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DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE PELLETS IN ORODISPERSIBLE TABLETS FOR PEDIATRIC USE

DEVELOPPEMENT ET EVALUATION DES MINIGRANULES À LIBERATION CONTRÔLÉE DANS LES COMPRIMÉS ORODISPERSIBLES A USAGE PEDIATRIQUE

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A mis padres
Quienes a pesar de la distancia
están siempre conmigo
y me animan a seguir adelante.

Si la vida da un cambio de rumbo,
conocerás otros lugares que también
pueden ser maravillosos.
(Playa y montaña, Emilio Aragón)

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LIST OF ABBREVIATIONS

°C	Celsius centigrade
°C/min	Celsius centigrade/minute
%	Percentage
ε	Porosity
µm	Micrometer
ADI	Acceptable daily intake
APAP	Acetaminophen
API	Active Principle Ingredient
BPCA	Best Pharmaceutical for Children Act
CHMP	Committee for Medicinal Products for Human Use
CI	Compressibility index
cm	Centimeter
DSC	Differential Scanning Calorimetry
EC	Ethylcellulose
EMA or EMEA	European Medicines Agency
Enpr-EMA	European Network of Pediatric Research at the European Medicines Agency
Eu	Eudragit®
EU	European Union
EuPFI	European Paediatric Formulation Initiative
Eu. Phar.	European Pharmacopeia
f_2	Similarity factor
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
g	Gram
GI	Gastrointestinal
GRAS	Generally Recognized as Safe
h	Hour
HR	Hausner's ratio
ICH	International Conference of Harmonization
IR	Immediate release

kg	Kilogram
kN	Kilonewton
l	Liter
Lac	Lactose
M	Molar
MCC	Microcrystalline cellulose
MHLW	Ministry of Health, Labour and Welfare
mg/l	Milligram/liter
MgSt	Magnesium stearate
ml	Milliliter
min	Minute
mm	Millimeter
mm/s	Millimeter/second
MPa	Megapascal
MUPS	Multiple-Unit Particulate System
MUP-ODTs	Multiple-Unit Orodispersible Tablets
N	Newton
NICHD	National Institute of Child Health and Human Development
nm	Nanometer
ODF	Orodispersible films
ODG	Orodispersible granules
ODP	Orodispersible pellets
ODT	Orodispersible tablets
ORL	Oral lyophilisates
OTC	Over the counter
PCO	Paediatric Committee
PeRC	Pediatric Review Committee
Ph. Eur	European Pharmacopoeia
PIP	Pediatric Investigation Plan
PmRN	Paediatric medicines Regulators Network
PREA	Pediatric Research Equity Act
PUMA	Pediatric Use Marketing Authorization
rpm	Revolutions per minute

s	Second
SD	Standard Deviation
SEM	Scanning Electron Microscopy
SPC	Supplementary protection certificate
STEP	Safety and Toxicity of Excipients for Pediatrics
σ	Tensile strength
TD	Tapped density
TEC	Triethyl citrate
TEDDY	Task-force in Europe for Drug Development for the Young
Tg	Glass transition temperature
US	United States
USPFI	Pediatric Formulation Initiative
USP	United States Pharmacopeia
UK	United Kingdom
Uv	Ultraviolet
V_o	Apparent volume
WHO	World Health Organization
WR	Written Report
w/v	Weight/volume
w/w	Weight/weight
XRPD	X-ray diffraction

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GENERAL INTRODUCTION

Research context

In the last decade, medical agencies have promoted a pediatric regulatory focusing on the development and availability of appropriate formulations suitable for age, size, physiological condition and treatment requirements for the pediatric population.

One of the greatest challenges in pediatric formulations has been the optimization of oral drug delivery route over other routes since it is convenient, economical, and user-friendly, however, swallowing ability is critical for these formulations.

In general, for long-term treatment, oral formulations are preferred in children, whereas parenteral administration still being the first option for neonates and emergency cases. The use of sustained release formulations can be an option to reduce the dose frequency and also can be practical for those patients who need to take their medication while they are at school or during the night.

In the matter of oral sustained release, formulations are designed to deliver the API through the gastrointestinal tract in a slow rate reducing the dose frequency compared to conventional formulations; nonetheless, not all the APIs are candidates to be formulated as sustained-release products because physiological conditions in children differ from those of adults. Factors such as solubility of the API in gastric and intestinal pH, emptying rate, intestinal motility, intestinal permeability and plasma elimination half-time can impact the pharmacokinetic parameters of the drug; therefore they have to be taken in account at the moment to develop a formulation.

Sustained release products are delivered in different dosage forms like multiparticulate systems which can be contained in sachets, capsules or as different types of tablets (e.g. coated, matrix or fast disintegration tablets). In the case of tablets and multiparticulate systems, it is necessary to present clear information on the label with specific information about their safety and efficacy measure such as those regarding that these formulations must not be broken or chewed or mixed with food or beverage in order to protect and do not compromise the coating and the efficacy and safety of the product.

Orodispersible tablets (ODT) hold a great promise for children as they are easy to swallow, do not require additional water and, present a uniform unit dose strength. Therefore, there are some challenges when an ODT is developed such as, taste-masking, rapid disintegration, mouth feel, manufacturing, tablet compression, and packaging.
Despite ODT formulations have a great success; there are currently few formulations that can deliver an active principle ingredient (API) in a sustained manner.

Multiparticulate drug delivery systems (MUPS), such as pellets, have several therapeutic and technological advantages over single-unit dosage forms; as they can distribute evenly in the gastrointestinal tract, control the drug release resulting in fewer adverse effects and also improve the palatability.

The potential to compress controlled release matrix-type pellets into tablets that rapidly disintegrate into small units could be a suitable dosage form for pediatric use owing to their facility of administration and flexibility of dosing (divided and reduced-size solid form), their reduced number of doses administered, leading to a better patient compliance and a reduced risk of overdose.

Objectives

The present study aimed to develop a Multiple-Unit Pellet Orodispersible Tablet (MUP-ODT) which allows the controlled release of acetaminophen (APAP), used as a model drug, contained in the pellets in an orodispersible tablets.

This work presents two lines of research: (i) the development of an orodispersible tablet (ODT) that uses safe excipients for children (GRAS excipients) and meets the Pharmacopoeial specifications and, (ii) the development of multiparticulate drug delivery systems in the form of pellets obtained by the extrusion-spheronization technique that are able to control the release of acetaminophen (APAP) and mask its taste for better acceptability.

Presentation of the work

The present work is composed of four chapters:

- The first chapter provides an overview of the legislative aspects, pharmacokinetic implications of the oral route of administration, dosages forms, drug delivery devices used and, particularities of the pediatric clinical assays involved in the pediatric drug development.

- The second chapter describes the materials and methodology followed on this research work.

- The third chapter corresponds to the results and discussions of this work. It is divided in four subsections to achieve the two main objectives.
  - The first part of this study examined the feasibility to compress uncoated MCC pellets with different orodispersible formulations to assess the influence of the percentage of pellets, type of disintegrants and compression force.
  - The second part determined the physical properties of APAP pellets produced by the extrusion-spheronization technique and containing different types of excipients and different drug load percentages to produce an immediate release matrix system. Then, the mechanical properties and dissolution of MUP-ODT were evaluated.
  - The third part was dedicated to the production of MUP-ODT which allowing for controlled-release of APAP using different percentages of Eudragit® to create the matrix system without significant changes in the release profile after compression.
  - The fourth part carried out a design of experiments to determinate the optimal parameters to produce MUP-ODTs.

- Finally, the fourth chapter provides a general conclusion and summarizes the aims achieved in this research work.

CHAPTER I

INTRODUCTION

1. Regulatory aspects of pediatric medicines

The pediatric population comprises about one-third of the world population (1); however, from the economical perspective, the pediatric market is unprofitable to pharmaceutical companies, because children represent a small proportion of the sick population (2). Therefore, for many years and up to date, the number of medical products labelled for pediatric use is limited. Hence, pediatricians have no alternative to prescribe off-label or unlicensed medicines to their patients. In consequence, the lack of information on dosage, potential toxicity, safety and efficacy in children increases the risk to develop adverse or undesired effects and to do not achieve or overpass the therapeutic drug concentrations (3–5). As a result, several initiatives around the world promote the development of pediatric medicines focusing on the suitability of age, size, physiological condition and treatment requirements for this population.

1.1 U.S. perspective

In the United States the first legislative initiative was put in effect in 1994 when the "Pediatric Labeling Rule" allowed pharmaceutical companies to review existing data in literature and determined whether they were sufficient to justify their pediatric use, but clinical trials were not required (6). Since, this approach was voluntary and it had a few impact, the FDA introduced the Pediatric Rule in 1997 and concluded in 1998.

At the same time in 1997, the Food and Drug Administration Modernization Act (FDAMA) published a list of drugs which included additional information that could be beneficial for pediatric use and also provided a financial incentive, exclusivity for six months, if the pharmaceutical companies conducted clinical trials to expand the benefit in pediatric use through a Written Request (7,8). This program expired in 2002 and was reauthorized the same year by the Best Pharmaceuticals for Children Act (BPCA) which renewed the exclusivity incentives and also expanded the provision to off-patent drugs involving government contracts for pediatric studies (9). Additionally in 2003, this regulatory framework was complemented by the Pediatric Research Equity Act (PREA) which required mandatory pediatric clinical trials, assessment for all new drug applications and biological license applications except orphan drugs and also addressed development of an age-appropriate formulation (10).

Both legislations the PREA and the BPCA were reauthorized from 2007 to October 2012. Additionally, the FDAAA introduced the Pediatric Review Committee (PeRC) which provides the preparation of consultation on and general review in pediatric plans, assessments, and pediatric studies to ensure quality and consistency (11). Also the PeRC is in charge to review all WRs, deferrals and waivers, and submitted studies in response to a WR (12).

As a response of the mandatory of the BPCA of 2002 and 2007, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), created in 2005 the Pediatric Formulation Initiative (PFI), this project aims: (i) to identify the scientific issues needed to develop appropriate pediatric medicines, (ii) to identify both international and national regulatory issues which affects the development and availability of pediatric medicines, (iii) to seek solutions to facilitate the development and approval for pediatric medications, and (iv) to promote interactive discussions, data exchange forums between academia, industry, sponsors and regulatory agencies (13).

1.2 E.U perspective

At the same time in 1997, the European Commission exposed to the European Medicines Agency (EMA) the necessity to strengthen the legislation to obtain pediatric information for medicines used in children and introduced an incentive system. And one year later, the Commission supported the discussion on the conduct of clinical trials in children under the International Conference of Harmonisation (ICH) principles (14,15).

By 2000, the E11 ICH guideline "Clinical investigation of medicinal products in the paediatric population" was approved and afterwards became in the European guideline in 2001 (16). At the end of this year, the European Health Council inquired the Commission a specific action to solve the problem of unauthorized medicinal products in the pediatric population and, in 2002 the paper "Better medicines for children- proposed regulatory actions on peaediatric medicinal products" was published by the Commission (17).

In 2005, the European Network of Excellence specialized in pediatric drug development was established, and the Task-force in Europe for Drug Development for the Young

(TEDDY), which mission is to expand and to promote research on the safe and effective use of medicines for children (18,19).

Finally in 2007, the Pediatric Regulation (European Commission No. 1901/2006) came into force. In general, the objective of the EU regulation is (i) to facilitate the development and access of medicines to the pediatric population, (ii) to ensure the quality and ethical research, evaluation and authorization of pediatric medicines available on the market, and (iii) to increase the availability information about the medicines used in children (6,20).

In order to achieve these objectives, the EU regulation conducts the following measures:

a) The Pediatric Committee (PCO)

The Committee, the counterpart to the PeRC in the US, covers all relevant areas in pharmaceutical development, clinical research, pharmacology, pharmacovigilance, ethics and public health. The tasks of the PCO involve (i) the evaluation and the approval of the PIP and to review exemption application and to report deferral related to PIP, (ii) to provide evidence about quality, safety and efficacy of medicines for pediatric use, (iii) to give recommendations about issues related to pediatric medicines (21,22)

b) The Pediatric Investigation Plan (PIP)

A PIP is a mandatory research and development program required for pharmaceutical companies when they apply for: (i) an application for a Pediatric Use Marketing Authorization (PUMA) for any new indications, (ii) new pharmaceutical forms, and (iii) new routes of administration (23). This plan must ensure that appropriate pediatric studies are carried out in order to obtain quality, safety and efficacy data to support the authorization of a medicine to be used in children (24,25). All PIP proposals are submitted to the European Medicine Agency and transmitted to the Pediatric Committee which evaluates the plan for acceptation or rejection.

It is expected a PIP includes: (23)

- A description of the studies and measures made to adjust the dosage formulation to demonstrate its safety, efficacy and acceptability in children
- All age groups defined by the ICH guideline E11 must be involved
- Define the timing of studies in children compared to adults

In some cases the PCO offers waivers to avoid unnecessary medical trials in children when the medicine is not effective or unsafe for the pediatric population (specially indicated for adults as menopause, Alzheimer's disease, etc.) (20).

Also a deferral can be granted if the authorized medicine demonstrates if its efficacy is well established on the basis of 10 years of medical use in the European Union in adults (23).

c) Rewards and incentives

If the data submitted in the PIP fulfill with all the regulatory requirements, the EMA provides rewards or incentives to the pharmaceutical laboratory which develops medicines for children (16,26). There are different awards depending on the group of drug involved (20):

- For new drugs and for licensed and covered by a patent or a supplementary protection certificate (SPC) medicines, an extension of six months on the SPC is granted.
- For medicines which are no longer covered by a patent, they may receive the benefit from a new exclusivity period of ten years. Also it is possible to use the same trademark for pediatric medicines approved for adults.
- For orphan medicines: two years more of market exclusivity is provided in addition of then ten years period if the required data completely fulfill the for pediatric use.

d) The European Network in Pediatric Research (EnprEMA)

In order to promote a high quality ethical research on pediatric medicines, the European Regulation created the European Network of pediatric clinical investigation which is in charge to coordinate the pediatric studies and, to bring both scientific and administrative skills in order to avoid unnecessary studies in the pediatric population (26,27).

Similar initiative as the US, the European Pediatric Formulation Initiative (EuPFI) – Formulating Better Medicines for children was stablished in London, UK in 2007. This consortium is formed by academia, hospital pharmacies, and pharmaceutical industry members having the European Medicine Agency (EMA) as an observer.

The EuPFI focuses on (i) identify the issues and challenges associated with development of pediatric medicines, (ii) promote early pharmaceutical considerations for development of pediatric formulations and (iii) improve the availability of the information of pediatric

medicines by five work-streams on extemporaneous preparations, taste-masking and testing, administration devices, age-appropriate formulations and excipients with a major database project, known as STEP (Safety and Toxicity of Excipients for Pediatrics), designed to provide information for the risk assessment of use of excipients in children (28).

Figure I-1 summarizes the important facts occurred in the pediatric regulation between the US and EU regulations in the last 20 years.

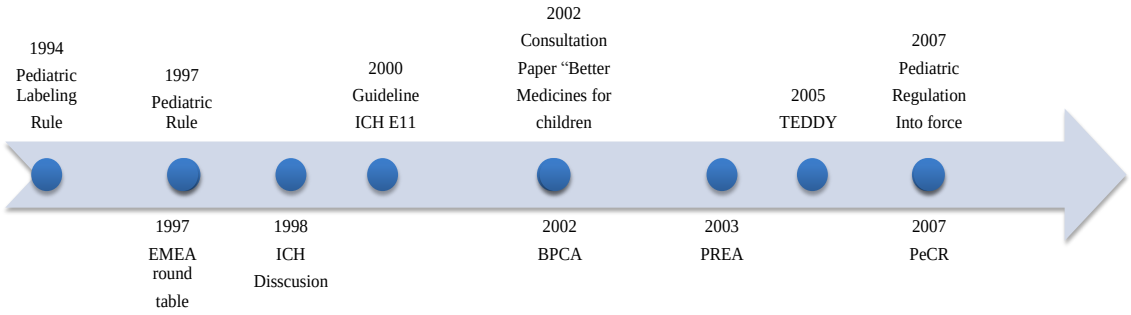

Figure I-1. Line time of pediatric regulations in US (top) and EU (below) actions.

1.3 The International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use (ICH)

In 2000, the first pediatric regulatory action took place in the context of the ICH between the EU, the US and Japan with the adoption of the ICH E11 guideline (29).

The aims of this document is to encourage and facilitate international timely drug development and to provide an outline of critical issues in pediatric drug development and approaches to a safe, efficient and ethical study of medicines in pediatrics (15). Despite this guideline has become an important instrument in the pediatric clinical design, it is not a mandatory requirement and it has not effect on pediatric submissions in Europe nor worldwide. Additionally, it is necessary an update of this guideline due to advances in the knowledge and understanding of pediatric drug development.

1.4 Other initiatives

Other countries have started to engage in regulatory initiatives development for example in Canada, a six month extension for data protection is granted to pharmaceutical companies which provide evidence to support a pediatric label indication (30).
In Japan, the Ministry of Health, Labour and Welfare (MHLW) provides to pharmaceutical companies as reward for develop pediatric medicines by not reducing the prices of those medicines, this program started in 2000 with the introduction of the Extension of Drug Re-examination and in 2006 was extended with the price premium for pediatric use (31,32).
Then in 2010, the Evaluation Committee on Unlicensed and Off-label Drugs introduced the premium for those pharmaceutical companies interested to promote pediatric drug development by expanding drug indications to pediatric use and by promoting the development of new drugs and eliminate off-label (31).

On the other hand, in 2008 the World Health Organization (WHO) launched the international program "Making Medicines Child Size" based on the list of essential medicines for children, which encourage pharmaceutical companies to develop accessible and appropriate quality pediatric formulations specially for emerging countries (32–34).

2. Oral drug development for pediatric population

2.1 Pediatric population

The childhood involves since the human been births until he reaches the adulthood, during this period the child presents continuous physical, metabolic and psychological changes. According to the ICH, the pediatric population is divided in groups (Table I-1) based on their physiological particularities (15).

As children should not been considered as "small adults", it is necessary to develop appropriate dosage forms suitable for age, size, physiological condition and, treatment requirement for each group as medical agencies suggest. Moreover, safe excipients, palatable formulations, sociocultural acceptability and clear product information are specifications demanded for pediatric medicinal products (35).

Table I-1. Groups of the pediatric population divided by age categories (36).

Group	Age	Average weight (kg)
Preterm newborns infants	< 37 weeks gestation	< 3.4
Term newborn infants	0-27 days	3.4
Infants and toddlers	1-23 months	3.4-12.4
Children	2-11 years	12.4-39
Adolescents	12- 16 or 18 years (dependent on the country)	39-72.1 (male)/60.3 (female)

2.2 Pharmacokinetic aspects

In general, the oral route of administration still being preferred over other routes since it is convenient, economical and user friendly (37,38). As the child is a continuous maturing organism, it is important to consider the gastrointestinal (GI) physiology differs to adults. In consequence, the drug administration requires keeping in mind the significant variability and constant changes in terms of pharmacokinetics experienced by the organism in this period.

2.2.1 Absorption

Each age group presents differences on gastric and intestinal pH, mobility, blood flow, tissue perfusion, surface area, pancreatic function, intestinal flora, transit time and, maturation of transporters and receptors (39). These factors are involved in drug release, solubility and absorption (40), thus, they need to be considered at the time a pediatric medicine is developed.

In the oral cavity, pediatric saliva presents a neutral pH (41,42). Most of the oral pediatric formulations are designed to be retained on the mouth; however it is important to consider the bioavailability of certain drugs (43): such as cases as poorly soluble weakly basic drugs, where they precipitate in neutral pH-conditions (44) or cases where the integrity of sensitive enteric coatings of tablets or sprinkles can be compromised if they keep in the mouth longer than the time expected and not swallowed immediately as there is indicated (45).

At birth, neonates present a neutral stomach pH value (6-8) due the presence of amniotic liquid. After a few hours, acid secretion occurs; this value decreases (1.5-3). By the 10^{th} day of being born, the pH value increases to 6-7 and remains standing until the 30^{th} day of life. The following months the acid secretion gradually increases until reaches the adult value at the age of 2 to 3 years (45,46).

In the case of the intestine, it presents an alkaline environment due the sodium bicarbonate which is secreted by the pancreas into the duodenum in order to neutralize the gastric acid from the stomach. The scarce data reports similar values of the intestinal pH between children and adults (pH 6-7.5) (46,47).
The colon, on the other hand, reports lower values than the small intestine (pH 6-6.5) due to the colonic bacteria which ferment unabsorbed carbohydrates into short-chain fatty acids. A study of neonates and infants reported that the type of milk (breast milk or formula milk) by which they were fed, affects the fecal pH due to difference in colonic bacteria (48,49).

Differences in pH at each age group can compromise some of the drug delivery oral dosage forms, such as drug precipitation out of suspension, pH sensitive coatings of tablets or multiparticulate drug delivery systems which can be released before or after anticipated time (40,45,50). Different pHs of the GI tract in different age groups in the fasted state are summarized on Table I-2.

Table I-2. pH of the gastrointestinal tract of different age groups in the fasted state (46,47).

Organ	Neonate (0-27 days)	Infants (1-23 months)	Child (2-11 years)	Adolescent (12-18 years)	Adult (>18 years)
Mouth	7	--	7.1	7.4	6-7.4
Esophagus	--	>5	>5	>5	5-6
Stomach	6-8	1.4	1.5-3	1.5	1-2.5
Duodenum	--	--	6.4	6.3-6.4	5-6.5
Small intestine	--	--	6.4-7.4	6.4-7.4	6-7.5
Cecum	--	--	5.9	5.9	6-6.5
Colon	--	--	5.9-6.5	5.9-6.5	7-7.5
Rectum/fecal matter	4.4-7.2	5.9-10.9	6.5-12.1	6.5	6.7-7.8

The gastric emptying in neonates follows a linear and slow behavior, within 6 to 8 months of age it reaches adults values: a rapid first state (10-20 min) followed by slower phase (39). Food has a significant impact on gastric emptying for instance, fat is absorbed in the small intestine, which decreases the gastric emptying rate, in consequence delays the onset of certain drugs. Also liquid food increases the rate of gastric emptying than solid food (51).

In infants the transit time for the small and large intestine ranges from 8 to 96 h compared to adults which ranges from 2 to 48 h. The small intestine is the major site where the drug absorption takes place and it is proportionally greater than in adults (46,52).
Intestinal mobility is irregular in neonates and infants, therefore the GI transit time should be considered as a controlling factor for drug absorption of oral dosage forms (45,46,53). The Table I-3 summarizes the GI tract transit time in pediatric populations.

Table I-3. GI tract transit time in pediatric populations (45–47).

Organ	Neonate (0-27 days)	Infants (1-23 months)	Child (2-11 years)	Adolescent (12-18 years)	Adult (>18 years)
Saliva secretion (ml/min)	0.03-0.04	0.47	0.25- 0.66	1.2	0.3-1.2
Esophagus (s)	3-4	4-8	5-8	5-8	10-14
Stomach (min)	54-82	12-70	12-70	12-138	5-120
Small intestine (h)	4	4	3-7.5	3-7.5	3-4
Colon (h)	28-96	32	17-34	17-34	2-48

2.2.2 Distribution

Drug distribution is closely related with the physicochemical properties of active principle, pH of physiological fluids, volume of body compartments, blood flow in each organ and tissue, extracellular water proportion, adipose tissue, membrane permeability and protein binding. During the maturation process, these factors suffer major changes (52,54).
Preterm neonates present high membrane permeability and it decreases as a function of age of the child. At birth the blood-brain barrier is functionally immature, in consequence, drug

readily diffuse through the cerebrospinal fluid and central nervous system with resultant toxicity (15,55).

In neonates and infants protein binding is reduced: total protein concentrations are 59 g/l comparing to adults 72 g/l. Moreover, these proteins present lower binding. At the moment of birth, albumin concentrations in plasma are 35-37 g/l and achieve normal adult values, 45-48 g/l, during the first year of life (56).

Lower body fat values are found in preterm neonates (3-12%) and neonates (12%) comparing to adults (18%). Thus, the volume of distribution of lipophilic drugs has to be contemplated due to its difference between children and adults. Higher liver blood flow rate is reported in neonates but, after 6 months of life it tends to decrease and reaches adult values (57).
Higher total body water presents neonates, where it contributes about 75% of total body weight (85% in preterm neonate) and decreases with age to around the value of adults (60%) by one year of life. In neonates and children, the percentage of extracellular water is higher than in adults, extracellular water represents about 45% of the total body weight of the newborn and it decreases with age to 25 % at one year and 15-20% at puberty. Intracellular water calculated by difference, represents 33% of the body weight in the newborn and, it increases during the first year and stabilized at 40%, therefore it is important to considerer that these changes produces higher volume of distribution of soluble water drugs in pediatric patients than in adults (56,58).

2.2.3 Metabolism

Bioavailability of drugs (e.g. midazolam, zidovudine, caffeine, theophylline, valproic acid, paracetamol, chloramphenicol, cimetidine and salicylamide) administered by the oral route can be affected by first pass metabolic inactivation in the intestine and the liver (51,59).

The intestinal flora plays an important role in the metabolism of the drug and in the course of maturation tending to change. At birth, neonate gut colonization is influenced by feeding and environmental factors (53) and it reaches adult values from 3 years old (43).

Bile acids and neutral sterols are metabolized through the lumen and their activity increases within age. The cholesterol metabolism carries out by bacterial biohydrogenation and followed by reduction manages similar adult values until the age of 4 years.

The bioavailability of many of drugs decreases due the metabolism in the gut lumen. However, the ontogeny of some enzymes can affect the fraction of drug absorbed in pediatric patients, which is the case of the aryl hydrocarbon hydroxylate which activity increases with age. Enzymes present in the small intestine such as CYP3A4, CYP3A5, glutathione S-transferase alpha-1 (GSTA1-1) and sulfotransferase (SULT) have showed higher activity in children compared to adults (43,60).

In general, children present a higher hepatic blood flood and liver size comparing with adults, therefore metabolic capacity can produce lower or higher drug plasma levels in both phase I enzymes and/or phase II enzymes (39,59).
Neonates present reduced levels of phase I enzymes during the first 2 or 3 week after birth, due a lower activity on the cytochrome P450 (CYP) and the NADPH-cytochrome c reductase, the presence of endogenous inhibitors from maternal origin, a reduced hepatic blood flow and relative hypoxemia. However the activity increases and the adult values are reached within 1 to 5 years depending on the isoform (57).
Phase II reactions are unevenly reduced at birth. Glycylconjugation and sulfoconjugation are mature at birth, while glucuronidation is reduced significantly; the values found in adults are only reached at the age of 24-30 months. Acetylation is functional during growth and at different stages according to the drug (52).

2.2.4 Elimination

Drugs and their metabolites are primarily eliminated by urine, bile, sweat, tears, saliva and breath. Drug urinary excretion by kidneys involves three mechanisms: glomerular filtration, tubular secretion and tubular reabsorption.

Renal blood flow increases conforming renal tube maturation (57). Glomerular function maturation reaches faster than tubular function, and it persists until the sixth month. The development of renal function depends on gestational age and sequential hemodynamic changes occurring during the first days of life. Complete maturation of glomerular and

tubular function is completed at the age of 6-8 months. In preterm neonates and neonates, glomerular filtration is reduced (15–40 ml/min/1.73 m^2) and achieve adult values (100 ml/min/1.73 m^2) around three months after birth (52,56).

Tubular secretion and tubular reabsorption get mature slower than glomerular filtration; they acquire adult levels at the age of two years. Therefore clinical implications have to be consider for drugs which glomerular filtration or tubular reabsorption are dependent of their elimination pathway in order to avoid an overdose or underdose (51,61).
Urinary pH in children presents lower values than adults, hence it may influence the reabsorption of weak organic acids and bases (39).

2.3 Excipients

Basically, medications contain a major proportion of excipients than the principle active ingredient. The functions of these inactive ingredients are mainly to improve stability, mask the bitter taste of the drug, control the drug release, improve the patient acceptability and/or to enhance the production (62). Nevertheless, particular adverse effects have been reported in some subpopulations of the pediatric broad, especially in neonates, infants and children as they present variations in their pharmacokinetics and pharmacodynamics than adults (63,64).

In the matter of formulation approval, guidelines stablish the use of the minimal amount of excipients; which should be declared in amount and justified its function, for each one used in the formulation, and also respect its acceptable daily intake (ADI) in order to avoid undesired effects (64–66). Both regulatory agencies EMA and FDA have published available guidelines related to the use and declaration of excipients for pediatric formulations available for consultation. Table I-4 enlists the main excipients with identified risks in children which should be considered before to develop a pediatric formulation (67,68). On the other hand, the European and US Pediatrics Initiatives work in collaboration to create the Safety and Toxicity of Excipients for Pediatrics (STEP) database with the purpose to provide literature evidence and evaluate the safety and toxicity information of excipients for children (35,69,70).

Table I-4. Excipients and associated adverse effects in pediatric.

Function	Excipient	Formulation	Acceptable daily intake	Associated adverse reaction	Reference
Solvent	Ethanol	Iron supplementations OTC cough syrups	0.5% < 6 years and 5% > 6-12 years	Chronic and acute toxicities in premature newborns	(64,67)
	Propylene glycol	Liquid Formulations	200mg/kg	Cardiovascular, hepatic, respiratory adverse events Toxic effects on CNS in newborns and infants	(64,67,71)
	Peanut oil	Intramuscular injections, Topical formulations	--	In some cases episodes of hypersensivity	(64)
Antioxidant/ Bacterial preservative	Benzyl alcohol	Nebulization solutions	5mg/kg	Metabolic acidosis, seizures and gasping	(63,67,71)
	Benzalkonium chloride	Nebulizer solutions, Nasal saline, nasal corticosteroids and nasal decongestant solutions	90mg/kg	Paradoxical bronchospasm in asthmatic children	(67)
	Sulfites	Inhaled medications for asthmatic patients	3mg/kg	Wheezing, dyspnea and chest tightness in asthmatic children	(63,64)
Filler/ Diluent	Lactose	Feed formula Tablets, capsules, lyophilized powders, liquid formulations, inhalations products	3g/kg	Lactose intolerant present gastrointestinal symptoms	(64,67)
Sweetener	Sorbitol	Liquid formulations	20g	Gastrointestinal disorders as diarrhea and malabsorption	(63,67)
	Sucrose	Liquid formulations	5g	Tooth caries formation Cariogenic at high concentration	(63,67)
	Fructose	Liquid formulations	50g	Increase blood level in diabetic patients; laxative effects, bloating and excessive flatus if administered in high doses	(63,67)
	Aspartame	Chewable tablets and liquid formulations	40mg/kg	Armful in patients affected by phenylketonuria	(63,71,72)

Table I-4. Excipients and associated adverse effects in pediatric (continue).

	Saccharin	Solid and liquid formulations	5mg/kg	Urticarial, pruritus, dermatitis and photosensitivity. Irritability, insomnia, opisthotonos and strabismus	(71,72)
Colorants	E102 tartrazine	Solid and liquid formulations	7.5mg/kg	Allergic reactions	(63,67,71,72)
	E104 quinoline yellow		10mg/kg		
	E110 sunset yellow		2.5mg/kg		
	E112 caromoisine		--		
	E129 allura red		7mg/kg		
	4RE142 ponceau		--		

In general, preservatives are used in syrups, injectable and ophthalmic dosage forms to prevent deterioration caused by microorganisms (bacteria, yeasts or molds). They are classified into two groups: preservatives originally made from mineral substances (nitrates and nitrites, sulfites, etc.) and preservatives from organic substances (benzoic acid and sodium benzoate) which should be avoided or carefully evaluated due to they increase the risk of jaundice in neonates (66).

Solvents as ethanol and propylene glycol (PG) are commonly used in liquid formulations; however, adverse effects to the central nervous system are being reported in infants and children at large doses as they present limited metabolic functions. Therefore, WHO recommends avoid their use to pediatric patients below the age of four years (67,73). On the other hand, the ICH stablishes as unacceptable criteria residual solvents in these pediatric medicines (51).

Lactose is a broadly filler used in oral solid dosage forms, liquid formulations, inhalations products and feeding formulas. It is a disaccharide derived from one molecule of β-D-galactose and one molecule of β-D-glucose which is hydrolyzed by the intestinal lactase before being absorbed to the intestine. When a lactose-containing medicine is administered in pediatric patients with lactose intolerance symptoms as prolonged diarrhea, dehydration or metabolic acidosis have been reported (67).

Sweeteners are used in pediatric medicines to modify their organoleptic properties as taste and smell to improve the palatability of the pediatric patient. In addition, special considerations should be taken into account as safety of the sweetener in relation to specific medical conditions such as laxative effect of poorly absorbed or non-digestible sweeteners at high concentrations (66).

Sweeteners are mainly classified in three groups: natural (sucrose and sorbitol), semi-synthetic (aspartame) and synthetic (saccharine).
In the case of sucrose (or saccharose) it is not recommended in children who suffer fructose intolerance. Formulations with a large amount of sucrose, such as syrups, should be excluded from pediatric therapeutics especially in patients with diabetes and replaced by another sweetener. On the other hand, the sugar causes a decrease in pH in the dental plaque thereby dissolving the enamel tooth and is as a promoter of dental caries (71).
Fructose is another sweeting agent which causes a rise in blood glucose levels in patients with diabetes; moreover this sugar is also contraindicated in children who suffer fructose intolerance by hereditary genetic disease. Fructose can cause laxative effects, bloating and excessive flatus if administered in high doses or over 50 g/day orally (67).

Polyols such as xylitol, mannitol and sorbitol are considered sugar-free agents to be substitute in formulations due to their safety for diabetic patients but also a weapon in preventing tooth decay (74). However, they have been associated with disorders of the GI tract as osmotic diarrhea with abundant flatulence because they are incompletely absorbed and slowly metabolized in the intestinal mucosa.

Aspartame is a synthetic dipeptide, product from L-aspartic acid and L-phenylalanine, which has a sweetening potency of 150-200 times more than sucrose and it, is widely used as a food additive, chewable tablets and liquid formulations. However, phenylalanine may be harmful for patients with phenylketonuria, therefore its use is prohibited in the manufacture of foods for infants and young children (under two years) (74).

Saccharin can be found in many pharmaceutical formulations because its higher sweetening power, however it has been demonstrated the existence of cross-reactions between saccharin and sulphonamides, hence children with a known sulphonamides allergy should not be treated with saccharin-containing drugs (71).

The organoleptic characteristics as flavor, color and sweetness play an important aspect in the acceptability of the pediatric patient. The flavor must be associated with the color to transmit the related information according to the European Community guidelines and the Federal Food, Drug and Cosmetic Act of 1938108 for its use in food products (72). Colorants widely used in oral formulations are azo dyes, quinolone dyes and xanthene dyes which hypersensitivity reactions and attention deficit hyperactivity disorder have been reported (71,75).

The drug label is another important issue to be considered, not only all excipients should be declared but also it case of the presence of harmful excipient for specific population, warnings signs should appear on the label (64).

2.4 Palatability and taste-masking of oral dosage forms

Another important aspect to be considered at the moment to develop an oral pediatric medicine is the palatability, which is an influential factor to acceptance and compliance of the patient.

Palatability is described as the overall perception of a medicinal product which is related to its smell, taste, texture and after taste specially in oral dosage forms (76).

The taste sense in humans is a chemosensory perception that comes from the stimulation of the taste receptors composed of modified epithelial cells located on the papillae of the tongue and all over the oral cavity. When compounds interact with these receptors once they are dissolved in saliva, one of the following five taste qualities are produced: sweet, sour, bitter, umami or salty (77).

During the 7^{th} and 8^{th} week of gestation taste receptors are developed and achieve their maturity by the 13^{th} and 15^{th} weeks. After birth, newborns are able to detect and tend to reject bitterness and prefer sweet or umami tastes (77).

As many active principles present a bitter taste, the taste-masking of the drug becomes a critical factor in patient compliance, especially in the case of acute or chronic illnesses, where the acceptability of the treatment is related to the pleasant taste of the medicines to be administered (78). The addition of sweeteners and flavors is often used to mask the undesirable taste of drug in pediatric formulations, especially in oral liquid forms (79).

Others techniques have been used to mask the undesirable taste of the active ingredients such as coating, complexation of the active ingredient with cyclodextrins or ion exchange resins, etc. The excipients used with these techniques should provide a safety profile and their bioavailability when are used in children (80).
In other cases, the palatability of the medicine might be improved by mixing it in soft food or beverages, nevertheless the aspects of acceptability, compatibility and stability of the product must be guaranteed (81).

Since the EU legislation on medicines for children became effective in 2007, the taste-making aspects are required by regulatory agencies, despite of the lack of guidance on the evaluation is still poor. Therefore, analytical in-vitro and in-vivo methods have been developed to assess the taste-masking efficacy.

a) Quantitative evaluation of taste-masking by analytical methods

Analytical methods as Uv-spectroscopy or HPLC are used to determine the amount of active ingredient released in an aqueous medium (e.g. artificial saliva) in a short period of time. Dissolution methodology is considered as an indirect test for taste-masking evaluation since it does not contribute in the evaluation of the flavor or sweetness of the formulations. This method is often used to assess the effectiveness of taste masking by coating or by complexation. Indeed, the taste of the active ingredient is considered hidden when during a short period of time (about 1-2 minutes) the active ingredient is not detected or detectable amount is below the threshold of human perception (82,83).

b) Quantitative evaluation of taste-masking by electronic taste analyzer

The electronic taste sensing system or electronic tongue detects taste attributes in an analogous manner such as human taste perception. Its principle is based on dissolved substances in the test solution that can produce changes in the electric potential of the analyzer sensors. These signals are based on the intrinsic properties of substances to be tested, including their taste (83).
The evaluation of taste-masking in a formulation, often as liquid form, is based on the comparison between the test solution and the placebo (84). This method presents a low cost advantage, easy to realize especially during the development stage (85).

c) Qualitative evaluation of taste by a taste panel

Despite the well standardized protocols for taste evaluation, there is still poor information to be used to perform an evaluation study of the taste-masking of medicines. A literature review realized by Pein et al., found different performed protocols specially on the panelist, the administration of the medicine and the time points to evaluate the taste-masking (83).

In accordance with the EU ad hoc committee, taste-masking studies are performed at phase I clinical studies should be performed in adults (86); however considering the sensory differences between adults and children, it is clear that children should be considered as the most appropriate target population for evaluate the taste in pediatric formulations (85,87).
The ethical question is often a major difficulty of such studies in children, which mainly requires safety tests. Moreover, it is required a consent informed from parents or persons responsible of the child for he/she participates. In order to avoid their confusion and fatigue the following aspects must be considered (87):

- A brief test related to attentional narrow window
- Limit the number of variants tested at up to four to ensure the reliability of evaluation
- Need for intrinsically motivating test and "fun" to do, given the easy distraction of the child
- Simplify the most the testing process to make it understandable even for very young children

2.5 Considerations for pediatric clinical trials

Clinical pharmacology studies are a challenge to conduct in pediatric patients due to ethical, technical and logistical difficulties. Pharmacokinetic data provided from adults clinical trials may be used to extrapolate clinical efficacy and safety to pediatric patients; however as the pediatric population presents different age groups, pharmacokinetic variations related with age, doses calculated based upon body-mass, requirements of measurable dosage forms, formulation preferences and taste issues might lead to dangerous errors (88).

The EMA in 2006 published the "Guideline on the role of pharmacokinetics in the development of medicinal products in the pediatric population" where advices on the use of pharmacokinetic studies during the drug development stage and the issues related with methodology in pediatric patients (89).

To perform a clinical trial, a detailed protocol must include a solid argumentation to convince them about the trial, the objectives of the assay, the principal and secondary evaluation criteria, describes in which phase it is performing (phase I, II or III), a detailed experimental design, the population studied, the number of patients included, risks and constraints to the volunteers. Additionally the WHO describes the specifications to consider in clinical trials (90):

- All the age groups must be represented in the clinical trial if they are concerned by the disease.
- The children acceptability (pain prevention, number of performed actions and their cumbersome, etc.)
- The comfort of the child and his quality of life must be preserved at the maximum. Also, it is important to describe all the procedures performed, the number of samples taken and also the amount of blood that generally should not exceed 5% of total volume in children every two weeks.
- Practical feasibility: there is not only the child education but also the availability of parents, coaching, schedules and, diet foods where impact for families can be different from one disease to another.
- The clinical trial cannot be done without the information and informed consent signed by the parents but the consent of the child it is also sought. The information leaflet for the child is not legally required, but it is recommended from the age of primary school. It must be adapted to the child understanding without causing additional stress at home. If the child refuses to participate to the clinical trial, the investigator cannot include the child.

3. Oral age dosages forms

The oral route of administration is well-liked over the other routes, nearly 90% of the marketed products are administered by this route, being liquid formulations the most supplied to newborns and infants due to their difficulties to swallow, and solid formulations to children and adolescents (91,92).

Due to the diversity of the pediatric population, it is a challenge to find one appropriate formulation for all age groups. Therefore, any desirable formulation must follow the basic criteria (93,94):

- The dose should contain the API amount adjusted to the age and needs of the child and show its sufficient bioavailability
- Demonstrate the use of safe excipients
- Have palatable and acceptable properties
- Meet the uniformity of content requirements
- Be easy, friendly and safe to administrate for both sides: patient and caregiver. Also the minimum manipulation prior to administration it is desirable
- The information about its use must be clear and precisely
- It has to be sociocultural acceptable

The EMA in the "Refection Paper on paediatric formulations" brings an overview about the most appropriate, available and acceptable oral dosage forms in relation to age and it is shown in Table I-5. Where codes 1 to 5 are assigned to indicate the potential of applicability and acceptability as a function of the age of the child:

- for youngers, the code represents essentially a physical capacity to use the considered form, a code 1 is assigned to the least suitable forms and code 5 to the most appropriate forms;
- for olders, referring child who is judged more and also is divided into "pre-school" and "school" children groups, the majority of dosage forms, if not all, are potentially acceptable, a code 1 being assigned to the less or not acceptable forms and code 5 to the most acceptable choice.

Table I-5. Preferred oral dosage forms as a function of the age of child (67,95).

	Preterm newborn (less than 37 weeks)	Term Newborn infants (0-27 days)	Infant and Toddlers (1-23 months)	Children		Adolescent (12-16/18 years)
				Preschool children (2-5 years)	School children (6-11 years)	
Liquid dosages forms						
Solution/drops/syrups [a]	2	4	5	5	4	4
Emulsion/suspension [a]	2	3	4	5	4	4
Effervescent formulation [a]	2	4	5	5	4	4
Solid dosages forms						
Powder/Multiparticulates [a]	1	2	2	4	4	5
Powder [b]	1	2	4	4	4	4
Granules [b]	1	3	4	5	5	5
Pellets [b]	1	3	4	5	5	5
Tablets [a]	1	1	1	3	4	5
Melting tablets [b]	1	1	3	4	5	5
Mini-tablets [b]	1	1	3	4	5	5
Capsules [a]	1	1	1	2	4	5
Orodispersible forms [a]	1	2	3	4	5	5
Melt-away films [b]	1	2	3	4	4	4
Sustained-release films [b]	1	1	2	3	4	5
Orodispersible tablets [b]	1	3	4	5	5	5
Lyophilisates [b]	1	3	4	5	5	5
Flash-release films [b]	1	3	4	5	5	5
Chewing tablets [a]	1	1	1	3	5	5

a) Recommendations from the European Committee for Medicinal Products for Human Use;

b) Added recommendations for novel formulations(95)

3.1. Liquid dosage forms

Liquid formulations are preferred to be administer to newborns and infants as they are easy to swallow avoiding the potential risk of choking associated with solid formulations (96), they can be supplied as solutions, suspensions, emulsions, elixirs, syrups and sprays where the API can be either dissolved or dispersed offering a higher bioavailability *in-vivo* comparing to solid dosage forms (95). In general, the main issues related with these dosage forms are stability, taste masking and dosage volume (79,97).

In the case of oral solutions, water is the standard vehicle used for high solubility drugs with agreeable taste. Nevertheless, for APIs with limited solubility the use of co-solvents and surfactants as mineral oil, glycerine, polyethylene glycol or alcohols are required; on

the other hand, it is important to consider all time the regulatory recommendations and limits stablished for pediatric formulations (98).

Suspensions are formulated when the solubility of the API cannot be modulated, or has an unpleasant taste; therefore the API is minimized in the solution form where not only the dosage volume is reduced but also the palatability is improved (99).
Another advantage of this dosage form is that it can be used to modify the drug release by coating, ion exchange resins or complexation (80).
In addition, in order to ensure a good compliance and homogeneity, the properly agitation must be indicated in the label product (100).

Emulsions are another kind of oral dosage used in pediatric population; these formulations consist in two-phase systems in which one liquid is dispersed throughout another liquid in the form of small droplets. The dispersion phase can be oleaginous material or aqueous solution and the addition of an emulsifying agent is required to concentrate in the interface between the droplet and the external phase and, to provide a physical barrier around the particle to coalescence. The presence of an antimicrobial agent is required due to the aqueous or oil phases are favorable to the growth of microorganism. The most common used include parabens, benzoic acid or quaternary ammonium compounds, therefore in every time the limit of daily doses for children should be considered (38,44). On the other hand, as suspensions, this kind of formulation presents the inconvenient of phase separation, therefore clear directions should be provided in order to ensure uniformity content and correct dosage (92).

Syrups are liquid formulations which are very often supplied in neonates and infants; those formulations are generally prepared with high concentrations of sucrose which ensures bacteriological conservation and masks the undesirable taste of some API, however when they are supplied on a regular basis and over long period of time the risk of dental caries and dental erosion exists (101). In order to reduce the high amount of sucrose used, several formulations have been developed using fructose, invert sugar, polyols and artificial sweeteners and thickeners to obtain syrup " sugar free" (102).

Usually to administer the right dose, an adjustment of the volume administered according to the concentration of the API is calculated based on the age and weigh of the child

(103,104); additionally, the EMA in the refection paper suggests that target dose volumes should be in the range of 5 mL for infants and children under 5 years and 10 ml for older children, in all cases larger volume than 10 ml might be inconvenient for both patient and caregiver (105).

Another aspect to be considering is the packing, which not only has to be designed to guarantee chemical and physical stability and to be protective from microbial contamination, but also it has to be child-resistant and to be handling for caregivers (106).
In most cases dosing devices must be provided by manufacturer in order to support accurate dosing by volume (106).

3.2 Solid dosage forms

Solid drug delivery forms present many advantages comparing to liquid dosage forms as they present long-term stability; enhance handiness, large dosing accuracy and low manufacturing. They also provide masking the undesirable taste and modified release of the API by coating technically more difficult than in liquid formulations. For adults, tablets and capsules are the most common solid dosages forms available on the market; however, the major inconvenient is the acceptability in younger children who can present difficulty to swallow big tablet sizes, on that account, it is important to adapt the size of the dosage forms according to the child abilities (107).

In the case of standard capsules size ranges from 11.1 to 23.3 in length. Nowadays there are no acceptable data in children, in consequence the capsules are opened and powders or granules contained inside them are mixed with food or liquids for an ease administration. In some cases unpleasant taste and change in the bioavailability may occur once the capsule is opened differing from the original product (108–110).

On the other hand, conventional tablets result inappropriate for pediatric use due to strength and size, therefore the recent EMA/CHMP draft “Guideline on pharmaceutical development of medicines for pediatric use” considers the acceptability of tablets as a function of the age and size of the children (See Table I-6) (76,105,111).

Table I-6. Suitability of tablets according to age and size of the children based on the "Guideline on pharmaceutical development of medicines for paediatric use" (76).

Subpopulation	Age	Acceptability of tablets
Neonates	0 – 30 days	None
	1 – 6 months	None
Infants and toddlers	6 – 24 months	Tablets are not acceptable, but powders, granules and pellets are accepted
Children		
- Preschool children	2 – 5 years	Tablets 3 – 5 mm in diameter
- School children	6 – 11 years	Tablets ≤ 10 mm in diameter
Adolescents	12 – 18 years	Tablets ≤ 15 mm in diameter

Table I-7 summarizes the principal advantages and disadvantages that liquid and solid formulations present.

Table I-7. Principal advantages and disadvantages that liquid and solid formulations.

Dosage form	Advantages	Disadvantages
Liquids forms	❖ Main route for long term treatments in children ❖ Acceptability form term birth ❖ Maximum dose flexibility Stability, portability, good dosage uniformity ❖ Options for different doses and modified release	❖ Fist pass effect ❖ Instability of multi-dose preparations ❖ Age appropriate dosing volume for full dose ingestion (5 ml in younger and 10 in older) ❖ Dose measuring device critical
Solid forms	❖ Better acceptability ❖ Dose flexibility ❖ Easy administration ❖ Low cost of production ❖ Solid state stability ❖ Modified opportunities ❖ Single or multiple packs	❖ Difficulty of swallowing for young children ❖ Risk of choking and chewing ❖ Limited dose flexibility ❖ Dose-measuring device needed ❖ Compatibility with food/drinks ❖ Taste masking requirements ❖ Special and child-resistant packing

3.3 Flexible oral solid dosage forms

The urgent need to provide age-appropriate oral dosage forms which meets not only all the quality attributes of conventional pharmaceutical products, but also offers high accuracy, dose flexibility and ease of swallowing with particular attention to conditions prevaile in the developing countries, have encouraged developing new technological platforms as multiparticulate systems (mini-tablets, granules, sprinkles and pellets) and dispersible forms into liquids or to be mixed with food (dispersible tablets, oral lyophilisates, orodispersible forms, lonzenges, buccal wafers and chewable formulations) (34,66,112).

3.3.1 Mini-tablets

As a response of the problematic related with swallowing issue and dosage strength, mini-tablets have been introduced as a new modality to deliver pediatric medicines.
Mini-tables are defined as tablets with a diameter ≤ 3 mm, since the pharmacotechnical point of view they are easily manufactured either by direct compression or wet granulation using an ordinary eccentric or rotary press machine with single or multiple tooling (113–115). Moreover, they offer size uniformity, regular shape, smooth surface, low porosity and enough attainable strength comparing with pellets, microspheres or granules (116). In any case, dose accuracy and drug content uniformity must be assured since mini-tablets can contain either low or high doses, especially for drugs with narrow therapeutic window (117).

Mini-tables can be found not only as uncoated or coated but also as single or multiple-unit systems which improve the swallowing and flexible dosage. In particular, due to their small size mini-tablets can be useful as coated multiple-unit systems (as modified or extended release systems, colon targeting, gastro-retentive system, pulsatile and bi-modal release) which offer multiple advantages as flexible dosage, improving the bioavailability of drugs comparing with single-unit systems, masking the bitter taste of APIs, or protecting the API through the gastrointestinal tract (118–120).

With regard to the acceptability of mini-tablets, in recent years studies conducted on pediatric patients particularly in children aged two years or less have demonstrated a well

acceptance of 2 mm uncoated tablets comparing with a sweet tasting syrup (111,121,122). The way that mini-tablets are administered is another aspect to consider, they could be given by dispersion using water as preference or drink as vehicle prior to uptake or by solid form when the patient are more than six months placing the mini-tablet on the mouth of the child or mixing with soft food (123,124). However, in case of mini-tablets are coated it is important indicate not to chew mini-tablets since the coating may compromise the drug release (125).

On the other hand, the package of mini-tablets plays an important role in order to conserver their integrity, they can be either filled inside with hard gelatin capsules, sachets or compacted into bigger tablets that after disintegration, mini-tablets will released into subunits as multiple dosage forms (116,119).

3.3.2 Multiparticulate systems

Multiparticulate formulations comprise pellets, granules, sugar seeds and, mini-tablets which their maximum size should be 2.5 mm as the FDA suggests in the guidance for sprinkle products (126). They can be manufactured by layering, cryopellitization, freeze palletization, extrusion spheronization and hot melt extrusion techniques (127).

Multiparticulates are provided in sachets, hard capsules or tablets that can be administered directly into the mouth of the patient, dispersed in a vehicle prior to administration (e.g. water, milk, juice) or sprinkle in the food (128,129).

They offer many advantages over single-unit dosage forms due to their multiplicity and small size. They are well distributed along the gastrointestinal track enhancing the bioavailability which reduces the risk of local irritation, the risk of toxicity and side-effects. Multiparticulates offer attractive opportunities to control drug release, mask the unpleasant taste of the drug and, to protect acid-labile drugs from possible degradation in the stomach as the API can be encapsulated or coated by one or more layers of polymers that provide extended, delayed or pulsed drug delivery, allowing the rate of release of the drug to be tailored as required (119). Moreover, in case for pediatric patients, multiparticulate formulations are ease of swallowing; however, in terms of grittiness or mouthfeel may affect their acceptability (130).

3.3.3 Orodispersible forms

Orodispersible formulations are designed to bring a rapid disintegration, without the use of water, once they are placed in the oral cavity drug solutions or suspensions are formed, this facilitate the ease administration and swallowing owing the benefit of compliance and acceptability of the patient compared to conventional formulations. These formulations include orodispersible tablets (ODT), orodispersible films (ODF), oral lyophilisates (ORL) and, orodispersible granules (ODG) (131,132).

a) Orodispersible tablets

Orally dissolving tablets which disintegrate quickly on the tongue without additional water intake were developed as a response to offer an easy oral administration and benefits to increase patient compliance. Different terms are used to refer to fast disintegrating tablets (e.g. mouth dissolving, orodispersible, fast dissolving, fast melt, rapid-dissolve, quick disintegrating, orally disintegrating, rapid-melt, fast melts, etc.) (133).

The FDA defines an "Orally Disintegrating Tablet" (ODT) as "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Additionally, the FDA Guidance for Industry: Orally Disintegration Tablets recommends that ODTs (i) should have an *in-vitro* disintegration time approximately 30 seconds or less and, (ii) the weight of the ODT should not exceed 500 mg (134). Whereas the European Pharmacopeia defines it as an orodispersible dosage form as having a disintegration time of less than 3 minutes (135).

ODTs offer several advantages from conventional tablets as good stability, accurate dosing, small packing size, ease handling, ease administration and minimal risk of suffocation as they do not require water and disintegrate within a few seconds. Therefore, they are beneficial for children, elderly, bedridden patients who have difficulty in swallowing conventional solid or liquid dosage forms (136,137). Moreover, recent studies on the administration of mini-tablets have demonstrated that this dosage form is well accepted in very young children (117).

It is well documented how ODTs could be prepared using various techniques like freeze drying, tablet molding, compression method, addition of tablet disintegrants, crystalline transition, sublimation, effervescence, spray drying and, cotton candy process and how

several companies have patented technologies for manufacturing ODTs (e.g. Zydis, Lyoc, QuickSolv, OraSolv, DuraSolv, WOW Tab, Flasdose, Frosta, FlashTab, Pharmaburst) (138–141).

As any dosage form, the development of ODTs presents challenges in the matter of taste-masking, a rapid disintegration, mouth-feel, manufacturing process, quality control (hardness/friability) and, packing. In the case of acceptability in children, the success of this depends on the flavor and the technology used to mask the bitter taste of the API (133,142).

b) Orodispersible films

Different terms are used to refer to oral films (e.g. wafer, oral film, thin strip, orally dissolving film, flash release wafer, quick dissolve film or melt-away film), however the EMA uses the term "orodispersible film" as the official one, whereas "soluble film" is the referred one by the FDA (143).

Orodispersible film (ODF) is described as a single or multi-layer thin hydrophilic polymer sheet that once is placed in the mouth it disintegrates or disperses within few seconds before being swallowed eliminating the need of water for its administration (144). Due to its fast disintegration, in some cases the API can be absorbed directly into systemic circulation, avoiding its degradation in the gastrointestinal tract and first pass effect (145).

In general an ODF must combine specific characteristics, by one side it should be a thin and flexible layer with a relative short time of disintegration, which also is stable and guarantees a robust manufacturing and packing process. Furthermore, as all oral dosages forms, it must masks the bitter taste of the API and provide a pleasant mouth feeling to improve its acceptability (133,143,145).

Manufacturing process of ODFs is very flexible, the most common is the solvent casting technique, but there are also other manufacturing process as hot-melt extrusion, rolling method, electrostatic spinning and ink-jet-printing, although the production cost is higher comparing to conventional tablets or capsules production (146,147). The main limitation of this approach is related with the amount of API loaded on the polymeric matrix, which is low (1-30% owing in a surface of 2-8 cm^2) thus only specific drugs can be successfully delivered by this dosage form (146). Recent researches have increased the drug load in

films, however as the thickness of the film increases, the disintegration time tends to be slower, therefore individual evaluations are required to their suitability (81,129).

In the matter of clinical and regulatory aspects, guidelines which stablish the methods for characterization, quality control, dissolution test and bioequivalence studies are required as ODFs are not yet listed in any pharmacopoeia (143,145).

c) Oral lyophilisates

The European Phamacopeia defines the oral lyophilisates (ORLs) as a subtype of tablets called "oral lyophilisates" which are produced from API dissolved or dispersed in an aqueous solution and freeze-dried directly in the aluminum blister pack (135).

The most common technology used to produce these products is Zydis®, where gelatin or mannitol are used as carrier material and, additional excipients as flavors and taste-masking agents can also be included (124,148).

The inconvenient with these products are related with the manufacture process as it includes several energy and time and also a special packaging is required. Therefore the price of these products tends to increase comparing to other orodispersible formulations. In addition, for the administration, patients or caregivers must be careful to not damage the ORL from the package at the moment to take if off (132).

d) Orodispersible granules

Orodispersible granules (ODG) are defined as a multi-particulate dosage form where the dose of API is distributed along multiple small-sized dose carriers which can be directly administered into the mouth of the patient or sprinkled on soft food prior oral administration (132). ODGs become into a suitable and user-friendly dosage form special populations as pediatric and geriatric who might present difficulties in swallowing.

ODGs can be prepared by granulation (149) or pelletization (150,151) techniques. Additionally superdisintegrants or effervescent agents might be included to accelerate the disintegration. Notwithstanding, as the remaining time of the ODGs in the mouth could be longer than a tablet, therefore it is necessary to mask the bitter taste of the API. Technologies as spry-drying (152,153) and hot-melt coating (154) are used to offer a pleasant taste.

3.3.4 Chewable formulations

Chewable formulations are designed to be chewed instead of swallowed which become a preferred formulation by pediatric patients, they can be found as chewable tablets, soft-chews and chewing gums (38). These formulations present the advantages of ease of administration, prolonged stability and flexible packing comparing to liquid or orodispersible formulations and good organoleptic properties (e.g. good taste and mouthfeel) (105,129).

Chewable tablets are designed for rapid disintegration into small particles in the moist environment of the trachea and large bronchi which prevent airway obstruction from an aspirated pill, followed by dissolution of the granules (155).
In order to avoid any risk of aspiration or injury, it is suggested that ideal chewable tablets should have near-neutral pH with a size and shape that facilitates swallowing and allows for easy rotation in the trachea if aspired (155).
Studies have demonstrate all of them are well accepted in children of two years old providing a safe dosage form and easy administration (156,157).

Chewing gums can be supplied for both local and systemic treatments. They present well acceptability for children of more than six years old. These formulations should not be swallowed and the chewing time must be indicated on the label, even though the complete release of the API takes around 10-20 minutes (51). The use of sugar-based fillers and sweeteners as sorbitol, sucrose, aspartame and sodium saccharine is necessary to mask increase the palatability over the entire chewing time (158), however it has to consider the potential for teeth erosion over long-term use (101,108).

As any dosage forms, chewable formulations present disadvantages one of them is related with the palatability, as these formulations present good taste, children tent to confuse with candies, so parents and caregivers should be warned about the danger of the excessive consumption of these products in order to avoid an overdose (51). On the other hand controlled release on these formulations can be a challenge as the formulations are subjected to a great mechanical stress upon administration (159).

4. Oral delivery devices

As it has been described, children, especially infants and young children, differ from adults in ways that extend beyond the obvious difference in size. Thus, these differences should be considered when designing, using and evaluating medical devices for drug administration in the matter of safety and effectiveness before and after marketing (160–162).

According to the EU Directive, a medical device is defined as "any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the following purposes: (a) diagnosis, prevention, monitoring, treatment or alleviation of disease; (b) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; (c) investigation, replacement or modification of the anatomy or of a physiological process; (d) control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means" (163).

Generally, there is a need in pediatrics to develop medical devices able to deliver the accurate dose in a simple and user friendly way (67). In all cases, designers of pediatric devices must be focused on the performance and the control depends on the dosage form, the age of patient and the route of administration chosen (164).
To obtain an approval from the FDA, pediatric devices have to overcome a variety of barriers due to specific needs of the pediatric population. These include (165):
- small sample size
- significant population heterogeneity (patients from different ages and sizes)
- limited financial incentive from device manufacturers
- ethical challenges related to high-risk medical device testing in children
- difficulty in establishing equipoise in the minds of families and clinicians
- logistical challenges

4.1 Oral pediatric devices

The oral pathway is still the most common route of drug administration for new born infants, toddlers and young children groups, where liquid dosage forms are the preferred option. Many of these products are packaged with dosage delivery devices such as droppers, measuring spoons and cups, oral syringes or graduated pipettes (38).
According to FDA (166) and EMA (167), these oral devices have calibrated units of measure marked on the device in order to dispense the accurate and precise dose to maximize the therapeutic benefit and decrease medication administration errors, many of which being due to dosing errors done by parents or caregivers using household spoons to dose liquid medicines (168–173).

In the case of spoons and cups their precision is limited by volumes of 5 to 15 ml where only drugs with relatively wide therapeutic range can use such system (174,175).
Graduated pipettes and oral syringes present greater accuracy which allow not only the control of the administration but also allow the administration of drugs with narrow therapeutic window (174).
Regarding the administration of small volumes, the use of droppers is preferred where the dosing accuracy depends on the strength of the device by the user as well as the formulations properties such as density and viscosity of the liquid form (67,109).

In a study conducted by Walsh et al., on behalf of EuPFI in six European countries, it was found that oral syringes were the most frequently supplied oral administration device followed by measuring spoons while droppers and dosing cups were the least often supplied (176).

In recent years, new devices have been developed to deliver syrups and suspensions to babies and infants by using modified feeding bottles (Medibottle®) and pacifiers with drug-loaded reservoirs (Mykundex®) in order to improve the palatability of oral solutions when they are mixed with milk or favorite liquid of the child. Another interesting approach are the plastic spoons with perforated film patents known by the following principle: once the spoon is immersed in water, the medicine tends to form a ready to take pulp with the appearance of baby food (Azithromycin Sandoz®).

The company Raumedic® manufactures the XStraw™ (DS Technology) for granulated dosage forms (such as pellets), which is an already pre-dosed straw drinking where the child tears open the sealed single pack, takes out the straw, puts it into his favorite drink and, takes off the end cap and sucks. The device contains a controller which goes up when drinking the medicine, once the complete dose is taken, this controller stays at the top of the device. Also, the same company distributes a Dose Sipping Syringe for liquid suspensions. Basically, the syringe is placed in contact with a pharmaceutical liquid suspension; it is dosed into the dose sipping syringe by pulling the piston. Then the dose sipping syringe is placed into a glass containing a favored drink, and finally the medicine can be taken by sipping at the mouthpiece on top of the piston (177).

Conclusion

In the pediatric medicines development effort many challenges were identified: pharmacological challenges due to the physiological heterogeneity of the pediatric population, ethical challenges by the necessity to conduct clinical studies in children, regulatory challenges to implement measures to encourage the development and research by industry and finally, pharmaceutical challenges by the need to adapt the dosage forms.
In all cases, the development of suitable formulations for the pediatric population can be a long and difficult process that requires a committed collaboration between the industry, regulatory agencies and academia.

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CHAPTER II

MATERIALS AND METHODS

Materials

a) Drug load pellets

To prepare drug load pellets, the following ingredients were used: Acetaminophen (APAP, Safic Alcan, India), Microcrystalline cellulose (Avicel PH 101, FMC BioPolymer, Belguim), Lactose monohydrate (Pharmatose 350M, DFE Pharma, The Netherlands), Ethylcellulose (Ethocel Standard 10 FP Premium, DOW Chemical Company, USA), Ammonio methacrylate copolymer type B (Eudragit RS PO, Evonik Industries AG, Germany), Ammonio methacrylate copolymer dispersion type B (Eudragit RS 30D, Evonik Industries AG, Germany), Triethyl citrate (TEC, Vertellus, France).

b) Orodispersible forms

The following materials were used to prepare orodispersible granules (ODG) and pellets (ODP): D-Mannitol (Pearlitol 50 CC, Roquette, France), Microcrystalline cellulose (Vivapur type 102, JRS, Germany), Crospovidone (Polyplasdone XL10, ISP, USA), Croscarmellose sodium (Ac-Di-Sol, FMC BioPolymer, Belgium), Sodium starch glycolate (Explotab, Roquette, France), Sucrose (Sol. Eurosucre, France), Magnesium stearate (Coopération Pharmaceutique Francaise, France).

2. Methods

2.1 Formulation and evaluation of acetaminophen pellets: influence of the matrix system on the controlled-release

2.1.1 Preparation of drug load pellets

APAP pellets were prepared using the composition shown in Table II-1. Dry powders were mixed in a tumbling mixer (Turbula, Basel, Switzeerland) for 10 min. Wet granulation was carried out in a planetary mixer (Keenwood Chief, Hampshire, UK) and demineralized water was used as wetting liquid. Then, the wet mass was extruded at 63 rpm through a cylinder extruder (Alexanderwerk GA 65, Remscheid, Germany) equipped with two counter-rotating rollers with standard screen of 1.0 mm diameter aperture. Then, extrudates were transferred to the spheronizer (Gabler R-250, Malsch, Germany) equipped with a crosshatch plate (1 mm) and processed at 750 rpm rotation speed until obtaining spherical shape. Pellets were dried overnight in an oven at 60°C. Finally, pellets were sifted on a vibratory sieve shaker (Retsch GmbH, Haan, Germany) and the 710–1000 µm fraction was retained for analyze.

Table II-1. Composition of APAP matrix pellets

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
APAP	12.5	25	50	75	12.5	25	50	75	12.5	25	50	75
MCC PH 101	43.75	37.5	25	12.5	43.75	37.5	25	12.5	43.8	37.5	25	12.5
Lactose	43.75	37.5	25	12.5	--	--	--	--	--	--	--	--
Ethylcellulose	--	--	--	--	43.75	37.5	25	12.5	--	--	--	--
Eudragit RS PO	--	--	--	--	--	--	--	--	23.58	20.21	13.47	6.735
Eudragit RS 30 D	--	--	--	--	--	--	--	--	18.94	16.23	10.82	5.41
Water (ml)	65	60	47	35	105	92	65	50	76	67	65	65

2.1.2 Pellet characterization

2.1.2.1 Particle size distribution

Dry sieving method-

The sieves used were 1250, 1000, 710, 500, and 355µm. Each test sieve was tared before the test. A sample of 100 g of pellets was placed on the top sieve. The nest of sieves was agitated in a vibratory sieve shaker (Retsch GmbH, Haan, Germany) for 5 min, and then

each sieve was removed from the nest and reweighted. The retained mass of pellets on each sieve was determined.

2.1.2.2 Aspect ratio

Pellet morphology was determined individually using a stereo-microscope (Nikon SMZ-800, Melville, US) equipped with a camera AxioCam Icc1. The images were then analyzed by AxioVision software (Carl Zeiss, Jena, Germany). Measurement was realized by determining the aspect ratio defined as the ratio of the longest Feret's diameter and its perpendicular diameter (n=50). The aspect ratio describes the pellet sphericity and is expected to be close to 1.

2.1.2.3 Moisture content

A sample of pellets (1 g) was accuracy weighed before and after heating up to 105°C for 30 min by using an oven (WTB Binder, Tuttlingen, Germay). The moisture content was calculated by the percentage of pellets weight loss (n=3).

2.1.2.4 Friability

One gram of pellets was placed into a 10 ml glass container together with 3 g of stainless steel beads and was subjected to oscillatory movements in a Turbula mixer (Bachofen Maschinenfabrik, Basel, Switzerland) at rotational speed of 27 rpm for 5 min. Afterwards, the fines were removed by sieving through a 355 μm mesh, the pellet friability was calculated by the percentage of pellets weight loss (n=3).

2.1.2.5 Hardness

Mechanical properties of single pellets were performed using a texture analyzer TA.XT Plus (Stable Micro System, Surrey, England). Single pellets were compressed on a stainless steel plate with a cylindrical stainless steel probe (diameter 3 mm) with a load cell of 5 kg. The parameters were fixed at a starting height 3 mm, downward cross-head speed of 0.03 mm/s, trigger force 1 g, elongation 0.5 mm and return speed 0.5 mm/s. Force–distance diagrams were recorded and evaluated with regard to maximal force and displacement (n=30).

2.1.2.6 Bulk and tapped density

Bulk density- method I- Measurement in a graduated cylinder.

A sample of 100 g was introduced into a dry 250 ml cylinder and read the unsettled apparent volume, V_o, the bulk density was calculated, in g per ml by the formula:

$$BD = \frac{M}{Vo}$$

Tapped density- method I- Measurement in a graduated cylinder.

A sample of 100 g without compacting was introduced into a dry graduated 250 ml cylinder and read the unsettled apparent volume, $V_{o.}$ The cylinder containing the sample was tapped using a tapping density and apparent volume tester (Pharma test PT-TD200, Hainburg, Germany) for 10, 500 and 1250 times in order to measure the tapped volume, V_a, V_b and V_f respectively. The tapped density was calculated in g per ml, by the formula:

$$TD = \frac{M}{Vf}$$

The compressibility index and Hausner ratio were measured by the following formulas:

- Compressibility index

$$CI = 100\frac{(Vo - Vf)}{Vo}$$

- Hausner's ratio

$$HR = \frac{Vo}{Vf}$$

2.1.2.7 Porosity

Total tapped porosity (ε%) was determined from the particle tapped density values and the apparent density of particles according to the following formula (1):

$$\varepsilon\% = \left(1 - \frac{\rho t}{\rho p}\right) \times 100$$

with the tapped density (ρt) calculated after 1 250 taps in a tapping density and apparent volume tester (Pharma test PT-TD200, Hainburg, Germany) using a 250 ml graduated cylinder according to Ph. Eur. recommendations. The apparent particle density (ρp) was determined with helium pycnometer (Micrometrics Accupyc 1330, Norcross, USA) (n=3).

2.1.2.8 Differential scanning calorimetric (DSC)

Thermograms were generated using a DSC 1 (Mettler Toledo, Greifensee, Switzerland). Approximately 5 mg of sample were placed into non-hermetic aluminum pans and scanned under a dry nitrogen purge from 25 to 250°C at 10°C/min. The reference was an empty aluminum pan. Temperature and enthalpy readings were calibrated using pure indium and zinc.

2.1.2.9 Drug content of pellets

A sample of 3 g of APAP pellets was weighed and finely powdered, 75 mg equivalent of APAP were weighed and transferred into a 100 ml volumetric flask with 25 ml of 0.1 M NaOH and then diluted with 50 ml of distilled water and shaken mechanically for 10 minutes. Sufficient distilled water was then added to produce 100 ml. After filtration, further dilutions were made with distilled water such that the final concentration of APAP in solution was 7.5 mg/l and then 2.5 ml of NaOH 0.1 M were added. The absorbance of the resulting solution was measured with the spectrophotometer (Shimadzu UV-1650PC sipper, Champs-sur-Marme, France) at a wavelength of 257 nm in a quartz cuvette of path length 1 cm using 0.1 M NaOH as the blank solvent (n=3).

2.1.2.10 Dissolution test

A sample equivalent to 80 mg of APAP pellets was weighed, and, dissolution test was performed according to the USP 37 dissolution paddle method at 50 rpm in 500 ml of distilled water, simulated gastric fluid (pH 1.5±0.1), and simulated intestinal fluid (pH 6.8±0.1) at 37±0.5°C using a USP dissolution tester (Sotax, Basel, Switzerland). 3 ml samples were withdrawn at given intervals and analyzed UV-spectrophotometrically (Shimadzu UV-1650PC sipper, Champs-sur-Marme, France) at 244 nm (n=3).

2.1.2.11 Taste masking

The test was carried out on a continuous flow system described by Hoang Thi et al. (2) (Figure II-1) that simulates the oral cavity conditions. The simulated saliva solution pH 6.9±0.1 (3) was supplied to the column inlet at 0.8 ml/min by PhD 2000 syringe pump (Havard Apparatus, Massachusetts, US) that simulates the rate of saliva in children. The column was heated at 37±0.5°C. Sampling was carried out by collecting the solution at the outlet of tubing at different time points: 1, 2, 3, 4, 5, and 10 min. The released quantity of

drug was analyzed by UV-spectrophotometry (Shimadzu UV-1650PC sipper, Champs-sur-Marme, France) at 244 nm (n=3).

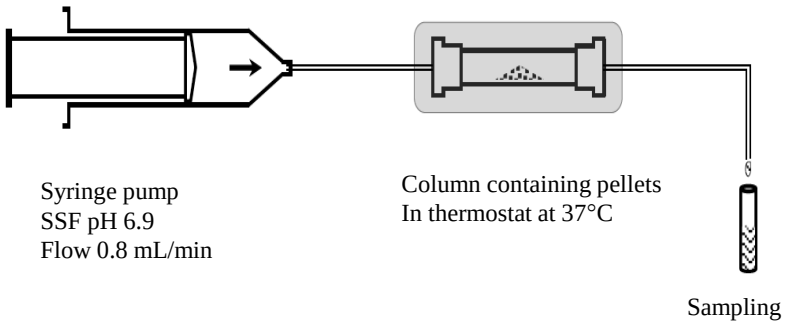

Figure II-1. Schematic illustration of continuous flow system for *in-vitro* drug release study.

2.2 Design and development of multiple-unit orodispersible tablets

2.2.1 Preparation of orodispersible granules

Orodispersible granules (ODG) were prepared by wet granulation using the excipients listed in Table II-2. Powders were weighed and mixed in a tumbling mixer (Turbula®, Basel, Switzeerland) for 10 min; wet granulation was carried out in a planetary mixer (Keenwood Chief, Hampshire, UK) using deionized water as wetting liquid. Then, the wet mass was passed through a 1.25 mm sieve in an oscillating granulator (Erweka FGS, Western, Germany) and dried in an oven (WTB Binder, Tuttlingen, Germay) at 60°C for 6 h. Granules were passed through a vibratory sieve shaker (Retsch GmbH, Haan, Germany) and the fractions from 500-1000 µm were used for further compression.

Table II-2. Placebo orodispersible granules formulation.

Ingredient	**FA**	**FB**	**FC**
Mannitol	76.15	76.15	76.15
MCC	15.0	15.0	15.0
Disintegrant*	5.0	5.0	5.0
Sucrose	3.0	3.0	3.0

*A) Crospovidone; B) Croscarmellose sodium; C) Sodium starch glycolate

2.2.2 Preparation of free-drug pellets

Free-drug pellets were prepared by mixing dry powders of MCC and lactose (ratio 1:1) in a tumbling mixer (Turbula, Basel, Switzeerland) for 10 min. Granulation was carried out with a blender mixer (Keenwood Chief, Hampshire, UK) using demineralized water as wetting liquid until obtaining a wet mass suitable for extrusion. Then, the wet mass was extruded through a cylinder extruder (Alexanderwerk GA 65, Remscheid, Germany) equipped with two counter-rotating rollers at 63 rpm, a standard screen having a 1.0 mm diameter aperture. The extrudates were transferred to the spheronizer (Gabler R-250, Malsch, Germany) equipped with a crosshatch plate (1 mm) and processed at 750 rpm rotation speed for 30 s. The resultant pellets were dried in an oven (WTB Binder, Tuttlingen, Germay) at 60°C overnight. Finally, dried pellets were sifted on a vibratory sieve shaker (Retsch GmbH, Haan, Germany) and the pellets retained on a 710 µm sieve were used for compression.

2.2.3 Compression of multiple-unit orodispersible tablets (MUP-ODTs)

a) Free-drug MUPs-ODTs

Placebo pellets from fractions 710-1000 μm were mixed with neutral orodispersible granules obtained by wet granulation at different percentages (Tablet II-3). Blends were transferred into the turbula mixer (Turbula, Basel, Switzeerland) and mixed at 54 rpm for 10 min. Then, lubricant was accurately weighed and added to the turbula jar and mixed for 5 min again. MUP-ODTs were manufactured on a single punch press machine (Korsch EKO/DMS, Berlin, Germany) with flat punches (diameter 5.0 mm) at three different compression forces in a 1-20 kN range.

Table II-3. Free-drug MUP-ODT formulations

Ingredient	% (w/w)		
MCC pellets	30.0	40.0	50.0
Orodispersible granules*	69.15	59.15	49.15
Mg-St	0.85	0.85	0.85

*A) Crospovidone; B) Croscarmellose sodium; C) Sodium starch glycolate

b) Drug load MUPs-ODTs

F2 APAP pellets (see *section 2.1.1*) were mixed with the orodispersible granules (Table II-4) in the Turbula mixer (Turbula, Basel, Switzeerland) at 54 rpm for 10 min. Then, lubricant was accurately weighed and added to the Turbula jar and mixed for 5 min again. MUP-ODTs were manufactured on a single punch press machine (Korsch EKO/DMS, Berlin, Germany) with flat punches (diameter 5.0 mm) in a 5-7 kN range of compression force.

Table II-4. Drug load MUP-ODT formulation .

Ingredient	%/(w/w)
Pellet MCC:API (25%)	40.00
Mannitol	45.44
MCC PH 102	8.94
Disintegrant*	2.98
Sucrose	1.79
MgSt	0.85
Total	100

Disintegrant*A) Crospovidone; B) Croscarmellose sodium; C) Sodium starch glycolate

2.2.4 Powder physical properties

Bulk density, tapped density, compressibility index and Hausner's ratio were performed as described in *section 2.1.2.6.*

2.2.5 Tablet testing

a) *Thickness* and *diameter* of tablets were measured with a portable dial hand micrometer (Mitutoyo, Tokyo, Japan) (n=20).
b) *Hardness*: Radial crushing strength was determined 24 h after compaction using a hardness tester (Dr. Schleuniger® Pharmaton AG, New Hampshire, USA) (n=10).
c) *Friability*: the weight loss of 20 tablets was evaluated in a Roche friability tester (Erweka® GmbH Tar 10, Heusenstamm, Germany) after tumbling for 4 min at 25 rpm.
d) *Disintegration time*: Disintegration of MUP-ODTs was determined according to Ph. Eur. with a PTZ-5 disintegration tester (Pharma test, Hainburg, Germany) in distilled water at 37.0±0.5°C using disks (n=6).
e) *Wetting time*: In a petri dish, with a 10 cm diameter circular tissue paper and 10 ml of water at room temperature. The tablet was carefully placed on the surface of tissue paper and the time required for water to reach the upper surface of the tablets was recorded as the wetting time (n=5) (4).
f) *Porosity*: True density (ρt) of the tablet was determined using a helium pycnometer (Micrometrics Accupyc 1330, Norcross, USA) (n=3).
g) *Mass variation and uniformity of content:* determined individually on 30 MUP-ODT according to the drug content procedure described in 2.9.40 of the Ph. Eur.

2.2.6. Drug content of MUP-ODT

Twenty MUP-ODTs were weighed and finely powdered. Amount of powder corresponding to 75 mg APAP was weighed and transferred into a 100 ml volumetric flask with 25 ml of 0.1 M NaOH and then diluted with 50 ml of distilled water and shaken mechanically for 10 minutes. Sufficient distilled water was then added to produce 100 ml. After filtration, further dilutions were made with distilled water such that the final concentration of APAP in solution was 7.5 mg/l and then 2.5 ml of NaOH 0.1 M were added. The absorbance of the resulting solution was measured with the spectrophotometer (Shimadzu UV-1650PC sipper, Champs-sur-Marme, France) at a wavelength of 257 nm in a quartz cuvette of path length 1 cm using 0.1 M NaOH as the blank solvent (n=3).

2.2.7 In-vitro drug release study

Dissolution test of MUP-s was performed according to the USP 37 dissolution paddle method at 50 rpm in 500 ml pediatric stimulated gastric fluid (pH 1.5) at 37±0.5°C using a USP dissolution tester (Sotax, Basel, Switzerland). 3 ml samples were withdrawn at given intervals and analyzed UV-spectrophotometrically (Shimadzu UV-1650PC sipper, Champs-sur-Marme, France) at 244 nm (n=3). Similarity factor (f_2) was calculated to compare differences in dissolution profile between pellets before and after compression, and also to compare the different behavior between the different matrices used and the marketed product.

$$f2 = 50 \times \log \left| \frac{100}{\sqrt[2]{1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2}} \right|$$

Where n is the number of time points, R_t is the dissolution value of the reference batch at time t, and T_t is the dissolution value of the test batch at time t. f_2 value greater than 50 indicates similarity between the two profiles and, more it approaches 100, better is the similarity.

2.3 Development of controlled release multiple-unit orodispersible tablets

2.3.1 Preparation of drug load pellets

APAP pellets were prepared using composition shown in Table II-5. Dry powders were mixed in a tumbling mixer (Turbula, Basel, Switzeerland) for 20 min. One hour prior, TEC was added to Eudragit® RS 30D and mixed with a low-shear mixer. Granulation was carried out in a mortar, the plasticized-Eudragit® RS 30D mixture was added slowly and then, demineralized water until obtaining a wet mass suitable for extrusion. Then, the wet mass was extruded through a cylinder extruder (Alexanderwerk GA 65, Remscheid, Germany) equipped with two counter-rotating rollers with standard screen of 1.0 mm diameter aperture at 63 rpm. Then, extrudates were transferred into the spheronizer (Gabler R-250, Malsch, Germany) equipped with a crosshatch plate (1 mm) and processed at 1 000 rpm rotation speed until obtaining a spherical shape (4-5 min). Pellets were dried in a fluidized bed (Aeromatic AG, Muttenz, Switzerland) at 25°C for 30 min and then in an oven (WTB Binder, Tuttlingen, Germay) at 60°C for 24 hours. Finally, pellets were sieved and the 710–1000 µm fraction was analyzed.

Table II-5. Composition of APAP pellets using Eudragit as matrix system.

Ingredient	E1	E2	E3	E4
APAP	25	25	25	10
MCC	37.5	25	15	10
Eudragit blend	37.5	50	60	80
Eudragit RSPO	20.21	26.09	31.3	41.675
Eudragit RS 30D	16.23	21.74	26.09	35
TEC	1.01	2.17	2.6	3.325
Total	100.0	100.0	100.0	100.0
Water (ml)	67	55	50	40
Solid total	88.6	84.8	81.7	75.5
Polymer	25.1	32.6	39.1	52.2
Drug content	25.0	25.0	25.0	10.0

2.3.2 Preparation of orodispersible granules

Orodispersible granules were prepared as described in the "*2.2.1 section*".

2.3.3 Compression of MUP-ODTs

APAP pellets were mixed with the orodispersible granules (Table II-6) in the Turbula mixer (Turbula, Basel, Switzeerland) at 54 rpm for 10 min. Then, lubricant was accurately weighed and added to the Turbula jar and mixed for 5 minutes again. MUP-ODTs were manufactured on a single punch press machine (Korsch EKO/DMS, Berlin, Germany) with flat punches (diameter 5.0 mm) in a 5-7 kN range of compression force.

Table II-6. Controlled release MUP-ODT formulations.

Ingredient	% (w/w)
APAP matrix pellet	40.00
Mannitol	45.44
MCC PH 102	8.94
Crospovidone	2.98
Sucrose	1.79
MgSt	0.85

2.3.4 Pellet characterization

Pellet characterization was performed as described in "*section 2.1.2* (2.1.2.1 to 2.1.2.10)".

2.3.4.1 X-ray diffraction (XRD)

X-ray powder diffraction was performed using a PANalytical X'pert Pro MPD diffractometer (λCu, Kα= 1.54 Å) in Bragg-Bretano θ-θ geometry (PANalytical, Almelo, the Netherlands) to study the physical state of APAP, polymer and drug-load pellets. Powders were placed into Lindemann glass capillaries (diameter 0.7 mm). The measurements were performed in transmission mode with incident beam parabolic mirror and X'celerator detector.

2.3.4.2 Scanning electronic microscopy (SEM)

The shape and the external morphology of the pellets were studied using a Hitachi S-400 scanning electron microscope (Hitachi High-Technologies Europe, Krefeld, Germany). Pellets were mounted with silver pain and covered with a fine chromium layer. Pictures were taken from the surface.

2.3.5 Tablet testing

Pharmacotechnical test were carried out as described in "*section 2.2.5 and 2.2.6*".

2.3.6 In-vitro drug release study

Dissolution tests of all APAP pellets and MUP-ODT were performed according to the USP 37 dissolution paddle method at 50 rpm in 500 ml of distilled water, simulated gastric fluid (pH 1.5±0.1), and simulated intestinal fluid (pH 6.8±0.1) at 37±0.5°C using a USP dissolution tester (Sotax, Basel, Switzerland). 3 ml samples were withdrawn at given intervals and analyzed UV-spectrophotometrically (Shimadzu UV-1650PC sipper, Champs-sur-Marme, France) at 244 nm (n=3).

Dissolution test of the commercial extended release tablets (Tylenol®8HR, McNeil Costumer Healthcare, US, lot 1390892) was performed for comparison following the same dissolution parameters. Similarity factor (f_2) was calculated to compare the differences between the dissolution profiles before and after pellets compression, and also to evaluate the effect of using different matrices and to compare our formulations with the marketed product.

2.3.7 Taste-masking evaluation

2.3.7.1 In-vitro dissolution

Taste masking was evaluated as mentioned above in "*section 2.1.2.11*".

2.3.7.2. Electronic tongue analysis

To determine the taste-masking, the different drug formulations were compared to the corresponding placebos. They were analyzed with little sample preparation to determine the effectiveness of the taste-masking. The closer the placebo matches the formulation with drug, the better the taste-masking is.

The Astree electronic tongue (Alpha MOS, Toulouse, France) was equipped with an Alpha MOS sensor set # 2, a 48-position auto-sampler and a stirrer. The sensor set consisted of seven cross-selective liquid sensors (ZZ, AB, GA, BB, CA, DA and JE) for pharmaceutical applications. An amount of each formulation of drug-load pellets or MUP-ODTs corresponding to 5 mg of APAP was weighed and dissolved in 50 ml deionized water at 37±0.5°C and stirred at 100 rpm for 3 min, then samples were filtered through a 0.45 μm nylon membrane filter using a vacuum pump. The solution obtained was poured directly in the beaker and analyzed by the Astree e-tongue.

The analytical conditions for the experiment were the following:

- Sample volume 25 ml
- Acquisition time 120 s
- Time per analysis 180 s

The e-tongue signal in each sample was measured at the equilibrium of 7 sensors (average between 100 and 120 s), three replicates were taken into account for the analysis. All data were generated on Astree system and treated using multidimensional statistics on AlphaSoft V14.3 software. The analyses are presented on a PCA graph. When there is no difference between the placebo and the drug formulation, the bitter taste has been masked. As the Astree is more sensitive than the human panel, the identified formulation will be correlated to the human ranking.

2.4 Feasibility of the compression of orodispersible pellets for pediatric use

2.4.1 Preparation of orodispersible pellets

Free-drug orodispersible pellets (ODP) were prepared using composition shown in Table II-7. Dry powders were mixed in a tumbling mixer (Turbula, Basel, Switzeerland) for 20 min. Granulation was carried out with a blender mixer (Keenwood Chief, Hampshire, UK) using demineralized water as wetting liquid until obtaining a wet mass suitable for extrusion. Then, the wet mass was extruded through a cylinder extruder (Alexanderwerk GA 65, Remscheid, Germany) equipped with two counter-rotating rollers at 63 rpm, the standard screen having a 1.0 mm diameter aperture. The extrudates were transferred to the spheronizer (Gabler R-250, Malsch, Germany) equipped with a crosshatch plate (1 mm) and processed at 750 rpm rotation speed for 1 min. The resultant pellets were dried in an oven (WTB Binder, Tuttlingen, Germay) at 60°C overnight. Finally, dried pellets were sifted and retained on 710 µm a sieve.

Table II-7. Free-drug orodispersible pellets formulation.

Ingredient	% (w/w)
Mannitol	76.25
MCC	15.0
Crospovidone	5.0
Sucrose	3.0

2.4.2 Preparation of free-drug MCC pellets

MCC placebo pellets were prepared as described in "*section 2.2.3*".

2.4.3 Pellet physical characterization

Pellet characterization was performed as described in "*section 2.1.2*".

2.4.4 Experimental design

A 3^3 full factorial design was used to prepare MUP-ODTs. The independent variables studied (X_1, X_2 and X_3) and their levels are shown in Table II-8. The chosen dependent responses (Y_1, Y_2 and Y_3) were mean hardness (N), disintegration time (s) and friability (%) respectively.

Table II-8. Independent variables: factors and levels for full factorial design.

Factors	LEVEL		
	-1	**1/3**	**1**
X1: Amount of API Pellets (%)	30	50	70
X2: Compression force (MPa)	0.8	1	1.4
X3: Amount of lubricant (%)	0.5	0.75	1

2.4.5 Tableting of MUP-ODTs

Both orodispersible and MCC placebo pellets from 710-1000 μm fractions were mixed at different percentages (Tablet II-9). Then, blends were transferred into the turbula mixer (Turbula, Basel, Switzeerland) and mixed at 54 rpm for 10 min. Finally, lubricant was accurately weighed and added to the turbula jar and mixed for 5 min. MUP-ODTs were manufactured on a single punch press machine (Korsch EKO/DMS, Berlin, Germany) with flat punches (diameter 5.0 mm) at three different compression forces in a 5-13 kN range. Hardness, friability and disintegration time were determined.

Table II-9. Free-drug MUP-ODT formulations.

Ingredient	F4	F5	F6	F7	F8	F9	F10	F11	F12
MCC pellet	30.0	30.0	30.0	50.0	50.0	50.0	70.0	70.0	70.0
ODP	69.5	69.25	69.0	49.5	49.25	49.0	29.5	29.25	29.0
MgSt	0.5	0.75	1.0	0.5	0.75	1.0	0.5	0.75	1.0

2.4.6 Tablet testing

Pharmacotechnical test were carried out as described in "*section 2.2.5*".

2.4.7 Statistical analysis of data

The effects of independent variables on each experimental response Y were modeled using a second order polynomial equation:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2$$

The models were simplified with a backward, stepwise linear regression technique. Only significant terms ($P<0.05$) were chosen for the final model. The modeling was performed

using SPSS (version) and related surface plots were obtained by STATGRAPHICS plus 3.0.

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CHAPTER III

RESULTS AND DISCUSSION

3.1 Formulation and evaluation of acetaminophen pellets: influence of the matrix system on the controlled-release

Multiparticulate drug delivery systems (MUPS) such as pellets have several therapeutic and technological advantages over single-unit dosage forms as they can distribute evenly in the gastrointestinal tract, control the drug release resulting in fewer adverse effects and also improve the palatability (1).
They can be administered orally either filled into hard capsules or compressed into rapidly disintegrated tablets. Although many studies have focused on protecting the coated pellets (reservoir system) from damages during tableting (2,3), only few studies have addressed on the compaction of uncoated pellets (matrix system), which potentially could provide fewer problems during compaction than coating pellets.

Classically, pellets produced by extrusion-spheronization are formulated with microcrystalline cellulose (MCC), considered as a standard pelletization aid by providing plasticity and cohesiveness to the wet mass prior to extrusion and spheronization. However, it may increase the disintegration time, therefore in this section we partially substituted the MCC with three different excipients in a (1:1) ratio: either lactose (Lac), or ethylcellulose (EC) or a blend of Eudragit (Eudragit RS PO/Eudragit RS 30 D) (Eu). These blends were associated with different drug loads i.e 12.5, 25, 50 and 75% (w/w) using the extrusion-spheronization technique to obtain a matrix system. Their mechanical and chemical properties as well as their influence on the controlled drug release were evaluated for further compaction. Acetaminophen (APAP) was used as a model drug.

3.1.1 Yield process and particle size distribution of pellets

Pellets were successfully produced with all tested formulations. All batches presented a high yield percentage over 80%: in the range of 83-87% for MCC:Lac formulations, 83-88% for MCC:EC formulations and 78.9-82% for MCC:Eu formulations. In a manufacturing process, the loss percentage should be considered; in our case, raw materials were lost mainly during the extrusion step where the wet mass adhered to the rollers surface. Only F1 (high percentage of lactose) and F8 (high % of drug associated with ethylcellulose) presented significant agglomeration or sticking pellets.

In all cases water was used as granulation liquid and, the amount required was adapted in function of the drug load to obtain pellets with desirable quality. The particle size of pellets was determinate by analytical sieving method based on the fraction retained. In general, the process produced pellets with a mean particle size in the range of 1250-710 μm as Figure III-1 illustrates it.

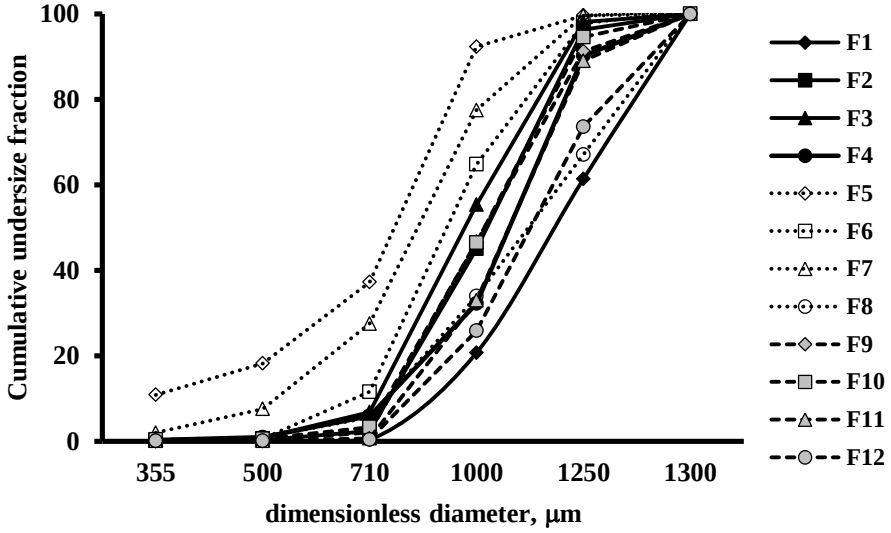

Figure III-1. Size distribution of APAP pellets using different type of excipients MCC:Lac (F1-F4), MCC:EC (F5-F8) and MCC:Eu (F9-F12) determined by sieve analysis.

For the purpose of this study, only the 710-1000 μm fraction was chosen because of its specific surface area, parameter important to consider in order to achieve a reproducible dissolution pattern of the API (4). Table III-1 summarizes the yield percentage obtained and the mean particle size from this fraction.

There is not relationship between the particle size distribution and the drug load ratio, however the particle size distribution and yield percent are related to the amount of water required to achieve a suitable wet mass.

Formulations prepared from MCC:Lac and MCC:Eu showed higher particle size than those from MCC:EC. A higher amount was added when EC was mixed with MCC whereas for Eudragit blends the amount of water used to prepare the wet mass was similar to the one used for the Lactose blends. As Eudragit is practically insoluble in water, this can be attributed to the type of acrylic polymers present in the Eudragit RS formulations. Indeed, Eudragit RS PO and Eudragit RS 30D contain quaternary ammonium substitutions which

provide an easy wettability of the blend; however, their spheronization time was greater than MCC:Lac or MCC:EC formulations.

Table III-1. Yield of the pelletization process, mean diameter size and aspect ratio from the 710-1000 μm fraction for different matrices and drug loading.

Formulation	Yield (%)	Diameter (μm ± SD)	Aspect ratio
F1	20.4	969±104	0.95±0.15
F2	42.6	988±191	0.94±0.15
F3	48.6	965±139	0.92±0.16
F4	26.3	983±136	0.86±0.09
F5	55.1	928±142	0.86±0.09
F6	53.2	925±101	0.91±0.06
F7	50.0	938±118	0.89±0.07
F8	28.3	982±141	0.88±0.06
F9	44.6	987±112	0.88±0.08
F10	43.2	959±126	0.90±0.08
F11	32.3	991±193	0.87±0.13
F12	25.4	1023±129	0.88±0.08

The level of drug incorporation is associated to the performance of the process. It was reported that higher drug loadings in extrusion/spheronization make the process more competitive even if it is more difficult to undertake. Hence, during formulation of pellets, the drug loading usually started at 50% and increased to in excess of 70% (5).

3.1.2 Pellet shape

Visual examination of pellets by microscopy indicated that pellets were generally spherical, with regular shape and a smooth surface. This is corroborated by the aspect ratio ranged between 0.86 and 0.95 (Table III-1), in agreement with the literature data suggesting that the aspect ratio of pellets should be lower than or equal to 1.2 (6).

The combination of MCC and Lac showed better sphericity compared to EC and Eu pellets (Figure III-2). It can be explained by the plastic deformation of MCC that allows the additional formation of hydrogen bonds between individual adjacent chains which

strengthen the structure and the recrystallization of lactose thus forming solid bridges with the fibrous nature of MCC during the extrusion/spheronization (7,8).

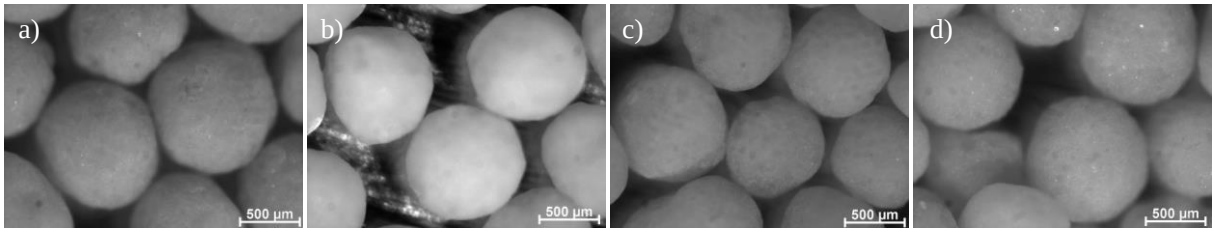

Figure III-2. Stereoscopic image of MCC:lac pellets at different drug loading: (a) F1 (12.5%), (b) F2 (25%), (c) F3(50%) and (d) F4(75 %) (Magnification 6X).

Ethylcellulose (EC) was used in powder form to produce the pellets. However, due to its hydrophobic nature, the wet mass showed low capability to be spheronized, so, it was necessary to blend it with MCC in the range of 12.5% to 43.75% to increase its plasticity during the extrusion and spheronization (9). With higher amount of the MCC:EC blend in the matrix and so less drug loading, pellets not only retained their spherical aspect, showed a rough surface but also they were harder than with a lower amount of MCC:EC (Figure III-3) (10).

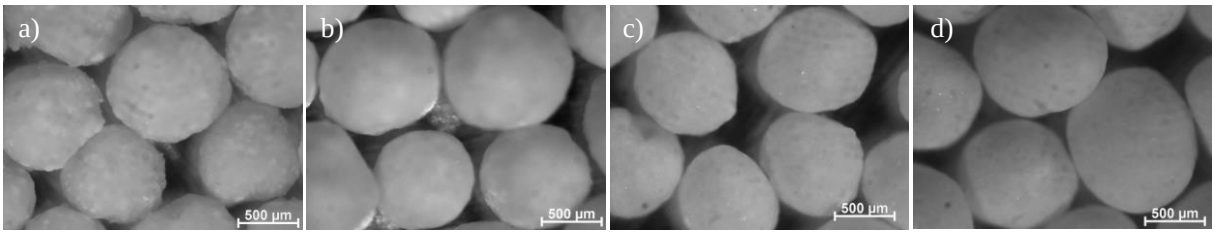

Figure III-3. Stereoscopic image of MCC:EC pellets at different drug loading: (a) F5 (12.5%), (b) F6 (25%), (c) F7(50%) and (d) F8 (75%) (Magnification 6X).

On the other hand, the shape and sphericity aspect of the pellets containing Eu were not altered by the increase in drug loading neither by the type of Eudragit® used as confirmed by Abbaspour et al. (Figure III-4) (11).

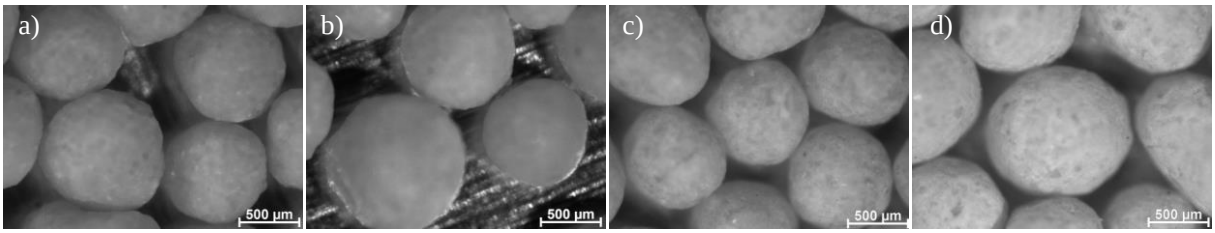

Figure III-4. Stereoscopic image of MCC:Eu pellets at different drug loading: (a) F9 (12.5%), (b) F10 (25%), (c) F11(50%) and (d) F12(75%) (Magnification 6X).

3.1.3 Pellet characterization

a) *Physical and mechanical properties*

Tables III-2 and III-3 summarize the physical and mechanical properties of pellets from the 710-1000 µm fraction of all batches produced for their further compaction. In all cases, the moisture content was below 2%: for formulations consisting of MCC: Lac (F1-F4) it was in the range of 0.9 to 1.5%, for matrices with MCC:EC (F5-F8) it was 0.1 to 0.9% and for matrices with MCC: Eu (F9-F12), 0.5 to 1.6%.

Table III-2. Physical characterization of APAP pellets as a function of the type of matrix used and drug load.

Formulation	Water loss on drying (% ± SD)	Friability (% ± SD)	Hardness (N ± SD)	Drug content (% ± SD)
F1	1.0±0.07	0.05±0.01	7.3±1.4	95.5±0.4
F2	1.5±0.07	0.06±0.01	9.6±3.1	95.6±1.1
F3	1.2±0.02	0.09±0.01	6.9±1.7	93.8±0.4
F4	0.9±0.1	0.1±0.06	4.1±1.0	93.6±0.8
F5	0.6±0.03	0.05±0.03	5.8±1.4	91.2±2.3
F6	0.9±0.04	0.00±0.00	4.1±0.6	96.6±0.6
F7	0.4±0.03	0.04±0.00	3.0±0.6	97.5±0.5
F8	0.1±0.1	0.0±0.00	3.2±0.7	97.8±0.7
F9	1.6±0.03	0.03±0.02	10.5±1.6	101.9±1.0
F10	1.3±0.07	0.02±0.02	9.0±1.6	109.8±1.1
F11	0.5±0.04	0.02±0.01	6.7±0.9	92.0±1.1
F12	0.6±0.07	0.01±0.01	5.3±1.4	102.2±2.4

All batches met the friability requirement of the Ph. Eur.; their values were below 1%, suggesting rugged pellets. Drug content of all formulations was found to vary from 95 to 109% w/w, which meets with UPS specification (90-110% w/w).

The values of hardness were in the range of 3 to 10 N which is satisfying for pellets of this size for any further handling step (e.g. filling into capsules, coating process or transportation).

Figure III-5 shows how the type of filler and quantity of drug load had and influence on the mechanical resistance of the matrix. Pellets containing MCC:Lac (a) showed sufficient mechanical strength in the range of 12.5 to 50% of drug load. In all cases, MCC:EC pellets (b) showed a weak mechanical behavior. MCC:Eu pellets presented better resistance to friction and higher hardness. In all cases, at high drug load pellets showed weak crushing strength.

Table III-3. Pharmacotechnical parameters of APAP pellets as a function of the type of matrix used and drug load.

	Bulk density (g/ml)	**Tapped density (g/ml)**	**Carr´s Index (%)**	**Hausner´s Ratio**	**Tapped porosity (ε%)**
F1	0.618	0.695	11.1	1.1	55.4
F2	0.713	0.744	4.2	1.0	53.2
F3	0.704	0.744	5.4	1.1	50.7
F4	0.667	0.718	7.1	1.1	49.0
F5	0.600	0.642	6.6	1.1	53.5
F6	0.566	0.601	5.9	1.1	55.4
F7	0.559	0.597	6.5	1.1	54.8
F8	0.565	0.592	4.5	1.0	55.5
F9	0.666	0.712	6.5	1.1	49.2
F10	0.652	0.697	6.5	1.1	50.9
F11	0.586	0.586	7.1	1.1	57.6
F12	0.647	0.647	6.0	1.1	52.1

All batches of pellets ensured good flow properties, as their Carr's Index values were below 15% which indicates the acceptable range. The density parameter should be considered, as it can influence the gastrointestinal transit time or the uniformity of their

filling into the die for further compression. Pellets presented tapped porosity (ε%) in the range of 49-55%, close to desirable values. Ideally, pellets might exhibit tapped porosity between 26 to 48%, however real pellets and beads are neither spherical nor uniform and higher values of tapped porosity are usually observed (7).

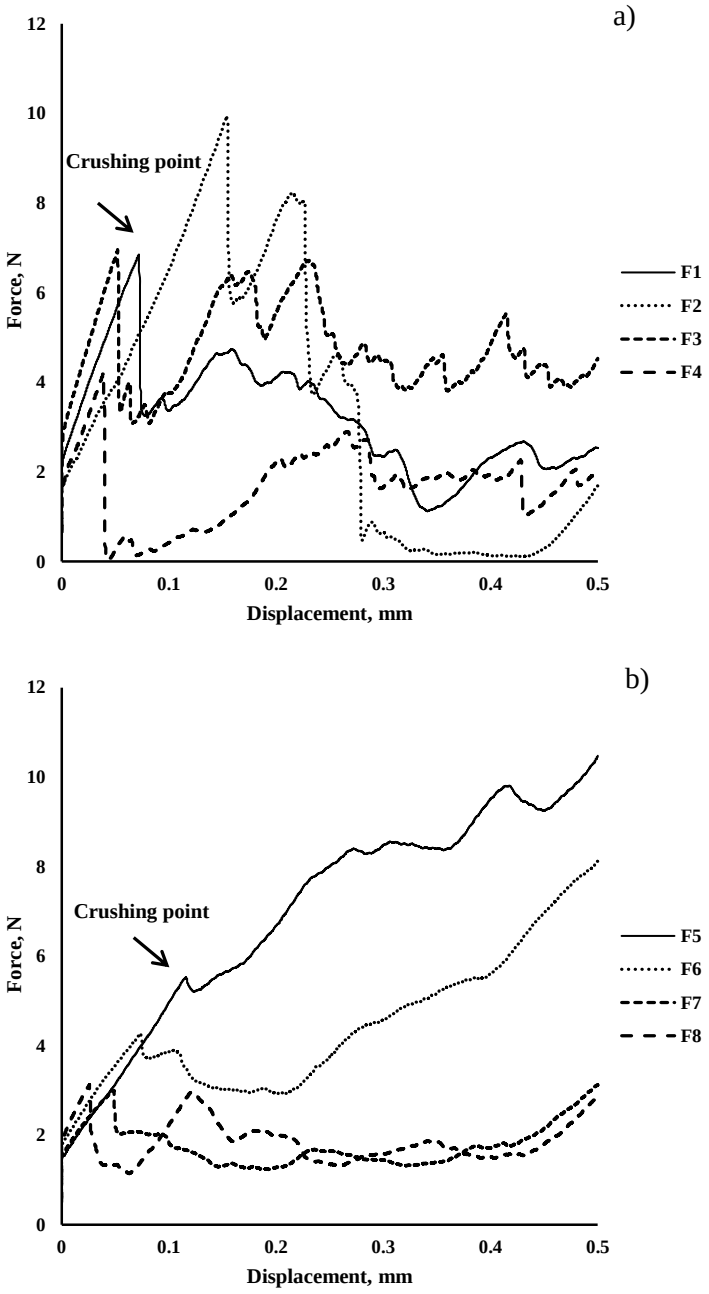

Figure III-5. Mechanical behavior of APAP pellets used at different type of excipients and drug loading (a) MCC:Lac, (b) MCC:EC, (c) MCC:Eu.

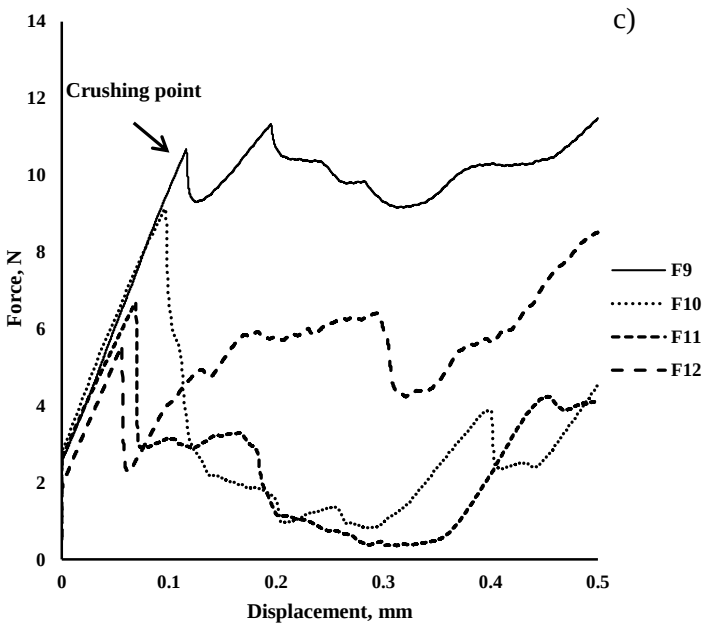

Figure III-5 continuation. Mechanical behavior of APAP pellets used at different type of excipients and drug loading (a) MCC:Lac, (b) MCC:EC, (c) MCC:Eu.

b) Thermal analysis

DSC thermograms of APAP, polymers and drug-polymer formulations were performed to evaluate any change in the properties of the drug. Figure III-6 illustrates the thermal behavior of APAP in MCC:Lac pellets, where pure APAP (a) thermogram showed a single sharp fusion peak at 170.03°C, that is characteristic of the APAP form I whose melting point is reported between 157-172°C (12,13). DSC analysis of Lactose (b) shows two sharp endothermic peaks, the first one at 147.59°C which represents a clear dehydratation of the α-monohydrate to the α-anhydrous form and there is no evidence of the recrystallization of the amorphous (which is evident at 167°C) and the second one at at 213.09°C which represents a characteristic sharp melting peak of the α-form (14,15). In DSC thermograms from formulations F1 to F4, APAP sharp peak was observed at 169.21, 169.78, 169.65 and 170.51°C respectively and showed a change in the broadness as the drug load increased in the formulation. In addition, characteristic sharp peaks of lactose were observed with negligible change in endotherm, which indicates that the excipients used in the formulation did not affect the thermal properties of the drug.

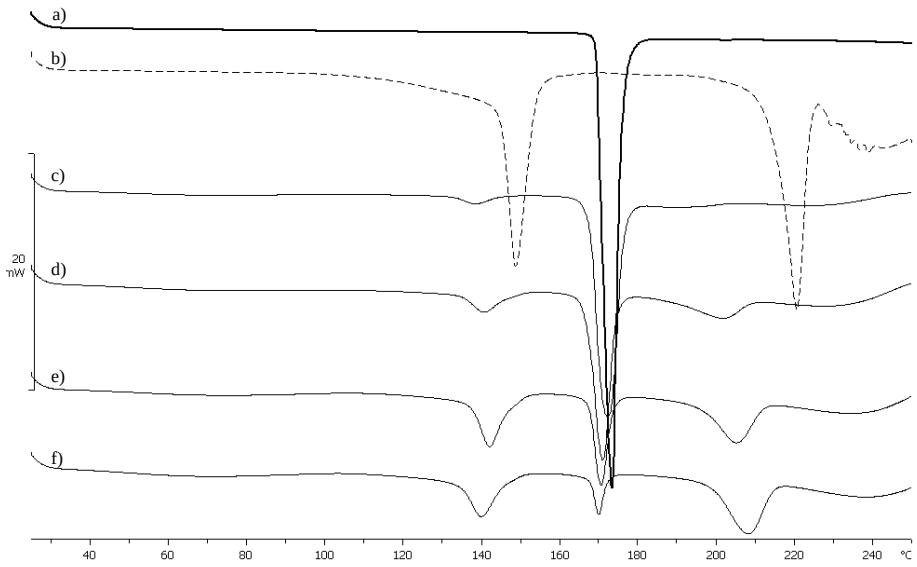

Figure III-6. DSC thermograms patters of APAP pellets at different drug loading using MCC:lactose as matrix system (a) APAP pure, (b) Lactose, (c) F4 (75%), (d) F3(50%), (e) F2 (25%) and (f) F1 (12.5%).

Figure III-7 shows the thermogram of EC (b) that did not show a specific endothermic peak. Thermograms of MCC:EC formulations (F5 to F8) showed the APAP sharp peak at 170.46, 169.93, 171.01 and 171.77°C respectively, similar behavior was observed in the broadness as the drug load increased in the formulation. The excipients used had not effect on the thermal properties of the drug.

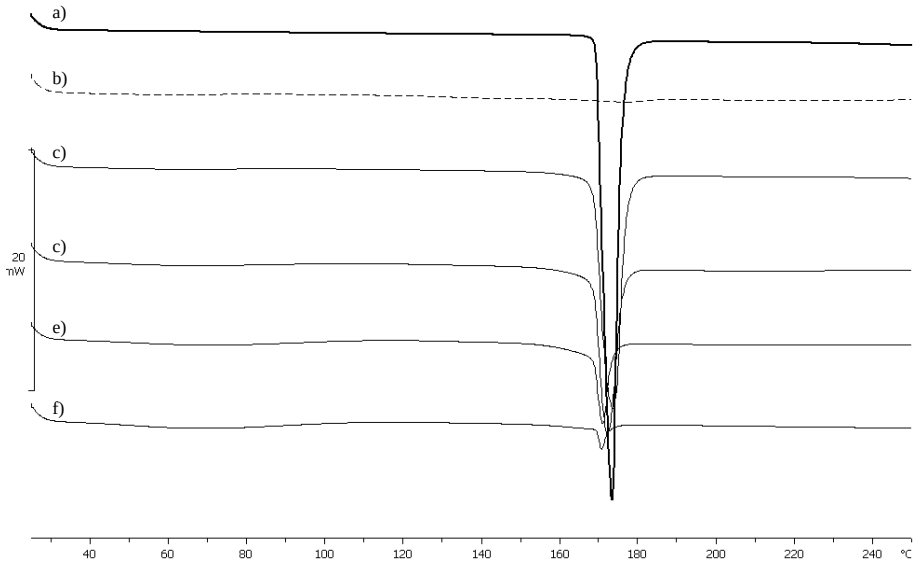

Figure III-7. DSC thermograms patters of APAP pellets at different drug loading using MCC:EC as matrix system (a) APAP pure, (b) EC, (c) F8 (75%) , (d) F7 (50%), (e) F6 (25%) and (f) F5 (12.5%).

On the other hand, Figure III-8 shows the thermograms of Eudragit RSPO/RS 30D that has not specific endothermic peak. In MCC:Eu formulations (F9 to F12), the sharp peak of APAP was observed at 168.84, 169.06, 169.93 and 170.62°C respectively. At low drug load concentrations, thermogram (e) showed a small modification in the thermal profile of APAP, this change may be due to drug-polymer interaction.

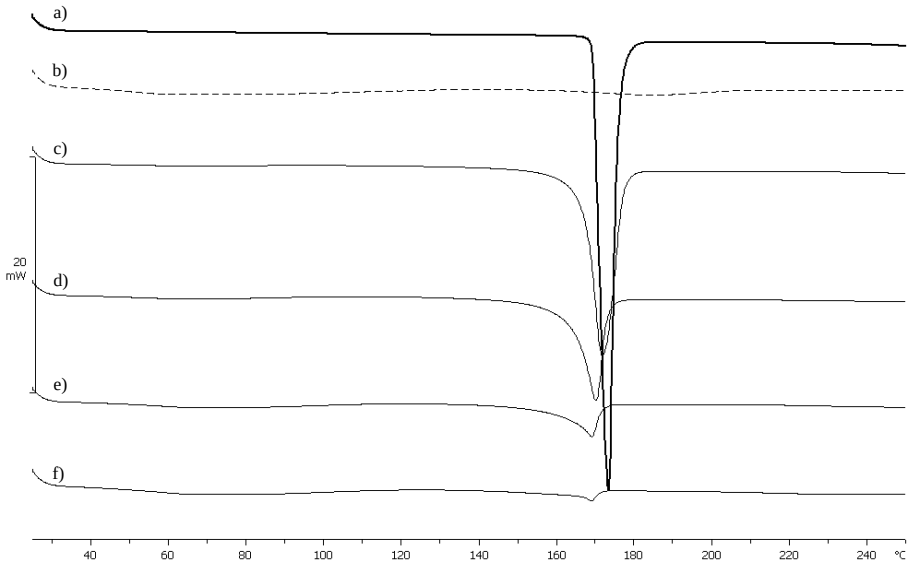

Figure III-8. DSC thermograms patters of APAP pellets at different drug loading using MCC:Eu as matrix system (a) APAP pure, (b) Eudragit blend, (c) F12 (75%), (d) F11 (50%), (e) F10 (25%) and (f) F9 (12.5%).

3.1.4 Drug release

In accordance with the USP specifications for APAP extended release tablets, the amount of API dissolved at 15 min should be between 45-65%, after 1 hour between 60-85% and, after 3 hours not less than 85%. Following these specifications, drug release profiles were performed from all pellets batches in order to find which formulation is suitable to use in our study. In addition, three different dissolution media, SGF pH 1.5, SIF pH 6.8 and water, were used.

In general, a rapid drug release from MCC:Lac pellets (F1-F4) was observed as Figure III-9 shows where 65-80% of APAP was achieved during the first 15 min and after 1 h 80-100% of the drug has been dissolved. It was also observed that neither the drug loading percentage nor the pH of dissolution media affected the dissolution rate of APAP. Due to

the solubility of lactose, the combination of MCC and lactose allowed the fast dissolution of the API, therefore this matrix cannot be considered as controlled release system.

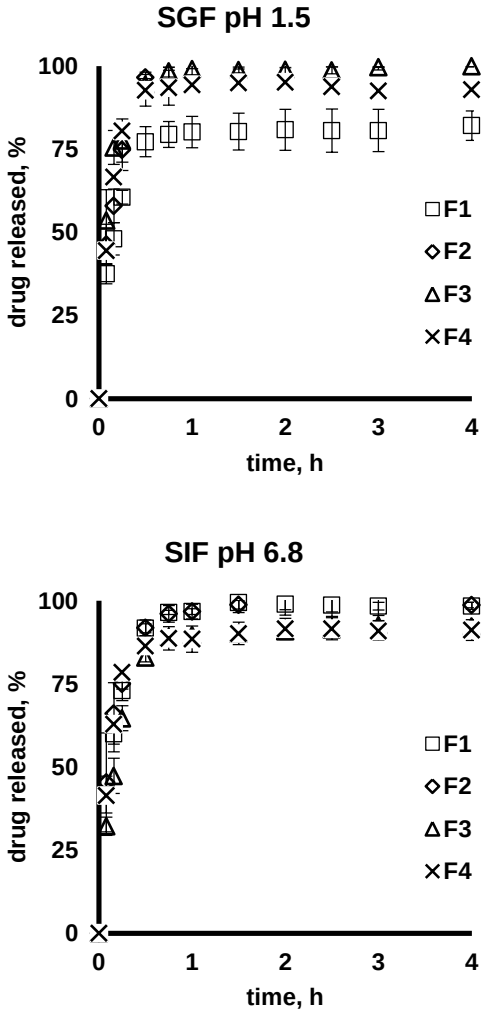

Figure III-9. Comparison of dissolution profile of APAP pellets containing MCC:Lac as matrix system at different drug loading. Apparatus 2, speed 50 rpm, volume 500 ml, medium (a) SGF pH 1.5, (b) SIF pH 6.8 and (c) water.

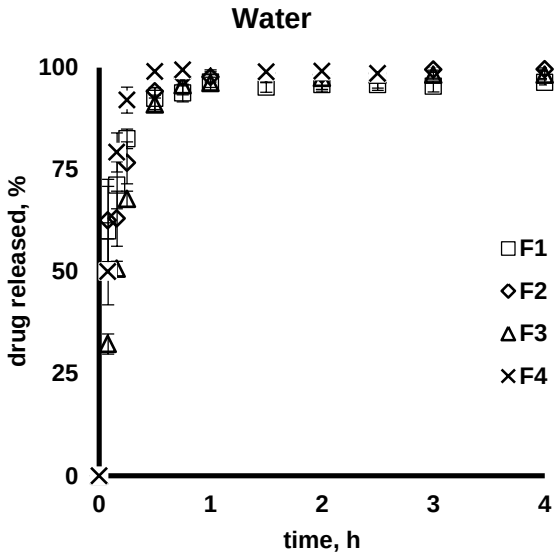

Figure III-9 continuation. Comparison of dissolution profile of APAP pellets containing MCC:Lac as matrix system at different drug loading. Apparatus 2, speed 50 rpm, volume 500 ml, medium (a) SGF pH 1.5, (b) SIF pH 6.8 and (c) water.

In the case of the MCC:EC formulations (F4-F8), pellets showed fast drug release and did not present marked variations with the different drug loading: in all formulations between 55 to 70% of APAP was released during the first 15 min and after 1 hour, all formulations achieved more than 90% of drug release, which did not meet with the USP specifications neither (Figure III-10). Because of the hydrophobic nature of EC, it was expected to obtain a slower drug release but as it was necessary to add MCC to increase their spherical properties, the EC based pellets lost their extended release properties. Mallipeddi et al. (16) report similar results with fine particle EC whose smaller diameter reduced the diffusion path length for the drug and the higher overall surface area of pellets, and this, combined with the hydrophilic properties of MCC, improved the fluid penetration resulting in an immediate release system (8,17).

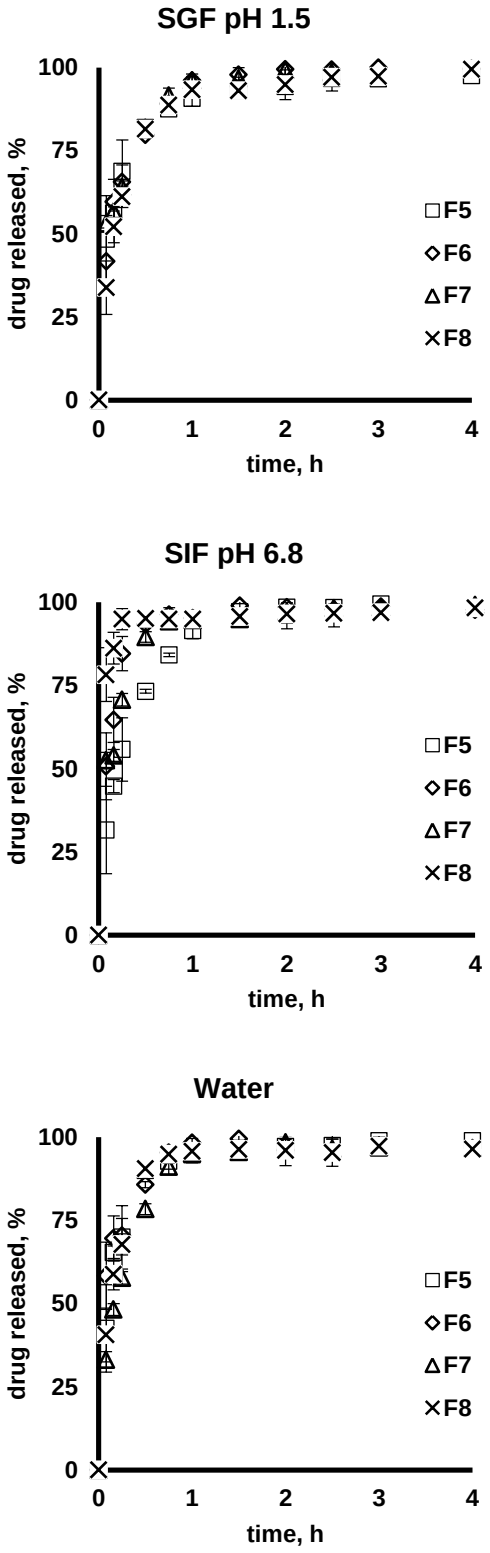

Figure III-10. Comparison of dissolution profile of APAP pellets containing MCC:EC as matrix system at different drug loading. Apparatus 2, speed 50 rpm, volume 500 ml, medium (a) SGF pH 1.5, (b) SIF pH 6.8 and (c) water.

As regards the MCC:Eu formulations (F9-F12), all pellets met the USP specifications at the first time, where APAP was released between 45-63% after 15 min. After 1 hour, only formulations with low dose strength (F9 (12.5%) and F10 (25%)) met the second point where the APAP release was between 79-85% and, by the third hour in all cases more than 95 of APAP had been released as Figure III-11 illustrates it. It is in agreement with the fact that at higher amount of polymer, lower porosity in the matrix was observed, therefore a slower drug release rate is achieved (18,19). The rate of entry of the medium is the limiting process in the drug release, even if APAP is a water-soluble drug. The dissolution rate was not affected by the solubility but it was similar to the rate of entry of the different mediums into the system (18).

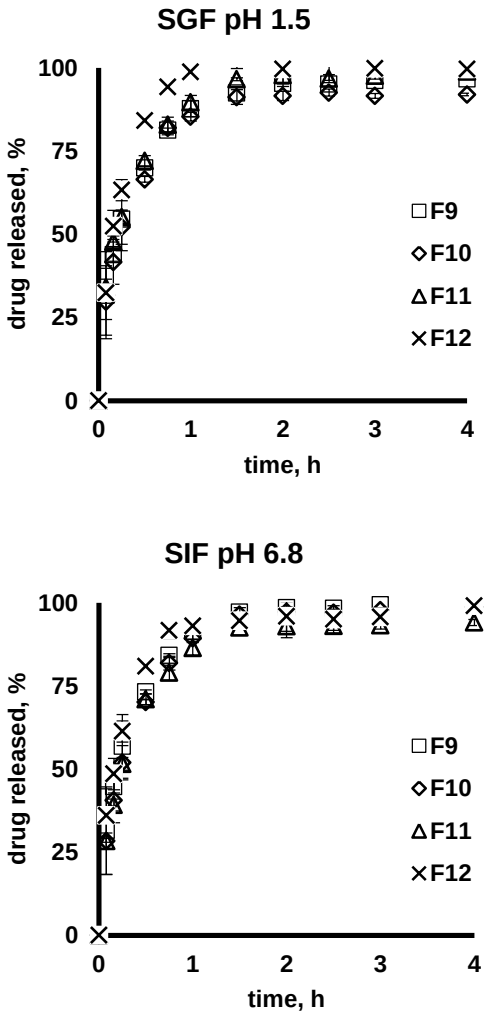

Figure III-11. Comparison of dissolution profile of APAP pellets containing MCC:Eu as matrix system at different drug loading. Apparatus 2, speed 50 rpm, volume 500 ml, medium (a) SGF pH 1.5, (b) SIF pH 6.8 and (c) water.

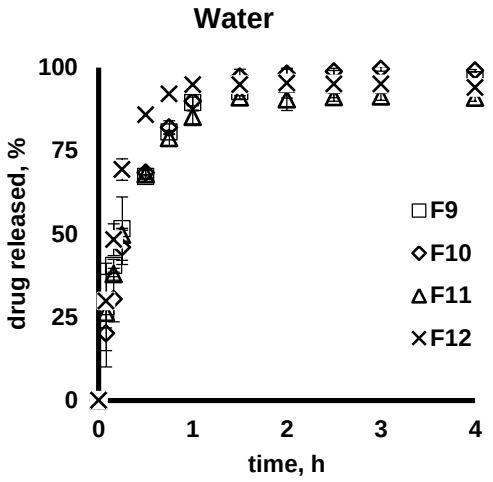

Figure III-11 continuation. Comparison of dissolution profile of APAP pellets containing MCC:Eu as matrix system at different drug loading. Apparatus 2, speed 50 rpm, volume 500 ml, medium (a) SGF pH 1.5, (b) SIF pH 6.8 and (c) water.

3.1.5 Taste masking

Human taste panel is the preferred method for taste assessment, however, it is quite difficult to perform a children taste panel because of safety, cognitive ability of the child, sociocultural difference, cost and ethical issues, etc. (20). *In-vitro* dissolution test can be performed to elucidate the taste masking capability by quantifying release of the drug in simulated oral cavity conditions (21,22).

APAP release from MCC:Lac, MCC:EC and MCC:Eu matrices was monitored using a continuous flow system that allows not only mimicking the realistic conditions in the mouth, but also predicting the taste masking effect. Figure III-12 shows the drug release profiles as a function of time for unmasked APAP as pure drug and pellets produced.
The amount of APAP released at the second minute was ranged between 11-27% for MCC:Lac pellets, 7-16% for MCC:EC pellets and 5-23% for MCC:Eu pellets, whereas the amount released for the pure drug was 29.8%. In general, pellets containing a higher ratio of polymer in the matrix showed a low release of APAP within the first 2 min, less than 10%, as these polymers are insoluble in saliva. So, in consequence the bitter taste of APAP can be masked during the first minutes (23).

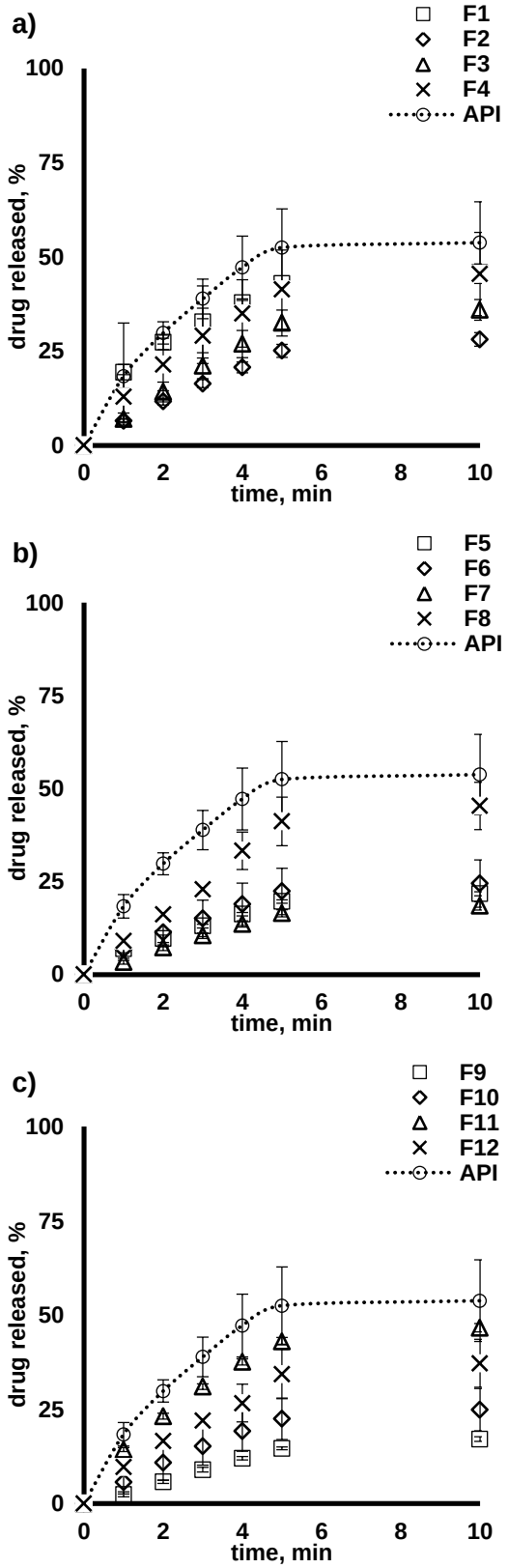

Figure III-12. *In-vitro* evaluation of APAP pellets containing using different matrices and drug loading by continuous flow system. Flow 0.8ml/min, medium SSF pH 6.9. (a) MCC:Lac, (b) MCC:EC and (c) MCC:Eu.

It is reported that 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. Nevertheless, the bitterness threshold reported in the literature is highly varying. Comparing our results with Albertini et al (24) where they reported within 41% and 55% of APAP release from taste masked granules at 3 min and Hoang Thi et al (25) who obtained a concentration release between 12% and 18% from taste masked powders, our matrices had a significant role in decreasing the drug release during the first 2 minutes, therefore they can be an approach for taste masking.

Conclusions

Different polymers were successfully used to produce APAP matrix pellets with different drug loading, all batches showed acceptable quality like low friability, good sphericity (aspect ratio ~1) and smooth surface. Especially formulation F10 (MCC:Eu, 25% drug) met with all desirable mechanical properties and controlled release parameters, therefore it will use for further compression and taste masking studies.

On the other hand, it was possible to produce spherical pellets containing 75% of APAP when associating lactose with MCC used as a spheronizing aid, which can be used as immediate release dose. However, their mechanical properties decreased, in particular the crushing strength, reducing their ability to be compressed. An alternative could be their incorporation in a multiparticulate counting device particularly interesting for the dose adjustment.

During the first 2 minutes, the pellets produced had a significant role in decreasing the drug release, limiting the contact between the bitter drug and taste buds in the mouth; therefore they can be an approach for taste masking.

3.2 Design and development of multiple-unit orodispersible tablets

In the development of pediatric medicines, three principal aspects must be regarded: (i) efficacy/ease of use, (ii) safety and (iii) patient access (26).
In the case of oral solid dosage forms, it is important to consider if the pediatric patient is able to swallow the tablet formulations. For this reason, the purpose of this study was to develop a multiple-unit orodispersible tablet which, once it is placed in the mouth of the child, disintegrates rapidly into the pellets constituting the tablet. This facilitates the swallowing, an important attribute to prevent airway obstruction from an aspirated pill, whereas the pellets will release the drug at different rates.

The first part of this study aimed to develop an orodispersible formulation that meets the specifications of Pharmacopoeia for ODTs. The second part determined the feasibility to compress free-drug uncoated MCC pellets with different placebo orodispersible formulations in order to obtain multiple-unit orodispersible tablets (MUP-ODTs), with the study of the influence of the percentage of pellets (30%, 40% and 50%), the type of disintegrant (crospovidone, croscarmellose and sodium starch glycolate) and the compression force (2-20 kN). The last part evaluated the mechanical properties and dissolution profile of MUP-ODT produced using acetaminophen as a model drug. For this study, the tablets produced had a diameter of 5 mm which is suitable for children aged from 3 to 5 years in accordance with the EMA/CHMP draft guidance (27).

3.2.1. Development of placebo orodispersible formulations

Mannitol was chosen as filler as it presents good mechanical properties, fast disintegration and pleasant mouth feel (28). Orodispersible formulations were prepared by the wet granulation method using different disintegrants. It is reported that the use of higher concentrations of disintegrant agent (10-20%) influences the relationship between the applied compression force and the disintegration time (29,30), therefore the percentage of disintegrant in the formulation was settle down at 5%. The physical properties of each formulation are shown in Table III-4. The resulted granules presented an irregular shape and in all cases the moisture content was below 2%. Bulk density was in the range of 0.32 to 0.41 g/cm^3 and the tapped density was found between 0.39 to 0.48 g/cm^3 for all

formulations. The Carr's index and Hauser ratio were calculated and were found in the range of 14.3 to 17.4% and 1.17 to 1.12 respectively; indicating that formulation FA presented good flowability properties meanwhile FB or FC were fair to passable. Thus orodispersible formulations could be ranked starting with the lowest value as follows, FA <FC< FB.

Table III-4. Characterization of placebo orodispersible granules.

	FA	**FB**	**FC**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
% loss on drying	0.26 ± 0.02	0.79 ± 0.05	0.49 ± 0.01
Flow (100 g/s)	9.5 ± 0.7	10.5 ± 2.1	9.0 ± 0.0
Bulk density (g/cm^3)	0.41 ± 0.01	0.32 ± 0.00	0.36 ± 0.00
Tapped density (g/cm^3)	0.48 ± 0.01	0.39 ± 0.01	0.43 ± 0.01
Carr's Index (%)	14.3 ± 0.2	17.4 ± 1.1	16.4 ± 1.0
Hausner's ratio	1.17 ± 0.00	1.21 ± 0.02	1.20 ± 0.01

The relationship between the compression profile and mechanical properties of directly compressed tablet formulations was examined using an instrumented tablet press. All orodispersible formulations showed a linear correlation between the compression force (2 to 14 kN) and the tablet tensile strength (0.5 to 6 MPa) (Figure III-13).

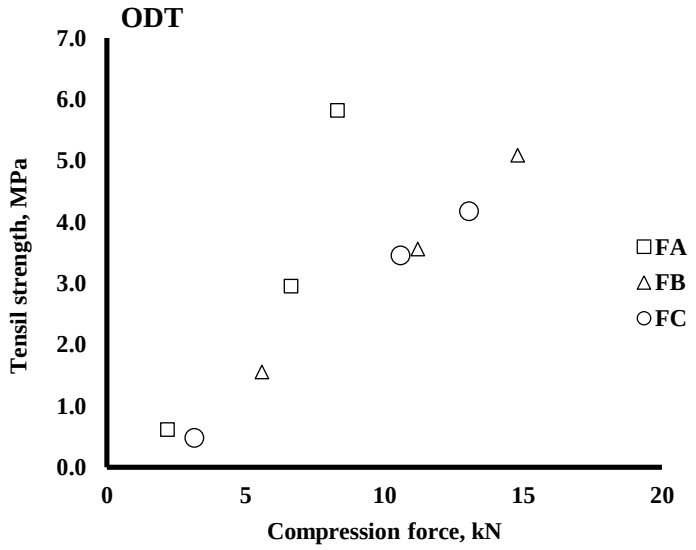

Figure III-13. Comparison of the compressibility of mannitol placebo formulations using different disintegrants (5 mm flat facetted single punch press).

Table III-5 summarizes the mechanical parameters, such as hardness, disintegration time and friability, used to select the best orodispersible formulation. All batches showed excellent hardness for all compression forces. In all cases, at medium and high compression forces, ODT met with friability criteria (less than 1%). The porosity of the tablet was affected by the increasing compression force therefore, disintegration time and wetting time which were recorded between 5 to 174 s and 4 to 120 s respectively were significantly affected by the increase in compression force. The overall results indicate that the processing parameter, compression force, affects the physical properties of the tablet formulation.

Table III-5. Pharmacotechnical test of placebo ODTs.

Formulation	Run	CF (kN)	Weight (mg)±SD	Hardness (N)±SD	Friability (%)	Disintegration time (s)±SD	Porosity (ε%)±SD	Wetting time (s)±SD
FA	1	2	46.5±0.9	10.7±2.5	1.55	5±1	49.4±2.8	4±1
	2	6	51.6±1.8	48.1±7.2	0.47	35±4	31.9±10.1	11±2
	3	8	46.7±2.9	54.5±13.1	0.44	113±4	1.5±19.3	22±4
FB	13	5	43.7±0.7	21.8±2.5	1.11	14±1	76.5±14.5	10±9
	14	11	44.2±0.7	49.5±4.6	0.36	51±6	42.4±8.9	28±5
	15	14	43.9±0.8	67.7±6.2	0.34	143±4	17.0±31.7	75±3
FC	25	3	49.6±2.0	8.7±2.5	5.94	10±2	45.5±6.3	10±1
	26	10	46.5±2.2	48.4±6.1	0.37	174±17	13.1±15.0	60±21
	27	13	48.5±0.5	61.0±2.7	0.53	160±2	8.2±4.8	120±32

CF: compression force

On the other hand, stereoscopic images (Figure III-14) showed that all ODTs produced present a smooth surface without any sticking or binding problem.

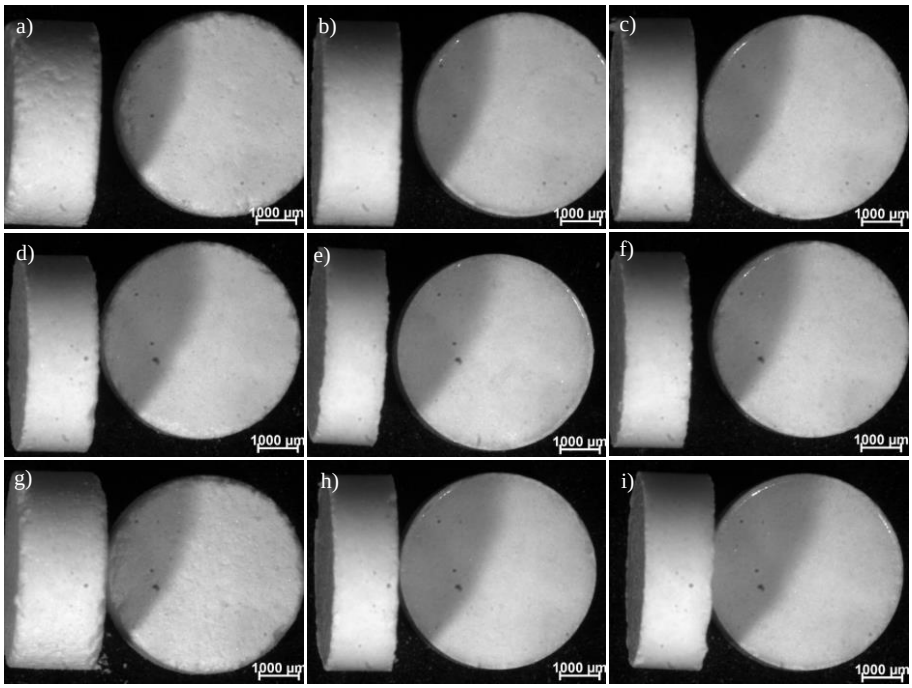

Figure III-14. Stereoscopic images of placebo ODTs formulations different compression forces, a-c) FA formulations, d-f) FB formulations and g-i) FC formulations (Magnification 2X).

3.2.2. Design of multiple-unit orodispersible tablets

To produce multiple-unit orodispersible tablets (MUP-ODTs), it is important to take into account the use of suitable compressible excipients with the purpose to improve the compactibility of pellets. The excipients used should offer a high dilution potential, the minimal segregation propensity, a cushion of the pellets during tableting and, the most important, they have to disintegrate rapidly in order to release the pellets, all this with minimal effect on the drug release kinetics (31). Moreover, they should meet the safety requirements for pediatric use.

3.2.2.1 Pre-compression parameters of multiple-unit orodispersible formulations

In this study, different percentages of MCC pellets from the 710-1000 μm fraction were added to placebo orodispersible granules with a narrow size similar to the one of pellets in order to avoid mass and content variations due to segregation problem which has been reported when smaller particle compressing agents are used (32,33). The physical properties of each formulation are shown in Table III-6.

Table III-6. Characterization of multiple-unit orodispersible formulations.

	FA-MUPS 30%	FB-MUPS 30%	FC-MUPS 30%	FA-MUPS 40%	FB-MUPS 40%	FC-MUPS 40%	FA-MUPS 50%	FB-MUPS 50%	FC-MUPS 50%
Flow (100g/s)	2.5	5.0	4.0	3.4	5.0	4.0	3.8	4.0	4.0
Bulk density (g/cm^3)	0.52	0.40	0.45	0.55	0.45	0.46	0.57	0.49	0.52
Tapped density (g/cm^3)	0.58	0.50	0.54	0.65	0.54	0.56	0.63	0.57	0.61
Carr's Index (%)	10.5	18.9	16.7	14.8	16.7	17.2	9.6	14.0	14.8
Hausner's ratio	1.1	1.2	1.2	1.2	1.2	1.2	1.1	1.2	1.2

Bulk density was in the range of 0.40 to 0.57 g/cm^3 and the tapped density was found between 0.50 to 0.65 g/cm^3 for all formulations. The Carr's index and Hauser ratio were found in the range of 9.6 to 18.9% and 1.1 to 1.2 respectively. In general, formulation FA still showed better flowability properties than FB or FC. On the other hand, the addition of 50% of pellets improved the flow properties of orodispersible formulations, meanwhile at 30% and 40% the formulations did not present any change in their flowability properties.

3.2.2.2. Effect of compression force and proportion of pellets on MUP-ODTs properties

In general, with multiple-unit orodispersible formulations it was possible to produce MUP-ODTs with sufficient crushing strength at low compaction forces. Compressibility assessments showed similar first rate tableting properties due to compactability and high dilution potential. Figure III-15 shows tablet tensile strength as a function of compression force, where low compression forces were required to compress different percentages of pellets in the formulation to obtain hard and easy handling tablets. MUP-ODTs from formulation FA required very low compression forces to obtain the desirable tablets comparing to FB or FC, this is due to crospovidone binder properties that shows an important advantage in this kind of tablet formulations.

On the other hand, by applying low compression forces not only help to protect the machine but also act as a tool against fast mechanical wear and prevent the blend from segregation in the feed hopper (34).

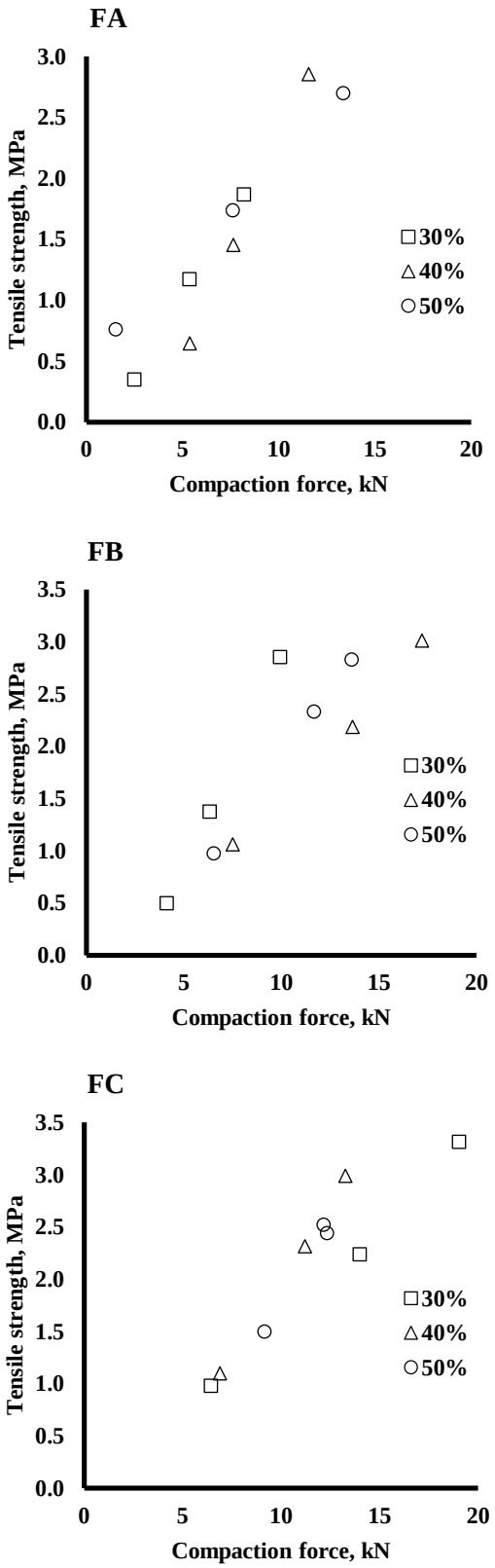

Figure III-15. Compaction behavior of multiple-unit orodispersible formulations at different percentage of MCC pellets.

In all formulations, the feasibility to compress different percentage of MCC pellets into multiparticulate orodispersible tablets was successful and their results are shown in Table III-7 to III-9.

a) Weight and Mass variation

The weight of MUP-ODTs was found in the range of 56-66 mg, it increased as the proportion of pellets increased. Besides, the MUP-ODT weight from different orodispersible granules varied due to their different densities. Nevertheless, the relative standard deviation from all batches was less than 6% and meets with the Ph. Eur. criteria of mass variation (Table III-7 to III-9).

b) Hardness

In all cases, harder MUP-ODTs were obtained as the compression force increased and as the proportion of pellets increased (Tables III-7 to III-9). In addition, there was a difference between the disintegrants used: MUPs-ODT containing starch glycolate yielded stronger MUP-ODTs than those containing croscarmellose or crospovidone. These results are similar to results obtained by Mehta et al. (31), where the interaction between starch pellets and croscarmellose or starch glycolate increased the hardness whereas the use of crospovidone decreased the hardness. In the case of orodispersible tablets, it is difficult to achieve enough mechanical strength after the compression process. Hence, the development of MUP-ODTs will bring a challenge: compress at lower range which facilitate both the further disintegration in the mouth and, have enough mechanical resistance to be able to withstand handling without substantial breakage (35,36).

c) Friability

Considering the brittle orodispersible tablets yielded by different processes, some authors have proposed increasing the percentage of friability until 1.5% for those tablets. However, there is not any official guideline which supports this statement yet (37,38). However, in this study, MUP-ODTs compressed at low compression forces (2-5 kN) showed friability values more than 1% and also, they completely fell apart into pellets and granules. MUP-ODTs compressed at medium compression forces (6-9 kN) showed less than 1% friability and, MUP-ODTs compressed at higher compression forces (10-17 kN) not only presented friability values less than 0.4% but also they were nearly intact after 2 min of test (Table III-7 to III-9) meeting the Ph. Eur. requirements.

Table III-7. Pharmacotechnical test of placebo MUPs-ODT using crospovidone as disintegrant agent.

FA							
Run	% Pellet	CF (kN)	Weight (mg)±SD	Mass Variation (%)	Hardness (N)±SD	Friability (%)	Disintegration time (s)±SD
4	30	3	57.1±1.6	2.8	7.5±1.2	11.28	5±0
5	30	5	58.7±2.9	4.9	20.9±7.9	1.05	11±3
6	30	8	57.7±2.2	3.7	33.9±7.0	0.64	14±1
7	40	5	63.1±1.1	1.7	13.8±2.2	5.32	6±1
8	40	8	62.8±1.7	2.7	29.1±5.3	0.94	10±1
9	40	12	66.2±1.3	2.0	55.0±5.6	0.32	121±23
10	50	2	66.4±1.9	2.9	16.4±3.6	7.76	10±1
11	50	8	66.3±2.5	3.7	34.9±7.6	0.81	22±2
12	50	13	66.5±1.0	1.5	52.5±6.3	0.48	201±5

Table III-8. Pharmacotechnical test of placebo MUPs-ODT using sodium croscarmellose as disintegrant agent.

FB							
Run	% Pellet	CF (kN)	Weight (mg)±SD	Mass Variation (%)	Hardness (N)±SD	Friability (%)	Disintegration time (s)±SD
16	30	4	52.9±2.1	3.9	8.5±2.0	16.19	7±1
17	30	6	52.9±1.4	2.6	23.0±5.1	0.54	28±3
18	30	10	55.3±2.4	4.3	46.4±3.7	0.18	107±1
19	40	8	56.9±2.8	4.9	19.7±3.2	0.53	9±1
20	40	14	57.4±2.3	3.9	38.8±8.5	0.26	57±3
21	40	17	55.0±1.3	2.3	50.1±5.9	0.29	115±6
22	50	7	59.9±2.8	4.7	18.4±6.7	0.89	17±2
23	50	12	60.5±1.0	1.6	41.7±5.0	0.33	106±4
24	50	14	61.4±3.0	4.9	51.2±3.9	0.34	247±11

Table III-9. Pharmacotechnical test of placebo MUPs-ODT using sodium starch glycolate as disintegrant agent.

FC							
Run	% Pellet	CF (kN)	Weight (mg)±SD	Mass Variation (%)	Hardness (N)±SD	Friability (%)	Disintegration time (s)±SD
28	30	7	56.9±1.7	3.0	18.1±3.5	1.18	22±4
29	30	14	56.9±1.8	3.2	38.5±6.1	0.57	75±3
30	30	19	55.6±1.4	2.6	53.4±4.5	0.22	198±7
31	40	7	58.5±1.9	3.2	20.3±6.6	0.63	30±2
32	40	11	58.5±1.8	3.1	40.8±6.5	0.56	131±6
33	40	13	57.9±0.8	1.4	50.9±4.9	0.29	225±11
34	50	9	62.2±2.1	3.5	28.4±5.1	0.75	71±4
35	50	12	64.4±2.1	3.2	47.2±2.8	0.41	257±18
36	50	12	64.5±2.6	4.0	46.0±6.1	0.50	302±10

d) Disintegration time

The time for disintegration of orodispersible tablets is generally less than 3 min according to Ph. Eur., but it is suggested that patients could experience ranges from 5 to 30 s (39). In most of the cases, MUP-ODTs showed fast disintegration times less than 3 min (Table III-7 to III-9); MUP-ODTs containing crospovidone (FA) showed faster disintegration than MUP-ODTs containing croscarmellose (FB) or starch glycolate (FC). The compression force applied and the type of disintegrant are able to affect directly the disintegration time independently of the amount of pellets in the MUP-ODT due to the weakening effect of each disintegrant. Those results were similar to those reported by Lundqvist et al. (40).

e) Porosity and Wetting time

Porosity and wetting time are parameters that can give information related to hardness and disintegration properties of the tablet; however these parameters may be unrelated (41).

It is reported that high tablet porosity facilitates the liquid penetration into the matrix and generates a faster disintegration, nevertheless, the rapid disintegration is related to the hydrophilic properties of the disintegrant agent (41,42). Figures III-16 to III-18 illustrate this situation, where MUP-ODTs from FA showed lower porosity (5-28%) comparing to FB (16-71%) or FC (15-80%) and, their wetting time achieved a faster liquid penetration (5-36 s) than the one of FB (12-67 s) or FC (21-247 s) formulations. The faster wetting time is reached, the quicker disintegration of the tablet will take place. This phenomenon can be explained because each disintegrant follows different disintegration mechanism. Crospovidone absorbs water in a rapidly way to generate a brisk volume expansion and in consequence, the hydrostatic pressure increases and finally tablet disintegration takes place (Douroumis 2011). Sodium croscarmellose swells and absorbs many times its weight in water which tends to increase the viscosity of the liquid within the tablet, therefore further water penetration may be delayed (36). A similar situation is observed for sodium starch glycolate which acts by water uptake followed by rapid and enormous swelling (44,45), as the swelling may be accompanied by gelling, this could occlude the pores in the tablet limiting further penetration of water into the tablet and so a delayed time has been observed (41).

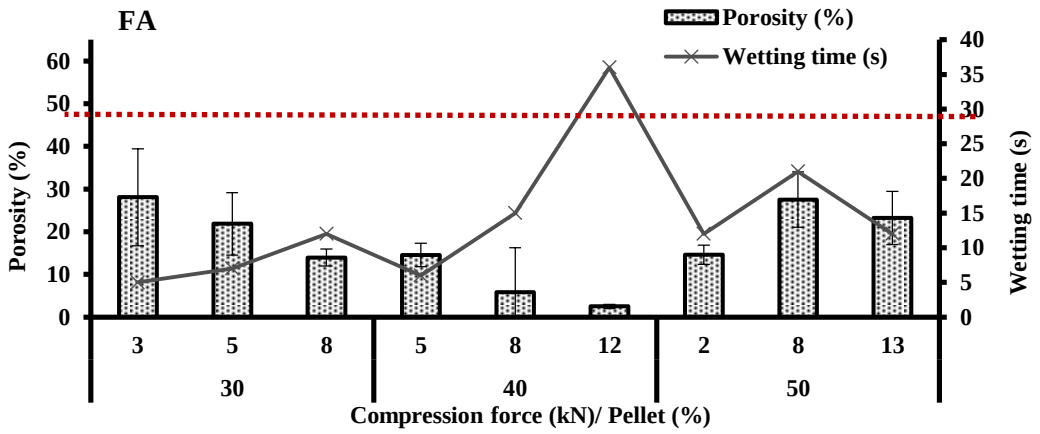

Figure III-16. Influence of pellet concentration and force de compression on the porosity and wetting time of MUP-ODTs using crospovidone as disintegrant agent.

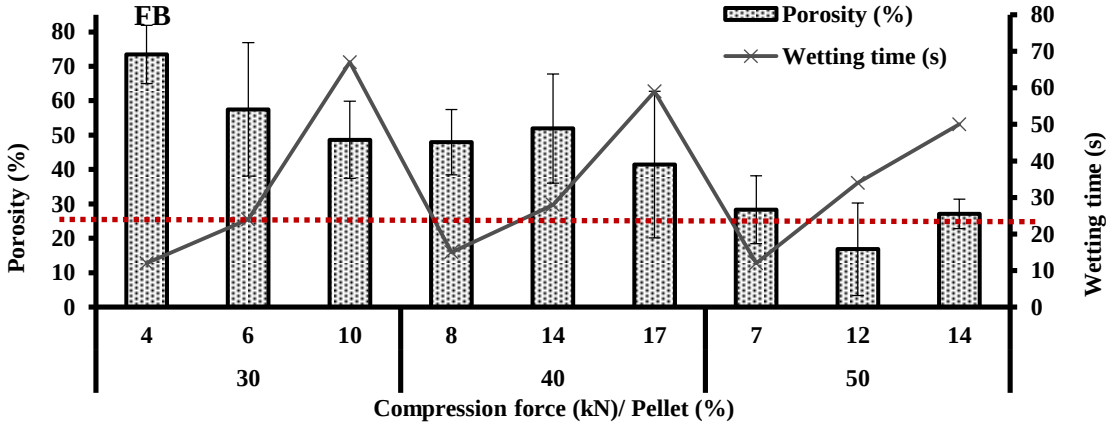

Figure III-17. Influence of pellet concentration and force de compression on the porosity and wetting time of MUP-ODTs using sodium croscarmellose as disintegrant agent.

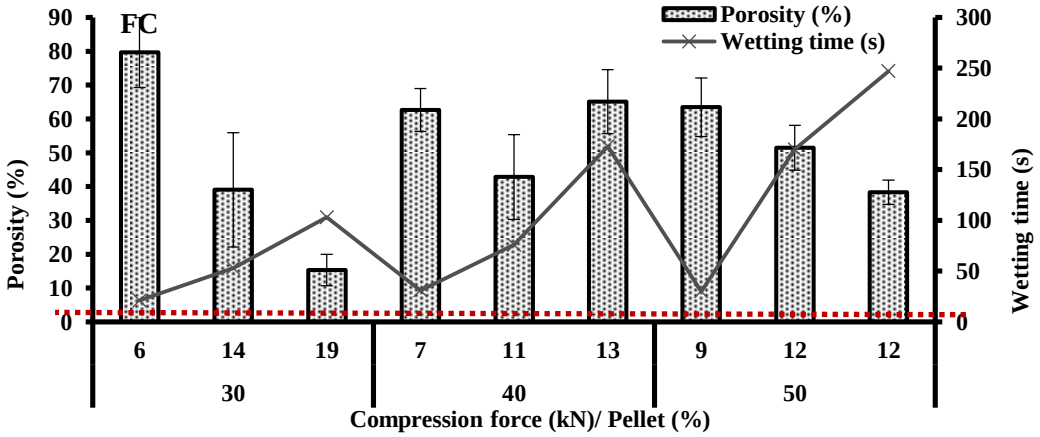

Figure III-18. Influence of pellet concentration and force de compression on the porosity and wetting time of MUP-ODTs using sodium starch glycolate as disintegrant agent.

In the case of 5 mm diameter tablet, the shape of individual pellets and the porosity of the tablet were affected by a high amount of pellets (up to 50%) and higher compression force applied resulting in irregular shape of pellets and increased disintegrations times. Meanwhile, the ratio 40% MCC pellets/60% orodispersible granules containing crospovidone (FA) as disintegrant was able to be compacted by plastic deformation and showed the best influence over croscarmellose (FB) or starch glycolate (FC) on their mechanical properties (Figure III-19): a compression force between 5-7 kN was sufficient to obtain tablets with acceptable hardness (29 N), acceptable friability (0.9%) and faster disintegration time (10 s). Therefore, this formulation was chosen for ing the drug release of acetaminophen contained in pellets.

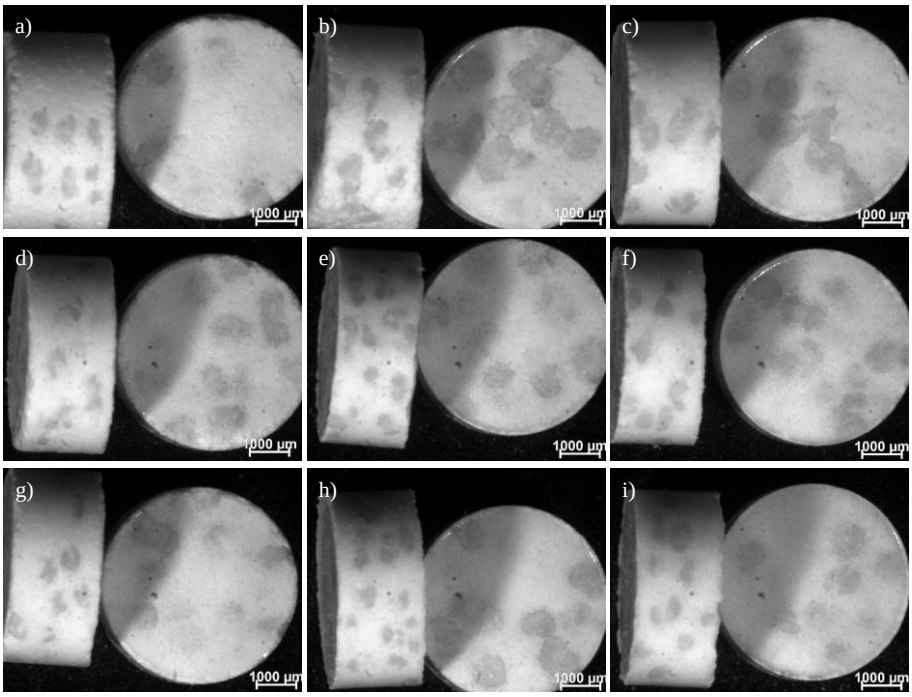

Figure III-19. Stereoscopic images of placebo MUPs-ODT formulations containing 40%of MCC pellets and 60% of orodispersible granules at different compression forces, a-c) FA formulations, d-f) FB formulations and g-i) FC formulations (Magnification 2X).

3.2.3 Influence of disintegrant on drug pellet release

All formulations were successfully compressed into ODTs meeting the Ph. Eur. specifications and the results are shown in Table III-10. MUPS-ODT presented similar hardness. FA and FC MUPS-ODT had friability less than 1% meanwhile FB failed. All MUP-ODTs showed faster disintegration and wetting time (less than 30 s) confirming that

tablets containing crospovidone (FA) presented also higher porosity and achieved faster disintegration compared to tablets containing croscarmellose sodium (FB) or sodium starch glycolate (FC). By using the same particular size for orodispersible granules and for pellets, content uniformity and weight variation met the Ph. Eur. specification.

Table III-10. MUPs/ODTs properties: influence of disintegrant agent.

	FA-MUPS	**FB-MUPS**	**FC-MUPS**
Hardness (N±SD)	19.1±9.2	22.5±12.4	25.1±10.4
Disintegration time (s±SD)	10±2	26±1	26±4
Friability (%)	0.76	1.23	0.85
Porosity (%±SD)	32.2±2.4	29.5±1.9	17.3±0.6
Wetting time (s±SD)	8±1	13±3	20±1
Drug content (%±SD)	100.0±9.5	100.0±4.3	100.7±8.6
Content uniformity (%CV)	9.5	4.3	8.6
Weight variation (%CV)	4.9	5.1	4.3

Figure III-20 shows that orodispersible granules met the purpose acted as cushioning agent during the compression and separated rapidly the pellets from each other and prevent their fusion. It can be observed that the main pellet deformation occurred on the tablet surface due to the contact with a hard surface of the punch or others pellets (46).

Similar drug release was found in all formulations. The dissolution profile of MUP-ODT was performed in pediatric stimulated gastric fluid (pH 1.5) where 75% of release was achieved at 15 min and more than 90% after 30 min. The similarity factor (f_2) values for drug release profiles of FA, FB and FC MUP-ODTs versus uncompressed pellets were 81, 82 and 74 respectively, which proved that pellets maintained their release properties and the orodispersible granules did not affected the drug kinetic (Figure III-21).

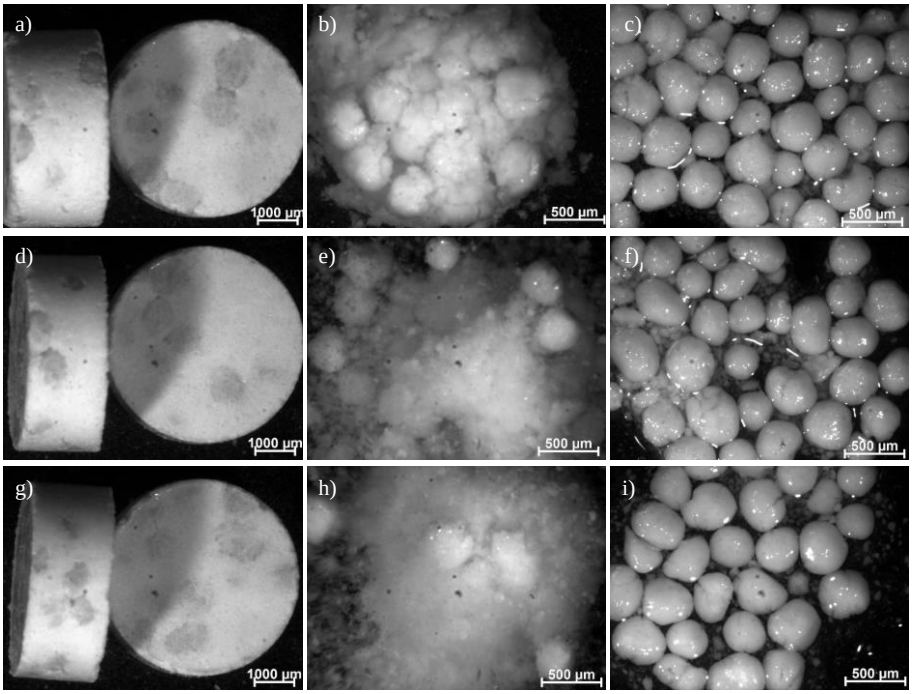

Figure III-20. Stereoscopic images of MUPs-ODT: influence of disintegrant agent on the pellet release from the tablet a-c) FA formulations, d-f) FB formulations and g-i) FC formulations (Magnification 2X).

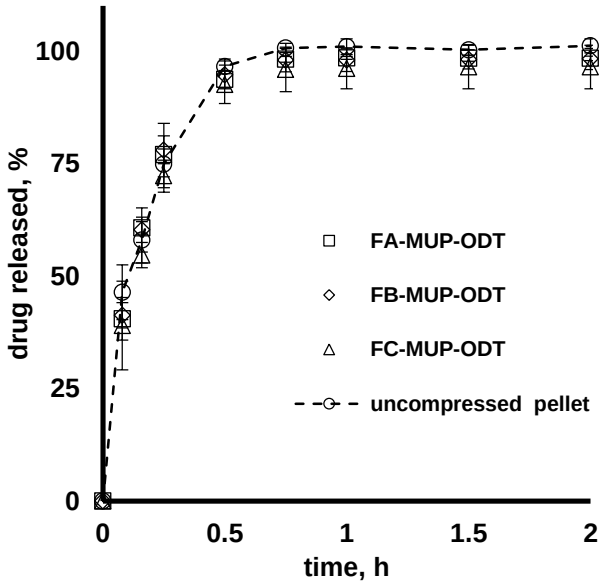

Figure III-21. *In-vitro* dissolution profile of APAP pellets contained into ODT using different disintegrants. Apparatus 2, speed 50 rpm, volume 500 ml, medium SFG pH 1.5.

Conclusions

Multiple Unit Orodispersible Tablets (MUP-ODTs) with a diameter of 5 mm were successfully produced for different percentages of pellets and compression forces, meting all specifications of the Ph. Eur. The optimal level of orodispersible granules to ensure an adequate disintegration was identified: 60% of placebo orodispersible granules and 40% of pellets making it possible to give tablets with desirable orodispersible characteristics.

By using matrix pellets, it was possible to vary the drug release profile into orodispersible tablets, avoiding the burst effect; therefore combination of both technologies can provide a novel dosage form for pediatric use, not only enable to give fast disintegration and modified properties but also to offer easy swallowing and dose flexibility.

3.3 Development of controlled release multiple-unit orodispersible tablets

Acetaminophen (APAP) is the most common non-prescription analgesic and antipyretic agent in infants, children, and adults. Most of the marketed children formulations of APAP are available as syrup, suspensions and tablets. Due to its short half-life, it is required to be administrated in a frequency of 4 to 6 times a day and only sustained release formulations are address to the need of adults and present a difficulty for administration to pediatric patients.

In the traditional extrusion-spheronization process, microcrystalline cellulose (MCC) has widely be used as standard excipient due to its proper rheological properties (47). Though, different types of Eudragit® have demonstrated their applicability as extrusion-spheronization aid (48). In our previous study, MCC:Eudragit matrix pellets showed good shape and mechanical properties, which indicated that Eudragit was a suitable palletization aid. Moreover, they showed slower release compared to MCC:Lactose and MCC:Ethylcellulose matrix pellets. The potential of pellets for controlled release and taste masking when they are incorporated into orodispersible tablets (MUP-ODT) can be investigated. Therefore, a formulation using acetaminophen as a model drug in an MUP-ODT with controlled-release should improve the patient acceptability and could also lead to the reduction of the number of doses administered; leading to better patient compliance, less chance of overdose and also, it could reduce the cost associated with the temporary relief or minor aches and pains.

The main objective of this study was to develop a Multiple-Unit Pellet Orodispersible Tablet (MUP-ODT) which permits the controlled-release of APAP contained in pellets into orodispersible tablets with sufficient hardness, good disintegration behavior and without significant change in the release profile after compression. The first part of this study determined the physical properties of APAP pellets using different percentages of Eudragit® to create the matrix system by extrusion-spheronization technique. The second part evaluated the mechanical properties and dissolution properties of MUP-ODT produced.

3.3.1. Pellets characterization

It was possible to produce pellets with different ratios of MCC and Eudragit RSPO. All batches presented an acceptable yield over 70% in the range of 70.2-78.9%. A proportion of water was substituted by Eudragit RS 30D, acting as binder during the wet granulation and as plasticizer and lubricant agent during the extrusion process. The blends presented sufficient plastic deformability to pass throughout the rollers and to support the spheronization process even though higher speed and time of spheronization were required to produce these pellets compared to the classical formulation. As a normal process, raw material was lost during the extrusion step where the wet mass adhered to the rollers surface.

The size of pellets showed a mean in the range of 710-1250 μm (Figure III-22), nonetheless for the purpose of compression, only the 710-1000 μm fraction was chosen for its specific surface area which is important to achieve a reproducible dissolution pattern of the API (4). Table III-11 summarizes the yield percentage obtained and the mean particle size from this fraction.

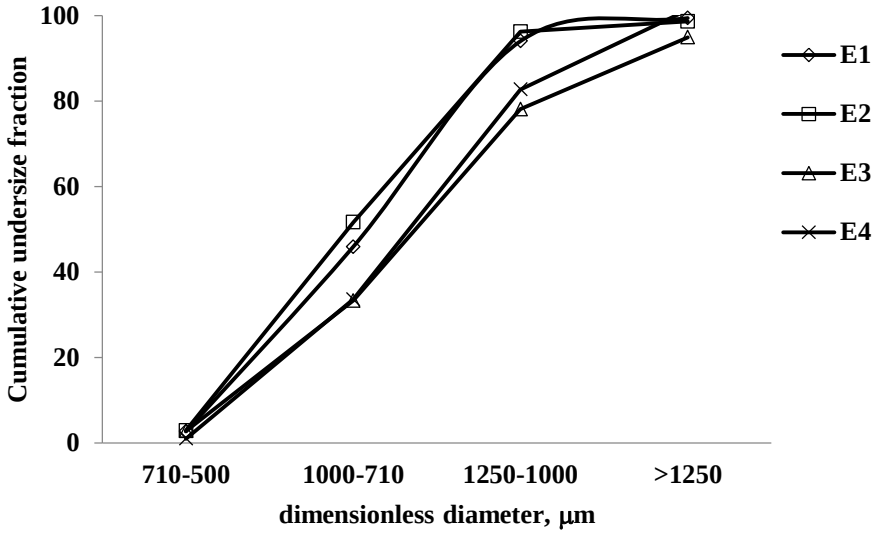

Figure III-22. Size distribution of APAP pellets using different ratio of Eudragit determined by sieve analysis.

There is not a correlation between the particle size distribution and the polymer ratio, neither between the amount of water required and the particle size distribution or yield

percent. However, by increasing the amount of Eudragit RS 30D, the amount of water required to get a suitable mass decreased. This can be attributed to the quaternary ammonium substitutions in Eudragit RS 30D providing an easy wettability to the blend during the granulation and acting as plasticizer and lubricant in the extrusion process (49).

Table III-11. Yield of the pelletization process, mean diameter size and aspect ratio from 710-1000 µm fraction from Eudragit matrices.

Formulation	Yield (%)	Diameter (µm±SD)	Aspect ratio
E1	48.1	954±97	1.04±0.11
E2	44.6	1007±117	1.08±0.14
E3	44.8	928±110	1.07±0.12
E4	49.1	951±149	1.09±0.14

Microscopy and scanning electron micrograph (SEM) examination indicated that pellets were generally spherical, with regular size, shape and smooth surface (Figure III-23). The aspect ratio ranged between 1.04 and 1.09, which is in agreement with the literature précising that the aspect ratio of pellets should be lower than or equal to 1.2 (6). Additionally, the shape and sphericity aspect of the pellets were not altered when the drug loading decreases as it has been reported in the literature (11).

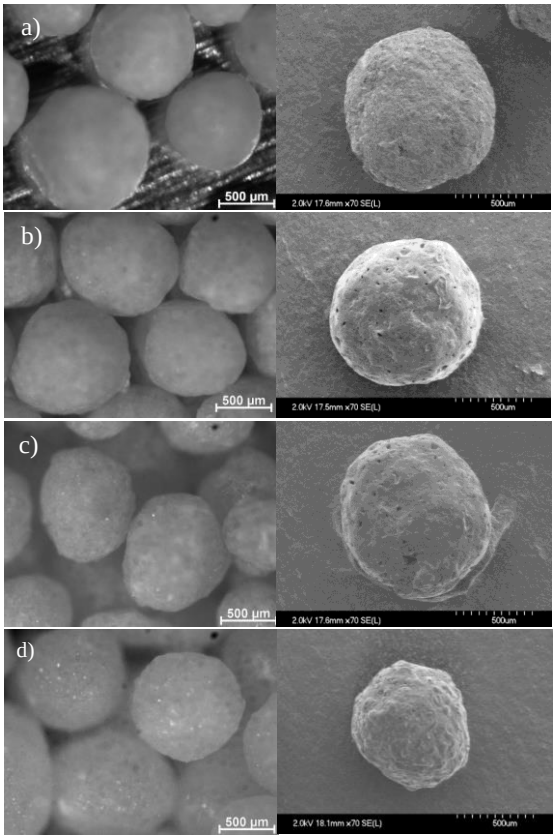

Figure III-23. Stereoscopic image (left) and SEM micrographs (right) of APAP pellets from different concentrations of Eudragit (a) E1, (b) E2, (c) E3 and (d) E4.

The physical properties of all pellets obtained from 710-1000 µm fraction prior to compression are shown in Table III-12. All formulations showed moisture content less than 2%, the range was of 1.2 to 1.9%. The drug content was found in the range of 102 to 110% w/w, which met with UPS specification (90-110% w/w).

Table III-12. Physical properties of Eudragit (RSPO/RS 30D) pellets.

	E1	**E2**	**E3**	**E4**
Water loss on drying (%±SD)	1.3±0.1	1.9±0.2	1.3±0.1	1.2±0.1
Hardness (N±SD)	9.0±1.6	10.1±2.3	12.2±1.9	15.4±2.7
Tapped porosity (ε%)	47.1	49.7	43.0	38.2
Drug content (%±SD)	109.8±1.1	102.9±4.0	109.0±1.5	104.4±4.3
Dissolution test (SGF)				
- Q = 45-65% at 15 min	52.2±2.0	48.2±0.8	49.8±3.3	36.1±1.6
- Q = 60-85% at 1 h	85.3±1.3	77.9±1.4	75.3±0.8	59.4±0.8
- Q ≥ 85% at 3 h	91.5±1.8	99.0±4.4	93.3±0.1	83.4±1.6

Eudragit pellets demonstrated values of hardness between 9 to 15 N, Figure III-24 illustrates the force-distance graphs obtained by texture analyzer, where the amount of Eudragit has a considerable effect on crushing strength of pellets due to its plastic nature. Pellets from formulation E1 showed a brittle behavior and they broke into fragments. By increasing the ratio of Eudragit, E2 and E3 produced harder matrices, whereas further increased in E4 showed high tendency to plastic deformation.

In addition, tapped porosity values were between 38 to 49%, which meet with desirable parameters (7). Both hardness and porosity parameters can be inversely related to the time and heat-treating performed after spheronization (2). It is reported that Tg of Eudragit RS 30D is 55°C and the one of Eudragit RSPO is 60°C (50). So, using higher temperatures than the Tg temperature during the drying step allows a rearrangement in the polymeric network through the matrix which decreases the porosity (51) and then, by increasing the ratio of Eudragit, the polymer provides more plastic mass which promotes densification of the matrix producing harder pellets after drying (11,51,52). On that account, our pellets would be able to support the compression force without significant damage after compression.

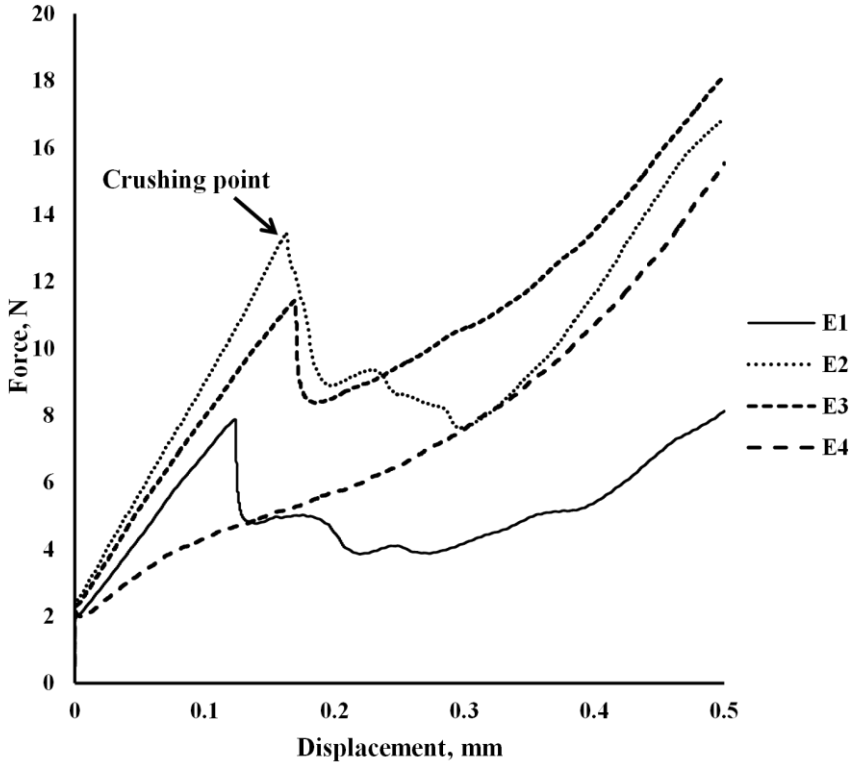

Figure III-24. Deformation behavior of individual Eudragit pellets under mechanical load.

DSC thermograms of APAP, polymers, drug-polymer physical mix and pellet after heat-treatment were carried out in order to evaluate any possible solid-state interactions between the polymer and the API. Figure III-25 presents the thermogram of APAP (a) that showed a single sharp fusion peak at 170.47°C, which is characteristic of the form I whose melting transition is reported in the range of 157-172°C (12,13). The thermogram of Eudragit RSPO/RS 30D (b) did not show a specific endothermic peak. The DSC patterns corresponding to E1-E4 pellets formulations after thermal heating reveled a small peak of fusion onset at 167.62 (c), 164.23 (d), 161.59 (e) and, 142.48°C (f) respectively. The modification in the thermal profile of the APAP may be due to drug-polymer interaction particularly in F4 where the API is dispersed into the higher content of polymer presented in the matrix system.

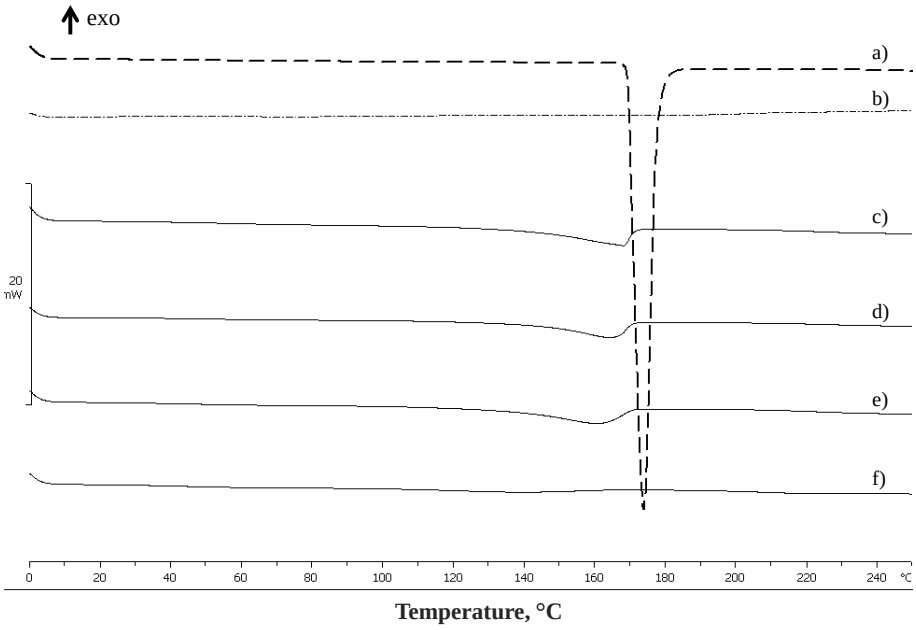

Figure III-25. DSC thermograms of Eudragit-APA pellets (a) APAP, (b) Eudragit, (c) E1, (d) E2, (e) E3 and (f) E4.

To evaluate the interaction between drug-polymer, X-ray diffraction of APAP, Eudragit, and pellets heat-treated were obtained. Figure III-26 shows that the X-ray diffraction peaks of pure APAP (a) occurred at 2Θ = 12.0 13.8, 15.5, 16.7, 18.1, 20.4, 20.8, 23.5, 24.3 and 26.5 meaning that APAP was in its crystalline form I (53). Eudragit (b) did not show any peak in its diffraction patter as it is an amorphous polymer (52). The physical mix (c) showed a diffraction peak at 2Θ = 22.0-22.7 which corresponds to the MCC. The diffraction peaks of APAP in heat-treated pellets (d-g) presented the same position which

indicates there was not any change in the crystalline form of the API during the heat-treatment as it was already confirmed by the DSC thermograms.

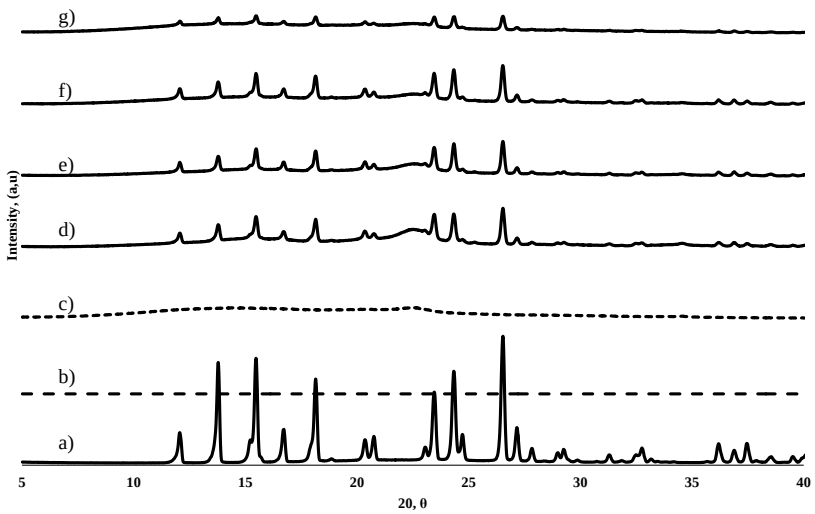

Figure III-26. XRPD patterns of Eudragit-APA pellets (a) APAP, (b) Eudragit, (c) placebo physical mix, (d) E1, (e) E2, (f) E3 and (g) E4.

3.3.2. Influence of the matrix formulation on drug dissolution

Drug release profiles from Eudragit pellets were compared in three different dissolution media: SGF pH 1.5, SIF pH 6.8 and water. Figure III-27 shows that similar drug release was observed in E1, E2 and E3 through which 46-55% of APAP was achieved during the first 15 min, 75-90% after 1 h, and 92-100% after 3 h in the three different mediums. Meanwhile E4 showed a slower APAP release compared to the other formulations: 36-41% at 15 min, 59-70% at 1 h and 83-94% after 3 h in the three media.

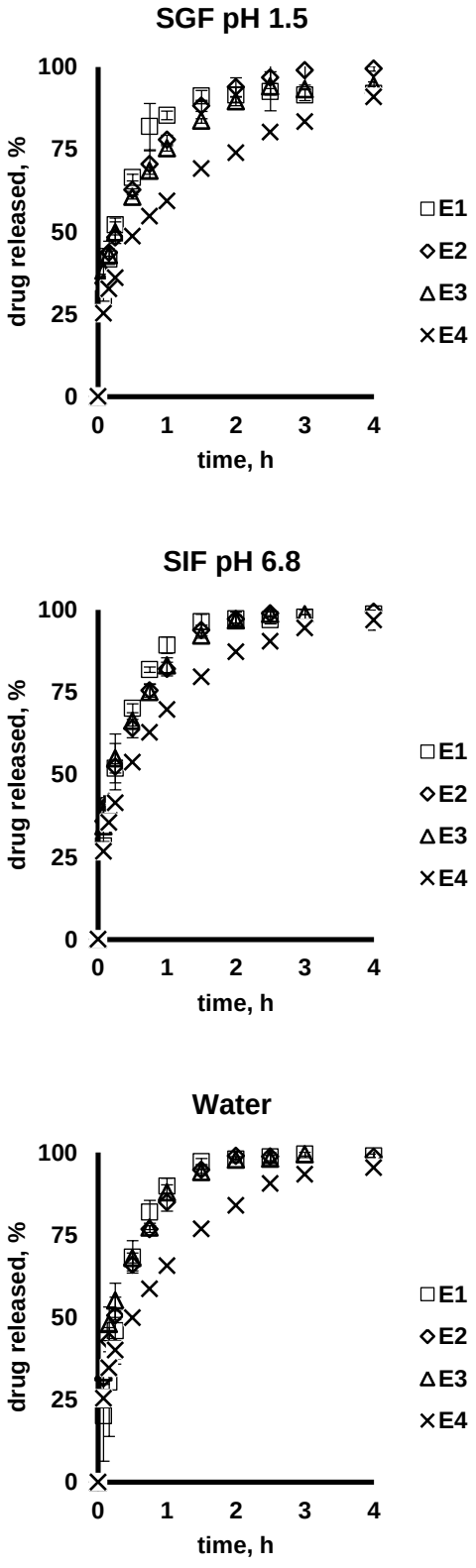

Figure III-27. Comparison of dissolution profile of APAP pellets contained in different matrices. Apparatus 2, speed 50 rpm, volume 500 ml, medium (a) SGF pH 1.5, (b) SIF pH 6.8 and (c) water.

Similarity factor (f_2) was calculated and formulations E1, E2 and E3 showed comparable values in each medium and between them as Table III-13 showed. On the contrary, dissolution profiles of E4 did not show similar dissolution. It is suggested that heat-treating below the Tg of the polymer does not alter the drug release rate, whereas applying greater temperatures than the Tg can modify the release rate due to the reorientation in the polymeric network, hence, it creates a barrier against drug release out of the matrix system (54). As APAP is a high water soluble drug, its dissolution rate was not affected by the pH of dissolution media. The differences in the drug release could be associated to the higher total polymer loading used in the pellets and the thermal heating which delayed the erosion process of the matrix system (55–57).

Table III-13. Similarity factor (f_2) in different mediums.

f_2	SGF pH 1.5	SIF pH 6.8	Water
E1 vs E2	69	71	65
E1 vs E3	63	73	60
E1 vs E4	43	50	46
E2 vs E3	81	91	82
E2 vs E4	47	55	48
E3 vs E4	50	54	46

3.3.3 MUP-ODT compression

To produce controlled release MUP-ODTs, as our preliminary study showed, 40% of drug load pellets were mixed with same particle size of mannitol based orodispersible granules in order to avoid and reduce the segregation problem (58). The compaction influence of pellets was studied and their physicochemical properties are shown in Table III-14. Only MUP-ODTs produced from formulations E1 and E2 met all the Ph. Eur. specifications, yielding similar values of hardness (26-29 N), friability below 1% (0.7%) and fast disintegration which was less than 3 min. The drug content, uniformity content and mass variations met the Ph. Eur. specifications, indicating uniform distribution of the API in the MUP-ODTs.

Table III-14. Multiple-Unit Pellet Orodispersible Tablet (MUP-ODTs) properties.

	E1	**E2**	**E3**	**E4**
Hardness (N±SD)	26.4±4.6	29.5±4.5	30.4±2.9	17.3±2.3
Disintegration time (s±SD)	45±2	67±9	31±1	19±1
Friability (%)	0.71	0.72	2.14	15.95
Porosity (%±SD)	33.2±8.0	43.5±8.6	29.3±2.0	36.4±2.8
Wetting time (s±SD)	27±10	55±29	42±8	25±3
Drug content (%±SD)	96.4±10.4	105.4±9.2	101.2±10.2	106.1±2.4
Uniformity of content (L2)	23.0	22.3	20.3	21.2
Mass variation (%CV)	3.3	2.2	2.8	3.2

Although MUP-ODT from formulations E3 and E4 presented an acceptable disintegration time (less than 60 s), tablets showed weak hardness values, which means that MUP-ODTs have no resistance to mechanical stress and therefore, high friability value was obtained. This effect could be attributed to yielded plastic pellets which presented a high crush point, therefore the deformation of pellets was not complete hindering the sufficient coalescent of orodispersible granules that surrounds the pellets (1).

After compression, pellets remained as coherent individual units as Figure III-28 shows, indicating that the orodispersible granules separate successfully the pellets from each other; Bashaiwoldu et al. report that the polymer used has an influence on the crushing strength and spherical shape of pellets after compression (59). The pellet deformation was produced not only when they are in contact with a harder surface, that is to say the punches for those at the surface or the other pellets for those inside the tablet, but it also depends on the amount by volume in the tablet (32).

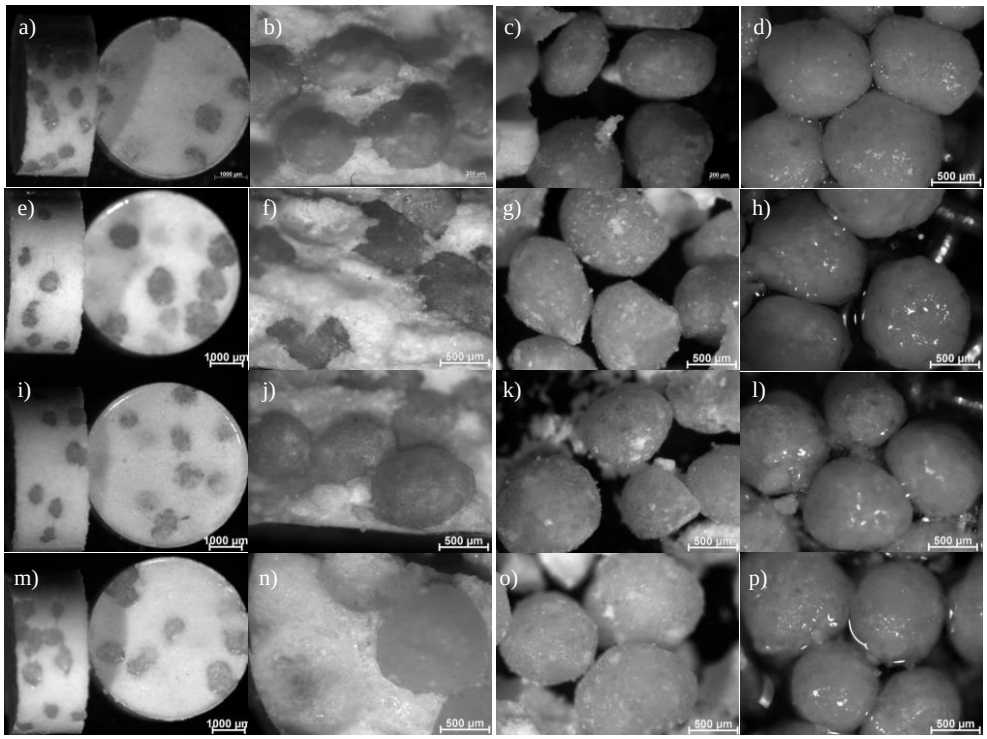

Figure III-28. Stereoscopic images of MUPs-ODT influence of the polymer in the matrix (Magnification 2X). Pellets after compression and disintegration a-d) E1, e-h) E2, i-l) E3 and m-p) E4 (Magnification 6X).

3.3.3.1 Drug release

Dissolution profile of MUP-ODT was performed under pediatric gastric conditions as the effects of gastric pH are further pronounced when gastric residence time is prolonged and dependent upon the characteristics of the drug (as pKa, solubility profile, etc.) (60). In this study, similar drug release was observed before and after compression of pellets into tablets: MUP-ODTs E1, E2 achieved 45-51% of APAP during the first 15 min, 85-90% after 1 h and complete release after 3 h. Meanwhile MUP-ODTs E3 and E4 showed a slower drug release after compression: 30-37% at 15 min, 57-78% at 1 h and 85-99% after 3 h (Figure III-29) probably because of the compression applied from all direct compression excipients reducing the pellet porosity (61). Nevertheless, the f_2 values compared with original pellets alone were 78, 64, 56 and 67 respectively, which proved that both formulations maintained their release.

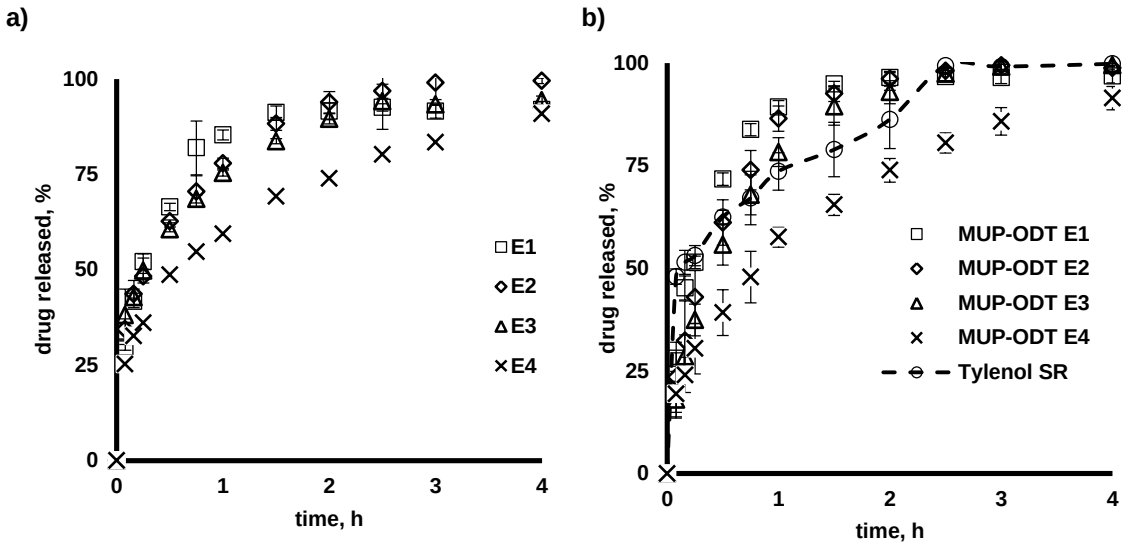

Figure III-29. *In-vitro* dissolution profile of APAP pellets before compression (a) and after compression (b). Apparatus 2, speed 50 rpm, volume 500 ml, medium SGF pH 1.5.

On the other hand, drug release profiles from MUP-ODT E1 and E2 showed a similar dissolution than Tylenol® in SGF pH 1.5 for which 50% of APAP was released during the first 15 min and controlled release observed afterwards. The similarity factor of MUP-ODT E1 and E2 respect to Tylenol® ER tablet was 51 and 50 which proved that both MUP-ODTs formulations are similar.

3.3.4 Taste masking

3.3.4.1 In-vitro dissolution

Different methods have been developed to evaluate the taste-masking properties of oral dosage forms. Human taste panel is the preferred method for taste assessment, however, due to the cognitive ability of the children it is quite difficult to perform a children taste panel (20). Dissolution test is one of the methods that can be performed by quantifying release of the drug in simulated oral cavity conditions (21,22). The drug release was monitored using a continuous flow system that allows not only mimicking the realistic conditions in the mouth, but also predicting the taste masking effect. Figure III-30 shows the release profiles as a function of time for unmasked APAP as pure drug and the pellet formulations E1-E4. It was found that the APAP amount released within the first 2 min was 10.8, 14.1, 21.6 and 10.2% respectively compared to the amount release for the pure drug which was 29.8%.

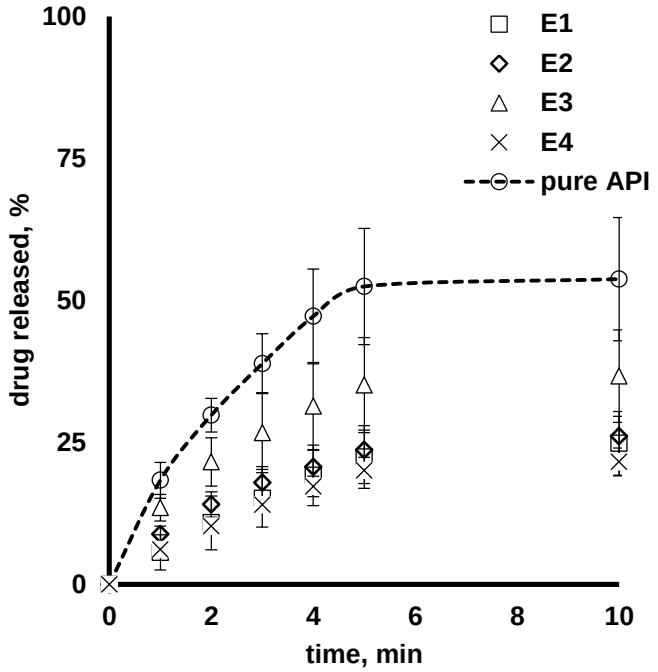

Figure III-30. *In-vitro* evaluation of APAP pellets containing using different matrices by continuous flow system.

According to literature, in case of orodispersible tablets, a drug release less than 10% within the first 5 min of dissolution may be used as a criterion to indicate a successful taste masking (62); in our case, formulations E1 and E4 were close to the limit. Anyhow, dwell a solid dosage form in the oral cavity of the child for 5 min could compromise the properties of multiparticulate systems like MUPS-ODTs designed to be swallowed without chewing. Therefore, as suggested Petrovick et al, the residence time should not exceed 60 s (63). Thus, 1 and 2 min of dissolution were chosen to investigate the drug release properties, where during the first minute the drug release ranged 5-10% and in the second minute 10-20% which means our pellets had a significant role in decreasing the drug release during the first minute, therefore they can be an approach for taste masking.

3.3.4.2 Electronic tongue analysis

The analysis was performed on pellets and on MUP-ODTs. Sample compositions for e-tongue analysis are indicated in Tables III-15 and III-16:

Table III-15 Pellet composition (710-1000 µm).

Ingredient	Concentration (% w/w)		
	F1-P1 (F1)	**F2-P4 (E2)**	**F3-P6 (E4)**
APAP	25	25	10
MCC PH 101	37.5	25	10
Lactose 350	37.5	---	---
Eudragit® (RSPO/RS30D)	---	50	80

Table III-16. MUP-ODT composition (5 mm).

Ingredient		Concentration (% w/w)	
		F4-T1 (F2)	**F5-T4 (F10)**
APAP pellet (40%)	APAP	10	10
	MCC PH 101	15	10
	Lactose 350	15	--
	Eudragit® (RSPO/RS30D)	---	20
ODG (59.15%)	Mannitol	45.44	45.44
	MCC	8.94	8.94
	Crospovidone	2.98	2.98
	Sucrose	1.79	1.79
0.85%	MgSt	0.85	0.85

For each formulation, a reference was also tested; it was the placebo that is to say the same formulation without the active drug.

The signal of each sensor on each assay was integrated in a matrix of data that could be computed by multidimensional statistic tools. A taste map based on Principal Component Analysis (PCA) can be generated using all sensors. It shows the relative repartition and proximity of taste of each formulation (Figure III-31).

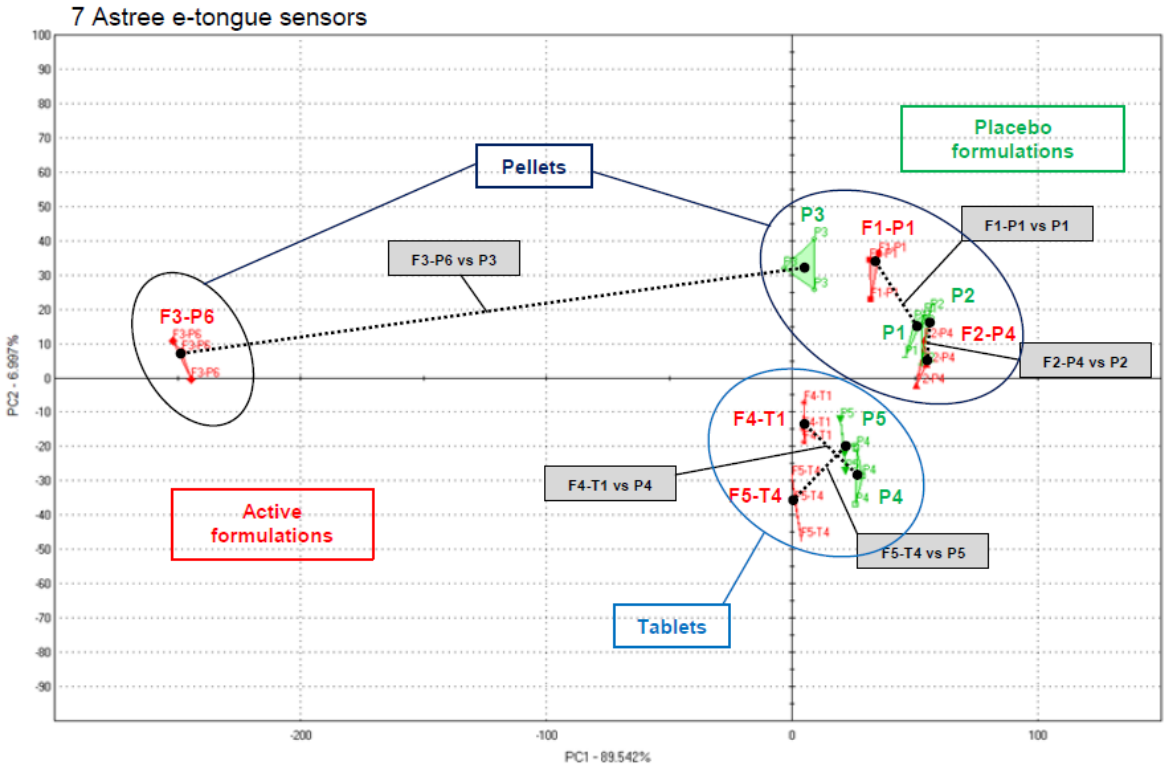

Figure III-31. Taste map based on principal component analysis (PCA) of active formulations and corresponding placebo.

The active formulations and placebos are discriminated along PC1 axis. Especially, samples are divided into three main groups:

- Group 1: samples under pellets form (F1-P1, P1, F2-P4, P2, P3)
- Group 2: sample F3-P6 under pellets form in which the API concentration per gram of pellets is lowest compared to other.
- Group 3: samples under tablets form (F4-T1, P4, F5-T4, P5)

The distribution of samples on the taste map allows seeing the impact of the API concentration on each formulation and the method of encapsulation effect on the resulting taste.

The distances between samples are indicatives of their taste proximity: the lower the distance, the closer the taste. Also, a Discrimination Index (DI in %) was determined for each formulation and the placebo. This indicator takes into account the average difference between the pairs to compare, as well as the dispersion of each sample. The closer index to 100%, the greater is the distance between the centers of gravity and the smaller the

dispersion within groups. The DI will help then to assess the significance of difference between the groups.

The results on distances histograms (Figure III-32) may be interpreted as follows:

- For four of the five distances (F1-P1/P1, F2-P4/P2, F4-T1/P4 and F5-T4/P5), each formulation is close to its placebo (DI < 90 %)
- Distance F3-P6/P3 represents the API impact (quantity of API in mg by gram of pellets) in the pellets formulation: F3-P6 is the formulation that is furthest from its placebo P3, the taste difference is significant (DI > 90 %) between the two samples.

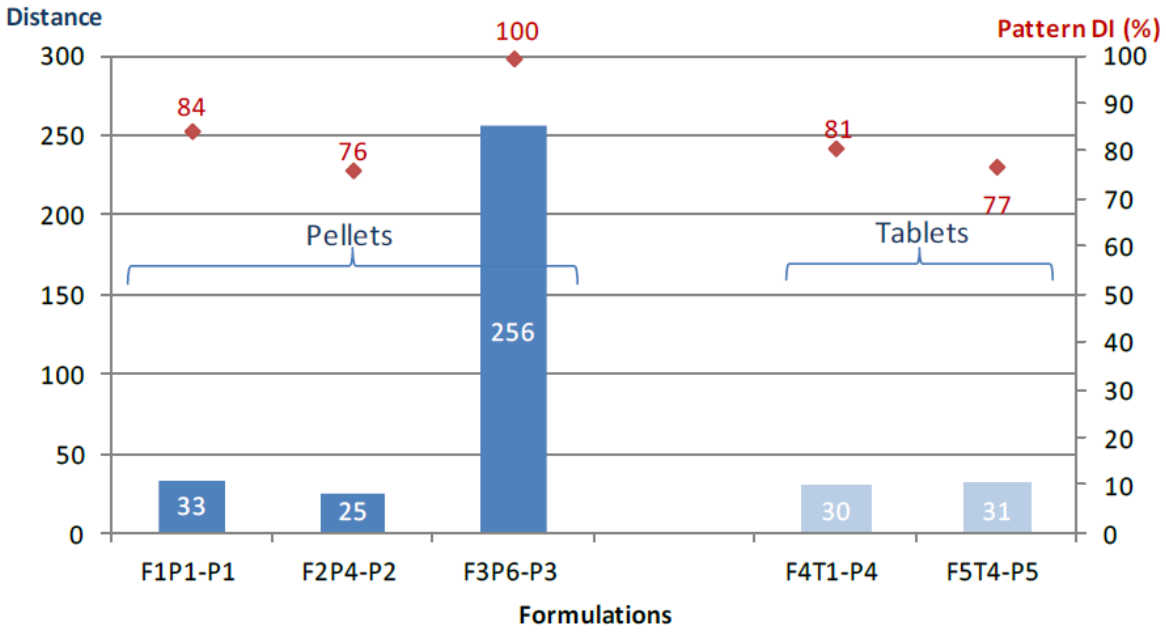

Figure III-32. Distances between active formulations F1-P1, F2-P4, F3-P6, F4-T1, F5-T4 and their respective placebos P1, P2, P3, P4 and P5.

On both PCA and distances histogram, the results show no impact of the formulation. It seems that there is no difference in taste between the active Acetaminophen and placebo formulations regardless of the formulation form (pellets or tablets).
In any case, the taste masking appears to be effective.

The only difference observed in taste is due to the amount of API present in the pellets upstream: F3-P6 formulation is furthest from its placebo P3 (100 mg API/g_{pellet}). All other formulations seem to have a similar taste.

Conclusions

Acetaminophen matrix pellets based on Eudragit RS PO and RS 30D were produced successfully using extrusion-spheronization technique. The resulted pellets showed acceptable mechanical properties.

As oral drug delivery systems, MUP-ODTs containing 40% of drug load pellets were successfully produced with good mechanical properties, friability less than 1% and disintegration time less than 60 s and met the requirements for controlled release dosage forms of the Ph. Eur. and the USP.

During the first 60 seconds, the pellets produced had a significant role in decreasing the drug release, limiting the contact between the bitter drug and taste buds in the mouth; therefore they can be an approach for taste masking.

Systems like pellets and MUP-ODTs can constitute an alternative approach in pediatric formulations not only because they enable both fast disintegration and controlled extended release properties, but also offer easy swallowing and flexible dosage.

3.4 Feasibility to compress orodispersible pellets for pediatric use

Multiparticulate dosage forms such as mini-tablets and pellets offer potential advantages for pediatric population compared to single-unit dosage forms (i) as they distribute fast through the gastrointestinal tract, thus reducing local irritation caused by the active ingredient, enhancing drug absorption and decreasing fluctuation of plasma peaks, (ii) they offer the possibility of being either filled into hard capsules or compressed into rapidly disintegration tablets (64,65), (iii) from the economical point of view, it is possible to produce tablets from pellets at lower cost than pellet-filled capsules and moreover (iv) it is possible to control the drug release rate, resulting in fewer adverse effects (1,66).

In our previous study, mannitol-base granules were used as cushioning agent to produce Multiple-Unit Orodispersible Tables (MUP-ODT) with desirable disintegration properties which could improve the palatability and acceptability in children. The feasibility to produce orodispersible pellets (ODP) by extrusion-spheronization can be an approach for new pediatric formulations.

The aim of this study was to produce drug-free ODP and, by a design of experiments explore the feasibility to compress drug-free ODPT and MCC pellets to obtain a Multiple-Unit Orodispersible Table (MUP-ODT) and determine the optimal level of formulation (percentage of MCC pellets and lubricant) and process factor (compression force). This study was carried out using tablets size of 5 mm in diameter which are suitable for children aged 3 to 5 years (27).

3.4.1 Drug-free mannitol based pellets

Different excipients have been investigated as alternatives to substitute MCC used as spheronisation aid and to promote a fast disintegration or drug release (47).

Mannitol is widely used as active ingredient, soluble drug model and filler for orodispersible formulations which presents ductile properties like MCC (28,67).

Mannitol-based pellets were successfully produced, with an acceptable high yield over 84%. A few amount of water was required to produce a suitable wet mass which was able to spheronize and to obtain desirable spherical pellets without agglomerations compared to the amount necessary to produce MCC pellets.

The particle size distribution was found to be in the range of 355-1250 μm. Figure III-33 shows a comparison between the particle size distribution of mannitol-based and MCC pellets. A high percentage of mannitol-based pellets was retained on the sieve 1000-1250 μm (45%) compared to classical MCC pellets (21.5%) but as regards the 710-1000 μm fraction, a higher percentage of MCC pellets (72%) was retained compared to mannitol-based pellets (38%). Pellet size is related to the amount of wetting liquid and drying method: a large amount of water tends to produce pellets with larger mass and median diameters whereas lower amount produces fine fractions (68). Similar results were reported by Goyanes et al. where when high concentrations of mannitol are used, the pellet size increases due to agglomeration during the spheronization step because of its viscous and sticker properties (69).

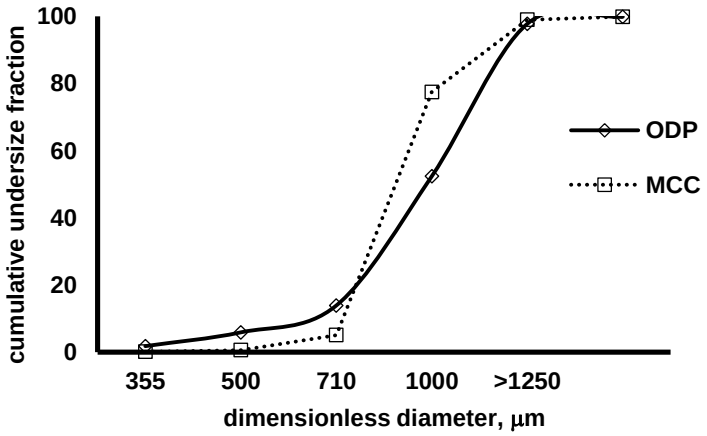

Figure III-33. Comparison of particle size distribution of mannitol-based (ODP) and MCC pellets determined by sieve analysis.

Physical properties of mannitol-based and MCC pellets are compared in Table III-17. Mannitol-based and MCC pellets showed values of 0.98 and 1.33% of moisture content, both are in agreement with desirable requirements (less than 2%).

Table III-17. Physical properties of mannitol-based and MCC pellets

Formulation	Water loss on drying (% ± SD)	Hardness (N ± SD)	Friability (%)	Tapped porosity (ε%)	Aspect ratio
Mannitol	0.98±0.04	5.0±1.8	0.05	38.4	0.92±0.35
MCC	1.33±0.67	8.9±2.3	0.00	55.4	0.97±0.12

Visual examination of mannitol-based pellets by microscopy indicated that pellets were generally spherical (Figure III-34), with regular shape, smooth surface and aspect ratio ranged between 0.92 and 0.97. In accordance with literature, data suggest that the aspect ratio of pellets should be lower than or equal to 1.2 (6).

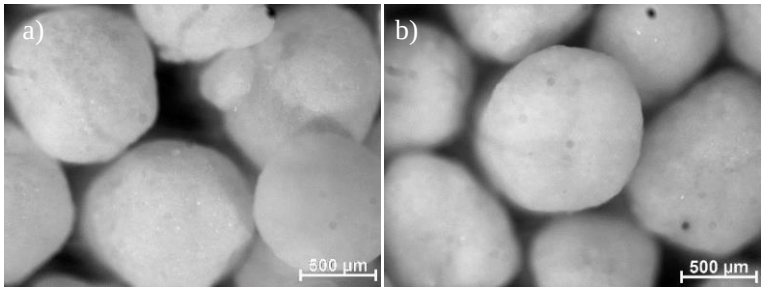

Figure III-34. Stereoscopic image of mannitol-based pellets (a) and MCC pellets (b) (Magnification 6X).

Both type of pellets showed friability values below than 1%, suggesting rugged pellets. It was observed that values of hardness were in the range of 5-9 N which indicate that they are easy to handle for further packing and transportation steps. Notwithstanding on Figure III-35 presenting the force-time graphs obtained by texture analyzer, mannitol-based pellets showed weaker crushing strength compared to MCC pellets which can influence their further compactability.

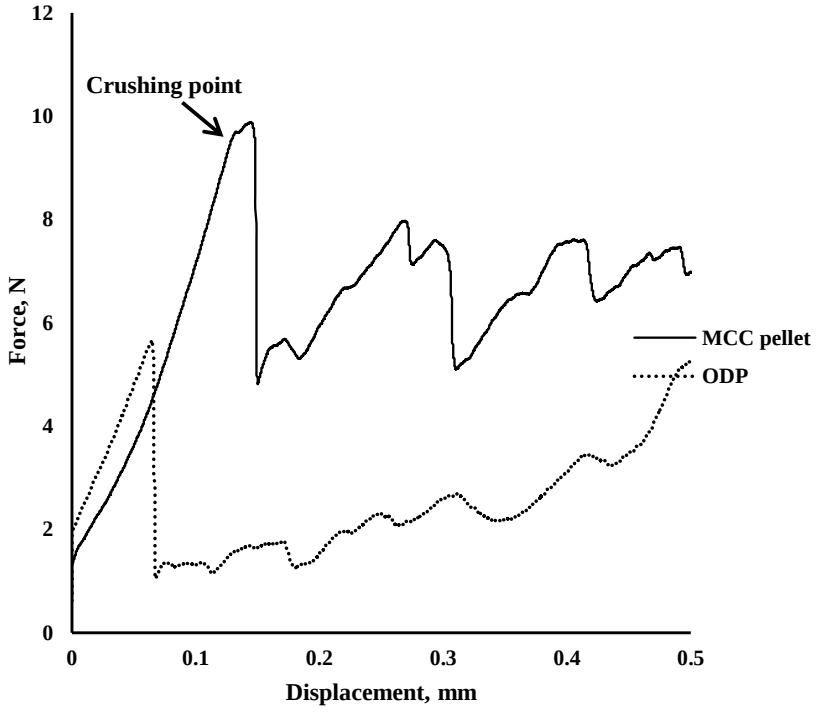

Figure III-35. Deformation behavior of individual pellets under mechanical load.

Mannitol-based pellets showed a tapped porosity (ε%) of 38.4% whereas it is 55.4% for MCC pellets. It is suggested that ideal pellets might exhibit a tapped porosity between 26 to 48%, which is far from the reality because real pellets and beads are neither spherical nor uniform and they have higher values of tapped porosity (7). So, our pellets tend close to desirable values.

3.4.2 Compression properties of MUP-ODT

3.4.2.1 Pre-compression parameters of multiple-unit orodispersible formulations

The influence of percentage of MCC pellets (30, 50 and 70%), amount of lubricant (0.5, 1.0 and 1.5%) and compression force (5-12 kN) were studied and the physical properties of each formulation are shown in Table III-18. Bulk density showed a range between 0.41 to 0.57 g/cm^3 and the tapped density was found between 0.48 to 0.65 g/cm^3 for all formulations. The Carr's index and Hausner ratio were found in the range of 9.3 to 14.3% and 1.1 to 1.2 respectively, suggesting that all formulations present excellent flowability properties.

Table III-18. Characterization of multiple-unit orodispersible formulations.

MCC pellets	**0%**	**30%**	**50%**	**70%**
Bulk density (g/cm^3)	0.41	0.52	0.55	0.57
Tapped density (g/cm^3)	0.48	0.58	0.61	0.63
Carr's Index (%)	14.3	10.5	9.3	9.6
Hausner's ratio	1.2	1.1	1.1	1.1

3.4.2.2 Effect of compression force and percentage of pellets on MUP-ODT

A simulation compaction study was performed in order to study the influence of the compression force on the tensile strength. Compression profiles exhibited a tensile strength increasing linearity through the range of compressed forces applied, the amount of MCC pellets and the lubricant added. Figure III-36 shows that in general, low compression forces from 5 to 12 kN were required to compress MUP-ODTs containing different percentages of MCC.

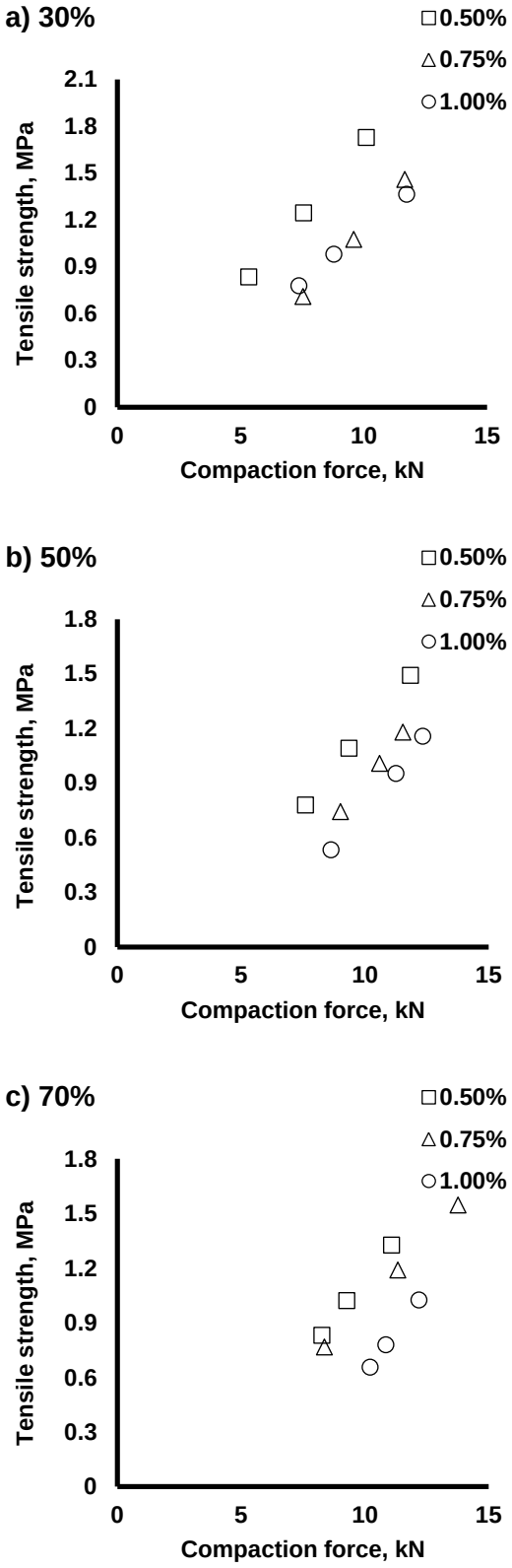

Figure III-36. Compaction behavior of MUP-ODTs formulations at different percentages of MCC pellets a) 30%, b) 50% and c) 70% with percentages of lubricant 0.5% (□), 0.75% (Δ) and 1.0% (○).

The design principle considers as successful formulation that one which is able to keep stable both kinds of pellets and exhibits adequate mechanical properties to handle the MUP-ODTs during the manufacturing process and further transportation until arrive to the customer and, shows a fast disintegration upon hydration. Therefore, experimental responses hardness (Y_1), disintegration time (Y_2) and friability (Y_3) were chosen as dependent variables. Table III-19 shows the results of MUP-ODTs obtained from the experimental design.

a) Hardness

In general, mannitol-based pellets showed an elastic deformation and brittle fragmentation which resulted in compacts with lower hardness as Tables III-19 indicates; however, they had not enough mechanical resistance to be able to withstand handling and showed substantial breakage (Figure III-37).

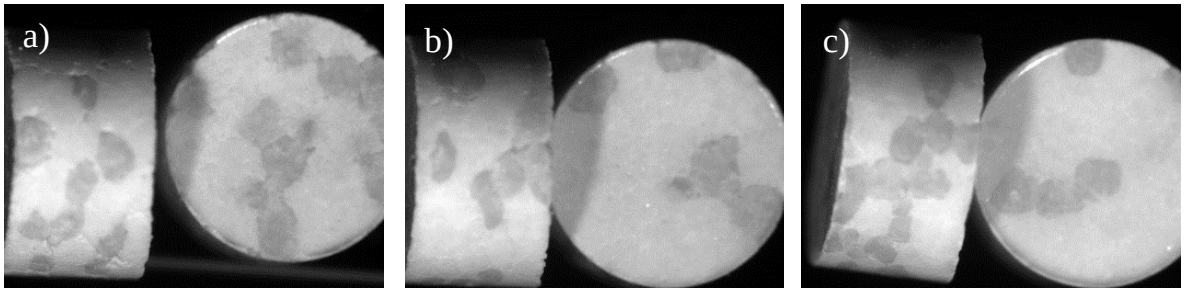

Figure III-37. Stereoscopic images example of placebo MUPs-ODT containing 30% of MCC pellets and 0.5% of lubricant at:(a) 0.8 MPa, (b) 1.0 MPa and, (c) 1.4 MPa (Magnification 2X).

As the proportion of lubricant increased, the values of hardness decreased. As the compression force increased, the hardness value increased. Similar values of hardness were found as the proportion on MCC pellets increased.

b) Disintegration time

In all cases, MUP-ODTs showed fast disintegration times less than 3 min (Table III-19) which are in agreement with Ph. Eur. specifications for orodispersible tablets. MUP-ODTs containing 30% of MCC pellets showed a rapid disintegration (less than 30 s) due to the major proportion of mannitol-based pellets which allows a faster disintegration.

On the other hand, the compression force applied was able to affect directly the disintegration time independently of the amount of pellets in the MUP-ODTs. At the same

time, the amount of lubricant had not influence on the disintegration, similar disintegration times were found in all MUP-ODTs.

c) Friability

MUP-ODTs showed high friability vales (>1%) completely falling apart into pellets after test. When increasing the compression force, the values of friability tended to decrease, meanwhile elevated friability values were showed when the amount of MCC pellets and lubricant increased. Therefore, as results suggest, the friability is strongly dependent on the independent factors.

Table III 19. Experimental responses for different formulations.

Test Run	X_1 MCC Pellet (%)	X_2 σ (Mpa)	X_3 MgSt (%)	Y_1 Hardness (N)	Y_2 Disintegration time (s)	Y_3 Friability (%)
1	30	0.8	0.50	19.3	16	79.4
2	30	0.8	0.75	16.5	14	94.8
3	30	0.8	1.00	18.2	19	100
4	50	0.8	0.50	18.4	13	89.8
5	50	0.8	0.75	17.3	12	100
6	50	0.8	1.00	12.4	17	100
7	70	0.8	0.50	19.5	17	100
8	70	0.8	0.75	17.9	20	85.3
9	70	0.8	1.00	15.4	14	100
10	30	1.0	0.50	27.9	37	1.4
11	30	1.0	0.75	24.0	29	27.6
12	30	1.0	1.00	21.9	26	66.1
13	50	1.0	0.50	24.6	26	42.6
14	50	1.0	0.75	22.8	28	75.5
15	50	1.0	1.00	21.6	34	78.0
16	70	1.0	0.50	23.3	29	89.8
17	70	1.0	0.75	26.9	40	75.3
18	70	1.0	1.00	17.8	34	100
19	30	1.4	0.50	37.8	102	0.3
20	30	1.4	0.75	31.5	86	7.1
21	30	1.4	1.00	29.6	64	22.2
22	50	1.4	0.50	33.3	107	25.6
23	50	1.4	0.75	26.1	108	70.0
24	50	1.4	1.00	25.4	101	88.8
25	70	1.4	0.50	30.1	110	71.7
26	70	1.4	0.75	34.3	119	42.9
27	70	1.4	1.00	22.8	90	100

3.4.2.3 Analysis of variance (ANOVA)

A quadratic statistical model was used to evaluate the influence of the independent variables on the dependent variables.

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2$$

Where Y_i was the response (dependent variable), b_0 was the arithmetic mean response of the 27 tests performed, the value of b_i was the coefficient for the relevant model terms, X_1 was defined as the percentage of MCC pellets (%), X_2 the tensile strength (MPa) and X_3 the amount of lubricant (%). The main effects X_1, X_2 and X_3 were represented by the average result changing one factor at a time from its low to high value. The terms of interaction X_1X_2, X_1X_3 and X_2X_3 demonstrated the change in the response when factors were varied in the simultaneous way. The terms X_1^2, X_2^2 and X_3^2 showed a non-linear correlation with the response.

Results of Table III-19 indicate a strong dependency of the response Y_3 on the independent factors. Therefore, an ANOVA was performed to evaluate the significance of the quadratic models based on the responses and estimate its quantitative effects. Table III-20 enlists the effect of the model terms and associated *p* values for the responses. The model was considered significant if *p*-values were less than 0.05. The manner of interpretation was the following: the sign and value of the quantitative effect indicated the tendency and the magnitude in terms of the influence on the response. A positive sign indicated an increase in the response value meanwhile a negative sign indicated a decrease in the response value.

In this analysis, 5 effects had *p*-values less than 0.05, indicating that friability (Y_3) was significantly influenced by the linear models of X_1 (%MCC pellets), X_2 (tensile strength) and X_3 (%lubricant), by the interactive model X_1X_2 (%MCC pellets- tensile strength) and by the polynomial model X_2^2 (tensile strength) at the 95.0% confidence level.

Table III-20. Results of regression of response Y_3 (friability) against X_1, X_2 and X_3.

Dependent variable (response)	**Predictors (factors)**	**Regression coefficients**	***p*- value**	**R^2**
Friability (Y_3)		54.7876 [C]		0.848
	X_1	21.7488	0.000	
	X_2	-23.3722	0.000	
	X_3	14.8006	0.0013	
	X_1X_2	12.6893	0.0135	
	X_1X_3	-5.725	0.2385	
	X_2X_3	5.95537	0.2129	
	X_1^2	-9.81667	0.1568	
	X_2^2	19.0957	0.0222	
	X_3^2	5.48333	0.4195	

Level of significance $p< 0.05$

The regression coefficients showed that the three factors X_1, X_2 and X_3 had an influence on the friability of the MUP-ODT; meanwhile the strong interaction of X_1X_2 and X_2^2 determined the tableting process as mannitol-based pellets played the role of crushing agent in order to protect the MCC pellets from deformation and fragmentation.
The following quadratic equation was derived from multiple linear regression analysis by the best fit method to describe friability (Y_3).

$$Y_3 = 54.8 + 21.7X_1 - 23.4X_2 + 14.8X_3 - 9.8X_1^2 + 12.7X_1X_2 - 5.7X_1X_3 + 19.1X_2^2 + 5.9X_2X_3 + 5.5X_3^2$$

A statistical analysis was performed to test the validity of the model. The R-squared statistic (R^2) indicated that the model as fitted explained 84.7943% of the variability in function of the friability. The adjusted R-squared statistic (R^2), which is more suitable for comparing models with different numbers of independent variables, was 76.7442%. The standard error of the estimate showed the standard deviation of the residuals was16.2328. The mean absolute error (MAE) was 10.5413 which belongs the average value of the residuals. The Durbin-Watson (DW) statistic tested the residuals to determine if there was any significant correlation based on the order in which they occurred in our data file. Since

the DW value was greater than 1.4, there is probably not any serious autocorrelation in the residuals.

Based on the friability equation, surface plots were generated to simulate the influence of the each independent variable on the response of friability. The graphs for compression force, amount of MCC pellets and lubricant are presented in Figures III-38-40. The plots provide a visual interpretation of the change in the response surface (Y_3) as a function of the independent factors as the individual and simultaneous manner, which offers values for further optimization of the formulation and understand its compaction behavior.

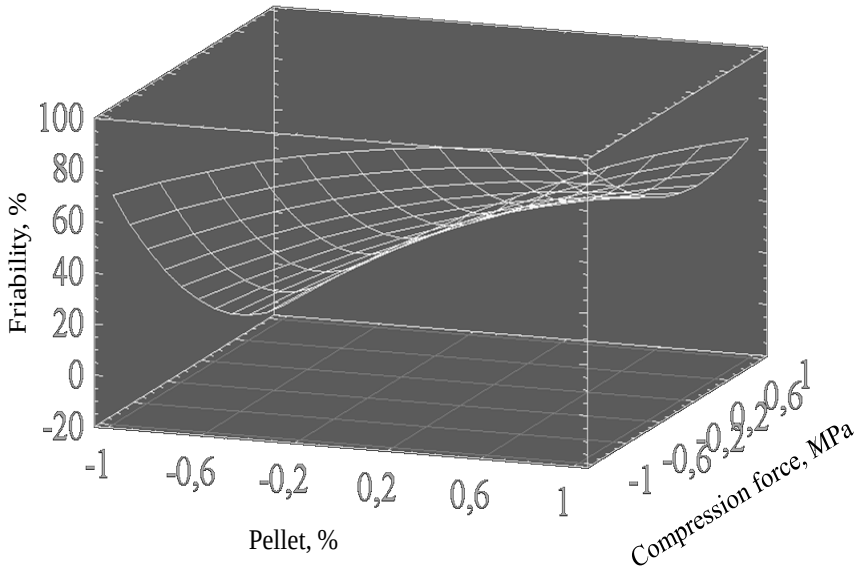

Figure III-38. Surface response plot showing the influence of the %MCC and compression force on the friability.

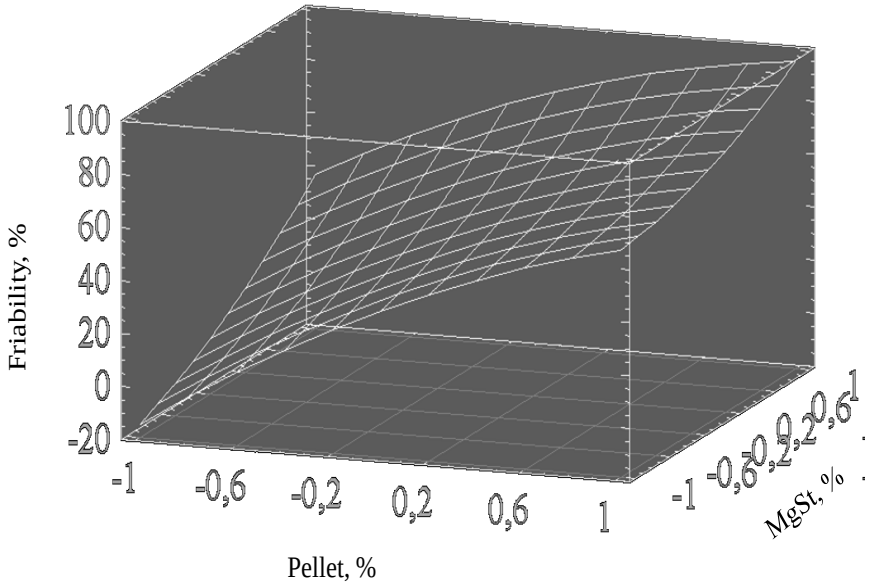

Figure III-39. Surface response plot showing the influence of the %MCC and % of lubricant on the friability.

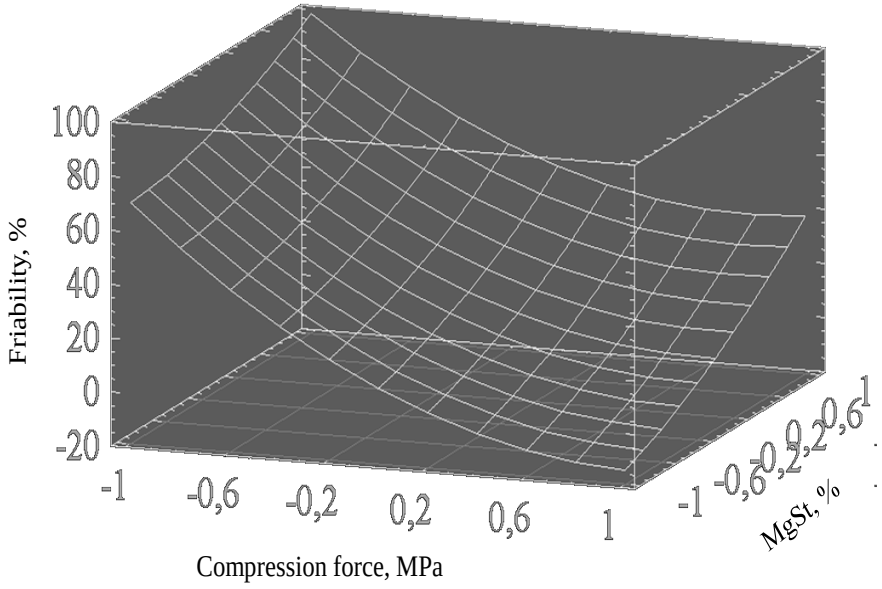

Figure III -40. Surface response plot showing the influence of % lubricant and compression force on the friability.

Based on the response surface plots, it is desirable to obtain an optimum formulation to produce MUP-ODT with characteristics which meet all the pharmacopeia specifications: friability less than 1% and disintegration time less than 3 min. The parameters which meet with these criteria to obtain a MUP-ODT of 5mm diameter are: 30% of MCC pellets, 0.5% of magnesium stearate at 10 kN as compression force.

As it was mentioned before, MUP-ODTs offer multiple advantages over single dosage forms, one of the ideal characteristics of this dosage forms is that they should offer ease to withstand physical parameters, stability, packing storage and transportation. Different soft materials or conventional granular excipients have demonstrated support and cushioning during the compression (70). In our previous study we have demonstrated that mannitol-based granules meet with this propose obtaining MUP-ODT with good quality properties. In this study, our formulation changed its form from granules to pellets. During the tableting process, mannitol-based pellets were designed to play the role of crushing agent in order to protect the MCC pellets from deformation and fragmentation. The compaction mechanism followed four stages described by Abdul et al, (i) the volume of the pellets was reduced by a rearrangement of the pellets to fill the inter-particle spaces, (ii) the pellet suffered a reduction of its volume due to its local surface deformation, (iii) a bulk deformation following by densification took place and (iv) finally a cessation of the volume reduction owing due to the low-inter and intra granular porosity (1).

Obtained MUP-ODTs presented a very low strength, due to the low elastic and brittle behavior of mannitol pellets which did not provide any protection enhancing the deformation of MCC pellets. Figure III-41 shows the distribution and the shape of the pellets changes after compression, where it is clearly that both mannitol and MCC pellets suffered significant change in their shapes and fragmentation. Therefore, from the manufacturing and the economical point of view, mannitol-based pellets are not candidates as cushioning agents for compression.

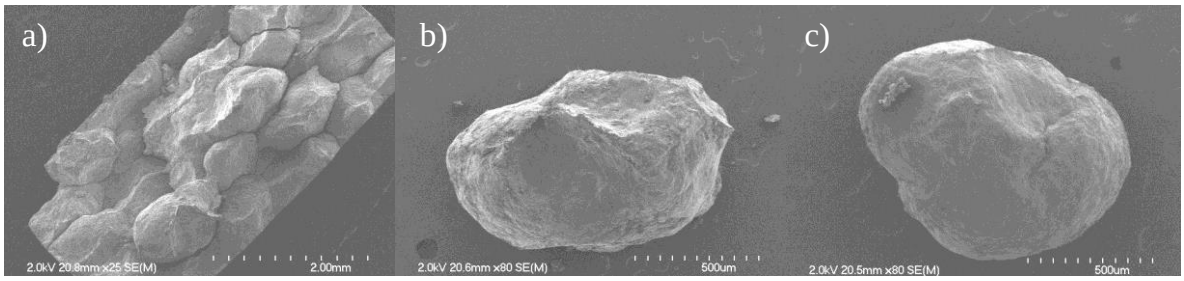

Figure III -41. SEM image of MUPs formulated with 30%MCC pellet, 0.5% of MgSt and 10 kN of compression force (a) fracture plane (b) Mannitol-base pellet, (c) MCC pellet after compression.

Conclusions

Mannitol-based pellets were successfully produced as orodispersible dosages forms. Pellets showed acceptable quality properties like good sphericity and smooth surface, low friability, and fast disintegration.

Through a design of experiments, proper parameters of formulation and process were determined to obtain MUP-ODTs which meet the Eu.Ph. specifications. However, from the manufacturing and the economical point of view, mannitol-based pellets are not candidates as cushioning agents for compression to produce MUP-ODTs.

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CHAPTER IV

DISCUSSION AND GENERAL CONCLUSION

The development of age appropriate drug delivery systems for pediatric use represents important challenges not only from the economical perspective as the distribution and commercialization of pediatric medicines are fewer comparing to the adult market, but also from the technological process aspect the selection and design of the appropriate dosage form for each subgroup which (i) includes the use of safe excipients, (ii) exhibits its security and efficacy, (iii) demonstrates the patient acceptability specially the palatability in oral dosage forms, (iv) shows a cost-effective in the manufacture process and, (v) meets the end-user requirements.

For the oral route of administration, orodispersible tablets and multiparticulate drug delivery systems as pellets can be considered as dosage form approaches to the pediatric population due to they offer ease of swallowing and dose flexibility which are desirable characteristics. Moreover, multiparticulate systems offer the advantages to control the drug release resulting in fewer adverse effects and also improve the palatability.

This study aimed the combination of both multiparticulate drug delivery systems and orodispersible formulations to create a Multiple-Unit Pellet Orodispersible Tablet (MUP-ODT) which was able to control the release of acetaminophen (APAP) and mask its taste for better acceptability. The main results are recapitulated:

1. Formulation and evaluation of acetaminophen pellets

Acetaminophen matrix pellets at different drug load were successfully produced using different polymers. All batches produced presented a high yield percentage over 80% with acceptable quality properties for further compression.

High drug load spherical pellets were produced using lactose and MCC as a spheronized aid, despite they showed a reduce ability to be compressed, they showed an appropriate immediate release behavior avoiding the undesirable burst effect which in recent years has been reported, particularly in acetaminophen ODT. On the other hand, this formulation can be incorporated in a multiparticulate counting device for the dose adjustment.

Formulation F10, which contains 25% of API in a matrix composed of Eudragit and MCC, meets with all desirable mechanical properties and the USP controlled release parameters for oral dosage form, so it was selected for further compression and taste masking studies.

A preliminary study demonstrated during the first 2 minutes of dissolution, drug load pellets showed a significant role decreasing the drug release, approaching the limit contact between the bitter drug and taste buds in the mouth; therefore they can be an approach for taste masking.

2. Design and development of multiple-unit orodispersible tablets

The excipients chosen to produce the orodispersible formulations contain mannitol as principal component due to it presents good mechanical properties, fast disintegration, pleasant mouth feel and also considered as safe excipient for children.

The resulted granules showed good flowability properties. Suitable 5 mm diameter Multiple Unit Orodispersible Tablets (MUP-ODTs) with different percentage of free-drug MCC pellets and compression forces were successfully produced meting all specification of the Ph. Eur. Formulations containing crospovidone (FA) as disintegrant required low compression forces, showed lower friability values (< 1%) and faster disintegration time (less than 30 s) than formulations containing croscarmellose (FB) or starch glycolate (FC) as disintegrants.

The optimal level for desirable MUP-ODTs was identified to be 60% of orodispersible granules and 40% drug MCC pellets. Similar drug release was found in all formulations before and after compression, which confirms that orodispersible granules met the function as support and cushioning agent during the compression providing protection against the deformation and fragmentation of MCC pellets, ensuring a fast disintegration which allows delivery the pellets for further ease swallowing and this without affecting the drug release kinetic.

3. Development of controlled release multiple-unit orodispersible tablets

Acceptable yield (> 70%) of acetaminophen matrix pellets based on different ratios of MCC and Eudragit RSPO were produced successfully using the extrusion-spheronization technique. Pellets showed good shape and mechanical properties, which indicated that Eudragit RSPO/RS 30D was a suitable palletization aid.

DSC thermograms and XRD confirmed there was neither any drug-polymer interaction in the matrix formed nor any change in the crystalline form of the API. The amount of Eudragit and the drying step after spheronization had an important influence over rearrangement in the polymeric network through the matrix which decreases the porosity. When increasing the ratio of Eudragit, harder matrices where produced. E4 that contains 70% of Eudragit showed a high tendency to plastic deformation supporting the compression force without significant damage after compression.

Drug release rate from Eudragit pellets was not affected by the pH of dissolution media. Formulations E1, E2 and E3 showed similar dissolution profile which 46-55% of APAP was achieved during the first 15 min, 75-90% after 1 h, and 92-100% after 3 h in the three different mediums. Meanwhile E4 showed a slower APAP release compared to the other formulations: 36-41% at 15 min, 59-70% at 1 h and 83-94% after 3 h in the three media. Differences on the drug release could be associated to the higher total polymer loading used on the pellet and the thermal heating which delayed the erosion process of the matrix system.

MUP-ODTs containing 40% of drug load pellets were successfully produced with good mechanical properties friability less than 1% and disintegration time less than 60 s; however only MUP-ODT containing pellets from formulations E1 and E2 met the requirements for controlled release dosage forms of the USP after compression.
Additionally, drug release profiles from MUP-ODT E1 and E2 showed a similar dissolution than Tylenol® in SGF pH 1.5. The similarity factor (f_2) of MUP-ODT E1 and E2 respect to Tylenol® ER tablet were 51 and 50 respectively which proved that both MUP-ODTs formulations are similar.
During the first 60 seconds, the pellets produced had a significant role decreasing the drug release (5-10%), therefore they can be an approach for taste masking.

4. Feasibility to compress orodispersible pellets for pediatric use

Mannitol-base pellets were successfully produced as orodispersible dosages forms. Pellets showed high yield (> 84%) with acceptable quality properties as good sphericity, smooth surface, low friability and fast disintegration.

Through a design of experiments, proper parameters of formulation (30% of MCC pellets and 0.5% of MgSt) and process (10 kN) were determined to obtain MUP-ODTs which meet the Ph. Eur. specifications: acceptable hardness (38 N), a low friability value (0.3%) and an acceptable time of disintegration (100 s). However, from the manufacturing and the economical perspective mannitol-base pellets are not candidates as cushioning agents for compression to produce MUP-ODTs as they did not provide any protection enhancing the deformation of MCC pellets.

In conclusion, by using matrix pellets, it was possible to vary the drug release profile of acetaminophen while avoiding the burst effect. The combination of both technologies multiparticulate drug delivery systems and orodispersible tablets can provide a novel dosage form for pediatric use not only enables both fast disintegration and modified properties but also offer easy swallowing and dose flexibility suitable for children aged from 3 to 5 years.

PERSPECTIVES

In view of the results obtained, it would be conceivable to require further investigations focus on the following points:

- ***Controlled release***
  - Elucidate the dissolution mechanism of Eudragit matrix.
  - Test other active principle ingredients

- ***Palatability and taste masking***
  - It is necessary perform an *in-vivo* evaluation to study the taste masking and grittiness effect of pellets and MUP-ODTs in different groups of pediatric population preferentially.

- ***Age dosage form***
  - Adapt the dose and table size according to the child age and design appropriate devices for each dosage form that are safe and easy to use for parents and caregivers.

RÉSUMÉ EN FRANÇAIS

Introduction

La situation générale des médicaments à usage pédiatrique

La population pédiatrique comprend environ un tiers de la population mondiale (1) mais d'un point de vue économique, le marché pédiatrique n'est pas rentable pour l'industrie pharmaceutique car les enfants représentent une faible proportion de la population malade (2). Par conséquent, pendant de nombreuses années et encore actuellement, le nombre de médicaments pédiatriques mis sur le marché est limité. De ce fait, les pédiatres n'ont pas d'autre alternative que de prescrire des médicaments non autorisés pour cette population à leurs jeunes patients. Ceci implique une manque d'information sur la posologie nécessaire ainsi que sur les aspects sécurité et efficacité chez les enfants ce qui augmente le risque de développer des effets indésirables pouvant être à l'origine de toxicité potentielle, ou de ne pas atteindre les concentrations thérapeutiques efficaces (3–5). En réponse à cette problématique, différentes initiatives à l'échelle internationale favorisent le développement de médicaments pédiatriques en prenant en considération la pertinence de l'âge, la taille, l'état physiologique et les exigences thérapeutiques de cette population.

En Europe, depuis 2007 le règlement pédiatrique (Commission européenne n ° 1901/2006) est entré en vigueur. L'objectif de cette réglementation consiste à (i) faciliter le développement et l'accès des médicaments à la population pédiatrique, (ii) assurer la qualité et la recherche éthique, assurer l'évaluation et l'autorisation des médicaments pédiatriques disponibles sur le marché, et (iii) augmenter l'information disponible sur les médicaments utilisés chez les enfants (6,7).

D'autre part, en 2008, l'Organisation Mondiale de la Santé (OMS) en mettant la priorité sur la liste des médicaments essentiels pour les enfants a lancé le programme international "Making Medicines Child Size", qui encourage les laboratoires pharmaceutiques à développer des formulations pédiatriques accessibles et de qualité particulièrement pour les pays en développement (8–10).

La population pédiatrique

La période de l'enfance est très large et s'étale de la naissance jusqu'à l'atteinte de l'âge adulte. Au cours de cette période, l'enfant présente continuellement des changements physiques, métaboliques et psychologiques. Selon la recommandation de l'ICH, la population pédiatrique peut se classer par groupes en fonction de leurs particularités physiologiques (Tableau 1) (11).

Tableau 1. Groupes de la population pédiatrique en fonction de leur âge (12).

Groupe	Age	Poids moyen (kg)
Nouveau-né prématuré	< 37 semaines de gestation	< 3.4
Nouveau-né à terme	0-27 jours	3.4
Nourrisson	1-23 mois	3.4-12.4
Enfant	2-11 ans	12.4-39
Adolescent	12- 16 ou 18 ans (en fonction des pays)	39-72.1 (H)/60.3 (F)

Les enfants ne peuvent pas été considérés comme des «petits adultes», raison pour laquelle il est nécessaire de développer des formes galéniques adaptées à leur âge, leur taille, leur état physiologique et les exigences thérapeutiques, comme le conseillent les organismes médicaux.

D'autre part, les médicaments pédiatriques doivent satisfaire des exigences telles que d'être formulés avec des excipients sûrs, de présenter une formulation agréable sur le plan gustatif, d'être acceptable d'un point de vue socioculturel et de présenter une information claire sur le produit (2,13)

La voie d'administration orale

1. Particularités des paramètres pharmacocinétiques de la population pédiatrique

En général, la voie d'administration orale est préférée aux autres voies d'administration, car elle est pratique, économique et facile à utiliser (14,15). Comme l'enfant est en maturation continue, il est important de considérer la physiologie gastro-intestinale (GI) qui diffère par

rapport à celle des adultes. En effet, lors de l'administration d'un médicament, des variations et des changements pharmacocinétiques significatifs peuvent être observés.

Chaque groupe de la population pédiatrique présente des différences en ce qui concerne le pH gastrique et intestinal, la motilité, la circulation sanguine, la perfusion tissulaire, la surface, la fonction pancréatique, la flore intestinale, le temps de transit et la maturation des transporteurs et des récepteurs (16). Ces facteurs sont impliqués dans la libération du médicament, la solubilité et l'absorption (17), par conséquent, ils doivent être pris en considération au moment d'élaborer et d'utiliser une forme pharmaceutique chez les enfants.

2. Le développement de médicaments pédiatriques

Fondamentalement, les médicaments contiennent une proportion importante d'excipients associés au principe actif. La principale fonction de ceux-ci est d'améliorer la stabilité du produit, de masquer le goût amer du principe actif et de contrôler sa libération, afin d'améliorer l'acceptabilité par le patient et/ou d'améliorer la production du médicament (18). Néanmoins, il y a des effets indésirables qui ont été rapportés dans certains groupes de la population pédiatrique, particulièrement chez les nouveau-nés, les nourrissons et les jeunes enfants, car ils présentent des variations au niveau des paramètres pharmacocinétiques et pharmacodynamiques comparativement aux adultes (19,20).

En matière d'approbation des formulations pédiatriques, les instances réglementaires conseillent d'utiliser la quantité minimale d'excipients et pour chaque excipient utilisé, la fonction doit être justifiée et la quantité utilisée doit être précisée en respectant la dose journalière admissible (ADI) afin d'éviter les effets indésirables (20–22). Les deux organismes de réglementation européenne et américaine, l'EMA et la FDA, ont publié des lignes directrices relatives à l'utilisation et la déclaration des excipients pour les formulations pédiatriques, qui peut être consultées sur leur site.

Un autre aspect important à considérer au moment de développer un médicament pédiatrique oral est la palatabilité, qui est un facteur influençant l'acceptabilité et l'observance du patient.

La palatabilité est décrite comme la perception globale d'un médicament qui est liée à l'odeur, le goût, la texture et l'arrière-goût après la consommation de formes pharmaceutiques orales (23).

Depuis que la législation de l'UE sur les médicaments pour les enfants est entrée en vigueur en 2007, les aspects du masquage du goût sont demandés par les organismes de réglementation. Toutefois, en raison de l'absence de directives sur l'évaluation, des méthodes d'analyse *in-vitro* et *in-vivo* ont été développés pour évaluer l'efficacité du masquage du goût.

Les études de pharmacologie clinique à effectuer chez les enfants sont un défi en raison de difficultés éthiques, techniques et logistiques. Les données pharmacocinétiques fournies par les essais cliniques chez les adultes peuvent être utilisées pour extrapoler l'efficacité clinique et la sécurité aux patients pédiatriques. Cependant, comme la population pédiatrique présente des différences entre les groupes, les variations pharmacocinétiques liées à l'âge, les doses calculées sur la base de masse corporelle, les exigences de formes mesurables, les préférences de formulation et de goût, pourraient conduire à des erreurs dangereuses (24,25).

L'EMA en 2006 a publié la «Directive sur le rôle de la pharmacocinétique dans le développement de médicaments pour la population pédiatrique". Il s'agit de conseils sur l'utilisation des études pharmacocinétiques pendant la phase de développement de médicaments et les questions liées à la méthodologie chez les patients pédiatriques (26).

3. Les formes pharmaceutiques orales

La voie d'administration orale est préférée aux autres routes d'administration. Près de 90% des produits commercialisés sont administrés par cette voie, les formulations liquides étant les plus administrées aux nouveau-nés et nourrissons en raison de leurs difficultés à avaler, et les formulations solides sont plutôt réservées aux enfants et adolescents (15,27,28).

En raison de la diversité de la population pédiatrique, il est difficile de trouver une formulation appropriée pour tous les groupes d'âge. Néanmoins, toute formulation envisagée doit suivre les critères de base suivants (29,30):

- La forme doit contenir la quantité de principe actif adaptée à l'âge et aux besoins de l'enfant et doit montrer que la biodisponibilité est suffisante
- Démontrer l'utilisation d'excipients sûrs
- Avoir des propriétés agréables au goût et acceptables
- Répondre aux exigences de l'uniformité de teneur
- Être facile, convivial et sûr lors de l'administration et ceci pour les deux acteurs: le patient et le personnel soignant. En outre, il est souhaitable qu'avant l'administration, la manipulation soit minimale
- L'information sur l'utilisation doit être claire et précise
- Il doit être acceptable au niveau socio-culturel

Les formulations liquides sont préférées pour l'administration aux nouveau-nés et nourrissons car elles sont faciles à avaler, évitant le risque potentiel d'étouffement associé aux formulations solides (31,32). Les formulations liquides peuvent être présentées sous forme de solutions, de suspensions, d'émulsions, de sirops, d'élixirs et de pulvérisations lorsque le principe actif peut être dissout ou dispersé, offrant une meilleure biodisponibilité *in-vivo* comparativement aux formes solides (33). En général, les principales questions liées à ces formes sont la stabilité, le masquage du goût et le volume de dosage (33,34).

Habituellement, pour administrer la dose correcte, il faut faire un ajustement du volume administré en fonction de la concentration du principe actif qui est calculée en fonction de l'âge et du poids de l'enfant (35,36). De plus, l'EMA dans son document de réflexion suggère que les volumes cibles devraient être de l'ordre de 5 ml pour les nourrissons et les enfants de moins de 5 ans, et de 10 ml pour les enfants plus âgés. Dans tous les cas, des volumes supérieurs à 10 ml peuvent être gênant pour le patient et personnel soignant (37,38).

Un autre aspect à envisager est l'emballage qui ne doit pas seulement être conçu pour garantir la stabilité physico-chimique du médicament. Il doit aussi protéger de la contamination microbienne et il doit être résistant aux enfants ainsi que facile à manipuler pour les parents et le personnel soignant (39).
Dans la plupart des cas, les dispositifs de dosage sont fournis par le fabricant afin de permettre un dosage précis en volume. Les appareils les plus couramment utilisés sont des cuillères mesures, des pipettes graduées ou des gobelets-doseurs (34,39).

Comparativement aux formes liquides, les formes solides orales présentent de nombreux avantages: elles présentent une stabilité à long terme, sont facile à manipuler, offrent une grande précision de dosage et elles sont de faible coût de revient pour la production. Également, elles permettent de masquer le goût indésirable du principe actif et il est possible de contrôler la libération du principe actif par enrobage mais la réalisation technique est plus difficile que pour les formulations liquides. Pour les adultes, les comprimés et les capsules sont les formes solides les plus courantes disponibles sur le marché. Cependant, le principal inconvénient est l'acceptabilité chez les plus jeunes enfants qui peuvent présenter des difficultés à avaler de grandes tailles de comprimés, de ce fait, il est important d'adapter la taille des formes pharmaceutiques en fonction des capacités de l'enfant (12,40).

D'autre part, les comprimés classiques sont inappropriés pour l'usage pédiatrique en raison des dosages et tailles qui existent actuellement sur le marché. C'est pourquoi, dans le récent projet publié par l'EMA/CHMP et intitulé «*Guideline on pharmaceutical development of medicines for pediatric use* », l'acceptabilité des comprimés en fonction de l'âge et la taille des enfants est considérée (Tableau 2) (23,37,41).

Tableau 2. L'adéquation des comprimés selon l'âge et la taille de l'enfant proposée par l'EMA/CHMP.

Sous-groupe	Age	Acceptabilité des comprimés
Nouveau-nés	0 – 30 jours	Aucun
	1 – 6 mois	Aucun
Nourrissons	6 – 24 mois	Les comprimés ne sont pas acceptables, mais les poudres et les mini-granules sont acceptés
Enfants	2 – 5 ans	Comprimés 3 – 5 mm en diamètre
	6 – 11 ans	Comprimés $\leq$ 10 mm en diamètre
Adolescents	12 – 18 ans	Comprimés $\leq$ 15 mm en diamètre

Synthèse

Il y a un besoin urgent de fournir des formes galéniques orales adaptées à l'âge qui répondent non seulement à tous les attributs de la qualité des produits pharmaceutiques classiques mais aussi, qui offrent une grande précision, une dose flexible, une facilité à

déglutir et surtout en prêtant une attention particulière aux conditions qui prévalent dans les pays en développement, Ceci a encouragé le développement de nouvelles plateformes technologiques comme les systèmes multi-particulaires (mini-comprimés, granules, et mini-granules) et les formes orodispersibles à utiliser sous forme de préparations liquides ou à mélanger avec des aliments (10,22,42).

En général, pour le traitement à long terme, les formulations orales sont préférées chez les enfants, alors que l'administration parentérale étant encore la première option pour les nouveau-nés et les cas d'urgence (38). L'utilisation de formulations à libération prolongée peut être une option pour réduire la fréquence des doses et peut également être pratique pour les patients qui ont besoin de prendre leurs médicaments alors qu'ils sont à l'école ou pendant la nuit (23,43).

En matière de libération prolongée par la voie orale, les formulations sont conçues pour délivrer le principe actif dans le tractus gastro-intestinal à un rythme lent en réduisant la fréquence d'administration par rapport aux formulations classiques. Cependant, tous les principes actifs ne sont pas des candidats pour être formulés sous forme de produits à libération prolongée en raison de conditions physiologiques différentes chez les enfants comparativement aux adultes (23). Il y a des facteurs tels que la solubilité du principe actif, le pH gastrique et intestinal, la vitesse de vidange gastrique, la motilité intestinale, la perméabilité intestinale et la demi-vie d'élimination que peuvent avoir un impact sur les paramètres pharmacocinétiques du médicament, ils doivent donc être pris en considération au moment de développer une formulation (12,16,44).

Les produits à libération prolongée existent sous différentes formes galéniques comme les systèmes multi-particulaires qui peut être contenus dans des sachets, des capsules ou des comprimés, ou comme différents types de comprimés (par exemple, pelliculés, système matriciel ou comprimés à désagrégation rapide) (15,45,46). Dans le cas des comprimés et des systèmes multi-particulaires, il est nécessaire de présenter des informations claires sur l'étiquette qui doit bien préciser que ces formulations ne doivent pas être brisées, mâchées ou mélangées avec de la nourriture ou des boissons afin de protéger l'enrobage, l'efficacité et la sécurité du produit (22,23).

Un grand défi pour les formulations pédiatriques a été l'optimisation de l'administration de médicaments pour la voie orale car elle est pratique, économique et facile à utiliser ; cependant, la capacité de déglutition est critique pour ces formulations.

Les comprimés orodispersibles (ODT) sont très prometteurs pour un usage pédiatrique parce qu'ils sont faciles à avaler, ne nécessitent pas d'eau et présentent une dose unitaire uniforme. Les principaux défis au moment de développer un comprimé orodispersible sont: le masquage du goût, la désagrégation rapide, la sensation en bouche, la méthode de fabrication, la compression et l'emballage.
En dépit de ces challenges, les formulations orodispersibles ont un grand succès; et actuellement il y a quelques formulations qui peuvent fournir le principe actif d'une manière contrôlée.

Les systèmes multi-particulaires (MUPS), tels que les mini-granules présentent plusieurs avantages thérapeutiques et techniques par rapport aux autres formes galéniques unitaires; ils peuvent se répartir uniformément dans le tractus gastro-intestinal, et contrôler la libération du principe actif entraînant ainsi moins d'effets indésirables et peuvent également améliorer la palatabilité.

Objectifs de la thèse

La compression de mini-granules à libération contrôlée dans un comprimé à désagrégation rapide qui disperse rapidement ces mini-granules pourrait permettre l'obtention d'une forme galénique appropriée à l'usage pédiatrique en raison de sa facilité d'administration et la flexibilité de dosage ainsi que la réduction de la fréquence des prises conduisant à un meilleur traitement du patient et moins de risques de surdosage.

Dans ce contexte, ce travail envisage le développement d'un comprimé orodispersible multi-particulaire (MUP-ODT) qui permet la libération contrôlée de l'acétaminophène (APAP) utilisé comme principe actif modèle.
Notre travail présente deux axes de recherche (i) le développement d'un comprimé orodispersible avec des excipients sûrs pour les enfants (excipients GRAS) et qui répond aux spécifications de la Pharmacopée Européenne et (ii) le développement de mini-granules obtenus par la technique d'extrusion-sphéronisation capables de contrôler la

libération de l'acétaminophène (APAP) et de masquer son gout pour une meilleure acceptabilité.

Matériel et méthodes

Le premier chapitre concerne la production des mini-granules par la technique d'extrusion-sphéronisation pour obtenir un système matriciel à libération contrôlée où la microcristalline cellulose (MCC) a été partiellement substituée par trois autres excipients dans un ratio (1:1): soit le lactose (Lac), l'éthylcellulose (EC) ou un mélange d'Eudragit (Eudragit RS PO/Eudragit RS 30D), et contenant différents taux de principe actif :12,5 ; 25 ; 50 et 75% (p/p). Les propriétés mécaniques et chimiques ainsi que leur influence sur la libération contrôlée de l'acétaminophène ont été évaluées.

Le deuxième chapitre de cette étude a examiné la faisabilité de comprimer des mini-granules non enrobés à base de MCC dans une formulation orodispersible neutre.

Les formulations orodispersibles neutres ont été préparées avec le mannitol comme principal composant de la formulation, associé à trois différents agents de désagrégation (crospovidone (FA), croscarmellose (FB) et glycolate d'amidon sodique (FC)). Les formulations ont été préparées par granulation humide et leurs paramètres de compression ont été évalués.

Ultérieurement, les formulations orodispersibles neutres ont été mélangées avec les mini-granules de MCC pour étudier l'influence du taux de mini-granules (30, 40 et 50%), du type d'agent de désagrégation (crospovidone, croscarmellose et glycolate d'amidon sodique) et de la force de compression (2-20 kN) pour obtenir un comprimé orodispersible multiparticulaire (MUP-ODT).

Tous les MUP-ODTs produits ont été évalués selon les essais de contrôle de qualité décrits à la Ph. Eur. (friabilité, temps de désagrégation, uniformité de masse et de teneur, et essai de dissolution).

Le troisième chapitre a été dédié à la production des MUP-ODTs qui permettent la libération contrôlée de l´acétaminophène en utilisant un mélange d'Eudragit RSPO/Eudragit RS 30D pour créer un système matriciel sans changement significatif du profil de libération après la compression.

Les mini-granules ont été fabriquées par la technique d'extrusion-sphéronisation en utilisant différents pourcentages d'Eudragit RSPO/Eudragit RS 30D et des taux de principe

actif de 10 et 25%. Leurs propriétés mécaniques, physico-chimiques et les profils de dissolution ont été évalués.

Pour l'obtention des MUP-ODTs, les mini-granules ont été mélangées avec des granulés orodispersibles neutres contenant la crospovidone (FA) comme agent de désagrégation, selon le ratio (40:60), puis comprimés à une force de compression de 5-7 kN. Tous les MUP-ODTs produits ont été évalués selon les essais de contrôle de qualité décrits à la Ph. Eur. (friabilité, temps de désagrégation, uniformité de masse et de teneur, et essai de dissolution).

L'évaluation du masquage de goût a été réalisée par deux méthodes: la langue électronique et la méthode de dissolution à l'aide d'une pompe à seringues qui utilise de faibles volumes de milieu afin de simuler le comportement dans la bouche d'un enfant.

La dernière partie de ce travail concerne la production de mini-granules orodispersibles à base de mannitol par la technique d'extrusion-sphéronisation et explore la possibilité de comprimer deux types de mini-granules (mannitol et MCC) pour obtenir un comprimé orodispersible multiparticulaire (MUP-ODT).

Un plan d'expérience a été effectué pour déterminer les paramètres optimaux de formulation (ratio mini-granules mannitol:MCC et lubrifiant) et le facteur procédé (force de compression). Cette étude a été réalisée à l'aide de comprimés de taille 5 mm de diamètre qui sont appropriés pour les enfants âgés de 3 à 5 ans.

Tous les MUP-ODTs obtenus ont été évalués selon les essais de contrôle de qualité décrits dans la Pharmacopée Européenne (friabilité et temps de désagrégation).

Résultats et discussion

1. Formulation et évaluation de mini-granules d'acétaminophène

Tous les lots de mini-granules fabriqués ont montré une qualité acceptable au niveau de la production, des propriétés mécaniques et ont satisfait les paramètres de contrôle de qualité spécifiés dans la Ph. Eur. (perte à la dessiccation, friabilité et uniformité de teneur en principe actif). Pour déterminer le profil de libération, des mini-granules ont été testés dans trois milieux de dissolution et les formulations à base de lactose (F1-F4) et d'éthylcellulose (F5-F8) ont montré une libération rapide du principe actif. Les formulations qui contiennent l'Eudragit (F9-F12) ont présenté des propriétés mécaniques

correctes et des profils de libération contrôlée pour des taux de principe actif de 12.5 et 25%.

D'autre part, il a été possible de produire des mini-granules contenant 75% d'acétaminophène associé à l'association lactose-MCC utilisée comme adjuvant de sphéronisation et permettant l'obtention de formes à libération immédiate. Cependant, nous observons une diminution de leurs propriétés mécaniques, en particulier la résistance à l'écrasement, ce qui réduit leur aptitude à pouvoir être comprimé. Néanmoins, ils peuvent être considérés comme une alternative pour l'ajustement de la dose et peuvent permettre une flexibilité de dosage notamment lorsqu'ils sont incorporés dans un dispositif distributeur de mini-granules.

Un essai de dissolution préliminaire à l'aide d'une pompe à seringues qui utilise de faibles volumes de milieu pour simuler le comportement dans la bouche de l'enfant a montré que les mini-granules préparés ont un rôle important dans la diminution de la quantité de principe actif libéré au cours des 2 premières minutes; par conséquent, ils peuvent être une approche pour le masquage du goût et plus particulièrement la formulation F10 qui est candidate pour une utilisation en compression avec masquage du goût.

2. Design et développement de comprimés orodispersibles multiparticulaires

Des formulations orodispersibles ont été préparées avec des excipients sûrs pour les enfants: le mannitol, composant majoritaire de la formulation, associé à trois différents agents de désagrégation. Les paramètres de compression des formulations préparées par granulation humide ont montré que les trois formulations ont de bonnes aptitudes à la compression et permettent l'obtention de comprimés qui répondent aux spécifications de la Ph. Eur. pour les formes orodispersibles.

Pour obtenir un comprimé orodispersible multiparticulaire (MUP-ODT) capable de délivrer des mini-granules en moins de 30 secondes et ainsi faciliter l'administration de comprimés chez l'enfant, nous avons utilisé des comprimés de taille de 5 mm de diamètre qui sont appropriés aux enfants âgés de 3 à 5 ans, conformément aux suggestions de l'EMA/CHMP.

En général, avec de faibles forces de compression il a été possible de produire des MUP-ODTs facilement manipulables, ce qui est favorable pour le futur conditionnement de ces

formes. La formulation avec le ratio 40% mini-granules de MCC et 60% granulés orodispersibles contenant la crospovidone (FA) comme agent de désagrégation a montré de meilleures propriétés comparativement aux formulations qui contiennent la croscarmellose (FB) ou le glycolate d'amidon sodique (FC). Pour ces formulations, la force de compression influence beaucoup les propriétés mécaniques des comprimés (dureté, friabilité, temps de désagrégation et porosité), et une force de compression entre 5-7 kN a été suffisante pour obtenir des MUP-ODTs de dureté et friabilité acceptables (29 N et 0,9 % respectivement) et avec un temps de désagrégation extrêmement rapide (10 s).

Afin de vérifier les paramètres expérimentaux optimaux définis au cours des différents essais, nous avons préparé des MUP-ODTs contenant 25% de principe actif dans les mini-granules. Les résultats de contrôle de qualité et de dissolution des MUP-ODTs répondent aux spécifications de la Ph. Eur. avec une friabilité inférieure à 1%, un temps de désagrégation et temps de mouillage plus rapide (moins de 30 s), une uniformité de masse et de teneur conformes.
Le facteur de similarité (f_2) des profils de libération des mini-granules avant et après la compression a démontré que le profil de libération des mini-granules n'est pas modifié par la compression et que la cinétique de libération de la forme MUP-ODTs n'est pas affectée.

3. Développement de comprimés orodispersibles multiparticulaires à libération contrôlée

Le troisième chapitre a démontré qu'il est possible de produire des mini-granules avec différents taux d'Eudragit RSPO/Eudragit RS 30D, en utilisant une quantité minime de MCC tout en conservant un rendement acceptable (> 70%). La quantité d'eau nécessaire pour obtenir une masse humide appropriée à l'extrusion/sphéronisation a diminué avec l'augmentation de la quantité d'Eudragit RS 30D ce qui peut être attribué aux substitutions d'ammonium quaternaire dans l'Eudragit RS 30D permettant une mouillabilité facile du mélange et agissant en tant que plastifiant et lubrifiant lors de l'extrusion (47).

Les mini-granules ont présenté de bonnes propriétés mécaniques, démontrant que l'augmentation de la quantité d'Eudragit dans les matrices et l'état de murissement ont un effet considérable sur la porosité et la résistance à l'écrasement en raison d'un réarrangement dans le réseau polymère ce qui diminue la porosité en favorisant la

densification de la matrice et ainsi les mini-granules seraient capables de supporter une force de compression sans dommage important dans leur structure (48–50).

Les analyses de calorimétrie différentielle à balayage (DSC) et diffractométrie de rayons X (XDR) ont confirmé qu'il n'existe pas d'interaction entre le polymère et la substance active à un taux de 25%.

Les profils de libération des mini-granules ont été réalisés et comparés dans trois milieux de dissolution différents: FSG pH 1,5, FIS pH 6,8 et l'eau. La libération de l'acétaminophène a été similaire pour les formulations E1, E2 et E3 (12,5; 25 et 50% d'actif respectivement), avec un taux de libération entre 46-55% au cours des15 premières minutes, 75-90% après 1 h et 100% après 3 h. La formulation E4 contenant 75% d'acétaminophène a montré un ralentissement de la libération du principe actif par rapport aux autres formulations: 36-41% à 15 min, 59-70% à 1 h et 83-94% après 3 h quel que soit le milieu.

Dans tous les cas, le facteur de similarité (f_2) a montré des valeurs comparables dans chaque milieu, indiquant que la dissolution de l'acétaminophène n'a pas été affectée par le pH du milieu de dissolution.

Les différences qui ont pu être observées pour la libération pourraient être associées au taux de polymère total utilisé dans la matrice et à l'état de murissement qui ont retardé le processus d'érosion (51–53).

Apres la compression, seuls les MUP-ODT produites à partir de formulations E1 et E2 (12,5 et 25% d'actif) ont satisfait à tous les paramètres de contrôle de qualité, avec des valeurs similaires de dureté (26-29 N), une friabilité inférieure à 1% (0,7%) et une désagrégation rapide (<3 min). L'uniformité de masse et de teneur sont acceptables indiquant une distribution uniforme du principe actif dans le MUP-ODT, la libération du principe actif est comparable.

D'autre part, les profils de libération de MUP-ODT E1 et E2 ont été comparé avec la spécialité commerciale Tylenol® dans le milieu FGS pH 1,5. Les f_2 des formulations MUP-ODT F1 et E2 comparées à la forme commercialisée sont de 51 et 50 et indiquent que les deux formulations du MUP-ODT sont similaires par rapport au comprimé commercial.

Pour l'évaluation du masquage de goût avec la méthode de dissolution, la libération d'acétaminophène est de 5-10% lors de la première minute et entre 10-20% lors de la

seconde minute, ce qui signifie que nos mini-granules ont un rôle important en diminuant la libération du médicament au cours de la première minute ce qui ils peuvent être une approche pour le masquage du goût. En effet, le masquage de goût est jugé efficace lorsque durant un court laps de temps d'environ 1 à 2 minutes, le principe actif n'est pas libéré ou la quantité libérée est en dessous du seul de perception de l'être humain.

L'évaluation du masquage de goût a également été réalisée à l'aide d'une langue électronique. Le principe consiste à comparer la distance du couple actif/placebo calculée sur la cartographie du gout. Plus cette distance est raccourcie, plus le goût de l'échantillon contenant la substance active est similaire à celui du placebo, c'est-à-dire ayant le goût neutre du placébo ou le goût masqué du principe actif.

L'évolution de la mesure des capteurs montre que les formulations de mini-granules contenant 25% de principe actif ont un masquage de goût efficace de même que les comprimés orodispersibles contenant des mini-granules à base Eudragit comme polymère et la crospovidone comme agent de désagrégation.

4. Faisabilité de comprimés de mini-granules orodispersible à usage pédiatrique

Des mini-granules à base de mannitol ont été produites avec un rendement acceptable (84%) mais la répartition granulométrique diffère par apport aux mini-granules de MCC. Des résultats similaires ont été rapportés dans la littérature lorsque de fortes concentrations de mannitol sont utilisées; la taille des granules augmente à cause de l'agglomération durant l'étape de sphéronisation en raison de ses propriétés de viscosité et autocollants (54). Les mini-granules de mannitol présentent une forme sphérique et des valeurs acceptables de friabilité (<1%) mais leurs valeurs de dureté indiquent une résistance plus faible comparativement aux mini-granules de MCC ce qui peut influencer leur aptitude à la compression.

Les profils de compression ont montré qu'il est possible de produire des MUP-ODTs en utilisant des forces de compression entre 5-15 kN, néanmoins les trois facteurs étudiés: taux de mini-granules de MCC, taux de lubrifiant et force de compression influencent directement la réponse de friabilité. Ceci s'observe à travers l'équation dérivée d'une analyse de régression linéaire multiple et le modèle de réponse de surface qui ont déterminé les paramètres expérimentaux souhaitables pour que la friabilité réponde aux critères de contrôle de qualité:

$$Y_3 = 54.8 + 21.7X_1 - 23.4X_2 + 14.8X_3 - 9.8X_1^2 + 12.7X_1X_2 - 5.7X_1X_3 + 19.1X_2^2 + 5.9X_2X_3 + 5.5X_3^2$$

Il apparait qu'un pourcentage de mini-granules de MCC de 30%, un taux de lubrifiant de 0.5% et une force de compression de 10 kN sont les paramètres optimaux pour obtenir un MUP-ODT avec une dureté acceptable (38 N), une faible friabilité (0,3%) et un temps de désintégration acceptable (100 s).

Conclusion

Les formes galéniques orales développées dans ce travail répondent aux spécifications de qualité pour les systèmes de libération contrôlée et les comprimés orodispersibles. Ces formes sont adaptées aux enfants de 3-5 ans en offrant une grande précision, une flexibilité de dosage et sont faciles à déglutir**.**

Les MUP-ODTs obtenus ont montré la faisabilité de leur production et l'obtention de bonnes propriétés mécaniques. Ils permettent la désagrégation très rapide et la possibilité de libération contrôlée de l'acétaminophène.

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Review article

- Martínez Terán M.E., Hoang Thi T.H., Flament M.P. Multi-particulate dosage forms for pediatric use. Pediatr Ther. (accepted)

- Martínez Terán M.E., Hoang Thi T.H., Flament M.P. Development and applications for paediatric medicines- A Review. (submitted)

Poster presentation

- Martínez Terán M.E., Flament M.P. Development of sustained release multiparticulate orodispersible tablets for paediatric use. 10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology. 2016 Apr 4-7. Glasgow, United Kingdom.

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Résumé

DEVELOPPEMENT ET EVALUATION DES MINIGRANULES À LIBERATION CONTRÔLÉE DANS LES COMPRIMÉS ORODISPERSIBLES A USAGE PEDIATRIQUE

Dans la dernière décennie, les autorités de santé ont promulgué une réglementation pédiatrique orientée sur le développement et la disponibilité des formulations adaptées à l'âge, la taille, l'état physiologique et les besoins de la population pédiatrique. Généralement, l'administration de médicaments par la voie orale est toujours préférée aux autres voies d'administration car elle est pratique, économique et bien acceptée. Au cours des dernières années, de nouvelles formulations solides ont été développés comme par exemple les comprimés orodispersibles car ils sont faciles à administrer, ne nécessitent pas d'eau et, dès lors que la dispersion est rapide, la biodisponibilité du médicament peut être significativement supérieure à celle observée avec les comprimés classiques offrant ainsi des solutions alternatives pour les enfants. D'autre part, les mini-granules présentent de nombreux avantages par rapport aux formes galéniques solides unitaires car ils se dispersent à travers le tractus gastro-intestinal, réduisant ainsi l'irritation locale du principe actif, et permettent l'amélioration de l'absorption du médicament ainsi que la diminution des fluctuations de concentration plasmatique. De plus, avec ces formes multiparticulaires, il est possible de contrôler la vitesse de libération du médicament, ce qui réduit les effets indésirables. Quelques études ont porté sur la compression des mini-granules non enrobés, ce qui pourraient limiter les problèmes pendant la compression comparativement aux mini-granules enrobés pour lesquels l'enrobage pourrait être détruit.

L'objectif global de ce travail était de développer un comprimé multiparticulaire orodispersible (MUP-ODT) qui permet la libération contrôlée d'acétaminophène (APAP), utilisé comme principe actif modèle, contenue dans les mini-granules des comprimés orodispersibles.

La première partie a déterminé les propriétés mécaniques des mini-granules d'APAP obtenus par la technique d'extrusion-sphéronisation en contenant différents types d'excipients et différents pourcentages de principe actif pour produire un système matriciel à libération contrôlée.

La seconde partie de cette étude a examiné la faisabilité de comprimer des mini-granules non enrobés à base de MCC dans différentes formulations orodispersibles et d'étudier l'influence du pourcentage de mini-granules, le type de désagrégeant et la force de compression.

La troisième partie a été dédiée à la production des MUP-ODTs qui permettent la libération contrôlée d'APAP en utilisant différents pourcentages d'Eudragit® pour créer un système matriciel sans changement significatif dans le profil de libération après la compression.

Enfin, dans la dernière partie, un plan d'expérience a été effectué pour déterminer les paramètres optimaux pour produire les MUP-ODTs. L'évaluation du masquage de goût a été réalisée par la langue électronique et la méthode de dissolution à l'aide d'une pompe à seringues qui utilise de fiables volumes de milieu afin de simuler le comportement dans la bouche d'un enfant. Plusieurs polymères ont été utilisés avec succès pour produire des mini-granules d'APAP de type matriciel avec différents pourcentages de principe actif. Les MUP-ODTs ont été obtenus en montrant la faisabilité de leur production et l'obtention de bonnes propriétés mécaniques. Ils permettent la désagrégation très rapide et la possibilité de libération modifiée, tout en offrant une déglutition facile pour un enfant et une flexibilité de posologie.

Mots clés : Mini-granules, Comprimée Multiple-Unit Orodispersible, Libération contrôlée, Masquage de gout, Formulation pédiatrique.

Abstract

DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE PELLETS IN ORODISPERSIBLE TABLETS FOR PEDIATRIC USE

In the last decade, medical agencies have promoted a pediatric regulatory focusing on the development and availability of appropriate formulations suitable for age, size, physiological condition and treatment requirements for the pediatric population. In general, oral drug delivery is still preferred over the other drug delivery routes since it is convenient, economical and user friendly. In recent years, a number of new solid oral drug delivery platforms such as orodispersible tablets have been developed as they are easy to administer, do not require additional water and, as long as dispersion is rapid, the bioavailability of the drug can be significantly greater than those observed in conventional tablet dosage forms offering a potential alternative for pediatric patients. In parallel, multiparticulate products present many advantages compared to single-unit dosage forms as they distribute fast through the gastrointestinal tract, thus reducing local irritation caused by the active ingredient, enhancing drug absorption and decreasing fluctuation of plasma peaks. Moreover, it is possible to control the drug release rate, resulting in fewer adverse effects. Only few studies have dealt with the compaction of uncoated pellets, which potentially could provide fewer problems during compaction than coated pellets, in particular by reducing damages on the coating.
The overall objective of this study was to develop a Multiple-Unit Pellet Orodispersible Tablet (MUP-ODT) allowing for the controlled release of acetaminophen (APAP), used as a model drug, which is contained in the pellets of the orodispersible tablets.
The first part determined the mechanical properties of APAP pellets produced by the extrusion-spheronization technique containing different types of excipients and different drug load percentages to produce a controlled release matrix system.
The second part of this study examined the feasibility to compress uncoated free drug MCC pellets with different orodispersible formulations to assess the influence of the percentage of pellets, type of disintegrants and compression force.
The third part was dedicated to produce MUP-ODTs which allowing for controlled-release of APAP using different percentages of Eudragit® to create the matrix system without significant changes in the release profile after compression.
Finally, a design of experiments was carried out to determinate the optimal parameters to produce MUP-ODTs.
Taste-masking evaluation was realized using the electronic tongue. Dissolution test was performed using a syringe pump and small volumes of aqueous medium at low flow rates to mimic the behavior in the mouth of the child.
Different polymers were successfully used to produce APAP matrix pellets with different drug loadings. MUP-ODTs were successfully obtained demonstrating their feasible production with good mechanical properties. They enable very fast disintegration and modified release properties, but also offer easy swallowing for children and dose flexibility.

Key words: Pellets, Multiple-Unit Orodispersible Tablets, Controlled release, Taste masking, Pediatric formulation.