

Accepted date: 13-12-2016

Please cite this article as: Richey, Roberta H., Hughes, Clare, Craig, Jean V., Shah, Utpal U., Ford, James L., Barker, Catrin E., Peak, Matthew, Nunn, Anthony J., Turner, Mark A., A systematic review of the use of dosage form manipulation to obtain required doses to inform use of manipulation in paediatric practice. *International Journal of Pharmaceutics* <http://dx.doi.org/10.1016/j.ijpharm.2016.12.032>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1 A SYSTEMATIC REVIEW OF THE USE OF DOSAGE FORM MANIPULATION TO  
2 OBTAIN REQUIRED DOSES TO INFORM USE OF MANIPULATION IN PAEDIATRIC  
3 PRACTICE.

4

#### 5 AUTHORS

6 Roberta H. Richey [1, 2] PhD, MRes, BSc, RGN. ([roberta.richey@thewaltoncentre.nhs.uk](mailto:roberta.richey@thewaltoncentre.nhs.uk) )

7 Clare Hughes [3] MPharmS.

8 Jean V. Craig [4] PhD, RSCN, RGN. ([Jean.Craig@uea.ac.uk](mailto:Jean.Craig@uea.ac.uk) )

9 Utpal U. Shah [1, 3, 5] PhD, MPharm.

10 James L. Ford [3] BSc, PhD, FRPharmS, FRSC. ([j.l.ford@ljmu.ac.uk](mailto:j.l.ford@ljmu.ac.uk) )

11 Catrin E. Barker [1, 5] MSc, PGDipClinPharm, MRPharmS. ([catrin.barker@alderhey.nhs.uk](mailto:catrin.barker@alderhey.nhs.uk) )

12 Matthew Peak [1, 5] PhD, MSc, BSc. ([Matthew.Peak@alderhey.nhs.uk](mailto:Matthew.Peak@alderhey.nhs.uk) )

13 Anthony J. Nunn [1, 3, 6] BPharm, FRPharmS, Hon FRCPC. ([a.j.nunn@liverpool.ac.uk](mailto:a.j.nunn@liverpool.ac.uk) )

14 Mark A. Turner [6, 7] PhD, MBChB, MRCPC. ([mark.turner@liverpool.ac.uk](mailto:mark.turner@liverpool.ac.uk) )

15

16 [1] Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool, L12 2AP

17 [2] The Walton Centre NHS Foundation Trust, Liverpool, L9 7LJ

18 [3] School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Byrom  
19 Street, Liverpool, L3 3AF

20 [4] Norwich Medical School, Faculty of Medicine and Health Sciences, University of East  
21 Anglia, Norwich Research Park, Norwich, NR4 7TJ

22 [5] Cheshire, Merseyside & North Wales Medicines for Children Local Research Network,  
23 Eaton Road, Liverpool, L12 2AP

24 [6] NIHR Medicines for Children Research Network Co-ordinating Centre, Institute of Child  
25 Health, University of Liverpool, L12 2AP

26 [7] Liverpool Women's Hospital NHS Foundation Trust, Crown Street, Liverpool, L8 7SS

27

28 Corresponding author: Professor James Ford, email: j.l.ford@ljmu.ac.uk

29 Conflict of interest statement: The authors have no conflict of interest to report.

30

31 Funding statement: This paper presents independent research commissioned by the National  
32 Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme  
33 (Grant Reference Number PB-PG-0807-13260). The views expressed are those of the authors  
34 and not necessarily those of the NHS, the NIHR or the Department of Health.

35

36 **ABSTRACT**

37 This study sought to determine whether there is an evidence base for drug manipulation to obtain  
38 the required dose, a common feature of paediatric clinical practice. A systematic review of the  
39 data sources, PubMed, EMBASE, CINAHL, IPA and the Cochrane database of systematic  
40 reviews, was used. Studies that considered the dose accuracy of manipulated medicines of any  
41 dosage form, evidence of safety or harm, bioavailability, patient experience, tolerability,  
42 contamination and comparison of methods of manipulation were included. Case studies and  
43 letters were excluded. Fifty studies were eligible for inclusion, 49 of which involved tablets  
44 being cut, split, crushed or dispersed. The remaining one study involved the manipulation of  
45 suppositories of one drug. No eligible studies concerning manipulation of oral capsules or  
46 liquids, rectal enemas, nebuliser solutions, injections or transdermal patches were identified.  
47 Twenty four of the tablet studies considered dose accuracy using weight and/or drug content. In  
48 studies that considered weight using adapted pharmacopoeial specifications, the percentage of  
49 halved tablets meeting these specifications ranged from 30% to 100%. Eighteen studies  
50 investigated bioavailability, pharmacokinetics or clinical outcomes following manipulations  
51 which included nine delayed or modified release formulations. In each of these nine studies the  
52 entirety of the dosage form was administered. Only one of the 18 studies was identified where  
53 drugs were manipulated to obtain a proportion of the dosage form, and that proportion  
54 administered. The five studies that considered patient perception found that having to manipulate  
55 the tablets did not have a negative impact on adherence. Of the 49 studies only two studies  
56 reported investigating children. This review yielded limited evidence to support manipulation of  
57 medicines for children. The results cannot be extrapolated between dosage forms, methods of  
58 manipulation or between different brands of the same drug.

59

## 60 INTRODUCTION

61 Many medicines given to children are used ‘off-label’ because the medicine has only been  
62 researched and authorised for adults. Often the dosage form (e.g., tablets, capsules,  
63 suppositories) is suitable for administration to adults but not to younger children (Waller, 2007).  
64 Age-appropriate formulations may not be commercially available to provide the wide range of  
65 doses required for neonatal and paediatric use (Olski et al, 2011; Fontan et al 2004; Nahata,  
66 1999). In order to tackle these problems medicines are routinely modified, whereby the dosage  
67 form is physically manipulated with the aim of achieving the required dose for administration.  
68 Differing definitions of ‘modification’ and ‘manipulation’ have been used (EMA 2013, Ernest et  
69 al, 2012). In the context of this study, a manipulation is defined as the physical alteration of a  
70 drug dosage form for the purpose of extracting and administering the required proportion of the  
71 drug dose. This work does not consider manipulations done for convenience or due to patient  
72 preference.

73 The Pharmaceutical industry invests considerable time and financial resource in the development  
74 of products designed for accurate and appropriate drug delivery. Legislation, in the form of the  
75 European Union Paediatric Regulation (2007) was established to drive the development of  
76 appropriately licensed and formulated medicines for children, through a system of requirements  
77 and incentives. Simultaneously the World Health Organisation (WHO, 2007) spearheaded a  
78 global campaign to raise awareness and accelerate action to address the need for improved  
79 availability and access to safe, child-specific medicines for all children under 12 years of age.  
80 Similar legislation has been enacted in the US (Turner et al, 2014).

81 However, it will be some time before the influence of this legislation and campaign strategy is  
82 realized and suitably formulated medicines are made available for children. Even when age-  
83 appropriate formulations are marketed, the need for manipulations will remain as drug  
84 development is not able to take account of all the possible circumstances of drug administration.

85 Table 1 provides examples of the type of dosage form manipulation used with the aim of  
86 achieving the required dose. Although drug manipulation is an acknowledged feature of  
87 paediatric clinical practice (Nunn, 2003), and a quantitative description of the situation in the UK  
88 in 2011 has been described (Richey et al, 2013a), previous studies have noted that there is a lack  
89 of information available on the extent to which manipulated drugs are being used (Skwierczynski

90 & Conroy, 2008; Conroy et al, 2000). Manipulations, such as halving tablets to obtain two doses,  
91 are used as a cost reduction measure in some jurisdictions (Berg & Ekedahl, 2010; Gee et al,  
92 2002; Fawell et al, 1999). In other vulnerable groups such as the elderly, those on intensive care  
93 and those receiving enteral feeds, manipulation is common to aid administration (Berg &  
94 Ekedahl, 2010; Gerber et al, 2008; Paradiso et al, 2002; Verrue et al, 2010). Whole tablets may  
95 be crushed and capsules opened and mixed with food or drinks to aid administration to children.  
96 Manipulations are time consuming, may be inaccurate, and the effects on the stability and  
97 bioavailability of the drug may be unknown (Skwierczynski & Conroy, 2008). It is thus possible  
98 to inadvertently administer toxic or sub-therapeutic doses. Manipulations may also increase the  
99 risk of drug errors because calculations are required to determine an amount to be administered  
100 and dose calculation errors at the point of administration have been identified as the most  
101 common type of medication error in neonatal and paediatric patients (Chua, 2010; Conroy et al,  
102 2007). Concerns about dose accuracy in other patient groups have also been highlighted (Berg &  
103 Ekedahl, 2010; Verrue et al, 2010).

104 This review focuses on manipulations conducted with the aim of obtaining the required dose.  
105 Given the lack of age appropriate doses or dosage forms for many drugs, the investigators are  
106 particularly interested in manipulations of drugs for paediatric and neonatal use. However, there  
107 may be situations where drugs relevant to paediatric practice are manipulated, for older patients.  
108 The aim of this systematic review is to establish the evidence base for drug manipulation to  
109 obtain the required dose.

## 110 **METHODS**

111 The systematic review protocol, including details of the iterative approach to developing the  
112 search strategy and refinement of a quality appraisal tool, has been previously published (Richey  
113 et al, 2012) The review was designed and completed with the support and advice of a steering  
114 group consisting of experts in formulation, research, medicine, pharmacy and nursing.

### 115 **Eligibility criteria**

116 This review excluded case studies, case reports and letters; it did not otherwise restrict on study  
117 design. Evidence was also taken from studies where drug manipulation was investigated without  
118 administration to patients as these laboratory-based studies considered the weight and/or drug

119 content of manipulated drugs. Studies investigating any drug, manipulated by any method were  
120 potentially eligible.

121 A hierarchy of outcomes was identified. The primary outcome was dose accuracy of the  
122 manipulated medicine as assessed by drug content assay or other relevant study specific methods  
123 such as weight. Secondary outcomes included: evidence of safety or harm (which the authors  
124 explicitly attribute to the manipulation); bioavailability, physical/chemical/microbial stability;  
125 patient experience of drug manipulation; tolerability/palatability/adherence (explicitly attributed  
126 to the manipulation); contamination of the areas of the manipulation/healthcare  
127 professional/patients/carer and any comparison of methods of manipulation used on similar  
128 dosage forms.

129 Manipulation of a medicine with subsequent administration of the entire dosage form was  
130 considered outside the remit of this review. An exception to this was tablets with a modified-  
131 release design. Where tablets have a modified-release design, crushing, splitting or dispersing of  
132 these tablets, may alter the bioavailability and safety of these tablets, even when the entire  
133 dosage form is administered. Studies that involved extemporaneous or compounding preparation  
134 within a pharmacy and those which were involved in the drug development process were  
135 excluded.

### 136 **Information sources and searches**

137 The Cochrane database of systematic reviews, MEDLINE (Internet interface PubMed),  
138 EMBASE, CINAHL and International Pharmaceutical Abstracts (IPA) databases were searched  
139 from inception of data base to August 2015. The review steering group and research and  
140 healthcare practitioners with expertise in medicines management were asked to provide  
141 references to any additional studies or unpublished data. The reference lists of included studies  
142 were checked for any additional eligible studies. The devising of the search strategy was  
143 complex as any drug or dosage form was potentially eligible. Furthermore manipulation to obtain  
144 the required dose does not have a standard term in databases of the medical and pharmaceutical  
145 literature therefore a list of free text descriptions for manipulation had to be identified. As the  
146 search strategy underwent a considerable review and revision process (Richey et al, 2012) a  
147 balance had to be made between the sensitivity and the precision of the search with the  
148 consequential risk that there may be studies that have not been identified. Therefore subsequent

149 narrower search strategies for three of the known manipulated drugs (omeprazole, captopril and  
150 warfarin) were devised and searches completed. The generic strategy has been described in the  
151 appendix of the published protocol (Richey et al, 2012). Initial searches were completed in  
152 August 2009; update searches were completed in August 2015.

### 153 **Study selection and data extraction**

154 Due to the considerable number of records identified by the generic search (39,762 hits) and the  
155 narrower drug-specific searches (4535 hits) an initial screen was undertaken by one reviewer  
156 (Richey et al 2012). A random sample of 5% the titles and abstracts was screened by a second  
157 reviewer to confirm the initial screening. Potentially eligible studies identified from the initial  
158 screen were independently considered and discussed by two reviewers and the full text of  
159 potentially eligible studies obtained. A third reviewer was available for any studies where  
160 agreement on inclusion could not initially be reached. Data for the included studies were  
161 extracted into data extraction tables by one reviewer, these were then independently assessed by  
162 the second reviewer and changes agreed. Drug specific searches did not yield any additional  
163 studies.

### 164 **Quality assessment**

165 An assessment of risk of bias of included studies was carried out at study, rather than outcome  
166 level using a bespoke quality assessment form derived from established checklists and  
167 supplemented with review specific criteria compiled by formulations, systematic review and  
168 healthcare professional experts (Richey et al, 2012). Two reviewers assessed studies  
169 independently and then discussed their decision-making to reach agreement on the quality  
170 criteria for the included studies. Overall quality ratings were then assigned to the studies using  
171 the symbols ++, + and – as described in Table 1. The authors, during the review processes,  
172 assessed the confidence/trust that can be placed on the outcomes of the studies. Thus in Table 1  
173 “considerable concerns” represents studies where a lot of risk of bias was apparent in the study  
174 design/methods or reported results/outcomes and meant that the study was considered as  
175 potentially unreliable. “Some concerns” indicates that some risk of bias in the design/methods  
176 was recognised that raised questions about the reliability of the reported results/outcomes. “With  
177 reasonable confidence” implies that the study design/methods are considered to have a lower risk  
178 of bias and the results/outcomes reported can be considered reliable.



179

**180 Data synthesis**

181 In order to capture as much data as possible that is relevant to clinical practice there was no  
182 restriction on study design, type of drug or method of manipulation. Accordingly, this review  
183 includes a heterogeneous set of studies. Because the studies were so heterogeneous, a narrative  
184 synthesis of the findings was used with no meta-analysis; the data from each study were  
185 extracted and tabulated, with studies grouped using the primary and secondary outcomes defined  
186 for this review. Results are generally presented descriptively

187

**188 RESULTS AND DISCUSSION**

189 Fifty studies were included and quality-assessed. Twelve (24%) studies were assigned a ++  
190 quality rating, 30 (60%) studies a + rating and 8 (16%) a – rating (Table 2).

191 Forty-nine studies were identified that met the inclusion criteria for tablets that were crushed,  
192 split or dispersed. These included 24 studies that had outcomes that included an assessment of  
193 the weight of split portions and/or their drug content and 10 studies that compared different  
194 methods of manipulation. Five studies had acceptance outcomes and included patient issues such  
195 as patient experience, adherence, taste or tolerability; nine studies had bioavailability outcomes.  
196 Though adverse effects are reported in the bioavailability studies there were no studies that  
197 specifically considered evidence of the safety or harm of manipulating medicines.

**198 *Primary outcome: dose accuracy of the manipulated medicines – weight and/or drug content***  
**199 *outcomes***

200 The dose accuracy of manipulated medicines was assessed by different studies through weight,  
201 dissolution profiles and/or drug content outcomes. In the absence of pharmacopoeial tests to  
202 establish uniformity of split tablets at the time that many of these studies were undertaken, some  
203 authors devised tests adapted from the then current pharmacopoeial criteria for intact (whole)  
204 dosage forms. These criteria mimic those currently found in the British Pharmacopoeia (2016)  
205 where tablets bearing break-marks that allow subdivision to provide required dose can be  
206 assessed. The efficacy of the break-mark(s) must be assessed during the development in respect  
207 of uniformity of mass of the subdivided parts. The test is based on 30 randomly selected tablets

208 which are broken by hand; one part is taken from each of the subdivided tablets and weighed.  
209 Each part is individually weighed and the average mass calculated. Compliance is agreed if not  
210 more than 1 individual mass is outside the limits of 85% to 115% of the average mass and that  
211 individual mass is not outside the limits of 75% to 125% of the average mass.

212 There were 24 studies that assessed the physical characteristics of halved tablets; 18 studies  
213 halved tablets and used adapted pharmacopoeial criteria. It might be assumed that any split  
214 fragment of a tablet will contain the fraction of the initial content proportional to the ratio of the  
215 fragment weight: whole tablet weight. Analysis of mercaptopurine tablets showed this to be the  
216 case (Footitt, 1983). However analysis of fragments from levodopa tablets (Walker et al, 1978)  
217 showed a highly significant difference in the variation of percentage of drug content between  
218 quarters and tablets.

219 Table 3 provides a summary of eight studies that were identified as assessing halved or quartered  
220 tablets using pharmacopoeial-based outcomes for weight and/or drug content uniformity. There  
221 is no assurance that halving or quartering tables provides uniform split products

222 One study (Horn et al, 1999) halved and quartered tablets and used pharmacopoeial-based  
223 outcomes for weight and/or drug content uniformity to compare two tablet splitters. Seven  
224 products were examined. These were scored clonidine (branded and generic), scored captopril,  
225 unscored amlodipine, unscored atenolol, scored sertraline and scored carbamazepine. Tablets  
226 from lots of each product were halved and quartered and assessed by weighing within  $\pm 15\%$ ,  
227 USP specification. The data in Table 4 clearly indicate the difference in batch performance, that  
228 different quality of portions may be obtained from different splitters and that the variation in  
229 quarters is greater than that for halved tablets.

230 In another study Stimpel et al (1985) halved 34 products which were scored tablets and  
231 contained antihypertensive drugs. The tablets were described as displaying excellent divisibility  
232 (7 products), good divisibility (11 products), moderate divisibility (10 products) or poor  
233 divisibility (6 products). One commercial controlled release tablet containing isorbide-5-  
234 mononitrate tablet of 60 mg is scored and designed to allow division into 20mg and 40 mg  
235 segments (Stockis et al, 2002)

236 Splitting tablets into two or three parts was reproducible with relative standard deviations of 0.8  
237 – 1.5 %. The presence of a score line does not guarantee an even subdivision of tablets (Footitt,

238 1983; Hill et al, 2009; Polli et al, 2003; Rashed et al, 2003; Rosenberg et al, 2002; Teng et al,  
239 2002; Zaid & Ghosh, 2011; Horn et al, 1999) (Table 3). Uniform splitting was related to the  
240 hardness, friability and shape of tablets (Zaid & Ghosh, 2011).

241 Splitting was also related to tablet shape, size & hardness and the depth of score lines. Tahaine  
242 & Gharaibeh (2012) split tablets (four products) with a knife and assessed the resulting half-  
243 tablets for weight uniformity using an adapted USP method. Split warfarin tablets were uniform  
244 in weight- which was attributed to hardness and the presence of a deep score line. Splitting  
245 digoxin, phenobarbital, and prednisolone tablet produced half tablets whose weights were highly  
246 variable (Tahaine & Gharaibeh, 2012). Splitting sixteen tablet products with a knife was  
247 assessed by Helmy (2015) using weight and content uniformity of half tablets. Dose variation  
248 exceeded a proxy USP specification for more than one-third of sampled half tablets of  
249 bromazepam, carvedilol, bisoprolol, and digoxin. Drug content in half tablets appeared to be due  
250 to weight variation due to fragment or powder loss during the splitting process. Tablet size,  
251 shape, hardness and presence of score lines were important variables. Quality control standards,  
252 other than mass uniformity and drug content may be used to assess the physical quality of  
253 manipulated tablets. Vranic & Uzunovic (2008) found that scored whole and halved tablets of  
254 four lisinopril products met Ph Eur adapted specifications for crushing strength, friability,  
255 disintegration time and mass uniformity. Costa et al (2000) halved and quartered three products  
256 containing captopril finding their hardnesses ranked as whole > halved > quartered tablets.

257 A variety of studies has extended splitting to include quartered tablets. The studies of Tuleu et al  
258 (2005) and Horn et al (1999) are discussed in Table 3 and below. Costa et al (2000) extended  
259 their studies into three captopril products and devised a divisibility assay value which was  
260 defined as the percent standard deviation divided by mean half or quarter weights, in effect a  
261 relative standard deviation. Values were 7.7, 5.8 and 8.3% for halves and 15.0, 8.8 and 16.9% for  
262 quarters for the three captopril products indicating decreased consistency of weight for quartered  
263 compared with halved tablets. In another study, Walker et al (1978) quartered tablets and  
264 considered that two products, each containing levodopa, showed no significant difference in  
265 weight variation between whole tablets and quarters whilst another levodopa product and a  
266 sulphamethoxypyridazine tablet showed significant difference in weight variation between whole  
267 tablets and quarters. For one of the levodopa products, significant difference in percentage  
268 content between tablets and quarters implied less homogeneity of drug distribution in un-

269 quartered tablets (Walker et al, 1978).

270 Eight studies (Costa et al, 2000; Erramouspe & Jarvi, 1997; Kayitare et al, 2009; Mandal, 1996;  
271 Shah et al, 1987; Simons et al, 1982; Stockis et al, 2002; Tuleu et al, 2005) used dissolution  
272 profiles to assess halved or segmented tablets. Each study identified differences in dissolution  
273 profiles between halved and intact tablets, and, with the exception of the work of Costa et al  
274 (2000), considered tablets with a modified-release mechanism. This latter study, examining three  
275 captopril products demonstrated that halving and quartering the tablets increased the speed of  
276 dissolution for the three tablets (Costa et al, 2000). Halved or quartered nifedipine modified  
277 release tablets had faster dissolution profiles than intact tablets (Tuleu et al, 2005).

278 Dissolution profiles of tablet fragments of Isorbide-5-mononitrate 60mg tablets differed by 10%  
279 or less relative to intact tablets (Stockis et al, 2002). Mean cumulative dissolution profiles of  
280 extended release methylphenidate tablets showed significant differences between halved and  
281 whole tablets from the same manufacturers and between halved brand and whole generic tablets  
282 (Erramouspe & Jarvi, 1997). Comparing the release of three aspirin products (sustained-release  
283 aspirin 800mg, , aspirin 325mg, extended-release aspirin 650mg, microencapsulated particles),  
284 Mandal (1996) showed that the dissolution rate of the split tablets of the 800mg tablets was  
285 significantly higher than that for whole tablets although the other tablets had similar drug release  
286 profiles over time with whole and split tablets. Brands of theophylline 300mg controlled-release  
287 had significantly different dissolution profiles between whole and half tablets in simulated  
288 gastric fluid and simulated intestinal fluid (Shah et al, 1987). Dissolution from halved sustained  
289 release theophylline 100mg tablets was significantly higher than from whole tablets (Simons et  
290 al, 1982)

291 Kayitare et al (2009) developed a novel fixed dose combination tablet, containing 300mg  
292 zidovudine and 160mg lamivudine, for paediatric HIV patients to allow easy breaking into a  
293 maximum of 8 subunits. The intact tablets and their subunits disintegrated within 20 s and in  
294 dissolution tests, > 95% of each drug was released after 30 min.

#### 295 Tablet shape Outcomes

296 Six studies (Helmy, 2015; Hill et al, 2009; Polli et al, 2003; Rosenberg et al, 2002; Teng et al,  
297 2002; Verrue et al, 2010) that included tablets which were not flat and round but were  
298 alternatively shaped (e.g., trapezoid, octagon, shield-shaped, ovoid-rectangular). Halves of these

299 tablets did not meet the specified USP weight specification. Another study (Zaid & Ghosh, 2011)  
300 showed that of 4 products examined, only one film-coated oblong shaped tablet passed the Ph  
301 Eur specification for weight uniformity of scored tablets whereas three other oblong-shaped  
302 tablets (one film-coated) did not. A square captopril product (Costa et al, 2000) subdivided into  
303 halves and quarters, met weight variation limits whereas two circular tablets did not, despite all  
304 three products having crossed grooves on one of their faces.

305 A novel fixed dose combination tablet, containing 300mg zidovudine and 160mg lamivudine,  
306 was developed for paediatric HIV patients (Kayitare et al, 2009). The novel product had a  
307 rectangular shape (22.4 mm long, 11.2 mm wide) with multiple score lines (depth 0.89 mm,  
308 angle 100°) to allow easy breaking into a maximum of 8 subunits. The tablets were subdivided  
309 along the score lines into 1/2 (along shortest axis of the tablet), 1/4 (along shortest axis), 3/4  
310 (along shortest axis) and 1/8 tablet. The average weights of the smallest pieces (1/8 of a tablet)  
311 were within the 85–115% range of the average mass limits as required by EP.

#### 312 Tablet dispersions

313 Apart from splitting tablets, dispersing tablets in water and taking an aliquot of the resulting  
314 suspension is used clinically to obtain reduced doses. Two studies assessed this practice using  
315 prior crushing and dispersion of nifedipine tablets (Tuleu et al, 2005) or dispersing dispersible  
316 aspirin 75 mg tablets (Broadhurst et al, 2008). Crushed nifedipine 10 mg modified release tablets  
317 were suspended in 10ml water. Samples were extracted using 1 or 5 ml oral syringes. Doses  
318 ranging from 2.9 to 5.7 mg and 0.6 to 1.5 mg were obtained using 5 ml and 1 ml syringes  
319 respectively compared to theoretical doses of 5 and 1 mg (Tuleu et al, 2005). Reproducing  
320 clinical practice, Broadhurst *et al* (2008) dispersed dispersible aspirin tablets in 10 mL water and  
321 found that, irrespective of dispersion time, the samples taken from the base of a 30 mL container  
322 were consistently closer to the intended dose (51-95% of the intended dose) compared with those  
323 taken from the highest zone at 8 mL mark of the container (23-80% of the intended dose), with a  
324 trend for the dose measured to decrease as the zones ascended up the beaker.

325

326 ***Secondary outcomes: comparison between weight loss, manipulation methods, bioavailability,***  
327 ***effectiveness, patient experience, adherence/compliance***

328 Comparison between manipulation methods:

329 Twelve studies were identified that compared methods of manipulating tablets (Table 5). Overall  
330 the use of a commercial tablet splitter (by some authors termed tablet cutter) was more accurate  
331 than other splitting methods such as scissors or knives, or splitting manually.

### 332 Weight loss during manipulation

333 Ten studies quantified the weight loss observed during the halving or quartering of tablets. Mean  
334 weight losses for mercaptopurine tablets varied from 0.24% to 2.64% depending on the operator,  
335 although individual losses as high as 11.7% were recorded (Footitt, 1983). Using tablet splitters,  
336 mean weight losses of between 0.1% and 1.3% were recorded for six commercial products (Hill  
337 et al, 2009) and 0% to 1.9% for 12 commercial products (Polli et al, 2003) although in the latter  
338 study a maximum weight loss of 7.3% was noted for one product and weight loss was not  
339 considered to be an indicator of the uniformity of split. Similar mean weight loss ranges were  
340 reported as 0.02% to 1.5% for 16 products (Helmy, 2015) 0.1% to 1.2% when halving or  
341 quartering captopril tablets (Costa et al, 2000) and 0.3% to 0.9% when quartering tablets made to  
342 a model formulation (van Vooren, 2002) where a maximum weight loss of 6.8% was recorded.  
343 Although a mean loss of 1.1% was noted for the loss following splitting of hydrochlorothiazide  
344 tablets (McDevitt et al, 1998), the range of loss varied from 0% to 19.4%. Recovery (in  
345 comparison to weight loss) of misoprostol tablets quartered by a pill splitter and by hand were  
346  $96.6 \pm 2.8\%$  and  $99.0 \pm 1.3\%$  respectively (Williams et al, 2002). The most comprehensive study  
347 (Verrue et al, 2010) compared three routine splitting methods (grouped as a splitting device,  
348 scissors or by hand, and a kitchen knife) to half or quarter eight commercial products.  
349 Statistically, the splitting device only produced the lowest weight loss of the three methods for  
350 the digoxin tablets when a mean weight loss of 1.4% was recorded as against 7.6% and 5.4% for  
351 the scissors/hand and kitchen knife respectively. For five products (warfarin, levodopa/carbidopa  
352 each halved; fenprocoumon, methylprednisolone and lisinopril, each quartered) the results  
353 obtained by the splitting device or scissors/hand) were statistically indistinguishable. Overall the  
354 splitting device produced the lowest weight loss but even with this method a weight loss as high  
355 as 26.6% was recorded when halving commercial metformin tablets. For digoxin tablets  
356 maximum weight losses of 37.0 and 37.6% were recorded using the scissors/hand and knife  
357 respectively (Verrue et al, 2010). Following subdivision of a novel fixed dose combination tablet  
358 capable of subdivision into 8 sub-units, weight loss was low ( $<0.4\%$ ) and independent of the  
359 subunit size (Kayitare et al, 2009).

360 These losses compare with those described by Green et al (2010) who discussed potential USP  
361 standards for the subdivision of scored tablets and indicated that to comply the mean loss of mass  
362 should not exceed 3%

### 363 Bioavailability

364 There were nine studies identified, all with adult participants, where modified-release tablets  
365 were split or crushed but, although the whole dose of the tablet was administered, the outcomes  
366 were considered relevant due to the potential to alter the drug release characteristics of the  
367 formulation Eight of these nine eligible studies were sustained-release formulations and one  
368 study used an enteric-coated formulation.

369 Crushing of pentoxifylline extended-release (Trental) 400mg and 600mg tablets (Cleary et al,  
370 1999) and theophylline matrix sustained-release (Theo-Dur) 300mg tablets (MacKintosh et al,  
371 1985) did not significantly change the bioavailability, though the time taken to reach peak  
372 concentration was shorter with crushed tablets than with intact tablets.

373 Five studies halved modified release tablets. No differences were found in bioavailability for  
374 halved and intact theophylline sustained-release (Theo-Dur) 100 mg tablets (Simons et al, 1982)  
375 and 300 mg tablets (Fagerström, 1980). One study used theophylline slow-release anhydrous  
376 (Uniphyllin®) 400 mg tablets (Primrose et al, 1983) and peak drug levels were significantly  
377 higher with halved than with intact tablets. Two studies used verapamil sustained-release 240 mg  
378 matrix tablets (McEwen et al, 1989; Moreland et al, 1989) and both studies found no differences  
379 in bioavailability for halved and intact tablets. One study involved cutting isosorbide-5-  
380 mononitrate tablets into thirds and found no significant differences in bioavailability though  
381 maximum peak concentration was higher with the trisected tablets than with intact tablets  
382 (Stockis et al, 2002). Ferron et al (2003) crushed enteric-coated tablets (pantoprazole 40 mg) and  
383 found that the resultant suspension was 25% less bioavailable than the whole tablet.

384 Two other studies were identified. There was no significant difference in pharmacokinetic  
385 parameters in a bioavailability study using adults between Duovir® and a novel fixed dose  
386 combination tablet, containing 300mg zidovudine and 160mg lamivudine, intended for paediatric  
387 HIV patients (Kayitare et al, 2009). Corbett et al (2010) manipulated a product to obtain a  
388 proportion of the original dosage form. This involved 18 HIV-infected children who received  
389 quartered, halved or three quartered generic tablet multiples of lamivudine (3TC) 300mg,

390 stavudine (d4T) 80 mg and nevirapine (NVP) 400 mg or a generic liquid or trade liquid in a  
391 crossover study. There was no significant difference in bioavailability between the different  
392 formulations and the time to maximum concentration was delayed for d4T and 3TC for the  
393 manipulated tablets compared with the liquid formulations.

394 Evidence of safety or harms, adverse effects:

395 Adverse effects considered to be related to the drug manipulation were relevant to this review.  
396 There were marginally more adverse effects reported in five of the nine bioavailability studies of  
397 modified release tablets with nausea/vomiting (Cleary et al, 1999; Primrose et al, 1983) and  
398 headache (Cleary et al, 1999; Primrose et al, 1983; Stockis et al, 2002) with crushed or split  
399 tablets than intact tablets. Two studies reported excellent tolerability with both split and intact  
400 tablets (Kayitare et al, 2009; Moreland et al, 1989). The one study which split enteric-coated  
401 tablets found both treatments to be well tolerated and considered the adverse effects reported to  
402 be related to nasogastric tube insertion rather than drug-related (Ferron et al, 2003). The number  
403 of adverse effects reported was small and conclusions cannot be drawn about whether  
404 manipulated medicines had more associated adverse effects.

405 Patient experience:

406 One study considered the experiences of children taking an oral solution compared with those  
407 taking a dispersion of crushed prednisolone tablets (Lucas-Bouwman et al, 2001). Taste assessed  
408 by visual analogue scores was significantly better for the oral solution than for the crushed  
409 tablets. Nine of the 78 children in the study also withdrew due to repeated vomiting while taking  
410 the crushed tablets.

411 There were a further five surveys identified that assessed adult participants' experiences of  
412 splitting tablets. Three studies used the same questionnaire or an adapted version of it for tablets  
413 split with a tablet splitter. Carr-Lopez et al (1995) surveyed 233 patients (all 55 years old, or  
414 older) splitting lovastatin, Gee et al (2002) surveyed 454 patients (average age 66 years old)  
415 enrolled in a statin splitting programme and Fawell et al (1999) surveyed patients (median age 65  
416 years old) splitting fosinopril. Across the three studies, a small percentage of respondents (4%  
417 (Fawell et al, 1999), 6.3% (Lopez et al, 1995), 7% (Gee et al, 2002)) felt that using the tablet  
418 splitter had an effect on their willingness to take the drug as prescribed. Some respondents (7%  
419 (Gee et al, 2002), 6% (Fawell et al, 1999), 14% (Lopez et al, 1995)) reported having missed



420 more split tablet doses in a month when compared to other medicines where the tablet did not  
421 have to be halved. One study surveyed 99 patients, the majority of whom were 50 years old or  
422 older, with hyperlipidaemia who used a tablet splitter and found that more than 90% agreed that  
423 they found that tablet splitting had not affected their willingness to take their medication and  
424 that 90% disagreed that they had missed more medication doses because of tablet splitting (Choe  
425 et al, 2007). In a survey of 28 patients, described as outpatient veterans, splitting lisinopril  
426 (method of splitting not reported) (Rindone, 2000), tablet splitting was bothersome ‘most’ of the  
427 time for 25% of participants; for ‘some’ of the time there were more than two pieces of the tablet  
428 following splitting for 54%, of the participants.

#### 429 Adherence:

430 Three identified studies considered aspects of adherence for 57 participants splitting fosinopril  
431 tablets (Fawell et al, 1999) and 111 (Choe et al, 2007) or 3787 participants splitting statin tablets  
432 (Parra et al, 2005) with a tablet splitter. There were no differences in adherence between those  
433 splitting tablets and those taking whole tablets whether self-reported (Choe et al, 2007),  
434 measured by tablet counting, refill history and self-reporting (Fawell et al, 1999) or prescription  
435 refills (Parra et al, 2005). A fourth study, which included patients with schizophrenia or  
436 schizoaffective disorder splitting risperidone, found that adherence increased with tablet splitting  
437 (Weissman & Dellenbaugh, 2007).

#### 438 Effectiveness

439 Tablets containing a statin have been frequently given as split tablets and clinical assessment  
440 made. No significant difference in total cholesterol, HDL, LDL or triglycerides between baseline  
441 levels and post splitting levels were found following split atorvastatin, simvastatin or pravastatin  
442 (Choe et al, 2007). In another study no significant difference in total cholesterol and triglycerides  
443 pre and post tablet splitting but significant small increases in HDL, AST and ALT and decreases  
444 in LDL were noted following the administration of split atorvastatin, lovastatin or simvastatin  
445 tablets (Gee et al, 2002). No significant difference in LDL between whole and halved tablets was  
446 found following administration of 5, 10, 20, or 40 mg simvastatin (Parra et al, 2005). Overall –  
447 significant decreases in total cholesterol and LDL pre and post splitting of simvastatin or  
448 atorvastatin (doses not specified) with half tablet dosing as effective as whole tablet taking  
449 (Duncan et al, 2002). For other classes of drugs, no significant difference in mean systolic and

450 mean diastolic blood pressure with tablet splitting of lisinopril was measured (Rindone, 2000)  
451 and no change in psychiatric or non-psychiatric admission rate was noted following the  
452 administration of splitting Risperidone tablets (Weissman & Dellenbaugh, 2007).

453 Direct observational study from the literature:

454 Mercovich et al (2014) reported observations of manipulation of solid oral dosage forms during  
455 medicine rounds in aged care facilities. From 160 observations across six medication rounds, 29  
456 residents had a total of 75 medications modified by the nursing staff prior to administration, with  
457 32% of these instances identified as inappropriate. Methods used for crushing and administration  
458 resulted in drug mixing, spillage and incomplete dosing. Staff reported adequate resources but a  
459 lack of knowledge on how to locate and use resources was evident. Mercovich et al (2014)  
460 concluded that improved staff training on how to use available resources was needed to reduce  
461 the observed high incidence of inappropriate modifications.

462 Non-tablet studies:

463 There were no studies identified through the systematic review which considered the  
464 manipulation of capsules, sachets, liquids for oral administration, nebuliser solutions,  
465 intravenous injections and injections for subcutaneous administration, enemas or transdermal  
466 patches. There was one study (Kim et al, 2005) identified through the systematic review which  
467 considered the manipulation of suppositories. This study asked anaesthesiologists to split  
468 paracetamol suppositories using the technique they would use in practice. This resulted in wide  
469 variation from the intended dose: intended dose 40 mg (range 30-78 mg), 53 mg (range 27-79  
470 mg), 60 mg (range 47-82 mg), 80 mg (range 38-92 mg), 162 mg (range 112-250 mg), and 217  
471 mg (range 113-259 mg)). The study concluded that the lack of accuracy and precision was a  
472 reason to use unaltered suppositories.

473 **GENERAL DISCUSSION**

474 This review has demonstrated that there is a dearth of evidence to support the widespread  
475 practice of drug manipulation in children. Where evidence was located it almost universally  
476 related to the manipulation of tablets for treating adult patients, with only one study which used  
477 any other dosage form. Only two studies had child participants (Corbett et al, 2010; Lucas-  
478 Bouwman et al, 2001) and, in one of these (Lucas-Bouwman et al, 2001), the taste scores of  
479 crushed tablets were considered. In the other study (Corbett et al 2010), the formulations were

480 well tolerated and 10% of children commented on the enjoyable taste of the liquid formulations.  
481 Splitting tablets was frequently unreliable. The clinical consequences of this finding are difficult  
482 to estimate but are likely to be important in medicines with a narrow therapeutic index. When  
483 splitting tablets, it is reasonable to expect that the weight or drug content of segments will vary  
484 no more than would be expected for intact tablets. Pharmacopoeial standards for intact tablets are  
485 well established and usually include tests to establish uniformity of weight or content. When  
486 many of these studies were undertaken there were no pharmacopoeial standards for the quality of  
487 segmented tablets. Most authors adapted the criteria and methodology for testing the uniformity  
488 of intact tablets. Whilst the detail of tests may vary they are essentially ensuring low variability  
489 of weight and/or drug content between dosage units and the absence of outliers. In 2002 the  
490 European Pharmacopoeia presented pharmacopoeial standards for the subdivision of scored  
491 tablets. These standards, which marked the first time this type of pharmacopoeial requirement  
492 was established, have been subsequently reviewed and revised (Green et al, 2010). The use of  
493 such standards within other pharmacopoeias has been discussed and a stimulus article discussed  
494 why standards should be included in the USP (Green et al, 2010) and are currently found in, for  
495 example, the British Pharmacopoeia (2016). Here, the efficacy of the break-mark(s) must be  
496 assessed during the development in respect of uniformity of mass of the subdivided parts where  
497 the selected tablets were broken by hand. Many of the citations in this study utilized tablet  
498 splitters or knives in the subdivision of tablets and their use has been broadly scientifically  
499 unestablished.

500 The results identified in this review varied but the majority of studies suggest a lack of  
501 uniformity of segment weight or drug content when splitting tablets into halves and even greater  
502 variation when splitting in to quarters. Such lack of uniformity is unacceptable for intact ‘whole’  
503 tablets. When weight and content uniformity were tested, of concern is that when weight  
504 uniformity was compliant content uniformity often was not, suggesting uneven drug distribution  
505 within some tablets. Although there were few comparisons there would appear to be differences  
506 in variability of segments between different tablet strengths and between branded and generic  
507 tablets. The clinical importance of unequal splitting of tablets cannot be estimated: Only one  
508 study was identified that reported bioavailability after a proportion of a tablet (an antiretroviral)  
509 had been administered to children. In all other bioavailability studies relevant to this review  
510 sustained release tablets were split or crushed and the whole dose administered. Though there

511 were only nine studies using ten sustained release products there is an indication from four  
512 studies that there may be an effect on the intended modified drug release mechanism and  
513 consequently on bioavailability following manipulation. Reduction in the time to reach peak  
514 concentration was the outcome predominantly affected by the tablet being halved or crushed  
515 prior to administration. The modified release mechanism is important in determining whether the  
516 release characteristics will be altered upon splitting.

517 Although results were inconsistent, tablets split using a tablet splitter were more likely to yield  
518 segments that had split more accurately than those split using methods including scissors, knife  
519 or manual splitting. Similarly scored tablets tended to provide segments closer to the intended  
520 weight. While these results can only be considered applicable directly to the products in the  
521 studies involved they do nonetheless suggest that use of a commercial tablet splitter and scored  
522 tablets may be beneficial if tablets must be split.

523 In general the segmenting of tablets does not appear to affect adherence in adults although the  
524 evidence is based on a limited number of drugs. We found only one study that had paediatric  
525 participants and this considered the taste and tolerance of crushed tablets rather than other  
526 aspects of manipulation (Lucas-Bouwman et al, 2001). This study concluded that the oral  
527 solution was better tolerated than the crushed tablets. The only study of a dosage form other than  
528 tablets showed substantial variation in size of the segments cut from paracetamol suppositories  
529 by anaesthetists leading the authors to conclude that such suppositories should not be split.

530 This study sought the evidence for an area of medical and nursing practice that could potentially  
531 include any drug and/or dosage form and therefore may be limited by its complex nature. We  
532 had specified that the only study type restrictions were on case series/studies, consequently  
533 included studies were heterogeneous not only in design and quality, but in terms of types of  
534 manipulations, drug types, dose forms, participants and outcomes investigated. Letters and case  
535 series excluded from this review may have included some of the anecdotal information on  
536 manipulation of dosage forms other than tablets and suppositories. It is also possible that clinical  
537 outcomes have been reported as case series or letters. For example, a letter suggesting  
538 satisfactory outcomes with split tablets of bosentan used for children with pulmonary  
539 hypertension followed an article and letter criticising the lack of information provided on the  
540 method of administration of bosentan tablets to young children (Rosenzweig et al, 2005).

541 Subsequently, regulatory submissions have included a formulation of bosentan tablets which is a  
542 quadrisectioned dispersible tablet containing 32 mg of bosentan to be dispersed in a teaspoon with  
543 water (EMA Report, 2012). Such regulatory reports were also not the subject of this review and  
544 individual summaries of product characteristics were not searched for information.

545 What emerges from this review is that there is little published information on manipulation of  
546 dosage forms to achieve the required dose and further work is needed to support what is a  
547 common practice (Berg & Ekedahl, 2010). The majority of the included studies related to tablets  
548 and it is difficult to draw firm conclusions from the outcomes since the products and method of  
549 manipulation varied considerably as did the outcomes in terms of compliance with standards for  
550 variability derived from those for intact tablets.

551 An optimum requirement would be studies where a drug was manipulated to obtain the required  
552 dose, administered to participants and outcomes reported. There were no studies identified which  
553 used this approach in children, the nearest being the study of Kayitare et al (2009) who  
554 developed a novel fixed dose combination tablet capable of subdivision to subunits containing a  
555 dose suitable for each 5 kg body weight. Biological characteristics were however established in  
556 adults.

557 Each formulation of each drug may provide different results when manipulated. Consequently  
558 the planning of future research becomes challenging. This may be aided by the identification of  
559 drugs which frequently require manipulations and represent a higher risk if an over or under dose  
560 is administered (such as those with a narrow therapeutic index (Shah et al, 2010) or where the  
561 adverse effects of a manipulated drug might be a concern or by the recognition of patient groups  
562 where a number of the commonly prescribed drugs may require manipulation. The use of  
563 standardised research methodologies would help to build a more comprehensive resource of  
564 evidence relating to drug manipulation to aid clinical decision-making.

565 No studies were identified that considered physical/chemical/microbial stability or contamination  
566 of the areas of manipulation.

567 Subsequent to the completion of data searching in August 2015, two publications were noted that  
568 considered drug manipulation in children. Mistry and Batchelor (2016) highlighted the need for  
569 support knowledge around the acceptability of age-appropriate medicines and presented an  
570 algorithm to aid in formulation selection based on age range. Andersson et al (2016) concluded

571 that tablets larger than 8 mm could be split only once to achieve an approximate half dose for  
572 paediatric use. The authors could not recommend that tablets be split more than once due to a  
573 lack of weight uniformity of the part tablets after splitting. Both Mistry and Batchelor (2016) and  
574 Andersson et al (2016) concluded that more age-appropriate dosage forms, including small  
575 tablets, should be available to children. Andersson et al (2016) considered that non-functional  
576 score lines should be avoided since both patients and health professionals falsely believed that a  
577 score line indicates the possibility of dividing the tablet in two equal parts.

578 A change in the manufacturing process of 10 mg hydrocortisone tablets, where an increased  
579 compression was used, led to reports (Saimbi et al, 2016) that the newer, harder tablets were  
580 more difficult to manipulate. Tablets were either manipulated by breaking along score lines to  
581 produce halved or quartered segments or 2mg doses were prepared by dispersing crushed tablets  
582 in 10 mL of water and taking a 2 mL aliquot; crushing was accomplished using a spoon onto a  
583 plate or a commercial crushing device (Saimbi et al, 2016). The harder tablets showed a better  
584 accuracy of split with weight ranges of 41 – 55% and 17 – 35% for halves and quarters  
585 respectively compared with weight ranges of 29–70% and 12–42%) for the less hard tablets.  
586 Conversely, the 2 mg dosing accuracy was better for both sets of tablets. The use of spoon / plate  
587 or the commercial device led to mean doses of 1.3 mg and 1.9 mg for the harder tablets and 1.7  
588 mg and 2.1mg for the less hard tablets. The authors concluded that parents or carers should be  
589 advised to crush the tablet into a fine powder, where possible, to improve dosage accuracy.

590 Nidanapu et al (2016) used caregivers to split tablets containing anti-epileptic drugs (phenytoin  
591 sodium, sodium valproate, carbamazepine and phenobarbitone) intended for adults but  
592 prescribed to paediatric patients. The caregivers performed the same splitting process that they  
593 normally followed in their homes. 168 caregivers participated and 1098 split tablets were  
594 analysed. In total 49.0% of the split parts were above the specified limit of the 2010 Indian  
595 Pharmacopeia (IP) for acceptable percentage weight deviation. 41.5% of the split parts were  
596 outside a specification for drug content. 253 split parts were outside the acceptable content  
597 uniformity range of >85% and <115%.

598 It is clear from the results in this paper that recommendations for the manipulation of products  
599 for children have to be advised by practices used in adults. Earlier iterations of the work  
600 described in this paper, in conjunction with other studies (Richey et al, 2012, 2013a, 2013b) were

601 used to develop a guideline (Manipulation of Drugs Required in Children (MODRIC)) for health  
602 professionals with recommendations for the Pharmaceutical Industry and regulators. Such  
603 recommendations include the need for the Pharmaceutical Industry to note the lack of evidence  
604 relating to the manipulation of medicines for the purposes of achieving a suitable dose for  
605 administration to children and to support practitioners in their requests for information around  
606 manipulations of medicines by recognising that children may require a range of doses that  
607 require manipulation of adult dosage forms. Regulatory authorities must recognise that  
608 manipulation is being undertaken in the paediatric population despite the lack of evidence and  
609 encourage the industry to provide evidence where reasonable and available.

610

## 611 **CONCLUSION**

612 Extensive searching yielded limited evidence to support the widespread clinical practice of  
613 manipulation of drugs with the aim of achieving the required dose. There is a need to conduct  
614 research about the impact of manipulation for dosage accuracy in all age groups. Future research  
615 should prioritise areas such as drugs with a narrow therapeutic index or clinical areas such as  
616 neonates or paediatric intensive care that are high risk because of manipulations, and should  
617 conduct standardised assessments of those manipulations. Where manipulations are a predictable  
618 use of a licensed product the effects of manipulations need to be included in drug development  
619 programmes.

620

621 **REFERENCES**

- 622 Andersson, AC, Lindemalm S, Eksborg, S. Dividing the tablets for children—good or bad? Pharm  
623 Methods, 2016; 7: 23-27
- 624 Berg C, Ekedahl A. Dosages involving splitting tablets: common but unnecessary? Journal of  
625 Pharmaceutical Health Services Research. 2010; 1: 137-141
- 626 Boggie DT, DeLattre ML, Schaefer MG, Morreale AP, Plowman BK. Accuracy of splitting  
627 unscored valdecoxib tablets. American Journal of Health-System Pharmacy. 2004; 61: 1482-  
628 1483
- 629 ‘Tablets’ In: British Pharmacopoeia (2016) Volume III – Formulated Preparations: General  
630 Monographs, Medicines & Healthcare products Regulatory Agency, UK.
- 631 Broadhurst EC, Ford JL, Nunn AJ, Rowe PH. Dose uniformity of samples prepared from  
632 dispersible aspirin tablets for paediatric use. European Journal of Hospital Pharmacy Science.  
633 2008; 14: 27-31
- 634 Carr-Lopez SM, Mallett MS, Morse T. The tablet splitter: barrier to compliance or cost-saving  
635 instrument. American Journal of Health-System Pharmacy. 1995; 52: 2707-2708
- 636 Choe HM, Stevenson JG, Streetman DS, Heisler M, Sandiford CJ, Piette JD. Impact of patient  
637 financial incentives on participation and outcomes in a statin pill-splitting program. American  
638 Journal of Managed Care. 2007; 13: 298-304
- 639 Chua SS, Chua HM, Omar A. Drug administration errors in paediatric wards: a direct  
640 observation approach. European Journal of Pediatrics. 2010; 169: 603-611
- 641 Cleary JD, Evans PC, Hikal AH, Chapman SW. Administration of crushed extended-release  
642 pentoxifylline tablets: bioavailability and adverse effects. American Journal of Health-System  
643 Pharmacy. 1999; 56: 1529-1534
- 644 Conroy S, Choonara I, Impicciatore P, Monh A, Arnell H, Rane A, Knoeppel C, Seyberth H,  
645 Pandolfini C, Raffealli MP, Rocchi F, Bonati M, Jong G, de Hoog M, van der Anker J. Survey of  
646 unlicensed and off label use in paediatric wards in European countries. British Medical Journal.  
647 2000; 320: 79-82
- 648 Conroy S, Sweis D, Planner C, Yeung V, Collier J, Haines L, Wong IC. Interventions to reduce



- 649 dosing errors in children: a systematic review of the literature. *Drug Safety*. 2007; 30: 1111-  
650 1125.
- 651 Cook TJ, Edwards S, Gyemah C, Shah M, Shah I, Fox T. Variability in tablet fragment weights  
652 when splitting unscored cyclobenzaprine 10mg tablets. *Journal of the American Pharmacists*  
653 *Association*. 2004; 44: 583-586
- 654 Corbett AH, Hasseinipour MC, Nyirenda J, Kanyama C, Rezk NL, Mkuoani P, Sichali D, Tien  
655 H, Kashuba ADM, Mwansambo C, Wiegel R, Kazembe P. Pharmacokinetics of generic and  
656 trade formulations of lamivudine, stavudine and nevirapine in HIV-infected Malawian children.  
657 *Antiviral Therapy*. 2010; 15: 83-90
- 658 Costa P, Amaral H, Sousa Lobo JM. Dissolution characteristics of divisible tablets. *S.T.P.*  
659 *Pharma Sciences*. 2000; 10: 373-377
- 660 Duncan MC, Castle SS, Streetman DS. Effect of tablet splitting on serum cholesterol  
661 concentrations. *The Annals of Pharmacotherapy*. 2002; 36: 205-209
- 662 Ernest TB, Craig J, Nunn A, Salunke S, Tuleu C, Breikreutz J, Rainer A, Hempenstall J.  
663 Preparation of medicines for children – a hierarchy of classification. *International Journal of*  
664 *Pharmaceutics*. (2012; 435:124–130 s
- 665 Erramouspe J, Jarvi EJ. Effect on dissolution from halving methylphenidate extended-release  
666 tablets. *The Annals of Pharmacotherapy*. 1997; 31: 1123-1126
- 667 European Medicines Agency. Assessment report for Tracleer (Bosentan). Procedure No.  
668 EMA/H/C/000401/X/0039 [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000401/WC500041604.pdf)  
669 [Assessment\\_Report\\_-\\_Variation/human/000401/WC500041604.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000401/WC500041604.pdf) [accessed 12/08/2016]
- 670 European Medicines Agency (EMA). Committee for Medicinal Products for Human Use  
671 (CHMP), Paediatric Committee (PDCO). Guideline on pharmaceutical development of  
672 medicines for paediatric use. EMA/CHMP/QWP/805880/2012 Rev. 2. 1 August 2013. [accessed  
673 23/09/16]
- 674 European Pharmacopeia Suppl 4.1, Tablets; Monograph 0478, Council of Europe, Strasbourg,  
675 France, 2002, 2433-2436
- 676 European Union Paediatric Regulation [<http://ec.europa.eu/health/files/eudralex/vol->

- 677 [1/reg\\_2006\\_1901/reg\\_2006\\_1901\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf), [http://ec.europa.eu/health/files/eudralex/vol-](http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf)  
678 [1/reg\\_2006\\_1902/reg\\_2006\\_1902\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf),  
679 [http://ec.europa.eu/health/files/paediatrics/2013\\_com443/paediatric\\_report-com\(2013\)](http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf)  
680 [443\\_en.pdf](http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf)] [Assessed: 12/10/2016]
- 681 Fagerström P-O. Pharmacokinetics of whole and half Theo-Dur tablets. *European Journal of*  
682 *Respiratory Diseases. Supplement 109, 1980; 61: 62-66*
- 683 Fawell NG, Cookson TL, Scranton SS. Relationship between tablet splitting and compliance,  
684 drug acquisition cost, and patient acceptance. *American Journal of Health-System Pharmacy.*  
685 1999; 56: 2542-2545
- 686 Ferron GM, Ku S, Abell M, Unruh M, Getsy J, Mayer PR, Paul J. Oral bioavailability of  
687 pantoprazole suspended in sodium bicarbonate solution. *American Journal of Health-System*  
688 *Pharmacy.* 2003; 60: 1324-1329
- 689 Fontan JE, Mille F, Brion F. Drug administration to paediatric patients. *Archives de Pediatrie.*  
690 2004; 11: 1173-1184.
- 691 Footitt R. Dose accuracy in paediatric medicine. *British Journal of Pharmaceutical Practice.*  
692 1983; 5: 16-17,20, 22, 26-27
- 693 Gee M, Hasson NK, Hahn T, Ryono R. Effects of a tablet-splitting program in patients taking  
694 HMG-CoA reductase inhibitors: analysis of clinical effects, patient satisfaction, compliance, and  
695 cost avoidance. *Journal of Managed Care Pharmacy.* 2002; 8: 453-458
- 696 Gerber A, Kohaupt I, Lauterbach KW, Buescher G, Stock S, Lungen M. Quantification and  
697 classification of errors associated with hand-repackaging of medications in long-term care  
698 facilities in Germany. *The American Journal of Geriatric Pharmacotherapy.* 2008; 6: 212-219
- 699 Green G, Berg C, Polli JE, Barends DM. Pharmacopeial standards for the subdivision  
700 characteristics of scored tablets. *Pharma Times.* 2010; 42: 15-24
- 701 Habib WA, Alanizi AS, Abdelhamid MM, Alanizi FK. Accuracy of tablet splitting: Comparison  
702 study between hand splitting and tablet cutter. *Saudi Pharmaceutical Journal* 2014; 22: 454–459
- 703 Helmy SA. Tablet Splitting: Is it worthwhile? Analysis of drug content and weight uniformity  
704 for half tablets of 16 commonly used medications in the outpatient setting. *Journal of Managed*

- 705 Care and Specialty Pharmacy. 2015; 21: 76-86
- 706 Hill SW, Varker AS, Karlage K, Myrdal PB. Analysis of drug content and weight uniformity for  
707 half-tablets of 6 commonly split medications. *Journal of Managed Care Pharmacy*. 2009; 15:  
708 253-261
- 709 Horn LW, Kuhn RJ, Kanga JF. Evaluation of the reproducibility of tablet splitting to provide  
710 accurate doses for the pediatric population. *The Journal of Pediatric Pharmacy Practice*. 1999; 4:  
711 38-42
- 712 Kayitare E, Vervaet C, Ntawukulilyayo JT, Seminegaa B, Van Bortel, Remon JP. Development  
713 of fixed dose combination tablets containing zidovudine and lamivudine for paediatric  
714 applications, *International Journal of Pharmaceutics* 370 (2009) 41–46
- 715 Kim TW, Rognerud CL, Ou C-N. Accuracy in the alteration of acetaminophen suppositories.  
716 *Anesthesia & Analgesia*. 2005; 100:1303-1305
- 717 Lucas-Bouwman ME, Roorda RJ, Jansman FG, Brand PL. Crushed prednisolone tablets or oral  
718 solution for acute asthma? *Archives of Disease in Childhood*. 2001; 84: 347-348
- 719 Manipulation of Drugs Required in Children (MODRIC); A guide for health professionals.  
720 [http://www.alderhey.nhs.uk/wp-content/uploads/MODRIC\\_Guideline\\_FULL-DOCUMENT.pdf](http://www.alderhey.nhs.uk/wp-content/uploads/MODRIC_Guideline_FULL-DOCUMENT.pdf)  
721 [Accessed 27 November 2016
- 722 MacKintosh DA, Baird-Lambert J, Buchanan N. Theo-Dur: No loss of sustained-release effect  
723 with chewing or crushing. *Australian & New Zealand Journal of Medicine*. 1985, 15: 351- 352
- 724 Mandal TK. Effect of tablet-integrity on the dissolution rate of sustained- release preparations.  
725 *Journal of Clinical Pharmacy and Therapeutics*. 1996; 21: 155-157
- 726 McDevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. *Pharmacotherapy*. 1998; 18: 193-  
727 197
- 728 McEwen J, Durnin C, McMurdo ME, Moreland TA. Sustained-release verapamil: multiple-dose  
729 pharmacokinetic comparison of 120mg and 240mg tablets and the effect of halving a 240mg  
730 tablet. *Journal of Cardiovascular Pharmacology*. 1989; 13 (Suppl 4): S57-S59
- 731 Mercovich N, Kyle GJ, Naunton M. Safe to crush? A pilot study into solid dosage form

- 732 modification in aged care. *Australasian Journal on Ageing* 2014; 33: 180–184
- 733 Mistry P, Batchelor H (2016) Evidence of acceptability of oral paediatric medicines: a review.  
734 *Journal of Pharmacy & Pharmacology*, doi 10.1111/jphp.12610
- 735 Moreland TA, McMurdo MET, McEwen J. Multiple dose comparison of a whole 240mg  
736 verapamil sustained-release tablet with two half tablets. *Biopharmaceutics & Drug Disposition*.  
737 1989; 10: 311-319
- 738 Nahata MC. Pediatric drug formulations: challenges and potential solutions. *Annals of*  
739 *Pharmacotherapy*. 1999; 33: 127-129.
- 740 Nidanapu RP, Rajan S, Mahadevan S, Gitanjali B. Tablet Splitting of Antiepileptic Drugs in  
741 Pediatric Epilepsy: Potential Effect on Plasma Drug Concentrations, *Pediatric Drugs* (2016) 18,  
742 451–463
- 743 Nunn AJ. Making medicines that children can take. *Archives of Disease in Childhood*. 2003; 88:  
744 369-71
- 745 Olski TM, Lampus SF, Gherarducci G, Raymond AS. Three years of paediatric regulation in the  
746 European Union. *European Journal of Clinical Pharmacology*. 2011; 67: 245-252
- 747 Paradiso LM, Roughead EE, Gilbert AL Cosh D, Nation RL, Barnes L, Cheek J, Ballantyne A.  
748 Crushing or altering medications: what’s happening in residential aged-care facilities? *Australian*  
749 *Journal on Aging*. 2002; 21: 123-127
- 750 Parra D, Beckey NP, Raval HS, Schnacky KR, Calabrese V, Coakley RW, Goodhope RC.  
751 Effect of splitting simvastatin tablets for control of low-density lipoprotein cholesterol. *The*  
752 *American Journal of Cardiology*. 2005; 95: 1481-1483
- 753 Polli JE, Kim S, Martin BR. Weight uniformity of split tablets required by a Veterans Affairs  
754 policy. *Journal of Managed Care Pharmacy*. 2003; 9: 401-407
- 755 Powers JE, Cascella PJ. Comparison of methods used to prepare tablets for nasogastric tube  
756 administration. *Journal of Pharmacy Technology*. 1990; 6: 60-62
- 757 Primrose WR, Clee MD, Moody JP, Hockings N. Alteration of pharmacokinetics after halving a  
758 slow-release theophylline tablet. *Pharmatherapeutica*. 1983; 3: 429-432
- 759 Rashed SM, Nolly RJ, Robinson L, Thoma L. Weight variability of scored and unscored split

- 760 psychotropic drug tablets. *Hospital Pharmacy*. 2003; 38: 930- 934
- 761 Richey RH, Craig JV., Shah UU, Ford JL, Barker CE, Peak M, Nunn, AJ, Turner M. The  
762 manipulation of drugs to obtain the required dose: Systematic review, *Journal of Advanced*  
763 *Nursing* 2012 68, 2103-2112
- 764 Richey RH, Shah UU, Peak M, Craig JV, Ford JL, Barker CE, Nunn AJ, Turner MA,  
765 Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not  
766 supported by guidelines or evidence. *BMC Pediatrics*. 2013a May 21;13:81. doi: 10.1186/1471-  
767 2431-13-81.
- 768 Richey RH, Craig JV, Shah UU, Ford JL, Barker CE, Peak M, Turner M, Nunn AJ. Estimating  
769 the requirement for manipulation of medicines to provide accurate doses for children, *European*  
770 *Journal of Hospital Pharmacy*, 2013b, 20:3-7
- 771 Rindone JP. Evaluation of tablet-splitting in patients taking lisinopril for hypertension. *Journal of*  
772 *Clinical Outcomes Management*. 2000; 7: 22-24
- 773 Rosenberg JM, Nathan JP, Plakoglannis F. Weight variability of pharmacist- dispensed split  
774 tablets. *Journal of the American Pharmaceutical Association*. 2002; 42: 200-205
- 775 Rosenzweig EB, Ivy DD, Widlitz A, Doran A, Claussen LR, Yung D, Abman SH, Barst RJ.  
776 Long-term bosentan treatment in children with pulmonary arterial hypertension - Reply– *Journal*  
777 *of the American College of Cardiology*. 2006; 47: 1915
- 778 Saimbi S, Madden V, Stirling H, Yahyouche A, Batchelor H. Comparison of hydrocortisone 10  
779 mg tablets: tablet hardness optimised for adult use has negative consequences for paediatric use ,  
780 *Arch Dis Child* 2016;101:e2 doi:10.1136/archdischild-2016-311535.17
- 781 Shah RB, Collier JS, Sayeed VA, Bryant A, Habib MJ, Khan MA. Tablet splitting of a narrow  
782 therapeutic index drug: a case with levothyroxine sodium. *AAPS PharmSciTech*. 2010;  
783 11:1359-1367
- 784 Shah VP, Yamamoto LA, Schuirman D, Elkins J, Skelly JP. Analysis of in vitro dissolution of  
785 whole vs. half controlled-release theophylline tablets. *Pharmaceutical Research*. 1987; 4: 416-  
786 419
- 787 Simons KJ, Frith EM, Simons FER. Dissolution and bioavailability studies of whole and halved

- 788 sustained-release theophylline tablets. *Journal of Pharmaceutical Sciences*. 1982; 71: 505-511
- 789 Skwierczynski C, Conroy S. How long does it take to administer oral medicines to children?  
790 *Paediatric and Perinatal Drug Therapy*. 2008; 8: 145-9.
- 791 Stimpel M, Vetter H, Küffer B, Groth H, Greminger P, Vetter W. The scored tablet – a source of  
792 error in drug dosing? *Journal of Hypertension*. 1985; 3 (Suppl 1): 97-99
- 793 Stockis A, De Bruyn S, Deroubaix X, Jeanbaptiste B, Lebacq E, Nollevaux F, Poli G, Acerbi D.  
794 Pharmacokinetic profile of a new controlled-release isosorbide-5-mononitrate 60mg scored tablet  
795 (Monoket Multitab®). *European Journal of Pharmaceutics and Biopharmaceutics*. 2002; 53: 49-  
796 56
- 797 Tahaineh LM, Gharaibeh SF. Tablet splitting and weight uniformity of half-tablets of 4  
798 medications in pharmacy practice. *Journal of Pharmacy Practice* 2012; 25: 471-476
- 799 Teng J, Song CK, Williams RL, Polli JE. Lack of medication dose uniformity in commonly split  
800 tablets. *Journal of the American Pharmaceutical Association*. 2002; 42: 195-199
- 801 Tuleu C, Grange J, Seurin S. The need for paediatric formulation: oral administration of  
802 nifedipine in children, a proof of concept. *Journal of Drug Delivery Science and Technology*.  
803 2005; 15: 319-324
- 804 Turner MA, Catapano M, Hirschfeld S, Giaquinto C; Global Research in Paediatrics. Paediatric  
805 drug development: the impact of evolving regulations. *Advanced Drug Delivery Review*, 2014;  
806 73:2-13.
- 807 van Riet-Nales DA, Doeve ME, Nicia AE, Teerenstra S, Notenboom K, Hekster YA, van den  
808 Bernt BJF. The accuracy, precision and sustainability of different techniques for tablet  
809 subdivision: Breaking by hand and the use of tablet splitters or a kitchen knife. *International*  
810 *Journal of Pharmaceutics* 2014; 466: 44–51
- 811 Van Vooren L, De Spiegeleer B, Thonissen T, Joye P, Van Durme J, Slegers G. Statistical  
812 analysis of tablet breakability methods. *Journal of Pharmacy and Pharmaceutical Sciences*. 2002;  
813 5: 190-198
- 814 Verrue C, Mehuys E, Boussery K, Remon JP, Petrovic M. Tablet-splitting: a common yet not so  
815 innocent practice. *Journal of Advanced Nursing*. 2010; 67: 26-32

- 816 Vranic E, Uzunovic A. Comparison of some physical parameters of whole and scored Lisinopril  
817 and Lisinopril / Hydrochlorthiazide tablets. *Bosnian Journal of Basic Medical Sciences*. 2008; 8:  
818 391-395
- 819 Walker J, Abdulsalam A, Theobald AE, Subrahmanyam R, Verma SK. Multiple-scored tablets.  
820 Weight and content uniformity of subdivisions and the distribution of active constituent within  
821 and between tablets. *Journal of Pharmacy and Pharmacology*. 1978; 30: 401-406
- 822 Waller DG. Off-label and unlicensed prescribing for children: have we made any progress?  
823 *British Journal of Clinical Pharmacology*. 2007; 64: 1-2
- 824 Weissman EM, Dellenbaugh C. Impact of splitting risperidone tablets on medication adherence  
825 and on clinical outcomes for patients with schizophrenia. *Psychiatric Services*. 2007; 58: 201-  
826 206
- 827 Williams MC, Tsibris JCM, Davis G, Baiano J, O'Brien WF. Dose variation that is associated  
828 with approximated one-quarter tablet doses of misoprostol. *American Journal of Obstetrics &  
829 Gynecology*. 2002; 187: 615-619
- 830 World Health Organisation (WHO). The selection and use of essential medicines. Report of the  
831 WHO Expert Committee, October 2007 (including the Model List of Essential Medicines for  
832 Children). [http://apps.who.int/iris/bitstream/10665/43887/1/WHO\\_TRS\\_950\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/43887/1/WHO_TRS_950_eng.pdf)[[accessed  
833 23/09/16]
- 834 Zaid AN, Ghosh, AA. Compliance of scored tablet halves produced by Palestinian  
835 pharmaceutical companies with the new European Pharmacopoeia requirements. *Archives of  
836 Pharmacal Research* 2011, 34, 1183-1189

837 Table 1: Criteria used to describe the three quality levels used in this study

| Quality level | Criteria   |
|---------------|--|
| ++            | Included studies where the reported methods and subsequent results and conclusions could be considered (with reasonable confidence) not to be biased. The process of the drug manipulations was at least adequately described. |
| +             | included studies where there were some concerns about the reported study methods or the methods were not reported with enough detail to permit sufficient assessment   |
| -             | included studies where there were considerable concerns about the reported methods or there was insufficient reporting of the methods for them to be assessed  |

838

839



840 Table 2. The quality ratings of the reported studies

| Reference                  | Quality | Reference                     | Quality |
|----------------------------|---------|-------------------------------|---------|
| Boggie et al (2004)        | +       | McEwen et al (1989)           | -       |
| Broadhurst et al (2008)    | +       | Mercovich et al (2014)        | ++      |
| Carr-Lopez et al (1995)    | +       | Moreland et al (1989)         | +       |
| Choe et al (2007)          | +       | Parra et al (2005)            | -       |
| Cleary et al (1999)        | ++      | Polli et al (2003)            | ++      |
| Cook et al (2004)          | ++      | Powers & Cascella (1990)      | +       |
| Corbett et al (2010)       | +       | Primrose et al (1983)         | +       |
| Costa et al (2000)         | +       | Rashed et al (2003)           | +       |
| Duncan et al (2002)        | +       | Rindone (2000)                | +       |
| Erramouspe & Jarvi (1997)  | +       | Rosenberg et al (2002)        | +       |
| Fagerström (1980)          | -       | Shah et al (1987)             | +       |
| Fawell et al (1999)        | +       | Simons et al (1982)           | +       |
| Ferron et al (2003)        | ++      | Stimpel et al (1985)          | +       |
| Footitt (1983)             | +       | Stockis et al (2002)          | +       |
| Gee et al (2002)           | -       | Tahaineh & Gharaibeh (2012)   | ++      |
| Habib et al (2014)         | ++      | Teng et al (2002)             | +       |
| Helmy (2015)               | ++      | Tuleu et al (2005)            | +       |
| Hill et al (2009)          | ++      | van Riet-Nales et al (2014)   | ++      |
| Horn et al (1999)          | +       | van Vooren (2002)             | -       |
| Kayitar et al              | ++      | Verrue et al (2010)           | +       |
| Kim et al (2005)           | -       | Vranic & Uzunovic (2008)      | +       |
| Lucas-Bouwman et al (2001) | -       | Walker et al (1978)           | +       |
| MacKintosh et al (1985)    | +       | Weissman & Dellenbaugh (2007) | +       |
| Mandal (1996)              | +       | Williams et al (2002)         | -       |
| McDevitt et al (1998)      | +       | Zaid & Ghosh (2011)           | ++      |

841

842 Table 3 Studies which halved or quartered tablets and used pharmacopoeial-based outcomes for weight and/or drug content uniformity

| Drugs  | Outcomes summary   | Ref                    |
|--|--|------------------------|
| One scored and one unscored product  | Both products did not meet the BP uniformity of weight specification   | Footitt (1983)         |
| Six products<br>2 scored, oblong, non-coated, scored<br>2 oval, film-coated, unscored<br>1 circular, non-coated, scored<br>1 oval, non-coated, unscored  | 43/180 (23.9%) of half tablets were outside of USP specification for drug content.<br>23/180 (12.8%) of half tablets were outside USP specification for weight<br>22.2% (20/90) of scored tablets were outside the USP specification for drug content compared with 25.6% (23/90) unscored tablets<br>11.1% (10/90) of scored tablets were outside the USP specification for weight compared with 14.4% (13/90) unscored tablets | Hill et al (2009)      |
| Twelve products<br>2 oval, unscored<br>1 oval, scored<br>3 round, scored<br>1 trapezoid, unscored<br>1 unscored<br>2 oblong, scored<br>1 shield-like, unscored<br>1 round/spherical, unscored. | 8/12 halved products passed adapted USP weight uniformity test; 6 out of these 8 products were scored.<br>4/12 did not pass adapted USP uniformity test; lovastatin, Each of these 4 products was unscored.  | Polli et al (2003)     |
| Five products<br>Three unscored<br>Two scored on one side  | Tablets halved.<br>Only one of the two scored products met the USP weight specification.   | Rashed et al (2003)    |
| 22 products<br>1 ovoid-rectangular, scored<br>5 capsule-shaped, scored<br>1 round, unscored<br>8 round, scored<br>1 oblong, scored   | Halved tablets.<br>6 scored and 1 unscored product met the USP weight specification including the extended release product<br>13 scored and 2 unscored products did not meet the USP weight specification;   | Rosenberg et al (2002) |

|   |   |                     |
|---|---|---------------------|
| 1 elliptical, scored<br>1 biconvex, scored, extended-release<br>1 modified-oval, scored<br>2 oblong, unscored<br>1 shield-shaped, scored                          |   |                     |
| 11 Products<br>3 oval, not flat, unscored<br>1 oval, not flat, scored<br>2 not oval, not flat, scored<br>1 not oval, flat, scored<br>4 not oval or flat, unscored | Halved tablets.<br><br>3 products met the USP weight variation specification; one product was scored and two were oval<br>8 Products did not meet USP weight variation specification; of these three were scored and two were oval  | Teng et al (2002)   |
| One sustained-release round unscored, product   | 38/40 tablet halves deviated from the percentage deviation allowed by the European Pharmacopoeia for uncoated or film-coated tablets of $\leq 80$ mg).<br>There was wide variability for half and quarter tablet weights  | Tuleu et al (2005)  |
| 14 scored products were studied<br>4 products were oblong of which 2 were film coated.<br>10 products were round  | Halved tablets<br><br>Only one film coated, oblong product met the European Pharmacopoeia specification for weight uniformity of scored tablets.<br>The remaining 13 products A following splitting had fragments outside of the 85-115% range of the average mass<br>Only four tablets following splitting (one film coated oblong; one oblong and two round had no fragments outside of the 75-125% range of the average mass | Zaid & Ghosh (2011) |

844 Table 4. The influence of cutter on the halving and quartering of 7 tablet products on the % halves or  
 845 quarters weighing within  $\pm 15\%$ , USP specification. 3 lots of each product were used and the range across  
 846 these lots is indicated (Taken from Horn et al, 1999)  
 847

| Product             | % halves or quarters weighing within $\pm 15\%$ |               |               |               |
|---------------------|---|---------------|---------------|---------------|
|                     | Halves  | Quarters      | Halves        | Quarters      |
|                     | First cutter;                                   | First cutter; | Second cutter | Second cutter |
| clonidine (brand)   | 52.5-100%                                       | 43.8-60%      | 85-90%        | 57.5-71.3%    |
| clonidine (generic) | 47.5-70%  | 37.5-45%      | 30-78.9%      | 25.0-48.8%    |
| Captopril           | 58.3-95%  | 37.5-55%      | 95-100%       | 26.3-36.1%    |
| Amlodipine          | 77.5-85.7%                                      |               | 76.9-90.5%    |               |
| Atenolol            | 62.5-95%  |               | 27.5-35%      |               |
| Sertraline          | 100%  |               | 90-100%       |               |
| Carbamazepine       | 87.5-92.5%                                      |               | 60-80%        |               |

848 Table 5: Summary of the twelve studies that compared the splitting of tablets using different techniques

| Observations  | Ref                         |
|---|-----------------------------|
| 8 products were examined. Tablets split with a tablet splitter had significantly lower deviation from theoretical weight and significantly less weight loss than those split by scissors (unscored)/hand (scored) or with a kitchen knife. There was no significant difference in weight between the scissors/hand and the kitchen knife. There was significantly less weight loss with the scissors/hand than with the kitchen knife.                              | Verrue et al (2010)         |
| A razor blade based cutting apparatus resulted in quarters where a large proportion were outside acceptable limits for uniformity of weight; non-uniformity was more marked with tablets broken by hand   | Walker et al (1978)         |
| Of 11 products halved with a razor blade, 3 passed USP uniformity of weight specification (2 unscored; 1 scored) and 8 failed ((5 unscored; 3 scored). 3 of the scored products which failed the uniformity specification when split with a razor blade, also failed when split by hand   | Teng et al (2002)           |
| Two commercial splitters were examined for halving and quartering tablets of 6 different drugs. Neither splitter yielded consistent results for tablet quarters or halves.  | Horn et al (1999)           |
| No significant difference between 100 unscored tablets halved with a tablet splitter and 25 tablets of the same drug which were split by hand   | Boggie et al (2004)         |
| Halves of round, film coated, unscored tablets, halved with a tablet splitter showed that 16% had a deviation of >15% from the theoretical weight compared with 58% of tablets were split with a kitchen knife  | Cook et al (2004)           |
| 33% of manually halved round, scored tablets but 40.2% tablet splitter halved tablets and were within 5% of the ideal weight  | McDevitt et al (1998)       |
| 2 methods of crushing whole tablets for nasogastric tube administration (pestle/mortar and between medicine cups) and dispersing whole tablets showed significant differences in the amount of drug delivered. Suspending the drug in the syringe delivered 18% more drug than crushing with medicine cups and 36% more than crushing with pestle and mortar.   | Powers & Cascella (1990)    |
| No significant difference in mean fragment weight was found between round unscored tablets quartered with a tablet splitter or manually cut with a razor blade. There was a significantly greater variance within the group produced from the tablet splitter than that quartered with the manually split tablets.  | Williams et al (2002)       |
| Flat, round, cross-scored tablets were manually halved and quartered, using four different tablet orientations or split using a knife. Fracturing to halves, the score-up orientation gave the lowest residual variance. The score-down orientation and the score-up knife halved tablets had the lowest person variability. The score-down break had significantly higher variability than for score-up break or score-up knife orientations for quartered tablets | van Vooren (2002)           |
| Tablets (round, flat, uncoated) were divided by hand or using 6 different proprietary tablet splitters or a kitchen knife. Only hand split half-tablets complied with weight requirements   | van Riet-Nales et al (2014) |

|   |                    |
|---|--------------------|
| A tablet splitter was superior to manual splitting in halving scored salbutamol tablets. Drug content variation in half-tablets appeared to be attributable to weight variation occurring during splitting. | Habib et al (2014) |
|---|--------------------|

849



WHO harmonised dose schedule for HIV drugs requires **half** tablet doses



Manipulation of dosage forms is often required to provide accurate doses for children



Systematic literature review



49/50 relevant papers referred only to tablets

Limited evidence of accurate dosing; cannot extrapolate between dosage forms, methods of manipulation or different brands of same drug.

