


REGULAR ARTICLE

Adjusting the dose in paediatric care by dispersing fragments of four different aspirin tablets

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Abstract

Aim: Tablets can be manipulated in several ways to obtain a fraction as the dose—a practice frequently seen in paediatric care due to lack of suitable formulations. Splitting tablets prior to fragment dispersion in a small volume of liquid is one such method. The objective of this study was to investigate the accuracy and precision of this method.

Methods: Four different types of aspirin tablets (two dispersible, one conventional and one chewing) were split with a tablet splitter into half and quarter fragments. The fragments were dispersed in a medicine measure or an oral syringe. The amount recovered was determined by UHPLC analysis.

Results: The largest quarter fragments ranged from 26.7% to 31.5% of the full tablet weight. Dispersing the fragment in an oral syringe, the amount recovered was greater than 90.8% of the fragment manipulated for all four tablet types, when rinsing was performed. Dispersing the fragment in a medicine measure, the amounts recovered spanned from 32.9% for the conventional tablets to 98.7% for one of the dispersible tablets.

Conclusion: Dispersion of half or quarter tablets directly in an oral syringe, but not a medicine measure, could give satisfactory recovery from fragments of all the investigated aspirin tablets.

KEYWORDS

aspirin, dose accuracy, drug manipulation, paediatric care, tablets

1 | INTRODUCTION

When caring for children in the clinic, it is frequently a practical problem that age-appropriate dosage forms are lacking. This has been a topic of concern for a considerable time.¹⁻³ To find practical solutions in this situation, drugs approved for use in the adult population are sometimes used off-label.^{3,4} Manipulation of drug form (eg

splitting and crushing tablets, opening capsules, dispersing the resulting powders) is one type of such off-label handling.^{5,6}

A recent study demonstrated that in 17% of all administrations to children, drug form is manipulated outside what is described in the Summary of Product Characteristics (SmPC) prior to administration.⁷ Although the manipulation is performed to achieve an accurate dose for the individual child, the actual dose obtained is often

Abbreviations: API, active pharmaceutical ingredient; SmPC, Summary of Product Characteristics; UHPLC, ultra-high-pressure liquid chromatography.

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unknown, and as tablet types differ in their characteristics, they could differ in their suitability for such handling. In a previous study, we investigated the accuracy and precision with respect to the intended dose that could be obtained for fractions when dispersing different aspirin tablets in a small liquid volume (10 mL) before a proportion (1–2 mL) was withdrawn⁸; a procedure arranged to mimic one kind of manipulation performed in the paediatric ward. Using the method of fraction extraction, marked variations in resulting aspirin amounts were observed, both between the different kinds of tablets, and for different extraction procedures (eg relating to the degree of mixing and the depth of extraction). For instance, when the 10 mL tablet dispersion was stirred in a standardised manner prior to extraction of a 1 mL volume, 13% or 83% of the fraction was recovered for a conventional and dispersible tablet, respectively, indicating a non-trivial differences between tablet types using a certain manipulation method.

Extraction of a fraction from a whole dispersed tablet, though in frequent use, is not the only method that can be used for tablet manipulation, however. When the MODRIC group (*Manipulation of Drugs Required in Children*) prepared their guideline on manipulation of dosage forms in paediatric care, they recommend splitting: 'Tablets should be split in preference to dispersing or crushing tablets and taking a proportion'.⁹

The aim of the study at hand was to investigate the suitability of a manipulation method for tablets more in line with the current MODRIC recommendation: splitting the tablets first, then dispersing the fragment—the last step often being required in paediatric care to aid administration. The aim was to explore factors of importance to the result obtained in such a manipulation: factors concerning the splitting itself, the device used for dispersion and the rinsing.

As the topic in question has received little attention, the study was initiated to obtain knowledge about manipulation effects of tablets, more in general. However, as in the previous study, the test subject was aspirin tablets—used in paediatric care for the antiplatelet action,¹⁰ and the results would shed light on manipulation effects for tablets containing this substance, in particular. In the treatment of neonates and children, aspirin has been recommended in doses of 1–5 mg/kg, up to 75 mg, for antiplatelet effect and prevention of thrombus formation.¹⁰ Because aspirin tablets typically contain 75 mg or more of the drug substance, manipulation to obtain a fraction will often be needed. In this study, to illustrate relevant dose adjustments performed in the clinics to tailor a paediatric dose, half and quarter tablets were investigated, as this would represent both relevant doses for some children from some tablets, and practically manageable splitting without weighing the fragments.

The same four aspirin tablets investigated previously with regard to the accuracy obtained with respect to the intended dose through fraction extraction⁸ were also investigated here, so that different methods of manipulation could be compared. Initially, aspirin tablets were chosen because such tablets have been found to be manipulated in the hospital ward,⁷ because several tablet types were

Key notes

- To simulate dose adjustment, four different aspirin tablets were split into half or quarter fragments, and dispersed in a medicine measure or an oral syringe.
- We investigated splitting accuracy and whether accurate aspirin amounts could be recovered from the dispersions.
- Both splitting and dispersion added to variability, and dispersion directly in the oral syringe gave the most accurate recovery for the half and quarter tablets.

available in the market and because manipulation has been shown to add dose variation for one aspirin tablet in the past.¹¹

As for the clinical relevancy of obtaining accurate aspirin doses, the drug is used over different ranges under different protocols,¹² and also regarded as 'well tolerated',¹³ indicating that accuracy with respect to the intended dose would be even more important for other drug substances, with a narrower therapeutic window. However, in conjunction with aspirin it has also been warned about significant adverse effects, many of which being dose-related,¹³ indicating that striving for an accurate dose is valuable.

2 | MATERIALS

Acetylic salicylic acid ($\geq 99.0\%$) and salicylic acid ($\geq 99.0\%$) were provided by Sigma-Aldrich Co., St. Louis, MO, USA. Ortho-phosphoric acid (85%) and potassium dihydrogen phosphate were provided by Merck KGaA, Darmstadt, Germany, or Sigma-Aldrich Co (Fluka), St. Louis, MO, USA. Methanol, HPLC grade, was provided by Rathburn Chemicals Ltd., Walkerburn, Scotland.

The tablets investigated were *Dispersible Aspirin* 75 mg, Aspar Pharmaceuticals Ltd., London, UK; *Bayer Chewable* 81 mg, Bayer Healthcare LLC, Morristown, NJ, USA; *Disprin* 300 mg, Reckitt Benckiser Healthcare (UK) Ltd, Hull, UK; and *Aspirin* 500 mg, Bayer AB, Solna, Sweden. None of the tablets had score lines. The tensile strength of the tablets was as follows: 1.45, 1.58, 1.22 and 0.87 N/mm², respectively, and the pH of one tablet dispersed in water for each of the tablets studied was 4.6, 3.0, 5.0 and 2.8, respectively. Further information regarding the tablets (concerning excipients, weight, dimensions, friability and disintegration time) has previously been published in more detail.⁸

3 | MANIPULATION STUDIES

The manipulation study design was inspired both by the routine for manipulation observed at our hospital ward, and by the MODRIC guidelines.⁹

3.1 | Tablet fragment dispersed in medicine measure

Half tablets: Tablets were split into two by use of a commercially available tablet splitting device (Apro tablet splitter, Karo Pharma AS). The largest half, judged by the eye, was weighed and placed in a 30 mL polypropylene medicine measure (D: 38 mm, H: 42 mm, Hammarplast Medical AB) with 2 mL purified water and left to disintegrate for 3 minutes. The measure was agitated gently for 10 seconds after half the time. The suspension was pumped into and out of the 5-mL oral syringe (Baxter Exactamed, Baxter Healthcare SA) four times before the whole fluid volume was drawn into the syringe. The 2 mL volume was ejected into a 100-mL volumetric flask, which was diluted to volume in mobile phase prior to quantification. **Quarter tablets:** The experiment was repeated as described for half tablets above, but this time, the tablet was split into four parts and the largest quarter fragment was dispersed. **Effect of rinsing:** The two experiments (above) were repeated, but this time, after emptying the 2 mL sample into the 100-mL volumetric flask, the medicine measure was rinsed with 1 mL purified water, which was drawn into the oral syringe and then added to the original 2 mL sample in the volumetric flask prior to quantification.

3.2 | Tablet fragment dispersed in oral syringe

The experiments were performed as described above, but this time, the largest half or quarter fragment was placed directly in a 5-mL oral syringe, 2 mL purified water was then drawn up, and the syringe was left horizontally for 3 minutes to allow tablet disintegration. The syringe was agitated gently for 10 seconds after half the time. The 2 mL volume was emptied into a 100-mL volumetric flask, which was diluted to volume with mobile phase. **Effect of rinsing:** Samples were also prepared with 1 mL rinsing being included. In these experiments, after ejection of the original 2 mL sample into the volumetric flask, 1 mL of water was first drawn into the syringe and then ejected into the volumetric flask, adding to the 2 mL already there. **Control samples:** For every tablet type and manipulation method, six samples were prepared. Three control samples consisting of tablet powder equal to one average tablet mass were also prepared for every manipulation experiment. The tablet powder in these samples always came from the same lot as the tablets manipulated in the same experiment.

3.3 | Splitting accuracy

The weight of both the whole tablet and the largest tablet fragment was recorded in all the manipulation experiments. In a separate experiment, to investigate splitting accuracy, tablets ($n = 8$) were split into halves and quarters and the weight was recorded. The weight of crumbles or fragments not included in any half or quarter was calculated (as weight of fragments subtracted from weight of the whole tablet).

3.4 | Quantification

For determination of aspirin, a previously described UHPLC method, validated for precision, specificity and linearity, was used.⁸

4 | EXPLANATION AND DEFINITION OF TERMS

A manipulation method to obtain a fraction of a tablet consisting of splitting tablets and dispersing the resulting fragments was the topic of investigation, and child-tailored doses were illustrated by tablet fragments equal to half and quarter tablets. In this work, the *intended* dose refers to the dose aimed at, that is, the *ideal* half or quarter tablet. Upon splitting, each fragment was weighed individually prior to further manipulation, and the *expected* values or amounts given refer to the recovered amount relative to each individual fragment weight. The accuracy obtained in the splitting process is given as per cent fragment weight of total tablet weight.

To help us extract general knowledge about the manipulation in question, the results from splitting and dispersion are discussed separately in this work, for the most part. The accuracy with respect to specific intended *doses* of aspirin will, of course, be influenced both by the splitting accuracy and by the recovery from the individual tablet fragment, but as this study is more general in scope, discussion of the specific effects on aspirin *doses* will be more limited.

No widely accepted limits of acceptable dose accuracy with respect to the intended dose for manipulated tablets are known to us. Deviations of $\pm 20\%$ have, however, been used in similar studies concerning tablets,^{8,14} and are also midway between the inner ($\pm 15\%$) and outer ($\pm 25\%$) acceptance limits for tablet parts from tablets intended for splitting¹⁵; as such, it is used to provide context to the observed variability in this work. In general, however, considerations regarding the safety aspects and acceptability of variation for the specific drug substance in question will also be of importance.

If not otherwise stated, the *accuracy* was defined as the closeness of the average recovered amount (%) to the theoretically expected amount from the individual half or quarter fragments, or the closeness of the average obtained value to the intended dose. The *precision* was defined as the variation around the average amount obtained, given as both lowest-highest value and standard deviation (sd).

Split-then-disperse refers to the manipulation methods performed in this study—all based on tablet splitting; *fraction-extraction* refers to a manipulation method described previously,⁸ consisting of first dispersing a whole tablet, then extracting a proportional fraction as the prescribed amount.

5 | RESULTS

5.1 | Control samples

For every assay performed, the content of three ground-up tablet masses ($n = 3$) equal to one whole tablet was determined, with no manipulation being performed. The recoveries obtained for these samples ranged around the declared amount with a maximum standard deviation of 2.2%: $100.2 \pm 2.2\%$ (mean \pm SD) ($n = 12$) for *Dispersible Aspirin* (75 mg), $100.1 \pm 1.8\%$ ($n = 12$) for *Bayer Chewable* (81 mg), $97.7 \pm 1.0\%$ ($n = 12$) for *Disprin* (300 mg) and $101.1 \pm 1.1\%$ ($n = 12$) for *Aspirin* (500 mg).

5.2 | Splitting accuracy

The splitting accuracy obtained for the four tablet types investigated—using a dedicated tablet splitter—is shown in Table 1. The difference in fragment mass was largest for the lowest strength tablet, *Dispersible Aspirin*. The largest quarter tablet fragments from this tablet were on average found to constitute 126% of the intended quarter, while the smallest fragment only constituted 39%. Tablet mass lost to crumbling—and not included in any of the four quarters (designated 'remaining')—constituted at least 6.7% of the tablet weight, for the chewable tablet, but could be up to 23.1%, for the lowest strength dispersible tablet. It can be noted that the tensile strength was highest for the chewable tablets with an average of 1.58 N/mm^2 , whereas the two dispersible tablets showed intermediate tensile strength at 1.45 and 1.22 N/mm^2 , respectively. In the manipulation study, only the largest fragment was chosen—and weighed. The masses of the quarter fragments actually used for manipulation constituted $31.9 \pm 10.3\%$ of the whole tablet for *Dispersible Aspirin*, $29.6 \pm 7.8\%$ for *Bayer Chewable*, $26.4 \pm 6.7\%$ for *Disprin* and $26.0 \pm 7.4\%$ for *Aspirin* ($n = 24$ for all tablets)—all in good agreement with the largest fragments given in Table 1. The largest tablet halves constituted $55.5 \pm 7.5\%$ of the whole tablet for *Dispersible Aspirin*, $55.7 \pm 6.0\%$ for *Bayer Chewable*, $50.9 \pm 5.6\%$ for *Disprin* and $52.4 \pm 5.5\%$ for *Aspirin* ($n = 24$ for all tablets).

5.3 | Accuracy and precision upon manipulation in medicine measure

The recovered amount upon dispersing the largest half and quarter fragments, respectively, in a medicine measure is shown in Table 2. The accuracy in recovery was best for the two dispersible tablets, where $>80\%$ of the fragments was always retrieved, even without any rinsing procedure. For the chewable tablet, a rinsing procedure could bring the recovery $>90\%$, while the recovered amount without this step was $<70\%$. For the conventional tablet, the average recovered amount never exceeded 33% of that expected from the individual fragment, regardless of rinsing. For this tablet, recovered

amounts could also span over a wider range (eg 12.6%–99.0%), demonstrating poor precision.

5.4 | Accuracy and precision upon manipulation in syringe

The recovered amount upon dispersing the half or quarter tablet fragment directly in a syringe is shown in Table 3. Using this method, the recoveries were comparable for all the four tablets. Upon rinsing, $>90\%$ of the expected half or quarter fragment was retrieved for all the four tablets, the exception being the conventional *Aspirin* tablet, where one sample contained only 26% of the amount expected from the fragment. The reason for this one sample deviating is not known.

6 | DISCUSSION

6.1 | General discussion

This study shows that the manipulation method consisting of splitting and dispersing tablets to obtain a fraction can give accurate and precise results when an accurate fragment is dispersed directly in an oral syringe. Even for a drug substance such as aspirin that is sparingly soluble (1:300 in water),¹⁶ the method is accurate and precise for several different tablet types, for tablets of various strengths and for both half and quarter tablets (Table 3). It is also accurate and precise for tablet suspensions where the pH is above and below pKa (3.5 for aspirin),¹⁶ where solubility is favoured or reduced, respectively (suspension pH has previously been documented above pKa for the two dispersible tablets (4.6–5.0), and below pKa for the chewable and conventional tablets (3.0–2.8)).⁸ Rinsing of the syringe after the first ejection may improve outcomes, but the results on this point were somewhat inconsistent.

Using an open medicine measure for dispersion of the tablet fragments has the advantage of providing the practitioner with some visual control over the dispersion process, as well as the opportunity to physically aid dispersion, if necessary. The variation added in recovered amount for different tablets could, however, be considerable using this method (Table 2). The recovered amounts for the two dispersible tablets, *Dispersible Aspirin* and *Disprin*, were $>80\%$ for both half and quarter tablets, even without a rinsing step. For the chewable tablet, rinsing of the medicine measure was required to give values exceeding 70% of the expected from the fragments, and for the conventional, highest strength *Aspirin* tablet, average values above 33% of the expected could not be retrieved, regardless of rinsing. The low solubility at the low pH in the suspensions of the latter two tablets could possibly contribute to sedimentation in the medicine measure, and following that, increased variability.

	Aspirin Dispersible, 'Aspar'	Bayer chewable, 'Bayer'	Disprin, 'Reckitt Benckiser'	Aspirin, 'Bayer'
Fragment 1	31.5 ± 5.8 (20.2-39.1)	31.7 ± 3.2 (26.4-36.7)	26.7 ± 0.9 (25.2-28.1)	27.2 ± 2.8 (21.0-29.7)
Fragment 2	21.2 ± 6.0 (8.5-28.5)	24.1 ± 2.9 (19.3-27.9)	24.8 ± 1.4 (22.7-26.6)	25.7 ± 2.8 (20.1-28.0)
Fragment 3	14.5 ± 4.5 (6.2-21.5)	19.7 ± 3.0 (14.6-23.3)	22.7 ± 1.6 (20.6-25.6)	21.1 ± 3.1 (15.8-24.2)
Fragment 4	9.7 ± 3.0 (5.1-13.6)	17.7 ± 3.4 (10.6-22.9)	18.2 ± 3.4 (11.2-22.8)	17.4 ± 2.4 (13.8-19.6)
Remaining	23.1 ± 11.7 (11.0-43.1)	6.7 ± 6.3 (1.9-21.3)	7.6 ± 4.7 (1.2-13.4)	8.6 ± 6.8 (1.1-20.0)

Note: Data are given as per cent of the whole tablets, from largest fragment (Fragment 1) to smallest quarter fragment (Fragment 4). 'Remaining' represents per cent of full tablet weight not included in any of the four fragments (ie crumbles) (n = 8).

	Half tablet	Half tablet, with rinse	Quarter tablet	Quarter tablet, with rinse
Dispersible Aspirin, 75 mg	83.0 ± 2.2 (80.1-85.9)	92.9 ± 4.8 (85.8-98.8)	85.2 ± 4.3 (77.9-89.3)	90.9 ± 2.9 (88.7-96.6)
Bayer Chewable, 81 mg	63.8 ± 11.0 (51.7-81.1)	93.9 ± 3.9 (88.7-99.6)	67.6 ± 8.3 (55.6-78.8)	93.9 ± 2.5 (90.4-98)
Disprin, 300 mg	93.4 ± 5.4 ^a (84.8-99.8)	97.2 ± 1.4 (94.6-98.6)	89.4 ± 2.6 (86.5-92.5)	98.7 ± 2.0 (96.7-102.5)
Aspirin, 500 mg	12.3 ± 7.3 (5.2-25.8)	14.9 ± 7.8 (7.5-29.6)	15.7 ± 8.7 (8.9-32.3)	32.9 ± 33.1 (12.6-99.0)

Note: Per cent of expected value ± SD (low-high value) (n = 6) is given. (Expected with regard to the individual, largest fragment manipulated).

^an = 5.

	Half tablet	Half tablet, with rinse	Quarter tablet	Quarter tablet, with rinse
Dispersible Aspirin, 75 mg	85.5 ± 3.7 (80.9-89.1)	94.6 ± 3.6 (90.5-100.0)	80.4 ± 1.3 (79.2-82.0)	94.1 ± 1.8 (91.1-96.1)
Bayer Chewable, 81 mg	92.0 ± 5.8 (81.6-97.8)	90.8 ± 3.8 (84.4-94.9)	85.3 ± 7.1 (74.8-94.2)	95.7 ± 4.3 (89.6-102.3)
Disprin, 300 mg	96.2 ± 1.8 (93.8-98.4)	97.7 ± 2.0 (94.7-100.7)	94.5 ± 1.1 (93.1-96.0)	97.9 ± 0.5 (97.1-98.6)
Aspirin, 500 mg	94.5 ± 1.9 (91.9-96.4)	91.0 ± 6.4 (85.1-98.8) ^a	95.7 ± 2.1 (93.3-99.1)	98.0 ± 1.7 (95.1-99.4)

Note: Per cent of expected value ± SD (low-high value) (n = 6) is given. (Expected with regard to the individual, largest fragment manipulated).

^an = 5 (unexplainable outlier not included). With outlier included, n = 6, 80.5 ± 26.2 (28.3-98.8).

Using the syringe has the advantage of omitting the transition step necessary when utilising a medicine measure—where the drug may be more prone to be lost to sedimentation. Indeed, dispersion of the fragments directly in the oral syringe gave accurate and precise values for most of the tablet fragments (Table 3). For the two low strength aspirin tablets—of most interest in paediatric care—more than 80% of the content from the individual fragments could be recovered, even without rinsing of the syringe, and introducing

a rinsing step brought the result to over 90% recovery for all tablet fragments.

On a general note, the suitability of a method based on dividing tablets prior to further manipulations (eg dispersion) depends on the characteristics of the tablets: both the splitting accuracy and the tendency to crumbling might influence outcomes. The selection of fragments for further manipulation should also be considered, as should the choice of splitting method or device—a

TABLE 1 Splitting accuracy of the different aspirin tablets (quarter fragments)

TABLE 2 Recovery from fragments dispersed in a medicine measure, with or without 1 mL rinse

TABLE 3 Recovery from fragments dispersed in an oral syringe, with or without 1 mL rinse

factor that could also influence the accuracy obtained, as has been shown for, for example, aspirin tablets.¹⁷ For several reasons, then, tablet splitting by itself can introduce variability with respect to the intended dose. This has been demonstrated several times before, for a variety of tablets,¹⁸⁻²⁰ and recently, for example, for hydrocortisone tablets.²¹ The results in our study are in line with such findings (Table 1). Thus, even though the recovery from the individual fragment can be acceptable when dispersion is performed directly in an oral syringe for a variety of tablets (Table 3), that may be of limited use if the fragment in question is off-target to begin with—for example constituting as little as 5% of the whole tablet, when a quarter (25%) is aimed at, as could be the case with *Dispersible Aspirin* (Table 1).

Table 1 illustrates that different tablet types can vary in their suitability for splitting—and, thus, suitability for manipulation through a *split-then-disperse* method. In general then, for some tablets and APIs, all fragments could possibly be considered suitable for further use, for others, only a few or only the largest fragment, and in this last instance, the risk of overdosing should also be considered. The fraction of the tablets lost as crumbles in the splitting process ('remaining'; Table 1) also varies between the tablets and could be considerable (eg 23% for *Dispersible Aspirin*). The tablet tensile strength may to a certain degree be linked to the tendency to crumble. Tablets intended for passive dispersion in water may not be manufactured with the highest tensile strength. Chewing tablets, on the other hand, will disperse after mechanical attrition and may be expected to have a higher mechanical strength, and the chewable tablets were found to have the highest mechanical strength (1.58 N/mm²) among the four types; however, the *Dispersible Aspirin* was among the intermediate tablets with a tensile strength of 1.45 N/mm², and the conventional tablets had the lowest tensile strength of 0.87 N/mm². This illustrates that tensile strength is not a simple characteristic to use for comparison between products from different manufacturers. As long as a tablet product has a suitable mechanical strength to comply with the company's specifications, the company defines the strength depending on the necessary processing steps and desired characteristics. When it comes to tablet splitting, discarding fragments and crumbles may not be a problem for some tablets—in other instances, however, administering all of every tablet is important, and a high rate of crumbling can make manipulation through splitting unacceptable. In such cases, a more suitable practice may be to pulverise the tablet and weigh out the dose equivalent tablet mass.

It is interesting to compare the results from the manipulation method investigated here, *split-then-disperse*, to the results from an alternative method investigated previously, *fraction-extraction*.⁸ In that study, the same four aspirin tablets included here were dispersed in 10 mL water, before a fraction (10 or 20%) was withdrawn as the prescribed amount. This method could produce aspirin >95% of that intended for the two dispersible tablets, *Dispersible Aspirin* and *Disprin*, under certain mixing conditions. For the other two tablets, *Bayer Chewable* and *Aspirin*, amounts >43%

of that intended could not be reached, regardless of mixing. The dispersions of these last two tablets had pH < pKa (3.5), where solubility is not favoured.

Taken together, manipulation through *fraction-extraction* could not produce accurate and precise aspirin amounts ($\pm 20\%$) for all the investigated tablets,⁸ while the recovery using the *split-then-disperse* method investigated here consistently could attain this level for the dispersion step, using oral syringes (Table 3). In this last instance, then, the final accuracy with respect to the intended dose will largely depend on the splitting accuracy of the tablet in question.

The use of a syringe to measure liquids accurately has previously been proven to be superior to using a medicine measure for both skilled and unskilled users.²² In line with this, and adding to the incentives to utilise oral syringes, the method of direct dispersion of a tablet fragment in a syringe, followed by rinsing step, also proved advantageous for all the different tablet types in this study. Average recovered amount from fragments of all four tablets fell within $\pm 20\%$ of the expected using a syringe for the manipulation (Table 3), while using a medicine measure did not reach this precision for several of the tablets (Table 2). From this, splitting and dispersing the fragment in a syringe could possibly constitute a promising default method for administering half or quarter tablets—applicable for a variety of different tablets, once suitability for splitting is established for the individual tablet. The only tool needed to establish splitting accuracy is a precision balance, this could be attainable in many hospital pharmacies who could aid the standardisation of procedures.

The results of this and our previous study⁸ indicate that tablet manipulation to obtain an accurate fraction can be done successfully, given enough knowledge about the tablet and drug substance. However, even though the practice is well intended, it also has the potential of introducing substantial dose inaccuracy, for example from uneven splitting or sedimentation of a poorly soluble substance. In view of this, the physicians need to consider the possibility of obtaining a theoretical best dose versus what is possible in the clinical setting: for example, in some scenarios administering closest half of quarter tablet could possibly be safer than aiming for an exact per cent fraction (eg 33%) in a *fraction-extraction*. In other scenarios where prescribed doses do not correspond to quarter tablets, the use of extemporaneously prepared products, such as oral mixtures or individual oral powders (filled in sachets or capsules), could be a better alternative.

Even though the study was initiated to gather general knowledge about manipulation effects in tablets, some conclusions about paediatric dosing of aspirin can also be extracted, focusing in particular on the two lower strength tablets in this study, that is most suitable in paediatric care (*Dispersible Aspirin* [75 mg] and *Bayer Chewable* [81 mg]). Considering the lowest strength *Dispersible Aspirin* tablets, the largest quarter fragment would on average constitute 31.5% of the whole tablet by mass (and theoretically 23.6 mg aspirin), and compensating for the loss in dispersion, an amount exceeding the ideal quarter tablet (18.75 mg)

by 19% would be obtained. A similar consideration for the *Bayer Chewable* tablets would give an amount 30% higher than the ideal quarter tablet. Thus, an easy-to-follow dosing algorithm, such as 'choose the largest fragment by eye, disperse directly in an oral syringe, and rinse', would be more accurate for the dispersible than the chewable tablet in this case. Better accuracy with respect to the intended dose could possibly be obtained by refining such an algorithm (eg regarding choice of fragment and the presence or absence of rinsing), but the algorithm could then also be more difficult to follow. From our previous study, on the aspirin amounts that can be recovered by *fraction-extraction* from these tablets,⁸ we know that 99% of the intended amount can be obtained for fractions of the dispersible tablets, while no more than 40% can be obtained for fractions of the chewable ones, even after mixing of the dispersion. For this reason, we now recommend using the dispersible tablet as this will give the most accurate amount, both by *fraction-extraction* and by *split-then-disperse*, given the use of the largest fragment.

The above considerations are undertaken given that aspirin is regarded as a well-tolerated substance.¹³ However, the prescribing physician should, as always, consider acceptable variation individually.

6.2 | Limitations

Only the largest fragment was chosen for the manipulations performed. This was done both to limit the number of variables and to ensure that a useable fragment could be obtained from each split tablet.

Only one active ingredient, aspirin, has been studied in this work. Other substances with different characteristics (eg pKa, solubility) could behave differently, the same could be said about tablet types not included in the study (melting tablets, coated tablets, etc)—and this limits generalisability of the results.

7 | CONCLUSIONS

Given sufficient splitting accuracy, the recovery from dispersions of chewable, dispersible and conventional aspirin tablet fragments is sufficient to give accurate and precise doses, when fragments are dispersed directly in an oral syringe. Introducing an additional step by first dispersing the fragments in a medicine measure introduces higher variability. Given good splitting accuracy, splitting and direct dispersion of fragments in an oral syringe seems promising as a manipulation method to obtain paediatric doses for a variety of tablets.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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