PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Paediatrics Open. The paper was subsequently accepted for publication at BMJ Paediatrics Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Content uniformity of quartered hydrocortisone tablets in comparison with mini-tablets for paediatric dosing
AUTHORS	Roberts, Matthew; Madathilethu, Jude; Peak, Matthew; Blair, Joanne; Prescott, Rebecca; Ford, James

VERSION 1 - REVIEW

REVIEWER	de Meijer, Mariska ACE Pharmaceuticals BV, The Netherlands Competing interests: None
REVIEW RETURNED	06-Sep-2017

GENERAL COMMENTS	The manuscript is clearly written and there is indeed a need for age-appropriate dosage forms, especially when different dosages are required for children, such as in the described patient group. The authors showed that quartering tablets can be regarded as suboptimal with regards to dosing, while dosage variation was within the specified limits with mini-tablets. Below are several comments/questions in order to improve the manuscript: Abstract: - The conclusion states that 'more accurate doses that meet the needs of paediatric patients' can be achieved with mini-tablets. When reading the abstract the needs (apart from accurate doses) do not become readily clear. You may want to add background information or delete this part. - Please check the spelling pharmacopoeia/pharmacopeia. Sometimes it is inconsistent (throughout the paper). Introduction: - The sentence 'no current oral hydrocortisone formulation meets the dosing requirements of children' seems too strict, because off-label use fills in the need currently (perhaps not adequately). Aims and objectives: - What do you mean by dose uniformity, since content uniformity is already mentioned? Materials and methods: - For the excipient Pharmatose the source is not mentioned? - Maybe you should shortly explain to the readers why you used USP criteria for content and Ph Eur for weight. Why have you not performed the breakability test according to Ph Eur? - Which percentage deviation was allowed for quartered tablets? Results: - Where does 'this specification' refer to (on p. 8 after Ph Eur monograph)?

	- You could add the totals for quartered tablets to table 2 for better comparison with the mini-tablets. Discussion: - Pharmacokinetics show intra- and interindividual variability. What content of hydrocortisone in a tablet quarter would be called underdosing? Does this correspond to your findings? - Obviously, different operators add variability in breaking tablets, in particular when the person is not trained nor experienced. In this study unexperienced operators splitted only 5 tablets. The issue is to some extent addressed in the manuscript. Would training and/or experience prevent dosing variation for hydrocortisone tablets (at least to acceptable levels)? In addition, did the operators find any crumbled or badly divided tablets that should have been disregarded?

REVIEWER	Almoazen, H. University of Tennessee, USA Competing interests: No competing interests
REVIEW RETURNED	15-Sep-2017

GENERAL COMMENTS	The research is not genuine enough for publications

REVIEWER	Mitra, Biplob Drug Product Development Celgene Corporation USA Competing interests: None
REVIEW RETURNED	01-Oct-2017

GENERAL COMMENTS	The authors did a great job in designing and executing the experiment, and presenting the results. This work should improve awareness about pediatric dosage forms among the manufacturer and caregiver. The manuscript can be published provided the comments are adequately addressed. 1. Page 4 Line 28-31: The author should specify the tablet strength for clarification. 2. Page 5 Line 7-8: What is the justification of using the specific source of 10 mg strength tablets? 3. Page 5 Line 39-48: How much granulation solution added for how long? How the drying endpoint was controlled (what was the LOD of the dried granules?)? Please clarify the phrase “sieve prior to separation”. Please consider moving the physical testing under separate subheading. 4. Page 6 Line 39-48: Please explain how Hausner ratio and flowability influence tablet tensile strength. 5. Page 6 Line 39-48: Please specify if a single tip or multi-tip tooling was used. Please also state the target minitablet physical properties. Please specify that 140-280 MPa is compression pressure. Please justify the wide range of compression pressure. 6. Page 7 Line 44: Absolute value of (M-X) should be used in equation 4. 7. Page 10 Line 12: The term “compressibility” only refers to densification not tensile strength of tablets. Please clarify the statement. 8. The conclusion should acknowledge that failure to meet weight limits is likely when splitting is not done by a professionally

	trained person. The broader conclusion drawn in this study needs to be supported by evaluating more than one commercial tablet source. Tablets quartered by trained professional should be used as control. Please also show weight and content uniformity data of quartered tablets prepared by compressing the minitablet formulation to 10 mg strength tablets and split them into four sections. 9. Please show hydrocortisone content (% label claim), weight adjusted hydrocortisone content (weight corrected % label claim), and weight of dosage form (% target weight) of individual tablets, quartered tablets, and minitablets in the same plot.

REVIEWER	Bagkeris, Emmanouil University College London, UK Competing interests: No competing interests
REVIEW RETURNED	04-Nov-2017

GENERAL COMMENTS	1. Was the distribution of weight and content uniformity normally distributed? Please state if so at the statistical analysis section to support the use of parametric statistics. 2. Avoid using the plus-minus symbol when reporting standard deviation both on text and tables. Instead state SD for standard deviation. 3. Add the use of correlation coefficient at the statistical analysis section. 4. Perhaps remove all decimal places of the percentages of weight reported. Reporting 41% does not convey a different message from 41.25%. 5. All acronyms (SD, CV%) should be explained in footnotes of table 2 and 3. 6. Figure 1 and 2 should have a title explaining in detail what they display. Reduce to two the decimal places reported for R squared in figure 1. 7. There is no reference of figure 2 in the main text.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Abstract:
- The conclusion states that 'more accurate doses that meet the needs of paediatric patients' can be achieved with mini-tablets. When reading the abstract the needs (apart from accurate doses) do not become readily clear. You may want to add background information or delete this part. Sentence reworded to 'more accurate doses for paediatric patients'
- Please check the spelling pharmacopoeia/pharmacopeia. Sometimes it is inconsistent (throughout the paper). Amended to pharmacopoeia throughout.

Introduction:
- The sentence 'no current oral hydrocortisone formulation meets the dosing requirements of children' seems too strict, because off-label use fills in the need currently (perhaps not adequately). Sentence amended to 'No current licensed oral hydrocortisone formulation adequately meets the dosing requirements of children.'

Aims and objectives:

- What do you mean by dose uniformity, since content uniformity is already mentioned? Dose uniformity replaced with 'content uniformity.

Materials and methods:

- For the excipient Pharmatose the source is not mentioned? Source now included.
- Maybe you should shortly explain to the readers why you used USP criteria for content and Ph Eur for weight. Why have you not performed the breakability test according to Ph Eur? The pharmacopoeial tests used in the study are adequately described and both Ph Eur and USP criteria are equally valid in our opinion. Due to their small size, determining the tensile strength of the mini-tablets was deemed to be more important for this study than testing breakability alone.

Which percentage deviation was allowed for quartered tablets? The same percentage deviation allowed for mini-tablets – this is now stated for clarity.

Results:

- Where does 'this specification' refer to (on p. 8 after Ph Eur monograph)? Sentence rephrased for clarity
- You could add the totals for quartered tablets to table 2 for better comparison with the mini-tablets. The authors feel that the data for quartered tablet weights provided in Table 2 along with the mean weight, SD and CV for whole tablets provided in the text on page 8 is sufficient.

Discussion:

- Pharmacokinetics show intra- and inter-individual variability. What content of hydrocortisone in a tablet quarter would be called underdosing? Does this correspond to your findings?

As the reviewer states, significant inter-individual variability is reported in patients treated with hydrocortisone, and a wide range of doses are required to achieve satisfactory cortisol replacement. For individual patients, doses are titrated against clinical symptoms, and on occasion measurements of cortisol and other surrogate markers of cortisol concentrations, for example 17 hydroxy-progesterone in children with congenital adrenal hyperplasia. Intra-individual variability can be addressed, in part, by standardising the dosing regimen for example the relationship between dosing and meal times. The data reported in this paper indicate that another layer of variability is introduced by the use of quartered hydrocortisone tablets. Doses ranged from 1.4mg to 3.4mg, and this unpredictability is likely to make the interpretation of clinical symptoms or biochemical measures unreliable, making dose titration and optimisation extremely difficult. A sentence has been added to the discussion to emphasise this point.

- Obviously, different operators add variability in breaking tablets, in particular when the person is not trained nor experienced. In this study unexperienced operators splitted only 5 tablets. The issue is to some extent addressed in the manuscript. Would training and/or experience prevent dosing variation for hydrocortisone tablets (at least to acceptable levels)? We have no evidence to suggest training would improve the dosing variation for hydrocortisone tablets to acceptable levels, including in our published systematic review of manipulation of adult dosage forms to obtain accurate doses in paediatric practice (ref 28), and the physical characteristics of the tablets would likely be the predominating factor. Other studies, as cited in the discussion, have highlighted the potential inter-operator variation obtained when splitting scored tablets.

In addition, did the operators find any crumbled or badly divided tablets that should have been disregarded? No crumbled or badly divided tablets needed to be discarded during the study.

Reviewer: 2

The research is not genuine enough for publications. NO COMMENT

Reviewer: 3

1. Page 4 Line 28-31: The author should specify the tablet strength for clarification. The authors are not clear why any tablet strength should be quoted in the aims and objectives section.
2. Page 5 Line 7-8: What is the justification of using the specific source of 10 mg strength tablets? These specific tablets are commonly prescribed and split (also see point 8, reviewer 3) and thus worthy of use in this study.
3. Page 5 Line 39-48: How much granulation solution added for how long? Details now added

How the drying endpoint was controlled (what was the LOD of the dried granules?)? LOD was not determined but drying time was kept constant for all batches of mini-tablets produced.

Please clarify the phrase "sieve prior to separation". Sentence rephrased for clarity

Please consider moving the physical testing under separate subheading. The tensile strength testing, weight uniformity testing are already under separate subheadings and the authors would prefer to keep the current sections.

4. Page 6 Line 39-48: Please explain how Hausner ratio and flowability influence tablet tensile strength. Flowability directly influences die filling, so when filling height is maintained at a constant level any fluctuation in fill weight will also result in variation in tablet thickness and therefore tensile strength also.
5. Page 6 Line 39-48: Please specify if a single tip or multi-tip tooling was used. Please also state the target minitablet physical properties. Please specify that 140-280 MPa is compression pressure. Please justify the wide range of compression pressure. Single-tip tooling now stated in text. Compression pressure now stated in text. There were no target physical properties for the mini-tablets, but the wide range of compression pressure is a direct result of the small punch-tip diameter as a small variation in compression force (kN) causes a large variation in pressure (MPa).
6. Page 7 Line 44: Absolute value of (M-X) should be used in equation 4. (M – X) = zero is now stated in the text.
7. Page 10 Line 12: The term "compressibility" only refers to densification not tensile strength of tablets. Please clarify the statement. The term compressibility has been replaced with compactibility in the text.
8. The conclusion should acknowledge that failure to meet weight limits is likely when splitting is not done by a professionally trained person. The broader conclusion drawn in this study needs to be supported by evaluating more than one commercial tablet source. Tablets quartered by trained professional should be used as control. Please also show weight and content uniformity data of quartered tablets prepared by compressing the minitablet formulation to 10 mg strength tablets and split them into four sections. Conclusion now states that " … quartering of 10 mg hydrocortisone tablets by untrained operators produces an unacceptable variation in the weight…". The commercial tablets studied are the most commonly prescribed and manipulated in the paediatric setting and were specifically chosen on this basis. The specific tooling design (convex, diamond shaped and quarter-scored) was not available to compress the mini-tablet formulation to 10mg strength tablets and the aim, as stated in the manuscript, was to produce a mini-tablet formulation that provides a 2.5mg dose for children so that tablet splitting is avoided. The aim was not to produce a tablet formulation to improve the process of tablet splitting.
9. Please show hydrocortisone content (% label claim), weight adjusted hydrocortisone content (weight corrected % label claim), and weight of dosage form (% target weight) of individual tablets, quartered tablets, and minitablets in the same plot. These data are provided in Table 2 and Table 3 and in response to editorial request to reduce length of manuscript, repetition of the data in an additional figure is not recommended.

Reviewer: 4

1. Was the distribution of weight and content uniformity normally distributed? Please state if so at the statistical analysis section to support the use of parametric statistics. Normal distribution of data confirmed in the statistical analysis section.
2. Avoid using the plus-minus symbol when reporting standard deviation both on text and tables. Instead state SD for standard deviation. ± symbol removed when indicating SD.
3. Add the use of correlation coefficient at the statistical analysis section. Use of R^2 value added to statistical analysis section.
4. Perhaps remove all decimal places of the percentages of weight reported. Reporting 41% does not convey a different message from 41.25%. Decimal places removed.
5. All acronyms (SD, CV%) should be explained in footnotes of table 2 and 3. Acronyms explained in footnotes.
6. Figure 1 and 2 should have a title explaining in detail what they display. Reduce to two the decimal places reported for R squared in figure 1. Figure titles are provided, R^2 value reported to 2 decimal places.
7. There is no reference of figure 2 in the main text. Figure 2 is referred to on Page 10, line 12