

BRIEF REPORT

Preparing paediatric medicines by dissolving tablets and extracting a portion may compromise dosing accuracy

Providing medicines for children with different ages, body weights and capacities poses clinical challenges. There is currently a lack of appropriately formulated medicines with suitable dosage forms and strengths to account for these variations including differences in absorption, distribution, metabolism and elimination of compounds. It is often necessary to crush and dissolve adult medicines to provide the prescribed dose, but healthcare staff or caregivers frequently must do this without supporting data in the market authorisations, which leads to uncertainty about the dose that is administered. Previous studies on how to dissolve a tablet and withdraw part of the solution found that the amount of acetylsalicylic acid recovered varied from 3% to 99%, depending on whether dispersible or not dispersible tablets were used and the extent of mixing.^{1,2}

In this report, we reflect on data from our laboratory and previous studies.^{3,4} The aim was to discuss two additional important aspects for dissolving tablets and using part of the solution. These were the proportion of the active pharmaceutical ingredients (APIs) in a tablet and the aqueous solubility of the active substance in relation to the intended concentration after dispersing the tablet in water according to a frequently used paediatric medicine preparation technique.

The first aspect is the amount of API in relation to the excipients, the non-active ingredients which are added to achieve the required tablet size and properties. High-dose APIs account for most weight of a tablet and one example is paracetamol, which accounts for 90% of the tablet (Figure 1). Low-dose APIs, with a high proportion of nonactive ingredients include clonidine where the API is only 0.08% of a tablet. This makes visual examination of low-dose tablet dissolution difficult, as only the successful dissolution of the nonactive ingredients is examined. It is likely that healthcare providers rarely reflect upon whether a tablet contains a low or a high dose API.

The second aspect is the maximum amount of API possible to dissolve (aqueous solubility) in relation to the intended concentration when a tablet is dispersed in water. If the APIs in Figure 1 were dispersed as tablets in 10 mL of water, for four out of the five substances, the solubility is lower than the intended concentration. Dispersing clemastine, with an aqueous solubility of 0.0004 mg/mL,⁵ it may look like most of the material has dissolved when a 1 mg tablet is placed in 10 mL of water, with the intended concentration of 0.1 mg/mL. The clear liquid lying above the solid, settled

material, can however never contain a higher concentration than the aqueous solubility (0.0004 mg/mL) unless the pH is adjusted or solubilising agents are added. There is a significant risk of underdosing if this procedure is performed, and part of the solution is administered. The major challenge for healthcare professionals to understand and assess this relates to the availability of information. In public databases such as PubChem,⁵ information about aqueous solubility can be found but it requires some specialist physicochemical knowledge and pharmaceutical skills to evaluate. There are both calculated, and experimentally measured, solubilities stated, and the pH and temperature of the dissolution media can affect solubility. Often, conventional tablets do not contain solubilising nonactive ingredients, rather the choice of specific salts is used to improve the solubility. In the example of clemastine above, the API is selected as a fumarate salt in the licensed product, likely providing a higher solubility; however, the information is not readily available in public literature.

Another example, paracetamol is available as a licensed 24 mg/mL oral solution in Sweden, which suggests that a 250 mg tablet dissolved in 10 mL of water would yield a 25 mg/mL solution. However, paracetamol has an aqueous solubility of around 14 mg/mL at room temperature⁵ and trying to dissolve such a tablet will leave undissolved material. The licensed oral solution, however, includes nonactive substances to increase the solubility to the labelled concentration and above. The study with acetylsalicylic acid also showed the importance of using nonactive ingredients, such as calcium carbonate, to achieve better homogeneity when dissolving tablets.²

If the APIs in Figure 1 were dispensed as tablets in 10 mL of water, the only soluble product would be clonidine with a solubility of 50 mg/mL.⁵ Taking a portion of a dispersed tablet with an API with sufficient solubility can be safe but relies on the API being uniformly distributed in the liquid. An additional complication in this case is that the tablet could contain nonactive ingredients, such as cellulose, which are insoluble in water. The resulting hazy fluid could falsely be interpreted as an insoluble API.

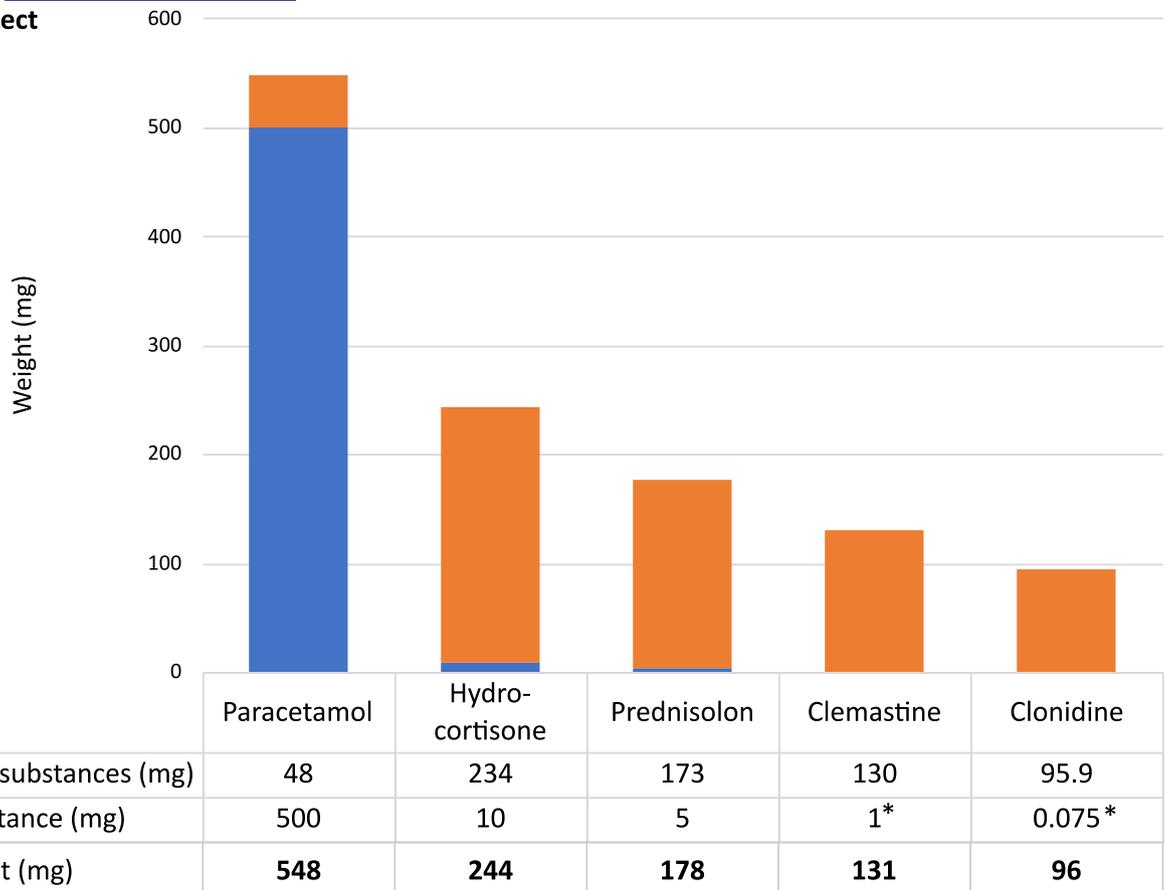
In the absence of appropriate, licensed, products for children, we propose the use of extemporaneously prepared products. The safe handling of APIs with narrow therapeutic windows is of the utmost concern. Tablets should only be dissolved in water, for partial

Abbreviation: API, active pharmaceutical ingredients.

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The First aspect



The Second aspect

*Properties dependent on the salt form of licensed products.

	Paracetamol	Hydrocortisone	Prednisolon	Clemastine	Clonidine
Intended concentration (mg/mL) tablet dispersed in 10 mL water	50	1	0.5	0.1*	0.0075*
Aqueous (intrinsic) solubility ⁵ (mg/mL)	14	0.3	0.2	0.0004*	50*

FIGURE 1 First aspect: Actual weight of tablets separated into weight of nonactive substances and labelled weight of active substance from published data.³ Second aspect: Intended concentration and aqueous solubility.⁵

administration, if the aqueous solubility is well above the intended concentration.

³Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

⁴Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

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None.

Correspondence

Mattias Paulsson, Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden.

Email: mattias.paulsson@kbh.uu.se

CONFLICT OF INTEREST STATEMENT

None.

Åsa C. Andersson^{1,2}

Per Nydert^{1,3}

Mattias Paulsson⁴

ORCID

Mattias Paulsson <https://orcid.org/0000-0002-2514-6618>

¹Karolinska University Hospital, Division of Paediatrics, Astrid Lindgren Children's Hospital, Stockholm, Sweden

²Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

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