FORMULATION DEVELOPMENT AND EVALUATION OF ORO-DISPERSIBLE PAEDIATRIC PARACETAMOL TABLETS

Maganga Bundala Maganga, B. Pharm

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FORMULATION DEVELOPMENT AND EVALUATION OF ORO-DISPERSIBLE PAEDIATRIC PARACETAMOL TABLETS

By

Maganga Bundala Maganga

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled; ***Formulation Development and Evaluation of Oro-dispersible Paediatric Paracetamol Tablets,*** in (partial) fulfillment of the requirements for Master of Pharmacy (Industrial Pharmacy) of Muhimbili University of Health and Allied Sciences.

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Prof. Eliangiringa A. Kaale

(Supervisor)

Date:_____

_____

Mr. Mathius Eulambius

(Supervisor)

Date:_____

DECLARATION AND COPYRIGHT

I**, Maganga Bundala Maganga,** declare that this **dissertation,** is my own original work, and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

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SUMMARY

Background: Paracetamol is a drug which is administered, both parenterally and orally though mostly orally, for management of pain and fever. Paracetamol liquid dosage forms for paediatrics (syrups and elixirs) dominate the local market despite containing solvents like alcohol and propylene glycol which are not recommended for children. Also, they require large space for storage, high transportation cost, have short shelve lives and are difficult to take accurate measurements at households. In some cases people have opted to cut conventional paracetamol tablets into pieces and administer to children.

Oro-dispersible paracetamol tablets are better dosage forms than the liquid preparations. They can be swallowed without using water. They are stable and have improved dissolution and they are a choice for people who have difficult in swallowing and those who refuse to swallow like paediatrics.

Objectives: The objective of this study was to develop and evaluate a formulation of oro-dispersible paediatric paracetamol tablets 120mg.

Methods: Binary mixtures of paracetamol and the excipients (lactose, starch 1500, crospovidone, croscarmellose, sacharin sodium, magnesium stearate, talc and avicel PH 102) were prepared and stored into the following conditions;-Oven (50^0C, closed bottle); Climatic chamber (40^0C/75% RH open bottle) and room condition (30^0C/75%RH) with open bottle. Samples were evaluated for changes in appearance and odour, assessed by NIR spectrometer and assayed by High Performance Thin Layer Chromatography (HPTLC) at the intervals of 0, 7, 14, 30, 60 and 90 days. Also, paracetamol powder flow was evaluated.

Trial formulations containing 80mg and 120mg per tablet of paracetamol were prepared by use of direct compressible excipients (starch 1500 and avicel PH 102). Also, trial batches of the formulation containing 120mg paracetamol were prepared by wet granulation method.

Results: Results indicated that paracetamol is compatible with the excipients. Though there were caking for paracetamol: crospovidone and paracetamol: sacharin blends stored at room, oven (50^0C) and climatic (40^0C/75%RH) conditions, assay results, NIR spectra and HPTLC

densitograms indicated no chemical degradation as there were no trend for assay results, NIR spectra showed no change in shape and there were no additional peaks in densitograms.

Also, results indicated that starch 1500 and avicel PH 102 did not improve the flow of paracetamol powder to enable direct compression while maintaining the content of paracetamol at the minimum of 15% w/w of tablet.

It was possible to prepare, by wet granulation, trial batches of oro-dispersible paediatric paracetamol tablets 120mg which had acceptable evaluation parameters.

Conclusion and recommendations: A formulation of oro-dispersible paediatric paracetamol tablet 120mg has been developed and characterized. This signifies that it is possible for local pharmaceutical manufacturers to develop medicines tailored for paediatrics.

Therefore, policy makers should set policy which will change the perspective of local pharmaceutical industries so that they strive to work on WHO recommendations with regard to paediatric formulations. These medicines will benefit paediatrics in terms of ease of use and safety but also minimize the use of resources like transportation cost, storage space and wastage due to stability issues.

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LIST OF ABBREVIATIONS

BNF	British National Formulary
BP	British Pharmacopoeia
CI	Compressibility Index
CMC CL	Cross linked carboxymethylcellulose
EMEA	European Medicines Agency
HPC	Hydroxypropyl cellulose
HPTLC	High Performance Thin Layer Chromatography
MUHAS	Muhimbili University of Health and Allied Sciences
mg	Milligrams
NIR	Near Infrared
nm	Nanometer
NSAIDS	Non-Steroidal Anti-inflamatory Drugs
ODPPT	Oro-dispersible paediatric paracetamol tablets
ODT	Oro-dispersible tablets
PCM	Paracetamol
PEG	Polyethylene glycol
PVPCL	Polyvinyl pyrollidine
QC Lab	Quality Control Laboratory
R&D	Research and Development Laboratory
1/R	1/Reflectance
SSR	Sum of Squares Regression
SST	Sum of Squares Total

TFDA	Tanzania Food and Drugs Authority
UK	United Kingdom
US	United States
WHO	World Health Organization

CHAPTER 1 : INTRODUCTION

1.1 Background

Paracetamol is a drug which is administered, both parenterally and orally though mostly orally, for management of pain and fever. The drug substance is sparingly water soluble, classified by WHO as BCS class I drug (1) and has a bitter taste. Others have classified paracetamol in BCS Class III despite having properties at the borderline to BCS class I. The permeability of paracetamol is just below the critical value of 90% while solubility is very high-23.7mg/ml at 37^0C (2).

Paracetamol has two official names; acetaminophen in US and paracetamol in UK. The two names originate from N-acetyl-para-aminophenol. It was discovered by chance in 80s of 19^{th} Century. This occurred after wrongly dispensing acetanilide instead of naphthalene (deworming agent) only to find that acetanilide lowered temperature significantly (3).

Acetanilide was introduced into the medical practice in 1886 under the name of antifebrin. However, it was found that it was toxic and this necessitated structural modification by chemists. The result of the modification was phenacetin and N-acetyl-p-aminophenol. Phenacetin was selected for use after studies incorrectly concluded that N-acetyl-p-aminophenol was as toxic as acetanilide (3).

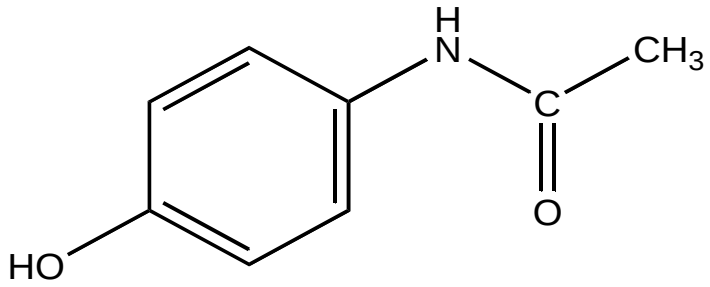

Figure 1: Structure of paracetamol (N-(4- Hydroxyphenyl) acetamide)

In 1948, Bernard Brodie and Julius Axelrod demonstrated that paracetamol was the main active metabolite of acetanilide and phenacetin and that methemoglobinemia was induced by another metabolite, phenylhydroxylamine. This was the beginning of the use of paracetamol.

Tylenol children's elixir was introduced into the market in 1955. The name tylenol is also derived from N-ace**tyl**-p-aminoph**enol**. According to WHO, paracetamol is recommended for all three categories of pain intensity; moderate pain, moderate to strong pain and strong pain to severe pain (3).

Physicochemical properties of paracetamol

The International Union of Pure and Applied Chemistry (IUPAC) name is N- (4-Hydroxyphenyl) acetamide. Paracetamol is white or almost white, crystalline powder and sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride. The melting point of paracetamol ranges from 168^0C to 172^0C(4). Paracetamol exhibits polymorphism (Form I, form II and Form III). The most stable form is monoclinic and orthorhombic is metastable and Form III is unstable. Most of the paracetamol drug samples belong to monoclinic, the most stable form. The melting point of monoclinic (Form I) is 167^0-169^0C and that for orthorhombic (Form II) is 156^0C (5).

Paracetamol is a weak organic acid and has a pka value of 9.5 and this implies that paracetamol is in the unionized form in the most part of the gastrointestinal tract (6).

Pharmacokinetics of paracetamol

At therapeutic concentrations, the pharmacokinetics of paracetamol are linear-that is independent of the dose and constant with repeated administration.

Absorption

Paracetamol is mostly taken orally and absorption in the gastrointestinal tract takes place by passive diffusion. There is very minimal metabolism of paracetamol in the gastrointestinal mucosa of the rats. In humans, paracetamol absorption is very little from the stomach but very rapid from the small intestine and the rate is dependent on the rate of gastric emptying. If gastric emptying is delayed due to presence of food, posture or drugs such as narcotics, absorption will be slowed although the extent absorbed is not affected (6).

Distribution

Paracetamol is uniformly distributed in the tissues. The ratio of concentrations in red blood cells and plasma is about 1.2:1 and binding to plasma protein is negligible. The apparent volume of distribution of paracetamol in man is about 0.9l/kg. (6).

Metabolism

Paracetamol is to a great extent metabolized in the liver while 2-5% of paracetamol administered is excreted unchanged in urine. Metabolism of the drug also occurs in the gut wall and kidney. The products of metabolism include sulphates and glucuronide conjugates. A small fraction of paracetamol is oxidized to highly reactive alkylating metabolites (6).

Excretion

The average renal clearance of paracetamol in healthy subjects given 20mg/kg was 13ml/ml. Paracetamol clearance depends on urine flow rate but not urine pH. It appears that paracetamol is filtered at the glomerulus with extensive tubular reabsorption. The mean renal clearance of paracetamol sulphate and glucuronide are 166 and 130mls/min (6).

Mechanism of action of paracetamol

The mechanism of action has not been elucidated until now. It has analgesic and antipyretic properties similar to NSAIDs but unlike NSAIDs it does not have any anti-inflammatory activity. However, in Literature, it has always been discussed together with NSAIDs. paracetamol suppresses prostaglandins just like the NSAIDs do (3).

Dose recommendation

According to Ji et al (3); the dose for under 2 years of age is as directed and supervised by a physician, 2-3 years (160mg in two divided doses); 4-6 years (240mg in three daily divided doses), 6-9 years (320mg in 4 divided doses) and 9-11years (320-400mg in 4 divided doses).

Also, according to the British National Formulary (BNF) (7), the oral dose for children between 1-5 years is 120-250mg every 4-6 hours and 6-12years is 250-500mg every 4-6

hours. For the neonates, the oral dose is 10-15mg/kg every 8-12 hours. Child 1-3 months the dose is 30-60mg every 8 hours as necessary and child 3-12 months, the dose is 60-120mg every 4-6hrs maximum 4 doses.

Paracetamol products are available on the market in the form of suspension, tablets, effeverscent tablets, powder to prepare oral liquid medicine (sachets) and rectal suppositories. Injectable paracetamol has also been in use especially in operations (3).

Tablet dosage form

Tablets are solid dosage forms that are most commonly used. It may be defined as a unit form of solid medicament which is prepared by compaction. Tablets are of various types and include; conventional tablets which are intended to be swallowed whole and then disintegrate and release the drug while in the Gastrointestinal tract, dispersible and effervescent tablets which are intended to disintegrate and dissolve in water prior to administration, chewable tablets which are chewed and then swallowed to ensure the drug disintegrate before reaching the site of action, Lozenges which are designed to dissolve slowly in the mouth, sublingual tablets which are placed under the tongue and tablets which are administered through the buccal cavity (between teeth and cheek) to avoid the first pass effect. The tablets may also be categorized based on their release mechanisms; either immediate release or controlled release (8).

Orodispersible tablets are tablets which are either placed in the mouth where they quickly dissolve or placed in a glass of water prior to ingestion (9). Dispersible tablets are also known as quick dissolves, fast melts, fast dissolving, rapid dissolve or Orally dissolving tablets (10) .

Children below 5 years of age have difficult or unable to swallow conventional oral dosage forms like tablets and capsules. Despite that liquid dosage forms have been developed, these dosage forms may be unstable and difficult to take accurate measurements. Liquids or powders for reconstitution require purified water for reconstitution and also refrigeration. This is not guaranteed in the third world.

There are several technical problems associated with development of paediatric medicines but one of them is acceptability of common excipients used in formulations. Also, the age range of the paediatric population from birth to 8 or 10 years of age is difficult to cover with one type of dosage form (11).

Orodispersible tablets have the advantage as they don't need water to swallow the dosage form. Also there is ease of administration to patients who cannot swallow such as the elderly, stroke victims, bedridden patients, patients who refuse to swallow such as paediatrics, geriatrics and psychiatric patients. Another advantage is rapid dissolution and absorption of the drug which result to quick onset of action. Orodispersible tablets also combine the advantages of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability (12). Examples of commercially available and patented oro-dispersible paediatric paracetamol tablets include Tempra Quicklets which uses Orasolv technology and manufactured by Cima Labs Inc., AdvaTab paracetamol manufactured using AdvaTab technology by Eurand International, Febrectol manufactured by Prographarm Chateauneuf in France, Jr. Tylenol Meltaways manufactured by Mc Neil Consumer Health care and rapidol (paracetamol 125mg) manufactured by Ethypharm Industries in France (13).

Development of oro-dispersible tablets

The basic approach in the development of fast dissolving /orodispersible tablets is the use of superdisintegrants. Direct compression method is an easy and confortable way as it requires small number of unit operations (14).

Disintegration of tablets prepared by direct compression method can be optimized by varying the concentration of disintegrants. It has been observed that there is a critical concentration of disintegrants below which, tablet disintegration time is inversely proportional to disintegrant concentrations. Also above this critical concentration level, disintegration time does not vary with increase of disintegrant concentration (15).

Optimization

The word “optimize” means to make as perfect, effective or functional as possible. Optimization is **a** useful tool to quantitate a formulation that has been qualitatively determined. Qualitative determination means rational selection of excipients and manufacturing steps for a given product (16).

There are several methods for optimization. In classical mathematical and search methods of optimization, the formulator is interested to understand the relationship between dependent variables (responses/product quality parameters) and independent variables (excipients /process variables). In most cases, this relationship is not known and hence necessitates the conduct of experiments (17).

Thus, the aim of the optimization of pharmaceutical formulations is generally to find the levels of the variables that affect the chosen response and determine the levels of the variable from which a robust product with high quality characteristics may be produced (18). Lagrangian method is one of the statistical methods which is useful only when not more than two independent variable are considered and the relationship between independent and response variable is to be established.

Optimization techniques are used to find either the best possible quantitative formular for a product or the best set of experimental conditions (input values) needed to run the process. Optimization techniques may be employed in the laboratory stage to develop the most stable, least sensitive formula or the qualification and validation stage of scale up in order to develop the most stable, least variable, robust process within its proven acceptable ranges of operation (19).

Response Surface Methodology

According to Oehlert, G.W (20), response surface methodology are the designs and models which are used for working with continuous treatments (independent variables) when trying to find the optima or describing the response.

Bolton, S. et al (21) describes the response surface as a geometrical representation of the response and the factors or independent variables which is similar to a contour map. According to Bolton, this representation in two dimensional space is possible only when there not more than two factors. In the case where more than two factors are involved, it is possible to take slices of the surface with all but two factors at a fixed level.

He also adds that; when one is looking for optimality, it is best to use a response equation which can reflect the presence of curvature in the response surface. To obtain an equation that will reflect curvature, one will have to conduct experiments with independent variables at more than three levels. In an equation this presence of curvature will be reflected by the presence of terms with a power more than 1 (e.g. X_1^2).

But, according to Oehlet, G.W. (20), simple models or equations using low order polynomial terms, that is, using terms with a power not more than 1 (first order model), is sufficient to describe sections of a response surface as models cannot describe the actual or whole surface. In other words, in a small region, polynomial models are usually a close approximation to the response surface that it is possible for us to use them in making inferences. He further elaborates that, first order models describes flat but tilted surfaces and the contour plots for these first order models are straight lines when two factors are involved and planes for more than two factors.

Contours or level curves are defined as set of design variables or independent variables that have the same expected response. Response surface designs are in most cases given by using coded values (20).

There are two aims for using response surface data; to find the settings for the design or independent variables that optimize (maximize or minimize) the response and to understand the “lie of the land”-where are the hills, valleys, ridgeline and so on that make up the topography of the response surface? It is possible to visualize the function f as surface of heights over the X_1, X_2 plane where X_1 and X_2 are independent variables, like a relief map showing mountains and valleys. A perspective plot shows the surface when viewed from the

side while a contour plot shows the contours of the surface, that is curves for X_1, X_2 pairs that have the same response value (20).

Factorial designs are formal experimental designs aimed at determining the effects of varying more than one factor. There are two types of factorial designs; simple factorial designs (Only two factors varied) and complex factorial designs where more than two factors are varied (22). These factorial designs of experiments are used in establishing data which are useful for establishing the response surface. They are thus the basis of response surface methodology.

Design space is a multidimensional combination and interaction of input variables (eg. material attributes) and process parameters that have been demonstrated to provide assurance of quality.

In a regulatory perspective, working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process (23).

1.2 Statement of the Problem

Paracetamol is a very important medicine which is commonly used in the management of acute and mild pain especially in pediatric patients. Despite lack of solid evidence on the benefit of using paracetamol in managing fever, in Tanzania, it is indicated for managing hyperpyrexia. In fact, it is preferred to non-steroid anti-inflammatory drugs (NSAIDs) when pyrexia is due to severe malaria.

Paracetamol liquid dosage forms for paediatrics (syrups and elixirs) have continued to dominate the local pharmaceutical manufacturing facilities and hence the local market despite the fact that they are formulated with solvents with unwanted side effects likes propylene glycol and ethanol. Although unpleasant taste of pediatric medicines can be easily masked in liquid pediatric formulations, accurate dose administration and stability of the medicines cannot be ensured with liquid formulations. They also require large space for storage and high transportation cost. In addition, liquids or powders for reconstitution require purified water for

reconstitution and also refrigeration which is not guaranteed in the third world. In some cases, people prefer to cut adult paracetamol formulation and administer with juice to paediatrics.

Oro-dispersible paediatric paracetamol tablet is the better dosage form than the liquid dosage forms in that it is stable, disintegrate rapidly when administered, easy to measure accurate dose and require small amount of water to swallow with. WHO in its document released in 2009 on the selection and use of essential medicines recommends that pediatric formulations be formulated in solid oro-dispersible dosage forms based on stability and accurate dose administration (24). Oro-dispersible fast dissolving dosage forms are important formulations since they are convenient for pediatric patients who have difficulty in swallowing conventional adult tablets or capsules.

With the given facts above, in this study, it is envisioned to develop and optimize a formulation of oro-dispersible paediatric paracetamol tablets which could provide better patient compliance, accurate dose, stability and palatability for pediatric patients.

Rationale of the Study

The study will give experience to the researcher on the formulation development and optimization of oro-dispersible tablets. The study, if successful will facilitate transfer of data and experience to local manufacturing facilities and help to provide an alternative to liquid paediatric paracetamol which has less advantages compared to oro-dispersible tablets. Experience gained could also be used later by the researcher in routine work. The study will use the direct compression method to manufacture oro-dispersible paracetamol tablets. This method is easy to use in the local setup. Lastly, most paracetamol tablet preparations are manufactured by wet granulation method which is a time consuming process.

1.3 Literature Review

According to EMEA (25), critical points for consideration when designing paediatric formulations include route of administration; appropriateness of dosage form; excipients choice, safety, level, side effects; acceptability and palatability; delivery devices; rate of infusion; volume to be administered and wastage.

Also, it is advised that when designing paediatric dosage forms or adult dosage forms which may have application in paediatric patients the use of excipients must be decided carefully. The preservative benzyl alcohol is used in injectables. Such injectables should not be given to neonates due to their immature metabolism. In products for young paediatric patients up to three years old, use of benzyl alcohol should carefully be evaluated. However, it is recommended to avoid it as it can cause pain at injection site (26).

In addition, the preservatives; benzoic acid, sodium benzoate and potassium benzoate when used in parenteral dosage forms may increase the risk of jaundice in neonates (26).

The use of sweeteners is one of the ways for masking taste of oro-dispersible tablets. There are two types of sweeteners; natural and artificial sweeteners. However, there is not a single sweetener which can suit all patients. According to EMEA, the sweeteners such as Sucrose which is hydrolysed in the intestine to absorbable monosaccharides fructose and glucose should be avoided in paediatric patients suffering from hereditary fructose intolerance. Also, formulations with high amounts of sugar should be avoided in therapy of paediatric patients, suffering from diabetes (26).

For preparations intended for long term use in paediatrics, large amount of sugar should be replaced by sugar free formulations because sucrose promotes dental carries. In addition, fructose is to be avoided in patients with hypoglycaemia or hereditary fructose intolerance as it may cause laxative effects when administered orally at high dose (26).

The sweeteners such as sorbitol and xylitol are considered safe for diabetics, however, they may cause osmotic diarhoea. Sorbitol is also metabolised to fructose. In severe cases, sorbitol may cause damage of the liver accompanied with coma and death in patients with hereditary

fructose intolerance and hypoglycaemia. It is also recommended to avoid intravenous administration of sorbitol (26).

The sweetener aspartame is 150-200 times as sweet as sucrose. It is a dipeptide of aspartic acid and a methyl ester of phenylalanine. The phenylalanine component may be harmful in patients with phenylketonuria. Cross reactivity to sulfonamides may also occur (26).

Lactose is a disaccharide of glucose. It is hydrolysed by intestinal lactase into glucose which is absorbed in the intestine. In infants and children with lactose intolerance, there may be prolonged diarhoea, dehydration and metabolic acidosis.

Direct compression method is the simplest tablet pressing method. However, according to Banker G.S et al (27), it has some challenges. For example, use of direct compression method for large doses may present problems if the drug itself is not compressible. This means that, in order to facilitate compression of the non-compressible large dose drug, the use of large amount of diluent may be required. Thus, it is recommended the drug to be limited to 30% of a direct compression formulation. Also, the use of large amount of diluent may increase cost and make the tablet (conventional tablets) difficult to swallow.

Banker G.S. et al explains that direct compression diluents such as Spray dried lactose may interact with amine compounds and form yellow discoloration. In this case, dextrose may be used to replace some spray dried lactose to reduce darkening.

They also add that equipment and procedures usually employed in direct compression method is basically screening or milling and mixing.

With regard to tablet size, the recommended tablets size is that with weight range of 120 to 700mg for standard density organic materials. However, for oval tablets, the weight may reach up to 800mg.

Also, according to Banker G. S. et al, anhydrous lactose is a low cost diluent which does not exhibit the maillard reaction but packaging of tablets need to be done carefully to avoid moisture. This information on anhydrous lactose is somehow contradictory as it has been stated by Kottke, M.K. et al (8) that anhydrous lactose can be used as a diluent particularly in

direct compression formulations where low moisture content is desirable since it has very good stability and a reduced tendency to colour upon aging. It has also been stated that it is insensitive to temperature changes and allows it to be reworked with relative ease. This information has also been supported by information that anhydrous crystalline lactose is not hygroscopic (28).

There are two methods for preparing oro-dispersible tablets by direct method; the use of disintegrants and the use of sugar based excipients. In the Literature, it has been stated that disintegrants are normally used in the following ranges; for croscamellose sodium (cross linked carboxymethyl cellulose), the range is 0.5 - 5.0%w/w), for crosspovidone (cross linked polyvinylpyrollidone) the range is 2-5%w/w and pre-gelatinized starch is used around 5%w/w. For these disintegrants to work effectively, they should not increase the viscosity significantly(29).

The usual range of lubricants; for magnesium stearate, the range is 0.25-0.5%w/w and Sodium lauryl sulfate/magnesium lauryl sulphate, the range is 1.0-2.0%w/w. The use of anionic surfactants has the advantage of improving the dissolution of poorly soluble drugs (29).

Excipients which are used for direct compression formulation and manufacture are diluents, compression aid, disintegrant and lublicants. Microcrystalline cellulose (avicel PH 102) is a commonly used compression aid(29).

Soluble lubricants like polyethylene glycols (PEGs) may be suitable for use as lubricants in dispersible tablets because they are both lubricating and hydrophilic and thus do not affect tablet dispersion. Also, the use of suspending agents or surfactants in dispersible tablets may be desired as more stable suspensions can be formed on dispersion (9).

Diluents for ODT are most commonly selected from cellulose derivatives and preferably microcrystalline cellulose, starches, lactose, polyols and preferably mannitol (12).

According to literature, tablets may have little dose variation if particle sizes are in the range of 800um (appro. 25 mesh size US standard). The particles should also not be less than 14um in size because flow through orifices may be impaired(9).

Colorants are part of the excipients for formulations. However, they do not contribute to therapeutic activity nor product bioavailability and stability. They only increase cost and complicate manufacturing process. Their main role is product identification and enhancing aesthetic appearance. Another challenge in colorants is that, there is no internationally agreed approved list of suitable colorants for ingestion (8).

With the difficulties seen in the choice of excipients for paediatric formulations, it has been recommended to use the minimum possible excipients in order to reduce the possible side effects (30).

Battacharyya, S. et al (31) prepared and evaluated orally disintegrating taste masking tablet of paracetamol with Kollicoat smart seal 30D by use of wet granulation technique but included so many types of excipients.

Anand et al (32) formulated rapid dispersible tablets of paracetamol with application of solid dispersion for solubility enhancement and polymer coating for bitter taste masking. Results indicated rapid release for formulations containing mannitol and betacyclodextrin as carriers and also showed acceptable organoleptic properties.

Prajapati B.G. et al (16) formulated and optimized successfully, domperidone fast dissolving tablets by wet granulation technique using factorial design. They used sodium starch glycolate as a super disintegrant and starch paste as a binder. It was shown that by adopting a systematic formulation approach, it was possible to attain an optimum point in the shortest time with minimum effort.

Vishal, M. et al (33) developed by wet granulation technique, using trial and error method, mouth dissolving tablets of lornoxicam by using KYRON T-34 (polacrillin potassium) as a novel superdisintegrant and menthol as a subliming agent. They also used mannitol as a diluent, aspartame as a sweetener, alcoholic solution of polyvinyl pyrollidone (PVP K-30) as binder and aerosil as flow promoter. Results showed that the use of the superdisintegrant and subliming agent gave promising results.

Kiran, N.R et al (34) formulated and developed, by direct compression method, without optimization, piroxicam orodispersible tablets using two types of superdisintegrants (crospovidone and sodium glycolate) each at a time at the concentration of 3% and 5% w/w. Only one type of disintegrant was used in each of the formulations. One formulation did not contain superdisintegrant. Other excipients which appeared in each formulation are microcrystalline cellulose, mannnitol, aspartame, magnesium stearate and menthol. The total tablet size was 200mg. Results indicated that piroxicam oro-dispersible tablets may be developed by direct compression method using super disintegrants (sodium starch glycolate and crospovidone).

ShobaKushnan et al (35) formulated oro-dispersible tablets of amlodipine by using direct compression method and superdisintegrants; sodium starch glycolate, croscarmellose sodium and crospovidone. The tablets were evaluated for weight variation, friability, hardness, drug content, in vitro disintegration time, wetting time and in vitro dissolution.

Results indicated that formulation with higher concentrations of sodium starch glycolate and crosspovidone as superdisintegrants showed better dissolution and disintegration. In this study, differential scanning calorimetry (DSC) and Fourier Transform Infrared Spectroscopy were used for drug excipient compatibility studies. Other excipients included in all test formulations were lactose, talc and magnesium Stearate. The active ingredient was 10% of the total weight 100mg.

Hirjau, M. et al (36), formulated and characterized orodispersible acetaminophen 120 mg tablets. The formulation was prepared by direct compression and wet granulation using various superdisintegrants. Materials used in the formulation included direct compressible acetaminophen, direct compressible lactose (tablettose 80), microcrystalline cellulose, polyvinylpyrollidine K30, sodium starch glycolate, croscarmellose sodium, magnesium stearate and colloidal silica. Characterisation of formulations showed that the optimal formulas were those containing sodium starch glycolate with sodium carboxymethylcellulose. For formulations to be regarded as optimal they had to show a balance between disintegration time and hardness.

Ugoeze et al (37), formulated and assessed paediatric dispersible paracetamol tablets containing lentinus tuber regium based co-processed filler –binder-superdisintegrant . The filler –binder-superdisintegrant was based on edible mushroom, lentinus tuber regium incorporated to trigger rapid dispersion of a paediatric dispersible tablet containing 125mg of paracetamol which was prepared by solvent evaporation of alcoholic wet massed excipients. Results indicated that the granules obtained were free from enteric or pathogenic organisms, flowable, compressible and its compression resulted to tablets which dispersed in 28 seconds in 10mls of water at 27 ± 2^0C.

1.4 Objectives

1.4.1 Broad Objectives

To develop and evaluate a formulation of paediatric oro-dispersible paracetamol tablet.

1.4.2 Specific Objectives

i. To conduct pre-formulation studies of potential excipients.
ii. To develop a formulation of paediatric oro-dispersible paracetamol tablet.
iii. To optimize the formulation by response surface methodology.
iv. To evaluate the optimized formulation.

CHAPTER 2 : MATERIALS AND METHODS

2.1 Materials and Equipment

2.1.1 Materials

Excipients which were used in the compatibility studies were microcrystalline cellulose (avicel PH102- FMC Biopolymer, USA), lactose monohydrate (Oxford Laboratory, India), magnesium stearate (donated by Shellys), talc (donated by Zenufa Laboratory Ltd), croscamellose sodium (donated by Zenufa laboratory Ltd), saccharin (donated by Zenufa Laboratories), crospovidone (donated by Shelys) and starch 1500. These are some of the common excipients (28). Paracetamol powder was also supplied by Zenufa laboratories.

2.1.2 Equipment

Equipment which were used include Near Infrared spectrophotometer (Lab Spec 5000 ASD inc.USA), and analytical balance (new classic MS Mettler Toledo Germany), HPTLC machine (Linomat 5 and CAMAG TLC Scanner 4), Twin trough development chamber, glass bottles (Fisher Scientific, Germany), Plastic bottles, Tubular mixer (Analytical Technology, Bangalore, India), Korsh EK 02 single station tablet press machine (Germany), Monsanto type tablet hardness tester (IEC, Mumbai, India), Roche Friabilator (electro lab, Bangalore, India), single pan balance (Shimadzu, AX200, Japan), Disintegration Apparatus USP (Electrolab, Bangalore, India), graduated cylinder (Fisher Scientific, Germany), sieve analyzer (Endecotts, Germany), glass bottles (Fisher Scientific, Germany), ERWEKA TBH machine (Heusenstamm, Germany), Kenwood planetary Mixer (Kenwood, United Kingdom), Dissolution tester (USP apparatus II (Paddle), ERWEKA DT 620, Heusenstamm, Germany), Kottermann 2712 Oven (Kottermann, W.German), normal lab ware and Densitometer (Flowmatics-India).

2.2 Methods

2.2.1 Pre-formulation studies

2.2.1.1 Preparation of binary mixture for drug –excipient compatibility Studies

Drug- excipient Compatibility studies were conducted as follows; 10.50g of each excipient was mixed with 10.50g of paracetamol powder (1:1 binary mixture) in order to prepare mixtures for assessment of chemical incompatibility. The mixtures were mixed by use of mortar and pestle in order to facilitate uniform mixing through finely milling of drug and excipient. Also, additional samples were prepared which contained paracetamol only and which contained paracetamol and all the excipients.

Each sample was divided into three transparent plastic containers which were labeled with the name of materials constituting the blend and also numbered as 1, 2 or 3. All samples bearing number 1 on the label were stored at room condition while opened; number 2 were stored in the Climatic Chamber ($40\ ^{0}$C / 75 % RH) with the bottles opened and those labeled number 3 were stored in the Oven at $50\ ^{0}$C with the bottles closed. All the samples were stored for a duration of three months (90) days.

2.2.1.2 Physical assessment of binary mixture

The binary mixtures which were prepared are as indicated in Table 1 below. The samples were physically observed for caking, liquefaction, discoloration and odour formation at the interval of 0, 7, 14, 30, 60 and 90 days of storage.

Table 1: Binary mixtures of paracetamol : excipients (1:1)

No.	Active Pharmaceutical Ingredient	Excipient	Ratio
1	Paracetamol	Starch 1500	1:1
2	Paracetamol	Lactose Monohydrate	1:1
3	Paracetamol	Sacharin	1:1
4	Paracetamol	Avicel PH 102	1:1
5	Paracetamol	Crospovidone	1:1
6	Paracetamol	Croscarmellose	1:1
7	Paracetamol	Magnesium stearate	1:1
8	Paracetamol	Talc	1:1
9	Paracetamol	All excipients	1:1
10	Paracetamol	-	

2.2.1.3 Qualitative assessment by Near Infrared Spectrometer

Near Infrared Spectroscopy (NIR) is a type of vibrational spectroscopy that makes use of photon energy in the range of 2.65 x 10^{-19} to 7.96 x 10^{-20}J (750 to 2500nm). This energy is sufficient to cause vibration in molecules but it is not sufficient to cause excitation of electrons, though with some exceptions.

This method has the following advantages; it is fast (takes one minute or less per sample), non- destructive, non-invasive, the probing radiation beam has high penetration power, suitable for in-line use, nearly universal application as all molecules containing C-H, N-H, S-H and O-H bonds can be analyzed and it requires minimum sample preparation demands (38).

Thus, assessment of chemical compatibility was also performed by use of NIR spectra to compare the consistency of the blend at day 0 with that of day 7, 14, 30, 60 and 90 under stated conditions. Ten small samples of each Paracetamol-Excipient blend were taken from the plastic containers and each small sample scanned three times to make a total of thirty scans for each sample at each time interval and storage condition and spectra recorded.

2.2.1.4 Assay of mixture of powders by HPTLC Method

HPTLC is the improved method of Thin Layer Chromatography (TLC) which utilizes the conventional techniques of TLC in more optimized way. It has the following benefits over the conventional Thin Layer Chromatography; it has been automated, there is full optimization, it uses selective detection principle and requires minimum sample preparation. HPTLC uses higher quality TLC plates with finer particle sizes in the stationary phase than that used in normal Thin Layer Chromatography (39). TLC is a chromatographic separation process in which the stationary phase consists of a thin layer applied to a solid substrate or support (40).

Thus, HPTLC method was selected instead of HPLC because of lack of appropriate column and standards for the HPLC machine and that HPTLC method is simple to use. This method is an in-house validated method.

At each interval, test samples and paracetamol standard samples were weighed into volumetric flasks and dissolved in methanol to make concentrations containing 0.35mg/ml of paracetamol.

These were spotted automatically by the Linomat 5 applicator on 20x10 HPTLC plates. This was then developed in a development chamber containing mobile phase of appropriate solvent mixture (toluene:methanol:acetone:glacial acetic acid-16:6:6:0.03).

2.2.1.5 Evaluation of flow properties of paracetamol powder

The flow ability of paracetamol powder was evaluated by measuring the compressibility index as per BP 2013.

The angle of repose of the powder was not measured as paracetamol powder exhibited poor floor and could not go through the funnel orifice. In this case angle of repose is not reliable because it does not give reproducible results and useful for materials with good flow only (41).

2.2.2 Formulation of oro-dispersible paediatric paracetamol Tablets

2.2.2.1 Formulation of oro-dispersible paediatric paracetamol tablets by direct compression

Powder blends for direct compression (Formulation F1 to F5) were prepared and evaluated for flow properties. These formulations (Table 2) were based on the dilution capacity of excipients. Formulation F1 to F3 were prepared based on normal excipients but formulation F4 and F5 (Table 2) were based on direct compressible excipients (starch 1500 and avicel PH 102). The formulations as shown in Table 2 below were then evaluated for flow properties before attempting compression. In these formulations finely milled paracetamol powder was limited to a minimum of 15% w/w. Details of the formulations are found in Table 2 below.

2.2.2.2 Formulation of oro-dispersible paediatric paracetamol tablets by wet granulation method

Trial formulations by design of experiments were prepared by use of non-direct compression materials as shown in Table 3 below. Formulation W2, W3, W4 and W5 were prepared for the purpose of selecting the appropriate superdisintegrant.

Factorial design was applied for formulations W8, W11, W12 and W14 which were then used to develop mathematical models. It was limited to two factors only as required for Lagrangian method of optimisation. Formulation W6 and W7 were developed to capture the effect of varying the concentration of avicel. Formulation W9 and W 10 were used to test the effect to disintegration time of using hydroxypropylcellulose as a binder instead of povidone. The details of these trial formulations are found in Table 9 to Table 21.

Table 2: Formulations F.1 to F.5

	Name of Ingredient	**F1**		**F2**		**F3**		**F4**		**F5**	
		Weight per tablet (mg)	**%**	**Weight per tablet (mg)**	**%**	**Weight per tablet (mg)**	**%**	**Weight per tablet (mg)**	**%**	**Weight per tablet (mg)**	**%**
1	Paracetamol	120	30	120	30	120	30	120	30	50	15
2	Talc	4.2	1	20	5	20	5	20	5	5.4	1
3	Magnesium Stearate	4.2	1	4	1	4	1	4	1	5.4	1
4	Microcrystalline Cellulose (Avicel PH 102)	83.3	20	80	20	130	32.5	190	47.5	207.05	38.3
5	Starch 1500	20.8	5	20	5	20	5	40	10	207.05	38.3
6	Lactose Monohydrate	156.3	37.5	130	32.5	80	20	-	-	-	-
7	Crosscarmellose	22.9	5.5	22	5.5	22	5.5	22	5.5	29.7	5.5
8	Sacharin	5	1.2	4	1	4	1.2	4	1	5.4	1
	Total	**416.7**	**100**	**400**	**100**	**400**	**100**	**400**	**400**	**540**	**100**

Table 3: Trial formulations W1 to W13

Name of Ingredient	Quantity per tablet (mg)											
	W2	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W13**
Inner phase												
Paracetamol (fine powder)	120	120	120	120	120	120	120	120	120	120	120	120
Microcrystalline Cellulose (Avicel PH 101)	35	35	35	35	17.5	70	86.7	70	94.5	86.7	35	35
Lactose Monohydrate	149	163.5	153.5	167	167	114.5	80.3	110.95	79.45	90.8	142.45	131.95
PVPCL	10.5	3.5	-		10.5	10.5	21	10.5	21	21	21	21
CMC CL	-	-	8.5	1.75	-	-	-	-	-	-	-	-
PVP K30	17.5	17.5	17.5	17.5	17.5	17.5	17.5	-	-	7	7	17.5
HPC	-	-	-	-	-	-	-	21	10.5	-	-	-
Sacharin	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Outer Phase												
PVP CL	10.5	3.5	-	-	10.5	10.5	-	10.5	-	-	-	-
CMC CL	-	-	8.5	1.75	-	-	17.5	-	17.5	17.5	17.5	17.5
Talc	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Magnesium Stearate	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Total	350	350	350	350	350	350	350	350	350	350	350	350

Table 4: Formulation F.1

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (600tablets)	Reason for Inclusion
1	Paracetamol	30	120	72	Active substance
2	Talc	1	4.2	2.5	Glidant
3	Magnesium Stearate	1	4.2	2.5	Lubricant
4	Microcrystalline Cellulose (Avicel PH 102)	20	83.3	50	Compression Aid
5	Starch 1500	5	20.8	12.5	Diluent
6	Lactose Monohydrate	37.5	156.3	93.8	Filler
7	Crosscarmellose	5.5	22.9	13.7	Disintegrant
8	Sacharin	1.2	5	3	Sweetener
	Total		416.7	250	

Table 5: Formulation F.2

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (600tablets)	Reason for Inclusion
1	Paracetamol	30	120	72	Active substance
2	Talc	5	20	12	Glidant
3	Magnesium Stearate	1	4	2.4	Lubricant
4	Microcrystalline Cellulose (Avicel PH 102)	20	80	48	Compression Aid
5	Starch 1500	5	20	12	Diluent
6	Lactose Monohydrate	32.5	130	78	Filler
7	Crosscarmellose	5.5	22	13.2	Disintegrant
8	Sacharin	1	4	2.4	Sweetener
	Total		400	240	

Table 6: Formulation F. 3

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (300tablets)	Reason for Inclusion
1	Paracetamol	30	120	36	Active substance
2	Talc	5	20	6	Glidant
3	Magnesium Stearate	1	4	1.2	Lubricant
4	Microcrystalline Cellulose (Avicel PH 102)	32.5	130	39	Compression Aid
5	Starch 1500	5	20	6	Diluent
6	Lactose Monohydrate	20	80	24	Filler
7	Crosscarmellose	5.5	22	6.6	Disintegrant
8	Sacharin	1.2	4	1.2	Sweetener
	Total		400	120	

Table 7: Formulation F.4

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (300tablets)	Reason for Inclusion
1	Paracetamol	30	120	36	Active substance
2	Talc	5	20	6	Glidant
3	Magnesium Stearate	1	4	1.2	Lubricant
4	Microcrystalline Cellulose (Avicel PH 102)	47.5	190	57	Compression Aid/Diluent
5	Starch 1500	10	40	12	Diluent
6	Crosscarmellose	5.5	22	6.6	Disintegrant
7	Sacharin	1	4	1.2	Sweetener
	Total		400	120	

Table 8: Formulation F.5

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (300tablets)	Reason for Inclusion
1	Paracetamol	15	80	24	Active substance
2	Talc	1	5.4	1.6	Glidant
3	Magnesium Stearate	1	5.4	1.6	Lubricant
4	Microcrystalline Cellulose (Avicel PH 102)	38.3	207.05	62.1	Compression Aid/Diluent
5	Starch 1500	38.3	207.05	62.1	Diluent
6	Crosscarmellose	5.5	29.7	8.9	Disintegrant
7	Sacharin	1	5.4	1.6	Sweetener
	Total		540	162	

Table 9: Formulation W1

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (750 tablets)	Reason for Inclusion
	Inner Phase				
1	Paracetamol (fine powder)	60%	120	90	Active Ingredient
2	Lactose Monohydrate	27 %	54	40.5	Diluent/Filler
3	PVPCL	3%	6	4.5	Disintegrant
4	PVP K30	5%	10	7.5	Binder
5	Sacharin	1%	2	2	Sweetener
6	Water			50	Solvent
	Outer Phase				
7	PVP CL	3%	6	4.5	Disintegrant
8	Talc	0.5%	1	1	Glidant
9	Magnesium Stearate	0.5%	1	1	Lubricant
	Total		200	150	

Table 10: Formulation W2

	Name of Ingredient	**%**	**Quantity per tablet (mg)**	**Quantity per Batch (g) (750 tablets)**	**Reason for Inclusion**
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	90	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	10%	35	26.25	Binder
3	Lactose Monohydrate	42.7%	149.45	112.09	Diluent/Filler
4	PVPCL	3%	10.5	7.9	Disintegrant
5	PVP K30	5%	17.5	13.1	Binder
6	Sacharin	1%	3.5	2.63	Sweetener
7	Water			58.2	Solvent
	Outer Phase				
8	PVP CL	3%	10.5	7.9	Disintegrant
9	Talc	0.5%	1.75	1.3	Glidant
10	Magnesium Stearate	0.5%	1.75	1.3	Lubricant
	Total		350	262.5	

Table 11: Formulation W3

	Name of Ingredient	**%**	**Quantity per tablet (mg)**	**Quantity per Batch (g) (750 tablets)**	**Reason for Inclusion**
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	90	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	10%	35	26.25	Binder
3	Lactose Monohydrate	46.7%	163.5	122.63	Diluent/Filler
4	PVPCL	1%	3.5	2.63	Disintegrant
5	PVP K30	5%	17.5	13.1	Binder
6	Sacharin	1%	3.5	2.63	Sweetener
7	Water			55.0	Solvent
	Outer Phase				
8	PVP CL	1%	3.5	7.9	Disintegrant
9	Talc	0.5%	1.75	1.3	Glidant
10	Magnesium Stearate	0.5%	1.75	1.3	Lubricant
	Total		350	262.5	

Table 12: Formulation W14

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (750 tablets)	Reason for Inclusion
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	90	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	10%	35	26.25	Binder
3	Lactose Monohydrate	43.9%	153.5	115.13	Diluent/Filler
4	CMC CL	2.5%	8.5	6.4	Disintegrant
5	PVP K30	5%	17.5	13.1	Binder
6	Sacharin	1%	3.5	2.63	Sweetener
7	Water			55	Solvent
	Outer Phase				
8	CMC CL	2.5%	8.5	6.4	Disintegrant
9	Talc	0.5%	1.75	1.3	Glidant
10	Magnesium Stearate	0.5%	1.75	1.3	Lubricant
	Total		350	262.54	

Table 13: Formulation W5

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (750 tablets)	Reason for Inclusion
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	90	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	10%	35	26.25	Binder
3	Lactose Monohydrate	47.7%	167	125.25	Diluent/Filler
4	CMC CL	0.5%	1.75	1.3	Disintegrant
5	PVP K30	5%	17.5	13.1	Binder
6	Sacharin	1%	3.5	2.63	Sweetener
7	Water			59	Solvent
	Outer Phase				
8	CMC CL	0.5%	10.5	7.9	Disintegrant
9	Talc	0.5%	1.75	1.3	Glidant
10	Magnesium Stearate	0.5%	1.75	1.3	Lubricant
	Total		350	262.5	

Table 14: Formulation W6

	Name of Ingredient	**%**	**Quantity per tablet (mg)**	**Quantity per Batch (g) (750 tablets)**	**Reason for Inclusion**
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	90	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	5%	17.5	13.1	Binder
3	Lactose Monohydrate	47.7%	167	125.2	Diluent/Filler
4	PVPCL	3%	10.5	7.9	Disintegrant
5	PVP K30	5%	17.5	13.1	Binder
6	Sacharin	1%	3.5	2.63	Sweetener
7	Water			58.2	Solvent
	Outer Phase				
8	PVP CL	3%	10.5	7.9	Disintegrant
9	Talc	0.5%	1.75	1.3	Glidant
10	Magnesium Stearate	0.5%	1.75	1.3	Lubricant
	Total		350	262.5	

Table 15: Formulation W7

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (750 tablets)	Reason for Inclusion
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	90	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	20%	70	52.5	Binder
3	Lactose Monohydrate	32.7%	114.5	85.5	Diluent/Filler
4	PVPCL	3%	10.5	7.9	Disintegrant
5	PVP K30	5%	17.5	13.1	Binder
6	Sacharin	1%	3.5	2.63	Sweetener
7	Water			84.7	Solvent
	Outer Phase				
8	PVP CL	3%	10.5	7.9	Disintegrant
9	Talc	0.5%	1.75	1.3	Glidant
10	Magnesium Stearate	0.5%	1.75	1.3	Lubricant
	Total		350	262.5	

Table 16: Formulation W8

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (710 tablets)	Reason for Inclusion
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	85.2	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	24.8%	86.7	61.56	Binder
3	Lactose Monohydrate	22.9%	80.3	57	Diluent/Filler
4	PVPCL	6%	21	14.9	Disintegrant
5	PVP K30	5%	17.5	12.42	Binder
6	Sacharin	1%	3.5	2.48	Sweetener
7	Water			97.7	Solvent
	Outer Phase				
8	CMC CL	5%	17.5	12.42	Disintegrant
9	Talc	0.5%	1.75	1.24	Glidant
10	Magnesium Stearate	0.5%	1.75	1.24	Lubricant
	Total		350	253.22	

Table 17: Formulation W9

	Name of Ingredient	**%**	**Quantity per tablet (mg)**	**Quantity per Batch (g) (750 tablets)**	**Reason for Inclusion**
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	90	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	20%	70	52.5	Binder
3	Lactose Monohydrate	31.7%	110.95	83.21	Diluent/Filler
4	PVPCL	3%	10.5	7.9	Disintegrant
5	Hydroxypropyl Cellulose (HPC)	6 %	21	15.75	Binder
6	Sacharin	1%	3.5	2.63	Sweetener
7	Water			116	Solvent
	Outer Phase				
8	PVP CL	3%	10.5	10.5	Disintegrant
9	Talc	0.5%	1.75	1.3	Glidant
10	Magnesium Stearate	0.5%	1.75	1.3	Lubricant
	Total		350	262.49	

Table 18: Formulation W10

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (415 tablets)	Reason for Inclusion
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	49.8	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	24.8%	94.5	39.2	Binder
3	Lactose Monohydrate		110.95	83.21	Diluent/Filler
4	PVPCL	6%	21	8.7	Disintegrant
5	Hydroxypropyl Cellulose (HPC)	3 %	10.5	4.3	Binder
6	Sacharin	1%	3.5	1.4	Sweetener
7	Water			65.5	Solvent
	Outer Phase				
8	CMCL CL	5%	17.5	7.3	Disintegrant
9	Talc	0.5%	1.75	0.73	Glidant
10	Magnesium Stearate	0.5%	1.75	0.73	Lubricant
	Total		350	145.2	

Table 19: Formulation W11

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (750 tablets)	Reason for Inclusion
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	49.8	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	24.8	86.7	36	Binder
3	Lactose Monohydrate	25.9%	90.8	37.7	Diluent/Filler
4	PVPCL	6%	21	8.7	Disintegrant
5	PVP K 30	2 %	7	2.9	Binder
6	Sacharin	1%	3.5	1.45	Sweetener
7	Water			53.3	Solvent
	Outer Phase				
8	CMC CL	5%	17.5	7.3	Disintegrant
9	Talc	0.5%	1.75	0.73	Glidant
10	Magnesium Stearate	0.5%	1.75	0.73	Lubricant
	Total		350	145.31	

Table 20: Formulation W12

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (750 tablets)	Reason for Inclusion
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	49.8	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	10%	35	14.5	Binder
3	Lactose Monohydrate	40.7%	142.45	59.1	Diluent/Filler
4	PVPCL	6%	21	8.7	Disintegrant
5	PVP K 30	2 %	7	2.9	Binder
6	Sacharin	1%	3.5	1.45	Sweetener
7	Water			51.3	Solvent
	Outer Phase				
8	CMC CL	5%	17.5	7.3	Disintegrant
9	Talc	0.5%	1.75	0.73	Glidant
10	Magnesium Stearate	0.5%	1.75	0.73	Lubricant
	Total		350	145.25	

Table 21: Formulation W13

	Name of Ingredient	%	Quantity per tablet (mg)	Quantity per Batch (g) (750 tablets)	Reason for Inclusion
	Inner Phase				
1	Paracetamol (fine powder)	34.3%	120	49.8	Active Ingredient
2	Microcrystalline Cellulose (Avicel PH 101)	10%	35	14.5	Binder
3	Lactose Monohydrate	37.7	131.95	54.8	Diluent/Filler
4	PVPCL	6%	21	8.7	Disintegrant
5	PVP K 30	5 %	17.5	7.3	Binder
6	Sacharin	1%	3.5	1.45	Sweetener
7	Water			45.3	Solvent
	Outer Phase				
8	CMC CL	5%	17.5	7.3	Disintegrant
9	Talc	0.5%	1.75	0.73	Glidant
10	Magnesium Stearate	0.5%	1.75	0.73	Lubricant
	Total		350	145.31	

2.2.2.3 Evaluation of flow properties of granules and powder blends for the formulations

All blends were evaluated for flow properties by determining the angle of repose and compressibility index.

Angle of Repose: The angle of repose was determined as per BP 2013.

Compressibility Index: Compressibility index of granules and blends were determined as per section 2.2.1.5. Granules/blends weighing 50g were poured into a 100mls measuring cylinder.

2.2.3 Tableting

Direct compression method

Direct compression is a method of tablet manufacture that involves compression of mixed powders into tablets without an intermediate granulating step. Excipients are available that are designed for this specific role. These excipients are called direct compression excipients (8).

All the excipients in the formulations (F1 to F5) except magnesium stearate were mixed together for 5 minutes by the turbular mixer. Then magnesium stearate was added after passing through 250µm sieve and the final mixture blended for 5 minutes. After this, the blend was tried for compression using Korsh EK 02 single station tablet press machine using 10 mm round punch.

Wet granulation method

This is a method of tablet compression which includes an intermediate step of granulation. This granulation step involves blending of dry ingredients, wet massing, screening and drying (8)**.**

Paracetamol was mixed for 5 minutes with some of formulation excipients by the Kenwood planetary mixer. Then granules were prepared by slowly adding a solution of binder (povidone or hydroxypropyl cellulose) while mixing for approximately 13 minutes. The end point of granulation was ascertained by the snow ball test.

Then the moist mass was passed through 4000µm sieve and the granules obtained were dried in the oven at 50^{o}C for 24 hours. After drying, the granules were evaluated for moisture content before and after passing through 1000µm sieve. For good compactibility, flow properties and quality of tablets the granules should have moisture content of less than 4% but not below 1% w/w (42).

After sieving the dried granules through 1000µm sieve to obtain granules size with good flow properties, the granules were evaluated for flowability and then blended with a disintegrant and talc for 5 minutes. Then a lubricant (magnesium stearate) was passed through 250µm

sieve and added to the blend. The final blend for each formulation was mixed for 5 minutes and then evaluated for flow properties before compression.

2.2.4 Evaluation of oro-dispersible paediatric paracetamol tablets

2.2.4.1 Weight variation

10 tablets were weighed individually, the average weight was calculated and the individual tablets weights were compared to the average.

The tablets met the test if no more than 2 tablets were outside the percentage limit of 5% and if no tablet differed by more than 2 times the percentage limit (27),(43).

2.2.4.2 Tablet hardness

10 tablets were crushed by a hardness tester (44), one at a time while maintaining the same direction with respect to application of force. The hardness tester was cleaned to remove all the fragments of the tablets before each determination.

2.2.4.3 Friability

A sample of ten pre-weighed tablets was placed in a friabilator which was then operated for 100 revolutions per 4 minutes (25rpm).

The tablets were then dusted and reweighed. Batches that lost less than 1.0% of their weight were considered acceptable. Also, if capping occurred during friability testing, the tablets were rejected.

2.2.4.4 Disintegration time

One tablet was placed in each of the 6 tubes of the disintegration test device and the basket rack was positioned in a 1 litre beaker of distilled water at $37^0C \pm 2^0C$. The time it takes for all particles to pass through the 10-mesh screen was noted for each tube/tablet.

2.2.4.5 Assay of oro-dispersible paediatric paracetamol tablets by HPTLC method

As per section 2.2.1.4

2.2.4.6 Comparative dissolution

A simple model independent approach which uses a difference factor (f 1) and a similarity factor (f 2) was used to compare the dissolution profiles. The difference factor (f1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/[\sum_{t=1}^{n} R_t]\}. 100$$

where n is the number of time points, R_t is the dissolution value of the reference (prechange) batch at time t, and T_t is the dissolution value of the test (postchange) batch at time t.

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f = 50 . \log \{[1+(1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} .100\}$$

For the dissolution profiles to be considered similar, the f 1 values should be close to 0, and f 2 values should be close to 100(45) .

Comparative dissolution was performed at three different conditions; hydrochloric acid pH 1.2, phosphate buffer pH 4.5 and phosphate buffer pH 6.8 (46). Innovator conventional paracetamol tablets (panadol 500mg) were chosen as a comparator because an innovator oro-dispersible product was not available.

Dissolution Machine Set up: Paddle, 50 Revolutions per minute (RPM), 37^{o}C, 900mls of buffer, 6 Individual units (tablets) and machine stopping time after 65 minutes. Only 6 instead of 12 individual units were taken because of time and instruments limitation.

Sampling interval (minutes): 10, 20, 30, 45 and 60.

Assay Method: UV method by using Specific Absorbance (A1%, 715) as per BP 2013.

2.2.5 Optimization of oro-dispersible paediatric paracetamol tablets

Optimization began by selecting the best disintegrant between crosspovidone and crosscarmellose. Four formulations were designed and developed. Two of the formulations contained one of the disintegrants at high and low levels and the remaining two formulations contained the other disintegrant at high and low values too (Formulations W2,W3,W4 &W5 in Table 3). The tablets obtained were evaluated for disintegration time and hardness.

Other formulations were prepared which contained both the disintegrants. Then from the different trial formulations, the one with minimum disintegration time was selected and further optimization was done to identify the design space by establishing mathematical models and plotting them.

CHAPTER 3 : RESULTS AND DISCUSSION

3.1 Pre-formulation Studies

3.1.1 Physical appearance and odour

Paracetamol: saccharin and paracetamol: crospovidone showed caking from day 7 in all storage conditions. Also, there was no change in colour for all the samples except paracetamol: sacharin which showed changes in colour (to off-white from white) in day 30 under oven condition. There were no change in odour of all the samples and no liquefaction was observed.

However, based on assay results (Table 22, 23 &24) and HPTLC densitograms, there were no evidence of chemical degradation for these blends. No new peaks were formed in the densitograms for paracetamol: saccharin (Figure 3 and Figure 4) and assay results indicated no specific trend as shown by Figure 2 below.

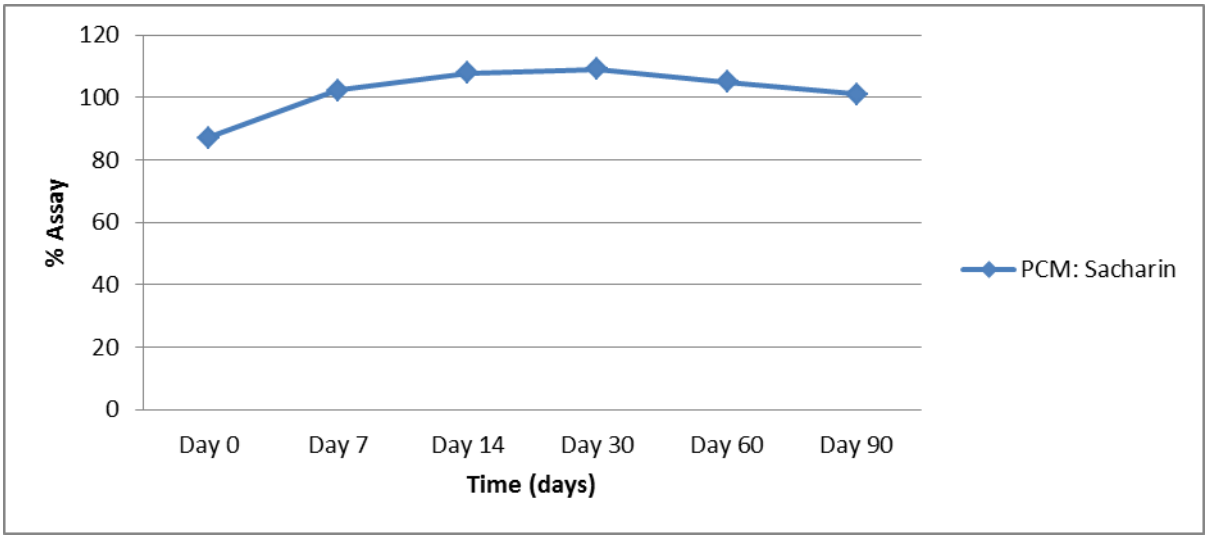

Figure 2: Plot of assay of PCM: Sacharin blend vs time for oven condition

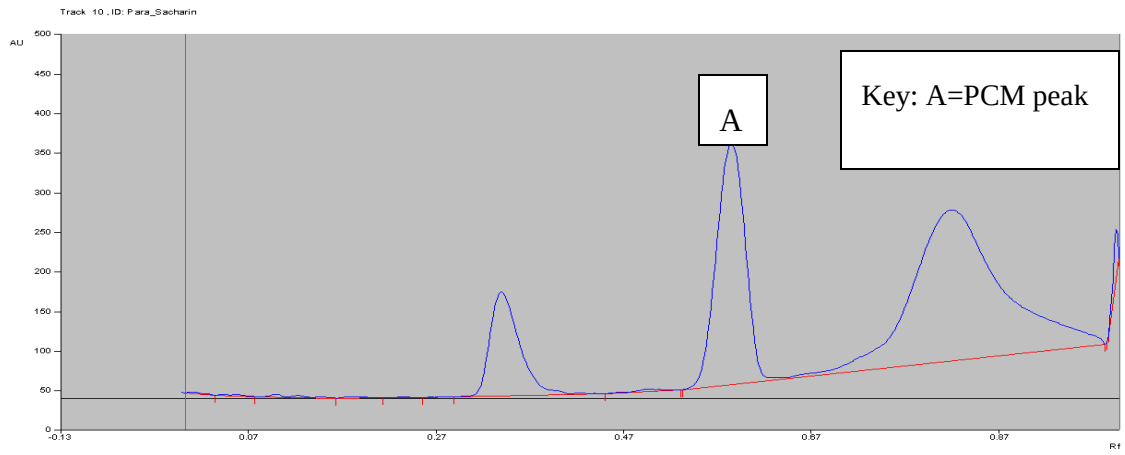

Figure 3: Typical densitogram of PCM: Sacharin 0.35mg/ml solution for day 0 developed in a mobile phase (toluene:methanol:acetone:glacial acetic acid -16:6:6:0.03 v/v) and detected at 254nm with sample application volume 5µl

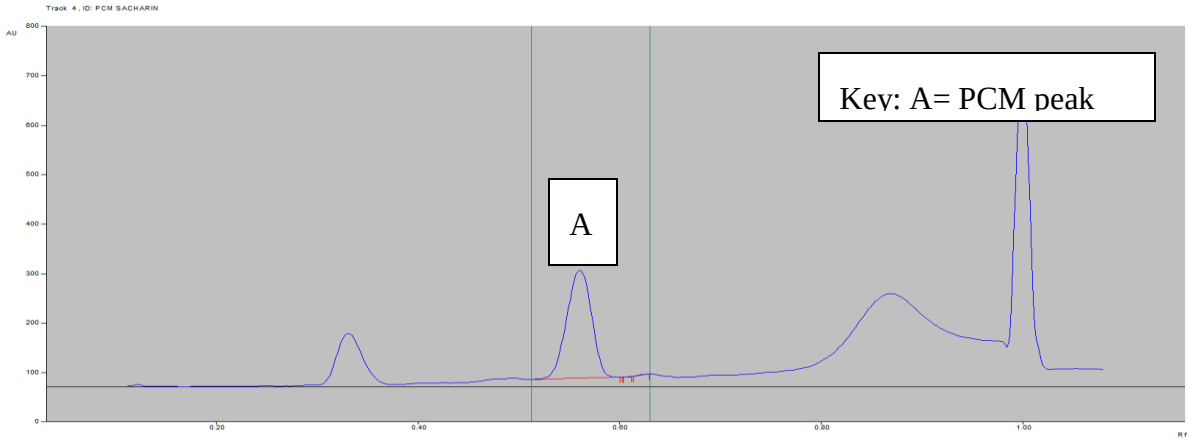

Figure 4: Typical densitogram of PCM: Sacharin 0.35mg/ml solution for oven condition in day 90 developed in a mobile phase (toluene:methanol:acetone:glacial acetic acid -16:6:6:0.03 v/v) and detected at 254nm with sample application volume 5µl.

Though there was caking for paracetamol:saccharin and paracetamol:crospovidone blends, the sample that contained all excipients did not show caking indicating that when the excipients are used in low levels do not cake and hence cannot affect flow of blends during in-process storage.

3.1.2 Near Infrared (NIR) assessment

The pattern of the spectra did not change indicating that the identity of materials remained the same (see sample spectra Figure 5 & Figure 6)**.** The observed differences in the position of the spectra were due to shifting of the baseline which could be due to differences in particle sizes or density of the blends as the tapping done before scanning may vary.

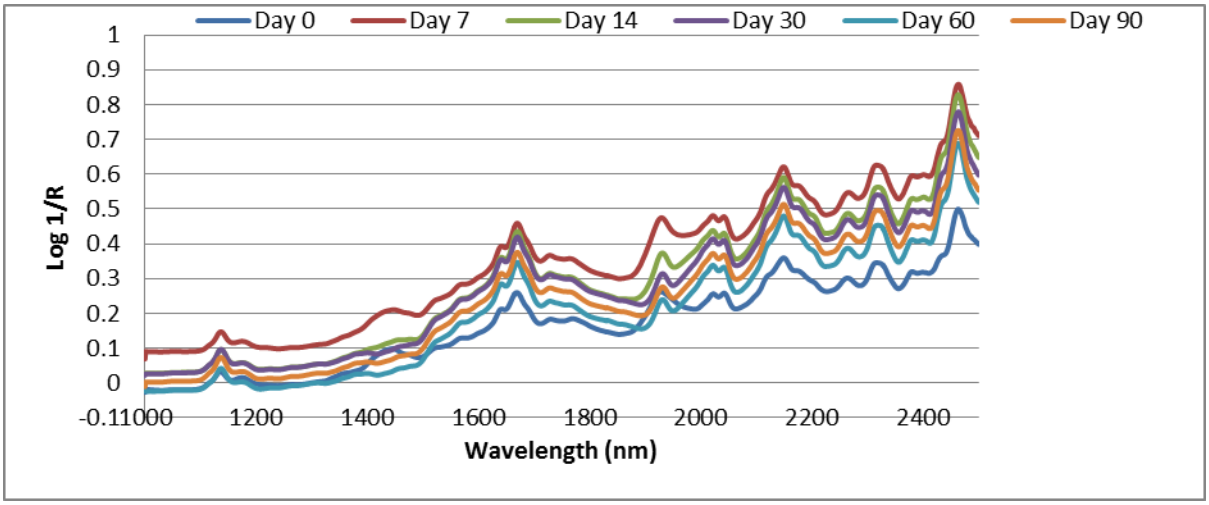

Figure 5: NIR spectra for PCM: Sacharin under oven condition

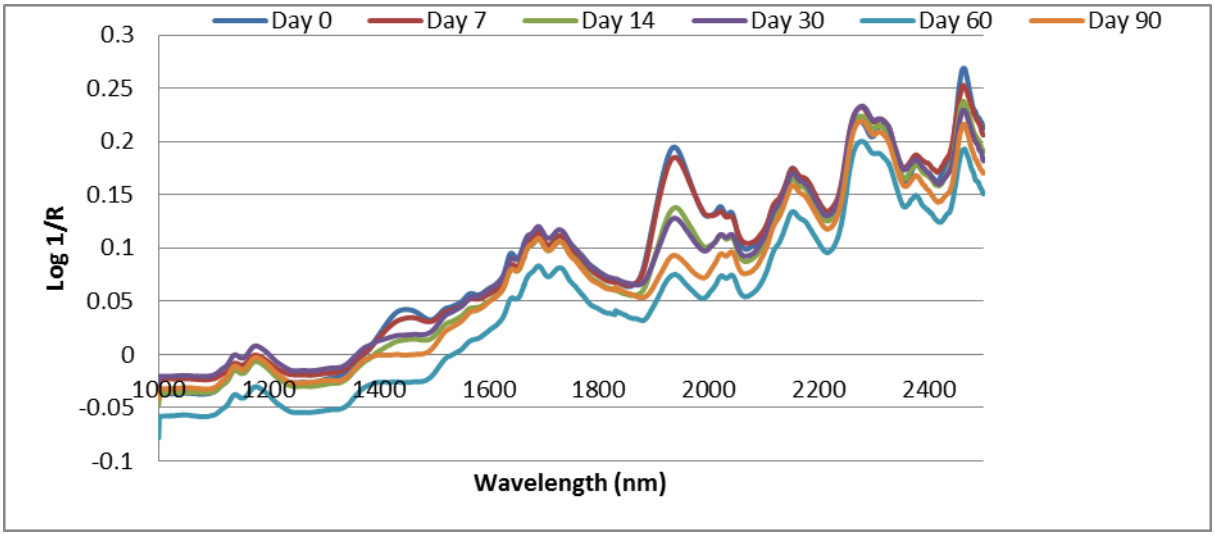

Figure 6: NIR spectra of PCM: Crospovidone blend under oven condition

3.1.3 Assay evaluation

Based on assay results, paracetamol was found to be compatible with the selected excipients. Results are as depicted in Table 22, Table 23 & Table 24 below. The acceptable limits were Not less than 95% and Not More than 105%. Though some of the results were outside these limits, no decreasing trend was observed (see Figure 7, Figure 8 & Figure 9 below) and hence the variation including out of specification results could be a result of errors in analysis and also due to mixing of the blend.

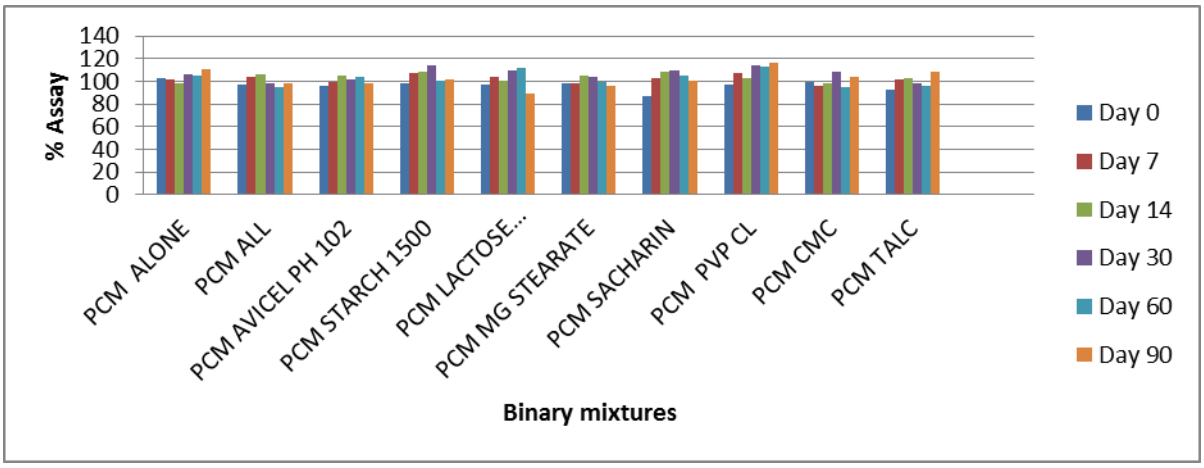

Figure 7: Assay results under oven condition

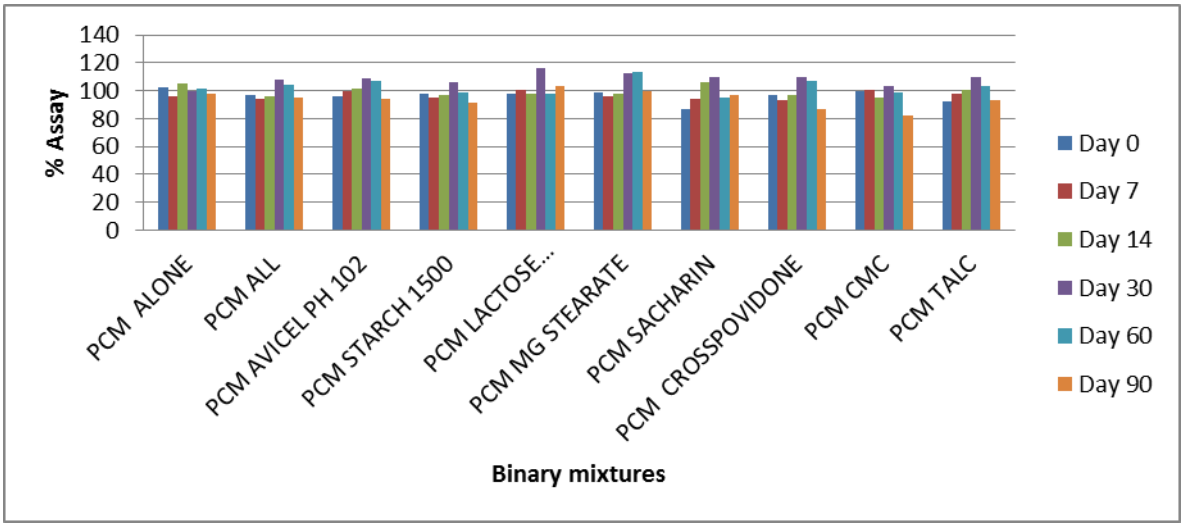

Figure 8: Assay results under climatic chamber

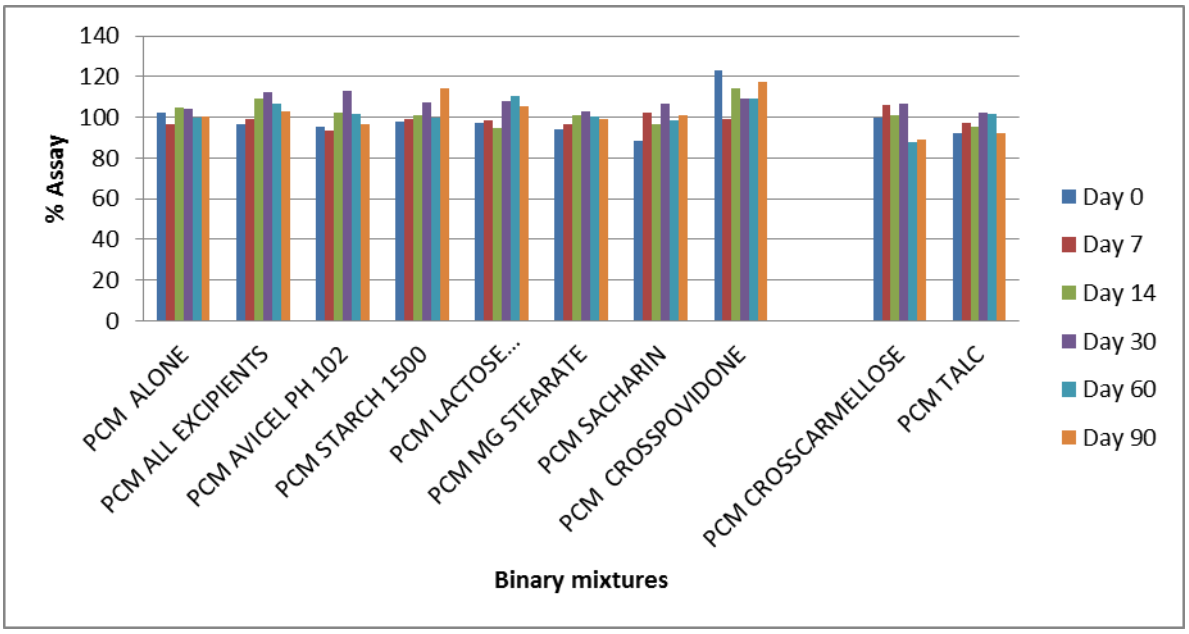

Figure 9: Assay results under room condition

Paracetamol and excipients did not show incompatibility at 50^0 C, closed bottle indicating that the excipients can be used in wet granulation method which required drying of granules at 50^0 C for 24 hours when dried by oven.

Also, based on stability at room and climatic chamber, not only that but tablets formulated by these excipients can be manufactured at room temperature as the blends were stable under such conditions.

Table 22: Assay results under room condition

	Sample	Assay %					
		Day 0	Day 7	Day 14	Day 30	Day 60	Day 90
1	PCM ALONE	102.6	96.7	105	104	99.9	100.6
2	PCM ALL EXCIPIENTS	96.5	99.2	109	112.1	106.5	103.2
3	PCM AVICEL PH 102	95.6	93.6	102.2	113	101.5	96.7
4	PCM STARCH 1500	97.8	99.3	101.1	107.2	99.9	114.3
5	PCM LACTOSE MONOHYDRATE	97.4	98.2	94.9	108.2	110.7	105.6
6	PCM MG STEARATE	93.96	96.9	101.1	103	100.5	99.1
7	PCM SACHARIN	88.6	102.5	96.7	106.8	98.5	101.1
8	PCM CROSPOVIDONE	123.3	99.1	114.1	109.1	109.3	117.1
9	PCM CROSSCARMELLOSE	99.7	105.8	101	106.9	87.8	88.9
10	PCM TALC	92.2	97.2	95.6	102	101.9	92.4

Table 23: Assay results for climatic chamber (accelerated) condition

	Sample	Assay %					
		Day 0	Day 7	Day 14	Day 30	Day 60	Day 90
1	PCM ALONE	102.6	96	105.4	99.8	101.9	98
2	PCM ALL	96.6	94.1	95.7	107.8	103.9	94.7
3	PCM AVICEL PH 102	95.6	99.4	101.3	109.2	107	94
4	PCM STARCH 1500	97.8	94.8	97.3	106.5	98.8	91.5
5	PCM LACTOSE MONOHYDRATE	97.4	100.5	97.5	116.6	97.9	102.9
6	PCM MG STEARATE	98.3	96.3	97.9	112.6	113.6	99.4
7	PCM SACHARIN	87	94.3	106.1	109.7	95.4	96.7
8	PCM CROSPOVIDONE	96.8	92.9	96.5	109.8	107.4	86.9
9	PCM CROSCARMELLOSE	99.7	100.7	95.5	103.4	98.6	82.3
10	PCM TALC	92.2	97.5	100.6	109.6	103.6	92.9

Table 24: Assay results for oven condition

	Sample	Assay %					
		Day 0	Day 7	Day 14	Day 30	Day 60	Day 90
1	PCM ALONE	102.6	101.4	98.1	105.7	104.8	110.7
2	PCM ALL	96.6	104.4	105.6	98.7	94.5	97.9
3	PCM AVICEL PH 102	95.6	99.1	105.4	101.9	104	98
4	PCM STARCH 1500	97.8	106.8	108.5	113.6	100.3	101.6
5	PCM LACTOSE MONOHYDRATE	97.4	104.2	100.4	109.2	111.3	88.7
6	PCM MG STEARATE	98.3	98.2	104.7	103.5	99.2	96.4
7	PCM SACHARIN	87.0	102.2	107.9	109.1	105	101
8	PCM CROSPOVIDONE	96.8	107.8	102.4	114.3	112.9	115.9
9	PCM CROSCARMELLOSE	99.7	96.3	98.5	107.9	95	103.8
10	PCM TALC	92.2	101.4	102.9	98.2	96.3	108.7

3.1.4 Flow properties of paracetamol powder

The sample of paracetamol powder that was available was a finely milled paracetamol powder that exhibited poor floor (compressibility index 30.3%). Angle of repose could not be established as the powder failed to flow through the funnel orifice. We thus rely on compressibility index to classify its flowability. This measure is sufficient as the angle of repose is not a reliable measure of powder flowability (41). Sieve analysis could also not be performed as it is suitable for powder with most particles (80%) above 75µm (47).

3.2 Results of Formulation Studies

3.2.1 Flow properties

All batches formulated by wet granulation had excellent flowability as indicated by both angle of repose and compressibility index (Table 25 & Table 26). The angle of repose is however

not a reliable means for determining flow (25) as in some cases even after blending with talc and magnesium Stearate the angle of repose remained the same while the compressibility index decreased in most cases.

Formulations for dry compression possessed poor flow as indicated by the compressibility index. The minimum compressibility index for dry compression formula was 20%. Direct compressible excipients (starch 1500 and avicel PH 102) could not improve the flow of paracetamol powder at the minimum inclusion of 15%w/w paracetamol (formulation F.5 in Table 2). Thus, even if one limits the drug to 30% of direct compression formulation, there is no guarantee that one will be able to compress tablets. Compression properties of blends depend on the property of direct compression excipients used and also the property of the active pharmaceutical ingredient.

Table 25: Flow properties

Ingredient	**Angle of repose**	**Comment**	**Compressibility Index**	**Comment**
Paracetamol	-	Flow very poor	30.35%	Poor flow
Microcrystalline Cellulose	33.27	Average	-	-
Starch 1500	30.70	Free Flowing	-	-
F.1	38	Average	20%	Fair to passable
F.2	47.6	Poor flow	33.9%	Poor Flow
F.3	47.6	Poor flow	31.45%	Poor Flow
F.4	38	Average	30.95%	Poor Flow
F.5	34.5	Average	25%	Poor Flow

Table 26: Compressibility index of formulation W1 to W14

Formulation	Compressibility Index of sieved dried granules	Compressibility Index (Carr's Index) of blends	Comments for blends
W.1	-	12.84%	Excellent
W.2	17.92%	13.64%	Excellent
W.3	11%	13.33%	Excellent
W.4	19.3%	13.83%	Excellent
W.5	13.27%	12.5%	Excellent
W.6	16.33%	12.79%	Excellent
W.7	15.25%	13.46%	Excellent
W.8	14.08%	13.56%	Excellent
W.9	16.03%	12.73%	Excellent
W.10	18.1%	12.07%	Excellent
W.11	21%	17.8%	Fair to passable
W12	14.4%	15.1%	Good
W13	14.2%	12%	Excellent
W14	19.4%	15.5%	Good

Table 27: Angle of repose of formulation W1 to W14

Formulation	Angle of repose of sieved dried granules	Angle of repose of blends	Comments for blends
W1	-	26.6	Free flowing material
W2	26.6	25.13	Free flowing material
W3	26.6	25.11	Free flowing material
W4	27.98	25.17	Free flowing material
W5	27.92	26.6	Free flowing material
W6	29.36	26.6	Free flowing material
W7	29.25	26.57	Free flowing material
W8	26.6	26.6	Free flowing material
W9	30.7	30.7	Free flowing material
W10	26.6^0	26.6^0	Free flowing material
W11	29.36^0	30.7^0	Free flowing material
W12	28^0	25.1^0	Free flowing material
W13	28^0	23.6^0	Free flowing material
W14	29.3^0	26.6^0	Free flowing material

3.2.2 Tablet Properties

Weight variation

Based on results for tablets weight variation (Table 28 below), all the formulations (W2 to W14) were within the limits for tablet weight variations (7.5% deviation allowed).

Table 28: Weight variation

Formulations	S/No.	1	2	3	4	5	6	7	8	9	10
W1	Tablet weight(mg)	340	340	320	340	340	340	330	340	330	340
	%Deviation	1.19	1.19	4.77	1.19	1.19	1.19	1.79	1.19	1.79	1.19
W2	Tablet weight(mg)	350	350	340	340	350	340	350	360	350	350
	%Deviation	0.57	0.57	2.3	2.3	0.57	2.3	0.57	3.45	0.57	0.57
W3	Tablet weight(mg)	370	360	370	380	370	370	380	380	370	370
	%Deviation	0.8	3.49	0.8	1.88	0.8	0.8	1.88	1.88	0.8	0.8
W4	Tablet weight(mg)	370	370	370	360	360	360	370	360	370	370
	%Deviation	1.09	1.09	1.09	1.64	1.64	1.64	1.09	1.64	1.09	1.09
W5	Tablet weight(mg)	370	360	370	360	360	360	370	360	360	370
	%Deviation	1.65	1.1	1.65	1.1	1.1	1.1	1.65	1.1	1.1	1.65
W6	Tablet weight(mg)	350	370	360	360	360	350	370	350	350	360
	%Deviation	2.23	3.35	0.56	0.56	0.56	2.23	3.35	2.23	2.23	0.56
W7	Tablet weight(mg)	350	350	360	340	350	350	350	350	340	350
	%Deviation	0.29	0.29	3.15	2.58	0.29	0.29	0.29	0.29	2.58	0.29
W8	Tablet weight(mg)	360	350	360	350	360	350	360	350	350	350

	%Deviation	1.69	1.14	1.69	1.14	1.69	1.14	1.69	1.14	1.14	1.14
W9	Tablet weight(mg)	340	350	350	350	350	350	360	340	350	350
	%Deviation	2.58	0.29	0.29	0.29	0.29	0.29	3.15	2.58	0.29	0.29
W10	Tablet weight(mg)	350	350	350	340	330	340	340	340	340	340
	%Deviation	2.34	2.34	2.34	0.58	3.51	0.58	0.58	0.58	0.58	0.58
W11	Tablet weight(mg)	360	360	360	350	360	350	360	350	350	360
	%Deviation	1.12	1.12	1.12	1.69	1.12	1.69	1.12	1.69	1.69	1.12
W12	Tablet weight(mg)	360	360	360	340	360	350	360	360	350	350
	%Deviation	1.41	1.41	1.41	4.23	1.41	1.41	1.41	1.41	1.41	1.41
W13	Tablet weight(mg)	370	350	350	350	350	350	350	360	350	360
	%Deviation	4.52	1.13	1.13	1.13	1.13	1.13	1.13	1.69	1.13	1.69
W14	Tablet weight(mg)	360	370	360	340	360	350	360	360	360	370
	%Deviation	0.27	3.06	0.27	5.29	0.27	2.51	0.27	0.27	0.27	3.06

Friability, hardness, disintegration time and assay

The formulations did not differ much in terms of friability as all were within limits. They differed in disintegration time and hardness. Formulation W3 possessed the highest hardness (26.03 kg/cm^2) while W1 (not detailed in this dissertation) showed the lowest disintegration time (less than 1 minute) and was softer than other formulations. Formulation W8 showed both acceptable hardness (7.85 kg/cm^2) and disintegration time (1.03 minutes). Formulation W11 had acceptable disintegration time and hardness but the flow ability (Table 25) of the blend was poor. There was no linear relationship between hardness and disintegration time possibly because of different levels of disintegrants, binders, other excipients and failure to measure the compression force and hence maintain it at a constant level for all the formulations. However, generally, we can say that formulations with lower tablets hardness (W8, W10 &W11) have lower disintegration time than those with higher hardness (W9, W12, W13 & W14).

Table 29: Test results for friability, hardness, disintegration time and assay of tablets

Formulation	Friability	Hardness	Disintegration Time (min.sec)	Assay
W8	0.28%	7.85±0.42	1:03	108.4%
W9	0%	11.5±0.4	1:45	112.2%
W10	0.86%	4.2±0.35	1:05	104.4%
W11	0%	6.55±0.37	0:53	124.6%%
W12	0%	11.35±2.9	1:55	118.4%
W13	0.28%	12.5±0.58	3:56	106%
W14	0%	10.3±1.2	2:18	-

3.2.3 Optimization

Based on formulations W2, W3, W4 and W5 crospovidone was shown to be a better super disintegrant than croscarmellose as indicated in Table 30 below;

Table 30: The effects of crospovidone vs croscarmellose on disintegration time

Disintegrant	levels	Disintegration time (min.)
Crospovidone	-1	16.03
	+1	3.28
Croscarmellose	-1	13.67
	+1	4.57

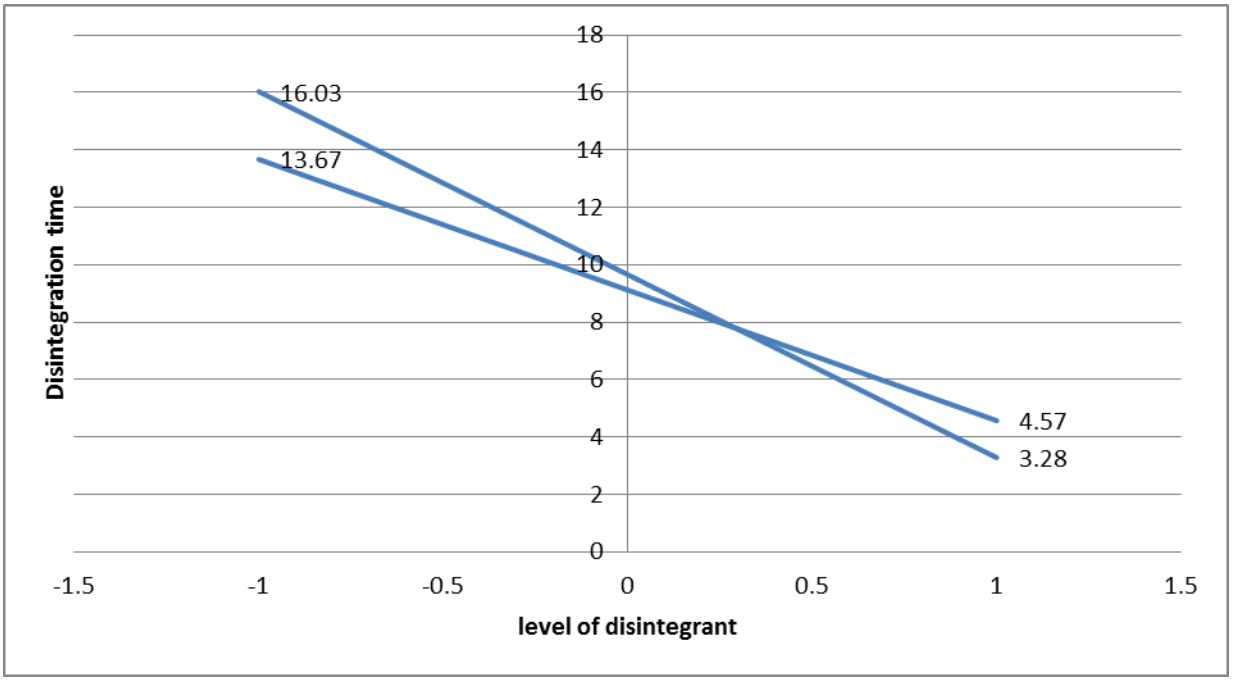

Figure 10: The effects of crospovidone vs croscarmellose on disintegration time

According to results in Table 30 above, when crospovidone was used at the low level it exhibited a highest disintegration time. But when used at high level it exhibited the lowest disintegration time of tablets (3.28 min.). On the graph (Figure 10), it is evident that the slope for the line indicating change of disintegration time with level of crospovidone is greater than that for croscarmellose. Thus, crospovidone has higher main effect on disintegration than croscarmellose. However, the formulation containing crospovidone which exhibited

minimum disintegration time is formulation W 7 (1.62 min.). This is within the acceptable limits but is not satisfactory because it is at the borderline of the upper limit which is 2 min.

The trial formulations which contained both disintegrants were shown to be better than those with only one disintegrant. Thus, it was decided to optimize a formulation containing two superdisintegrants.

Table 31: Hardness (dependent response) for formulations at different levels of independent variables (levels have been coded)

	Variable X_1 (Avicel)	**Variable X_2(binder)**	**X_1X_2**	**Total**	**Hardness (Kg/cm2)**	
					observed	**predicted**
W8	+1	+1	+1	+1	7.85	7.85
W11	+1	-1	-1	+1	6.55	6.55
W12	-1	-1	+1	+1	11.35	11.35
W13	-1	+1	-1	+1	12.5	12.49
Coefficients ($\sum xy/2^n$)	-2.36	0.61	0.04	9.56		
	β1	β2	β12	β0	Av.=9.56	

Model for hardness: $YH = -2.36X_1 + 0.61X_2 + 0.04X_1X_2 + 9.56$

Testing fitness of the model: SSR = 5.898 SST = 5.9159

SSR/SST = 0.997 $r^2 = 0.997$

Based on these results (r^2=0.997), it was concluded that the model for hardness is a useful model. If r^2 was equal to zero, this could mean that there was no relationship between hardness and the independent variables as hardness could be constant irrespective of the levels of avicel and the binder (povidone).

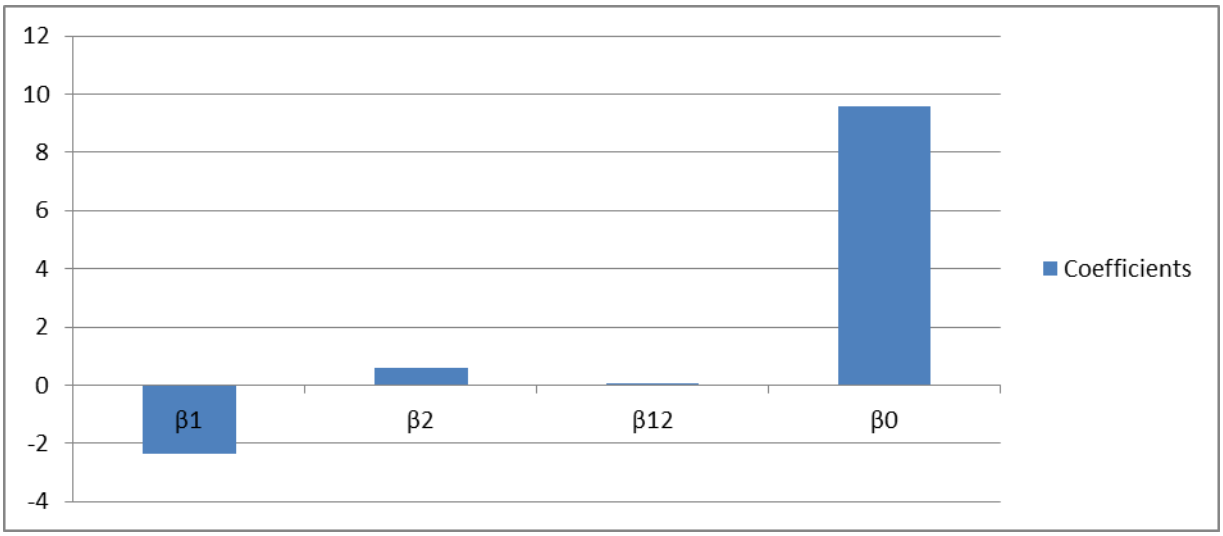

Figure 11: Effects (coefficients) of the variables on hardness response

Table 32: Disintegration time (dependent responses) for formulations at different levels of independent variables (levels have been coded)

	Variable X_1	Variable X_2	X_1X_2	Total	Disintegration time (min.)	
					Observed	Predicted
W8	+1	+1	+	+1	1.05	1.06
W11	+	-1	-1	+1	0.88	0.88
W12	-1	-1	+1	+1	1.92	1.92
W13	-1	+1	-1	+1	3.94	3.94
Coefficients ($\sum xy/2^n$)	-0.98	0.55	-0.46	1.95		
	β1	β2	β12	β0	Av.=1.95	

Model for Disintegration time: $YD = -0.98X_1 + 0.55X_2 - 0.46X_1X_2 + 1.95$

Testing fitness of the model: SSR = 23.7732

SST = 23.8319

SSR/SST = 0.997 $r^2 = 0.997$

Also, in this case, r^2 = 0.997 indicating that the model for disintegration time is useful. In Figure 11 above, it can be seen that, when you increase the level of avicel, you tend to decrease the tablet hardness while when you increase the level of the binder, you tend to increase the tablet hardness (see the negative coefficient for avicel and the positive coefficient for the binder (povidone). However, the two factors have an interaction that tends to increase tablet hardness.

In Figure 12 below, the effects for the factors on disintegration time are similar to that on hardness except that interaction tends to decrease the disintegration time.

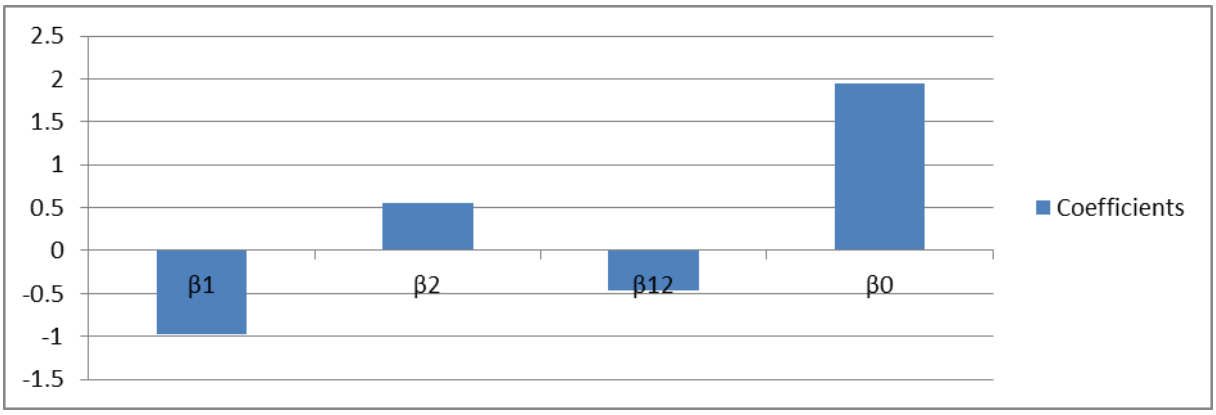

Figure 12: Effects of factors on disintegration time

Testing of the Models

An additional formulation (at the center point) was prepared with both Avicel (17.4%) and Binder (3.5%) at 0 levels. The observed disintegration time was 2.3minutes and hardness was 10.3±1.2 kg/cm^2. Substituting zero for the variables in the model for disintegration time and hardness, the result we get is 1.95 and 9.56. The deviation for disintegration time is 17% and that for hardness is 7.74%. This is a significant difference but in this case it could be acceptable due to the fact that compression force could not be maintained at a constant level in all formulations bearing in mind that disintegration time is a function of tablet hardness and material properties while hardness is a function of compression force and material properties.

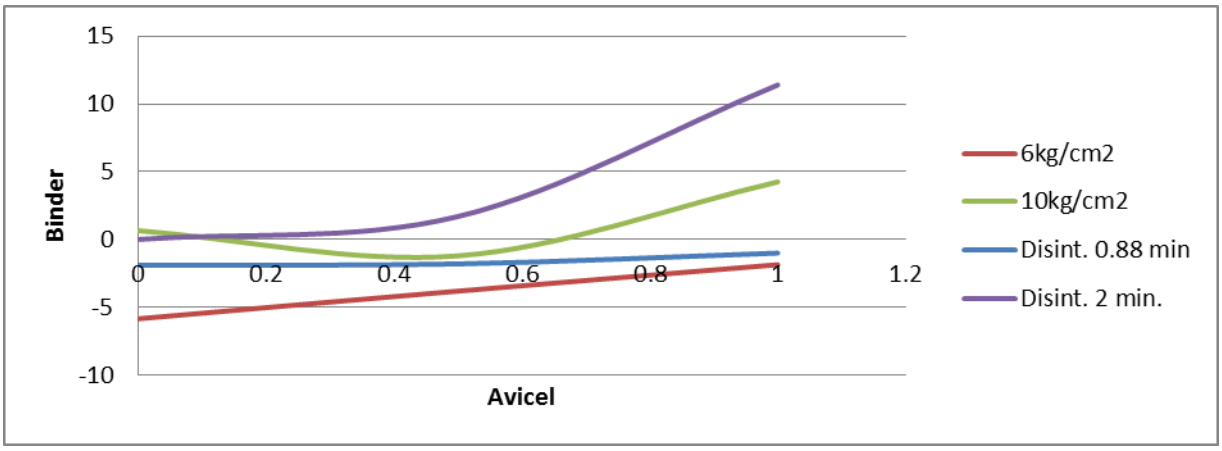

Figure 13: Contour plot of hardness and disintegration time with all other independent factors being constant except the levels of avicel and povidone (binder)

In the graph (Figure 13), there are four lines. The first line from top (purple coloured) is the lines that connect pairs of X1 and X2 that give Disintegration time of 2 minutes. Pairs below this line will give a disintegration time of less than 2 minutes.

The second line (green coloured) connect pairs of X1 and X2 that give a hardness of 10kg/cm2 and below this line the pairs give a hardness of less than this value.

The third line (blue coloured) is for disintegration time of 0.88 minutes above which we get Disintegration time above 0.88 minutes.

The last line (red) is for hardness of 6kg/cm2 above which we get hardness above 6kg/cm2. The two middle lines provide boundaries for the design space (Figure 14) within which pairs give acceptable disintegration time and hardness.

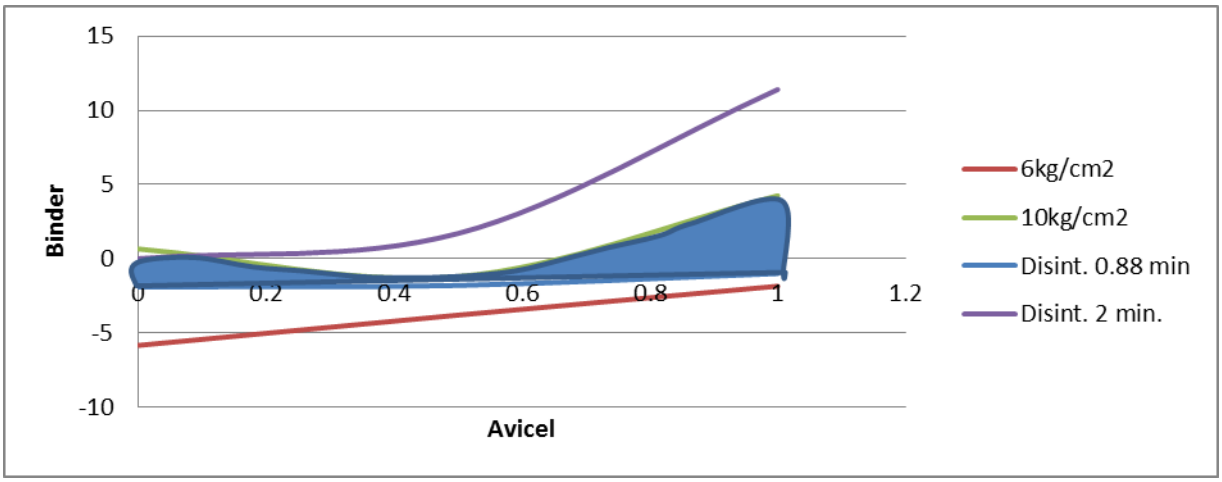

Figure 14: Design space for ODPPT 120mg when all other factors are kept constant while the level of avicel and binder (povidone) are varied

3.2.4 Comparative dissolution of Formulation W8 and panadol 500mg

Results of comparative dissolution, in a regulatory perspective, indicate that the products are similar at all the three pH conditions because more that 85% of each product had dissolved within 15 minutes as data in annex I indicates. However, just for the purpose of quantifying the differences and similarities, f1 and f2 factors were calculated as shown below in Table 33.

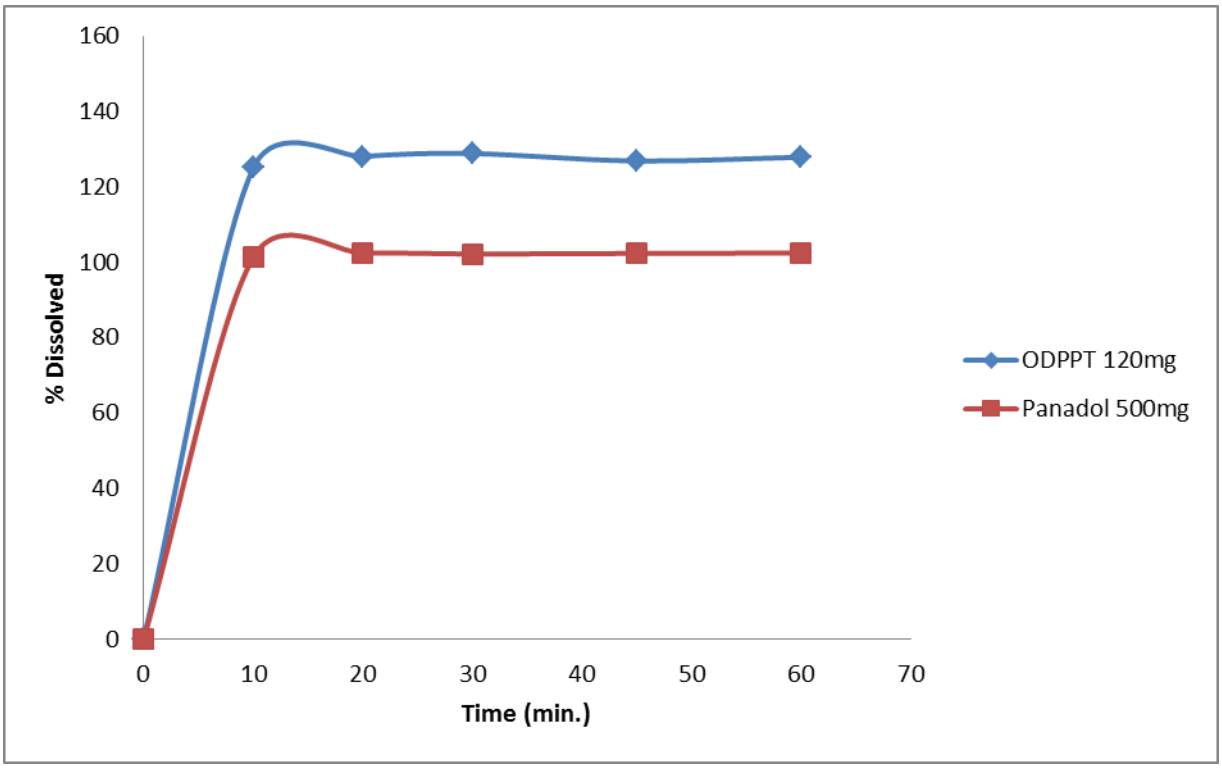

Figure 15: Dissolution profiles at pH 1.2 hydrochloric acid

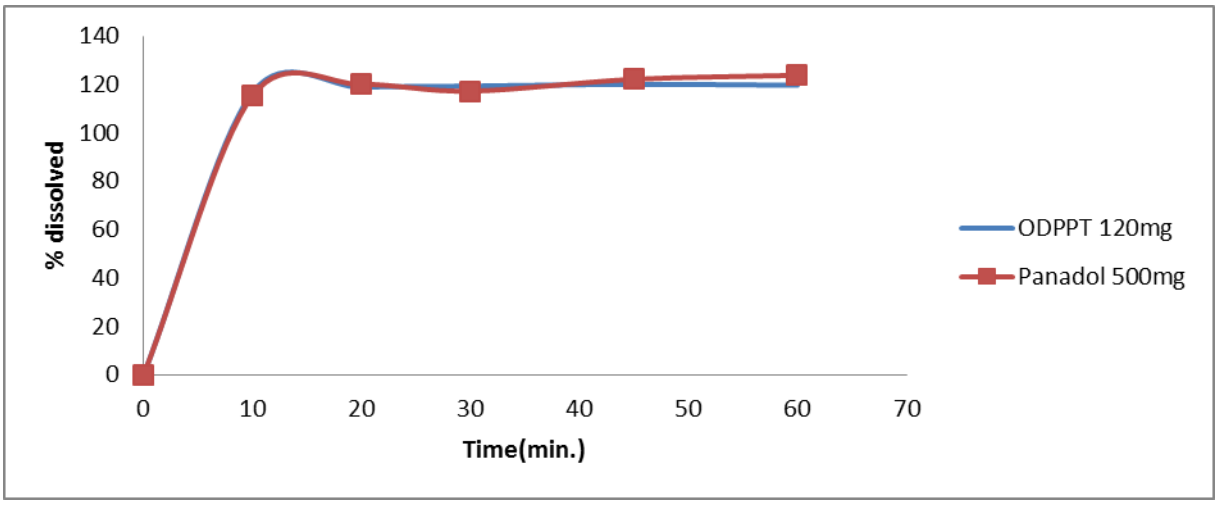

Figure 16: Dissolution profiles at pH 4.5 phosphate buffer

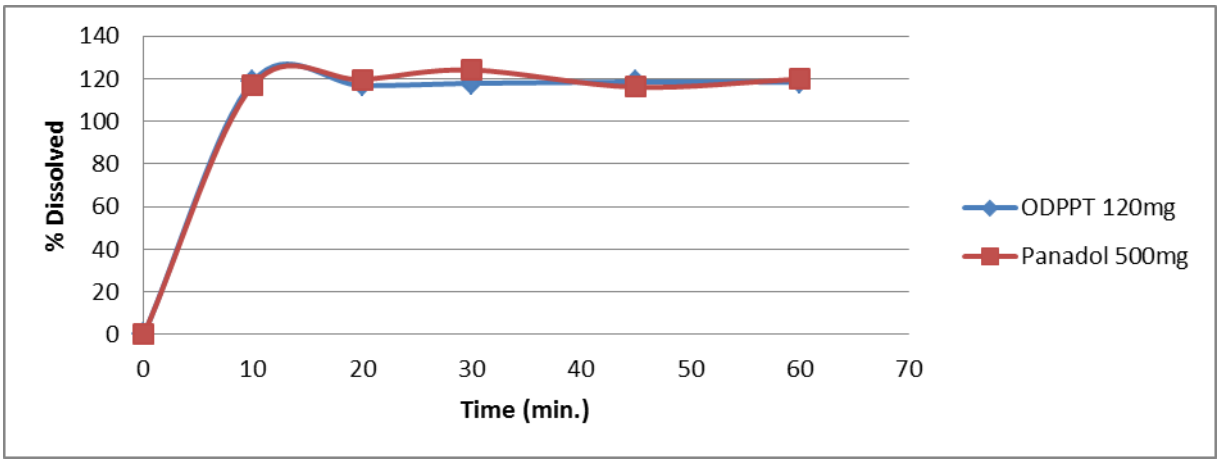

Figure 17: Dissolution profiles at pH 6.5 phosphate buffer

Table 33: Summary of comparative dissolution results

condition	f 1	f 2
pH 1.2	24.66	29.9
pH 4.5	1.67	79.4
pH 6.5	2.47	72.4

At PH 4.5 and 6.8 f1 values were very close to 0 and f2 values were very close to 100 (Table 33**).** Thus the two products were similar at these conditions. At PH 1.2, f1 value was much greater than 0 and f2 value was much less than 100. In this condition, the dissolution was high for oro-dispersible paediatric paracetamol tablets 120mg. We can thus conclude that this formulation was superior in terms of dissolution to the comparator (innovator conventional product) product in terms of dissolution as is expected for oro-dispersible tablets. However, as said above, in a regulatory perspective or under the existing practice, it does not mean that the two products are different.

3.3 Limitations

Experiments involved were done successfully except for the following limitations;-

- Mainly linear effects were addressed.
- The Size of tablet was limited by availability of appropriate punch size.
- Taste, process parameters and solvent for granulation was not optimized as it was not within the scope of this dissertation research.
- Direct compression formulations were based on available direct compression materials (starch 1500 and Avicel PH 102).Other excipients with better flow properties than these (eg. spray dried lactose, anhydrous lactose and granulated lactose) were not available.
- Achieving constant compression force was a challenge due to defective compression force measuring device. Thus, the models may be affected by differences in compression force. Example, hardness is a function of compression force and nature of active ingredient and excipients employed.
- Time was also a limiting factor.

3.4 Conclusion and recommendations

A formulation of oro-dispersible paediatric paracetamol tablet 120mg has been developed and characterized. This signifies that it is possible for local pharmaceutical manufacturers to develop medicines tailored for paediatrics.

Therefore, policy makers should set policy which will change the perspective of local pharmaceutical industries so that they strive to work on WHO recommendations with regard to paediatric formulations. These medicines will benefit paediatrics in terms of ease of use and safety but also minimize the use of resources like transportation cost, storage space and wastage due to stability issues.

Annex I: Dissolution data for ODPPT 120mg and Panadol 500mg at pH 1.2, 4.5 and 6.8

ODPPT 120mg pH 1.2 HCL

	1	2	3	4	5	6	Avg.	Max.	Min.	RSD
10 min.	118.04	139.49	122.7	121.77	123.1	124.94	125.01	139.49	118.04	5.96
20 min.	124.94	124.2	121.59	151.42	124.94	122.33	128.24	151.42	121.59	8.92
30 min.	132.4	124.38	125.13	123.45	131.1	136.5	128.83	136.5	123.45	4.10
45 min.	131.28	124.01	125.87	128.3	124.38	127.37	126.87	131.28	124.01	2.15
60 min.	127.74	126.81	130.54	126.81	126.25	129.04	127.87	130.54	126.25	1.28

Panadol 500mg pH 1.2 HCL

	1	2	3	4	5	6	Avg.	Max.	Min.	RSD
10 min.	98.09	102	101.26	99.58	104.62	102.19	101.29	104.62	98.09	2.23
20 min.	101.63	103.31	100.33	100.33	105.36	103.68	102.44	105.36	100.33	1.97
30 min.	101.45	101.26	102.94	101.82	102.38	103.31	102.19	103.31	101.26	0.81
45 min.	102.75	101.63	103.5	99.95	101.82	104.24	102.32	104.24	99.95	1.49
60 min.	102.19	102.38	102.94	102	102.94	102.19	102.44	102.94	102	0.40

ODPPT 120mg pH 4.5 Phosphate buffer

	1	2	3	4	5	6	Avg.	Max.	Min.	RSD
10 min.	113.38	115.24	117.3	114.87	121.21	117.86	116.64	121.21	113.38	2.38
20 min.	118.04	118.23	118.97	118.04	119.53	120.28	118.85	120.28	118.04	0.77
30 min.	118.41	119.16	119.35	117.67	121.96	119.53	119.35	121.96	117.67	1.22
45 min.	119.35	120.84	121.03	116.55	122.14	120.47	120.06	122.14	116.55	1.62
60 min.	118.79	119.35	117.67	119.16	121.96	121.03	119.66	121.96	117.67	1.31

Panadol 500mg pH 4.5 Phosphate buffer

	1	2	3	4	5	6	Avg.	Max.	Min.	RSD
10 min.	103.68	113.57	109.84	106.11	117.86	141.91	115.50	141.91	103.68	12.04
20 min.	117.48	123.64	112.07	118.6	120.65	127.37	119.97	127.37	112.07	4.40
30 min.	121.77	113.75	115.99	118.6	115.43	118.04	117.26	121.77	113.75	2.41
45 min.	116.73	120.65	119.35	118.97	125.5	131.66	122.14	131.66	116.73	4.50
60 min.	129.6	117.86	112.45	121.96	128.3	132.59	123.79	132.59	112.45	6.24

ODPPT 120mg pH 6.8 Phosphate buffer

	1	2	3	4	5	6	Avg.	Max.	Min.	RSD
10 min.	113.75	140.23	112.82	115.8	114.5	115.8	118.82	140.23	112.8	8.88
20 min.	114.87	116.36	115.8	118.6	117.48	117.67	116.80	118.6	114.87	1.17
30 min.	115.99	117.3	115.99	118.23	118.6	120.84	117.83	120.84	115.99	1.56
45 min.	117.11	118.6	117.3	117.86	119.72	120.28	118.48	120.28	117.11	1.10
60 min.	117.86	118.41	117.3	119.91	118.41	118.6	118.42	119.91	117.3	0.74

Panadol 500mg pH 6.8 Phosphate buffer

	1	2	3	4	5	6	Avg.	Max.	Min.	RSD
10 min.	120.09	109.65	113.19	118.04	123.08	118.23	117.05	123.08	113.19	4.14
20 min.	127.74	117.3	118.79	117.11	114.5	122.33	119.63	127.74	117.11	3.95
30 min.	124.38	146.57	120.84	115.24	117.48	120.47	124.16	146.57	115.24	9.19
45 min.	116.74	118.6	115.8	113.19	122.14	110.02	116.08	122.14	110.02	3.63
60 min.	121.96	117.48	122.33	116.55	123.64	117.3	119.88	123.64	116.55	2.58

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