Adjusting the dose in paediatric care: dispersing four different aspirin tablets and taking a proportion

Jørgen Brustugun, Nikolai Notaker, Lasse Holtan Paetz, Ingunn Tho, Kathrin Bjerknes

ABSTRACT

Objectives When caring for children in a hospital setting, tablets are often manipulated at the ward to obtain the right dose. One example is manipulation of tablets containing the slightly water-soluble substance aspirin, used in paediatric care as an antiplatelet agent. The evidence base, however, for choosing certain tablet formulations and manipulation methods over others for extraction of proportions is lacking. The aim of this study was to investigate the effect of tablet formulation and manipulation technique on the dose accuracy and precision attained when dispersing different commercially available aspirin tablets and extracting a small proportion suitable for children.

Methods The manipulation methods investigated simulated those observed in the paediatric clinic. Four tablet formulations—one chewable, one conventional and two dispersible—were dispersed in 10 mL water in a medicine measure. On (1) passive dispersion, (2) mixing by stirring with the syringe, or (3) stirring and pumping the dispersion in and out of the syringe, respectively, proportions (1 mL or 2 mL) were extracted and the doses recovered were determined using a validated UHPLC (ultra high-pressure liquid chromatography) method.

Results Fractions from the four different dispersed aspirin tablet formulations varied from 99% to 3% of that intended with the lowest degree of mixing, and from 96% to 34% of that intended with the highest degree of mixing. Only the dispersible tablets gave average doses within 20% of the intended dose.

Conclusions Fraction extraction from dispersed aspirin tablets only gave doses within 20% of intended for the dispersible tablets, and then only for some of the manipulation methods: ‘passive dispersion’ for the 75 mg dispersible tablet and ‘stirring and pumping’ for the 300 mg dispersible tablet. The tablets not intended for dispersion gave unsatisfactory results, outside 20%, regardless of manipulation method. The findings underline the importance of considering both tablet formulation and dose extraction technique when manipulations are required.

INTRODUCTION

Children are often left without documented and approved medicines because medicines may be developed for use in the adult population only; furthermore, the dosage forms and formulations that are available on the market are frequently not suitable for use in children. This lack of age-appropriate formulations has been a topic of concern for a considerable time.1-3 Authorities have tried to improve the situation, for instance through the European Union Paediatric Regulation,4 a regulation that intends to encourage the development of formulations appropriate for children in the European market. Although some progress has been made through the last decade, the situation still leaves a lot to be desired,5 and it has been suggested that it will still take decades before the availability of documented and approved medicines for children is comparable with that for adults.6 In this situation, medicines are regularly administered off-label.7-9 For instance by having the dosage form...
Aspirin has previously been found to be manipulated in paediatric care in our clinic. In this population, aspirin is used as an antithrombotic agent and was treated with aspirin for the antiplatelet effect. Aspirin has previously been found to be manipulated in paediatric care in our clinic. In this population, aspirin is used as an antithrombotic agent and was treated with aspirin for the antiplatelet effect.

Off-label and unlicensed use of medicines has received some attention through the years, but the practice of manipulation seems to have received less so. In the instances where manipulation has been studied, the focus has mainly been on the effect of tablet splitting. The British initiative Manipulation of Drugs Required in Children (MODRIC) – A Guide for Health Professionals has provided useful guidance on the manipulation of tablets to children, recommending for instance that ‘Tablets should be split in preference to dispersing or crushing tablets and taking a proportion’. In paediatric care, however, the splitting of tablets is often just the first step in the administration; further or other manipulations, like dispersion and dose extraction, may be required. For questions relating to this, MODRIC recommends consulting ‘Manufacturers and/or pharmacists’. And indeed, the question is often raised in the daily life in the clinic, but the evidence base for making recommendations regarding different formulations is limited, also for the hospital pharmacist.

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The tablets investigated were Dispersible Aspirin 75 mg (Aspar Pharmaceuticals, London, UK); Bayer Chewable 81 mg (Bayer Healthcare, Morristown, New Jersey, USA); Disprin 300 mg (Reckitt Benckiser Healthcare (UK), Hull, UK); and Aspirin 500 mg (Bayer, Solna, Sweden). Further information regarding the tablets is summarised in table 1.

Table 1 Description of the four tablets included in the study: formulation type, aspirin content and excipients

<table>
<thead>
<tr>
<th>Formulation type</th>
<th>Dispersible Aspirin (Aspar)</th>
<th>Bayer Chewable (Bayer)</th>
<th>Disprin (Reckitt Benckiser)</th>
<th>Aspirin (Bayer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin content</td>
<td>Acetylsalicylic acid.</td>
<td>Acetylsalicylic acid.</td>
<td>Acetylsalicylic acid.</td>
<td>Acetylsalicylic acid.</td>
</tr>
<tr>
<td>75 mg</td>
<td>81 mg</td>
<td>300 mg</td>
<td>500 mg</td>
<td></td>
</tr>
<tr>
<td>Calcium carbonate.</td>
<td>Corn starch.</td>
<td>Citric acid.</td>
<td>Corn starch.</td>
<td></td>
</tr>
<tr>
<td>Citric acid.</td>
<td>Sodium saccharine.</td>
<td>Sodium saccharine.</td>
<td>Sodium lauryl sulfate.</td>
<td></td>
</tr>
<tr>
<td>Colourants: D&amp;C Red No 27</td>
<td></td>
<td></td>
<td>Polyvinylpolypyrrolidone.</td>
<td></td>
</tr>
<tr>
<td>Lake, FD&amp;C (Food, drugs and cosmetics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red No 40 Aluminium Lake.</td>
<td></td>
<td></td>
<td>Lime flavour.</td>
<td></td>
</tr>
</tbody>
</table>
polypropylene medicine measure (Diameter: 38 mm, Height: 42 mm, 30 mL) from Hammarplast Medical (Linköping, Sweden).

**Validation of the chromatographic method**

Linearity ($r^2 > 0.999$) was demonstrated over the sample concentrations $0.5 \mu g/mL \text{ to } 0.125 \text{ mg/mL}$, and the limit of quantification was $<0.5 \mu g/mL$, as a ratio of signal to noise (S/N) >10 was found at this concentration. Specificity was validated with regard to tablet excipients of all four tablets, and by subjecting aspirin to heat, hydrogen peroxide (3%) or alkaline conditions. The stress conditions produced salicylic acid. Resolution between aspirin and salicylic acid was $>8$ for all samples. The precision was demonstrated determining the aspirin content of powdered Bayer Chewable tablets. The relative SD was <1% (n=3 samples), <1% (n=3 days) and 0.3% (n=6 injections from the same sample vial). Sample stability was established for (n=3 samples), <1% (n=3 days) and 0.3% (n=6 injections from the same sample vial). Precision was demonstrated determining the aspirin content of Bayer Chewable, up to at least 154% for Disprin and Aspirin, to up to at least 154% for Bayer Chewable, and up to at least 166% for Dispersible Aspirin.

**Tablet characterisation**

The crushing strength (N), disintegration time (s) and friability were tested according to European Pharmacopoeia (9.0) (PhEur). To allow for comparison between tablets with various dimensions, tensile strength (N/mm²) was calculated from breaking strength (N), tablet diameter (mm) and height (mm), according to Fell and Newton. The pH of the dispersion resulting from dispersing one tablet in purified water (10 mL) was recorded; the pH of purified water was 6.28 ± 0.61 (mean ± SD, n=7).

**Manipulation studies**

The manipulation procedures in this study were designed to be a standardised representation of various non-standardised manipulation practices that are performed in our hospital wards. Observation of manipulations being performed on the ward, as well as interviews with both nurses and clinical pharmacists, provided information regarding the normal procedures used. Doses of 10% and 20% of the full tablets were chosen as representatives of ‘small tablet fractions not covered by half or quarter tablets’.

In line with Broadhurst et al., in a 30 mL graduated plastic medicine measure, a single aspirin tablet was placed in 10 mL purified water for 3 min. Three minutes was chosen in our study as it was a time sufficient for all four tablet types to disintegrate—and a time that would facilitate comparison with the bottom (zone 1) to the top (zone 5), as outlined by Broadhurst et al.—the syringes were held vertically and the fraction was extracted from ‘Zone 2’ of the medicine measure (ie, at the 2 mL mark) (figure 1). Six medicine measures, each containing one tablet, were prepared both for each tablet formulation and each type of manipulation. One sample was withdrawn from each medicine measure and the aspirin content of the sample was determined in triplicate. The content of each extracted dose was determined as described in the Preparation of samples from extracted tablet fractions section.

From samples both stirred and subjected to ‘pumping’ treatment, 1 mL samples were also withdrawn from zone 1 and zone 5, respectively, to explore the effect of extraction zone.

**Preparation of samples from extracted tablet fractions**

The sample—the dose’, for example, a suspended tablet proportion withdrawn with an oral syringe—was transferred to a 100 mL volumetric flask. Mobile phase (70–80 mL) was added and the flask was vigorously shaken for 1 min. The flask was ultrasonicated at ambient room temperature for 30 min. It was again vigorously shaken for 1 min before mobile phase was added to a final volume of 100 mL. The liquid was again mixed thoroughly. Of the sample solution, 5 mL was transferred to a 10 mL test tube and centrifuged (2500 rpm (rotations per minute)) for 5 min. The supernatant was transferred undiluted to an injector vial, or further diluted in mobile phase—when necessary—to target concentrations of 0.075 mg/mL (Dispersible Aspirin), 0.081 mg/mL (Bayer Chewable) or 1.00 mg/mL (Disprin and Aspirin).

For every manipulation experiment, three control samples consisting of tablet powder equal to one average tablet mass were prepared as described above. The tablet powder in these samples always came from the same lot as the tablets manipulated in the same experiment. A new standard curve from a freshly prepared stock solution was prepared for each new chromatographic analysis. One hundred milligrams (≥99.0%) of aspirin were dissolved in mobile phase in a 100 mL volumetric flask. This 1.00 mg/mL aspirin solution was further diluted to 0.2 mg/mL in mobile phase. From this stock solution the standard curve was prepared.

**Definitions**

Dose accuracy was defined as the closeness of the average dose obtained (%) to the intended dose (a fifth or a tenth of a tablet). Dose precision was defined as the variation around the average dose obtained and the result is given as both the lowest–highest value and SD.

**RESULTS**

**Physical properties of the tablets**

The physical properties of the tablets are presented in table 2. The pKa of aspirin was 3.5, and the pH of a dispersed tablet was above the pKa value for two of the tablets (Dispersible
Table 2 Characteristics of the four aspirin tablets included in the study

<table>
<thead>
<tr>
<th>Tablet Type</th>
<th>Weight (g)*</th>
<th>Dimensions, diameter × height (mm)†</th>
<th>pH of dispersed tablet</th>
<th>Friability (%)§</th>
<th>Disintegration time (s)¶</th>
<th>Tensile strength (N/mm²)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dispersible Aspirin (Aspar)</td>
<td>0.150±0.003</td>
<td>7.03×2.90</td>
<td>4.60</td>
<td>0.44 (n=42)</td>
<td>31 (25–38)</td>
<td>1.45 (1.26–1.62)</td>
</tr>
<tr>
<td>Bayer Chewable (Bayer)</td>
<td>0.228±0.002</td>
<td>8.00×4.25</td>
<td>3.02</td>
<td>0.07 (n=29)</td>
<td>34 (26–40)</td>
<td>1.58 (1.21–1.78)</td>
</tr>
<tr>
<td>Disprin (Reckitt Benckiser)</td>
<td>0.473±0.003</td>
<td>12.80×2.70</td>
<td>4.96</td>
<td>0.84 (n=14)</td>
<td>30 (23–35)</td>
<td>1.22 (1.03–1.36)</td>
</tr>
<tr>
<td>Aspirin (Bayer)</td>
<td>0.597±0.003</td>
<td>12.06×4.90</td>
<td>2.84</td>
<td>0.11 (n=11)</td>
<td>6 (5–10)</td>
<td>0.87 (0.78–0.93)</td>
</tr>
</tbody>
</table>

*Mean (g)±SD (n=8).
†Mean, n=3; SD% <1.5%.
§PH of one tablet suspended in 10 mL purified water (n=1); pH of purified water: 6.28±0.61 (average±SD) (n=7).
¶Per cent lost on friability testing (PhEur 9.2) (n, according to PhEur).
§Average time (s) to disintegrate (n=6) (low–high).
**Calculated from breaking strength (N), diameter (mm) and height (mm). Average values are given (n=10) (low–high).

Aspirin and Disprin) and below the pKa for the other two tablets. The tablets varied in tensile strength; the strongest (Bayer Chewable) were approximately double the mean tensile strength of the weakest (Aspirin). Regarding friability, all tablets showed less than 1% weight loss generally accepted in PhEur. The tablets with the lowest tensile strength (Aspirin) disintegrated faster than the rest of the tablets. All tablets disintegrated well within 3 min—the hold time in the manipulation experiments (figure 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 following were the recoveries obtained for these samples (mean (SD) (lowest–highest value)): 100.3% (0.9) (98.7–101.3) (n=15) for Dispersible Aspirin (75 mg), 98.5% (1.6) (97.3–101.2) (n=12) for Bayer Chewable (81 mg), 99.3% (1.9) (97.3–103.0) (n=12) for Disprin (300 mg), and 99.9% (4.5) (88.8–104.4) (n=12) for Aspirin (500 mg).

Dose accuracy and precision on extraction of a tablet fraction
Manipulating aspirin tablets to obtain paediatric doses by extraction of a part from a dispersed tablet led to variations in dose accuracies both between the tablet formulations manipulated and the manipulation methods used (tables 3 and 4).

Dose accuracy
The tablet formulation giving the most accurate dose was the dispersible tablet, Dispersible Aspirin. For this tablet, the accuracy varied between 71.1% and 98.7% (mean, n=6) of the intended dose for the three different mixing methods explored. The least accurate doses were observed when the conventional aspirin tablet (Aspirin) was manipulated, where an average dose of 3.4% was found (table 3). Doses extracted after more extensive mixing were generally more accurate; the exception to this was the dispersible tablet, Dispersible Aspirin, where more mixing gave a less accurate dose (table 3).

Dose precision
The dose precision also showed substantial variation depending on the formulation type and mixing method. For the method with the highest accuracy (98.7%, obtained by direct extraction from the lowest dose dispersed tablet), the dose range for six equally treated samples was found to be approximately 20% above or below the intended dose (80.0%–117.3%, n=6). More substantial variations in the doses obtained were found for other tablets, particularly for the chewable tablet and the conventional tablet (table 3). In one instance, doses ranging from 14.8% to 116.0% of that intended were found for the same manipulation method and tablet type (‘mixing by stirring’ of the chewable tablets).

Extraction of the sample at different levels in the medicine measure also contributed to variation in the achieved dose (table 4). In general, extracting the dose from near the bottom (zone 1) resulted in a higher, more accurate dose than extracting near the top (zone 5). The differences seen between 1 mL and 2 mL samples, a tenth and a fifth of a tablet, respectively, were less noteworthy (table 3).

DISCUSSION
The results obtained in this study illustrate that both dose accuracy and dose precision may be compromised when a small dose is extracted as a proportion of a dispersed tablet (tables 3 and 4). Thus, in general it appears that the value of prescribing a small

Table 3 Dosage accuracy and precision attained after suspending a tablet in 10 mL water and extracting a fraction: 1 mL or 2 mL, a tenth or a fifth of a tablet constituting the intended dose

<table>
<thead>
<tr>
<th>Tablet Type</th>
<th>Volume extracted</th>
<th>Direct extraction</th>
<th>Direct extraction</th>
<th>Stirring</th>
<th>Stirring and pumping</th>
<th>Stirring and pumping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dispersible Aspirin (Aspar)</td>
<td>1 mL</td>
<td>98.7±14.5 (80.0–117.3)</td>
<td>92.2±13.3 (76.0–113.3)</td>
<td>83.4±8.4 (70.7–92)</td>
<td>71.1±4.3 (66.7–78.7)</td>
<td>72.9±3.1 (69.3–77.3)</td>
</tr>
<tr>
<td>Bayer Chewable (Bayer)</td>
<td>2 mL</td>
<td>9.3±6.4 (6.2–22.2)</td>
<td>12.4±9.6 (4.9–28.4)</td>
<td>36.2±39.5 (14.8–116.0)</td>
<td>39.9±17.0 (23.5–66.7)</td>
<td>34.2±6.6 (23.5–42.0)</td>
</tr>
<tr>
<td>Disprin (Reckitt Benckiser)</td>
<td>1 mL</td>
<td>45.7±2.6 (43.3–49.9)</td>
<td>55.0±3.6 (50.7–60.8)</td>
<td>73.4±9.3* (67.2–89.5)</td>
<td>80.9±5.3 (80.5–95.8)</td>
<td>95.5±2.7 (92.7–98.9)</td>
</tr>
<tr>
<td>Aspirin (Bayer)</td>
<td>1 mL</td>
<td>3.4±1.1 (2.5–5.6)</td>
<td>7.7±4.1 (3.3–14.4)</td>
<td>13.0±7.3 (9.2–27.8)</td>
<td>43.2±12.4 (20.9–54.1)</td>
<td>37.3±21.8 (20.6–79.8)</td>
</tr>
</tbody>
</table>

*Mean (g)±SD (lowest–highest value) (n=6) is given. All samples were extracted from zone 2 of the medicine measure.

* n=5.

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Table 4  Effect of extraction zone: dosage accuracy and precision attained after suspending a tablet in 10 mL water and extracting a fraction: 1 mL, a tenth of a tablet being the intended dose

<table>
<thead>
<tr>
<th>Zone 1, bottom</th>
<th>Zone 5, top</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dispersible Aspirin 75 mg</strong></td>
<td>83.4±11.1 (71.3–101.3)</td>
</tr>
<tr>
<td><strong>Bayer Chewable 81 mg</strong></td>
<td>44.9±13.9 (27.2–65.4)</td>
</tr>
<tr>
<td><strong>Disprin 300 mg</strong></td>
<td>94.2±8.2* (85.5–105.6)</td>
</tr>
<tr>
<td><strong>Aspirin 500 mg</strong></td>
<td>72.4±8.3* (10.4–209.5)</td>
</tr>
</tbody>
</table>

Per cent of intended dose ±SD (lowest–highest value) (n=6) is given for dose extractions from zone 1 (bottom of dispersion) or zone 5 (top of the dispersion). All samples were agitated (stirred and pumped) before the extraction.

*Estimated value, outside validated range.

The tablet fraction should always be weighted against the risk of obtaining an inaccurate dose, and sometimes a gravely inaccurately one, at that. The results further illustrate that several factors may be important when tablets are manipulated. For drug substances with challenges regarding solubility, such as aspirin in the tablets investigated here, the type of formulation, the mixing procedure and the details concerning the extraction procedure could affect the result. Because of this, it is important both to select the most suitable tablet formulation and to standardise the manipulation procedure to make therapy safe, in particular for children.

In the absence of a generally accepted level of accuracy for fraction doses from manipulated tablets, ±20% from intended dose was chosen. This interval was recently used by Watson et al25 to judge the acceptability of fraction doses obtained from dispersed hydrocortisone tablets. A level of 20% is also midway between the inner (±15%) and outer (±25%) acceptance limits for tablet parts from tablets with break marks outlined in PhEur,26 and although none of the tablets in this study were approved for splitting these pharmaceopial limits were deemed to provide additional context regarding acceptable deviation in dose for fractions of tablets.

Regarding the different formulations in this study, the dispersible tablet Dispersible Aspirin gave the most accurate dose on extraction of a fraction (98.7% of the tenth of a tablet aimed at). As this is a tablet made with dispersion in mind, this finding may not be surprising. The poor result obtained for the conventional tablet (Aspirin), even after mixing (at best 43.2%), is more noteworthy. Notable too is the poor results obtained for the chewable tablet (Bayer Chewable)—a tablet that with its low dose (81 mg) could be thought attractive in a paediatric care setting. For this tablet, only 39.9% of the intended dose was attained on average, even after the most extensive mixing procedure used. As a general notice, fraction extraction only gave satisfactory doses for the dispersible tablets, and then only when certain manipulation methods were used—passive dispersion for Dispersible Aspirin, and stirring and pumping for Disprin; for the tablets not intended for dispersion, fraction extraction gave unsatisfactory results, outside ±20% of the intended dose, regardless of manipulation method.

The variations observed are probably influenced by formulation excipients. For example, the two dispersible tablets both contained citric acid and calcium carbonate, a system developing carbon dioxide gas that through agitation will improve homogeneity of the tablet dispersion. The dispersions resulting from the different tablets also had different pH values, probably caused by individual excipients such as calcium carbonate. In this study, the tablet dispersions spanned two pH units, from 3.0 to 5.0, a range encompassing the pKa of the active ingredient in question, aspirin, with its pKa of 3.5. This could explain some of the variations in accuracy observed as the solubility of aspirin depends on its protonation—the solubility of aspirin itself being given as 1 g in 300 mL water (ie, 33.3 mg in 10 mL), while inorganic salts of the substance are stated to be ‘soluble’.23 Defining ‘soluble’ as 1:10–1:30,22 a solubility of 1 g in 10–30 mL is reached (ie, 1000 mg–333 mg in 10 mL), and as the aspirin content in the tablets fell between 75 mg and 500 mg, the 10 mL water used in the experiments would not be sufficient to dissolve the protonated aspirin at pH values below pKa. At pH values above the pKa, however, as at pH 4.6–5.0 seen for dispersions of the dispersible tablets, better solubility would be expected, and with that better dose accuracy—as is indeed observed even for the 300 mg dispersible tablet (Disprin). On the other hand, reduced solubility at low pH may well have contributed to the low dose accuracy for both the conventional aspirin tablet (Aspirin) and the chewable tablet (Bayer Chewable) as the pH was 3.0 or lower for the dispersions of these tablets (table 2). With reduced solubility, increased sedimentation and dose inhomogeneity could be suspected. The observed differences between doses from the top and bottom zones—being more pronounced for the low pH dispersions, and in particular for the highest dosed Aspirin (table 4)—support this.

In general, defining sink conditions as 3–10 times the solubility, the volumes needed to dissolve drug substances in paediatric manipulations will sometimes be prohibitive considering a neonatal stomach can only contain a limited volume, sometimes estimated to 20 mL.26 Because of this, it is likely that some active ingredients will always remain undissolved during a tablet manipulation. The results for the chewable and conventional tablets in this study (tables 3 and 4) illustrate that the dose accuracies obtained in such situations may be poor indeed—and that mixing of the tablet suspensions only has a limited effect. ‘Stirring’, ‘stirring and pumping’, and ‘pumping’ with a 1 mL oral syringe or a 5 mL oral syringe all gave doses below 50% of that intended. Thus, in our experiments, mixing could not compensate if an unsuitable tablet formulation was chosen to begin with.

The samples discussed above (table 3) were all extracted from zone 2 of the medicine measure. The situation is further complicated when dose extractions from zone 1 or 5 are considered (table 4 and figure 1). As pointed out, the effect of extraction zone was most pronounced for the tablets where the solubility, because of pH and aspirin amount, was not favoured. In particular, this is illustrated by the conventional Aspirin tablet where doses extracted from near the bottom of the medicine measure showed a very high variability (table 4). The difference between doses from the lowest and uppermost zones approached 50 per cent points for this conventional tablet, even after mixing. This far exceeds the 20 per cent point difference between these zones previously demonstrated on passive dispersion of a dispersible tablet,22 a further illustration of the different behaviours of different tablet formulations.

As both this study and the study by Broadhurst et al22 investigated manipulation of dispersible 75 mg aspirin tablets, an estimate of practitioner variability can also be made. In this study the passive dispersion for 3 min of the dispersible 75 mg tablet followed by extraction of a 1 mL dose from zone 2 with a 1 mL syringe yielded 98.7% of the intended dose. The dose retrieved under comparable conditions by Broadhurst et al22 was 58.3%. This difference could be a genuine expression of person-to-person variability, or possibly an effect of steps in the manipulation process not standardised; it could also be an effect of factors not tied to the manipulation itself, such as differences in the analytical method.
In general, quantitative determination of the active ingredient in the extracted dose was essential to judge on the success of the manipulations. The physical characteristics (eg, friability, tensile strength and so on) seemed not to be promising candidates as stand-in parameters for ‘suitability for manipulation’ (table 2). This study illustrates that the dose accuracy obtained in extracted proportions of dispersed tablets may be influenced by both the manipulation method used, the individual physicochemical properties of the drug substance in question and the type of tablet. Effects of individual excipients and variation between practitioners could possibly come in addition to these.

For the aspirin tablets investigated in this study, only a combination of certain tablets (the dispersible ones) with certain manipulation procedures (which could vary) would give doses both accurate and precise. Accepting a deviation from an intended dose of 20%, only passive dispersion of the Dispersible Aspirin tablet and ‘stirring and pumping’ of Disprin met the criterion. This highlights the importance of standardising the manipulation practice, both in the method used and the tablet formulation chosen.

Limitations
Because the different types of tablets were not available in equal strength, tablets with different aspirin content (75–300 mg) were investigated in the study. Comparing the content with the solubility limits, this may have influenced the results to some extent. The main trend did not follow the content gradient, however (table 3): doses deemed acceptable could be extracted both from the lower (75 mg) and higher (300 mg) dispersed tablets.

The results from the chewable and conventional tablet in this study could possibly be generalised to other drug substances with challenges regarding solubility. However, individual concerns regarding dose, solubility and pH of the test substance, aspirin, could limit generalisability, and the study of other drug substances in similar or alternative tablets is of interest.

An additional limitation is that this study only investigated one main manipulation method: dispersing a tablet and withdrawing a fraction from the resulting dispersion. Although this method is not encouraged by the European Medicines Agency,6 it was found by MODRIC to be a common practice, constituting more than 50% of reported tablet manipulations in their survey study.19 Alternatives to this method exist, however—for instance, splitting the tablet first before dispersing the fragment and treating the full volume as the dose. Further investigation is therefore necessary to give advice for best practice at the ward.

CONCLUSIONS
Fraction extraction from dispersed aspirin tablets only gave satisfactory doses, here defined as within 20% of the intended dose, for the dispersible tablet formulations, and then only for some of the manipulation methods used: ‘passive dispersion’ for the 75 mg dispersible tablet and ‘stirring and pumping’ for the 300 mg dispersible tablet. For the tablets not intended for dispersion, fraction extraction gave unsatisfactory results, regardless of manipulation method used. The findings underline the importance of considering both tablet formulation and dose extraction technique when manipulations are required.

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Contributors JT, JB and KB: conceived the project, supervised data collection and data analysis, and wrote the manuscript. LHP and NN (equal contributions): performed tablet manipulations, collected, analysed and interpreted the data, and reviewed the manuscript.

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