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PAEDIATRIC MINI-TABLETS OF ENALAPRIL: FORMULATION AND ACCEPTABILITY ASSESSMENT

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Abstract

Children are often given adult medicines that have been crushed, split or dispersed, and enalapril is a typical example. This narrative review examines what the published literature says about paediatric mini-tablets of enalapril, covering the clinical need, the principles of mini-tablet design and manufacture, quality and stability issues, and the evidence on acceptability. It reports no new data and describes no formulation or acceptability experiment. Trials in neonates, infants and preschool children suggest that small uncoated tablets are well accepted, often better than syrups. Few of these studies involved enalapril or sick children, however, and data on content uniformity, stability and caregiver dosing accuracy for this drug remain sparse.

1. INTRODUCTION

Children are still given many medicines that were never designed for them. A pharmacist handed a prescription for a three-year-old with heart failure will often be working from an adult tablet, a calculator and a mortar. The shortage of suitable paediatric formulations has been documented for two decades, and surveys of community prescribing showed early on that many drugs given to children had no licensed child-friendly form [1, 2]. Liquids are the traditional answer, yet they bring problems of stability, taste, dose accuracy, excipient exposure and storage that become obvious once one tries to supply them at scale [3, 4]. Solid oral forms small enough for a young child to swallow have therefore attracted attention as a way round some of these difficulties.

Enalapril is a good test case. It is an angiotensin-converting enzyme inhibitor used in children for hypertension, heart failure, congenital heart disease and some kidney conditions, and it has been prescribed in paediatric practice for many years even though adult tablets dominate the market [5, 6, 7]. Doses are calculated by body weight and may be very small. Hospital pharmacies have usually met the need by crushing tablets or preparing suspensions, a process that adds variability and carries stability risks [8]. A mini-tablet is a tablet with a diameter of roughly two to three millimetres, and several can be counted out to make up a dose. The concept looks well matched to a potent drug that has to be given in many different strengths.

This review examines what the published literature says about mini-tablet formulation and acceptability, using enalapril as the worked example. It reports no new data, and no formulation work or acceptability trial is described. The sections that follow cover the clinical need for an enalapril paediatric product, the principles of mini-tablet design and manufacture, quality and stability considerations, the evidence on acceptability in different age groups, and the regulatory framework. Findings from studies of other drugs are used where enalapril-specific data are missing, and this is stated where it matters. The purpose is to give formulation scientists and hospital pharmacists a balanced account of what is known, and of what would need to be shown before such a product could be relied upon.

2. CLINICAL RATIONALE FOR PAEDIATRIC ENALAPRIL

Enalapril maleate is a prodrug. After absorption it is hydrolysed in the liver to enalaprilat, the active diacid that inhibits the angiotensin-converting enzyme and lowers angiotensin II production. The result is vasodilatation and reduced aldosterone secretion. In hypertensive children aged six to sixteen, a placebo-controlled dose-response study showed dose-related reductions in blood pressure with enalapril, supporting its use in this age group [5]. Paediatric hypertension guidelines from North America and Europe list angiotensin-converting enzyme inhibitors among the drugs suitable for children, particularly where there is proteinuric kidney disease or diabetes [6, 7]. The pharmacology is thus familiar, and the need for a convenient dosage form follows from the established use.

Evidence from heart disease is more mixed. A multicentre randomised trial of enalapril in infants with a single functional ventricle, run by the Pediatric Heart Network, found no improvement in somatic growth or other secondary outcomes compared with placebo [9]. That result tempered earlier enthusiasm for routine use in this population, but it did not reduce the number of children who receive the drug for other cardiac conditions, such as cardiomyopathy and left-to-right shunts with heart failure. For the formulation scientist, the lesson is that the target population is wide, running from neonates to adolescents, and that doses may vary by more than an order of magnitude between the youngest and oldest patient [6, 9].

Such a range creates the formulation problem. A single fixed-dose tablet cannot serve a neonate and a teenager, and splitting adult tablets into fractions is inaccurate, especially for the small amounts needed at low body weight. Surveys of paediatric practice have documented how often tablets are manipulated by crushing, dispersing in water or cutting [1, 10]. The practice introduces dose error, and for a drug with a narrow window between effective and hypotensive dose, as can occur with ACE inhibitors in volume-depleted infants, this is not a trivial concern. The requirements for a good paediatric product are therefore flexibility of dose, small size, easy administration and reliable content uniformity [3, 11].

The alternatives to a solid form each have drawbacks. Oral solutions and suspensions allow fine dose adjustment, but they require preservatives, flavours and sweeteners, which can themselves be unsuitable for infants, and they need a measuring device that caregivers may use poorly [3, 4]. Syrups can be bulky, short-lived once opened and troublesome to transport. Reviews of commercially available paediatric oral products show that liquids make up the majority of the formulations marketed for children, which reflects

convenience for manufacturers as much as clinical preference [10]. Where a drug is stable as a solid and is needed in small, adjustable doses, a multiple-unit solid form offers a credible way of avoiding most of these difficulties [4, 10, 12].

Liquid enalapril has long been prepared extemporaneously in pharmacies, and published stability work exists for such preparations. A study of enalapril maleate in three extemporaneously prepared oral liquids examined retention of potency over time and found that stability depended on the vehicle and storage conditions [8]. The finding is useful, but it applies to a particular preparation made in a particular way. Variation between suspending agents, pH values and storage temperatures means that a shelf life established in one pharmacy cannot be assumed for another, and that is a standing argument for a manufactured solid form.

3. MINI-TABLET DESIGN AND MANUFACTURE

Mini-tablets are defined by size, with a diameter generally at or below three millimetres, and they are made on conventional rotary presses fitted with multi-tip tooling. A single punch station can produce many tablets in one stroke, which keeps output at a practical level despite the tiny size. Formulations are commonly based on direct compression, using fillers and binders with good flow and compactibility, because granulation is not always needed and each additional step adds cost [12, 13, 14]. Small die diameters make powder flow critical, since fill depth and die filling are the main determinants of weight variation. A formulation that flows well on a large press may segregate or bridge when asked to fill a die only a couple of millimetres across.

Content uniformity is the central challenge for a potent drug like enalapril. When the tablet weighs only a few milligrams and the dose is a fraction of that, small differences in blend uniformity translate into large relative differences in drug content. The pharmacopoeial test for uniformity of dosage units sets limits that are demanding for such systems [15]. Strategies include using a drug of controlled particle size, geometric dilution during blending, and adding a carrier that helps the drug distribute evenly. Where the drug is moisture-sensitive, as enalapril maleate is, humidity control during manufacture also matters. These measures are standard practice in solid dosage design, but their margin for error is smaller when the unit is small [14, 15].

Other design choices follow from the intended age group. Uncoated mini-tablets are simple and avoid the extra cost, solvents and time of coating, and the trials in young children generally used uncoated tablets of about two millimetres [16, 17, 18]. Taste masking may be needed for bitter drugs, and where it is, coating or incorporation of the drug into a matrix is required. Orodispersible mini-tablets, which disintegrate in the mouth in seconds, have been proposed for children who cannot swallow reliably, though their disintegration time and mechanical strength have to be balanced against each other [19]. Choice of excipient is another limiting factor: lactose, sugars, benzyl alcohol, propylene glycol and certain colourants can pose problems in young children, and a short, simple excipient list is preferred [3, 11, 20].

Handling and dosing are the final design questions. A dose of, say, eight mini-tablets has to be counted correctly by a caregiver, and a single miscount is a dose error. Dispensing containers and devices can help, including counting cards, blister packs with the dose marked, and dispensers that release a fixed number of units at a time. A survey of delivery devices for paediatric formulations discussed the options and the lack of evidence that any one design is best [21]. Dose by count also assumes tablets of equal strength, so manufacturers must keep each mini-tablet at a defined and consistent content. Neither problem is unsolvable, but each requires deliberate design and, ideally, testing with real caregivers [21, 22].

Sensory properties deserve attention at the design stage. Tiny tablets have a small surface, so exposure of the tongue to the drug is brief, which helps with bitter compounds, yet any residue left on the tongue or between the teeth can still produce an aftertaste. Research with adult volunteers on multiparticulate systems showed that particle

size and vehicle influenced grittiness and preference, which suggests that physical form affects acceptance independently of taste [23]. Children cannot always express such preferences, and observational scoring is used instead. The practical message is that a mini-tablet should be smooth, round and uniform in size, since irregular or rough units are more likely to be refused or to stick in the mouth [19, 23, 24].

Mini-tablets also give flexibility that liquids rarely offer. A single product strength can be dispensed as one, two, five or ten units, so one pack can serve patients across a wide weight range. Titration up or down becomes a matter of changing the count. For a drug where dose adjustment is routine, as with an ACE inhibitor started low and raised according to blood pressure and renal function, that property has obvious appeal. It also means that a hospital can stock one strength and need not hold several concentrations of liquid, with the associated risk of selection errors [6, 12, 13].

4. QUALITY AND STABILITY CONSIDERATIONS

Enalapril maleate has well-characterised degradation pathways. In the presence of moisture it hydrolyses to enalaprilat, and by an intramolecular cyclisation it forms a diketopiperazine derivative, with the rate of each pathway influenced by pH, temperature and excipients. This behaviour explains why the stability of extemporaneous liquids is limited and variable [8]. In solid dosage forms the same pathways operate more slowly, but they remain relevant to excipient choice and to packaging. Basic or hygroscopic excipients can accelerate degradation, and a formulation developed for adult tablets cannot simply be scaled down without checking compatibility. The reaction chemistry is a reminder that stability for a mini-tablet is an experimental question, not a theoretical one [8, 25].

Stability testing follows international guidance. The World Health Organization guidance on stability testing sets out conditions for long-term, intermediate and accelerated studies, as well as the number of batches and the attributes tested [25]. For a mini-tablet the relevant attributes include assay, degradation products, dissolution or disintegration, hardness and water content. A moisture-sensitive product may need high-barrier packaging, such as aluminium blisters or a container with desiccant, and the pack must still allow convenient dispensing of small units. The tiny surface-to-volume geometry of mini-tablets means that they take up and lose moisture faster than larger tablets, so packaging claims need to be justified and not assumed [14, 25].

Mechanical quality is a further concern. Standard friability tests were designed for tablets of conventional size, and applying them unchanged to mini-tablets may give misleading results because of their low mass and high surface area. Pharmacopoeial methods exist for friability, disintegration and uniformity [15], but the validity of the first of these for tablets of a few milligrams is debatable, and developers have often modified the procedure or relied on other evidence of robustness. Dissolution testing of many small units also demands care in sampling. These points are not objections to the dosage form. They indicate that its quality control needs to be adapted rather than copied from larger tablets [14, 15, 19].

5. EVIDENCE ON ACCEPTABILITY

The strongest data on mini-tablets come from studies conducted by German and other European groups in young children. A randomised controlled trial of infants and preschool children compared uncoated mini-tablets with a syrup and found that acceptability was clearly higher for the mini-tablets, which most children swallowed without difficulty [16]. An earlier exploratory crossover study in young children had pointed the same way, finding uncoated mini-tablets to be accepted by the large majority of those who took part [17]. A pilot study in preschool-aged children evaluated multiple mini-tablets given together, and indicated that several units could be swallowed in one dose [26]. These studies used placebo or non-drug units, and results are summarised in table 1 and grouped in fig. 1.

Neonates are the most demanding group. A randomised trial examined uncoated

mini-tablets in neonates against an oral solution and reported that the tablets could be given safely, with acceptability comparable to that of the liquid [18]. Many clinicians had assumed that newborns could not handle solid forms, and the result challenged the assumption. The study was relatively small, took place in specialist units, and used a simple placebo product, so its findings should not be over-extended. Even so, they raised the lower age limit for which mini-tablets can be considered, and they bear directly on enalapril, which is prescribed in the first weeks of life for some cardiac and renal conditions [9, 18].

Table 1: Published evidence relevant to enalapril mini-tablets for children

Study or topic	Principal finding reported	Ref.
Mini-tablets versus syrup infants and preschool children	Acceptability higher for uncoated mini-tablets than for syrup	[16]
Crossover study young children	Uncoated mini-tablets accepted by most participants	[17]
Neonates mini-tablets versus oral solution	Tablets could be given safely with acceptability similar to the liquid	[18]
Several mini-tablets at once preschool children	Multiple units swallowed in one dose in a pilot study	[26]
Two and four millimetre minitablets preschool-aged children	Both sizes could be swallowed	[13]
Orodispersible mini-tablets	Rapid disintegration in the mouth possible, balanced against mechanical strength	[19]
Enalapril maleate in extemporaneous liquids	Stability depended on vehicle and storage conditions	[8]
Enalapril in hypertensive children dose-response study	Dose-related reductions in blood pressure	[5]
Enalapril in infants with single ventricle randomised trial	No improvement in somatic growth versus placebo	[9]
Regulatory guidance EMA and WHO	Flexible solid oral forms encouraged where age-appropriate	[27, 28, 29]

Earlier work from the United Kingdom showed that preschool-aged children could swallow minitablets of both two and four millimetres, supporting the general idea that small solids are manageable [13]. At the same time, comparisons between studies are difficult because the methods differ: some scored swallowing by a trained observer, some used caregiver reports, and the definitions of acceptable varied. Reviews of the acceptability literature note this heterogeneity and call for standard methods [22, 24]. A large survey of children and caregivers also revealed that preferences differ markedly by age and by the cultural setting, which means that a product accepted in one country may be viewed differently elsewhere [22, 30].

Knowledge gaps are plain. Most data derive from trials with placebo mini-tablets in children who were otherwise well, and there are few studies in sick children, who may be nauseated, dehydrated or fearful. The information on chronically treated children, in whom acceptance over months matters, is limited. Whether ten or more units per dose would still be acceptable for the larger dose bands is not established. Nor is it clear how well caregivers cope with counting and administering units at home rather than in a supervised research setting. For enalapril specifically, no published acceptability work in the target patient population was identified in the sources consulted for this review [22, 24, 26, 30].

Technique may change the outcome. In the trials, children were generally offered the tablets with a drink or with a spoonful of food, and the way a unit was presented seemed to affect acceptance. Putting a few mini-tablets on a spoon and letting the child swallow with water was easy to demonstrate, whereas placing several on the tongue was less reliable. Caregiver training therefore forms part of the product, and a clear leaflet or demonstration will probably be needed whatever the formulation, and nurses on paediatric wards are well placed to provide it [16, 17, 21].

6. REGULATORY FRAMEWORK AND PRACTICE

Regulatory documents have moved in the same direction as the science. The European

Medicines Agency reflection paper on formulations of choice for the paediatric population set out the principle that the formulation should suit the age group [31], and its guideline on pharmaceutical development of medicines for paediatric use asks developers to justify the choice of dosage form, excipients, dose flexibility and acceptability [27]. The World Health Organization's points to consider make a similar case and recommend flexible solid oral forms where appropriate [28]. The European Paediatric Regulation created obligations and incentives for companies to study medicines in children [32]. Together these documents encourage the kind of age-appropriate product a mini-tablet represents [29, 33].

Regulators also expect evidence of acceptability. A regulatory perspective on acceptability testing emphasises that studies should be built into development and should match the age of the intended users, using suitable measures of swallowing, palatability and handling [33]. Review articles on marketed paediatric products show that few manufactured solid forms are designed for very young children, and most authorised products for children are still liquids or adult-strength tablets [4, 10]. For hospital pharmacists, the practical implication is that a licensed mini-tablet product, when available, would replace extemporaneous preparations that now fill the gap, with the benefit of defined quality and assay [8, 10, 29].

Hospital supply chains matter as well. In the absence of licensed products, pharmacies prepare liquids from adult tablets or from raw materials, each batch carrying its own assay uncertainty and a short shelf life [8]. Community surveys have found that children often receive medicines for which no suitable formulation exists [2], and the problem is more acute outside specialist centres. A licensed mini-tablet would be easier to distribute and could reach community pharmacies, where preparation is less feasible. Whether it would be affordable is another matter, since small-volume paediatric products are not always attractive commercially, and incentives under the European regulation were designed partly to address this problem [1, 2, 32].

7. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations apply to this synthesis. It is a narrative review and does not follow a systematic protocol, so relevant studies may have been missed. Evidence on acceptability comes mostly from non-enalapril trials, and extrapolation to enalapril rests on the assumption that acceptability depends mainly on size and palatability, not on the active ingredient. Data on stability of enalapril in the solid state in tiny units, and on the effect of packaging, are sparse in the sources consulted. The age range of children studied narrows towards the youngest, and older children have been neglected, though they may prefer different presentations. All of these points restrict the weight that can be placed on any single claim [8, 18, 22, 25].

Future work should connect the strands that are currently separate. Formulation studies could report content uniformity and stability data for enalapril mini-tablets against pharmacopoeial and international stability standards [15, 25]. Acceptability studies should include children with cardiac and renal disease and use standard outcome measures, as recommended in the reviews [22, 24]. Studies of dosing devices and caregiver counting accuracy would address the practical side [21]. Economic comparison with extemporaneous liquids has not been performed. Until these gaps are filled, mini-tablets of enalapril are best viewed as a promising and plausible concept supported by indirect evidence, and not as a settled replacement for current practice [16, 18, 29].

8. CONCLUSION

The published evidence supports the view that mini-tablets are a plausible dosage form for enalapril in children. Randomised and exploratory studies in neonates, infants and preschool children show that small uncoated tablets can be swallowed and are often better accepted than syrup [16, 17, 18, 26]. The drug's known degradation pathways and the weakness of extemporaneous liquids give a practical reason to prefer a manufactured solid form [8, 25], while regulatory guidance asks developers to justify dose flexibility and

acceptability [27, 28, 33].

The evidence also has clear limits. Acceptability data come mainly from placebo products in children who were not acutely ill, and no enalapril-specific acceptability study was found. Content uniformity, moisture sensitivity, packaging and caregiver counting accuracy all need to be shown for the individual product [15, 21]. Until they are, mini-tablets of enalapril should be regarded as a well-founded proposal, and hospital pharmacists should continue to rely on documented stability data for any preparation they supply [8, 29].

9. ABBREVIATIONS

ACE-Angiotensin-converting enzyme, EMA-European Medicines Agency, WHO-World Health Organization, ICH-International Council for Harmonisation, ODMT-Orally disintegrating mini-tablet

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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