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FORMULATION OF IMMEDIATE RELEASE & SUSTAINED RELEASE PELLETS FOR PAEDIARTIC APPLICATION

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ABSTRACT

Paediatrics formulation design is complicated because it requires an understanding of the developmental physiological changes that occur during childhood and their influence on medication absorption. Paediatric dosage modifications are often predicated on obtaining pharmacokinetic or pharmacodynamic characteristics similar to those seen in adult populations. However, changes in how children manage adult medications, as well as the usage of tailored pediatric formulations, can lead to unanticipated pharmacokinetic drug profiles and changed clinical effectiveness.

Differences in medication formulations must be appreciated by healthcare professionals who prescribe, administer, or dispense pharmaceuticals to children in order to provide appropriate guidance and assure therapeutic results. This concern is not limited to oral medications, but applies to all modes of administration used in pediatric care.

There is significant interest in enhancing the acceptability of solid oral dose forms (SODF)in pediatric populations. Combination medicines provide a unique way to mix two active medicinal components. This study found that a binary combination of pediatric SODF can improve formulation swallow ability and palatability.

We used the Paediatric Soft Robotic Tongue (PSRT), an in vitro device inspired by the anatomy and physiology of 2-year-old children, to study the oral phase of swallowing multi-particulate formulations such as pellets (350 and 700 µm), mini tablets (1.8 mm), and binary mixtures (BM). We measured oral swallowing time, fraction of particles swallowed and post-swallow residues.

Adding pellets to the carriers enhanced shear viscosity but had no influence on shear thinning. Xanthan gum-based solutions improved pellet swallowing rates(≥75%),particularly at high concentrations of 0.5and1%, promoting pellet transport while minimizing post-swallow residues.

Keywords- Paediatrics, Pellets, minitablets, binary mixture, flexible solid oral.

INTRODUCTION

Medical organizations have supported a paediatric regulatory framework for the past ten years, emphasizing the creation and accessibility of formulations that are appropriate for the pediatric population's age, size, physiological state, and therapeutic needs.

Optimizing the oral drug delivery route over alternative routes has shown to be one of the biggest hurdles in paediatric formulations. This is because oral drug delivery is convenient, cost-effective, and easy to use, but swallowing ability is crucial for these formulations.

While parenteral administration is still the first choice for babies and emergency situations, oral formulations are often recommended for long-term treatment in children. For patients who must take their medication at night or while attending school, the use of sustained release formulations may be a practical way to lower the frequency of doses.

Because children's physiological conditions differ from adults', not all APIs are suitable candidates for formulation as sustained-release products. In the case of oral sustained release, formulations are made to deliver the API through the gastrointestinal tract at a slower rate than conventional formulations, lowering the dose frequency. When developing a formulation, it is important to consider factors that can affect the drug's pharmacokinetic parameters, such as the API's solubility in gastric and intestinal pH, emptying rate, intestinal motility, intestinal permeability, and plasma elimination half-time. Different dose forms, such as multiparticulate systems, which come in sachets, capsules, or various tablet forms (such as coated, matrix, or fast disintegration tablets), are used to give sustained release products. It is essential to provide explicit information on the label of tablets and multiparticulate systems about their safety and effectiveness measures. For example, it should state that these formulations should not be broken, chewed, or combined with food or drink in order to preserve the coating and ensure the product's safety and effectiveness. Compared to single-unit dosage forms, multiparticulate drug delivery systems (MUPS), like pellets, offer a number of therapeutic and technological benefits. These include improved palatability, controlled drug release that reduces side effects, and even distribution of the drug in the gastrointestinal tract.

‘Pediatrics is the branch of medicine dealing with the health and medical care of infants, children, and adolescents from birth up to the age of 18. The word “paediatrics” means “healer of children”; they are derived from two Greek words: (pais = child) and (iatros = doctor or healer). Paediatrics is a relatively new medical specialty, developing only in the mid-19th century. Abraham Jacobi (1830–1919) is known as the father of paediatrics’.

Compared to single-unit dosage forms, multiparticulate drug delivery systems (MUPS), like pellets, offer a number of therapeutic and technological benefits. These include improved palatability, controlled drug release that reduces side effects, and even distribution of the drug in the gastrointestinal tract.

a. Children and their particular requirements-

Children's medication development has long been overlooked. Up until the latter half of the 20th century, it was widely believed that clinical research involving children should be avoided for ethical grounds. Other obstacles also exist, despite the current consensus that children should have access to medications that have been suitably assessed for their intended purpose. The pediatric population, which includes premature neonates and adolescents, is too diverse to be treated as a homogeneous group. In addition to posing practical challenges for study design, smaller populations also translate into reduced returns for businesses. Consequently, there is a dearth of medications that are intended and researched for use in children. At the end of 2006, on a European scale, of the As of the end of 2006, 43% of the 317 centrally authorized medications had potential pediatric use but were not approved in this way (1).

Infants, toddlers, pre-schoolers, school-age children, adolescents, and new-borns (term or pre-term) comprise the diverse population of children (1). Pharmacotherapy is made more difficult by the physiological changes that occur during childhood. Regarding the age ranges that characterize infancy, childhood, and puberty, there isn't total agreement. Individuals between the ages of 0 and 18 have been referred to as "children" in a broad sense.

From a biological perspective, a child (plural: children) is typically a human being between birth and adolescence. Age groupings are used in accordance with developmental phases in the guideline on clinical evaluation of medicinal items in the pediatric population. The early growth spurt, the progressive growth from ages 2 to 12, the pubertal and teenage growth spurt, and the development towards adult maturity are all examples of biological changes that are reflected in it. Children's physiological composition varies within their own age group as well as from that of adults. Saliva production, body composition (such as body water and fat content, protein binding properties), organ weight, and maturity (such as renal and hepatic maturation) all vary over the first several weeks and months of life (3). This may have an impact on how medications and excipients are absorbed, distributed, metabolized, and excreted, which may lead to toxicity (4).

b. Kids and their medications-

One major issue facing the pediatric population is the absence of approved medications and the resulting off-label use of adult medications. Given their frailty and even smaller patient numbers, neonates present a unique set of difficulties. Why are children given adult medications "off-label" if they are not young adults? A youngster does not profit from authorized medications that are not on the market. As people age, the proportion of approved, dosage-capable medications with appropriate dosage forms rises. According to the American Academy of Pediatrics, doctors "must frequently either not treat children with potentially beneficial

medications or treat them with medications based on adult studies" as a result of the paucity of pediatric research.

Research involving children is crucial if children are to fully benefit from advancements in medical science, as research conducted on adults cannot be easily extended or generalized to newborns, children, and adolescents. Research in pediatrics is more difficult than research in adults due to a number of factors, such as the comparatively small number of children with serious medical issues, the requirement for developmentally appropriate outcome measures for children of various ages, the difficulties of parental involvement and family decision making, and the modifications needed in research procedures and settings to accommodate children's physical, cognitive, and emotional development.

Additionally, children typically offer a smaller market for commercial research sponsors than adults. The expenses of creating new preventive, diagnostic, and therapeutic alternatives for children may not be covered by their commercial worth, particularly in the case of rare disorders. While the widespread usage of off-label medications does not encourage firms to fund pediatric research on medications that are already approved for use by adults, there are a number of formulation, clinical, and regulatory requirements for producing pediatric formulation. The rarity of many childhood disorders, population variability, and consent concerns are obstacles to conducting five pediatric studies.

AIM AND OBJECTIVE

The goals of paediatric research are to minimize newborn and child mortality, restrict the spread of infectious illness, promote healthy lifestyles for a long disease-free life, and assist in the treatment of children and adolescents with chronic disorders.

Paediatricians diagnose and treat a variety of illnesses among children, including:

- Injuries and infections.
- Genetic and congenital conditions.
- Cancer, organ illnesses and dysfunctions.

Paediatrics is concerned with not just the immediate care of the unwell kid, but also the long-term repercussions on quality of life, impairment, and survival. Paediatricians are concerned with the prevention, early identification, and management of disorders such as:

- developmental delays and disorders
- behavioral problems
- functional disabilities
- social stresses
- mental disorders including depression and anxiety disorders

Objectives:

- Creating sustained release pellets using polymers such as ethyl cellulose and eudragits.
- Coated pellets are evaluated and optimized for in vitro drug release over a 12-hour period.
- In vivo testing of drug-loaded pellets in an appropriate animal model, such as a rabbit.

PLAN OF WORK:

- Design of dosage forms
- Ingredients
- Handling

THE PROFILE OF DRUGS AND EXCIPIENTS

DRUG AND EXCIPIENT PROFILE: This chapter summarizes the physicochemical properties of 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.

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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.

Excipients Essentially: pharmaceuticals have a greater amount of excipients than the primary active component. These inactive chemicals' primary purposes are to improve stability, hide the harsh taste of the medicine, regulate drug release, improve patient acceptance, and/or increase production (62). Nonetheless, specific adverse effects have been observed in several subpopulations of the pediatric population, particularly in neonates, babies, and children, who have different pharmacokinetics and pharmacodynamics than adults (63,64).

Guidelines for formulation approval establish the use of the smallest quantity of excipients, which must be reported in amount and justified by function for each one used in the formulation, as well as respect its recommended daily intake (ADI) in order to minimize undesirable effects (64-66). Both regulatory authorities, the EMA and the FDA, have produced guidelines for the use and disclosure of excipients in pediatric formulations that are open for comment. Table I-4 outlines the principal excipients associated with known concerns in children that should be evaluated when developing a pediatric formulation (67,68). On the other hand, the European and US Pediatrics Initiatives collaborate to develop the Safety and Toxicity of Excipients for Pediatrics (STEP) database, which aims to offer literature evidence and evaluate the safety and toxicity of excipients for children (35,69,70).

Table I-1. Excipients and associated adverse effects in pediatric

Function	**Excipient**	**Formulation**	**Acceptable daily intake**	**Associated adverse reaction**
Solvent	Ethanol	Iron supplementations OTC cough syrups	0.5% < 6 years and 5% > 6-12 years	Chronic and acute toxicities in premature new borns
Antioxidant/ Bacterial preservative	Benzalkonium chloride	Nebulizer solutions, Nasal saline, nasal corticosteroids and nasal decongestant solutions	90mg/kg	Paradoxical bronchospasm in asthmatic children
Filler/ Diluent	Lactose	Feed formula Tablets, capsules, lyophilized powders, liquid formulations, inhalations products	3g/kg	Lactose intolerant present gastrointestinal symptoms

Sweetener	Fructose	Liquid formulations	50g	Increase blood level in diabetic patients; laxative effects, bloating and excessive flatus if administered in high doses
Colorants	Solid and liquid formulations	2.5mg/kg	Allergic reactions	

MATERIALS AND METHODS

Materials:

a) Drug load pellets To create drug load pellets, the following substances were used: Acetaminophen (APAP, Safic Alcan, India), Microcrystalline cellulose (Avicel PH 101, FMC Biopolymer, Belgium), 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), Trieth.

b) Orodispersible forms.

The following materials were used to make 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).

Methods:

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

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	--	--	--	--	--	--	--	--	18.94	16.23	10.82	5.41
Water (ml)	**60**	**65**	**47**	**35**	**105**	**92**	**65**	**50**	**76**	**67**	**65**	**65**

Pellet characterization

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.

Aspect ratio-

Individual pellet morphology was assessed using a stereo microscope (Nikon SMZ-800, Melville, US) with an AxioCam Icc1 camera. The photos were then examined using AxioVision software (Carl Zeiss, Jena, Germany). The aspect ratio was calculated as the ratio of the longest Feret's diameter to its perpendicular diameter (n=50). The aspect ratio specifies the pellet sphericity and is anticipated to be close to one.

Moisture content-

A 1 g pellet sample was accurately weighed before and after heating in an oven at 105°C for 30 minutes (WTB Binder, Tuttlingen, Germay). The moisture content was determined as a percentage of pellet weight loss (n=3).

Friability-

One gram of pellets was put in a 10 ml glass container with 3 g of stainless steel beads and oscillated in a Turbula mixer (Bachofen Maschinenfabrik, Basel, Switzerland) at 27 rpm for 5 minutes. Fines were sieved through a 355 µm screen, and pellet friability was evaluated based on weight loss % (n=3).

Hardness-

A texture analyzer, TA.XT Plus (Stable Micro System, Surrey, England), was used to determine the mechanical characteristics of individual pellets. Single pellets were squeezed on a stainless steel plate using a cylindrical stainless steel probe (diameter 3 mm) and a load cell weighing 5 kg. The settings were set at a starting height of 3 mm, a downward cross-head speed of 0.03 mm/s, a trigger force of 1g, elongation of 0.5 mm, and return speed of 0.5 mm/s. Force-distance graphs were recorded and analyzed for maximum force and displacement (n=30).

Thermograms were created using a DSC-

1 (Mettler Toledo, Greifensee, Switzerland). Approximately 5 mg of material was deposited in non-hermetic aluminum pans and scanned using a dry nitrogen purge from 25 to 250°C at 10°C/min. The reference was an empty metal pan. Temperature and enthalpy measurements were calibrated with pure indium and zinc.

Design and development of multiple-unit orodispersible tablets-

Production of orodispersible granules-

The excipients described in Table II-2 were used to create orodispersible granules (ODG) using wet granulation. Powders were weighed and combined in a tumbling mixer (Turbula®, Basel, Switzerland) for 10 minutes. Wet granulation was done in a planetary mixer (Keenwood Chief, Hampshire, UK) with deionized water as the wetting liquid. The wet material was passed through a 1.25 mm screen in an oscillating granulator (Erweka FGS, Western, Germany) and dried in an oven (WTB Binder, Tuttlingen, Germay) at 60°C for 6 hours. Granules were passed through a vibrating sieve shaker (Retsch GmbH, Haan, Germany), and fractions between 500-1000 ìm were employed for 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

Preparation of free drug pellets-

To make free-drug pellets, dried powders of MCC and lactose were mixed 1:1 in a tumbling mixer (Turbula, Basel, Switzerland) for 10 minutes. Granulation was done with a blender mixer (Keenwood Chief, Hampshire, UK) and demineralized water as a wetting liquid to create a moist material appropriate for extrusion. The wet mass was extruded using a cylinder extruder (Alexanderwerk GA 65, Remscheid, Germany) with two counter-rotating rollers at 63 rpm and a standard screen with a 1.0 mm 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 .

RESULTS

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.

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 amanufacturing 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.

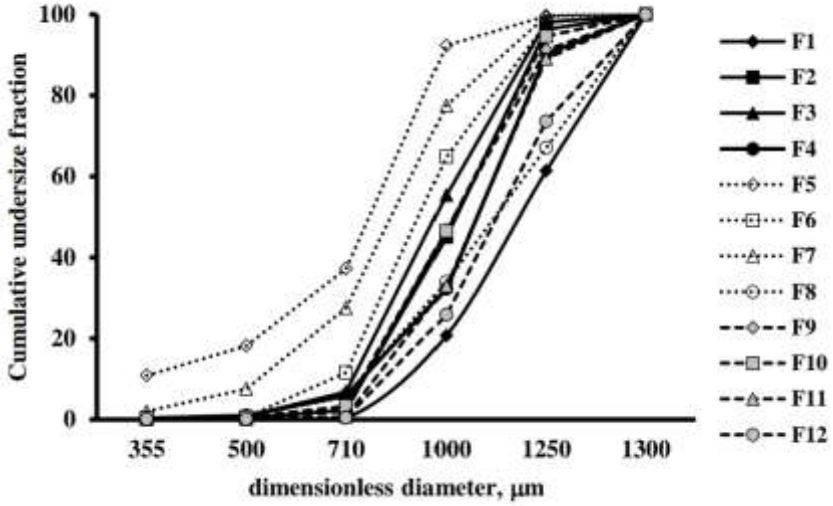

Figure III-1. Size distribution of APAP pellets using different type of excipients MCC:Lac (F1-F4), MCC:EC (F5-F8) and MCC:Eu (F9-F12) determined by sieve analysis.

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.

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**

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