DEVELOPMENT AND EVALUATION OF PEDIATRIC ORALLY DISINTEGRATING PARACETAMOL TABLETS

NGUGI SAMUEL GITAU

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DEPARTMENT OF PHARMACEUTICS AND PHARMACY PRACTICE

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UNIVERSITY OF NAIROBI

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DECLARATION

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I declare that this research work is my original work and has not been submitted to the University of Nairobi or any other institution for examination purposes of awarding a Master's degree or publication.

Signature……. Date……

Ngugi Samuel Gitau

U53/88934/2016

Department of Pharmaceutics and Pharmacy Practice

School of Pharmacy, University of Nairobi

Supervisors

This reasearch dissertation has been submitted with our approval as University supervisors:

1. Signature……. Date……

   Dr. Nasser Nyamweya

   Department of Pharmaceutics and Pharmacy Practice

   University of Nairobi

2. Signature……. Date……

   Dr Njogu P. Mbugua

   Department of Pharmaceutical Chemistry

   University of Nairobi

DECLARATION OF ORIGINALITY

Name of student:	Ngugi Samuel Gitau
Reg No:	U53/88934/2016
College:	Health Sciences
School:	Pharmacy
Department:	Pharmaceutics and Pharmacy Practice
Course Name:	Master of Pharmacy in Industrial Pharmacy
Title of work:	Development and evaluation of pediatric orally disintegrating paracetamol tablets

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I dedicate this work to my loving family for the support and prayers throughout my research.

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ABBREVIATIONS AND ACRONYMS

CMC	Carboxymethyl cellulose
COX-2	Cyclooxygenase type 2
GRAS	Generally recognized as safe
ICH	International Conference on Harmonization
IUPAC	International Union of Pure and Applied Chemistry
L-HPC	Low substituted Hydroxypropyl Cellulose
MCC	Microcrystalline cellulose
NAPQI	*N*-acetyl-*p*-benzoquinone imine
NSAIDS	Non-steroidal anti-inflammatory drugs
ODTs	Orally disintegrating tablets
OTC	Over the counter
PVP	Polyvinyl Pyrrolidone
QTPP	Quality target product profile
SD	Standard deviation
US-FDA	United States Food and Drug Administration
USP	United States Pharmacopeia
PODTs	Pediatric orally disintegrating tablets

ABSTRACT

The aim of this study was to develop pediatric orally disintegrating tablets (PODTs) of acetaminophen that would be appropriate for pediatric patients. The limitations of commercially available paracetamol formulations precisely: 1) stability and portability (commercial paracetamol suspensions) and 2) non-pediatric friendly excipients and costly manufacturing processes (commercially available paracetamol orally disintegrating tablets) were addressed by developing tablets using generally regarded as safe (GRAS) status excipients and a direct compression process. A total of eight batches with 60-mg and 120-mg paracetamol strengths of PODTs were successfully prepared by a simple cost-effective direct compression process. The tablets contained crospovidone (5 or 10 %) and/or effervescent excipients (10 or 20%) as disintegrants for fast oral disintegration.

The formulated tablets were assessed for uniformity of weight, breaking force, thickness, friability, disintegration time, dissolution, wetting time, water absorption ratio, content and content uniformity. Tablet disintegration rates were found to correlate well with tablet water absorption ratios and to a lesser extent with tablet wetting times. There was no correlation between tablet disintegration times and tablet mechanical and physical properties such as the tablet breaking force (hardness) or friability. Batches that contained 5 or 10% crospovidone disintegrated at a faster rate (of less than 30 seconds) than the effervescent excipients containing batches.

The PODT-2 batch with 10% crospovidone was selected as the best batch based on its fast mean disintegration time profile of about 12 seconds. It also had a mean breaking force of 45.8 N as well as a mean friability of 1.6 %. The batch was therefore selected for optimization to reduce its friability and improve its palatability. The batch was successfully optimized as the obtained breaking force led to a reduction in friability without affecting the disintegration time. The palatability was also improved with the addition of sweeteners.

CHAPTER ONE

INTRODUCTION

1.1 Background of the study

Oral drug delivery remains the most common and preferred route of drug administration compared to the other routes as it is flexible, easy to use, convenient, promotes accuracy in dosing and is cost-effective (Sarfraz *et al.*, 2015). Additionally, drugs meant for the oral route do not require sterile environments during manufacture. The popularity of oral drug delivery has promoted extensive research to provide more effective and patient appropriate oral drug dosage forms suitable for pediatrics, geriatrics as well as patients with swallowing difficulties. Orally disintegrating tablets (ODTs) are among the products that have been developed to address this need (Saigal *et al.*, 2008), (Sharma *et al.*, 2012).

Orally disintegrating tablets disintegrate rapidly in the mouth, typically in less than 60 seconds. In some cases, the observed fast disintegration and dissolution may increase drug bioavailability compared to that of conventional tablets (Siddiqui, Garg and Sharma, 2010). The rapid disintegration in most ODTs is associated with fast water penetration inside the tablet structure facilitated by super-disintegrants such as crospovidone, sodium starch glycolate, low hydroxyl propyl cellulose and croscarmellose sodium (Schwing *et al.*, 2014). Therefore, incorporation of suitable super-disintegrants and/or highly water-soluble excipients is an important pre-requisite in the development of ODTs (Nagar *et al.*, 2011), (Tanuwijaya, 2013). Other methods that promote fast disintegration include: addition of effervescent mixtures, lyophilization, sublimation, spray drying, phase transition, cotton candy process and use of low compression force (Roy, 2016), (Toor *et al.*, 2018).

Direct compression of powders to produce ODTs (with addition of super-disintegrants and/or effervescent mixtures) is not only the easiest method of production of tablets, but it is also less expensive and effective in comparison with other tablet manufacturing procedures. This method is compatible with conventional tablet manufacturing and packaging equipment. In addition, the availability of directly compressible excipients with excellent flow and disintegration properties

has further enhanced its use. Attempts to improve the method have led to the development and patenting of various technologies like Flashtab®, Wowtab®, OraSolv® and Durasolv®.

OraSolv® and DuraSolv® are compression technologies that have been patented by CIMA Labs Inc. to develop ODTs. However, the OraSolv® technology tablets were associated with low mechanical strength (breaking force) which required special packaging (PakSolv®). The observed low mechanical strength in OraSolv® technology tablets was improved by development of DuraSolv® technology. In the DuraSolv® technology, higher compression pressures were applied to produce stronger tablets which are compatible with conventional packaging. However, the aforementioned ODT technologies as well as many other utilize compressed coated particles making the formulation process expensive, complicated and tedious. Flashtab® and Wowtab® patented by Ethypharm and Yamanouchi (currently Astellas) used alternative proprietary process. Elimination of the coating process would provide a more cost-effective and simple formulation process for ODTs (Parkash *et al.*, 2011). The use of ODTs in pediatrics can lead to improved patient compliance due to elimination of the need to take drugs with water especially for travelling patients as well as improved drug absorption and overcoming swallowing difficulties compared to conventional oral solid dosage forms (Saigal *et al.*, 2008), (Kundu and Sahoo, 2008), (Abay and Ugurlu, 2015).

Paracetamol has been in use as an analgesic and antipyretic drug since 1951 upon approval by United States Food and Drug Administration (US FDA) as (Tylenol®). Since approval, paracetamol has been among the most popular and well tolerated drugs, either by prescription or as an OTC drug for the management of mild-to-moderate pain and fever in children. It is also common and well tolerated across all ages. Efforts to formulate the drug into an effective and patient friendly formulation such as ODTs are therefore vital. Although its mechanism of action is not well understood, it is believed to be a cyclooxygenase-2 (COX-2) inhibitor like Non-Steroidal Anti-inflammatory Drugs (NSAIDS) despite it not showing anti-inflammatory activity like NSAIDS (Graham and Scott, 2005).

The wide use of paracetamol has warranted research which has ascertained short-term safety and efficacy justifying its use as an OTC drug for the general population leading to the availability of various formulations. These include: tablets, powders for reconstitution, suspensions, enemas and

solutions for injection. However, paracetamol has a mild bitter taste when taken orally (Albertini *et al.*, 2004) and thus require taste masking during formulation to improve patient compliance. Most taste masking procedures are complex unit operations requiring specialized equipment and proficiency (Chauran, 2017). The addition of flavors and sweeteners are the simplest methods of taste masking for mildly bitter tasting drugs and also helps to complement other taste masking methods (Hirani, Rathod and Vadalia, 2009), (Nagar *et al.*, 2011), (Badgujar and Mundada, 2011), (Moriarty and Carroll, 2016), (Roy, 2016).

1.2 Statement of the problem

Paracetamol suspensions have been widely used in the management of mild to moderate pain and fever in pediatric patients. The widespread use of the suspensions has not been without challenges. For example, Calpol® suspension is bulky, requires special storage conditions to prevent instabilities, does not allow for accurate dosing relative to solid dosage forms and contains excipients which do not have generally regarded as safe (GRAS) designation which may be harmful to the patients (Table 2). The observed stability challenges are however almost shared by all suspensions that are currently in the market.

Other research studies such as one conducted at the University of Bangladesh by Azam and Haider to investigate dissolution characteristics among ten brands of paracetamol suspensions showed that dissolution of the suspensions was affected by the type of suspending agents used and their concentrations, the viscosity of the suspension, flocculation extent, zeta potential, and complexation (Dey and Maiti, 2010).

The rate and extent of dissolution is a rate-limiting step for drug bioavailability in suspensions. Since the concentration and type of the suspending agent may affect the dissolution of drugs formulated into suspensions, there is therefore a need to formulate paracetamol for pediatrics into an effective and patient friendly solid dosage formulation that will be more preferable than the widely used paracetamol suspensions. Orally disintegrating tablets will therefore help to overcome dissolution challenges observed in paracetamol suspensions (Azam and Haider, 2008). In addition, the ODTs would help to overcome the other challenges associated with the suspensions as they are easier to administer, more stable, easier to handle and less bulky.

Most paracetamol suspensions such as Calpol® suspension, Panadol® Baby and Infant suspension and Children's Panadol® Elixir have an upper storage limitation temperature of 25°C. The limitation is a concern especially in tropical climates where normal prevailing temperatures are usually above this limit. The presence of water in these formulations coupled with extreme temperatures above 25°C promotes drug degradation through hydrolysis (Zhou, Porter and Zhang, 2017). Orally disintegrating tablets provide an approach by which the limitations of paracetamol suspensions can be addressed. This study will seek to provide PODTs with 60-mg and 120-mg of paracetamol strengths using a simple cost-effective approach with less restriction on storage.

1.3 Study justification

This study seeks to develop a dosage form (tablet) that significantly improves on the currently existing ODT technologies. Most of these technologies require coating which is a complicated technique that requires expensive equipment and technical skills (Rao *et al.*, 2008), (Sujitha *et al*., 2014).

Therefore, the study will help to formulate less expensive and effective ODTs for the pediatric population with appropriate mechanical properties and disintegration times using equipment that is widely available in pharmaceutical manufacturing (as opposed to the specialized processes used in the aforementioned technologies). Furthermore, the tablets that will be developed in this work will use excipients that have less toxicological concerns, a factor that is of great importance in pediatric drug therapy.

These low dose ODTs will be suitable for pediatric patients because of the ease in dose measurements for children less than 12 years of age. This will help in preventing dosing variations observed with paracetamol suspensions, thus helping to minimize cases of under-dosing and over-dosing. The formulated tablets will be less bulky making them easy to store, transport, handle, dispense, use and pack. The absence of water in the formulation makes orally disintegrating paracetamol tablets reduce the potential for microbial spoilage if well formulated, packed and stored.

Short disintegration time is a critical factor when developing ODTs because it helps in rapid exposure of the drug for dissolution and absorption. For an oral dosage form to be able to disintegrate within the shortest time possible, the breaking force of the tablet will have to be compromised as seen in most commercially available ODTs where tablets have a lower breaking force than conventional tablets. This concern can however be addressed by careful packaging or by using specialized blister packaging such as PakSolv® by CIMA Labs Inc. However, none of the processes/technologies produces tablets with all the desired qualities. Additionally, many of the commercially available processes are expensive, tedious and complicated (Krishnaveni and Dhanalakshmi, 2014), (Badgujar and Mundada, 2011). This study will therefore aim at the formulation of uncoated PODTs containing paracetamol with satisfactory disintegration time and breaking force for easy packaging and handling.

1.4 Objectives

1.4.1 General objective

This study aims to formulate orally disintegrating paracetamol (120 mg and 60 mg) tablets for use in pediatrics using pediatric appropriate excipients.

1.4.2 Specific objectives

The study will seek to fulfill two key specific objectives:

1. Development of orally disintegrating paracetamol tablets using crospovidone and/or effervescent excipients as a disintegrant.
2. Quality evaluation of the formulated orally disintegrating paracetamol tablets.

1.5 Significance and anticipated outcome

Paracetamol is a safe and effective analgesic and antipyretic drug for all age groups, including pediatric patients below the age of 5 years. However, overreliance on paracetamol suspensions for management of pain and fever in children below the age of 5 years especially in public hospitals in Kenya has not been without challenges. These challenges are formulation bulkiness, inaccurate dosing, instabilities and storage conditions restrictions. Therefore, formulation of PODTs with 60 mg and 120 mg paracetamol using a less expensive and simple direct compression method with GRAS status excipients for children below 5 years of age will help to overcome the challenges associated with the use of suspensions in this age group.

CHAPTER 2

LITERATURE REVIEW

2.1 Background

2.1.1 Definition of orally disintegrating tablets

Orally disintegrating tablets may also be referred to as oro-dispersible or mouth dissolving tablets. They are tablets which rapidly break up in the patient's buccal cavity upon contact with saliva without chewing or co-intake water (Pawar *et al.*, 2011). They break up into small particles or dissolve into a gel-like matrix form resulting in the patient swallowing a solution or a suspension of the dispersed drug product in a saliva-based medium. According to European Pharmacopeia, ODTs are *"uncoated tablets intended to be placed in the mouth where they disperse rapidly (within 3 min) before swallowing"*. However, *"a solid dosage form which contains a medicinal substance/active ingredient which disintegrates rapidly within a matter of seconds when placed upon a tongue"* is an ODT according to US FDA (Fu *et al.*, 2004), (Siddiqui *et al.*, 2010), (Toor *et al.*, 2018).

2.1.2 Prominent features of orally disintegrating tablets

Orally disintegrating tablets should disintegrate rapidly (preferably instantly or within one minute) when in contact with saliva and without additional water or chewing. The disintegrated tablet should transform into a soft mass, solution or a suspension with a good mouth feel and that which is easy to swallow. Since the ODTs disintegrate/dissolve in close proximity to taste buds, drugs/API that have undesirable taste should be taste-masked with techniques which are compatible with the formulations while tasteless or drugs with no undesirable taste should dissolve to leave minimal or no residue after swallowing.

When designing ODTs, careful selection of APIs and/or excipients by the formulator is important for their appropriateness in properties such as solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density in order not to significantly affect tablet properties such as disintegration and breaking force. The water uptake of ODTs should be enhanced with the use of high wettability excipients to aid in fast water absorption for fast disintegration/dissolution. However, since the breaking force of a tablet is directly proportional to

the pressure from the compression machine while permeability (porosity) is affected negatively by the pressure from the compression machine; it is prudent to attain tablet porosities that are suitable for rapid penetration of water into the structure of a tablet without compromising on the required breaking force. Likewise, extremely 'soft' tablets should be avoided for easy packing and handling although special packaging containers can be used to handle fragile tablets. The tablets should have minimal sensitivity to humidity as many of the excipients are hydrophilic to promote rapid dissolving properties. An appropriate container closure system should be utilized in cases of moisture sensitive products (Fu *et al.*, 2004).

2.1.3 Benefits of orally disintegrating tablets

Orally disintegrating tablets possess the entire benefits associated with regular oral tablets and capsules, such as good stability, precise dosing, easy production, low bulkiness, and easy handling by patients. Likewise, they possess the benefits associated with liquid products, such as ease of administration and reduced threat of choking from physical blockage by a product. They are therefore suitable for pediatrics, geriatrics, bedridden/disabled patients as well as patients with developmental disorders and those with swallowing difficulties such as in Parkinsonism. These dosage forms do not require co-intake water for administration making them suitable for patients with limited access to water such as those in arid and semi-arid regions. Administration without water also allows for flexibility in administration time and location especially for travelling patients who would have been forced to carry bulky liquid formulations or water to swallow as in cases of conventional oral solid dosage forms (Fu *et al.*, 2004), (Siddiqui et al., 2010), (Roy, 2016), (Toor *et al.*, 2018).

2.1.4 Challenges in development of orally disintegrating tablets

Orally disintegrating tablets ought to have a fast disintegration time upon contact with saliva. However, fast disintegration is somehow inversely related to the breaking force (crushing strength) of a tablet necessitating a compromise between producing strong tablets and fast disintegration during formulation. Most ODTs therefore have a low crushing strength for fast disintegration leading to the requirement of careful handling during processing and packing, or in extreme cases special packaging due to the often-observed high friability issues.

Since the drug product disintegrates in the mouth, efficient taste-masking is a necessity as most drugs are known to have a bitter or undesirable taste (Pandey and Dahiya, 2016). Additionally, there should be minimal or no residue after swallowing, a requirement also for tasteless or drugs with no undesirable taste. Taste-masking techniques such as fluid bed coating or ion-exchange interaction are complex manufacturing unit operations. Some of the excipients used to mask the taste cannot be designated as generally regarded as safe (GRAS). The said excipients may be acceptable for adult patients, but concerns have arisen in pediatric use. These concerns are warranted due to differences in physiology, anatomy as well as organ and tissue development in pediatric patients compared to adult patients (Kearns *et al.*, 2003), (Batchelor and Marriott, 2015). This therefore warrants the need to use few excipients and those with known and/or minimal pediatric safety concerns.

2.2 Rapid disintegration strategies

2.2.1 Available technologies and methods

There are several proprietary technologies that have been used to formulate commercially available ODTs. These technologies are usually categorized depending on the method of manufacture utilized for development such as compression (either direct or with prior wet/dry granulation), lyophilization, molding, melt granulation, phase-transition, effervescence, sublimation, spray-drying among others.

The existing technologies include: OraSolv® and DuraSolv® (Cima Labs, USA), Wowtab® (Yamanouchi Pharma Technologies, USA, currently Astellas Pharma Inc.), Flashtab® (Ethypharm, France), Zydis® (Catalent, USA), Lyoc® (Cima Labs Inc. a subsidiary of Cephalon, USA), Quicksolv® (Janssen Pharmaceutica, Beese, Belgium), NanoCrystal™ (Elan, currently Perrigo, Ireland), Dispersible tablet (Lek, Yugoslavia), Pharmaburst® (SPI Pharma, USA), Frosta® (Akina, West Lafayette, Indiana), Quick-dis™ (Lavipharm, Canada), AdvaTab™ (Eurand, currently Adare Pharmaceuticals, USA), Oraquick® (KV Pharmaceutical, St. Louis, Missouri), Shearform (Biovail, currently Valeant, Canada) and Ziplet® technology (Passano con Barnago, Italy). Although the aforementioned technologies produce dosage forms that possess distinct required qualities of ODTs even though not all, not a single one of them has all the preferred qualities. The qualities of the resulting products are related to the method of manufacture used. As a result, there may be product-to-product variation in physicochemical properties such as breaking force, stability, dissolution, bioavailability and taste (Fu *et al.*, 2004).

2.2.2 Direct compression method

Direct compression is a compaction method. It is usually preferred because of its simplicity, cost effectiveness, few numbers of processing steps and availability of directly compressible excipients with acceptable flow and disintegration properties. In addition, the method is compatible with conventional manufacturing machinery and equipment. The OraSolv® and DuraSolv® technologies are direct compression methods with proprietary rights to Cima Labs Inc. to produce the commercially available ODTs. However, there are other compression based technologies which have been patented for use in the formulation of ODTs but with prior granulation such as Wowtab® and Flashtab® technologies (Dey and Maiti, 2010), (Razak *et al.*, 2015), (Toor *et al.*, 2018).

2.2.3 Lyophilization

Lyophilization (freeze drying) process involves removal of a solvent from a frozen drug solution or suspension matrix through sublimation under high vacuum and temperatures below freezing point of water (Saharan, 2017). The process produces feathery and highly permeable tablets with quick dissolution and fragmentation. The tablets disintegrate instantaneously to release the incorporated drug when in contact with saliva. The process is carried out at low temperatures to prevent adverse thermal effects that may lead to drug instability for thermal sensitive drugs. Storage of the lyophilized ODTs in a dry state prevents the likelihood of drug instabilities leading to extension of their shelf lives. Formation of a glassy amorphous matrix of excipients and API during the lyophilization process enhances the dissolution rate of the formulated product. Although the process produces fast disintegrating/dissolving tablets, it is expensive and the resultant tablets are unstable at high temperatures and humidity. Zydis® (Catalent, USA), Quicksolv® (Janssen Pharmaceutica, Beese, Belgium), Lyoc® (Cima Labs Inc. a subsidiary of Cephalon, USA) and NanoCrystal™ (Elan, currently Perrigo, Ireland) are examples of lyophilization process technologies (Fu *et al.*, 2004).

2.2.4 Molding

The molding method mostly utilizes hydrophilic ingredients. The powder blend is wetted with aqueous solvents and is subsequently air dried before tableting at lower compression force than that of conventional tablets. Water and ethanol are normally the wetting solvents. The use of low compression pressure helps to maintain high porosity for fast dissolution. Dissolution can also be enhanced via particle size reduction of the powder blend (Roy, 2016).

2.2.5 Melt granulation

Melt granulation involves formation of granules from powder particles using a meltable binder. This method avoids the use of granulation liquids such as water or organic solvents as in the case of conventional wet granulation methods. High-shear mixers are usually used, where the powder blend is heated to temperatures above the melting point of the binder through a heating jacket or by heat of friction generated by the blades. Hydrophilic waxy binders such as Superpolystate® and PEG-6-stearate have been successfully used as melt granulation binders (Roy, 2016).

2.2.6 Spray drying

Spray drying is a fast and cost-effective method of drying of pharmaceutical and biochemical powders. It provides small particle size powders with high porosity suitable for the formulation of ODTs. Spray dried powders for the formulation of ODTs usually contain supporting agents (such as hydrolyzed and non-hydrolyzed gelatins), bulking agents (such as mannitol) and super-disintegrants (such as crospovidone, sodium starch glycolate and croscarmellose sodium). Addition of effervescent excipients further increases the disintegration as well as dissolution of the dosage forms. Tablets that have been prepared by compression of spray dried powders have been observed to have a disintegration time of approximately 20 seconds (Parkash *et al.*, 2011), (Pandey and Dahiya, 2016).

2.2.7 Sublimation

The presence of highly water-soluble excipients in a solid dosage form impedes water penetration into the tablet matrix due to low porosity which may lead to a decrease in dissolution rate. Incorporation of volatile excipients into such formulations followed by compression into tablets using conventional tableting machines promotes formation of extremely porous structures when they sublime. The increase in porosity promotes fast disintegration of the tablets. Volatile excipients which are normally used include: urea, ammonium carbonate and camphor. Other excipients such as menthol, thymol and organic acids have been used as sublimating agents although in a few cases (Pandey and Dahiya, 2016).

2.2.8 Mass extrusion

In mass extrusion, a powder mix containing the API and the excipients is softened using a combination of hydrophilic polyethylene glycol and ethanol. An extruder or a syringe is then used to force out the softened mass into cylindrical pieces which are then cut into even segments to form tablets (Pandey and Dahiya, 2016), (Roy, 2016).

2.2.9 Phase transition

In the phase transition method, ODTs are formulated by compressing a powder blend containing two sugar alcohols such as erythriol and xylitol followed by heating at a temperature between their melting points. The heating process boosts inter-particulate bonding to provide tablets with higher mechanical strengths due to increased compatibility. The increase in mechanical strength does not affect the DT of the tablet (Roy, 2016), (Toor *et al.*, 2018).

2.2.10 Nanonization

Nanonization method is basically a particle size reduction wet-milling technique mainly for poor water-soluble drugs developed in the recent past as technologies such as Nanomelt® technology (Perrigo, Ireland). The formed API nanocrystals are adsorbed onto selected stabilizers to prevent coalescence and are then used to formulate ODTs. Nanoparticles promote fast disintegration/dissolution leading to enhanced absorption which translates to higher bioavailability and reduced dose (Roy, 2016), (Toor *et al.*, 2018).

2.2.11 Candy floss process

Candy floss (cotton candy) process exploits an exceptional process involving simultaneous rotating and flash melting to provide a fuzz-like crystalline matrix similar to cotton candy and hence the name. The formed matrix is recrystallized (to improve flow properties and compressibility), milled and blended with the API and other excipients before compression into ODTs. This process allows for high drug loading and improved breaking force. However, it is unsuitable for thermal sensitive drugs due to the high processing temperature involved (Roy, 2016), (Toor *et al.*, 2018).

2.2.12 Effervescence

The addition of alkali metal carbonates salts and organic acids into formulations meant for oral disintegration leads to evolution of carbon dioxide gas when in contact with saliva as evident in the OraSolv® formulations. The release of the gas and subsequent volume expansion promotes disintegration of ODTs as well as a sensation for further release of more saliva for an increased disintegration and dissolution rates (Desai, Valeria Liew and Wan Sia Heng, 2016).

2.2.13 Fast dissolving films

This is a relatively new method that has been developed to provide fast dissolving films as ODTs (Dixit and Puthli, 2009). In this technique, a homogenous viscous hydrophobic solution containing a film forming polymer, the API and other excipients is prepared and dried to get rid of the solvents to form fast dissolving films. The films dissolve rapidly in the mouth releasing the drug in suspension or solution forms (Roy, 2016), (Toor *et al.*, 2018).

2.2.14 Super-disintegrants

Super-disintegrants are excipients incorporated in solid dosage forms at low concentrations to promote fast disintegration in an aqueous environment thereby enhancing dissolution. Rapid disintegration is an important factor in the production of ODTs. Efficiency of disintegration is realized with super-disintegrants' strong interaction with water, ability of the super-disintegrants to overcome tablet binder effects and compression forces that form the tablets. Super-disintegrants act by promoting swelling and/or wicking and/or deformation of solid dosage forms to cause release of drug molecules when in contact with aqueous environment. Super-disintegrants are incorporated in granulated solid dosage forms "intragranularly", "extra granularly" or as a combination of the two to promote breakdown to powder particles thereby enhancing dissolution of drug molecules. However, in directly compressed tablets, they are blended together with other tablet excipients (Mohanachandran *et al.,* 2011), (Chhote et al., 2014). Table 1 gives a summary of mechanisms of tablet disintegration associated with commonly used super-disintegrants.

Table 1: Types of disintegrants incorporated in mouth disintegrating tablets

Disintegrant	Nature	Properties	Mechanism
Crospovidone	Cross-linked polyvinyl pyrrolidone (PVP)	Swells 7-12 times in less than 30 seconds. Hydrophobic, compressible in nature to form porous tablets with pleasant buccal feel.	Swelling and wicking
Croscarmellose sodium	Cross-linked cellulose	Hydrophobic, has a pleasant buccal feel. Swells two-dimensionally and at 4-8 times < 10 seconds.	Swelling
Sodium starch glycolate	Cross-linked starch	Hydrophobic, swells 7-12 folds < 30 second and in three dimensions.	Water uptake followed by swelling
Acrylic acid derivatives	Poly (acrylic acid) super porous hydrogel	Insoluble in organic solvents, disperses in cold water and settles as a highly saturated layer.	Wicking
Effervescent mixture	Citric acid, tartaric acid, sodium bicarbonate	Crystalline in nature. Release CO_2 in contact with fluid.	Effervescence
Sodium alginate	Sodium salt of cross-linked alginic acid	Slowly soluble in water, hygroscopic in nature	Swelling
NS-300 (Ozeki *et al.*, 2003).	Carboxy- methylcellulose (CMC)	Particle size approximate 106 µm, DT approximate 20 seconds.	Wicking
ECG-505 (Ozeki *et al.*, 2003).	Calcium salt of CMC	DT is approximately 80 seconds.	Swelling
L-HPC	Low hydroxyl propyl cellulose	DT is approximately 80 seconds	Swelling and wicking
Isphagula husk		*Plantago ovata* seed shell with swelling properties and gives even and fast disintegration.	Swelling

Adopted from (Fu *et al.*, 2004), (Rao *et al.*, 2008).

2.3 Patented technologies

2.3.1 OraSolv® technology

OraSolv® technology is a patented direct compression process from CIMA Labs Inc. USA which produces ODTs with low mechanical force (6-25N). The tablets disintegrate mainly by an effervescent method with release of carbon dioxide gas upon contact with saliva. Release of carbon dioxide creates a sensation which further promotes saliva production enhancing disintegration. The effervescent effect is as a result of presence of an acid source (citric, tartaric, malic, fumaric, adipic, or succinic acids) and a carbonate source (sodium bicarbonate, sodium carbonate, potassium bicarbonate or potassium carbonate). The effervescent excipient pair is incorporated at about 20-25% of the maximum tablet weight. Apart from the effervescent excipients, other excipients such as fillers, disintegrants, lubricants, flavors and colors make up the final product.

OraSolv® technology uses conventional tablet manufacturing machines and equipment to produce ODTs that have comparable pharmacokinetic profiles to conventional tablets. The ODTs disintegrate within 10 to 40 seconds with a maximum strength of 750 mg. However, this technology produces soft and delicate tablets which require a special packaging system to keep the tablets intact during transport and storage. CIMA Labs Inc. developed PakSolv®, which is a special child resistant blister package that not only holds the tablets in position, but also protects the tablets from moisture and light (Fu *et al.*, 2004), (Pawar *et al.*, 2011).

2.3.2 DuraSolv® technology

DuraSolv® technology is a second-generation direct compression technology from CIMA Labs Inc. USA developed to improve the OraSolv® technology. It produces tablets with increased breaking force of about 15 to 100 N able to withstand packaging in blisters or multi-dose containers. The formulations are comparable to that of OraSolv® technology. Non-direct compression fillers (such as dextrose, mannitol, sorbitol, lactose or sucrose at approximately 60-95% of the total tablet weight promote dissolution and smooth texture of the tablets) are crucial ingredients in DuraSolv® technology. The appropriate particle size distribution of the non-directly compressible fillers should be between 20 to 65 µm and over 100 µm for at least 85% of directly compressible fillers.

DuraSolv® technology produces ODTs at strengths of about 125 µg to 500 mg capable of disintegrating within 10 to 50 seconds to release the taste-masked API microparticles prior to dissolution. This technology allows for incorporation of higher percentages of hydrophobic lubricants at 1 to 2 % together with the non-direct compression fillers compared to 0.2 to 1 % in conventional tablets. It also allows for extended lubricant mixing period of about 10 to 25 mins without affecting disintegration. Like the OraSolv® technology, it is also compatible with conventional tablet manufacturing machines and equipment. The formed tablets have a friability of about 2 % or less as per USP specifications and disintegration times (DT) below 60 seconds (Fu *et al.*, 2004), (Dey and Maiti, 2010), (Kumar, Sharma and Sharma, 2011), (Pandey and Dahiya, 2016), (Roy, 2016), (Toor *et al.*, 2018).

2.3.3 Wowtab®

Wowtab® (Yamanouchi Pharma Technologies, Norman, Oklahoma currently Astellas Pharma Inc.) produces tablets with appropriate physical and mechanical integrity able to withstand normal processing procedures. In Wowtab® technology, a low moldability saccharide (such as mannitol, xylitol, lactose, glucose and sucrose) is granulated in a fluid-bed granulator together with high moldability saccharide (such as sorbitol, maltose, maltitol and oligosaccharides) which acts as a binder. The low moldability saccharides are however the main components. The granules are blended with lubricants and flavoring agents and the resultant blend is compressed into tablets.

The formulated tablets can be packed in both conventional bottles and blisters unlike OraSolv® and Zydis® formulations. Smooth-melt action, a patented taste-masking technology is employed to give a good mouth feel for Wowtab® products. Physical blending of the two saccharides or simultaneous granulation before tableting will not guarantee tablets with the required qualities of Wowtab® ODTs (Fu *et al.*, 2004), (Parkash *et al.*, 2011), (Roy, 2016).

2.3.4 Flashtab® technology

Flashtab® technology (Ethypharm, France) produces ODTs by compression of pre-coated API blended with pre-granulated disintegration enhancing excipients as well as other GRAS status excipients. The disintegration enhancing excipients are prepared by either dry or wet granulation. The excipients are categorized as 1) disintegrating agents such as carboxymethyl cellulose, crospovidone, croscarmellose sodium or insoluble reticulated polyvinylpyrrolidone and 2)

swelling agents such as starch, modified starch, carboxymethylated starch, microcrystalline cellulose and 3) readily directly compressible sugars. Highly aqueous sugar alcohol binders such as mannitol, sorbitol, xylitol and maltitol can replace the swelling agents if need arises. The formed tablets have sufficient mechanical strength to withstand manufacturing and packaging processes as well as short disintegration time which is usually within a minute (Fu *et al.*, 2004), (Hirani, Rathod and Vadalia, 2009), (Dey and Maiti, 2010), (Badgujar and Mundada, 2011), (Nagar *et al.*, 2011), (Roy, 2016).

2.3.5 Zydis® technology

Zydis® technology (Catalent, USA) is the most popular lyophilization method for the production of ODTs. The Zydis® formulations contain a mixture made up of three components including a drug, saccharide and a polymer in a matrix which is made into a solution/suspension. The solution/suspension is transferred into blister cavities that are then put under a specially designed liquid nitrogen freezing process. This guarantees correctly sized crystals suitable for the formation of a porous structure in the tablet for fast disintegration. The frozen blisters are then dried using large-scale freeze dryers by sublimation before sealing with a heat seal process.

There is no requirement for addition of preservatives since the resultant products have low water content to sustain microbial growth. However, they are very sensitive to moisture and may degrade at humidity greater than 65%, hence a minor damage to the packaging material will affect the product. The fillers that are used in Zydis® technology should be chemically inert, water insoluble and with particle sizes below 50 µm (Fu *et al.*, 2004), (Dey and Maiti, 2010), (Roy, 2016).

2.3.6 Lyoc® technology

In Lyoc® technology (Cima Labs Inc. a subsidiary of Cephalon, USA), an emulsion containing the API (as bulk or as micro-particles) is freeze-dried to porous tablets with rapid disintegration rates. The API is mixed together with excipients such as fillers, thickeners, surfactants, sweeteners and non-volatile flavoring agents and made into an emulsion. The liquid preparation is transferred into blister cavities before lyophilization to porous solid ODTs. To prevent non-uniformity of the formulation during the lyophilization, a large proportion of the filler is required to increase the viscosity of the suspension (Fu *et al.*, 2004). Preservatives are not required in ODTs prepared by

this technology unlike in the other freeze-dried dosage forms. The formulations are however known to have low mechanical strengths (Dey and Maiti, 2010), (Roy, 2016), (Saharan, 2017).

2.3.7 Quicksolv® technology

Quicksolv® (Janssen Pharmaceutica, Belgium) is a lyophilization method of production of ODTs coupled with solvent extraction of moisture from the frozen matrix containing the dissolved drug. A suspension/solution of a drug is freeze-dried to a porous solid dosage form. The moisture in the frozen dosage form is extracted using excess alcohol in a solvent extraction process to produce highly disintegrating tablets with uniform porosity and appropriate crushing strength for handling. However, this technology can only be used for low drug content products insoluble in the extracting solvent (Fu *et al.*, 2004), (Dey and Maiti, 2010), (Roy, 2016), (Saharan, 2017).

2.3.8 NanoCrystal™

NanoCrystal™ (Elan, currently Perrigo, Ireland) technology produces ODTs comprising of a matrix of nanoparticles (particle sizes are less than 2 μm). A colloidal dispersion of the drug nanoparticles together with hydrophilic excipients are filled into blisters and lyophilized to ODTs. This technology is mainly used in lab-scale preparation of ODTs for extremely potent or lethal ingredients to avoid risk of exposure to aerosolized particles from manufacturing operations such as mixing and packaging. This technology ensures minimal wastage of the API due to limited manufacturing processes. The formed tablets have adequate robustness for packaging in blisters or multi-dose bottle container closure systems with a maximum of 200 mg of the API per unit (Fu *et al.*, 2004), (Saharan, 2017).

2.3.9 Dispersible tablet technology

Dispersible tablet technology (Lek, Yugoslavia) produces tablets with enhanced dissolution as a result of inclusion of organic acids and disintegrating agents in the formulations. The tablets disintegrate within a minute because of the use of multiple disintegrating agents which promote rapid wicking and swelling. The most commonly used disintegrating agents include starch, modified starch, MCC, alginic acid, cross-linked sodium carboxymethyl cellulose and cyclodextrins. This technology has been successfully used to manufacture dispersible tablets of dihydroergotoxine and cimetidine (Fu *et al.*, 2004), (Parkash *et al.*, 2011).

2.3.10 Pharmaburst® technology

Pharmaburst® technology (SPI Pharma, USA) employs the use of co-processed excipients to develop ODTs that dissolve rapidly between 30 to 40 seconds (Moqbel *et al*., 2016). The rate of dissolution is dependent on the type and strength of the API per unit dose. The API also determines the amount of Pharmaburst® required in a formulation for the preferred mouth feel and disintegration rate. The API, lubricants and flavors are dry blended before compression on a typical tablet press with stock tooling. The tablets can be packed in normal bottles and blisters (Kaushik *et al*., 2004), (Fu *et al.*, 2004), (Parkash *et al.*, 2011).

2.3.11 Frosta® technology

Frosta® technology (Akina, USA) basically involves compression of pre-granulated plastic granules at low pressure to produce cost-effective highly porous but robust ODTs. The granules are composed of a porous and plastic material, water permeation enhancer and a binder. The porous and plastic materials are essential for interparticulate bonding which help in formation of tablets at low pressure as a result of plastic deformation. They are also hydrophilic in nature to promote fast dissolution upon contact with water. The water permeation enhancer is incorporated to prevent the formation of a viscous barrier on the surfaces of the granules especially in the cases of polymeric plastic materials. The binder prevents the segregation of the two components during the granulation process. This technology produces fast disintegrating tablets with disintegration times usually below 30 seconds depending on the tablet size (Fu *et al.*, 2004), (Parkash *et al.*, 2011), (Roy, 2016).

2.3.12 Quick-dis technology

Quick-dis™ technology (Lavipharm, Canada) produces a thin, flexible and fast disintegrating oral film. The technology uses solvent casting method to produce a homogenous viscous solution containing hydrocolloids using a high-shear mixer. The homogenous solution is then degassed under a vacuum before transferring onto casting films. Excess water in the films is removed by drying in an oven prior to appropriate size reduction and shaping as per the application. A 2-mm thick film normally disintegrates within 5-10 seconds. The excipients that are commonly incorporated in these formulations include: hydrophilic inert fillers, plasticizers, wetting agents,

taste-modifying agents, buffers, preservatives, colorants, emulsifying agents, stabilizers and solubilizing agents (Parkash *et al.*, 2011), (Roy, 2016), (Pandey and Dahiya, 2016).

2.3.13 AdvaTab™

AdvaTab™ (Adare Pharmaceuticals, USA) is a phase separation method technology that produces ODTs that have the API pre-coated via a microencapsulation process for taste-masking. Adare owns the proprietary rights to Microcaps technology responsible for the microencapsulation process. The technology has a special lubrication system which involves internal addition of lubricants unlike in conventional tablets. The lubricants are also 10 to 30 times less hydrophobic than in conventional tablets which result in 30 to 40 % increase in breaking force. As a result, the formulations do not require special packaging because they are appropriate for packaging in normal bottles and blisters. Nevertheless, the increased breaking force does not obstruct liquid uptake upon contact with saliva. Other excipients in addition to the lubricants such as sugar alcohols, saccharides and disintegrants are utilized in the technology (Fu *et al.*, 2004), (Parkash *et al.*, 2011).

2.3.14 Oraquick® technology

The Oraquick® technology (KV Pharmaceuticals, USA) uses its proprietary MicroMask® microsphere taste-masking technology to produce microencapsulated drug particles for ODTs. The taste-masking technology hastens the production as it does not involve the use of solvents. The technology is also suitable for heat sensitive drugs because it is less exothermic. The microcapsule is able withstand high compression pressure to achieve appropriate breaking force without disrupting taste masking (Pandey and Dahiya, 2016), (Roy, 2016).

2.3.15 Shearform technology

The shearform technology (Biovail, currently Valeant, Canada) is a cotton candy method and involves exposure of raw materials containing a sugar carrier to flash heat processing to form a matrix known as “Shearform matrix”. The matrix results from concurrent exposure of the sugar to centrifugal force and temperature gradient, which leads to an increase in temperature of the mass creating an internal flow condition allowing part of the bulk to flow with respect to the mass. The amorphous matrix is milled and recrystallized before mixing with other excipients and the API for compression into tablets (Roy, 2016).

2.3.16 Ziplet® technology

Ziplet® technology (Passano con Barnago, Italy) involves prior coating of hydrophobic drugs into micro-particles before mixing with appropriate amounts of combined hydrophilic inorganic excipients and disintegrating agents. The combination promotes appropriate breaking force as well as ideal disintegration time of the formed tablets. The hydrophilic inorganic excipients promote faster disintegration whereas the water-soluble sugars or salts promote dissolution prior to disintegration (Roy, 2016).

2.4 Commercially marketed paracetamol products for pediatrics

Oral dosage forms of paracetamol for pediatrics exist commercially as liquid or solid dosage forms. Table 2 shows a list of some common commercially available pediatric paracetamol oral liquid dosage products. The oral liquid dosage products are more popular notwithstanding the related observed challenges. Dosing accuracy is a major challenge as these products must have their dose measured before administration. Many of these products such as those listed have an upper storage limitation temperature of 25°C to maintain drug stability. Storage under such temperature is a major challenge in tropical climates such as in Mombasa, the second largest city in Kenya, where the calculated mean kinetic temperature using the formula shown in Equation 1(Global, 2019) based on average high and low recorded temperature (Climat, 2019), (Climate-Data.org) is 31.5°C. Additionally, these liquid paracetamol products use some excipients such as parabens, polysorbates and colors that are not of GRAS status.

$$TK\ (K) = \frac{\frac{-\Delta H}{R}}{\ln\left\{\sum_1^n \exp\left(\frac{-\Delta H}{R \cdot Tn}\right)\middle| n\right\}} \quad \text{.....Equation 1}$$

*Where: $\boldsymbol{T_K}$ is the mean kinetic temperature in Kelvins (K), $\Delta\boldsymbol{H}$ is the activation energy =83.14472 KJ/Mol , **R** is the universal gas constant = 8.3144*10^{-3} KJ/Mol/K, **T** is the temperature in degrees K, **n** is the equal total number of time periods over which the data was collected = 12 times.*

Table 3 shows a list of commercially available pediatric paracetamol oral solid dosage form products and one adult paracetamol ODT product. The listed products have special instructions on use from the manufactures specifying that: Children's Tylenol® Chewables are chewable tablets; Panadol® Children Chewable tablets may be chewed or allowed to disintegrate orally; and both Calpol® Sixplus™ Fast Melts and Paralyoc® tablets disintegrate orally. These products are associated with less restriction on storage temperature limits when compared with the liquid formulations. However, specialized unit operations with specialized equipment appear to have been used in the manufacture of the aforementioned solid dosage form products. A particle coating process most likely involving a fluid-bed coater appears to have been used for the manufacture of the pediatric products while the adult dosage is manufactured by a lyophilization process. These

complex processes add to the cost of the finished product. Additionally, the particle coating based products use specialty excipients which have not been used for long in pediatric formulations. Toxicity issues may arise from potential ionic interactions between ionic polymers excipients (specialty excipients) and functional groups in the body tissues (Walsh *et al.*, 2014).

Table 2: Commercially Marketed Pediatric Paracetamol Oral Liquid Products

Product	**Excipients**	**Limitations**
Calpol® Suspension (Paracetamol 120 mg/5 mL) Reference: (McNeil, 2016a).	Sucrose, Sorbitol Liquid (Non-Crystallising) (E420), Glycerol, Xanthan Gum, Dispersible Cellulose, Polysorbate 80, Acesulfame Potassium, Propyl Parahydroxybenzoate (E216), Ethyl Parahydroxybenzoate (E214), Strawberry Flavour 500018E, Methyl Parahydroxybenzoate (E218), Carmoisine (E122), Purified Water	• Uses parabens • Uses polysorbate 80 • Uses colors • Liquid – dosing accuracy • Do not store in temperatures exceeding 25°C
Panadol® Baby and Infant Suspension (Paracetamol 120 mg/5 mL) *Reference:* (GlaxoSmithKline, 2014b).	Malic acid, xanthan gum, hydrogenated glucose syrup (maltitol syrup), 70% sorbitol liquid crystallizing, sorbitol powder, anhydrous citric acid, nipasept sodium (Ethyl-methyl-propyl-hydroxybenzoate), water, azorubine, strawberry flavor and purified water	• Uses parabens • Uses colors • Liquid – dosing accuracy • Store below 25°C
Children's Panadol® Elixir (Paracetamol 240 mg/mL) *Reference:* (GlaxoSmithKline, 2014a).	Glycerol, propylene glycol, macrogol, saccharin sodium, potassium sorbate, sorbitol solution (70% crystallizing), water purified, Allura red AC, benzoic acid, raspberry flavor, imitation candied sugar	• For patients 5 – 12 years of age • Uses colors • Liquid – dosing accuracy • Store below 25°C

Table 3: Commercially Marketed Pediatric Paracetamol Oral Solid Products

Product	Excipients	Limitations
Children's Tylenol® Chewables (previously Tylenol Meltaways) (Paracetamol 160-mg) *Reference:* (Johnson, 2016).	Grape Flavor anhydrous citric acid, cellulose acetate, crospovidone, D&C red no. 7 calcium lake, D&C red no. 30 aluminum lake, dextrose, FD&C blue no. 1 aluminum lake, flavor, magnesium stearate, povidone, sucralose Bubble gum Flavor anhydrous citric acid, cellulose acetate, crospovidone, D&C red no. 7 calcium lake, dextrose, flavor, magnesium stearate, povidone, sucralose	• Uses colors • Non-GRAS excipients • Store at 15 to 30°C
Panadol® Children Chewable 3+ Years Tablets (Paracetamol 120-mg) *Reference:* (GlaxoSmithKline, 2018).	Mannitol, Starch –maize, Ethylcellulose, Stearic acid, Saccharin sodium, Cherry Trusil Artificial flavour 5-909834179	• Complex manufacturing process • Store below 30°C
Calpol® Sixplus™ Fast Melts Tablets (Paracetamol 250-mg)	Mannitol (E421), Crospovidone, Aspartame (E951), Strawberry flavouring E. 9620941, Magnesium stearate, Basic butylated methacrylate	• For patients 6 years and above • Non-GRAS excipients • Complex manufacturing process

Reference: (McNeil, 2016b).	copolymer, Polyacrylate dispersion 30%, Colloidal Anhydrous Silica	• (no specific storage conditions indicated)
Paralyoc® (500-mg Paracetamol) Reference (MonCoinSanté, 2017).	Micro encapsulated paracetamol: 500 mg. (oral lyophilisate). Other ingredients: Aspartame, polysorbate 60, Xanthan gum, dextran 70, orange flavouring, mono hydrous lactose.	• For patients 8 years and above • Complex manufacturing process (lyophilization) • (no specific storage conditions indicated)
Flashtab (Paracetamol 500 mg) Reference (FarmaciaRisparmio, 2019).	Coated paracetamol crystals: basic butylated methacrylate copolymer, polyacrylate dispersion 30%, silica (colloidal hydrophobic). Tablet: Mannitol (granules, powder), Crospovidone, aspartame (E951), currant flavor, magnesium stearate	• For adult patients • Non-GRAS excipients • Complex manufacturing process • (no specific storage conditions indicated)

2.5 Paracetamol active pharmaceutical ingredient

2.5.1 Molecular structure and nomenclature

The molecular structure of paracetamol is shown in Figure 1. The chemical formula is $C_8H_9NO_2$ while its relative molecular mass is 151.2. Its chemical name is *N*-(4-Hydroxyphenyl) acetamide, while the systemic name recommended by International Union of Pure and Applied Chemistry (IUPAC) is 4`-Hydroxyacetanilide. Other commonly used synonyms for paracetamol are 4-Acetaminophenol; acetaminophen; 4-hydroxyacetanilide; 4-(*N*-acetylamino) phenol; *N*-(4-hydroxyphenyl) acetamide and 4-(acetylamino)phenol.

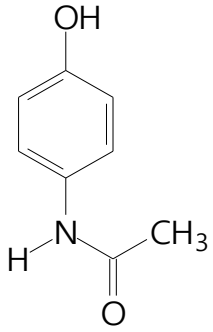

Figure 1: Paracetamol molecular structure.

2.5.2 Chemical and physical properties of paracetamol

Paracetamol is a white crystalline powder with a melting point of 170°C and density of 1.293 g/cc. It has an aqueous solubility of 14.7 mg/mL at 20°C, 14.3 mg/mL at 25°C (Afrasiabi *et al.*, 2003) and 23.7 mg/mL at 37°C (Shaw *et al.*, 2005). It is however soluble in ethanol and slightly soluble in methylene chloride. Paracetamol has n-octanol/water partition coefficient (log P) value of 0.2. However, fragmental methods of calculations based on atomic contributions to lipophilicity gives log P values of 0.31 and 0.89 while ClogP program (version 3.0, Biobyte corp., Claremont, CA) gives a value of 0.49 (Kasim *et al.*, 2004), (Kalantzi *et al.*, 2006).

2.5.3 Pharmacokinetics

Absorption of paracetamol through the gastrointestinal tract (GIT) system is rapid, leading to a fast attainment of maximum plasma concentration in about 30 to 90 minutes. At therapeutic levels, there is minimal paracetamol plasma protein binding (about 10 to 25%). Distribution occurs throughout all body tissues except fat.

Paracetamol has a half-life of about 4 to 6 hours. It is metabolized in the liver via phase 1 & 2 reactions. In phase 1, it is oxidized by cytochrome P450 enzymes (CYP2E1) to an active and toxic metabolite known as *N*-acetyl-*p*-benzoquinone imine (NAPQI). NAPQI is conjugated with glucuronic acid and sulfuric acid in Phase 2 reactions. However, sulfation is the prominent route of conjugation in children below the age of three years while glucoronidation is prominent in adults. Other metabolic pathways include hydroxylation and deacetylation. However, children have a reduced capacity to glucoronidation than adults which worsens paracetamol toxicity in case of overdose (Kearns, Leeder and Wasserman, 2000). There is a reduced clearance of a paracetamol in pediatrics due to lower weight and reduced metabolism compared to adults (Anderson, Woollard and Holford, 2000). Nevertheless, children, adolescents and adults have a comparable pharmacokinetic exposure profile while for neonates and infants, the pharmacokinetic exposure are much higher. Therefore, to achieve similar pharmacokinetic exposure of paracetamol in neonates and infants as the rest of the subpopulations, dose reductions of 33 % and 50 % in infants and neonates respectively are required (Gibb and Anderson, 2008).

Paracetamol is eliminated via kidneys in urine within one (1) day after administration. Most of the metabolites are excreted in the conjugated form (> 90%) while the rest is excreted in the unconjugated form (< 5%).

2.5.4 Paracetamol toxicity

Oxidation of paracetamol by cytochrome p450 enzymes produces NAPQI, an active and toxic substance. NAPQI is detoxified via combination with glutathione in the hepatocytes in phase 2 reactions. In case of high single dose or repeated high doses of paracetamol, the concentrations of glutathione in the hepatocytes are depleted leading to increased levels of the toxic NAPQI. The unbound NAPQI binds to liver cells causing necrosis of the liver cells and severe liver damage.

Additionally, high levels of NAPQI further reduce the levels of glutathione in the liver, amplifying the problem (Mitchell *et al.*, 1973), (Kozer *et al.*, 2003).

The threshold of paracetamol toxicity in children is thought to be around 150 - 200 mg/kg body weight although it is subject to individual variation. Younger children are more predisposed to paracetamol toxicity than children above the age of 5 years according to pharmacokinetics data. Apart from age, starvation and pre-existing liver disease increase the risk of toxicity.

2.5.5 Paracetamol dosing in children

Paracetamol is used for its analgesic and antipyretic properties in children above the age of two months, and for the management of post-vaccination fever in infants between the ages of 2 to 3 months. It is largely available as a liquid preparation for children in two strengths: 120 mg/5 mL and 250 mg/5 mL. However, some brands like Junior Tylenol suspension (160 mg/mL) are also available.

The therapeutic dose of paracetamol is based on milligram paracetamol per kilogram bodyweight. Studies have shown that a dose of 10 to 20 mg/kg bodyweight is effective for analgesic and antipyretic effect. Table 4 shows the dosing and dosing frequency of paracetamol suspensions in children below six years of age.

Table 4: Infant paracetamol (120 mg/ 5 mL) dosing in children

Age	Dose (mL)	Dose (mg)	Dosing frequency
2 to 3 months	2.5	60.0	Once or twice daily if necessary
3 to 6 months	2.5	60.0	6 hourly
6 to 24 months	5.0	120.0	6 hourly
2 to 4 years	7.5	180.0	6 hourly
4 to 6 years	10.0	240.0	6 hourly

2.6 Mechanisms of tablet disintegration

Tablets may disintegrate via swelling, deformation, particle-particle repulsive forces as well as effervescence and wicking mechanisms depending on the type of disintegrant used.

2.6.1 Swelling

Swelling action is as a result of increase in size of certain adhesive disintegrating agents in an aqueous environment thereby promoting disintegration. Adhesion forces within the tablet matrix are reduced leading to tablet break up/ disintegration. Starch, sodium starch glycolate and *Plantago ovata* cause disintegration by swelling (Pahwa and Gupta, 2010), (Mohanachandran *et al.*, 2011), (Mangal *et al.*, 2012).

2.6.2 Deformation

This mechanism relies on the elastic behavior of known disintegrating agents like starch grains. When under pressure, the elastic agents deform, but later return to their original shape upon withdrawal of pressure. However, starch grains go through permanent deformation when compressed, storing a lot of energy which is released upon contact with water. Release of the energy lead to breakdown of the tablets (Pahwa and Gupta, 2010), (Mangal *et al.*, 2012).

2.6.3 Particle-particle repulsive forces

Particle repulsion theory explains the swelling of tablets caused by disintegrants that are not able to swell but are able to impart disintegration. A study conducted by Guyot-Herman and J. Ringard to evaluate disintegration mechanisms of tablets containing starches showed that, tablets containing swelling and non-swelling carboxymethyl starches had comparable disintegration times when in contact with water/fluid (Guyot-Hermann and Ringard, 1981). They also observed that some carboxymethyl starches which exhibit less swelling when exposed to gastric fluid gave more reduced disintegration times in the said fluid. Therefore, the swelling effect could not be responsible for the observed disintegration as a result of the presence of the non-swelling carboxymethyl starches. It was therefore concluded that the disintegration could have resulted from breakdown of cohesive bonds between the tablet particles due to electric repulsive forces in presence of water/fluid. Therefore, particle-particle repulsive forces accompany wicking mechanism to cause disintegration of tablets (Mohanachandran, Sindhumol and Kiran, 2011), (Pawar *et al.*, 2011), (Mangal *et al.*, 2012).

2.6.4 Effervescence

Effervescence results from the reaction between an acid (such as tartaric acid and citric acid) and a base (such as bicarbonates) in presence of water leading to the release of carbon dioxide gas. Release of the gas increases the pressure inside the tablet leading to disintegration. Liberation of carbon dioxide enhances drug dissolution as well as taste masking of bitter tasting drugs. Tablets disintegrating by this method are very sensitive to humidity and temperature and therefore strict adherence to both is vital during manufacture/formulation (Pahwa and Gupta, 2010).

2.6.5 Wicking

Tablet disintegration by wicking occurs through enhancement of porosity and capillary action. The porous structure creates voids where fluids penetrate the tablet matrix via capillary leading to breakdown of interparticle bonds which cause tablet breakdown. Crospovidone and croscarmellose sodium cause disintegration via a wicking mechanism (Pahwa and Gupta, 2010), (Mohanachandran *et al., 2011)*, (Mangal *et al.*, 2012).

CHAPTER 3

MATERIALS AND METHODS

3.1 Study design

This was a laboratory-based comparative experimental study.

3.2 Study location

The study was carried out in the Pharmaceutics Laboratory in the Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi, Kenya.

3.3 Equipment /apparatus

A manually operated single punch tablet compression machine Type EP – 1 (Erweka, India), disintegration testing machine (Type ZT3, Shimadzu, Tokyo, Japan), friability tablet testing machine (Model EF2/EF2W, Electrolab, India), vernier calipers, Schleuniger-2E tablet hardness tester (Schleuniger & Co., Germany), analytical weighing balance (Model R200D, Sartorius, England), Fourier Transform Infrared (FT-IR) Spectrophotometer (Shimadzu, Tokyo, Japan), GENESYS™ 10S UV-Vis spectrophotometer (Model G10S UV-Vis, Shimadzu, Tokyo, Japan), Dissolution tester (Model EDT-08LX, Electrolab, India) and a 3510 pH meter were used in this study.

3.4 Materials

Paracetamol powder and anhydrous citric acid were donated by Regal Pharmaceuticals Limited. Microcrystalline cellulose (100 µm mean particle size), mannitol, colloidal silicon dioxide, magnesium stearate, potassium dihydrogen phosphate and crospovidone were provided by the Pharmaceutics Laboratory, School of Pharmacy at the University of Nairobi, Kenya. The reagents used for the analytical tests were provided by the Pharmaceutical Chemistry Laboratory, School of Pharmacy at the University of Nairobi.

3.5 Quality target product profile

The quality target product profile (QTPP) specifies what characteristics and properties the drug product should have. It helps the formulator to visualize the end product in mind before formulation. The QTPP for the paracetamol PODT is summarized in Table 5.

Table 5: Target Product Profile for the Paracetamol PODT

Product Attribute	Absolute requirements	Preferences
Route of Administration	Oral, tablet is capable of being easily swallowed by pediatric patients	Oral, tablet disintegrates in the oral cavity
Paracetamol Dose Range	60 – 120-mg	60 – 120-mg
Total Tablet Weight (as a % of paracetamol dose)	< 200%	100 – 200%
Excipients	GRAS	GRAS, Compendial
Manufacturing method	Direct compression, dry or wet granulation	Direct compression, anhydrous process
Tablet Disintegration Time	< 30 seconds	< 15 seconds
Tablet Dissolution	• Meets USP specifications for acetaminophen tablets (chewable tablets) • No less than 75% drug dissolved in 45 minutes	• Meets USP specifications for acetaminophen tablets (chewable tablets) • No less than 75% drug dissolved in 45 minutes
Tablet Friability	Sufficient for standard or specialized blister packaging	Sufficient for standard blister packaging
Taste	Palatable	Palatable with a pleasant taste, flavor and mouth feel
Product Intellectual Property	Patentability not an absolute requirement	Patentable formulation

GRAS = generally regarded as safe

3.6 Formulation Compositions

The functionality and the regulatory status of the excipients that were used are shown in Table 6. The ingredients that made up the prepared formulations are shown in Table 7 (% w/w) and Table 8 (weight in mg). Excipients were selected on the basis of safety for use in pediatric patients and for the functionality required to manufacture an orally disintegrating tablet. Drug-excipient compatibility was justified based on prior use of each excipient with paracetamol in commercially marketed solid dosage forms. Powder blends of all the components except the lubricant were mixed manually for 15 minutes in a plastic container. The powder blends were then mixed with magnesium stearate for 3 minutes for lubrication.

Table 6: Functionality and Regulatory Status of the Excipients

Ingredient	Function	Regulatory Status
Mannitol	Filler, sweetener, mouth feel enhancing agent	GRAS listed. Accepted for use as a food additive in Europe
Microcrystalline Cellulose	Filler, dry binder, disintegrant	GRAS listed. Accepted for use as a food additive in Europe
Crospovidone	Super-disintegrant	Accepted for use as a Food additive in Europe
Sodium Bicarbonate	Effervescent disintegrant with citric acid	GRAS listed. Accepted for use as a Food additive in Europe
Anhydrous Citric Acid	Effervescent disintegrant with sodium bicarbonate	GRAS listed. Accepted for use as a food additive in Europe
Colloidal Silicon Dioxide	Glidant	GRAS listed. Approved by the FDA as a food additive.
Magnesium Stearate	Lubricant	GRAS listed. Accepted as a food additive in the USA and the UK.

GRAS = generally regarded as safe.

Table 7: Composition of the Pediatric Orally Disintegrating Tablets (% w/w)

Ingredient	PODT-1	PODT-2	PODT-3	PODT-4	PODT-5	PODT-6	PODT-7	PODT-8*
Paracetamol	48.0	48.0	48.0	48.0	48.0	48.0	48.0	48.0
Mannitol	26.0	21.0	16.0	21.0	11.0	31.0	36.0	21.0
Microcrystalline Cellulose	20.0	20.0	20.0	20.0	20.0	-	10.0	20.0
Crospovidone	5.0	10.0	5.0	-	-	10.0	5.0	10.0
Sodium Bicarbonate	-	-	5.0	5.0	10.0	5.0	-	-
Anhydrous Citric Acid	-	-	5.0	5.0	10.0	5.0	-	-
Colloidal Silica	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

* PODT-8 had the same composition as PODT-2 but the tablets were half the weight to obtain a 60-mg paracetamol dose.

Table 8: Composition of the Pediatric Orally Disintegrating Tablets (mg)

Ingredient	PODT-1	PODT-2	PODT-3	PODT-4	PODT-5	PODT-6	PODT-7	PODT-8*
Paracetamol	120.0	120.0	120.0	120.0	120.0	120.0	120.0	120.0
Mannitol	65.0	52.5	40.0	52.5	27.5	77.5	90.0	26.25
Microcrystalline Cellulose	50.0	50.0	50.0	50.0	50.0	-	25.0	25.0
Crospovidone	12.5	25.0	12.5	-	-	25.0	12.5	12.5
Sodium Bicarbonate	-	-	12.5	12.5	25.0	12.5	-	-
Anhydrous Citric Acid	-	-	12.5	12.5	25.0	12.5	-	-
Colloidal Silica	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Magnesium Stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Total	250.0	250.0	250.0	250.0	250.0	250.0	250.0	250.0

* PODT-8 had the same composition as PODT-2 but the tablets were half the weight to obtain a 60-mg paracetamol dose.

3.7 Powder characterization

The prepared powder blends were characterized by evaluation of powder flow properties.

3.7.1 Assessment of powder flow characters

The flow characters of the powder blends were assessed through determining micromeritic properties such as angle of repose, bulk density, tapped density, compressibility index and Hausners' ratio.

3.7.2 Angle of repose

The angle of repose provides information on the frictional forces in a loose powder. Methods available for determination of angle of repose are tilting box, fixed-funnel, revolving cylinder or fixed-bed cone method. However, the results of the tests are dependent on the method used. The angle of repose was determined using the fixed-funnel method. Approximately 25 grams of the powder blend from each batch was poured through a funnel fixed at a vertical height of 4 centimeters. The powder was allowed to flow onto a clean flat surface free from vibrations into a cone shaped heap of powder. The radius of the heaped powder was measured to determine the angle of repose as shown in Equation 2.

$$\mathbf{Tan\ \alpha = \frac{h}{r}} \quad \text{..... Equation 2}$$

Where: α = Angle of repose, h = Height of the cone powder, r = Radius of the cone powder.

3.7.3 Bulk and tapped density

The bulk density was determined by gently filling 25 grams of the powder blend from each batch into a 100 cc graduated measuring cylinder. The corresponding capacity occupied by the powder and the mass were then used to determine the bulk density as shown in Equation 3.

$$\mathbf{Bulk\ density} = \frac{\mathbf{Mass\ of\ the\ blend}}{\mathbf{Volume\ of\ the\ blend}} \quad \text{..... Equation 3}$$

The powder that was used for the determination of bulk density was subsequently tapped using a glass rod to remove spaces within the powder until there was no further change in its volume to

determine the tapped density. The final volume of the powder was recorded to determine the tapped density as shown in Equation 4.

$$\textbf{Tapped density} = \frac{\textbf{Mass of the blend}}{\textbf{Volume occupied in the cylinder}} \quad \textbf{..... Equation 4}$$

3.7.4 Compressibility index

The compressibility index is an indication of how easy a powder can flow once induced to do so. It was calculated using the formula shown in Equation 5.

$$\boldsymbol{Compressibility\ index\ (I)} = \frac{\boldsymbol{Tapped\ density - Bulk\ density}}{\boldsymbol{Tapped\ density}} * \mathbf{100} \quad \textbf{...Equation 5}$$

3.7.5 Hausner Ratio

Hausner ratio is an indirect index that indicates the ease of powder to flow. It was calculated using the formula shown in Equation 6.

$$\textbf{Hausner Ratio} = \frac{\boldsymbol{Tapped\ density}}{\boldsymbol{Bulk\ density}} \quad \textbf{..... Equation 6}$$

3.8 Tablet compression

Direct compression method using a manually operated single punch tablet compression machine type EP-1 (Erweka, India) equipped with 10-mm round tooling was used to produce round flat-faced tablets. The die was carefully filled with a powder blend equivalent to the weight of one tablet using a spatula. 250-mg or 125-mg of the powder blends were compressed to yield tablets with paracetamol dose strengths of 120-mg or 60-mg, respectively and an average breaking force ranging from approximately 20 to 60 N.

3.9 Evaluation of the compressed tablets

3.9.1 Parameters

Physical and chemical parameters of the compressed tablets were assessed as per compendia specifications to check for their quality.

3.9.2 Physical Quality Assessment

3.9.2.1 Appearance

The tablets were assessed for shape and texture.

3.9.2.2 Weight uniformity

Twenty tablets from each batch were randomly sampled and weighed individually on a Sartorius Analytical Lab Scale Digital Balance (Model R200D, England). The average weight of the tablets ± standard deviation (SD) of individual tablets was calculated.

3.9.2.3 Breaking force

The breaking force/hardness was carried out individually on ten randomly sampled tablets from every batch using a Schleuniger-2E tablet hardness testing machine (Schleuniger & Co., Germany). The mean crushing strength and the sample SD were determined. The test measures the capability of the tablets to withstand mechanical stresses.

3.9.2.4 Friability test

The friability test was assessed on twenty (20) randomly sampled ODTs from each batch using an EF2/EF2W Friability tester (Electrolab, India) set to rotate at a rate of 25 revolutions per min (rpm) for 4 min. The tablets were weighed before (initial weight) and after (final weight of intact tablets) the test. If tablets cracked, cleaved or broke after the test, the sample was recorded as 'Failed' for friability test. The percentage friability was calculated using Equation 7. The test was performed as a measure of confidence to show that the tablets would be able to tolerate the mechanical stress during processing, handling, and shipment.

$$\%\ \mathbf{Friability} = \frac{\mathbf{W\ (initial)} - \mathbf{W\ (final)}}{\mathbf{W\ (final)}} \qquad \text{..... Equation 7}$$

3.9.2.5 Thickness

The thickness of each tablet in the samples of 10 from each batch was measured using a pair of vernier calipers.

3.9.2.6 Wetting time and water absorption ratio

The wetting time test was performed on three (3) randomly sampled tablets from each batch. In the test, each tablet was gently placed on a double folded piece of tissue paper in a Petri dish containing 6 mL of water. The time required for the water to completely cover the top surface of the tablets was recorded as the wetting time. The subsequent weights of the tablets after complete wetting were determined to calculate the water absorption ratio as per Equation 8.

$$\mathbf{WAR = 100\frac{[Wa-Wb]}{Wb}} \quad \text{..... Equation 8}$$

Where WAR is the water absorption ratio, $\mathbf{W_a}$ is the weight of the wet tablet while $\mathbf{W_b}$ is the weight of the dry tablet.

3.9.2.7 Disintegration time

Disintegration rate was determined in each batch from six randomly selected tablets using a Shimadzu ZT3 disintegration testing machine (Shimadzu, Japan). The medium for the test was distilled water at 37°C ± 0.5°C. The tablets were placed individually in each of the six disintegration cylinders immediately prior to immersion and the time taken for complete disintegration was recorded. The average and SD of the disintegration times of the sampled tablets were determined.

3.9.3 Chemical Quality Assessment

3.9.3.1 Phophate buffer preparation for dissolution test

The phosphate buffer solution was prepared by accurately weighing 7.14 g of disodium hydrogen phosphate and 49.5 g of potassium dihydogen ortho-phosphate in a beaker. The two components were dissolved in 6 L of distilled water while stirring to make 6 L of the phosphate buffer for each batch. The pH of the prepared buffer solution was determined using a pH meter. The pH was

adjusted with ortho-phosphoric acid to attain the required pH of 5.8 as per Pharmacopoeial specifications.

3.9.3.2 *In vitro* dissolution test

The USP test method of dissolution for acetaminophen tablets (chewable tablets criteria) was used (USP, 2005). A USP dissolution apparatus 2 (Model EDT-08LX, Electrolab, India) was used with 900 mL phosphate buffer at pH 5.8 thermostatically controlled at 37°C ± 0.5°C as the dissolution medium. The dissolution tester paddles were set to rotate at 75 revolutions per minute for 45 minutes. The samples were analyzed for paracetamol content at λ max 243 nm (USP, 2005) using a UV-Visible spectrophotometer (Model G10S UV-Vis, Shimadzu, Japan) against a paracetamol standard.

The standard was made using 130 mg of paracetamol standard in a 100 mL volumetric flask and made to volume using the phosphate buffer solution. From the stock solution, 5 mL were pipetted into a 100 mL volumetric flask and made to volume with the buffer solution. One milliliter of the prepared solution was subsequently pipetted into a 10 mL volumetric flask and made to volume to provide the working standard solution containing 0.0065 milligrams of paracetamol per milliliter solution.

3.9.3.3 Content uniformity test

Ten tablets from each batch were randomly selected for the content uniformity test. The tablets were assayed individually as per the BP 2017 to determine their paracetamol content using a UV-Vis spectrophotometer at 257 nm (Pharmacopoeial Secretariat, 2017). The percent drug content was calculated using Equation 9. The batches were said to be compliant if all the ten values were within the limits 95 to 105% and failed if more than one value fell outside the limits.

$$\%\ \textbf{Drug content} = \frac{\textbf{A sample}}{\textbf{A 1\%}} * \frac{\textbf{dilution factor} * \textbf{Average weight (g)}}{\textbf{weight equivalent to 0.12 g paracetamol}} * \textbf{100}$$

……..…. ….Equation 9

Where: **A 1 %** is the absorptivity coefficient (715) of 1 g/ 100 mL solution of standard paracetamol in 1 cm cuvette.

3.9.3.4 Assay by use standard absorptivity value (A (1 %, 1 cm))

Assay by use of standard absorptivity value (E value) is the recommended method of assay of soluble paracetamol tablets. The standard absorptivity value/coefficient of paracetamol is 715 as per BP 2017 monograph on paracetamol assay (Pharmacopoeial Secretariat, 2017). This means that a solution of 1 g/100 mL paracetamol standard has an absorbance of 715 at 257 nm wavelength of UV – Visible light in 1 cm cuvette (Pharmacopoeial Secretariat, 2017).

Twenty tablets from each batch (of about 25 g) were selected randomly and their total weight recorded. The tablets were pulverized to fine powder with a mortar and pestle. A powder sample corresponding to 200 mg paracetamol was weighed in a 250 mL volumetric flask and dissolved with 50 mL of 0.1M sodium hydroxide and 100 mL of distilled water consecutively. The resulting solution was sonicated for about 15 min and made to volume with distilled water. The resultant solution was filtered using a Whatman® filter paper. Ten milliliters of the filtrate was pipetted into a 100 cc volumetric flask and made to volume with distilled water. Ten milliliters of the solution were added to 10 mL of 0.1M sodium hydroxide in a 100 mL volumetric flask and made to volume with distilled water. The absorbance of the resultant solution was determined in a UV spectrophotometer set at 257 nm (Pharmacopoeial Secretariat, 2017). The assay of paracetamol was calculated using 715 as the absorptivity value (A (1 %, 1 cm)) at 257 nm as shown in Equation 10.

$$\%\ \textbf{drug content} = \frac{\textbf{A sample}}{\textbf{A 1}\%} * \frac{\textbf{dilution factor} * \textbf{Average weight (g)}}{\textbf{weight equivalent to 0.2g paracetamol}} * \textbf{100}$$

…… **Equation 10**

Where: **A 1 %** is the absorptivity coefficient (715) of 1 g/100 mL solution of standard paracetamol in 1 cm cuvette.

3.9.3.5 Assay by calibration graph/working standard curve

In calibration curve method, the absorbances of several solutions of working standard at concentrations covering the sample concentrations were determined, to generate a standard graph.

One hundred and sixty milligrams of paracetamol working standard (potency 99.95%) were accurately weighed in a 100 mL volumetric flask, dissolved with 20 mL 0.1 M NaOH and 40 mL distilled water. The resultant solution was sonicated for about 15 min and made to volume with

distilled water. Ten milliliters of the solution were pipetted into a 100 mL volumetric flask and made to volume with distilled water to a obtain 0.16 mg/mL stock solution. Paracetamol standard solutions at 0.0026, 0.004, 0.006, 0.008, 0.0096, 0.012 and 0.016 mg/mL were prepared from the stock solution representing expected paracetamol content of 32.5, 50, 75, 100, 120, 150 and 200 %, respectively, as shown in Table 9. The absorbance of the obtained standard solutions was determined in a UV spectrophotometer at 257 nm as shown in Table 10 (Pharmacopoeial Secretariat, 2017). A standard curve was plotted using the obtained data as shown in Figure 2.

Table 9: Procedure for the preparation of the dilutions of the paracetamol standard

Concentration (mg/mL)	% content	Procedure
0.0026	32.5	Twenty-five milliliters of the 0.006 mg/mL (75 %) was pipetted into a 50 mL volumetric flask and made to volume with distilled water.
0.004	50	Twenty-five milliliters of the 0.008 mg/mL (100 %) was pipetted into a 50 mL volumetric flask and made to volume with distilled water.
0.006	75	Two milliliters of the stock solution and 5 mL of 0.1 M NaOH were pipetted into 50 mL volumetric flask and made to volume with distilled water.
0.008	100	Five milliliters of the stock solution and 5 mL of 0.1 M NaOH were pipetted into 100 cc volumetric flask and made to volume with distilled water.
0.0096	120	Three milliliters of the stock solution and 5 mL of 0.1 M NaOH were pipetted into 50 mL volumetric flask and made to volume with distilled water.
0.0128	150	Two milliliters mL of the stock solution and 5 mL of 0.1 M NaOH were pipetted into 25 mL volumetric flask and made to volume with distilled water.
0.016	200	Ten milliliters of the stock solution and 10 mL of 0.1 M NaOH were pipetted into 100 cc volumetric flask and made to volume with distilled water.

The calibration curve was then used to determine paracetamol content in assay samples by extrapolation, whereby the concentration of paracetamol in the samples was read from the graph as the concentration corresponding to the measured absorbance of the sample solution.

Table 10: Standard concentration and absorbance values

Standard (mg/mL)	Absorbance
0.0026	0.215
0.004	0.273
0.006	0.444
0.008	0.541
0.0096	0.654
0.012	0.867
0.016	1.066

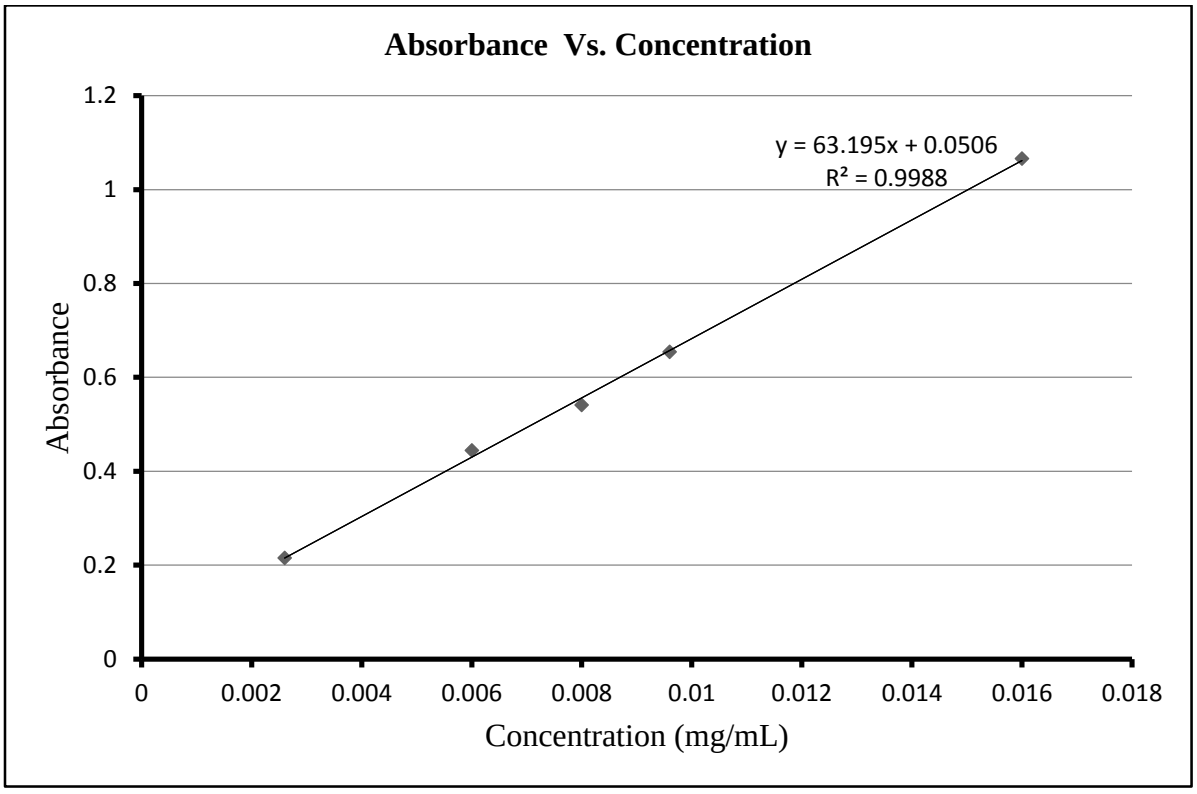

Figure 2: Standard curve for the paracetamol API working standard.

3.10 Statistical Analysis

Where applicable, test results were subjected to statistical analysis using analysis of variance (ANOVA) with a p-value of 0.05. Excel (Microsoft Corporation, USA) data analysis was used to conduct the ANOVA as well as multiple linear regression analysis while spreadsheets were used to perform post-hoc (Tukey's HSD) testing. The null and alternative hypotheses for the ANOVA were:

H_0: $\mu_1 = \mu_2 = \ldots = \mu_k$ *(where μ refers to the formulation mean test values and k refers to the number of formulations)*

H_A: *at least two of the means differed*

The multiple regression statistics equation used for the analysis was:

$Y = B_0 + B_1X_1 + B_2X_2 + B_3X_3 + B_4X_4 \ldots\varepsilon$

Where:

Y = *the predicted mean disintegration times (dependent variable)*

B_0 = *Y-intercept*

X_1, X_2, X_3 *and* X_4 = *the mean formulation values of friability, breaking force, wetting time and water absorption ratio (independent variables)*

B_1, B_2, B_3 *and* B_4 = *the coefficients for the respective independent variables.*

ε = *error*

CHAPTER 4

RESULTS AND DISCUSSION

4.1 Micromeritic tests on powder blends

Table 11 shows the results of the micromeritic tests for the eight formulations. Although the Hausner ratio and the compressibility index values for the powders fell in the poor powder flow range, the values of angle of repose were in the fair to passable range for powder flow. The angle of repose values for the powder blends in this study ranged from 38 to 44°. The United States Pharmacopoeia indicates that powders with angles of repose up to the 40 – 50° range have been successfully used in manufacturing (USP, 2012a). It is recognized however, that these tests cannot independently be used to assess powder flow, but may be useful in comparing and ranking different formulations. There is however a need to optimize powder flow during the scale up process. Table 12 shows the flow characters and the corresponding angles of repose while Table 13 shows the scale of flowability for powders as per the USP 2012 specifications (USP, 2012a).

Table 11: Micromeritic test results

Test	**PODT -1**	**PODT -2**	**PODT -3**	**PODT -4**	**PODT -5**	**PODT -6**	**PODT -7**	**PODT -8**
Bulk Density (g/cc)	0.4	0.4	0.4	0.5	0.5	0.4	0.4	0.4
Tapped Density (g/cc)	0.7	0.6	0.6	0.7	0.7	0.7	0.7	0.6
Hausner Ratio	1.6	1.6	1.5	1.6	1.6	1.7	1.6	1.6
Compressibility Index (%)	38.5	38.7	31.2	37.0	37.5	40.0	39.1	38.7
Angle of Repose (°)	42.8	38.5	42.3	43.6	38.0	41.3	42.5	38.5

Table 12: Flow properties and corresponding angle of repose

Flow property	Angle of repose (degrees)
Excellent	25 - 30
Good	31 – 35
Fair – aid not needed	36 – 40
Passable – may hang up	41 – 45
Poor – must agitate, vibrate	46 – 55
Very poor	56 - 65
Very, very poor	> 66

Table 13: Scale of flowability

Compressibility Index (%)	Flow Character	Hausners' Ratio
≤10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59
>38	Very, very poor	>1.60

4.2 Tablet characterization

The results for the tablet characterization tests are shown in Table 14. Figure 3 shows the order of the *in vitro* dispersion test that was performed prior to the disintegration time test to predict the disintegration time. Samples of the prepared tablets are depicted in Figures 4 and 5.

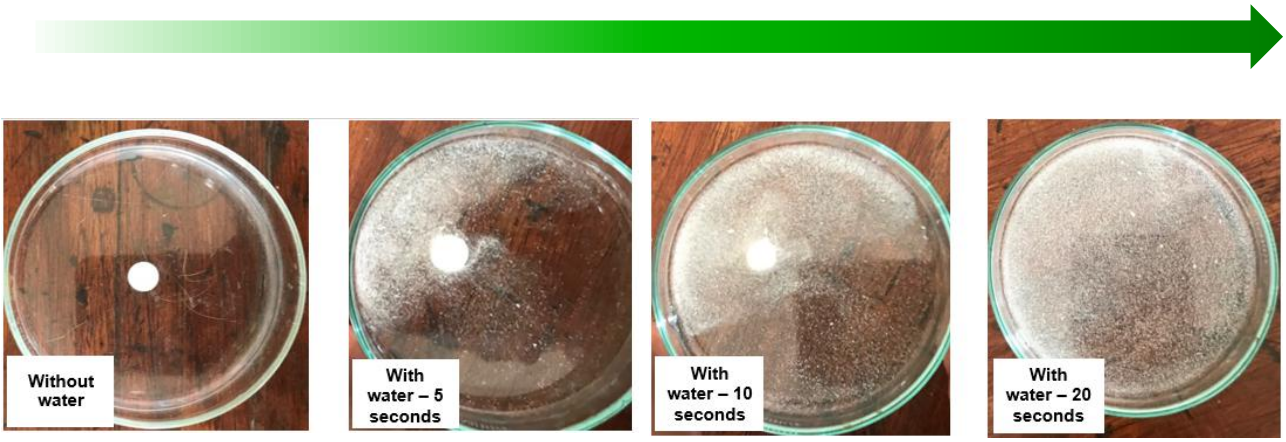

Figure 3: Pictorial illustration of the *in vitro* tablet dispersion test.

Figure 4: Physical appearance of 120 mg paracetamol tablets.

Figure 5: Physical appearance of 60 mg paracetamol tablets**.**

4.2.1 Weight deviation

The prepared ODTs had weights ranging from (250.4 ± 4.7 mg, PODT-5) to (253.1 ± 4.8 mg, PODT-2) and 127.0 ± 2.8 mg for the 60-mg PODT-8 batch. All formulations were within the pharmaceutical specifications for weight variation (USP, 2012c).

4.2.2 Assay and content uniformity

The results of the assay test in Table 14 showed that all the batches apart from PODT-4 complied with the assay for paracetamol chewable tablets as per BP 2017. The standard curve method of assay was a confirmatory test for the BP method of assay. Similarly, all the tablets complied with the uniformity of content test set at 95 - 105% label claim for paracetamol chewable tablets as per BP 2017 (Pharmacopoeial Secretariat, 2017).

4.2.3 Thickness variation

The prepared ODTs had an average thickness ranging from (2.47 ± 0.08 mm, PODT-4) to (3.11 ± 0.11 mm, PODT-6) and 1.36 ± 0.05 mm for the 60-mg PODT-8 batch. The achieved thickness is suitable for pediatric patients.

4.2.4 Breaking force

Breaking force is a common test for ODTs notwithstanding there being no generally recommended range values for ODTs. The breaking force is determined by the compression force applied to form tablets as well as the type and amount of binder present in the formulation. The pressure from the tableting machine was adjusted to attain a targeted breaking force in the range of 20 to 60 N. The variations in the attained breaking force could be attributed unequal compression forces as the press was manually operated as well as the quantity of the binder used. Batches containing microcrystalline cellulose (MCC) at 20 % of the total tablet weight had higher average breaking forces ranging from 42.4 to 53.0 N while those with less or no MCC had markedly low average breaking forces (33.3 N for 10 % MCC in PODT-7 and less than 10 N in PODT-6 which lacked MCC).

4.2.5 Friability

There was no capping or breakage of tablets during the friability test in all other batches except in PODT-6 which lacked MCC. Tablets in PODT-6 broke into a powder during the test signifying a 'failed' test. However, PODT-7 tablets, which contained half the level of MCC in comparison to the other batches, gave the highest friability (5.4%) results. The rest of the batches were less friable with friability values ranging from 1.5 to 4.8 %, suggesting that MCC was functioning as a dry binder in the formulations. The incorporation of the effervescent excipients pair in PODT-3, PODT-4, PODT-5 and PODT-6 batches also seemed to have a negative effect on the tablet friability as these four formulations had friability values greater than 2% as opposed to crospovidone-only formulations. All the batches however had higher than the recommended

friability for a typical oral tablet of 1% (USP, 2012b). This concern can however be addressed by careful packaging or specialized blister packaging in cases of extremely 'soft' tablets. Besides, high mechanically 'soft' tablets are available commercially with mechanical issues being handled by suitable packaging.

4.2.6 Wetting time and water absorption ratio

Wetting time and water absorption ratio tests are related (Figure 9) because they are performed using the same procedure. Wetting time is a key determinant for disintegration properties of tablets (Velmurugan and Vinushitha, 2010). It is closely associated with internal structure of the tablets as well as the hydrophilicity of the excipients (Abdelbary ., *et al* 2009). From the results of the wetting time (Table 14), it was observed that all the batches containing crospovidone alone (PODT-1, PODT-2, and PODT-7) gave acceptable wetting time values (5.3 ± 0.6, 5.3 ± 0.6 and 6.0 s), respectively. Batches which had the crospovidone combined with the effervescent excipients pair (PODT-3 and PODT-6) also gave acceptable but significantly longer wetting time results (11.3 ± 3.2 and 13.3 ± 1.5 s), respectively, whereas PODT-4 and PODT-5 did not give acceptable wetting time results since their wetting time results were 56.0 ± 3.0, 48.3 ± 2.9 s respectively.

The values of the water absorption ratio test in Table 14 showed that batches containing crospovidone alone as a disintegrant (PODT-1, PODT-2, and PODT-7) had low water absorption ratio values (2.2 ± 0.6, 2.3 ± 0.3 and 1.6 ± 0.5 s), respectively. The same was evident in batches containing both crospovidone and effervescent excipients pair ((PODT-3 and PODT-6), which had 2.3 ± 0.7 and 2.5 ± 0.3 s respectively, as values for the water absorption ratio test. However, the PODT-4 and PODT-5 gave higher water absorption ratio values of 5.5 ± 0.2 and 3.7 ± 0.3, respectively.

The short wetting time and low water absorption ratio observed in batches containing crospovidone alone is as a result of the swelling and wicking effect from the super-disintegrant (Schwing *et al.*, 2014). The slight increase in wetting time and water absorption ratio in batches with combined disintegrants (crospovidone and effervescent excipients pair) may be attributed to the interference effect of the effervescent disintegrants. The marked increase in wetting time and water absorption ratio in batches containing the effervescent excipients pair as disintegrants alone confirmed the effect on the tablets. The observed effect of crospovidone on wetting time and water absorption

ratio indicates that the said batches require only a little amount of water for disintegration to occur. In contrast, batches containing effervescent pair disintegrants required more water for effective disintegration.

4.2.7 Disintegration rate

Fast disintegration is a vital tablet property that enhances the *in vivo* performance of ODTs. According to Kuno et al, the disintegration time of ODTs is usually 1 min or less, preferably approximately 30 s or less (Kuno *et al.,* 2005), (FDA). Disintegration time depends on the type and amount of disintegrants, water soluble excipients among other formulation factors (Mizumoto *et al.,* 2005). All the prepared batches disintegrated within 30 s except PODT-4 which had an average disintegration time of about 51 s. PODT-4 contained the least amount of the effervescent excipients pair (10%) and lacked the super-disintegrant crospovidone as disintegrating agent. The excipients used in PODT-5 were however similar to those in PODT-4 but the percentage of the effervescent excipient pair was higher (20%). Although the average disintegration time for PODT-5 was below 30 s, it was significantly higher than in the rest of the batches which contained crospovidone as a disintegrant. The observed difference in disintegration time between the two batches and the rest could be attributed to the absence of crospovidone in the two batches.

Effervescent forming combinations of alkali metal carbonate salts and organic acids contribute to tablet disintegration through generation of carbon dioxide and consequent volumetric air expansion (Desai, Valeria Liew and Wan Sia Heng, 2016). Combining crospovidone with the effervescent excipients as in PODT-3 and PODT-6 batches did not appear to provide any benefit towards faster disintegration rates. The insignificant effect on disintegration could have arose from the low level (5 – 10% of the total tablet weight) at which they were incorporated in the PODT formulations. Excipients for pediatric formulations (especially tablets) should have a low contribution to the final weight of the formulations due to size restrictions. Since disintegration time is a key factor during formulation of ODTs and can be influenced by other formulation factors other than effect of disintegrants, the disintegration test results were taken through additional statistical analysis.

In order to test the hypothesis that the formulation composition had an effect on tablet disintegration times, ANOVA was performed on the disintegration results for the eight formulations using Microsoft 2010 excel package. The between groups ANOVA showed that

there was a statistically significant effect with $F(7, 40) = 9.77$, $p < 0.05$. Tukey's HSD post-hoc test was performed to determine which formulations had significantly different results on disintegration. The PODT-4 batch was found to have significantly higher average disintegration time (51 seconds) than all the other batches, which all disintegrated in less than 30 seconds. There were no statistically significant differences between the disintegration times of any of the other formulations.

In order to check the relationship between the tablets' disintegration times with other tablet parameters such as breaking force/crushing strength, friability, water absorption ratio and wetting time, a correlation analysis using tablet disintegration times against the aforementioned parameters was conducted as shown in Figures 6 to 9. However, PODT-6 was excluded in the graphs in figures 6 and 7 because there were no continuous numeric values obtained for its breaking force and friability (Table 14). The correlation coefficient (R^2) was used to assess the strength of the relationship between the disintegration time and the tablet parameters.

The R^2 values for the relationship between the tablet disintegration time and breaking force, friability, water absorption ratio and wetting time were 0.022, 0.018, 0.829, and 0.696, respectively. The R^2 value observed in the case of water absorption ratio and wetting time indicated strong relationships compared to the rest of the other parameters. Interestingly, the relationship was stronger with the water absorption ratio than with the wetting time, even though the two methods are rather similar according to the strong correlation (R^2=0.887) observed between them in the graph in Figure 9.

There was no observed relationship between both breaking force and friability with the tablet disintegration times. There is however a general expectation that tablets with higher breaking force will frequently have prolonged tablet disintegration times as the corresponding high density from increased solid fraction may prevent entry of water inside the tablet core. Likewise, tablet friability would be expected to be highly associated with tablet disintegration times, whereby highly friable tablets would be expected to have faster disintegration times due to weaker inter-particulate bonding.

From the correlation analysis results, it may be concluded that the tablet-water interaction rate and the corresponding amount of water taken up by the tablet have a greater impact on disintegration time than tablet mechanical properties such as breaking force and friability. Previous report by

Yang et al confirms the observed close relationship between the water absorption ratio and wetting time with the tablet disintegration time (Yang *et al.*, 2018). Additionally, a study that was conducted by Pabari and Ramtoola showed that rapid wetting and disintegration of ODTs are not essentially related to tablet porosity (Pabari and Ramtoola, 2012). Figures 10 to 12 compares the disintegration time, wetting time and water absorption ratio graphically.

In order to check which parameters among the four would be used to best predict the disintegration time of the tablets shown in Table 15, a multiple regression analysis at $p = 0.05$ (at 95% confidence interval) was conducted using Microsoft 2010 excel package between the values of the four parameters (predictor or independent variables) and the disintegration time results (predicted or dependent variable). The predictive analysis model containing all the four predictor variables gave p values of 0.08, 0.31, 0.18 and 0.27 for mean water absorption ratio, wetting time, friability and breaking force respectively as shown in Figure 13.

All the observed values were greater than 0.05 showing that at 95% confidence interval, none of the mean predictor values could be used to best predict the disintegration times of the formulations. However, the p value for the water absorption ratio (0.076) in the model was only slightly higher than 0.05 and therefore could be used to predict the disintegration time results although minor interference would be expected. Interestingly, the p value of the wetting time (0.31) in the model was higher than that of the water absorption ratio despite the similarity between the two tests. However, when the analysis was conducted with the mean values of water absorption ratio together with breaking force and friability, the model gave an acceptable p value of 0.007. Likewise, when the analysis was conducted with the mean wetting times values, breaking force and friability, the corresponding model gave an acceptable p value of 0.05.

The observed interference in the strength of the analysis model to predict the disintegration time by the effect of water absorption ratio values and wetting time values when used in the same model is due to multicollinearity effect as the two predictor variables are somewhat similar (Daoud, 2017). From the analysis therefore, at 95% confidence interval, the water absorption ratio and wetting times values have a strong relationship with the disintegration time and can be used to accurately predict the disintegration times of the formulations.

4.2.8 *In vitro* dissolution studies

Although fast disintegration is an important property for ODTs, drug dissolution is the most important factor that influences *in vivo* drug absorption (Zhao and Augsburger, 2005). All the tablets complied with the dissolution test for chewable paracetamol tablets, which according to USP specifications, more than 75% of the paracetamol is expected to be released within 45 minutes (USP, 2005).

Table 14: Tablet Characterization Test Results

Test	PODT -1	PODT -2	PODT -3	PODT -4	PODT -5	PODT -6	PODT -7	PODT -8
Thickness (mm)	2.5 (0.1)	2.8 (0.2)	2.7 (0.2)	2.5 (0.1)	2.6 (0.1)	3.1 (0.1)	2.6 (0.1)	1.4 (0.1)
Breaking force (Newtons)	47.3 (3.5)	45.8 (5.8)	46.2 (14.7)	42.4 (3.6)	53.0 (6.4)	<10.0	33.2 (4.2)	29.0 (5.8)
Friability (%)	1.5	1.6	4.6	2.9	4.9	Failed	5.4	1.6
Wetting time (seconds)	5.3 (0.6)	5.3 (0.6)	11.3 (3.2)	56.0 (3.0)	48.3 (2.9)	13.3 (1.5)	6.0 (0.0)	2.7 (0.6)
Water absorption ratio	2.2 (0.6)	2.3 (0.3)	2.3 (0.7)	5.5 (0.2)	3.7 (0.3)	2.5 (0.3)	1.6 (0.5)	1.6 (0.1)
Disintegration time (seconds)	13 (3.2)	12 (3.4)	11 (3.1)	51 (29.7)	21 (6.9)	10 (1.1)	18 (6.1)	7 (0.6)
% Drug Dissolved at 45 minutes	94.7 (3.5)	90.7 (2.3)	110.9 (5.5)	102.4 (3.4)	91.3 (1.2)	90.1 (0.7)	93.3 (1.9)	104.7 (2.5)
Uniformity of content (%)	97.9 (1.9)	97.5 (2.2)	95.8 (1.4)	98.9 (3.8)	95.2 (1.2)	94.8 (0.5)	99.0 (2.9)	100.5 (4.7)
Assay with standard absorptivity (%)	98.5 (1.4)	101.2 (6.1)	95.8 (0.6)	111.8 (9.5)	104.6 (8.1)	94.9 (6.1)	100.4 (6.5)	99.3 (6.6)
Assay with standard curve (%)	101.5 (1.7)	104.1 (3.7)	98.4 (0.7)	116.5 (6.2)	108.3 (5.4)	95.3 (3.7)	103.6 (4.9)	102.3 (4.4)
Weight uniformity (mg)	251.9 (3.4)	253.1 (4.8)	252.3 (6.1)	251.6 (3.9)	250.4 (4.7)	250.5 (6.3)	251.5 (4.8)	126.9 (2.8)

Results are recorded as mean values ± SD.

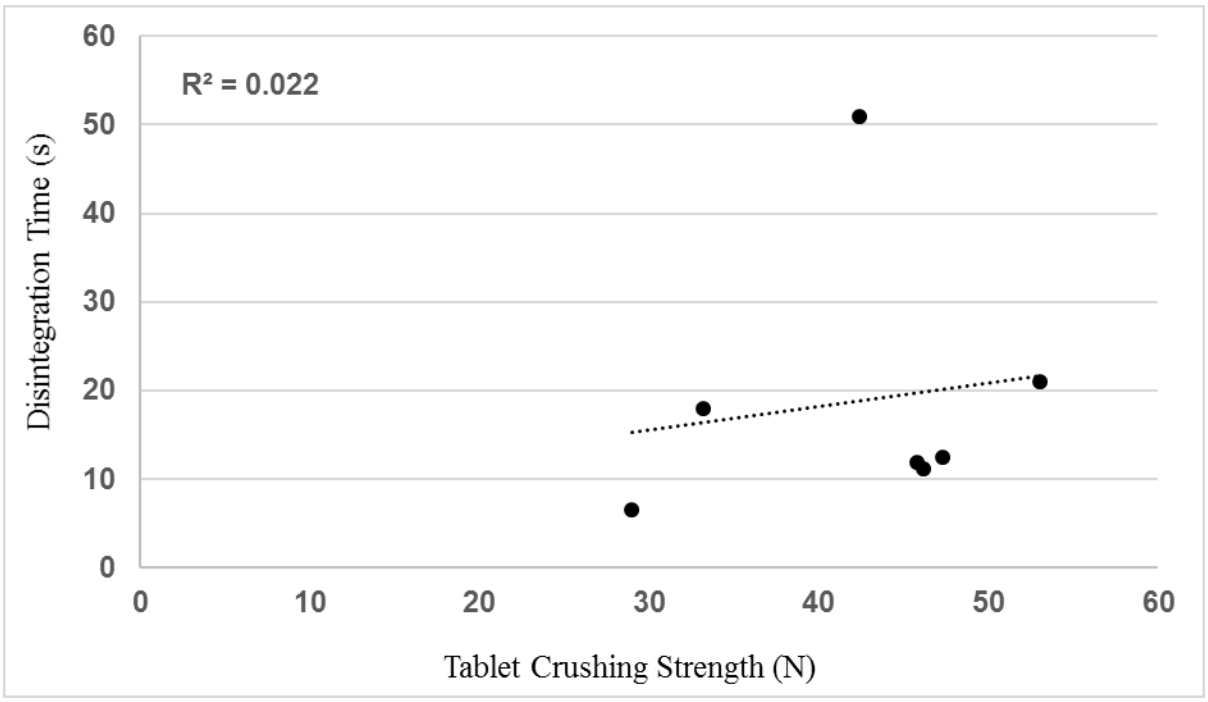

Figure 6: Disintegration time plotted as a function of tablet crushing strength.

R^2 = correlation coefficient

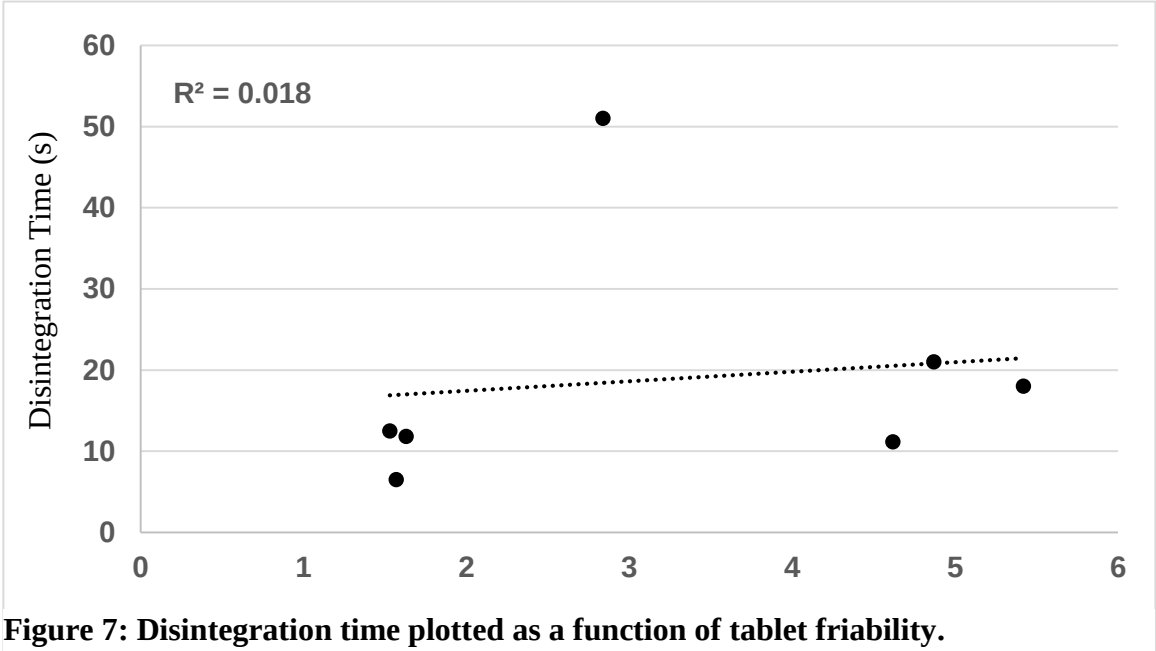

Figure 7: Disintegration time plotted as a function of tablet friability.

R^2 = correlation coefficient

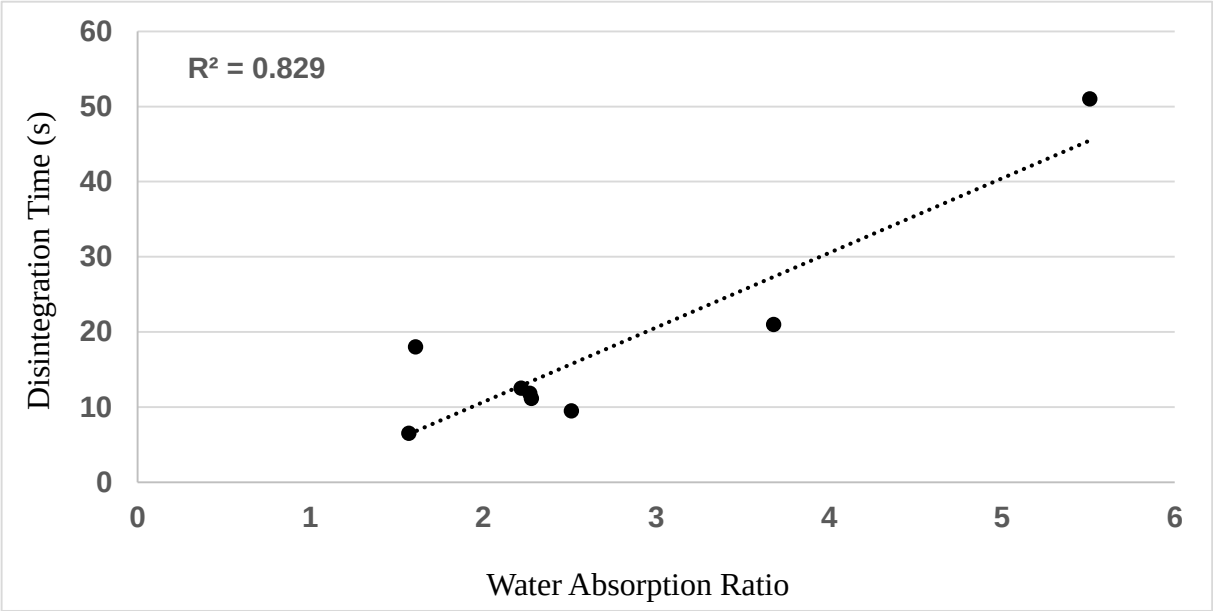

Figure 8: Disintegration time plotted as a function of tablet water absorption ratio.

R^2 = correlation coefficient

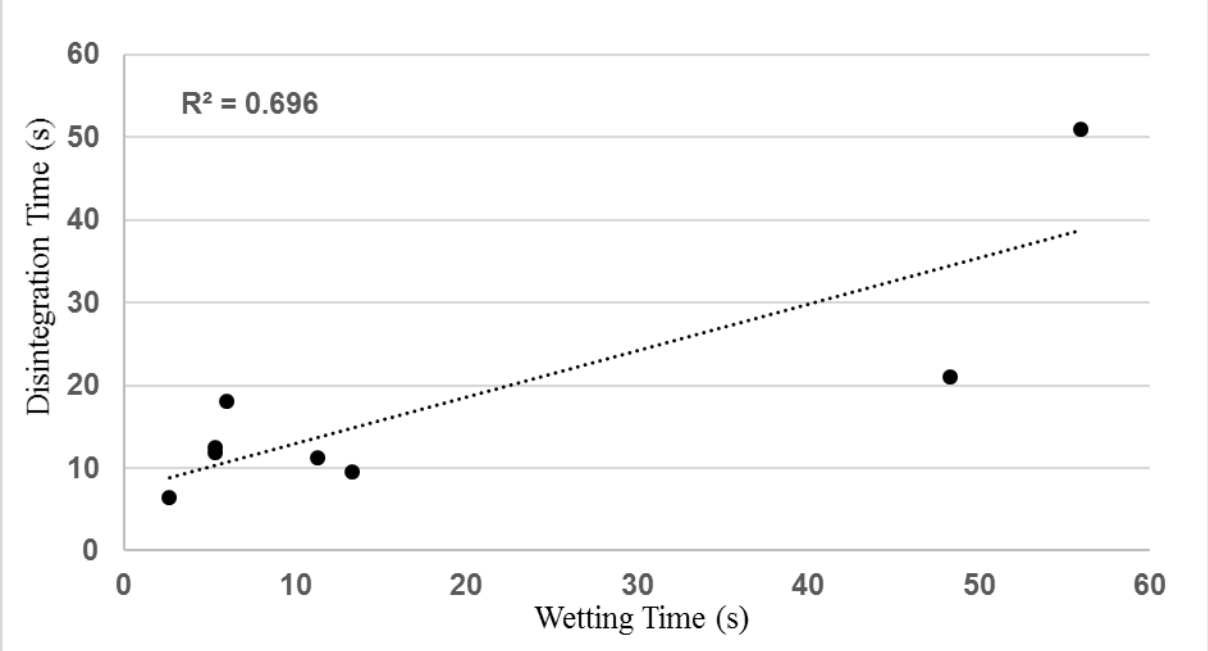

Figure 9: Disintegration time plotted as a function of tablet water wetting time.

R^2 = correlation coefficient

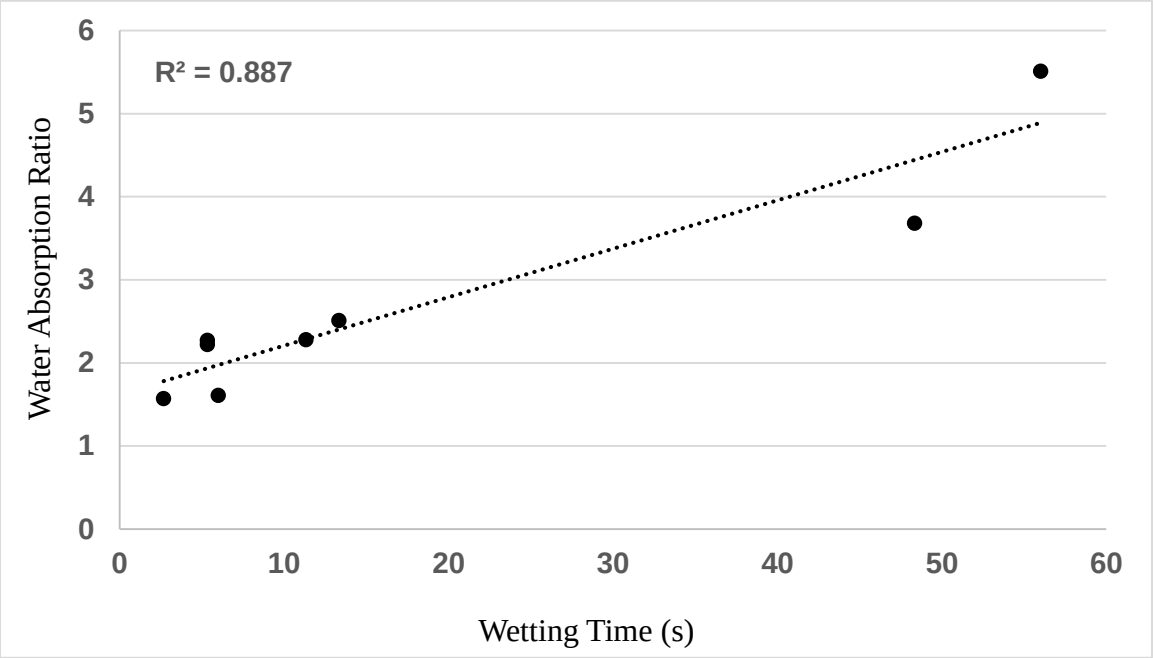

Figure 10: Water absorption ratio plotted as a function of tablet wetting time.

R^2 = correlation coefficient

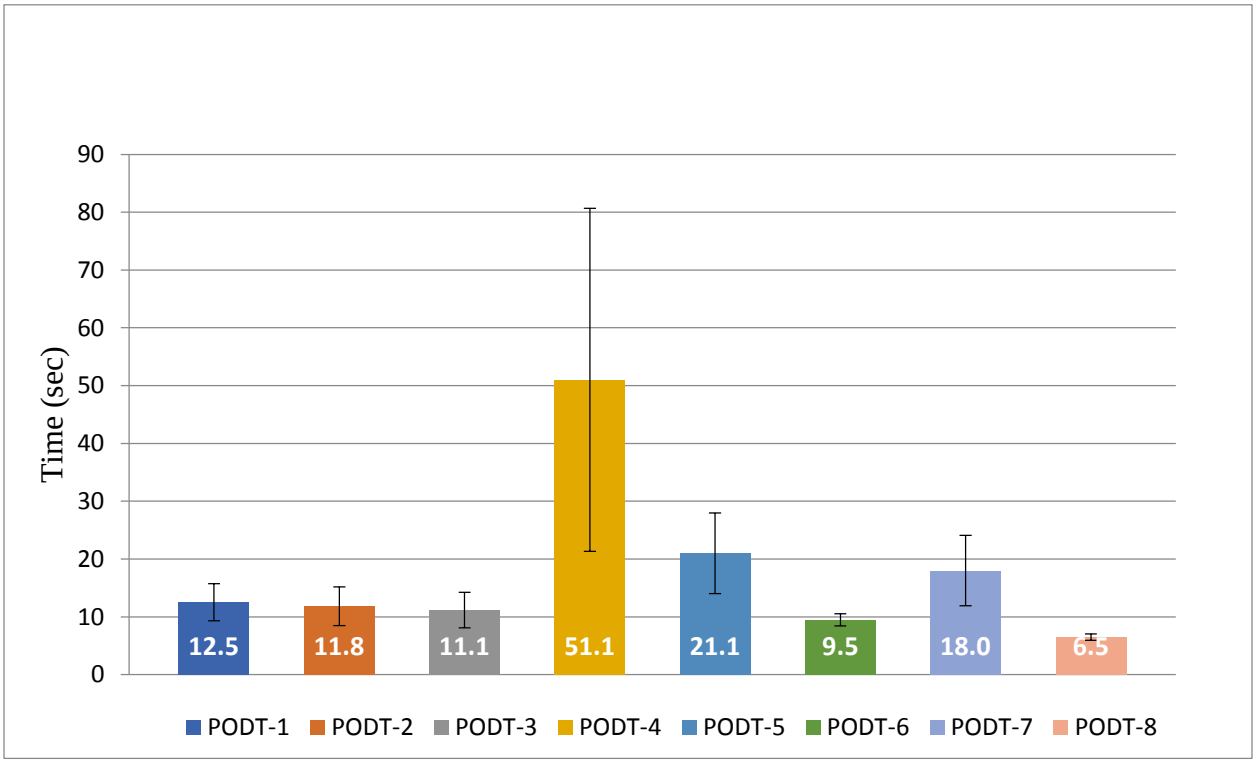

Figure 11: Disintegration times of ODTs formulated using various disintegrants. Data expressed as mean ± SD.

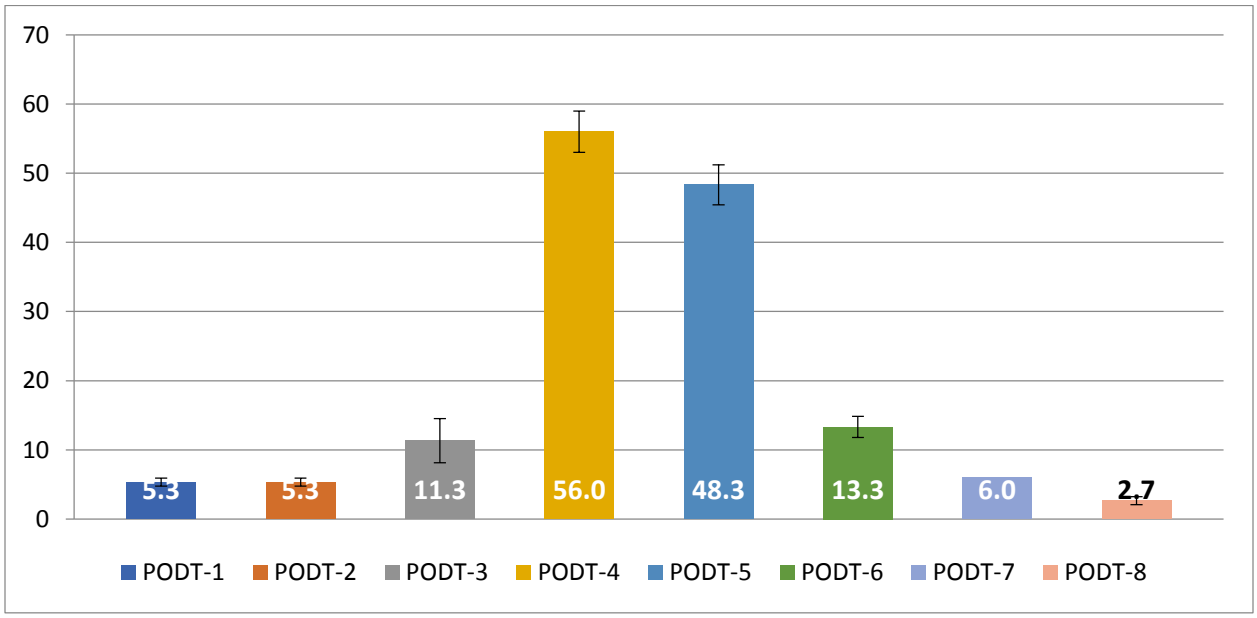

Figure 12: Wetting times of ODTs formulated using various disintegrants. Data expressed as mean ± SD.

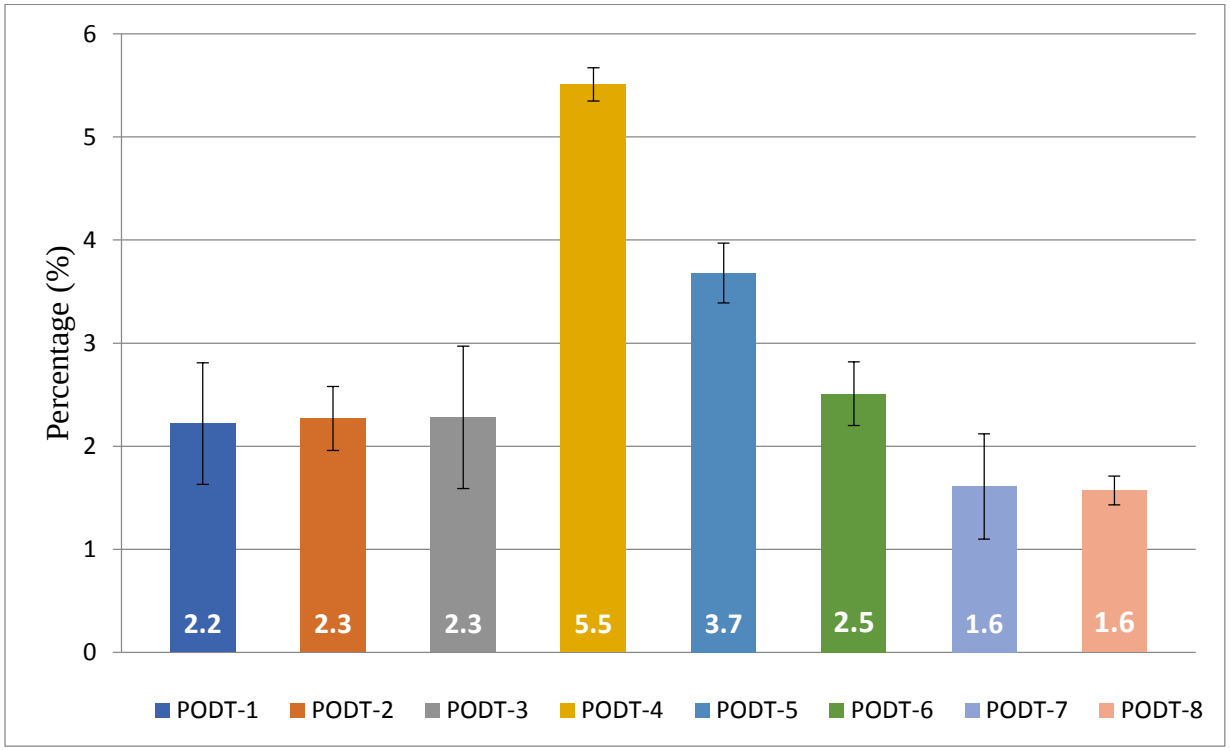

Figure 13: Water absorption ratio of ODTs formulated using various disintegrants. Data expressed as mean ± SD.

Table 15: Formulations mean values for disintegration times (dependent variable), water absorption ratio, wetting time, friability and breaking force

Batch	Disintegration time (s)	Water absorption ratio	Wetting time (s)	Friability (%)	Breaking force (N)
PODT-1	12.5	2.2	5.3	1.5	47.3
PODT-2	11.8	2.3	5.3	1.6	45.8
PODT-3	11.2	2.3	11.3	4.6	46.2
PODT-4	51.0	5.5	56.0	2.8	42.4
PODT-5	21.0	3.7	48.3	4.9	53.0
PODT-7	18.0	1.6	6.0	5.4	33.2
PODT-8	6.5	1.6	2.7	1.6	29.0

Table 16: Multiple linear regression analysis model to predict disintegration times using water absorption ratio, wetting time, breaking force and friability values

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.98
R Square	0.97
Adjusted R Square	0.90
Standard Error	4.73
Observations	7

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	4	1295.39	323.85	14.50	0.07
Residual	2	44.68	22.34		
Total	6	1340.08			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	-7.04	15.36	-0.46	0.69	-73.12	59.05	-73.12	59.05
WAR (%)	18.05	5.31	3.40	0.08	-4.82	40.92	-4.82	40.92
WT (sec)	-0.47	0.34	-1.36	0.31	-1.95	1.01	-1.95	1.01
Breaking force (N)	-0.52	0.26	-2.02	0.18	-1.61	0.58	-1.61	0.58
Friability (%)	2.32	1.52	1.53	0.27	-4.21	8.86	-4.21	8.86

Where:

***Multiple R** = coefficient of multiple regression.*

***R^2** = the proportions of the variance of the mean disintegration time values that is explained by all the predictor variables (breaking force, friability, wetting time and water absorption ratio).*

***Adjusted R** = measure of the predictive power of the regression.*

Table 17: Multiple linear regression analysis model to predict disintegration times using water absorption ratio and breaking force and friability values

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.97
R Square	0.94
Adjusted R Square	0.87
Standard Error	5.36
Observations	7

ANOVA

	Df	*SS*	*MS*	*F*	*Significance F*
Regression	3	1253.89	417.96	14.55	0.03
Residual	3	86.18	28.73		
Total	6	1340.07			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	8.66	11.53	0.75	0.51	-28.03	45.34	-28.03	45.34
WAR (%)	11.11	1.71	6.48	0.01	5.65	16.56	5.65	16.56
Friability (%)	0.94	1.28	0.73	0.52	-3.14	5.02	-3.14	5.02
Breaking force (N)	-0.55	0.29	-1.9	0.15	-1.46	0.37	-1.46	0.37

Where:

***Multiple R** = coefficient of multiple regression.*

***R^2** = the proportions of the variance of the mean disintegration time values that is explained by all the predictor variables (breaking force, friability, wetting time and water absorption ratio).*

***Adjusted R** = measure of the predictive power of the regression.*

Table 18: Multiple linear regression analysis model to predict disintegration times using wetting time, breaking force and friability values

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.88
R Square	0.77
Adjusted R Square	0.54
Standard Error	10.04
Observations	7

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	3	1037.66	345.89	3.43	0.17
Residual	3	302.41	100.80		
Total	6	1340.07			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	30.04	22.95	1.31	0.28	-42.98	103.07	-42.98	103.07
WT (sec)	0.65	0.21	3.13	0.05	-0.01	1.31	-0.01	1.31
Friability (%)	-0.97	2.48	-0.39	0.72	-8.87	6.94	-8.87	6.94
Breaking force (N)	-0.49	0.54	-0.90	0.44	-2.21	1.24	-2.21	1.24

Where:
***Multiple R** = coefficient of multiple regression.*
***R^2** = the proportions of the variance of the mean disintegration time values that is explained by all the predictor variables (breaking force, friability, wetting time and water absorption ratio).*
***Adjusted R** = measure of the predictive power of the regression.*

4.3 Batch optimization

PODT-1 and PODT-2 were selected as the most appropriate formulations for further development to improve tablet breaking force, friability and taste. Since PODT-8 was comparable to PODT-2 in terms of percentage composition, optimization of PODT-2 may be extrapolated to the batch. The PODT-2 tablets were prepared at half the total weight to yield 60-mg paracetamol tablets as PODT-8 batch. The use of a common blend to manufacture tablets of different dose strengths is helpful because it does not require a separate manufacturing process before the tablet compression step.

4.3.1 Tablet composition

PODT-1 and PODT-2 were comparable on tablet excipient compositions with a difference only in the percentage of the crospovidone used. The two batches therefore had comparable wetting time and water absorption ratio values. Interestingly, PODT-2 gave a shorter mean disintegration time of 11.8 ± 3.4 seconds. The PODT-2 therefore provided better pharmacopoeial parameter results suitable for ODTs based on the disintegration times. The batch was therefore selected for optimization to improve tablets' breaking force, friability and palatability. Table 19 shows the compositions of the optimized PODT-2 as a percentage weight while the compositions in Table 20 are in milligrams.

Table 19: Composition of the optimized Pediatric Orally Disintegrating Tablets (% w/w)

Ingredient	PODT-2A	PODT-2B	PODT-2C	PODT-2D
Paracetamol	48.0	48.0	48.0	48.0
Mannitol	21.0	20.0	17.0	0.0
Crospovidone	10.0	10.0	10.0	10.0
Sucrose	0.0	0.0	0.0	20.0
Microcrystalline cellulose	20.0	20.0	20.0	20.0
Colloidal silicon dioxide	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5
Aspartame	0.0	1.0	4.0	1.0
Total	100.0	100.0	100.0	100.0

Table 20: Composition of the optimized Pediatric Orally Disintegrating Tablets (mg)

Ingredient	PODT-2A	PODT-2B	PODT-2C	PODT-2D
Paracetamol	120.0	120.0	120.0	120.0
Mannitol	52.5	50.0	42.5	0.0
Crospovidone	25.0	25.0	25.0	
Sucrose	0.0	0.0	0.0	50.0
Microcrystalline cellulose	50.0	50.0	50.0	50.0
Colloidal silicon dioxide	1.25	125	1.25	1.25
Magnesium stearate	1.25	1.25	1.25	1.25
Aspartame	0.0	2.5	10.0	2.5
Total	250.0	250.0	250.0	250.0

4.3.2 Tablet characterization

The results for the tablet characterization tests (uniformity of weight, disintegration time, breaking force and friability) for the optimized batches are shown in Table 21. All the tablets complied with the uniformity of weight test where none of the tablets had a weight which varied with more than 7.5 SD from the mean weight. The optimized batches also complied with the disintegration test for ODTs as all of them disintegrated in less than thirty seconds. The tablets had improved mean breaking force values ranging from 59.4 ± 4.5 to 72.6 ± 2.1 N. The increase in breaking force led

to a reduction in friability which was less than 1.5 % in all the batches. Interestingly, batches containing aspartame as a sweetener had the lowest friability of less than 1.2%. Most importantly, the observed increase in breaking force did not affect the disintegration times of the tablets as all the batches disintegrated within 30 seconds

The palatability of the tablets was improved by incorporation of aspartame as a sweetener in PODT-2B, PODT-2C and PODT-2D as shown in Table 19 and 20. Mannitol was replaced with sucrose as a filler-sweetener to further improve the taste in PODT-2D for more pleasantly tasting tablets. Sucrose is known to be sweeter than mannitol according to the ratio scale of sweetness and would therefore provide more palatable tablets, (Moskowitz, 1970), (Moskowitz, 2015). The formulated tablets had a pleasant sweet taste with no after taste and therefore suitable for pediatric patients.

Table 21: Pharmacopoeial results for the optimized batches

Batch	**PODT-2A**	**PODT-2B**	**PODT-2C**	**PODT-2D**
Weight uniformity (mg)	245.1 (1.7)	245.9 (4.0)	244.6 (3.2)	250.7 (5.2)
Disintegration time (sec)	11.7 (1.6)	9.0 (0.9)	14.0 (1.4)	7.7 (1.4)
Breaking force (N)	72.6 (2.1)	61.0 (6.8)	62.4 (3.9)	59.4 (4.5)
Friability (%)	1.3	1.1	1.2	1.3

Results are recorded as mean ± SD

4.4 Dosing

The prepared ODTs have a better dosing compared to the suspensions as the dosage form offer for accurate and simple dosing. The tablets are also easy to handle because they are less bulky and therefore would be preferred to the suspensions. The equivalent dosing between Calpol® infant suspension 120 mg/5mL and the prepared paracetamol ODTs for children below the age of 6 years is shown in Table 22.

Table 22: Equivalent dosing between Calpol® infant suspension 120 mg/5mL and the prepared paracetamol orally disintegrating tablets for children below the age of 6 years

Age	Dose (mL)	Dose (mg)	Dosing frequency (in 24 hours)
2 to 3 months	2.5	60.0	Once or twice if necessary
3 to 6 months	2.5	60.0	6 hourly
6 to 24 months	5.0	120.0	6 hourly
2 to 4 years	7.5	180.0	6 hourly
4 to 6 years	10.0	240.0	6 hourly

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

The aim of the study was to evaluate the feasibility of direct compression of paracetamol formulations to manufacture PODTs for children below the age of 6 years using few GRAS status excipients. The formulated PODTs would be a more appropriate alternative for paracetamol suspensions in the management of pain and fever in children below 6 years. Despite the wide use of paracetamol suspensions, they are bulky, physically unstable at temperature above 25°C, cannot guarantee accurate dosing and require storage below 25°C away from light. Therefore, formulation of paracetamol PODTs as an alternative will help to overcome the challenges associated with the suspensions.

Existing literature on already formulated paracetamol dosage forms with comparable excipients can be used to justify that the excipients are compatible with the API because no incompatibilities have been reported. Evaluation on powder flow suggested a passable flow character on all powder blends although there is possibly need to improve powder flow to facilitate manufacturability. The direct compression method which is the simplest and most cost-effective method was used to formulate all the batches.

Out of the 8 batches formulated, PODT-1, PODT-2, PODT-3 and PODT-8 (60-mg paracetamol ODT) complied with the *in vitro* disintegration test of less than 30 seconds for orally disintegrating tablets with corresponding breaking force of 47.3 ± 3.5, 45.8 ± 5.8, 46.2 ± 14.7 and 29.0 ± 5.8 respectively. These batches had crospovidone as a super-disintegrant at 5 to 10 % which shows that crospovidone provides fast and effective disintegration at that percentage range because the aforementioned batches had comparable average disintegration time. However, PODT-2 (with 10 % crospovidone) had the shortest DT and least friability compared with the other batches. It was therefore optimized to reduce friability and improve palatability by addition of aspartame as a sweetener. The optimized batches which included PODT-2A, PODT-2B, PODT-2C and PODT-2D were pleasantly/sweet tasting and less friable with friability values of 1.3, 1.1, 1.2 and 1.3 % respectively. The friability concern can however be solved by careful packaging and in extreme cases specialized blister packaging is an option.

5.2 Recommendations

Paracetamol PODTs were successfully formulated using direct compression method. There is therefore a need to scale up the production of the formulated PODTs to pilot for commercial manufacturing. Even though the prepared batches did not give upon testing, friability results which were below the recommended limit for oral tablets of 1 %, the tablets were strong for packaging in normal bottles or blister packs in extremely cases.

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