THE FORMULATION OF FUROSEMIDE DISPERSEABLE TABLETS FOR USE IN PEDIATRICS

BY

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A dissertation submitted in partial fulfillment of the requirements for the award of the degree of Master of Pharmacy in Industrial Pharmacy of the University of Nairobi.

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This dissertation contains my original work which has not been submitted to any university/institution for the award of a degree.

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DEDICATION

This work is dedicated to my family; you have taught me how to love, to persevere and to appreciate the most important things in life. My nephew Walcott and nieces Hadassah and Vuyanzi you have taught me that no matter how far I go or how high I climb, to you I am simply “Auntie”, one of the hats that give me the greatest joy.
ABBREVIATIONS AND ACRONYMS

WHO - World Health Organization
ADI - Acceptable Daily Intake
QTPP - Quality target product profile
TPP - Target product profile
CQA - Critical Quality Attributes
FDA - Food and Drug Administration
API - Active Pharmaceutical Ingredient
IST - Isothermal Stress testing
HPLC - High Pressure Liquid Chromatography
USP - United States Pharmacopeia
BP - British Pharmacopeia
RSD - Relative Standard Deviation
DEFINITION OF TERMS

Formulation: The systematic combination of excipients and active pharmaceutical ingredients to produce a drug product.

Active pharmaceutical ingredient: A substance that is incorporated into a drug product and is the one responsible for the pharmacological activity of the drug product.

Excipient: Inactive substances incorporated into a drug product.

Acceptable daily intake: An acceptable amount of a compound expressed on a body mass basis that is allowed for intake without causing harm to the body.

Freeze drying/ Lyophilisation: The process of dehydration whereby substances are dried under vacuum.

Hygroscopic substances: Substances that absorb moisture from the air.

Super disintegrants: Excipients added to tablet to facilitate very fast disintegration.
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ABSTRACT

Introduction: Furosemide is a loop diuretic used in the management of hypertension in both adults and children. Its use in Kenya is limited by lack of a registered pediatric formulation thus patients have been treated with extemporaneously prepared medicines, increasing the cost of treatment due to frequent trips to the pharmacy. Most companies avoid developing pediatric formulations since most of them are liquid dosage forms which present a challenge to the development scientist and also clinical trials involving children are governed by more stringent rules further hindering development. WHO has encouraged the development of solid dosage forms for use in pediatrics since this will ensure availability of pediatric medicines. Some regulatory bodies have also offered incentives to drug development companies to encourage launching of both pediatric and adult formulations at the same time. The objective of this study was therefore to formulate Furosemide dispersible tablets which can be used in pediatrics.

Materials and method: The materials used were of pharmaceutical grade obtained as a gift from the Laboratory and allied limited company. The lactose was granulated with starch at 10% concentration as a binder. Colloidal silicon dioxide was used as a glidant at 0.1%, talc and magnesium stearate were used as lubricants at 1% and 0.5% concentration respectively. The level of active ingredient was based on the dosing in pediatrics such that 4mg of the active ingredient was incorporated per tablet. To facilitate fast disintegration two superdisintegrants were added per formulation at 4% concentrations with each incorporated at 2%. The superdisintegrants used were cross carmellose, crospovidone and sodium starch glycollate. The tablets were then tested for quality as per the USP monographs for tablets.

Results and discussion: White tablets with an average weight of 500mg were obtained. The tablets croscarmellose with crospovidone and those with sodium starch glycollate with crospovidone were found to comply with the physical tests. They disintegrated in 10ml of water to give a white suspension and on assay contained between 90-110% Furosemide. They underwent dissolution to release at least 80% of the drug in 60minutes. These tablets were found to give the best formulation for Furosemide dispersible tablets for use in pediatrics.

Conclusion and recommendations
The Furosemide dispersible tablets were formulated successfully. The formulation can be further improved by adding flavouring and thickening.
1.0 INTRODUCTION

1.1 BACKGROUND

Liquid dosage forms have been the formulation of choice in pediatrics for a long time. This is because they are convenient to administer to children especially in comparison to solid dosage forms like tablets which may not be easily swallowed especially for children below preschool age. In a study carried out by Thomson et al(1) on the ability of preschool aged children between 2-6 years to swallow mini tablets, they found that the ability to swallow the mini tablets increased with age. However, as much as preschoolers are encouraged to swallow tablets there is still an age where liquid dosage forms are a necessity hence their place cannot be totally ruled out. The pediatric population ranges from neonates, toddlers, preschoolers to adolescents and the younger children in this population will still require liquid dosage forms.

Despite their usefulness, the liquid dosage forms have quite a number of challenges which include need for taste masking, reduced stability and bulkiness (1). This makes it extra challenging for the formulation scientist to come up with child friendly liquid formulations (2). Lack of pediatric formulations forces healthcare providers to use some medicines off license to treat children. For these patients the drug ends up being prepared extemporaneously by the pharmacist to facilitate ease of use in children (3). There is therefore a need to come up with formulations that can overcome the challenges of both liquids and solid oral dosage forms in pediatrics. This means a formulation that can remain stable and at the same time be easily administered to children of all ages without interfering with the formulations’ integrity.

WHO has stressed the importance of using solid dosage forms in the pediatric population to help curb some of the challenges encountered with the liquid dosage forms (4).

Some of the solid formulations that have been used in children include: dispersible tablets, multiparticulates, mini tablets, orally disintegrating tablets, chewable tablets and chewing gums, oral wafers, and special formulations like gummy bears and lollipops (5).
1.2 PROBLEM STATEMENT

Furosemide is a diuretic agent used in the management of hypertension and edema. It majorly exerts its activity on the loop of Henle hence the name loop diuretic. Furosemide has been used both in the pediatric and adult population although in the pediatric population it has been used off license. Currently in Kenya, Furosemide is only available as tablets since there is no oral liquid formulation or any other pediatric friendly formulation that is currently registered by the Pharmacy and Poisons Board of Kenya (6). The children who have this drug prescribed for them have to have the dose approximated by splitting the tablets or for the ones who can afford it they get it extemporaneously prepared in some of the hospitals. However, due to a problem with stability the patients have to keep coming back for a refill since only a small amount can be prepared at time to cover for the period when it is stable. The trips back and forth from the hospital increase the cost of the treatment and in addition to this; the extemporaneously prepared drug is much more expensive compared to the tablets themselves.

This study is aimed at formulating Furosemide dispersible oral tablets that can be comfortably used in children hence enhance convenience where pediatrics are concerned. Tablets are continually being favored over liquid dosage forms since they have been found to be more advantageous. In the informal expert meeting in 2008 in Geneva, WHO recommended the formulation of more pediatric solid dosage forms. The advantages listed for the solid dosage forms over the liquid dosage forms were based on their stability, dosing and administration (4).

In this study if the formulation is successful it will serve to;

- Increase ease and convenience of administration
- Reduce the cost of production since tablets are cheaper to produce,
- Ensure stability since solid dosage forms have better stability than liquids,
- Reduce bulk since the liquid dosage forms are bulkier than the solid dosage forms
- Increase commercial viability since tablets can be produced in bulk
1.3 OBJECTIVES

1.3.1 GENERAL OBJECTIVE
To formulate Furosemide into tablets that can be dispersed in water to facilitate use in pediatrics.

1.3.2 SPECIFIC OBJECTIVES
- To come up with a target product profile for Furosemide dispersible tablets.
- To carry out pre-formulation studies on Furosemide
- To carry out formulation optimization studies
- To carry out tabletting of Furosemide dispersible tablets
- To test the quality of the formulated Furosemide dispersible tablets

1.4 SIGNIFICANCE AND ANTICIPATED OUTCOME
The dispersible Furosemide tablets are expected to be formulated such that they can be dispersed in water to give a pleasant tasting liquid that can be conveniently taken orally by children. This will reduce the challenges experienced with pediatric patients especially when they have to be discharged from the hospital on medication.

1.5 DELIMITATIONS
A target product profile for Furosemide shall be set up
Compatibility of different excipients with Furosemide shall be determined to ensure the most compatible excipients are used.
Different formulations shall be made and used to determine the optimum formulae for making the Furosemide dispersible tablets.
The optimum formulae shall be used to make the Furosemide dispersible tablets which shall then be evaluated for quality.

1.6 LIMITATION
Long term stability of the formulated tablets will not be tested since this requires that they be stored for a period and their quality monitored over this period. This will not be done since the time within which the project is to be carried out will not give enough time for stability study to be done.
2.0 LITERATURE REVIEW

2.1 INTRODUCTION

Pharmaceutical formulations are formulations containing active pharmaceutical ingredients which are formulated in such a way that they facilitate convenient administration of a medication to patients. They can be solid dosage forms or liquid dosage forms depending on the target population. The solid dosage form represents the most convenient dosage form both to the patient and the formulation scientist. This is because it is generally less susceptible to degradation compared to the liquid dosage form. This stems from the fact that the commonest solvent or diluent used in formulation is water and since many drugs have ester and amide bonds they tend to undergo hydrolysis when in solution which results in the degradation of the compound (7). In addition, it is easier to mask the taste and smell of obnoxious drugs in solid dosage forms hence taste and smell is not a big challenge.

The WHO in the informal expert meeting in 2008 held in Geneva recommended the formulation of more pediatric solid dosage forms. They listed stability, dosing and administration as some of the advantages that made the solid dosage forms preferred to the liquid dosage forms(4). In this meeting requirements for pediatric dosage forms were also identified as follows:

- The frequency of administration must be low
- The impact on the life style must be very minimal
- The formulation should not contain toxic excipients
- It should not be bulky and should be easy to transport
- It should have stability in various climates
- It should not be expensive
- It should have commercial viability
- It should be easy and convenient to administer, whereby health professionals need not have to manipulate it further before administration.

The solid dosage forms were found to satisfy most of these requirements therefore the WHO recommended that more pediatric formulations be made in solid dosage forms(4).
2.2 MAIN REVIEW

2.2.1 PEDIATRIC SOLID DOSAGE FORMS

Pediatric solid dosage forms are dosage forms that can be comfortably and conveniently taken by children despite being in solid form. They have to be specially formulated to ensure safety and stability. Children due to the fact that they are still growing can be easily affected by different excipients used in formulations. The excipients used in these pediatric formulations have to be chosen with care to ensure that they are not harmful and will in no way interfere with the normal development and growth in children(5). Special care has to be taken when choosing a formulation and the excipients that will go with it. Other than the safety of excipients there is also the acceptable daily intake (ADI) for different excipients. This value gives the limit of excipients that is allowed for daily intake. These values are used to ensure that harmful levels are not exceeded.

The excipients used in any formulation will determine the kind of formulation that is prepared since different excipients play different roles in a formulation. Some of the solid dosage formulations that have been used in pediatrics include; multi particulates, mini tablets, orally disintegrating tablets, lyophilates, chewable tablets, chewing gums, oral wafers, gummy bears, lollipops and dispersible tablets(5).

**Multiparticulates**

This is a formulation that consists of small particles which could be granules or pellets of less than 2mm in diameter. Usually these are administered by sprinkling on food or given directly. The advantage with multi particulates is that it is possible to carry out taste masking of unpleasant tasting drugs and in addition to this, different drugs can be combined for administration since they will be in separate pellets. Artequin® from Mepha is one of the products that have been prepared using this formulation(5).
Orally disintegrating tablets
These are tablets that disintegrate in the mouth within 5-30sec without any need for water. They are especially suitable for patients with swallowing difficulties, however taste is a very important factor in this case(5).

Lyophilates
This is a formulation produced through the technique of freeze drying. The lyophilized drug once put in the mouth quickly disintegrates. However, due to the technology used to produce it, it tends to be hygroscopic and hence will require special packaging(5).

Chewable tablets
These are tablets that can be chewed before swallowing and can comfortably be taken without water. Taste is very important in their formulation since if the taste is unpleasant then adherence will be compromised. Singulair ® 4mg from Merck Sharp and Dohme is one of the formulations on the market that has been prepared using this technology(5).

Chewing gums
In this formulation the medicament is incorporated into a chewing gum. The advantage with this is it can be used both for local effect in the mouth and systemic effect. As the gum is chewed the medication is released. The gum itself should not be swallowed therefore this can only be used in children above six years. Taste is very important here since it has to be pleasant tasting otherwise adherence will be compromised(5).

Minitablets
These are tiny tablets of a diameter less than 3mm. They are easy to swallow and taste masking of unpleasant drugs can be achieved by coating. In a study carried out by Thomson et al(1), they found that preschool children could swallow the mini tablets however the ability to swallow increased with age form 2years and upwards. Therefore this is a formulation that can be exploited for this population. One challenge with this formulation however is that special technology is required to manufacture the mini tablets (5).

Oral wafers
These are thin films and strips of wafers in which medicament has been incorporated. Water is not required for their administration since they can be placed directly on the tongue where they disintegrate or dissolve to release the medicine within a few seconds. The wafer adheres to the mucosa and this is advantageous since it cannot be spat out(5).
Gummy bears and Lollipops
Here the active ingredient is incorporated into the lollipop or gummy bear and the children can suck it like a sweet. They are very attractive to children hence it is not hard to convince the children to take them. However being attractive makes them disadvantageous since children can mistake them for sweets and this can result in poisoning or overdose. They have to be stored securely from children(5).

Dispersible tablets
These are tablets that can be dispersed in water before administration and will disintegrate within 3min to form a suspension or a solution that is palatable. The advantage with this formulation is that it can be used by all ages from neonates to geriatrics since the tablets can be swallowed whole as well as dispersed in water. In addition to this, the production of this formulation requires no special equipment since the standard tabletting and packaging equipment and technology can be used. One of the formulations on the market where this technology has been used is the Coartem® dispersible tablets which can be used for children as small as 5kg and at the same time taken by adults(5).
To facilitate this fast disintegration the dispersible tablets have a super disintegrant incorporated into them, making their disintegration much faster than the disintegration of the other tablets.

2.2.2 PHARMACEUTICAL PRODUCT DEVELOPMENT
Pharmaceutical product development is the process of designing a quality product as well as outlining its manufacturing process such that the process can consistently produce a product that will consistently achieve its intended purpose. The information obtained during the development process is used to establish the specifications, the manufacturing controls and the design space for that product. Design space gives the range of parameters within which the manufacturing process can be carried out without affecting the quality of the product. When the design space is established any combination of parameters within it will give a product of desired quality(8).
The pharmaceutical development process ensures that the critical steps and critical process parameters to any manufacturing process are identified and consequently controlled to ensure quality. In this way the quality of the product is designed right from the start such that quality is built into the product. Testing is consequently carried out just to prove this quality.
When the critical aspects are identified and scientifically understood, their effects on the product outcome can also be controlled. Some of these aspects include: Characteristics of the drug substance, the excipients used, the container closure systems and the manufacturing processes. Product development can be very useful since when well documented the information obtained can be used for risk assessment during the manufacture of the product such that the effect of varying any aspect will be considered versus the risk to the quality of the product. In addition, this information can also be used as part of the information submitted during product registration(8).

The pharmaceutical product development involves several elements which include:

- The definition of the quality target product profile
- The identification of the critical quality attributes of the drug product
- Risk assessment
- Setting of the design space
- Setting of the control strategy
- Management of the product lifecycle with continual improvement(8)

**The definition of the quality target product profile**

A quality target product profile (QTPP) is a development tool that is prepared to summarize the development goals of a drug product. Each goal in the QTPP is correlated to a completed development activity. It is basically helping the formulator to start the formulation process with the end product in mind. In this way the main goals are achieved without major diversion from the main purpose. The components of a target product profile as per the FDA Guidance for Industry on the TPP include the following(9)

- Indications and usage
- Dosage and administration
- Dosage forms and strengths
- Contraindications
- Warnings and precautions
- Adverse drug reactions
- Drug interactions
• Use in special populations like nursing mothers, pediatrics, geriatrics, renal impairment
• Drug abuse and dependence
• Over dosage
• Description of the product
• Clinical pharmacology
• Non clinical toxicology such as carcinogenesis, mutagenesis, fertility impairment and animal toxicology
• Clinical studies
• Labeling
• References
• How supplied including storage and handling requirements
• Patient counseling information

The identification of the critical quality attributes (CQA) of the drug product
The critical quality attributes of the drug product are identified. In this case any characteristics of the API, excipients, intermediate material that will affect the quality of the product are studied and their effects are documented(9).

Risk assessment
Risk assessment is carried out such that the CQA of the drug product are linked to the material attributes and process parameters. Assessment of risk will look at process parameters, equipment parameters and the input material parameters and their potential risk on the quality of the product. The significant parameters are identified and then studied further to get a better understanding of them(9).

Setting up of the design space
The design space which is the range of parameters within which the manufacturing process can be carried out without affecting the quality of the product is determined by looking at the relationship between the CQA and the inputs. These inputs will include both the material characteristics and the process parameters. The effect of varying any parameter must be documented and any parameters that are not studied should also be documented to ensure that the design space is well defined (9).
Setting of the control strategy
Control is important to ensure consistency in the production of a quality product. From the information gained in the experiments and the effects of different parameters on the quality of the product, a control strategy is set up such that controls are put in place to ensure and maintain quality. The controls can be in terms of the input materials, the intermediates, the container closure systems and even the drug product itself. Unit operations can also be controlled to ensure quality. These controls are monitored through testing at regular intervals to verify quality (9).

Management of the product lifecycle with continual improvement
Here the product is continually monitored and as more information is gathered from the routine manufacture further improvement can be made to the drug product (9).

2.2.3 PREFORMULATION STUDIES

Preformulation is the process of characterization of the physicochemical properties of a drug substance during pharmaceutical product development. Preformulation allows for important information that relates to the stability of the API in different conditions to be gained which can be helpful in the formulation of the drug product. Information gained through these preformulation studies gives the basis for the formulation developed and it helps to ensure that the formulation produced is stable and easily produced en masse. Preformulation studies also help the formulation scientist to understand the characteristics important to the stability of a compound and relate them to the expected performance of the finished product.

Generally in preformulation there are important parameters that are studied and evaluated to understand the API. These include solubility, dissolution behavior, stability, partition coefficient, ionization constants, solid state properties such as polymorphism, water sorption, particle size, and shape (10).

Preformulation will also help to give information on the degradation process of the API hence the formulation scientist can think of ways to control the degradation.

The information gained from these studies can then be used in the selection of a drug candidate especially where an API has different polymorphic forms. The excipients that would best be used in the formulation can also be decided upon based on the information gained from the
preformulation studies. For instance, a drug that degrades in basic medium can be formulated using excipients that will ensure the presence of an acidic environment to prevent this and buffers would also be incorporated to ensure the pH is maintained on the lower end hence ensure stability. A moisture sensitive drug would be formulated to exclude moisture both in its formulation its manufacture and even its packaging. The container closure system and retest periods can also be decided based on the information from the preformulation studies. For a new drug candidate there is a lot that needs to be studied in the preformulation studies. In the case of a generic formula most of the information is available since most of the work has been done on the innovator product, hence the work is less tedious.

2.2.3.2 COMPATIBILITY STUDIES
For the preformulation studies involving a generic formulation the important things to note include the compatibility of the excipients with the API especially if new excipients, are being introduced in the formulation, which have not been used before.

When developing a generic product, the use of excipients that have been successfully used with the API to give stable formulations helps to reduce the time required to carry out preformulation compatibility studies. However the use of any new excipients with the API has to be justified through compatibility studies. This ensures that the new excipients will not be detrimental to the stability of the API in the formulation. Although excipients-excipients interactions are also important to consider, they are not as common as drug-excipients interactions, therefore preformulation studies will major on drug-excipients interactions.

Compatibility studies can be carried out in different ways with the most resource sparing being computational method. In this case the chemical compatibility is predicted using a comprehensive database containing the reactive functional groups of the drug and excipients. The compatibility is predicted based on the knowledge of the reactivity of the functional groups. This method cannot be used solely since it can be misleading(11).

Another approach to compatibility studies is the use of binary mixtures of the API and the excipients. This can be done with or without water where they are prepared as slurries or dry mixtures. The mixtures are then stored under stress conditions. This is known as isothermal stress testing (IST). After this, they are analyzed using a stability indicating method like HPLC. Incompatibility with the API is concluded if degradation of the API is shown.
2.2.3.3 PROCESS OPTIMIZATION

This is the stage in product development where the process parameters are monitored to check the effect of varying various parameters on the quality of the formulation. This is done to ensure that the process is developed to give the best results. Some of the parameters looked at are; effect of mixing time, type of equipment used and the quantity of some excipients. The effects of these parameters on the quality of the formulation are monitored and a report prepared to form part of the product development report.

2.2.4 TABLETS AND THE TABLETING PROCESS

A tablet is a compressed solid dosage form containing a single dose of one or more active ingredients produced by compressing uniform volumes of particles(12). They are usually intended for oral administration although their use is not limited to this. The oral tablets can be swallowed whole, chewed and swallowed, dissolved or dispersed in water before administration or even placed in the mouth under the tongue where absorption occurs. The mode of administration will be determined by the type of tablet.

Tablets can be grouped into several types which include; the chewable tablet, the sublingual tablet, the effervescent tablet, the buccal tablet, lozenges, dispersible tablet, sustained release tablet and delayed release tablet. The tablet type is majorly determined by the types of ingredients in the tablet and the manufacturing process it goes through. Depending on the API they can be administered for local activity in the mouth or for systemic activity(13).

Tablets have been favored as a dosage form because;

- The oral route is convenient and relatively safe for drug administration
- Compared to liquid dosage forms tablets have general advantages in terms of the chemical and physical stability of the dosage form
- The preparation procedure enables accurate dosing of the drug
- They are convenient to handle and can be prepared in a versatile way with respect to their use and the delivery of the drug
- They can be cheaply produced en mass with robust and quality controlled production procedures giving elegant preparations of consistent quality
- They are less bulky compared to liquid dosage forms or even bulk powders
Some of the disadvantages associated with tablets include:

- Low bioavailability of poorly water soluble or poorly absorbable drugs
- Local irritation and harm to the gastrointestinal mucosa
- They cannot be used in the very young and the very sick patients since they can lead to choking.

Tablet types are mainly determined by the tablet excipients used in the formulation of the tablet. Some of the commonly used tabletting excipients include:

**Diluents /filler**

Diluents are excipients that are used to give the formulation bulk or dilute it. This is especially so for formulations where the API is very potent such that the dose is minute hence cannot be formulated by itself. The diluent gives it bulk and facilitates tabletting.(13).

**Binders**

Binders are substances that impart cohesiveness to the tabletting mixture and facilitate the formation of a compact tablet (13).

**Lubricants**

These are substances added to the formulation to reduce friction between the tablet and the die walls hence facilitate smooth ejection of the tablet after compression(13).

**Ant adherents**

These prevent the sticking of the granulate to the die wall during the tabletting process(13).

**Glidants**

Glidants are excipients that allow the granulate to flow freely from the hopper to the die cavity hence facilitate uniform flow of the powder and consequently uniformity in the tablet weights(13).

**Disintegrants**

These are excipients that facilitate the breaking up of a tablet into its primary components such as powder or granules. Disintegrants can facilitate this through various modes of action like;

*Capillary activity:* In this case the disintegrants pull water into the pores of the tablet disrupting the physical bonds between particles in the tablet. The water drawn into the pores can also be absorbed by the disintegrant causing it to swell and further disrupting the physical bonds in the tablets leading to disintegration.
**Particle to particle repulsive forces:** Some disintegrants on contact with water acquire an electric charge which results in the disintegrant particles repelling each other hence breaking up the tablet.

**Deformation:** Some of the disintegrants get deformed on contact with water and this causes a disruption in the tablet structure causing disintegration.

**Release of gases:** Release of gases is majorly used in effervescent tablets whereby on contact with water there is a reaction that leads to gas production and as the gas escapes it breaks up the tablets. Usually citric acid and bicarbonate are used in this kind of tablet and in the presence of water they react to release carbondioxide gas which is responsible for the effervescence and breakage of the tablet.

**Enzymatic activity:** For enzymatic disintegration an enzymatic reaction is facilitated on contact with water. An enzyme that facilitates the breakdown of a binder in the formulation is incorporated during tabletting and on contact with water the binder is broken down interfering with the tablet bonds leading to disintegration(13).

Other excipients that also find use in tabletting include Adsorbents, Dissolution retardants, Dissolution enhancers, Wetting agents, Ant adherents, Buffers, Chelating agents, Antioxidants, Preservatives, Coloring agents, Flavoring agents and Coating agents

**Tabletting**

The tabletting process involves the compression of either powders or granules to form a compact tablet. Tabletting can be carried out through direct compression using dry powders or alternatively the powders can be first granulated to form granules after which the granules are tabletted. When granulation is done, the granules can either be generated through the process of wet granulation or dry granulation. In the case of dry granulation the granules are formed through the formation of a slug or through roller compaction. These compact rolls and slugs are then milled and screened to form granules. When wet granulation is carried out a liquid usually water is used to carry out wet massing after which the wet mass is forced through screens to form the granules which are then dried and sized.

Tabletting involves several steps which are generally determined by whether direct compression, dry granulation or wet granulation is being used. In wet granulation the steps involved are

- Weighing of the materials
• Sizing of the materials
• Blending of the materials
• Wet massing
• Wet screening
• Drying of the granules
• Dry screening of the dried granules
• Blending with the lubricant and the disintegrant
• Tablet compression
• Dedusting
• Coating (if required)
• Packaging of the tablets

Tabletting proper happens in two major steps
• Compression
• Consolidation

In compression, the bulk volume of the material is reduced through the elimination of void spaces and results in bringing the particles close and into contact with one another.
Consolidation brings the particles close together resulting in inter particle interactions hence increase in the mechanical strength of the tablet.

Quality testing
During the manufacture of any dosage form quality assurance is very important. This is because quality determines the safety and efficacy of the product. To ensure that quality is maintained different aspects of the product are monitored during production. Each product will come with specifications that are set during product development. For tablets in general there are some specifications that must be achieved as part of the requirements for quality.
Some of the general specifications for tablets include:
• The correct dose
• The elegant appearance with a consistent weight, size and general appearance
• Controlled and reproducible drug release profile
• Biocompatibility with no harmful excipients and microorganisms
• Mechanically strong enough to withstand fracture and erosion during handling
- Chemical physical and microbiological stability throughout the tablets lifetime
- Patient acceptability
- Safe packaging

These specifications are checked through some quality tests that are specified in the pharmacopoeia. These are;

- Tablet weight uniformity
- Tablet content uniformity
- Friability test
- Disintegration test
- Dissolution test

**Tablet weight uniformity**
This test is used to check if the tablets fall within the same narrow range of weight and is usually an early indication of content uniformity issues. This is because if there is a large variation in weight even the content will be affected.

The test is done by randomly selecting 20 tablets then getting their average weight after which the individual weights of the tablets are also obtained and compared to the average weight. For the tablets to pass no more than 2 of the tablets should deviate in weight from the average weight by; more than 10% in case of tablets weighing less than 80gm, or no more than 7.5% for those between 80-250gm and no more than 5% for those of average weights greater than 250gm(14).

**Tablet content uniformity**
Here a suitable analytical method for the API is chosen after which 10 tablets are picked randomly then individually analyzed for the content of the active ingredient. The tablets are considered to have passed the test if all the 10 values fall within the range of 85-115% of the average tablet dose(14).

**Friability test**
This is a test used to check for the ability of the tablet to withstand stresses due to handling and transportation. This test is carried out using a friability tester. The tablets are counted dedusted and weighed, and then they are placed in the friability tester which is then set to rotate at 100
revolutions in 4 minutes. The tablets are then dedusted and reweighed. They are said to have passed the test if the percentage weight loss is less than 1%(12).

**Disintegration test**
Disintegration is the breakdown of a tablet into its primary tablet components which could be either the granules or the powder. Disintegration ensures that the surface area is increased to facilitate dissolution. This test is therefore useful in checking if the tablet is capable of breaking down once it is swallowed since if it does not break down then the release of the API will be hindered.
The test is carried out in a disintegration tester and here 6 tablets are picked at random and individually placed in a tube in the tester. The tubes are immersed in a water bath maintained at 37°C. The machine is then set to start. The tubes are raised and lowered 28-32 times per minute. The tablets are observed and they are said to pass the test if all the tablets will have completely disintegrated within the specified time for each type of tablet. For instance for dispersible tablets, they should disintegrate within 3 minutes and for the uncoated tablet within 15 minutes(14).

**Dissolution testing**
This is a test that is used to check if the tablet is capable of releasing the active drug into solution once swallowed. This is important because only the drug in solution is capable of crossing the biological membranes for absorption.
This test is carried out using a dissolution testing machine which could have either paddles or baskets. The baskets would be used for those dosage forms that tend to float hence the baskets would ensure the product is submerged throughout the test period.
The dissolution machine has beakers filled with 900ml of buffer set at 37°C. 6 tablets are picked at random and individually placed in the beakers and the machine is started. Samples are withdrawn at prescribed intervals usually, 45 minutes and the volume of withdrawn liquid is replaced with an equal amount of buffer.
The amount of API in the sample is determined using a suitable method and the tablets are said to have passed if by 45 minutes more than 70% of the API has dissolved(14).
2.2.4 EXCIPIENT SAFETY IN PEDIATRICS

The pediatric population is unique compared to the rest of the population when it comes to formulation development. This is because they are still growing and developing and in addition to that their organ function may not be fully developed. Due to this, care has to be taken in the choice of compounds used in their formulations to ensure that none will interfere with the growth and development. The substances should also be adequately cleared from the body as part of the safety measures to prevent build up. For most medications especially the potent ones, majority of the formulation is made up of excipients. These excipients will play different roles in the formulation such as ensuring stability, increasing bioavailability of the API and also ensure ease of dosing. Since they are seen to not exert any pharmacological effect, excipients have been loosely termed as inert although they can have effects on the body. Like all chemicals they have a potential for toxicity. Care therefore has to be taken when choosing any excipients to be used in medicines and special care should be taken where pediatric medicines are concerned.

When an excipient is proposed for use in a pharmaceutical formulation it is required that the manufacturer demonstrates safety to the FDA (15). The incident in 1937 where diethyleneglycol was used to solubilize sulfanilamide causing the deaths of 100 children made the congress pass a law to ensure safety testing is performed on products before marketing (15). For excipients that have been in use, safety issues can be addressed through; citation of regulatory status of the compound, marketing history, and existing non clinical and clinical databases. In cases where there are gaps in information on the safety of the excipients then studies on their safety must be done.

The safety of excipients is considered based on:

- The duration of use or exposure
- Levels of exposure, whether local or systemic
- The targeted patient population such as geriatrics and pediatrics
- Known effects of other compounds in the same class as the excipients in question

These aspects are used in the risk benefit assessment of excipients (15)

For the formulation of Furosemide dispersible tablets the excipients proposed for use are starch, crospovidone, croscarmellose, sodium starch glycollate, lactose, talc, magnesium stearate, colloidal silica and sugar. These have been used in various marketed pediatric
dosage forms before and thus are considered safe for use in a pediatric pharmaceutical formulation.

The only issue that could arise would be in children with lactose intolerance who could react to the lactose in the formulation.

2.2.5 PREVIOUS WORK ON DISPERSEIBLE TABLETS

Among the work that has been done on dispersible tablets, includes the work by Kuchekar et al (16) on the formulation of Noflorxacin dispersible tablets using natural substances as disintegrants. In the study natural gums were used and found to work effectively. The disintegrants were Isphagula husk, *Cassia tora* and *Cassis nodosa*.

Aceclofenac dispersible tablets have also been formulated. This work was done by Someshwara(17) and superdisintegrants were used to facilitate disintegration. The compounds used were croscarmellose, crospovidone and sodium starch glycollate and the effect of the different superdisintegrants at different concentrations in the formulations were observed and compared.

Coartem dispersible tablets have also been formulated and marketed for use in pediatrics for malaria treatment. This has been done by Novartis. In these tablets the superdisintegrants crospovidone and croscarmellose sodium have been used.

With the WHO recommendation to encourage solid dosage forms in pediatric medicines, dispersible tablets are gaining more ground in pediatric use. It is hoped that Furosemide will be counted among the formulations that can be conveniently dispensed to pediatrics without worrying about convenience of dosing or stability.
3.0 METHODOLOGY

3.1 STUDY DESIGN
This was an experimental study.

3.2 STUDY LOCATION
The study was carried out in the laboratory at the School of Pharmacy, University of Nairobi in the departments of Pharmaceutics and Pharmacy Practice and Pharmaceutical Chemistry.
The raw materials were obtained as a gift from Laboratory and Allied Limited Company.
The materials were pharmaceutical grade raw materials.

3.3 MATERIALS AND EQUIPMENT

3.3.1 RAW MATERIALS
The raw materials used in the formulation are listed in table 1.

Table1: Table of raw materials

<table>
<thead>
<tr>
<th>Material</th>
<th>Quantity(gm)</th>
<th>Quantity in (mg) per 500mg tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Furosemide</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>2 Lactose</td>
<td>500</td>
<td>418</td>
</tr>
<tr>
<td>3 Maize starch</td>
<td>500</td>
<td>50</td>
</tr>
<tr>
<td>4 Talc</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>5 Magnesium stearate</td>
<td>30</td>
<td>2.5</td>
</tr>
<tr>
<td>6 Colloidal silicon dioxide</td>
<td>30</td>
<td>0.5</td>
</tr>
<tr>
<td>7 Sodium starch glycollate</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>8 Croscarmellose</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>9 Crospovidone</td>
<td>50</td>
<td>10</td>
</tr>
</tbody>
</table>

Each of the formulations had a combination of two super disintegrants.
3.3.2 EQUIPMENT
The equipment used during the formulation of the Furosemide dispersible tablets included.
Sifter
Tabletting machine - Erweka single punch automatic tabletting machine
Weighing balance - Shimadzu
Friability tester - Erweka
Electronic tablet hardness tester – Schleuniger
Dissolution testing machine type 2
HPLC machine – Prominence auto sampler, Sil-20AHT-from Japan
Vernier calliper

3.4 EXPERIMENTAL SECTION

3.4.1 TARGET PRODUCT PROFILE
The target product profile was set as shown in table 2 below.

Table 2: Table of Target Product Profile

<table>
<thead>
<tr>
<th>QUALITY ATTRIBUTE</th>
<th>TARGET</th>
<th>CRITICALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Tablet</td>
<td></td>
</tr>
<tr>
<td>Potency</td>
<td>4mg</td>
<td>Critical</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Immediate release tablet</td>
<td>Critical</td>
</tr>
<tr>
<td>Appearance</td>
<td>Elegant tablet consistent in appearance</td>
<td>Critical</td>
</tr>
<tr>
<td>Identity</td>
<td>Positive for Furosemide</td>
<td>Critical</td>
</tr>
<tr>
<td>Assay</td>
<td>90-110%</td>
<td>Critical</td>
</tr>
<tr>
<td>Weight uniformity</td>
<td>Meets USP standards</td>
<td>Critical</td>
</tr>
<tr>
<td>Content uniformity</td>
<td>Meets USP standards</td>
<td>Critical</td>
</tr>
<tr>
<td>Disintegration</td>
<td>Not more than 3min</td>
<td>Critical</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Not less than 80% released within 60minutes</td>
<td>Critical</td>
</tr>
</tbody>
</table>
3.4.2 PREFORMULATION STUDIES

The characterization of the API was not carried out since this has already been carried out as Furosemide is a product already on the market as both tablets and injection. It has been characterized as follows

*Chemical name*
4-chloro-N-Furfuryl-5-Sulphamoylanthranilic acid

*Pharmacological class*
Loop diuretic

*Solubility*
Aqueous solubility at room temperature has been found to be 0.0825mg/ml and this solubility increases with increase in pH

*Polymorphism*
Furosemide has been found to have 7 polymorphic forms although polymorphism has not been reported to affect bioavailability.

*pKa*
Furosemide has a pKa value of 3.8. It is weakly acidic.

*Partition coefficient*
The partition coefficient in n-octanol/ water has been reported as 2.29 (18).

3.4.3 COMPATIBILITY STUDIES

The excipients chosen for the development of this formulation have all been previously used in other oral Furosemide formulations on the market. Therefore the assumption made was that since these marketed formulations are stable, the excipients are compatible with the API (18). A compatibility study was therefore not necessary before formulation began.
3.4.4 FORMULATION

3.4.4.1 GRANULATION

The granulating process begun with the sieving of lactose to ensure that the material was of uniform size. Granulation of lactose was carried out using starch as a binder at 10%. The lactose was wet massed with starch paste after which the wet mass was screened to break the wet mass into wet granules. These granules were spread out onto a flat surface and allowed to air dry for 24 hours to give white dry granules as shown in picture 1.

The dried granules were then screened and sized to obtain a size of between +250 to 500. The sized granules were then lubricated with magnesium stearate at a concentration of 0.5% and Talc at 1%. Colloidal silicon was also added to the formulation as a glidant. These were then mixed to ensure a uniform mix.

The granules were then divided into 3 batches and to each batch a combination of two different super disintegrants were added whereby:

To batch 1
2% of sodium starch glycollate and 2% of crospovidone were added.
To batch 2
2% of sodium starch glycollate and 2% of croscarmellose were added.
To batch 3
2% of crospovidone and 2% of croscarmellose were added.

Each batch was mixed to ensure a uniform mix.

Plate 1: Picture of Sized granules
3.4.4.2 TABLETTING

The settings on the tabletting machine shown in picture 2 were adjusted to give tablets of the required quality. The tablets were checked for weight, hardness and friability to ensure the settings on the machine were right. Dummy tablets were then prepared from the granules. The dummy tablets were then weighed and an average tablet weight obtained. This weight was used as the desired tablet weight and used to calculate the quantity of the Active pharmaceutical ingredient (Furosemide) to be incorporated into each batch. The weight of the Furosemide to be incorporated into each batch was calculated based on the amount required per tablet.

The dose to be incorporated into each tablet was based on the dosing of furosemide in children which is 2mg/kg. Therefore 4mg per tablet was picked since this figure is divisible by 2 and if the tablet is scored it can even be given in smaller doses.

The required Furosemide was then weighed out and added to the mix through triturating to ensure a uniform mix ready for tabletting.

The three batches were then tabletted and then taken through quality testing to check for their compliance with quality standards.

Plate 2: Picture of the single punch tabletting machine
3.4.5 QUALITY TESTING

Uniformity of weights
20 tablets were picked at random and individually weighed as the tablet weights were recorded. The average weight of the tablets was then calculated. The percentage deviation from the average weight and from the expected weight by the tablets with the least and the most weight was calculated to check for compliance with the uniformity of weight test.

Tablet hardness
This test was carried out using the electronic tablet hardness tester shown in picture 3. One tablet was placed inside the machine at a time then the machine was set and the reading for the hardness was read in kilopascals (kPa).

Plate 3: Picture of the electronic tablet hardness tester
**Friability**

20 tablets were randomly picked from each batch and dusted to remove any loose particles. These were weighed and the weight recorded after which they were placed in the friability tester, shown in picture 4, and the machine was then set to rotate for 100 revolutions. The tablets were then removed from the friability tester dusted and then re weighed and the weight recorded. The percentage weight loss was then calculated and the results used to check if the tablets passed the friability test.

**Plate 4: Picture of the friability tester**

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**Disintegration**

6 tablets were randomly picked and individually placed in 10ml of cold water. The time it took for disintegration of the tablet to occur was checked and recorded.
Dissolution testing
Dissolution testing was carried out as per the USP method using dissolution test apparatus type 2. But the analysis was done using HPLC instead of UV analysis. Phosphate buffer solution at pH 5.8 was used as the dissolution medium. The phosphate buffer was prepared by dissolving 1.19g of disodium hydrogen orthophosphate dehydrate and 8.25g of potassium dihydrogen orthophosphate in sufficient water to produce 1000ml. This solution was checked for pH and the pH adjusted with phosphoric acid to the required one.
6 tablets were then picked from each batch and individually placed in the dissolution apparatus each of which contained 900ml of the phosphate buffer at 37°C. The machine was then set to run at 50 rpm for 1 hour then samples were withdrawn for analysis. The samples were protected from light since Furosemide is sensitive to light.
For analysis the standard was prepared by first dissolving it using a diluting solution made from water: acetonitrile: Glacial acetic acid mixture in 70:30:1 proportions after which an aliquote was taken and diluted in the phosphate buffer of pH 5.8 to give a concentration equivalent to the concentration of one tablet in 900ml. The samples and standards were then analyzed by HPLC and the chromatograms compared to check the extent of the dissolution by the Furosemide dispersible tablets.
Assay
The assay was carried out according to the USP monograph on Furosemide tablets.
The standard preparation was prepared by accurately weighing USP Furosemide RS (Furosemide BP working standard number v/ws/fr 02/30, Batch number 0080710 manufacturing date 05/06/2012) and dissolving it in the diluting solution made from water: acetonitrile: Glacial acetic acid mixture in 70:30:1 proportions to give a solution with a concentration of 1.0mg/ml.
To make the assay preparation, 20 tablets were powdered then an amount equivalent to 25mg of the active ingredient was weighed from this powder and placed in a 25ml volumetric flask. 15ml of the diluting solution was added to this and sonicated for 10 minutes after which more diluting solution was added to volume and mixed. The preparation was filtered, discarding the first 10ml of the filtrate.
Equal volumes of the standard and assay preparation were separately injected into the chromatograph. The chromatograms were then recorded and the peak responses measured at
254nm. The quantity in mg of Furosemide in the portion of the tablets taken was calculated using the formula $25C \left( \frac{R_u}{R_s} \right)$

Where $C$ is the concentration in mg/ml of USP Furosemide RS in the standard preparation

$R_u$ is the peak response of the assay preparation

$R_s$ is the peak response of the standard preparation
4.0 RESULTS AND DISCUSSION

4.1 APPEARANCE

The tablets were smooth, shiny, circular and white in colour as shown in picture 5 with size ranging between 4.85mm to 5.05mm.

Tablets have to be taken through evaluation after production to ensure that they comply with the set standards. Most of these tests involve the use of machines and lab equipment, however before being taken through the barrage of tests one of the simple ways they are evaluated is through appearance. Appearance gives an initial indication of quality through simple observation. Usually the specifications for products include size, shape and colour. If the tablets do not conform to the standards of appearance then there may be no need to take them through laboratory testing. However if they comply with the set standards for appearance then they can be taken through the rest of the tests.

Apart from the shape and size, colour is also a good indicator of quality especially after storage. Some drugs degrade over time resulting in by products that may be coloured. Therefore colour may be used as an indicator of degradation. In addition to this poor storage can cause tablets to acquire spots due to growth of mould. These aspects can be checked through simple observation.

Consumer acceptability is very important when products are placed on the market. The main way to achieve this is to have appearance standards that are consistent over time.

Using the above criteria the tablets were found to be acceptable and consistent in their appearance therefore they were taken through the other quality tests for tablets.

**Plate 5: Picture of the formulated tablets**
4.2 UNIFORMITY OF WEIGHTS

The results from the uniformity of weights test were as shown in table 2

Table 3: Table of results for uniformity of weights test

<table>
<thead>
<tr>
<th>UNIFORMITY OF WEIGHTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BATCH NUMBER</td>
</tr>
<tr>
<td>Number of tablets</td>
</tr>
<tr>
<td>Average weight (mg)</td>
</tr>
<tr>
<td>STD Deviation</td>
</tr>
<tr>
<td>RSD</td>
</tr>
<tr>
<td>% deviation of tablet with min weight</td>
</tr>
<tr>
<td>%deviation of tablet with max weight</td>
</tr>
<tr>
<td>Projected tablet weight (mg)</td>
</tr>
<tr>
<td>% deviation from projected weight</td>
</tr>
<tr>
<td>Calculated API content</td>
</tr>
</tbody>
</table>

The British pharmacopoeia specifies that in the test for uniformity of weights the tablets are said to have passed the test for uniformity of weights if, for tablets of average weights greater than 250mg no more than 2 tablets weighed are deviating in weight from the average weight by more than 5%.

The test done on the three batches showed that batch number 1 and 3 complied with the test while batch number 2 did not comply with the test since the tablet with the least weight deviated from the average weight by more than 5%. This test is important since it is indicative of the uniformity of content in the tablet. From the projected weight of 500mg, the calculated API content in the batches was found to be acceptable however batch number 2 was on the borderline for the lower limit. Tablet weight is a good indicator of content since if the weight of the tablet reduces then the content will also reduce and if it increases the content will also increase. When looking at the content uniformity tablet weights can give an early indication of content. With a uniform mix it is a much easier indicator to use for setting the machine for tabletting. Therefore the batches 1 and 3 were found to comply with the test for the uniformity of weights test.
4.3 TABLET HARDNESS

Table 4: Table of results for tablet hardness test

<table>
<thead>
<tr>
<th>TABLET HARDNESS</th>
<th>BATCH NUMBER</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tablets</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Average hardness</td>
<td>6.3</td>
<td>5.9</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>STD Deviation</td>
<td>2.2</td>
<td>0.639</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>RSD</td>
<td>34.92</td>
<td>10.83</td>
<td>20.31</td>
<td></td>
</tr>
</tbody>
</table>

Tablet hardness is a test indicative of the tablet’s strength and its resistance to mechanical stress. The harder the tablet is, the better its resistance to friability. However for ordinary tablets, tablet hardness can interfere with their disintegration since if they are too hard then they can fail to disintegrate within the required time thus compromise the release of the active ingredient hence affect the performance of the tablet. Therefore a compromise has to be reached so as to give tablets that are resistant enough to mechanical stress but not too hard to affect disintegration. This test is not covered in the compendia however limits for it are usually set in house for each product. This test is an early indication of possible issues with friability therefore when working on the settings of the machine this can be used in the initial setting to obtain required hardness that can strike a balance between mechanical strength and ease of disintegration.

The tablet hardness for the formulation was set at between 5-11 kPa. The three batches were all found to comply with the specifications set.

4.4 TABLET FRIABILITY

Table 5: Table of results for tablet friability test

<table>
<thead>
<tr>
<th>TABLET FRIABILITY</th>
<th>BATCH NUMBER</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>% FRIABILITY</td>
<td>0.98</td>
<td>2.6</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>
Friability is a test that is indicative of the tablets resistance to mechanical stress. Tablets once produced have to be transported to the end user. They go through warehouses, distributors, wholesalers and retailers. In between all these handlers, the tablets undergo transportation. It is important that the integrity of the tablets is maintained throughout up to the end user. To withstand the stresses involved in transportation the tablet have to have adequate mechanical strength. The BP specifies that for the test for friability the tablets are said to have passed if the loss in weight is less than 1%. The 3 batches were tested for friability and batches 1 and 3 were found to comply with the requirements whereas batch number 2 did not comply. This implies that batch 1 and 3 have the mechanical strength to withstand the stresses throughout the shelf life and thus these can be considered for release if it was a commercial batch.

4.5 DISINTEGRATION

Table 6: Table of results for disintegration test

<table>
<thead>
<tr>
<th>Batch</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average disintegration time (seconds)</td>
<td>62</td>
<td>137</td>
<td>69</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>4.082</td>
<td>14.024</td>
<td>10.206</td>
</tr>
<tr>
<td>RSD</td>
<td>6.58</td>
<td>10.24</td>
<td>14.79</td>
</tr>
</tbody>
</table>

Dispersible tablets are special tablets that are supposed to disintegrate when placed in water at room temperature to give a palatable suspension that can be taken directly by children. The BP specifies that when placed in water the dispersible tablet should disintegrate within 3 minutes to give a suspension. The three batches formulated were tested and found to all disperse within 3 minutes. The tablets dispersed in 10ml of water to give a white suspension as shown in pictures 6 and 7.

Plate 6: Pictures of disintegrating tablets

A (20 seconds)  B (60 seconds)
Plate 7: Picture of suspension of dispersible tablet after disintegration

4.6 ASSAY

Table 7: Table of results for assay test

<table>
<thead>
<tr>
<th>ASSAY RESULTS</th>
<th>BATCH 1</th>
<th>BATCH 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVERAGE %CONTENT</td>
<td>100.99</td>
<td>108.81</td>
</tr>
<tr>
<td>STD DEVIATION</td>
<td>0.21656078</td>
<td>0.998649</td>
</tr>
<tr>
<td>RSD</td>
<td>0.21</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Assay testing for any formulated product is important to help establish the quantity of the API in the formulated product. During the formulation of any product there is a quantity of API that is targeted to be contained in the product, which is known as the label claim. It is expected that the quantity of the API on the label claim can achieve a certain pharmacological action. Therefore after formulation the quantity of the API is established through assay. The Furosemide tablets were assayed using HPLC and chromatograms as shown in figure 1 obtained. The results as shown in table 7 showed that the tablets complied with the specifications for assay of the content.
of Furosemide in the dispersible tablets. The USP specifies that the tablets should not contain less than 90% and not more than 110% of the stated label claim. Therefore from the results it shows that the tablets formulated complied with the specification meaning they contain the stated amount.

Tablets can fail to comply with test in which case they would not be cleared for release and use. Failure to comply with the assay in the case of a uniform mix could be due to a lower tablet weight than intended or a higher one than intended in which case the content ends up being either lower or higher respectively. Failure to comply can also be due to inadequate mixing or over mixing resulting in a non uniform mix. This means some tablets will end up having more API content than others. For some molecules which may readily undergo degradation during processing may show less API content if not processed in the required conditions to prevent this degradation. To ensure that tablets produced comply with the assay specifications it is important that all this precautions are taken to consideration to give a product that will have the amount of API on the label claim when assayed.
Figure 1: Figure of chromatograms obtained from the assay of Furosemide dispersible tablets

Furosemide (4 mg) Dispersible Tablets
Assay and Dissolution Report

<table>
<thead>
<tr>
<th>Title</th>
<th>Sample Name</th>
<th>Sample ID</th>
<th>Ret. Time</th>
<th>Area</th>
<th>Theoretical Plateing Factor (IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C:\LabSolutions\HPLC\FUROSEMIDE DISP TABLETS</td>
<td>Batch 1 A</td>
<td>6.428</td>
<td>38067746</td>
<td>41122831</td>
<td>1.277</td>
</tr>
<tr>
<td>C:\LabSolutions\HPLC\FUROSEMIDE DISP TABLETS</td>
<td>Batch 1 A</td>
<td>6.773</td>
<td>40721761</td>
<td>4133773</td>
<td>1.292</td>
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<tr>
<td>C:\LabSolutions\HPLC\FUROSEMIDE DISP TABLETS</td>
<td>Batch 1 A</td>
<td>5.859</td>
<td>34787471</td>
<td>3977119</td>
<td>1.218</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.353</td>
<td>37858993</td>
<td>4074574</td>
</tr>
<tr>
<td>%RSD</td>
<td></td>
<td></td>
<td>7.269</td>
<td>7.852</td>
<td>2.087</td>
</tr>
</tbody>
</table>
Figure 2: Figure of chromatograms obtained from the dissolution of Furosemide dispersible tablets.

**FUROSEMIDE (4 mg) DISPERSIBLE TABLETS**
**ASSAY AND DISSOLUTION REPORT**

12Sep2014

![Chromatograms](image)

Summary (Compound)

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Sample ID</th>
<th>Ret. Time</th>
<th>Area</th>
<th>Theoretical Pct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch 1 tablet 1</td>
<td>5.759</td>
<td>165645</td>
<td>6058.200</td>
<td></td>
</tr>
<tr>
<td>Batch 1 tablet 1</td>
<td>5.682</td>
<td>168096</td>
<td>6460.998</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>5.720</td>
<td>166871</td>
<td>6259.599</td>
<td></td>
</tr>
<tr>
<td>%RSD</td>
<td>0.959</td>
<td>1.038</td>
<td>4.550</td>
<td></td>
</tr>
</tbody>
</table>

**Title** | **Sample Name** | **Sample ID** | **Ret. Time** | **Area** | **Theoretical Pct** |
---|----------------|----------------|---------------|---------|---------------------|
| C:\LabSolutions\HPLC\FUROSEMIDE DISP TABLETS | Batch 1 tablet 1 | 5.759 | 165645 | 6058.200 |
| C:\LabSolutions\HPLC\FUROSEMIDE DISP TABLETS | Batch 1 tablet 1 | 5.682 | 168096 | 6460.998 |
| Average | 5.720 | 166871 | 6259.599 |
| %RSD | 0.959 | 1.038 | 4.550 |

**Ing Factor (1G)**
1.207
1.278
1.242
4.053

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4.7 DISSOLUTION

<table>
<thead>
<tr>
<th>DISSOLUTION RESULTS</th>
<th>BATCH 1</th>
<th>BATCH 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVERAGE DISSOLUTION (%)</td>
<td>95%</td>
<td>82%</td>
</tr>
<tr>
<td>STD DEVIATION</td>
<td>15.3</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Dissolution testing was carried out on the batches 1 and 3. This was because batch 2 had not passed all the physical tests. This was carried out to ensure that the formulated tablets were capable of releasing the API as expected once ingested. The chromatograms obtained from the dissolution test were as shown in figure 2 and these were used to calculate the amount of API released. The USP specifies that not less than 80% of the labeled amount of Furosemide should be released after 60 minutes. The test results as shown in table 8 showed that at least 80% of the drug was released after 60 minutes therefore the tablets complied with the test for dissolution meaning that when ingested they can release the drug hence achieve required activity. The batch number one showed a better profile than batch number 3.

5.0 CONCLUSION

The formulation process was successful. The Furosemide dispersible tablets for use in pediatrics were formulated, checked for quality and found to be satisfactory. The set target profile was met since the criteria set in table 2 were achieved.

It was shown that the combination of sodium starch glycollate and crospovidone as well as that of croscarmellose and crospovidone can be used successfully in the formulation to give a good product. This product however did not undergo stability testing to check for its stability over prolonged storage times and varied storage conditions due to time constraints. Before any product is approved for marketing it has to be shown that the formulation is stable throughout its intended shelf life. Hence there is more work that should be done on the formulation before it can be considered for use. In addition to this, being a pediatric product flavoring can be considered for addition to the product to make it more palatable. Since the materials are not bad
tasting sweetening may not be necessary. With a few improvements this formulation can be suitable for consumption hence commercial use. This would give a formulation convenient for manufacture, storage, transportation and administration hence fit perfectly into the recommendations given by WHO for pediatric formulations.


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