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1 **Research Paper**

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4 **Challenge of paediatric compounding to solid dosage forms sachets and hard capsules –**
5 **Finnish perspective**

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25 **Abstract**

26

27 **Objectives:** The study evaluated the quality of compounded sachets and hard gelatine capsules and
28 their feasibility in paediatric drug administration.

29 **Methods:** Commercial tablets were compounded to sachets and capsules in hospital environment,
30 and the uniformity of content and simulated drug dose were determined.

31 **Key findings:** Compounded formulations were successfully obtained for a range of drug substances;
32 dipyridamole, spironolactone, warfarin and sotalol formulations were within acceptable limits for
33 uniformity of content, in most cases. Though, some loss of drug was seen. The type and amount of
34 excipients were found to affect uniformity of content; good conformity of capsules was obtained
35 using lactose monohydrate as filler, whereas microcrystalline cellulose was a better choice in sachets.
36 In capsules, content uniformity was obtained for a range of drug doses. If the drug is aimed to be
37 administered through a nasogastric tube, solubility of the drug and excipients should be considered,
38 as they were found to affect the simulated drug dose in administration.

39 **Conclusions:** Compounded sachets and capsules fulfilled the quality requirements in most cases. In
40 compounding, the choice of excipients should be considered as they can affect conformity of the
41 dosage form or its' usability in practice. Quality assurance of compounded formulations should be
42 taken into consideration in hospital pharmacies.

43

44

45 *Keywords:*

46 Capsule, Compounding, Content uniformity, Nasogastric tube, Paediatric, Sachet

47 **Introduction**

48 The lack of age-appropriate formulations for paediatric medications is faced in everyday work
49 in hospitals. Also, off-label use of medicines is common (1,2). In medication, *extemporaneous*
50 preparations have to be used, although these have certain risks such as dosing inaccuracy or errors,
51 excipient toxicity or modified bioavailability (3). Dosage forms and formulations are needed for
52 paediatric use. In dosage forms, critical issues are dosing flexibility, accuracy and their practical
53 handling. It has been evaluated that these issues concern even a quarter of existing dosage forms (3).
54 Improvement needs concern even half of the marketed drug products when the ease of intake and
55 palatability of the dosage form are taken into account. In improving the pharmaceutical quality of
56 paediatric medicines the priority is on the youngest age groups, neonates and infants. Fortunately, an
57 increased trend in the marketing authorisation procedures has been seen recently (4).

58 Thus far, the need for compounding commercial products to paediatric dosage forms prevail
59 in hospitals. The choice of dosage form type vary in different European countries (5). Liquid
60 preparations are predominant in England and Sweden, capsules in France and powders in Finland.
61 Also other manipulations, such as tablet splitting into segments or opening capsules are often
62 necessary in paediatric medications (6), but risk for dose inaccuracy and changed bioavailability is
63 apparent in these manipulations (7,8,9). Facilities, time and expertise in hospital pharmacies limit the
64 choice of what kind of compounded dosage forms are usually prepared (5). The practice in
65 manufacture varies in the hospitals throughout Europe and there is little harmonisation of
66 formulations. Many formulations are developed in-house, based on the literature available (if any).
67 The quality of the formulations is usually evaluated indirectly, based on the batch records of
68 procedures and ingredients. Often limited facilities are available for quality assurance, such as
69 analytical equipment for evaluations of uniformity of content or stability of the drug.

70 In Finland, compounding to solid dosage forms is common in hospital pharmacies; a
71 commercial tablet is crushed and diluted with an appropriate filler and redistributed in smaller

72 strength sachets (powder paper) or capsules to obtain appropriately sized dosage units for paediatric
73 medication (10). In practice, compounding to solid dosage forms has been considered feasible
74 because solids are suitable for drug substances that are unstable in aqueous environment and thus
75 cannot be compounded to suspensions or solutions (11). In general, solid dosage forms are expected
76 to have better stability of the drug, although only few results of stability studies have been published
77 for compounded capsules (12,13). Additionally, solid dosage forms may be preferable because less
78 excipients are needed (14). This is important because many common excipients exhibit potential risk
79 for toxicity in paediatric patients (15).

80 However, little published information exists on compounded oral solid dosage forms, sachets
81 and capsules. The information is in-house knowledge, and may be limited due to the lack of
82 analytical facilities in hospital pharmacies. A Finnish research group has studied compounded sachets
83 and hard gelatine capsules of one drug, nifedipine (10,16,17). They concluded that the optimum
84 powder mass in sachets should be 300 mg or more, in smaller powders drug loss during manufacture
85 increase the risk for non-conformity and low drug recovery. On the other hand, it was possible to
86 prepare small capsules (size numbers 3 and 4), which complied the standards for uniformity of
87 content. A French study evaluated the effect of the amount of the active ingredient on conformity of
88 capsules, concluding that small amounts of drug increase the risk for non-conformity (18).

89 *Extemporaneous* formulations that meet the quality standards could be compounded in these studies,
90 but not all the formulations were such. It is evident that more information is needed, on more drug
91 substances as well as on formulations containing different kinds of excipients. Although compounded
92 formulations should be avoided, they still need to be used in hospitals. Thus, all the work towards
93 compounded products which would be safe in use is extremely important.

94 In the present study, the real life compounding of solid dosage forms in hospital pharmacy
95 was mimicked, using the procedures and facilities available. The quality of sachets and hard gelatine
96 capsules was evaluated, by determining their content uniformity as described in the European

97 Pharmacopoeia. Furthermore, the usability of the compounded solid dosage forms in paediatric drug
98 administration was evaluated by mimicking the real administration procedure in hospitals (drug
99 administration via nasogastric tube). In practice, the dosage form is opened before administration and
100 the contents are administered with fluid or food (5). In the younger patients, the contents are
101 suspended in water and administered through a nasogastric tube. Administration has been found
102 challenging due to occasional blockage of the tube (19,20). The present study evaluated whether the
103 formulation could explain difficulties in administration.

104 Commercial tablets were compounded to sachets and capsules with different drugs and
105 excipients in formulations. Drug substances were chosen based on their prevalence as commonly
106 modified products in Finnish hospital pharmacies; dipyridamole, spironolactone, warfarin and
107 sotalol. Additionally, warfarin and spironolactone were chosen based on their status as drugs
108 included on the WHO Model List of Essential Medicines for Children (21). Although these drug
109 substances are widely used in paediatric medication, no published information on the quality of
110 compounded sachets or capsules is available. The risk for non-conformity was expected to be most
111 evident with small-dose drugs (18). Thus, the effect of drug amount was studied with spironolactone
112 and warfarin, which have the lowest therapeutic dose (of the four drugs). Sachets and capsules of
113 different sizes were prepared, by varying the amount of filler in the formulation. Microcrystalline
114 cellulose and lactose monohydrate were chosen because they are both widely used as excipients in
115 paediatric medicines. Different grades of excipients were evaluated; microcrystalline cellulose,
116 silicified microcrystalline cellulose and two grades of lactose monohydrate. These were chosen on
117 the basis of their particle size and flow properties, which are expected to be important variables in
118 preparation of the sachets and in the filling procedure of capsules which is standardized by volume
119 (10). The effect of excipient grade was evaluated in more detail with sachets of the smallest weight.
120 As the sachets are filled with weight, small weight sachets are expected to be most sensitive to dose
121 non-conformity.

122

123 **Materials and methods**124 *Materials in compounding*

125 Commercial tablets were compounded to sachets and hard gelatine capsules. Drug substances
126 in these were dipyridamole (Dipyryn 75 mg, Ratiopharm; Merckle, Germany), spironolactone (Spirix
127 25 mg, Takeda Pharma, Denmark), warfarin as a sodium salt (Marevan forte 5 mg, Orion Pharma,
128 Finland) and sotalol as a hydrochloride salt (Sotalol Mylan 80 mg, Mylan; Gerard Laboratories,
129 Ireland).

130 Microcrystalline cellulose (MCC; Avicel PH-102, FMC Biopolymer, Ireland), silicified
131 microcrystalline cellulose (SMCC; Prosolv 50, Penwest Pharmaceuticals Co, USA) and two grades
132 of lactose monohydrate (Pharmatose, 200M and 80 M, DMV International, Netherlands) were used
133 as fillers in formulations. Lactose monohydrate is freely but slowly soluble in water (1 in 5.24)
134 whereas the celluloses are practically insoluble in water (22). In the MCC the average particle size
135 was 100 μm and the values for bulk density and tapped density were 0.32 g/cm^3 and 0.48 g/cm^3 ,
136 respectively. In the SMCC the corresponding values were 60 μm , 0.31 g/cm^3 and 0.39 g/cm^3 . In
137 Pharmatose 200 M the particle size was < 250 μm (fine particle fraction 60% < 45 μm) and values
138 for bulk and tapped densities were 0.55 g/cm^3 and 0.85 g/cm^3 , respectively. In Pharmatose 80 M the
139 particle size was < 355 μm (fine particle fraction 10% < 100 μm), and the respective values for bulk
140 and tapped densities were 0.76 g/cm^3 and 0.91 g/cm^3 .

141

142 *Compounding to sachets and hard capsules*

143 Preparation of the sachets and hard capsules were done according to the standard protocol for
144 *extemporaneous* compounding of dosage forms in hospital pharmacy, using the equipment and
145 facilities available (Helsinki University Hospital, Finland, Päijät-Häme Central Hospital, Finland).
146 Manufacturing procedures are the same in these units, but the choice of excipients in formulations

147 differ slightly (lactose is preferred in the first unit whereas MCC in the second).

148 The commercial tablets were crushed manually and carefully ground into a fine powder, with
149 a pestle in a non-porous mortar. The pestle was held firmly and downward pressure was exerted with
150 it while the pestle was moved in concentric circles. Geometric amounts of filler were added to
151 achieve a final drug concentration in formulation. Sachets were prepared to total weight of 200 mg
152 (dipyridamole), 300 mg (sotalol) or 500 mg (spironolactone or warfarin). The theoretical amount of
153 each drug was 5 mg (dipyridamole), 4 mg (sotalol), 0.5 mg (spironolactone) and 0.1 mg (warfarin).
154 Each powder was weighed individually using an analytical balance (precision ± 0.05 mg) and
155 transferred into waxed powder papers (Ulvila Paper Mill, Finland). One batch of each formulation
156 was prepared for the production of 100 sachets.

157 In preparation of the capsules, the amount of filler needed to fill the capsule was calculated
158 and geometric amounts of filler were added to ground tablet mass to achieve the final volume of
159 capsules. Hard gelatine capsules number 0 (volume 0.68 ml) were used for spironolactone and
160 warfarin formulations, and capsules number 1 (volume 0.5 ml) were used for sotalol formulation. The
161 theoretical amount of the drug in capsules was the same as in the sachets. Additionally, capsules
162 containing higher amounts of drug were prepared for spironolactone and warfarin. Drug doses were 4
163 mg for sotalol, 0.5 mg, 3 mg and 6 mg for spironolactone and 0.1 mg, 0.2 mg and 2 mg for warfarin.
164 Capsules were filled with the Feton Fastlock capsule filling machine (Feton International, Belgium).
165 Parallel batches were prepared for the production of 100 hard capsules. Because the capsules are
166 filled with volume, variation in the powder mass and thus variation in the filling procedure may result
167 in batch to batch variability.

168 As a comparison to the semi-automated procedure (Feton) which is commonly used in
169 Finnish hospitals, capsules were prepared with an automated procedure. These capsules were
170 manufactured by Mettler Toledo GmbH (Switzerland), using an automated Quantos capsule filling
171 device (QH012-LNM, Mettler Toledo AG, Switzerland). The powder mass was prepared in hospital

172 pharmacy, as described previously, and the obtained drug powder was sent to Mettler Toledo for
173 capsulation. The reference capsules contained the lowest amount of drug; spironolactone (0.5 mg) or
174 warfarin (0.1 mg).

175

176 *Drug analysis by HPLC*

177 Drug concentrations were determined by means of high performance liquid chromatography
178 (HPLC). Previously described methods with slight modifications were used in analysis (dipyridamole
179 (23), spironolactone (24); warfarin sodium (25); sotalol hydrochloride (26)). Samples containing
180 sotalol hydrochloride were analysed in the Department of Environmental Sciences, all the other drugs
181 were analysed in the Division of Pharmaceutical Chemistry and Technology.

182 The HPLC system (Shimadzu Corporation, Japan, for sotalol hydrochloride; Thermo
183 Separation Products TSP, USA, for the other drugs) consisted of degasser (Shimadzu DGU-20 A5;
184 TSP Spectra System SCM 1000 vacuum membrane degasser), a pump (Shimadzu LC-20AT; TSP
185 Spectra System P4000), autosampler (Shimadzu SIL-20-A; TSP Spectra System SA 3000), a UV-
186 VIS detector (Shimadzu SPD-20A; TSP Spectra System UV 6000 LP) and a computerized data
187 analysis system (Shimadzu Corporation LabSolutions 5.57 SP1, Japan; CromQuest 4.2.32, Thermo
188 Scientific, USA).

189 Sample separation was carried out in a reverse phase C-18 column (Synergi Hydro-RP 4.6
190 mm x 25 cm; 4 μ m, USA for sotalol hydrochloride; Supelco Discovery 4.66 mm x 15 cm; 5 μ m, USA
191 for the other drugs). Retention times varied from 4.3 to 4.7 minutes for the analytes.

192 The mobile phase consisted of methanol and phosphate buffer pH 4.6 (in a ratio of 75:25) for
193 dipyridamole. For spironolactone, the mobile phase was methanol and HPLC grade water (65:35).
194 For warfarin sodium, the mobile phase consisted of acetonitrile and HPLC grade water with 0.05% of
195 trifluoroacetic acid (55:45). For sotalol hydrochloride, the mobile phase was acetonitrile and
196 phosphate buffer pH 4.6 (75:25). The flow rate of the mobile phase was 1.0 ml/min.

197

198 *Uniformity of content*

199 Content uniformities of dosage units (commercial tablets and compounded solid formulations
200 thereof) were determined by method established in the European Pharmacopoeia. The dosage unit
201 complied the test if not more than one of 10 individual contents was beyond $\pm 15\%$ of the average
202 content and if none were beyond $\pm 25\%$ of the average content. If two or three individual contents
203 deviated more than $\pm 15\%$ (but less than $\pm 25\%$), the individual contents of another 20 dosage units
204 were determined. The drug concentrations were analysed in triplicate by HPLC.

205

206 *Statistical analysis*

207 Statistical analysis were carried out in SPSS (IBM SPSS Statistics, Ver. 23, United States)
208 using non-parametric Kruskal-Wallis analysis of variance. Individual differences were identified
209 using Dunnet's two-tailed t-test as a post hoc test. The value $P < 0.05$ was considered as statistically
210 significant.

211

212 *Simulation of drug administration*

213 Dosage form administration to paediatric patients in hospitals was simulated mimicking the
214 administration procedure through a nasogastric tube (Helsinki University Hospital, Finland, Päijät-
215 Häme Central Hospital, Finland). Individual contents of the dosage forms were emptied to a
216 medicine cup and suspended to HPLC grade water. The volume of water varied depending on the
217 procedure that they use in the hospital; 1.5 millilitres of water was used for suspending the contents
218 of size 1 hard gelatine capsules, and for suspending the contents of size 0 hard gelatine capsules or
219 sachets the volume was 3 millilitres. The suspension was thoroughly stirred with the tip of an oral
220 syringe (volume 5 ml) after which the formed suspension was withdrawn into the syringe for drug
221 administration. Nasogastric tube (Nutrisafe 2, size 06 French/50 cm, internal diameter 1.2 mm,

222 external diameter 2 mm, VYGON, France) was first rinsed with 2 millilitres of water, after which the
223 drug suspension was administered through the tube. Finally, the tube was rinsed with 2 millilitres of
224 water. All contents were led to a volumetric flask and after diluting the sample to a known volume,
225 the amount of drug was analysed by HPLC. The simulated drug dose passed through the nasogastric
226 tube was expressed as percentage of the average amount of the drug in formulation. The procedure
227 was repeated in triplicate for each formulation.

228

229 **Results**

230

231 *Content uniformity of commercial tablets*

232 All commercial tablets complied the test for uniformity of content, as expected. The average
233 contents of drug in tablets were $77.6 \text{ mg} \pm 3.5 \text{ mg}$ (SD) for dipyridamole (103.5% of the theoretical
234 drug amount, which was labelled to be 75 mg), $24.2 \text{ mg} \pm 0.3 \text{ mg}$ for spironolactone (98% of the
235 labelled amount 25 mg), $4.96 \text{ mg} \pm 0.08 \text{ mg}$ for warfarin (99.2% of the labelled amount 5 mg) and
236 $72.1 \text{ mg} \pm 1.4 \text{ mg}$ for sotalol (90.1% of the labelled amount 80 mg).

237

238 *Content uniformity of compounded sachets*

239 The content uniformity of sachets, compounded with different fillers as excipients, complied
240 the test for uniformity of content for most formulations (Table 1). However, if lactose of smaller
241 particle size ($< 250 \mu\text{m}$) or microcrystalline cellulose were used as fillers, the formulation failed to
242 comply with the test. In case of MCC formulations, two individual contents were outside the limits
243 85 per cent to 115 per cent of the average content, and one was outside the limit of 75 per cent to 125
244 per cent, in which case the deviation was 26.3% of the average content. For lactose formulation
245 (particle-size grade $< 250 \mu\text{m}$), one content was outside the limit of 75 per cent to 125 per cent
246 (measured value -30.7%). The average drug content in formulations containing the different

247 excipients (MCC, SMCC or lactose, two grades) was found statistically significantly different
248 ($P < 0.05$) (Table 1).

249 Although most of the formulations complied the test for uniformity of content, the mean drug
250 content in compounded sachets was in most cases less than the theoretical drug content (Table 1).
251 The difference was statistically significant ($P < 0.05$) for most of the formulations (5/7). The
252 adsorption of the drug in powder paper seemed one possible explanation for the loss of active
253 ingredient, as visualised in Figure 1 for the yellowish drug dipyridamole. At highest, 16% (0.8 mg;
254 $SD \pm 0.13$ mg; $n=5$) of the labelled dose of dipyridamole was recovered from the sachet paper
255 (formulation containing lactose particle-size grade < 355 μm). In analysis, the paper was rinsed with
256 water and the drug analysed by HPLC. The drug loss was smallest when SMCC was used as filler in
257 sachets, 3.8% (0.2 mg; $SD \pm 0.02$ mg; $n=5$) of the labelled dose of dipyridamole was recovered from
258 the sachet paper. The rest of the missing dose was assumed to be on the manufacturing tools.

259

260 *Content uniformity of compounded capsules*

261 The content uniformity of hard capsules compounded using lactose as filler complied the test
262 for uniformity of content (Table 2). Content uniformity of hard capsules of spironolactone and
263 warfarin were studied at three different dose levels. The largest single-capsule deviation from the
264 mean content was 21% for capsules that contained the lowest amount of spironolactone (0.5 mg). The
265 measured mean drug content in the batch was 0.42 mg which was lower ($P < 0.05$) than the theoretical
266 amount of drug (84.4% of the labelled dose). Also for warfarin, the highest single-capsule deviation
267 (-8.2%) was observed with a batch of capsules which contained the lowest amount of drug (0.1 mg).
268 In the batch, the measured mean drug content was 90% of the theoretical amount of drug, although
269 the effect was not statistically significant in this batch.

270

271 If microcrystalline cellulose was used as a filler in hard capsules (drug sotalol), one batch out

272 of three did not comply the test for uniformity of content (Table 2). The highest single-capsule
273 deviation was 25.2% which was slightly above the upper acceptance limit. In all batches the
274 measured mean drug content was lower compared to the theoretical amount of the drug (4 mg). The
275 average amount of drug varied from 3.7 mg (SD \pm 0.09 mg, $P < 0.05$) to 3.72 mg (SD \pm 0.39 mg,
276 $P < 0.05$), which corresponded 92.5% to 93.0% of the theoretical amount of the drug.

277 In most cases, no statistically significant effects were found in relation to batch to batch
278 variation. Only two batches out of 15 parallel batches differed significantly ($P < 0.05$) in the average
279 drug content (Table 2).

280 Capsules were also prepared with an automated Quantos capsule filling device, as a
281 comparison to the conventional method (Feton). The batches prepared using Quantos complied with
282 the content uniformity test specified in the European pharmacopoeia, as expected. Segregation of
283 powder components during the filling process was not observed (Figure 2). The filling method had
284 no effect on the quality of the capsules, and no statistically significant differences were found in the
285 average drug content if capsules filled with Quantos were compared to capsules filled with the
286 conventional method. The largest single-capsule deviation from the mean content was 10%
287 (spironolactone 10.24%; warfarin 10.20%; filler lactose). The average amount of drug in capsules
288 was 0.41 mg (SD \pm 0.017 mg) for spironolactone and 0.093 mg (SD \pm 0.0038 mg) for warfarin,
289 which corresponded 82.0% and 93.0% of the theoretical amount of the drug (0.5 mg and 0.1 mg for
290 spironolactone and warfarin, respectively). The difference in drug amount was statistically significant
291 ($P < 0.05$) for spironolactone (no statistical effects were found for warfarin).

292

293 *Simulation of drug administration through a nasogastric tube*

294 The loss of drug was evident when suspended formulations were lead through a nasogastric
295 tube, mimicking the procedure used in hospitals in administering the drug to the paediatric patient.
296 The lowest simulated drug doses were obtained with sachets that contained celluloses (MCC or

297 SMCC) as fillers, compared to formulations that contained lactose. In these, the amount of
298 dipyridamole passed through the nasogastric tube (n=3) varied from 46.5% (SMCC) and 62.0%
299 (MCC) to 77.5% (lactose < 355 µm) and 86.1% (lactose < 250 µm) of the average drug content.

300 In compounded hard gelatine capsules the drug loss was smaller than 12% of the average drug
301 content in all cases. For size 0 hard gelatine capsules, the drug dose passed through the nasogastric
302 tube (n=3) was 88.1% for spironolactone and 96.4% for warfarin (as sodium salt), calculated of the
303 average drug content in the capsules. The filler in these capsules was lactose (particle-size grade <
304 355 µm). For size 1 hard gelatine capsules, 90.3% (n=10, P<0.05) of the drug dose passed through
305 the tube (drug sotalol hydrochloride, filler MCC).

306 Blockage of the nasogastric tube during drug administration was occasional, in most cases
307 with no clear correlation to the type of the formulation. However, some tendency towards more
308 frequent blockage was observed with formulation in which there was a combination of the slightly
309 soluble drug dipyridamole and the practically insoluble, but swellable excipients MCC or SMCC.

310

311 **Discussion**

312 Finnish studies have presented *extemporaneously* compounded oral powders and capsules as a
313 feasible choice for delivering paediatric medications (nifedipine) in hospital environment (10,16,17).
314 The results of the present study demonstrate that, when needed, compounded solid dosage forms can
315 successfully be obtained also for a range of other drug substances which are commonly used in
316 paediatric medication in Finnish hospitals; in most cases, formulations of dipyridamole,
317 spironolactone, warfarin and sotalol were found to be within acceptable limits for content uniformity,
318 as described in the European Pharmacopoeia. In statistical analysis, no significant differences existed
319 in average drug content when sachets were compared to capsules, indicating that both dosage forms
320 are as good as a choice. However, the actual drug content in both dosage form types, sachets and hard
321 gelatine capsules, was generally smaller than the theoretical amount of the drug. In 19 batches out of

322 24 the difference was statistically significant ($P < 0.05$).

323 The findings on lower drug contents compared to the theoretical drug amount could partly be
324 explained by the fact that the commercial tablets, which were used as a source of the active drug
325 substance, may have contained less drug than labelled. Although the amount of drug was on an
326 acceptable level in all products, the commercial tablets are allowed to have this kind of specific
327 variation in drug content. Additionally, the drug adsorption on the surface of the dispenser or the loss
328 of drug during the preparation process are possible explanations for low drug recovery (10,16). The
329 drug loss has been found to be more marked with small size oral powders (mass 50 mg or 100 mg)
330 dispensed in sachets, in which the drug recovery was only 62-77% of the theoretical value. A total of
331 75% of the missing drug dose was found on the sachet paper (16). In compounded capsules (capsule
332 shells size 1, 3 or 4) the drug recovery was satisfactory, which apparently related to the smaller
333 surface area of the dispenser; capsule shell compared to sachet paper (10). In our study, the dosage
334 units were in general larger (mass in the sachets varied from 200 mg to 500 mg, and the capsule shell
335 size from 1 to 0) than in the previous study and thus, not so marked drug loss was expected.
336 However, the phenomenon of drug adsorption on the surface of the sachet paper was easily visualised
337 with the yellowish drug dipyridamole. In analysis, at highest 16% of the theoretical dose was found
338 on the sachet paper (formulation containing lactose as filler). The risk of drug loss should be kept in
339 mind in sachet formulations, especially if small sachets are prepared. Also, further studies would be
340 beneficial in evaluations on whether other sachet materials than waxed powder paper could result in
341 smaller drug loss, such as plastic laminates or foil.

342 Although sachets and hard gelatine capsules were successfully compounded from commercial
343 tablets in most cases, our results emphasize that the type and amount of excipients in the formulation
344 should be considered as they can affect conformity of the dosage form. In statistical analysis, the
345 effect of excipient was found significant in all cases, and formulations which contained the different
346 excipients (MCC, SMCC and lactose, two grades) differed in average drug content. If the quality of

347 the formulations was evaluated as described in the European Pharmacopoeia, in total of three batches
348 (out of 24 batches) failed to pass the test for content of uniformity; two of these were compounded as
349 sachets (weight 200 mg) and one was a batch of hard gelatine capsules (capsule size 1). The sachets
350 are filled by weight, and therefore inaccuracy of weighing procedures of the small amounts may be a
351 challenge (10). Consistently in our study, the non-conformity in sachets was observed in the smallest
352 sachet mass. Drug adsorption on the surface of the sachet paper or the equipment during preparation
353 seemed possible explanations for non-conformity, as discussed earlier for sachets containing lactose
354 (drug dipyridamole). It has been proposed that use of microcrystalline cellulose as filler could yield
355 in better conformity in sachets (10). The smaller density of MCC results in larger volume of powder,
356 which may protect against the drug adsorption to the sachet paper. Our results emphasise that in
357 addition to density, also other powder characteristics may be important. The best drug recovery and
358 less variation in uniformity of content of dipyridamole was obtained with silicified MCC, in which
359 case not only the small density of the filler but also the surface properties of the excipient, such as
360 hydrophobicity, may explain the results.

361 Whereas the sachets are filled by weight, capsules are filled with volume. Thus, in preparation
362 of capsules good flow properties of the filler are expected to result in better conformity (10). In
363 general, higher density grades of fillers have improved flow properties (27). In addition, the amount
364 of drug is known as a critical variable in compounded capsule formulations, and small amounts of
365 drug increase the risk for non-conformity (18). In the present study, all 14 batches of capsules which
366 contained lactose as filler complied the test for uniformity of content. On the other hand, in MCC
367 capsules one batch of capsules out of three failed the test. The good conformity of lactose capsules
368 may be explained by the high bulk and tapped densities of lactose, which could result in uniform
369 filling of capsule shells during the manufacturing process. It was noteworthy, that content uniformity
370 (as described in the European Pharmacopoeia) was obtained for a range of drug doses (from 0.1 mg
371 to 2 mg for warfarin and from 0.5 mg to 6 mg for spironolactone), including the small doses of the

372 drug. In most cases, no statistically significant effects were found in relation to batch to batch
373 variation. This indicates that compounding of such formulations is rather reproducible. However, it
374 should be noted that the measured drug content in the batches was predominantly significantly lower
375 than the theoretical amount of the drug, although the batches met the pharmacopeial requirements.
376 Discrepancy between the results could be explained by the fact that the limits of acceptance are
377 calculated of the average drug content of the batch (instead of labelled drug amount).

378 The last part of the study evaluated the practical usability of compounded sachets and
379 capsules. Both sachets and capsules, whose contents are emptied for use, seem feasible choice from
380 quality perspective (uniformity of content), and are a practical choice for manufacture in hospital
381 pharmacies. In comparison to sachets, manufacture of capsules is faster as serial production can be
382 utilised. This increases the usability of compounded capsules even further. Capsules filled with the
383 Feton Fastlock filling machine were as good in quality as the reference capsules which had been
384 filled using the automated Quantos capsule filling device. Despite of these favourable properties,
385 there might be some concerns in practical use of compounded sachets and capsules. Including the
386 capsules prepared with the Quantos capsule filling device, the risk of drug loss in manufacture and
387 consequent possibility to under dosing should be considered. In addition, administration of these
388 kinds of solid dosage forms (suspended in fluid) through the nasogastric tube has been found
389 challenging (19,20). The volume of water (or other fluid such as milk) in which the solid powder is
390 suspended, should be rather small as the daily intake of fluids in the neonates is limited. The small
391 volume of fluid increases, however, the risk of blockage of the nasogastric tube. In our study, the
392 administration through a nasogastric tube resulted in loss of drug. The lowest simulated drug doses
393 were obtained with sachets which contained the slightly soluble (but swellable) excipient,
394 microcrystalline cellulose, compared to formulations which contained the more readily soluble
395 lactose. Similarly, the amount passed through the tube was slightly less for the insoluble drug
396 spironolactone **than for** the readily soluble warfarin sodium. Such drug loss in administration,

397 together with the fact that the actual dose of drug was in most formulations less than the theoretical
398 dose, increases the risk for under dosing in practice, especially for the drugs of narrow therapeutic
399 index (such as warfarin in the present study).

400 The results emphasize that in compounded sachets and capsules (if the dose is aimed to be
401 administered through a nasogastric tube) solubility of the drug and excipients should be considered.
402 The amount of solid contents should also be as small as possible as the amount of liquid used for
403 suspending cannot be increased due to physiological reasons. This is supported by findings for size 1
404 capsules, in which the drug administration through nasogastric tube resulted in high simulated drug
405 dose, even though the formulation contained the slightly soluble excipient MCC. Also from the
406 therapeutic point of view, smaller amount of excipients would be preferable as the safety of many
407 excipients in the very young patients is not known (15). In practice, this means preference for
408 compounding sachets of small weight and capsules of small size. The risk of drug loss should,
409 however, be kept in mind.

410 It is evident that more studies are needed in evaluations on how the formulation and
411 excipients, or their administration procedure to the patient affect bioavailability of *extemporaneous*
412 formulations. Also, *in vitro* studies predicting biological properties of the developed formulations are
413 needed, such as dissolution studies. Unfortunately, the lack of facilities (analytical facilities,
414 dissolution apparatus etc.) in hospital pharmacies has limited conductance of these studies.

415

416 **Conclusions**

417 Our results indicate that compounded formulations, which meet the quality requirements for
418 uniformity of content as described in the European Pharmacopoeia, can successfully be obtained for a
419 range of drug substances. The results emphasize, however, that the type and amount of excipients in
420 the formulation should be considered. Good conformity of capsules was obtained using lactose
421 monohydrate as filler, whereas microcrystalline cellulose seemed a better choice in sachets. In lactose

422 capsules content uniformity could be obtained for a range of drug doses, including the very small
423 doses. If the drug is aimed to be administered through a nasogastric tube, solubility of the drug and
424 excipients should be considered, as they were found to affect the simulated drug dose in
425 administration. The risk of drug loss should be considered in manufacture and administration. It is
426 noteworthy that even though the formulations met quality requirements for uniformity of content, in
427 most cases the measured drug content was statistically significantly lower than the theoretical amount
428 of the drug.

429 Both sachets and capsules could be a practical choice as solid dosage forms to be prepared in
430 hospital pharmacies. Capsules are faster to manufacture, which increases their value even more
431 compared to sachets. It is obvious, however, that validation of manufacturing procedures and quality
432 assurance systems are important in hospital pharmacies, as the conformity is affected by the
433 formulation. In compounding, the risk of drug loss should be kept in mind and analytical methods
434 would be needed to determine the drug amount in quality analysis, or the influence of procedures
435 (crushing the tablets) on drug. Additionally, compatibility and stability studies are needed if
436 compounded formulations are manufactured for storage, in addition to *extemporaneous* preparation.
437 Dissolution studies would be needed to predict the biological properties of the developed
438 formulations.

439

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445

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TABLES

Table 1. Uniformity of content in compounded sachets. Individual contents of at least 10 units were determined, as described in the method by European Pharmacopoeia.

Drug; Excipient	Average drug content (mg)	Acceptable \pm 15% limits (mg)	Largest individual deviation (mg)	Maximum deviation (%)	Amount of drug (% of theoretical)
Dipyridamole ^a					
MCC	4.52 ^{f,g}	3.84 – 5.20	1.18	+26.3	90.4
SMCC	5.33 ^{f,g}	4.54 – 6.13	0.69	-12.9 ^e	106.6
Lactose (< 355 μ m)	4.04 ^{f,g}	3.43 – 4.65	0.52	+12.9 ^e	80.8
Lactose (< 250 μ m)	4.46 ^{f,g}	3.79 – 5.13	1.37	-30.7	89.2
Spirolactone ^b					
Lactose (< 355 μ m)	0.44 ^f	0.37 – 0.51	0.04	+9.0 ^e	88.0
Warfarin (as sodium salt) ^c					
Lactose (< 355 μ m)	0.092	0.078 – 0.106	0.009	+10.2 ^e	92.0
Sotalol (as hydrochloride salt) ^d					
MCC	3.69	3.14 – 4.23	0.17	-4.6 ^e	92.2

Theoretical drug content (powder mass) ^a 5 mg (200 mg); ^b 0.5 mg (500 mg); ^c 0.1 mg (500 mg); ^d 4 mg (300 mg); ^eComplies with the test for Uniformity of Content (European Pharmacopoeia);

^fStatistically significantly different (P<0.05) from the labelled amount of drug; ^gStatistically significantly different (P<0.05) when one excipient (MCC, SMCC or lactose) is compared to the other excipient.

Table 2. Uniformity of content in compounded hard gelatin capsules. Individual contents of at least 10 units were determined, as described in the method by European Pharmacopoeia.

Drug; Theoretical drug content	Average drug content (mg)	Acceptable ± 15% limits (mg)	Largest individual deviation (mg)	Maximum deviation (%)	Amount of drug (% of theoretical)	Average capsule content (mg)
Spironolactone^a						
0.5 mg	0.424 ^d	0.360 – 0.487	0.089	+21.0 ^c	84.4	552.4
0.5 mg	0.402 ^d	0.342 – 0.462	0.006	-1.7 ^c	80.4	556.3
0.5 mg	0.426 ^d	0.362 – 0.489	0.017	-4.0 ^c	85.2	553.3
3 mg	2.58 ^d	2.19 – 2.97	0.24	-9.4 ^c	86.0	545.6
6 mg	5.25 ^{d,e}	4.47 – 6.04	0.43	+8.1 ^c	87.5	536.1
6 mg	4.88 ^d	4.15 – 5.61	0.25	-5.2 ^c	81.3	545.8
6 mg	5.02 ^d	4.27 – 5.77	0.18	-3.5 ^c	83.7	544.4
Warfarin (as sodium salt)^a						
0.1 mg	0.082 ^{d,e}	0.070 – 0.095	0.006	-7.0 ^c	82.0	530.1
0.1 mg	0.094	0.080 – 0.108	0.001	-1.2 ^c	94.0	522.1
0.1 mg	0.090	0.076 – 0.103	0.007	-8.2 ^c	90.0	486.5
0.2 mg	0.187 ^d	0.160 – 0.216	0.010	-5.5 ^c	93.5	512.1
2 mg	1.89 ^d	1.60 – 2.17	0.07	+3.5 ^c	94.5	509.2
2 mg	1.84 ^d	1.56 – 2.11	0.12	-6.5 ^c	92.0	521.0
2 mg	1.86 ^d	1.58 – 2.14	0.07	+3.7 ^c	93.0	521.7
Sotalol (as hydrochloride salt)^b						
4 mg	3.72 ^d	3.16 – 4.28	0.13	-3.5 ^c	93.0	186.8
4 mg	3.70	3.14 – 4.25	0.93	-25.2	92.5	180.6
4 mg	3.70 ^d	3.15 – 4.26	0.38	-10.4 ^c	92.5	173.0

^a Capsule size 0, filler lactose monohydrate, particle-size < 355µm; ^b Capsule size 1, filler MCC, particle size < 100µm, ^cComplies with the test for Uniformity of Content (European Pharmacopoeia)

^dStatistically significantly different (P<0.05) from the labelled amount of drug; ^eStatistically significantly different (P<0.05) when the batch is compared to parallel batches. When capsules were compared to sachets containing the same drug substance, at the same dose (Table 1.), no statistically significant effects were detected (N.S.).

515 **Figure legends**

516

517 **Figure 1.** Visualisation of the adsorption of the yellowish drug dipyridamole on the sachet paper.

518 Formulations (powder mass 200 mg) were dispensed in sachets, similarly as in preparation of the

519 compounded solid dosage forms, and emptied for analysis. Formulations contained the different

520 excipients (order of emptied sachet papers from front to back); SMCC, lactose monohydrate (particle

521 size < 250 μm), MCC and lactose monohydrate (particle size < 355 μm).

522

523 **Figure 2.** Drug content of capsules prepared using the automated Quantos (Mettler Toledo) capsule

524 filling device; upper panel spironolactone (theoretical drug amount 0.5 mg, n = 30), lower panel

525 warfarin (theoretical drug amount 0.1 mg, n = 20). The batches complied with the content uniformity

526 test, as specified in the European pharmacopoeia. The acceptance $\pm 15\%$ limits were 0.340 mg –

527 0.472 mg and 0.079 mg – 0.107 mg for spironolactone and warfarin, respectively. For

528 spironolactone, the drug amount was found significantly different ($P < 0.05$) from the labelled amount.

529 No statistical effects were found for warfarin (N.S.).