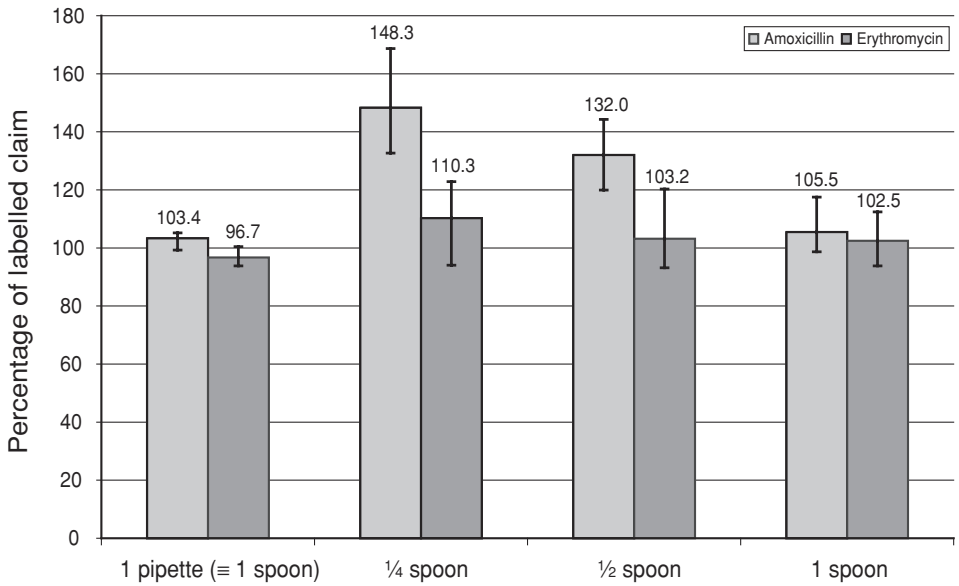


Figure 1 Dosing accuracy of commercially available amoxicillin (*n*=49) and erythromycin (*n*=14) oral suspensions on the German market showing the median and the interquartile range.

Table 3 Dosing accuracy of commercially available clarithromycin (n=8) showing the actual doses (mg) and the drug content expressed as percentage in reference to the declared amount (%) upon administration with ¼, ½ and full spoon

Declared clarithroymcin conc / full syringe	Dosing accuracy of measuring devices provided with clarithromycin (syringe) ¼ syringe (%)	¼ syringe (mg)	½ syringe (%)	½ syringe (mg)	full syringe (%)	full syringe (mg)
125 mg	*	*	98.5	92.3	101.5	126.9
	*	*	98.1	92.0	96.5	120.6
	*	*	101.5	95.2	105.8	132.3
250 mg	91.6	57.3	103.3	129.1	101.9	254.8
	101.4	63.4	102.6	128.3	104.5	261.3
	102.0	63.8	104.1	130.1	100.5	251.3
	*	*	101.3	126.6	99.5	248.8
	*	*	98.3	122.9	102.6	256.5
Median (%)	**101.4**		**101.4**		**101.7**	
Dosing range (%)	**91.6–102**		**98.1–104.1**		**96.5–105.8**	

* Indicates the absence of the respective graduation on the measuring spoon

deviation from the labelled claim was observed using ¼, ½ and 1 units of the syringes. The corresponding median drug contents are presented in Figure 2.

Influence of the shaking behaviour of patients/parents on the dosing accuracy on the sample of amoxicillin suspensions

Based on the experience that laymen often do not exactly follow the licensed instructions for drug preparation, *the effect of not shaking the reconstituted suspension before dispensing* on dosing accuracy has been investigated on the basis of six most frequently prescribed amoxicillin suspensions. Depending on the viscosity of the suspensions, the six sedimentation profiles of the unshaken formulations could be combined to three different profiles, which are represented in Figure 3. Suspensions of very low viscosity apparently sediment within a few hours. This was reflected by the low amoxicillin concentration not exceeding 8% of the labelled claim measured at five hours in sedimentation profile 1. On the other hand, suspensions of higher viscosity mimic a visually stable suspension and separation of phases becomes clearly visible only after 24 hours. However, this apparent stability within the first 24 hours is not reflected by the concentrations measured, which declined up to 50% within five to ten hours in sedimentation profile 2. After 24 hours the amoxicillin content was only 5.7% and remained constant for the following three days, rising up to concentrations above 100% in the residual doses at the end of the investigation period because of cumulated and sedimented amoxicillin. Finally, suspensions of very high viscosity give the impression of being stable over the whole investigation period of five days showing no apparent separation of phases, but in reality also in these cases invisible segregation takes place as can be demonstrated from the continuous decrease in the amoxicillin concentrations in the first 48 hours in sedimentation profile 3.

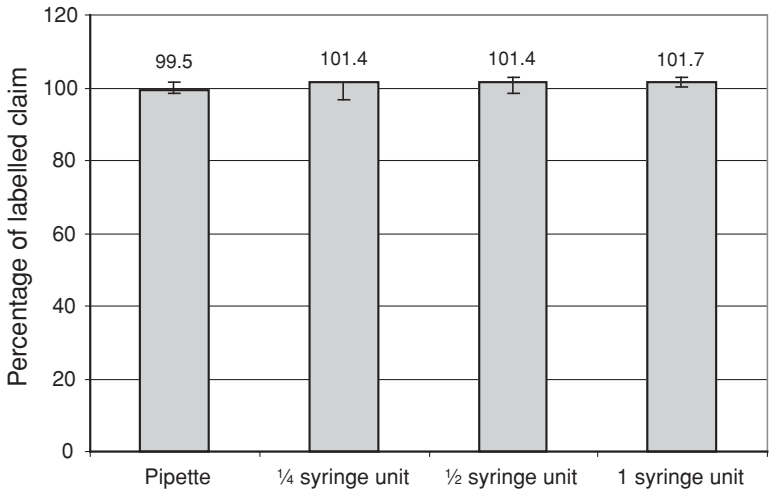


Figure 2 Dosing accuracy of all commercially available clarithromycin oral suspensions with 125 mg/5 ml showing the median and the interquartile range.

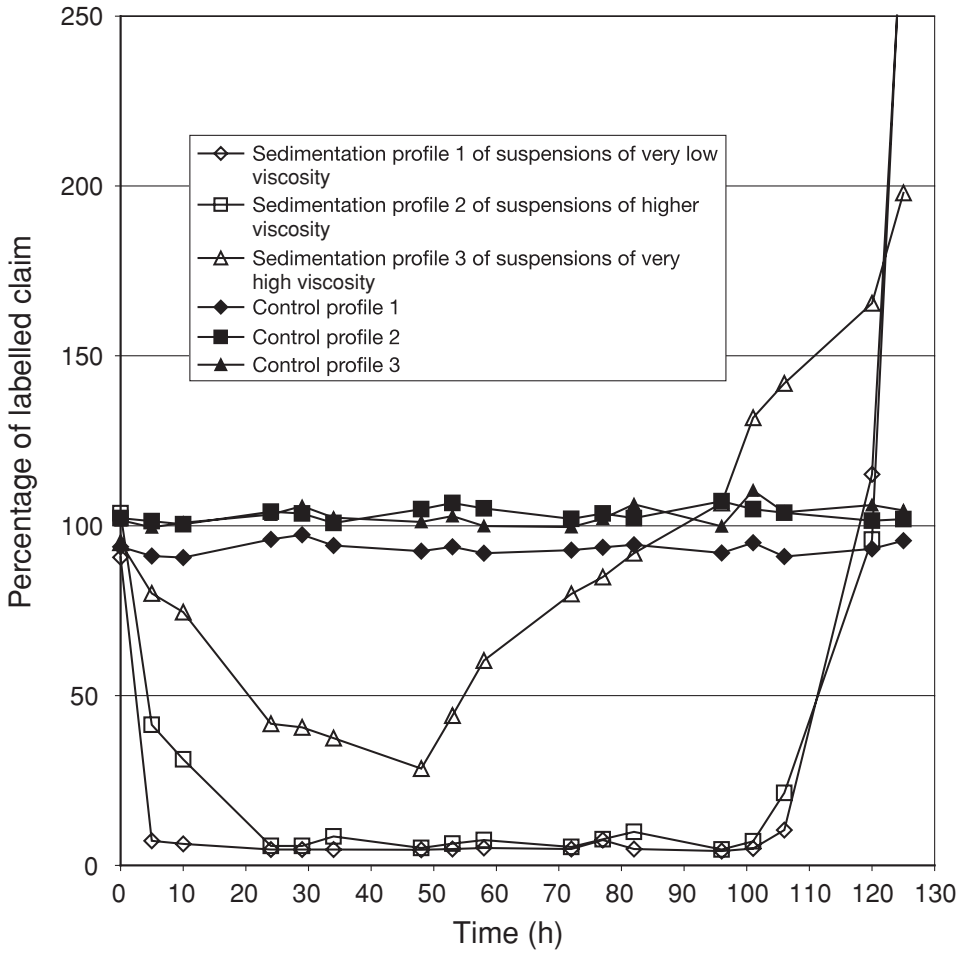


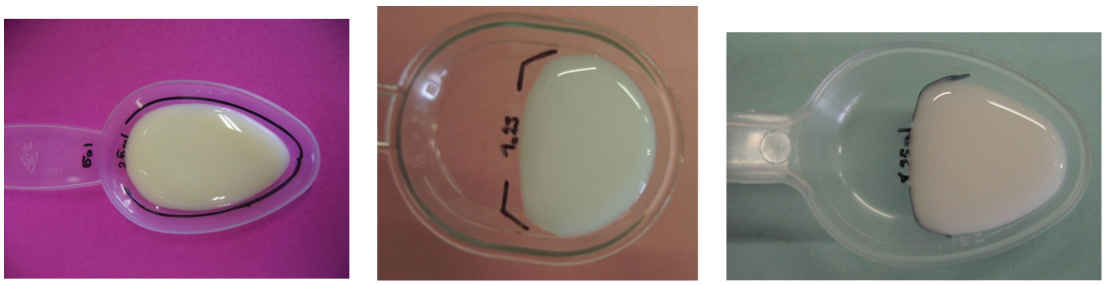
Figure 3. Sedimentation profiles of reconstituted oral suspensions not shaken before dose withdrawal compared to the sedimentation profile of regularly shaken suspensions. The points on the graph represent the percentage of the anticipated concentrations in shaken and unshaken samples. Open symbols represent unshaken, filled ones are controls (shaken formulations).

Discussion

This study shows that dosing of suspensions using the measuring devices provided with the product may constitute a significant source for the lack of dosing accuracy. The overall results reveal, that using the ½ and ¼ graduation marks at the dosing spoon manifest overdosing can be observed. The deviation was larger the smaller the volume measured. This was greatest with amoxicillin suspensions.

Thereby the magnitude of the dosing error correlated with an increase in the base area of the measuring spoon. Very flat measuring spoons having a large base area lead to manifest overdosing (up to 160.8%) as can be seen in Figure 4a, clearly pointing out the difference in volume obtained by exactly measuring a 2.5 ml dose using a certified pipette compared to the use of the ½ marking of the measuring spoon. Similar discrepancies between the nominal and actual volumes were also obtained using flat and broadly based measuring spoons provided with erythromycin suspensions (Figure 4b). However, in general, the measuring spoons provided with erythromycin products performed better than those supplied with amoxicillin products because of their smaller base area. Nevertheless, exact dosing of small volumes may be also obtained with measuring spoons, if they are deep enough and have a small base area as can be seen in Figure 4c. Moreover, it was shown that measuring cups generally ensure better dosing accuracy than measuring spoons. This may be attributed mainly to their greater depth and smaller base area.

As can be deduced from the results obtained with clarithromycin suspensions, dosing with syringes should be preferred, since they provide more accurate dosing. The syringe presented in Figure 5, which is supplied with a clarithromycin suspension, is not just characterised by high dosing accuracy but also facilitates dosing because of the two graduation scales applied on the syringe, being devoted on the one hand to the volume and on the other hand to the weight of the child. In contrast to usual syringes the design of this syringe prevents the attachment of a luer



(a) (b) (c)

Figure 4 The discrepancy between the nominal and actual volume of different measuring spoons. (a) Difference in volume obtained when measuring a 2.5 ml dose with a pipette compared to the use of the ½ graduation of a measuring spoon supplied with amoxicillin. (b) Difference in volume obtained when measuring a 1.25 ml dose with a pipette compared to the use of the ¼ graduation of a measuring spoon supplied with erythromycin. (c) Example of a measuring spoon enabling exact dosing at 1.25 ml dose.

needle, thus eliminating potential errors from wrong-route administration of oral liquid medication. Moreover, using proper adapters may ensure drip-free filling of the medication. Since the doses may only be withdrawn by turning the bottle upside down, the formulation is automatically shaken. Hence extra shaking prior to dose dispensing is no longer necessary, thus reducing the incidence of dosing errors assigned to unshaken suspensions. Although syringes are already routinely used in the United Kingdom, the worldwide use of syringes today is still limited, mainly because of economic reasons. Nevertheless, progress in developing new dosing devices proceeds rapidly in view of the observed inaccurate dosing associated with several measuring devices. For example, a novel patented drug delivery system using the SIP-technology (originating from 'sipping a liquid with a straw') for the precise and easy oral administration of clarithromycin to children has been introduced recently into the market, thus extending the spectrum of dosing devices[10]. This technology provides premeasured doses as solid pellets in a drinking straw, which are dissolved by adding a specified volume in the straw and are finally sipped by the child with the aid of the straw.

Figure 5 Dosing syringe supplied with clarithromycin suspensions that facilitates dosing because of the two graduation scales applied on the syringe, being devoted on the right to the volume and on the left to the weight of the child.

However, it is not only the devices used for dose delivery that play a crucial role in assuring accurate dose measurement, but also the homogeneity of suspensions. Thus the attention of the parent/patient should be directed towards the necessity of shaking the suspensions prior to dose dispensing. The present study revealed manifest dosing errors, if the suspensions were administered without shaking. This may be attributed to the sedimentation of the drug at the bottom, leaving a very diluted solution of the antibiotic, often not exceeding 10% of the labelled content, which is actually dispensed, if the suspension has not been shaken before. This is very critical, since too low doses may lead to the failure of antibiotic treatment, at the same time promoting the development of resistance towards antibiotics. Therefore, communication between pharmacists and parents is of vital importance, especially in the case of highly viscous suspensions which mimic a visually stable suspension, in order to ensure the best possible outcome for children.

In summary, it could be shown in the present study that in view of the inadequate dosing accuracy of many measuring spoons provided with oral suspensions, there is a clear need for action. Although accuracy to the nearest of 0.1 ml is not required for all medications, accurate measuring tools should be provided with the medication to prevent dosing errors reaching up to 219%. Therefore the device selected should be appropriate to the type of formulation and volumes to be measured.

Based on these results some pharmaceutical companies have already started to substitute the formerly used measuring spoons with syringes for the delivery of their oral medication. Nevertheless, in the future higher demands regarding the investigations on the accuracy of graduation on dosing aids should be made. A basis therefore is already provided by the EMEA draft guideline on the suitability of the graduation of delivery devices for liquid dosage forms, which demands that graduation should be applied to the dosing device in such a manner that accurate and precise dosing is guaranteed.

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CrossRefs are available in the online published version of this paper:
http://www.librapharm.com
Paper PPDT-0185_2, *Accepted for publication:* 12 July 2007
Published Online: 20 August 2007
doi:10.1185/146300907X178950