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Multi-Particulate Dosage Forms for Pediatric Use

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Abstract

In recent years, regulations on pediatric medicines have induced an increased need for research into novel child-appropriate dosage forms. Indeed, children cannot be considered as « small adults » as they present different anatomical and physiological characteristics. Whatever the route of administration, the age-appropriateness of the formulation is of major importance and has to be taken into consideration. The development of new pediatric dosage forms encounters technical complexities such as dose modification, ease of administration/swallowing, taste-masking, chemical and physical stability, preservation, considerations of a multi-phase and/or multi-use product, packing, providing/designing the measuring device. Innovations are important and the research of new ways to deliver medicines tends to improve compliance, convenience and pharmacokinetic. Recently, the World Human Organization recommended that small sized solid forms or orally disintegrating solid forms should be favored. Solid multi-particulate systems such as pellets have the advantage to cover a broad range of doses for different patients. Dose adjustment can be accurately done by means of dosing device such as a multi-particulate counting device. Developing multi-particulate dosage form with fast disintegration can be useful for children as they present both advantages of solid and liquid formulations. This led to the concept of Orally Disintegrating Tablet which disintegrates rapidly in the mouth into small particles or pellets. Their small size enables them to be well distributed along the gastrointestinal tract improving the bioavailability while reducing local drug concentration, risk of toxicity and side effects. They offer easy swallowing and dose flexibility for pediatric patients and caregivers. The promising results of our fast disintegrating pellets used in multi-particulate dosage forms indicate that they might be the base of a solid platform technology for pediatric medicines.

Keywords: Regulation; Multi-particulate dosage forms; Mini-tablets; Orally disintegrating tablets; Pediatric formulations

Introduction

In recent years, both European and United States regulations on pediatric medicines and recent World Human Organization recommendations have induced an increased need for research into novel child - appropriate dosage forms [1]. Indeed, children cannot be considered as « small adults » as they present different anatomical, physiological and psychological characteristics and these influence the therapeutic approach that is taken.

The age-appropriateness of the formulation is also to be taken into consideration, whatever the route of administration. Indeed, the pediatric population is extremely heterogeneous as regards age, weight and physiological development. An arbitrary age classification was defined in the guidelines on the clinical investigation of medicinal products in the pediatric population [2].

To strengthen the development of pediatric drug formulations, a new legislation was introduced in the United States and Europe. Specific guidelines and requirements from, in particular, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) form the regulatory framework [3]. This new regulation was necessary in order to consider the specific requirements and needs of the pediatric population. The regulation provides new obligations for the pharmaceutical industry, coupled with rewards and incentives [4]. The objectives of the regulation were to improve the health of children by (i) Increasing high quality, ethical research into medicines for children (ii) Increasing availability of authorised medicines for children (iii) Increasing information on use of medicines in children and this, without unnecessary studies in children and without delaying authorisation for adults.

The measures proposed are to assess quality, safety and efficacy of the product and these are the conditions to obtain the Market authorization.

The aim of the present paper is to describe the recent progress in the development of pediatric formulations. In a first part, we approach why there is a specific need for pediatric formulations and the challenges associated with the development of pediatric medicines, then, we describe the recent solid dosage forms suitable for children and finally, we develop an example of fast disintegrating pellets used in multi-particulate dosage forms that might be the base of a solid platform technology for pediatric medicines.

Challenges associated with the development of a pharmaceutical product for pediatric use

There is a number of challenges associated whit the development of a pharmaceutical product intended for pediatric use. These challenges are to provide dose flexibility and dose accuracy to overcome dysphagia, to meet the needs of a population with a wide range in physiological size and maturity and to ensure patient adherence for example by taste masking of the formulation.

Child-appropriateness of a dosage form is indicated by easy administration, palatability, possibility for weight-based dosing and

dose titration, convenient handling as well as the use of safe, well-established and stable excipients [1]. This facilitates formulation acceptability and medication adherence.

Oral drug delivery remains the most widely accepted and preferred route of administration and a large part of pediatric dosage forms are for an oral administration. Table 1 presents the dosage form acceptance versus age for the oral route established by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) [5].

	Preterm newborn	Term newborn 0-28 days	Infants and Toddlers 1-23 months	Preschool Children 2-5 years	School children 6-11 years	Ado 12-16 or 18 years
Solution/Drops	2	4	5	5	4	4
Suspension	2	3	4	5	4	4
Capsules	1	1	1	2	4	5
Tablets	1	1	1	3	4	4
Chewable tablets	1	1	1	3	5	5
Multi-particulate	1	2	2	4	4	5
Oro-dispersible	1	2	3	4	5	5

Table 1: Dosage form acceptance versus age for the oral route [5].

The code used in the matrix can be interpreted in the following way [5]:

For the early ages the code indicates mainly the applicability of the route and the dosage form:

1. Not applicable.
2. Applicable with problems.
3. Probably applicable, but not preferred.
4. Good applicability.
5. Best and preferred applicability.

For the higher ages more or less all dosage forms might be principally applicable, but with an increased age, the preference of the children becomes more important:

1. Not accepted.
2. Accepted under reserve.
3. Acceptable.
4. Preferred acceptability.
5. Dosage form of choice.

Age-appropriate dosage forms for children from 0 to 2 years usually constitute of concentrated solutions and suspensions in order to reduce the volume of drug required per dose. For children of 2 to 12 years old, all dosage forms are appropriated, but as regards tablets, 6 years old is generally considered as the age at which children can safely swallow a solid oral dosage form, although this varies according to the child.

In 2008, a WHO expert forum proposed a shift toward pediatric oral solids in view of stability problems and the high transportation and storage costs involved in liquid formulations [1,6]. From then, flexible oral solid dosage forms, such as orodispersible tablets and/or tablets used to prepare oral liquid preparations suitable for younger children, have become the recommended pediatric dosage forms worldwide.

To obtain flexible solid dosage forms, a solid platform technology for multi-particulate is required. Multi-particulates consist in pellets, beads, or granules that can be sprinkled on food or can be further processed to produce other solid form including tablets and dispersible preparations.

Multi-particulate dosage forms

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics.

The active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. They provide many advantages over single-unit systems because of their small size.

The subunits of multiple-unit preparations distribute readily over a large surface area in the gastrointestinal tract and these small particles (<2 mm) behave like liquids leaving the stomach within a short period of time. Their small size also enables them to be well distributed along the gastrointestinal tract that could improve the bioavailability, which potentially could result in a reduction in local drug concentration, risk of toxicity and side-effects [7]. Inter and intra-individual variations in bioavailability caused for example by food effects are reduced. Pellets can be coated to modify the drug release. Taste masking is also possible by coating the particles.

They can be used for immediate or modified release. When they are used for modified release, pellets are of two different types: One consisting of coated pellets (reservoir systems) and the other prepared by compaction of matrix and/or uncoated drug pellets.

They can be used in different pharmaceutical dosage forms such as oral suspension (ready to use, dry suspension), sachet, capsule, mini-tablets or orally disintegrating tablets 'ODTs).

Mini-tablets are defined as tablets with a diameter inferior to 4 mm. They enable flexible dosing and administration and could potentially overcome swallowing difficulties. They may also be applicable for other populations such as geriatric patients with dysphagia.

Figure 1 presents spherical mini-tablets of 3.6 mm diameter tablets made in our laboratory.

Figure 1: Spherical mini-tablets for pediatric use (3.6 mm diameter).

But miniaturization of the tablets causes difficulties during the compaction. In particular, delaminating of the tablets appeared, particularly when they are spherical (Figure 2).

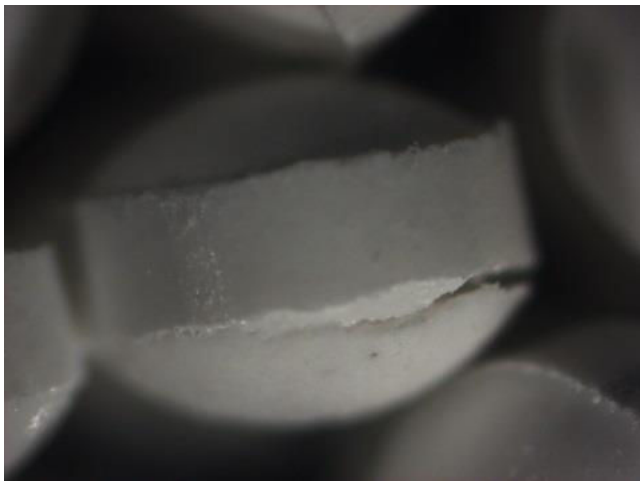

Figure 2: Delaminating on spherical mini-tablets.

After mini-tablets, a new concept was developed with orally disintegrating tablets. Indeed, oral solid dosage forms are convenient, economical and user-friendly. But sometimes, difficulties of swallowing may exist. So, a dosage forms which disintegrates rapidly in the oral cavity within a small amount of saliva might be a suitable dosage form, even for infants and toddlers. This leads to a second approach for pediatric solid dosage forms: the ODT which disintegrates in the mouth in a few seconds [7]. They present:

1. Good stability
2. Accurate dosage
3. Small packing size
4. Easy handling
5. Easy administration
6. Minimal risk of suffocation
7. No need of water

ODTs are defined in the European Pharmacopoeia as uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed [8]. Orodispersible tablets disintegrate within 3 min in the disintegration test described in the Pharmacopoeia.

FDA defined ODT as a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when they are placed upon the tongue. Tablet weight is below 500 mg and the disintegration time determined according to the USP specifications is below 30 seconds [9].

For ODTs, the challenges of formulation are:

1. Taste-masking
2. Rapid disintegration
3. Mouth feel
4. Manufacturing
5. Packaging

Discussion

Development of fast disintegrating pellets used in multi-particulate dosage forms

Multi-particulate dosage forms may offer a flexible dosing system that allows covering a broad range of doses for different age groups. Since each individual unit contains a small amount of drug, dose adjustment can be accurately done by means of dosing device e.g. multi-particulate counting devices or volume/weight measuring devices. On the other hand a fast disintegrating system is the most convenient mode of medicine administration for pediatric population and other patients with dysphagia. Such dosage form can disintegrate and/or dissolve spontaneously in the oral cavity, resulting in a solution or suspension that can be easily swallowed [10]. In this context, our study attempt to evaluate the feasibility of combining two well-established technologies i.e., extrusion/spheronization and freeze-drying in order to produce pellets that have fast disintegration and better mechanical strength as a novel dosage form for pediatric use. An instantaneous disintegration of the pellets while maintaining their mechanical strength would be interesting for pediatric orodispersible solid dosage forms. Acetaminophen was used as a model drug.

First of all, the drug was coated in a spray-drying process in order to mask the unpleasant taste of the drug. Lecithin and sodium caseinate were used as coating agents because they are considered as GRACE substances that can be used in the pediatric population [11]. Spray-drying is a well-established, inexpensive and straightforward technology which permits to mask the unpleasant taste of certain ingredients through encapsulation. During this process, appropriate encapsulating materials enable the film formation at the droplet surface as water evaporates (Figure 3). The functional properties of encapsulating agent have an important role on resultant product characteristics e.g. solubility and therefore the taste masking efficiency.

Taste assessment is approached *in vitro* by an indirect method through drug release studies. We developed a method with a syringe pump using small volumes of aqueous medium and low flow rates, to mimic the behavior in the mouth (Figure 4). Taste-masking is achieved if, within the frame of 1-2 min, drug substance is either not released or

the released amount is below the human threshold for identifying its bad taste. This method gave results comparable to those obtained with the Astree electronic tongue analysis (Alpha Mos, Toulouse, France).

Pellets containing the drug taste-masked (25, 50 or 75% w/w) and microcrystalline cellulose were manufactured by extrusion-spheronization. Drying was realized by freeze-drying. Figure 5 presents the pellet manufacturing process.

The process developed was successful in preparing pellets with acceptable quality e.g. high drug loading, good sphericity, low friability (Figure 6).

Importantly, freeze-dried pellets were shown to exhibit an instantaneous disintegration within 5 seconds as well as a rapid drug release (Figure 7).

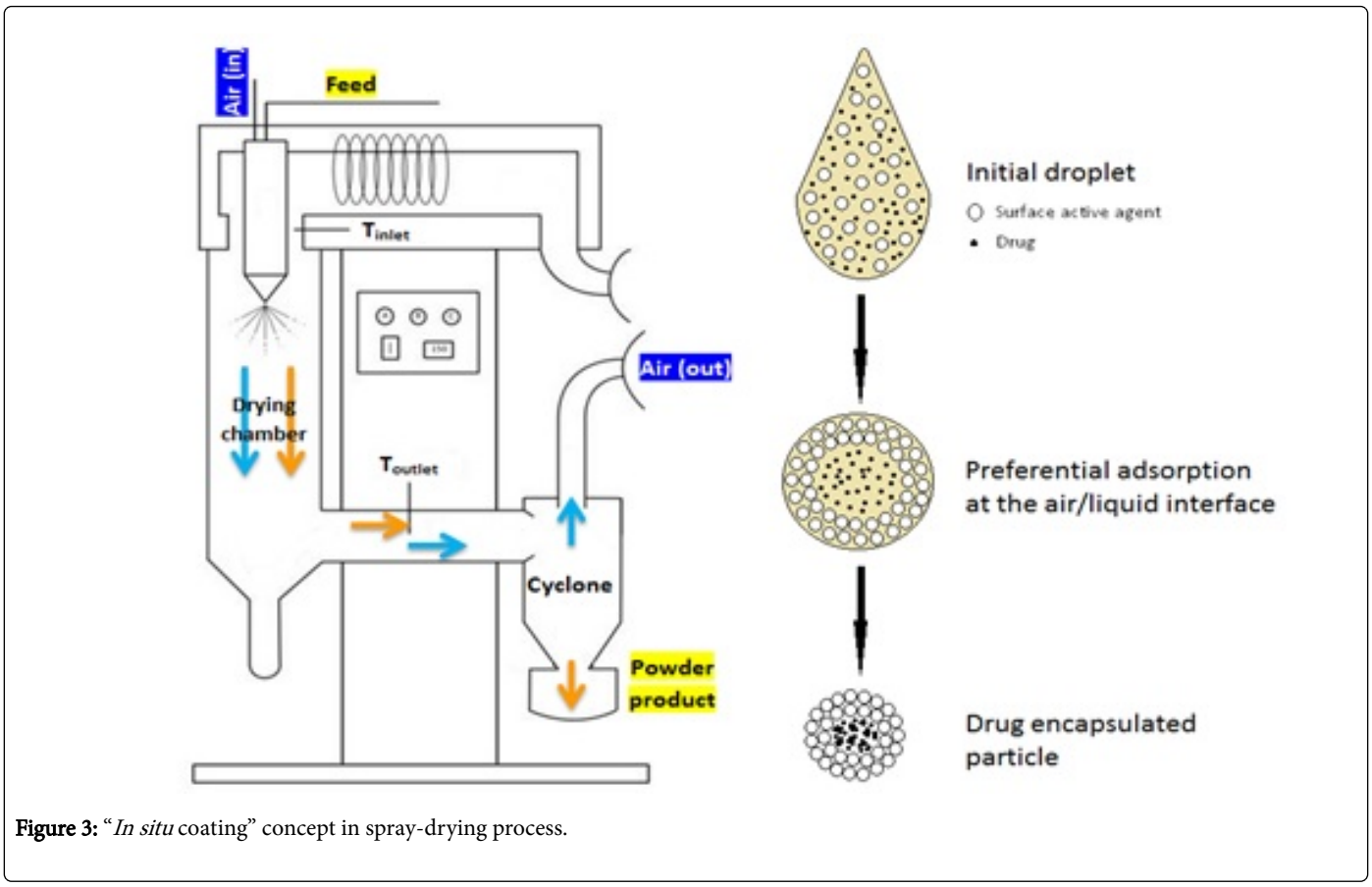

Figure 3: "*In situ* coating" concept in spray-drying process.

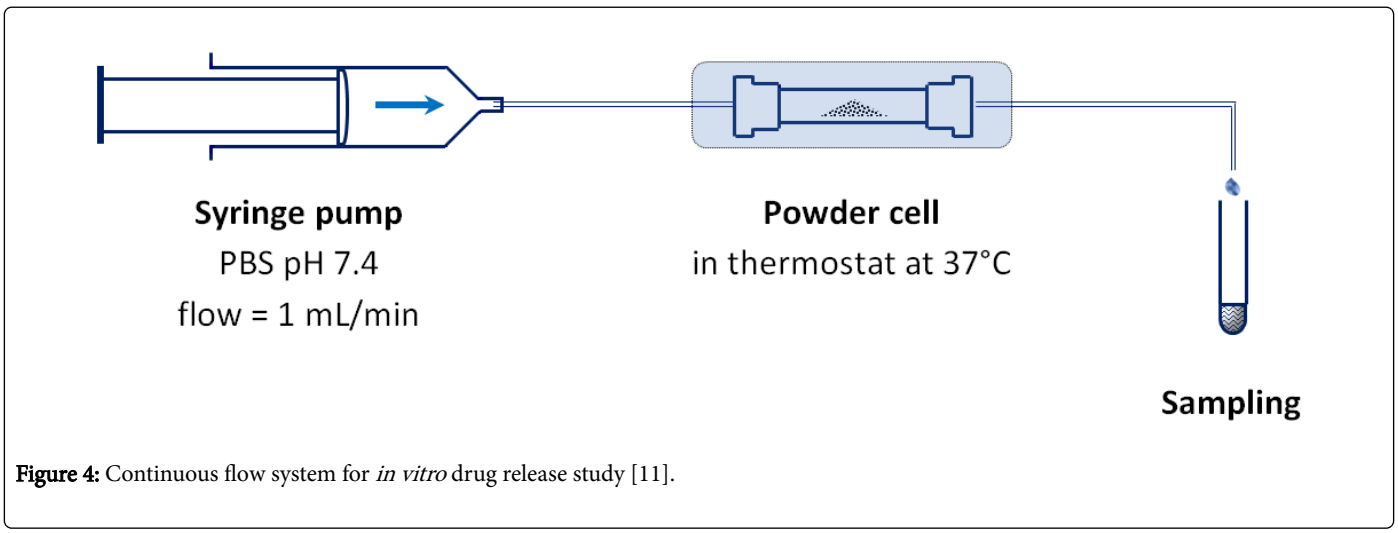

Figure 4: Continuous flow system for *in vitro* drug release study [11].

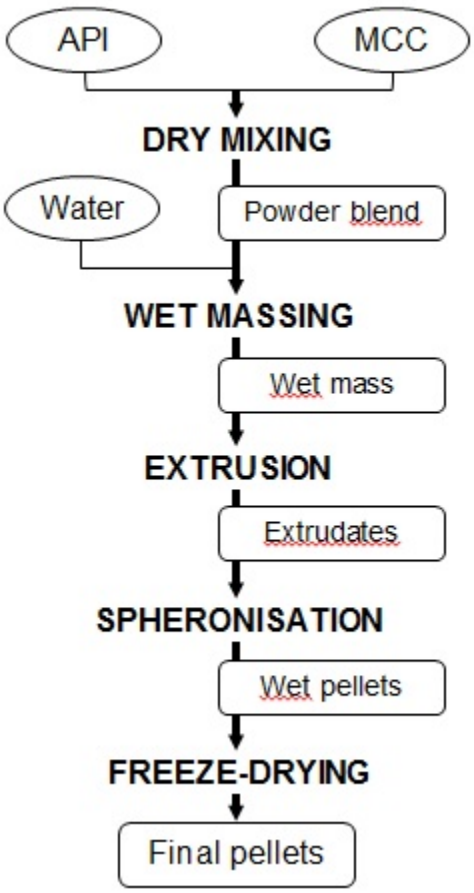

Figure 5: Pellet manufacturing process [10].

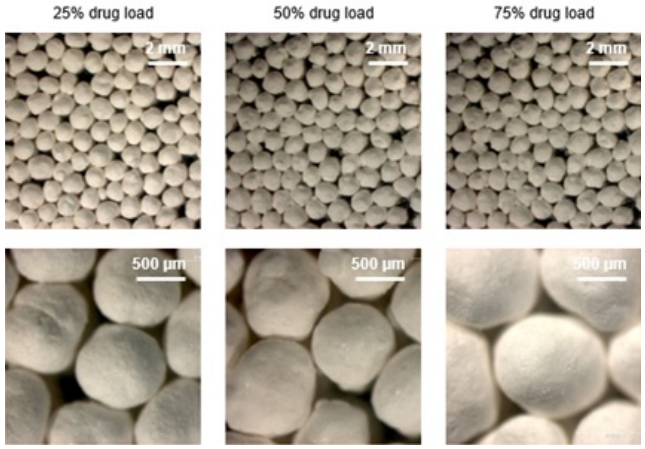

Figure 6: Optical micrographs of freeze-dried drug loaded pellets [10].

The rapid drug release that is determined by the dissolution test: More than 90% of drug is released within 15 min for all batches. The incorporation of acetaminophen did not really delay the disintegration time of the pellets, even with a percentage of 75%. This is promising for the development of very fast disintegrating orodispersible solid dosage forms.

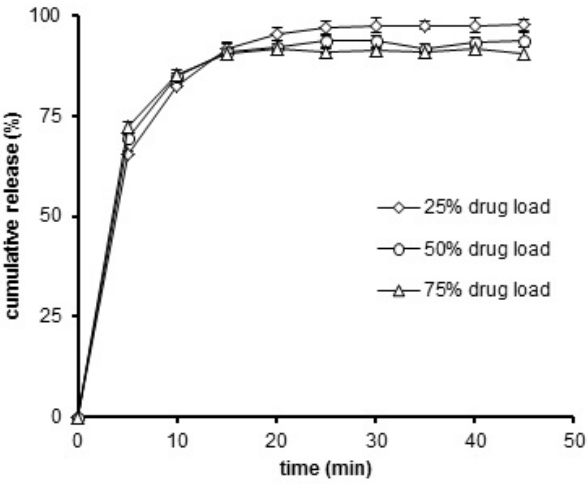

Figure 7: Dissolution profiles of freeze-dried drug-loaded pellets [10].

Then, orally disintegrating tablets (ODTs) were obtained by mixing the previous pellets with neutral granules prepared by wet granulation. Composition of the tablets is presented in Table 2.

	Ingredients	ODTs (% w/w)
Pellets	Acetaminophen pellets	40
Neutral granules	Mannitol	45.44
	MCC	8.94
	Crospovidone	2.98
	Sucrose	1.79
Lubricant	Magnesium Stearate	0.85

Table 2: Composition of the orally disintegrating tablets.

The formulation was successfully compressed into ODT meeting the European Pharmacopoeia specifications. The physicochemical properties of the ODTs are shown in Table 3. The ODTs show low friability value (less than 1%) and fast disintegration time (less than 60 s). Figure 8 presents stereoscopic images of the ODTs and of the pellets after compression.

During compression, pellets are submitted to deformation but are not crushed. They keep their shape. After disintegration of the ODTs, the pellets are distributed in the gastrointestinal tract and can release the active drug. By formulating the pellets with suitable polymer, they could constitute an approach to obtain extended release system in pediatric formulations.

Weight (mg) ± SD	Thickness (mm) + SD	Hardness (N) + SD	Disintegration time (s) + SD	Friability (%)	Porosity (%) + SD	Drug content (%) + SD	Mass variation (% CV)
59.3 ± 2.9	2.61 ± 0.03	17.1 ± 4.9	30 ± 2	0.76	32.2 ± 2.4	97.5 ± 11.3	4.4

Table 3: Physical properties of the ODTs.

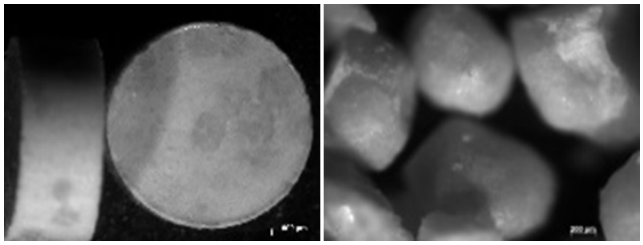

Figure 8: Stereoscopic images of the ODTs and of the pellets after compression.

Conclusion

Age-appropriate formulations of medicines for children are not always available. With orally disintegrating mini-tablets (ODMTs), a novel solid oral dosage form was developed, fulfilling all current demands for child appropriate dosage forms such as easy administration, flexible dose titration and safe excipients. ODMTs combine the advantages of liquids, like ease of application and individual dose adaption, with the advantages of solids such as good stability and low transport and storage costs. Multi-particulate dosage forms have several therapeutic and technological advantages over single-unit dosage forms, they can distribute evenly in the gastrointestinal tract, resulting in fewer adverse effects. Further research is required to develop more pediatric formulations.

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