FORMULATION AND EVALUATION OF A CO-PROCESSED EXCIPIENT FOR DIRECT COMPRESSION OF GLIMEPIRIDE TABLETS.

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BEING A PROJECT SUBMITTED TO THE DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY,

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THE FACULTY OF PHARMACY

UNIVERSITY OF BENIN

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CERTIFICATION

This is to certify that this study was carried out by CLARA ONOJIASUN IKEBOH (PHA1808382) in the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin-city, Edo State.

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DEDICATION

To God Almighty, for His uncommon wisdom and guidance during the course of this project. And also to my parents, guardians and siblings.

ACKNOWLEDGEMENT

I acknowledge God's grace over my life. Without His uncommon help and empowerment, I would not have been where I am today. My gratitude to God is by no means boundless.

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I love you all.

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ABSTRACT

Co-processed excipients have been developed to enhance the performance of poorly soluble drugs like Glimepiride.

Varying ratios of the API (Glimepiride) was mixed with the co-processed excipients and from the results, there was improved flowability, compressibility and disintegration properties, optimizing tablet formulation and bioavailability.

Studies have demonstrated reduced lubricant sensitivity and enhanced drug release profiles. Co-processed excipients offer improved dilution potential, mechanical strength and faster manufacturing processes making co-procession a valuable advancement in pharmaceutical technology.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Tablets

Tablets are solid dosage preparations intended for oral administration and consists of a mixture of Active Pharmaceutical Ingredient(s) and a variety of excipients, compressed into a convenient and uniform shape with a design to release the active ingredients at a concise and controlled rate in order to produce a therapeutic effect.

“Tablets are solid dosage forms containing medicinal substances with or without suitable diluents and are obtained by compressing uniform volumes of particles.” (Aulton M.E). Tablets were introduced by Thomas Brockedon in 1843 and glyceryl trinitrate tablets were the first to appear in the British Pharmacopoeia in 1885

Tablets are made up of Active Pharmaceutical Ingredients (API) and excipients which are usually in powdered form, then pressed and compacted from the powder into a solid dosage form.

Excipients used in pharmaceutical preparations include;

Binders---, gelatin, hydroxypropyl methylcellulose (HPMC), Polyvinylpyrrolidone (PVP), microcrystalline cellulose, tragacanth

Disintegrants--- sodium starch glycolate, crospovidone, croscarmellose sodium, microcrystalline cellulose

Fillers--- lactose, starch, silica, talc, polyethylene glycol

glidants and lubricants (flow aids)--- magnesium stearate, zinc stearate, polysorbate 80, glyceryl palmitostearate

coating agents--- carnauba wax, sucrose, cellulose acetate phthalate (CAP)

colourants--- tartrazine yellow, iron oxide, beetroot red, caramel, erythrosine

flavourants--- peppermints, raspberry, saccharin

preservatives--- benzyl alcohol, parabens, silica gel, calcium silicate

sweeteners--- Natural sweeteners (sucrose, fructose, glucose, honey, maple syrup), Artificial sweeteners (aspartame, sucralose, acesulfame potassium, neotame), Sugar substitutes (maltitol, xylitol, mannitol, sorbitol), and other sweeteners such as glycerin and monk fruit sweeteners.

Excipients are added to tablets preparations in order to aid the tabletting process, disintegrants to make the tablets release the active ingredients while in the digestive tract, fillers to add bulk to the preparation.

According to a research by Debora Futoro on percentage of pharmaceutical forms of medicines prescribed research gate Compact tablets are the most prescribed dosage forms with about 62.5% of all prescriptions being in tablet dosage form.

During the process of tablet manufacturing, a deliberate groove known as a scoreline is inserted on the surface and it serves to enable easy breaking as well as improve dosing flexibility. A tablet on which a scoreline has been inserted is said to be “Scored”. Tablets may be identified by sizes or shapes. Tablets size ranges from 3mm-25mm in diameter and shapes may range from round to oval to caplets. The shape of a tablet is based on the content of medicinal substances and its intended route of administration. The shape is essential to aid swallowing, to identify the specific brand, to enhance tablet stability and to meet specific packaging requirements.

1.1.1CLASSES AND TYPES OF TABLETS

Tablets can be classified on the basis of:

A. Route of administration

i. Oral tablets
ii. Sublingual tablets
iii. Buccal tablets
iv. Implantable tablets
v. Vaginal pessaries
vi. Rectal tablets

B. Manufacturing design

i. Sugar coated tablets

ii. Film coated tablets

iii. Chewable tablets

iv. Effervescent tablets

v. Compressed tablets

vi. Multiple compressed tablets

C. Drug delivery system

i. Sustained release tablets

ii. Immediate release

iii. Delayed release tablets

1.1.1.1 TABLETS USED IN ORAL CAVITY

Tablets are formulated in different ways and are intended for different purposes.

I. Lozenges: these include cough and antacid lozenges such as menthol and calcium carbonate respectively

II. Buccal tablets: they are tablets designed to be placed under the cheek where they disintegrate and release their medicinal contents. These includes fentanyl and testosterone tablets

III. Orally disintegrating tablets (ODTs): such as antihistamines containing diphenhydramine and analgesics containing ibuprofen

IV. Chewable tablets: vitamin C tablets and antacids are examples

V. Dental cone: these are tablets shaped like a cone and designed for oral action such as breath freshening effects. Examples are chlorhexidine cones, benzocaine cones

VI. Sublingual tablets: They are placed under the tongues where they dissolve into systemic circulation and produce effects. Examples of sublingual tablets are nitroglycerin and vitB12 tablets.

1.1.1.2 TABLETS FOR NON-ORAL ROUTES

I. Vaginal tablets/ pessaries

II. Rectal tablets

III. Implantables

1.1.1.3 TABLETS FOR ORAL INGESTION

I. Delayed release tablets

II. Film-coated tablets

III. Compressed tablets

1.1.1.4USED TO PREPARE SOLUTIONS/SUSPENSIONS

I. Effervescent tablets

II. Dispersible tablets

1.1.2 QUALITIES OF TABLET DOSAGE FORM

The most important quality of a tablet is dose uniformity. Other are:

a) Tablets should be hard enough to withstand pressure such that they don't break in a container; however friable enough to disintegrate in the stomach
b) The tablet must release the active ingredient in a consistent manner (this is evaluated by dissolution test method)
c) In appearance, tablet must be elegant and free from capping, lamination, physical defects, microbial molds and cracks
d) Tablets should be physically stable and meet its proposed shelf life
e) Tablets should be strong enough to withstand mechanical stress of handling and packaging
f) Tablets should be portable in order to facilitate handling and transportation

1.1.3 ADVANTAGES OF TABLETS AS A DOSAGE FORM

a. tablets afford convenience and simplicity in design

b. uniformity of dose which leads to dosing flexibility especially if the tablet is scored

c. it can be easily identified through colour coating, embossed marking, printing and specific shapes

d. during the formulation process, the tablets may be conferred certain properties such as sustained release tablets

e. its stability to physical, chemical and microbiological elements increases its range of use

f. the dose can be adjusted into equals, as in scored tablets

g. large scale production per batch is possible and comes with a low manufacturing cost compared to other dosage forms

h. in terms of packaging, tablets are easy to package because they are light and occupies a low volume

i. tablets have a wide range of application; from oral, to sublingual, to vaginal and rectal administration

j. the side effects of tablets can be minimized by the control of the drug release

1.1.4 DISADVANTAGES OF TABLETS AS A DOSAGE FORM

i. The bioavailabilty of tablets poses a hindrance to its widespread use
ii. Drugs such as aminopeptides and insulin are degraded by stomach acid hence unsuitable for oral administration
iii. Drugs with slow dissolution profile and high GIT absorbance may not be formulated as tablets
iv. Amorphous Active ingredients and/or excipients are incompressible
v. Certain health conditions render a patient unable to swallow as in coma, vomiting, dysphagia
vi. The first pass metabolism deactivates some drugs when transported from the GIT to the hepatic site
vii. Except with the emergence of ODTs, tablets have a high onset of action. This makes it unsuitable for emergency conditions
viii. The cost of production is significantly enhanced because drugs with bitter taste/odour may be coated or encapsulated

1.1.5 TABLET INGREDIENT

Every tablet is made up of two key components viz:

A. Active pharmaceutical ingredients

B. Excipients, also known as additives. These excipients may further be classified into:

   i. Excipients that enhances compression characteristics such as binders, lubricants, diluents

   ii. Excipients that imparts additional desirable characteristics to the end-product tablet. These include sweeteners, colourants, flavourants.

1.1.5.1TABLET EXCIPIENTS

These are pharmacologically inert substances deliberately incorporated into tablet formulations to facilitate the manufacturing processes, enhance the stability and bioavailability of the active pharmaceutical ingredients (API), as well as optimize the tablets physical and organoleptic properties, thereby ensuring the delivery of a precise and efficacious dose of medication to the consumer.

Excipients are substances other than the drug or prodrug which are included into pharmaceutical preparations in order to enhance product stability, bioavailability or patient acceptability or to aid product manufacture and/or identification. This excipient must be non-toxic, non-sensitizing and non-irritating and should be compatible with all the other ingredients in the formulation. Excipients are indispensable in the process of drug formulation; it facilitates the flowability of active substances, confers non-sticky properties

on the overall preparation, aids in *invitro* prevention of particle aggregation or structure denaturation over the expected shelf life.

Below are examples of excipients used in pharmaceutics

1.1.5.2BINDERS

Binders are adhesives used to bind diluents and drugs together in a cohesive mix during granulation and compaction of solid oral dosage They are pharmaceutical excipients that impart cohesion and mechanical strength to tablet formulations by forming non-covalent bonds between particles which aids the transformation of powder blends into compact and uniform tablets with optimal physical and mechanical properties.

Binders are characterized based on the manufacturing process intended viz:

i. Dry tablet binders: they are intended for direct compression and must exhibit cohesive and adhesive forces such that when compacted, the particles agglomerate. Examples are cellulose, methyl cellulose
ii. Wet tablet binders are hydrophilic and soluble in water. They are first dissolved in water to form a wet mass and then granulated. Some examples of these binders are gelatin, cellulose, polyvinylpyrrolidone

However, dry or wet binders are incorporated into the preparation in a concentration not exceeding 2-10%

Binders used in pharmaceutical preparations include:

i. Gums like tragacanth gum and acacia gum
ii. Starch paste
iii. Poluvinylpyrrolidone (PVP)

iv. Sugars such as molasses, lactose, glucose, sorbitol and sucrose

v. Extract from irish moss

vi. Sodium alginate

vii. Cellulose and its derivatives such as Hydroxypropylmethylcellulose, carboxylmethylcellulose, methylcellulose, hydroxypropylcellulose

viii. Gelatin

ix. Waxes, alcohol and water may also be considered to be bind

1.1.5.4 DISINTEGRANTS

Disintegrants are excipients that promotes the breaking of tablets/capsules into particles in order for the active ingredient to be rapidly released thereby facilitating dissolution and absorption of the drug.

Based on the mechanism of disintegration, disintegrants are classified into:

a. Disintegrants that absorb water and swell. This swelling creates pressure in the tablets and causes breakage thereby releasing its content

b. Disintegrants that reduces interfacial tension between the tablet and the dissolution medium thereby making breaking of the tablets easier

Examples of disintegrants are:

i. Starch and starch derivatives such as primogel and explotab (1-8%)

ii. Cellulose and cellulose derivatives such as sodiumcarboxymethylcellulose

iii. PVP (polyvinylpyrrolidone), crosslinked polymers like crospovidone

iv. Alginate

v. Microcrystalline cellulose

vi. Clays-veegum HV, bentonite 10% (in coloured tablets only)

1.1.5.4 EMULSIFYING AGENTS

They are also called Emulsifiers or Emulgents and acts by facilitating the mixing and stabilization of two or more immiscible liquids such as oil and water. Emulsifying agents helps to stabilize blends, improve bioavailabilty and solubility. They constitute 0.05-15% by weight of the final formulation.

Emulsions include Natural emulsifiers (lecithin, gum Arabic, tragacanth), synthetic emulsifiers (sodium lauryl sulphate, polysorbate 80) and semi-synthetic emulsifiers (hydroxylated lecithin)

1.1.5.5 GLIDANTS AND LUBRICANTS

Glidants are excipients that enhance flow properties of powders, granules or tablets by facilitating the smooth and consistent movement through hoppers and dies. They are used for direct compression of tablets and in granulation process (before tabletting) to enhance flowability of the granules.

Glidants include but not limited to silica, talc, starch, calcium silicate, Cab-O-Sil, syloid, aerosol.

Lubricants are excipients incorporated into pharmaceutical preparations in order to reduce friction, prevent stickiness, improve flow and enhance tablet ejection. Examples of lubricants are magnesium stearate, sodium stearyl fumarate, glycerin, palmitostearate. Before choosing a lubricant, it is essential to consider compatibility factors, concentration and type suitability.

There are two known types of lubricants viz:

Hydrophilic lubricants: they are considered poor lubricants because they have no glidant or anti-adhesive properties

Hydrophobic lubricants: have glidant and anti-adherent properties. Hydrophobic lubricants are generally good lubricants and are effective even at concentrations.

1.1.5.6 FLAVOURANTS AND SWEETENING

Flavours are beautifully scented substances used to conceal unpleasant tasting active ingredients and to make the appearance appealing. The effects of flavouring translates to patients adherence to medication course. Flavourings may be natural or artificial flavours. In order to improve taste, the following may be considered:

Mint, anise or cherry to conceal bitter taste

Liquorice, peach or apricot in order to conceal salty taste

Liquorice or apricot to conceal sour taste

Vanilla to conceal an excessively sweet taste

Sweeteners are agents used to enhance and improve the taste of a drug product. Examples include:

Sugar and mannitol (for chewable tablets)

Aspartame, an artificial sweetener however unstable in the presence of moisture

Saccharine, an artificial sweetener which is 500x sweeter than sucrose.

1.1.5.7FILLERS

Tablet fillers which may also be called diluents or bulking agents are inactive substances added to a formulation in order to increase the bulk, dilute the API, improve flow and support compressibility. The presence of diluents ensures improved cohesion, direct compressibility and promotes flowability.

Usually, fillers are inert and do not alter the therapeutic efficacy of the API. However, they influence the physical and mechanical properties of a tablet which include its hardness, friability and disintegration time. Examples of fillers are:

i. Lactose-anhydrous and spray dried lactose
ii. Microcrystalline cellulose-Avicel (PH101 and PH 102)
iii. Dextrose
iv. Mannitol
v. Dibasic calcium phosphate hydrate
vi. Calcium sulphate dehydrate
vii. Hydrolysed starch-Emdex and cellutab
viii. Sorbitol
ix. Sucrose-sugar tab, Dipac, Nutab

An approved Filler for pharmaceutical use has the following characteristics:

1. It should be physically inactive
2. It must not alter the bioavailability of the drug
3. It must be non-toxic
4. It must be free from microbial contamination
5. It should be commercially available in acceptable grade
6. It should be physically and chemically stable by itself and when in combination with other drugs
7. An hygroscopic substance is unsuitable as a filler
8. Its compatibility and dilution capacity should be rated good

9. The most commonly used filler is lactose because it fills the above criteria and has a pleasant taste, in addition. However, lactose intolerance symptoms may arise from patients who are lactose intolerant. These symptoms are abdominal cramps, nausea, vomiting, diarrhoea, bloating.

1.1.5.8 COLOURANTS AND DYES

Colourants and dyes are excipients used in tablet formulation in order to harmonize the colour of a drug into a more appealing form, to identify the product, improve its elegance and overall enhance patience compliance.

Colouring agents must be tested, approved and certified by the FDA. The colouring agents may be added prior to or during compression processes. These colourants are of two types ---- FD & C and D & C dyes. Some examples of colouring agents are:

i. FD & C green 3—fast green
ii. FD& C yellow 5—tartrazine
iii. FD& C yellow 6—sunset yellow
iv. FD & C blue 1—brilliant blue
v. FD& C blue 2—indigo carmine
vi. D & C red 3—erythrosine
vii. D & C red 22—eosin Y

1.1.5.9 PRESERVATIVES

Excipients and additives used in pharmaceutical preparations to inhibit or prevent the proliferation of microorganisms – bacteria, yeast, mold. Preservatives are incorporated into drug formulations to conserve its safety, stability, efficacy and shelf-life.

Typical preservatives used in pharmaceutical formulations include:

i. The parabens (methyl paraben, propyl paraben)

ii. The amino acids--- cysteine and methionine

iii. Antioxidants – vitamin A, vitamin C, retinyl palmitate, selenium

iv. Citric acid and sodium citrate

1.1.5.10 COATINGS

Tablet coatings are additives which protects tablets ingredients from deterioration by moisture in the air, it also makes large or unpleasant tablets appealing and hence easier to swallow. Cellulose ether such as HPMC film coating free from sugar and allergens is used for coating. Shellac, corn protein zein, gelatin can also be used in coating.

1.1.5.11 VEHICLES

This applies mostly to liquid and gel formulation. A bulk excipient conveying the active ingredients is known as the vehicle.

1.2 METHOD OF TABLET PREPARATION

Tablet manufacturing is a complex multi-stage process during which the starting raw materials change their physical properties multiple times before the end stage product is achieved. Traditionally, tablets are made by granulation –a process of converting powders to granules. It imparts two primary requisites viz fluidity and compressibility.

In tablet preparation, the foremost step is MILLING & MIXING. Numerous unit processes are involved in tabletting processes such as blending, particle size reduction, granulation, drying, compressing and coating. Each of these processes are critical and influences bioavailability, content uniformity, stability.

The most critical essence of tablet formulation is to ensure content uniformity in relation to the API and excipient ratio. The content uniformity is achieved by the use of free flowing, relatively dry powder or granules and a particle of relatively uniform size.

Powders having a wide range of particle sizes will segregate during manufacturing process into their various particle densities. This can be handled by processing the powder into granules of similar sizes before compaction. Granulation also enhance the flow of such powders.

Powders which mix well with good flow properties can directly be compressed into tablets. Other powders are granulated either by wet or dry granulating methods.

1.2.1 DRY GRANULATION METHOD

This involves granulating powders into granules without incorporating a liquid medium because the product may be sensitive –to moisture and heat. Dry granulation involves densifying and compressing the primary powder particles aggregated under high pressure. A High-shear mixer granulator is used for this type of granulation.

1.2.2.1 ADVANTAGES OF DRY GRANULATION METHOD

1. Granules produced by this method is consistent with high quality
2. The tablets can be easily handled, stored or transported due to high bulk density
3. Flowability of the tablet is enhanced; unlike powders that break and cake. The tabletting is more efficient
4. This method gives room for control of particle sizes to meet precise product requirements
5. It saves time and energy and it affords a simpler and continuous process than wet granulation

1.2.2.1 LIMITATIONS OF DRY GRANULATION METHOD

1. Less yield is obtained due to the production of non-compacted powder with fines, because liquid binder was not used

2. tablets produced by this method shows low tensile strength and frail ability

1.2.2 WET GRANULATION METHOD

This is a granulation method in which granules are formed by the addition of a granulation liquid to a powder bed under the influence of an impeller. The system is then set into agitation along with the wetting of the components which results in the aggregation of the primary powder particles to produce wet granules.

The granulation fluid must be non-toxic & contain a volatile solvent which can be removed by drying. Such fluids include isopropyl alcohol, ethanol, water either alone or as a combination. The fluids mixed with the powders form bonds between powder particles and are strong, enough to bind them one to another.

When polyvinyl pyrrolidone (PVP) is used, it is dissolved in water or other suitable solvents and then added to the process. PVP forms a bond with the powders during the process while the water (or solvent) evaporates. When the solvent has evaporated, the powders form a densely held mass which is further subjected to milling. The process results in granules formation.

1.2.2.1 ADVANTAGES OF WET GRANULATION

1. This method is preferred by pharmaceutical industries because it improves flow and cohesion, reduces dust and chances of cross-contamination 2.it allows the handling of powder blends without loss of homogeneity.

3. Wet granulation reduces segregation of the powder components during processing and handling.

4. the dissolution of an insoluble drug can be enhanced by wet granulation

5. a lesser compression pressure is required for the tabletting process; thereby reducing the wear and tear of the machine

1.2.2.2 DISADVANTAGES OF WET GRANULATION

The disadvantages of wet granulation is itemuized below:

1. Water is commonly used as a solvent in this method and therefore poses the materials to hydrolysis
2. The chances of contamination is increased compared to direct compression method (Bandelin 1989)
3. There are several steps involved in this method and requires temperature and humidity control which may be cumbersome
4. Decrease in yield with each of the several stages

5. Drying of the granules accelerates hydrolysis and disintegration. Drying increases the cost of production
6. Control and validation of the steps is difficult because of the complexities in each step
7. Incompatibility between formulation components is aggravated with wet granulation

1.3 COMMON PROBLEMS IN TABLET PRODUCTION

During tabletting, certain problems may arise as a result of improper machine adjustment, tooling or granulation malady.

Major problems during tablet production include:

1.3.1 CAPPING AND LAMINATION

Capping is an occurrence whereby the upper part of a tablet separates from the main body of the tablet. Capping is as a result of expansion of trapped air in the compressed tablet following the release of the compression pressure, or due to the presence of large amount of fines during granulation, or the insufficiency of space between the punch and die wall.

Lamination is the separation of a tablet into two or more layers usually due to weak bonding force between the granules or particles. Lamination of a tablet occurs due to weak compression forces, excessive moisture content, use of poor quality excipients, inadequate granulation.

To overcome the problem of Capping and Lamination;

1. Binder concentration should be increased
    i. Use an optimized granulation procedure
    ii. Change, increase or decrease lubricant concentration

1.3.2 STICKING, PICKING & FILMING

When poorly lubricated or improperly dried granules are compressed, they stick to the punch faces. This leads to the production of tablets with dull, scratched or pitted faces.

Picking is a special form of sticking whereby granules stick to the punch faces and increases at each press revolution thereby causing a hole on the tablet surface.

To overcome sticking, picking and filming:

i. Properly dry and lubricate the granules
ii. Polish the punch faces
iii. Adding of an adsorbent such as aerosol, silica gel

1.3.3 MOTTLING

Mottling refers to unequal distribution of colour shades on a tablet with different spots in a supposedly uniform surface. Mottling in a coloured drug occurs when the colour of the excipients differ from the colour of the degradation product. Improper mixing of dye or colourants is a chief cause of mottling.

To overcome mottling:

Mix the colourants/dyes properly and reduce the particle size to prevent segregation

Also, endeavour to use appropriate colourants

1.3.4 BINDING TO THE DIE

A tablet is said to be binding to the die when it is resistant towards the ejection by the die accompanied by characteristic squeaking sound leading to the production of rough and forcefully scored tablets.

Binding to the die may be due to insufficient lubrication, wet/moist granules, blemished die.

To overcome binding to the die:

Increase the concentration of lubricant/ use a better alternative

Compress at optimum humidity and temperature

Reduce the compression pressure

1.3.5 FORMATION OF SOFT TABLETS

This is an occurrence whereby tablets produced have a hardness of less than 5kpa. Soft tablets are products of low compression pressure, wet/moist granules, high concentration of lubricants.

This can be handled by applying optimum compression pressure, properly dry granules and the use of lubricants in acceptable proportion.

1.3.6 FLUCTUATION OF API CONCENTRATION

Due to uneven distribution of the active ingredient in the powder blend, the API concentration may not be even in consecutive tablets. However, this can be overcome by proper mixture of the API with other powders, possibly by the use of ball mill or V-blenders for industrial scale production

1.3.7 TABLET WEIGHT VARIATION

Inconsistency in powder or granules density, large range of particle size are major determinants of the variations in tablet weight.

1.4 TESTS CARRIED OUT ON TABLETS

1.4.1 TABLET THICKNESS TEST

This is an unofficial test. It is measured using a vernier caliper/ micrometer screw gauge. The thickness can range from 2.5mm to 6.5mm (±5%)

1.4.2 TABLET HARDNESS TEST

Hardness is the amount of load needed to crush a tablet when on its edges. This test is done to evaluate the structural integrity and yield point of a tablet under various conditions such as handling, storage, transportation before it gets to the final consumer.

Tablets should be mechanically strong to withstand stress during handling but not too hard to hinder timely drug release (COOPER 1972). The hardness of a tablet is influenced by the binder used, compression force applied and the granulation method employed. The hardness of a tablet can be determined by the following:

i. Monsanto or Stokes hardness tester
ii. Erweka tester
iii. Pfizer hardness tester
iv. Strong cob hardness tester

1.4.3 TABLET WEIGHT

This is the volumetric fill of the die cavity after compression. It is determines using a weighing balance to weigh 20 tablets individually and calculate the average weight. Not more than two tablets should differ from the average by double the weight of the acceptable percentage

1.4.4 TABLET DISINTEGRATION TEST

This is the time taken by a tablet to breakup in a liquid medium and release its active ingredients. A high disintegration time is indicative of a high compressibility index and a low disintegration time is indicative of soft tablets/with poor binding characteristics. If a tablet batch disintegrates over a wide range of time, it implies batch inconsistency and non-uniformity.

Fluids like water, simulated gastric/intestinal juice can serve as liquid medium in a disintegration test. The British Pharmacopoeia specifies 15 minutes and 1 hour maximum for uncoated and coated tablets respectively.

1.5 OVERVIEW OF CO-PROCESSING OF EXCIPIENTS

Co-processing of excipients refers to the process whereby two or more compatible excipients are combined in order to give rise to a novel excipient with hybrid characteristics. Co-processing does not alter the chemical characteristics of the novel excipients.

According to Gohel and Jogani 2005; Gohel *et al,* 2005) Co-processing refers to the process of combining two or more established excipients by an appropriate process. According to International Pharmaceutical Excipient Council (IPEC), Co-processed excipient is “any mixture of compendial or non-compendial excipients that has been designed to be physically coprocessed in a way which results in functional performance attributes when used in a drug application and which are not seen if the excipients are combined using simple mixing”.

Excipients are co-processed in order to:

1. Mask undesired properties of individual materials
2. Improve or retain specific properties of individuals in order to enhance performance

3. Obtain a product with increased value compared to its ratio and functionality/price
4. Co-processing of excipients produces a synergistic effect by exhibiting improved functions in compaction, enhanced flow properties

Raw materials can be classified as Elastic, plastic and brittle on the basis of their response to applied force. Although, raw materials cannot absolutely be categorised in a singular class because pharmaceutical excipients demonstrate the properties of the three with one property being dominant. A combination of plastic and brittle material is required for an optimum tabletting process and this can efficiently be achieved by co-processing.

1.5.1 ADVANTAGES OF CO-PROCESSING EXCIPIENTS

Co-processed excipients retain their individual chemical properties, therefore, there are no regulatory concern

1. They display less weight variation than simple mixture of the parent materials hence it is suitable for use for direct compression
2. The pressure-hardness relationship of filler-binder co-processed excipients when plotted and compared with simple physical mixtures showed a marked improvement in the compressibility profile (Sherwood and Berker,1998; Schmidt and Rubensdorfer,1994; Belda and Mielckm 1996)
3. Mouth feel of chewable tablets produced with co-processed excipients have been reportedly plausible than when produced with the constituent excipients
4. They possess better physico-mechanical properties than the constituent excipients. E.g Cellactose possesses flow properties better than a mixture of lactose and cellulose of the same particle size distribution

5. Co-processed excipients have enhanced dilution potential, than a physical mixture of the excipients
6. When co-processed, the excipients can be used both for wet granulation and direct compression unlike some of the individual components
7. they are generally referred to as “safe” because their chemical property is not affected during co-processing
8. this method saves cost as the excipients required for the formulation of a tablet is fewer.

1.5.2 LIMITATIONS OF CO-PROCESSED EXCIPIENTS

1. The process is not recognized by the official books such as Pharmacopoeia

2. fixed ratio of the constituent excipients whereas in the development of new formulation, a fixed ratio will not be optimum for the API and dose

1.5.3 EXAMPLES OF COMMERCIALLY AVAILABLE CO-PROCESSED EXCIPIENTS

Table 1.1

EXCIPENTS	COMPOSITION	PROPERTIES
Pharmatose DCL 40®	Lactitol and b-lactose	Has a low lubricant sensitivity and a high compressibility index
Formaxx®	Calcium carbonate, sorbitol	Improved particle size distribution
Cellactose®	Microcrystalline cellulose, lactose	Improved compressibility, better tableting at low cost
Starlac®	Lactose, corn starch	Direct compressibility, better disintegration, good glow
Avicel CE-15®	Guar gum and microcrystalline cellulose	Less chalkiness, creamier mouth-feel, enhanced palatability
ludipress®	PVP, Crospovidone, lactose	Less hygroscopicity, good flow properties

Adapted from (Bansal and baker 2008)

1.5.4 AIM/OBJECTIVES OF THE STUDY

The aim of this study was to:

i. formulate and evaluate co-processed excipient for direct compression of Glimepiride

The objectives were to:

i. formulate the co-processed excipients using cassava starch, sodium starch glycolate and HPMC
ii. characterize the novel excipients and assess its flow properties
iii. formulate Glimepiride tablets with the novel excipients for direct compression.

CHAPTER TWO

2.O MATERIALS AND METHODS

2.1 MATERIALS

Sodium starch glycolate (ROQUETTE, France), cassava starch (GOODWAY, Nigeria) and HPMC (ADDAGE, India) were obtained from Edo Pharmaceuticals. and tested physically and chemically in order to validate the label ingredient claim.

2.2 PREPARATION OF CO-PROCESSED EXCIPIENT

3g of hydroxypropylmethycellulose (HPMC) was wetted with sufficient amount of water and stirred for 2 minutes. Then, 4g of sodium starch glycolate and 3g of cassava starch were weighed using an electronic weighing balance (OHAUS Corporation, Pine brook NJ USA) and homogenized for about 15 minutes using a homogenizer (QSONICA Ultrasonic). The mixture was subsequently poured on a tray and dried in a pre-heated hot air oven (Morgan & Grundy Ltd) at 75ºc for 8 hours. The resulting mass was sieved with a SETHI sieve of 1.6mm and dried again for one hour. After the second drying, the resulting granules were characterized and then tabletted using a Manesty type 3 (Manesty Machines UK). Other materials used included T70 UV/VIS Spectrophotometer (PG Instruments Ltd England), Mosanto hardness tester, Erweka Friabilator. All reagents used were analytical grades and all glasswares were borosilicate.

2.3 CHARACTERIZATION OF NOVEL EXCIPIENTS

2.3.1 Determination of Bulk and Tapped density

Weighed 10g (W) of the novel excipient was measured into a clean 50ml measuring cylinder and the volume was recorded as V1. The measuring cylinder was subjected to tapping 100times on a hard table top and the tapped volume was recorded as V2.

The experiment was done in triplicates and the Bulk and Tapped densities were calculated for, as the ratio of mass to volume.

2.3.2 DETERMINATION OF ANGLE OF REPOSE

Weighed 8g of the co-processed novel excipient was poured into a clean glass funnel mounted on a retort stand at a perpendicular height of 7cm from the table surface, the funnel was blocked with a cotton wool. The cotton wool was removed and the height of the powdered heap of H (cm) was formed. The diameter of the powdered heap circumference was determined and the radius was calculated from it.

2.3.3 FLOW RATE

The amount of a substance which flows through an orifice of a funnel per unit time (g/sec) is the flow rate. Under the influence of gravity, 10g of the co-processed excipient was allowed to flow through a funnel of 0.85cm diameter and the time taken for the flow was recorded.

2.3.4 CARR'S COMPRESSIBILITY INDEX

This measures the compressibility of the powder as a percentage of the volume lost during compression.

Using the Bulk density, V1 and Tapped density, V2 value. The Carr's compressibility index was calculated for:

Carr's index= $\left(\frac{Bulk\ density - tapped\ density}{bulk\ density}\right) x\ 100$ _____ (1)

2.3.5 HAUSNER'S RATIO

This is the ratio of tapped to bulk density of a powder. It is an index of the flowability of a powder.

$Hausner's\ ratio = \frac{Tapped\ density}{bulk\ density}$ _____ (2)

2.4 BATCH PRODUCTION OF TABLETS

The Glimepiride tablets were prepared via Direct Compression using the ratio below for API, Co-processed excipient and filler respectively:

Table 2.2: Formula used for preparation of tablets using novel excipients

	BATCHES				
Ingredients (mg)	A	B	C	D	E

API (Glimepiride)	20	20	25	30	35
Novel excipient	150	200	250	300	350
Filler (lactose)	430	380	325	270	215

A total of five (5) batches were prepared containing the API (Glimepiride), co-processed excipients (cassava starch, sodium starch glycolate & HPMC) and filler (lactose) in the ratio given above using the Doubling-up method for mixing powders. Then, 600mg of the powder blend was individually weighed and transferred quantitatively into the die of the compressing machine at a compression force of 6-8 metric tonne.

2.4 TESTS CONDUCTED ON TABLETS

2.4.1 TABLET WEIGHT AND DIMENSION

The weight of each of the 40 tablets in a batch was measured using a weighing balance (OHAUS Corporation, pine book, USA).

The diameter/ thickness of five (5) tablets each were measured using a micrometer screw gauge and the average was calculated for.

2.4.2 TABLET CRUSHING STRENGTH TEST

A Monsanto hardness tester was used to determine the hardness of the tablets. The crushing strength of 5 tablets per batch were measured and recorded.

2.4.3 TABLET FRIABILITY TEST

Using a Roche friabilator, 10 tablets from batch A were previously weighed as W1a and placed in a friabilator revolving at 25 rpm (revolution per minute) for 100 revolutions. After which the tablets were dusted and weighed again as W2a. This was repeated for all other batches and recorded.

2.4.4 TABLET DISINTEGRATION TEST

Using a MK IV, Manesty machine UK disintegration tester, six tablets were introduced into the tablet compartment of the machine containing distilled water at a temperature of 37.0±0.5ºc.

The tablets were rotated upward and downward by the device and the time taken for all pieces of the tablet to pass through the machine mesh was recorded as the disintegration time.

This was repeated for all batches.

2.5 TABLET PRODUCTION STAGES

Drug → mix granulation→ granules → screen drying→ mixing → tablet blend→ tableting→ tablet

CHAPTER THREE

3.0 RESULTS AND DISCUSSION

3.1 RESULTS OF THE PHYSICAL PROPERTIES OF THE CO-PROCESSED NOVEL EXCIPIENTS

The physical properties of the different batches of co-processed excipients are given in the table below:

Table 3.1 Physical properties of co-processed HPMC, Cassava starch starch glycolate

PARAMETER	STANDARD	RESULT
Bulk density (g/ml)	>0.5 (excellent flow)	0.75
Tapped density (g/ml)	>0.86 (excellent flow)	0.86
Carr's compressibility index (%)	11-15 (good flow)	14.5
Hausner's ratio	1.12-1.18 (good flow)	1.15
Angle of repose (º)	31-35 (good flow)	32.70
Flow rate (g/sec)	>20 (excellent flow)	0.8

3.1.1 BULK AND TAPPED DENSITY

From the table above,the bulk density of the novel excipient was calculated to be 0.75. Kindly refer to method for the process description.

3.1.2 CARR'S INDEX

The Carr's compressibility index for the formulated novel excipient was 14.5% and according to Carr 1965, an index between 11-15 indicates a good flow.

3.1.3 HAUSNER'S RATIO

Frpm table 3.1 above, the Hausner's ratio of the formulated granules was determined to be 1.15 and is within the range for a "good" flow

3.1.4 ANGLE OF REPOSE

From table 3.1, the angle of repose was 32.7 degrees and depicts a good flow.

3.1.5 FLOW RATE

The granules under evaluation have an excellent flow rate. With a flow of 0.8g/second.

3.2 PHYSICOCHEMICAL PROPERTIES OF COMPRESSED GLIMEPIRIDE TABLETS

Table 3.2: Characterization of the physicochemical properties of the different batches of Glimepiride tablets produced with co-processed excipients.

	A	**B**	**C**	**D**	**E**
Tablet weight (mg)	550-594	**520-597**	**580-605**	**530-591**	**555-610**
Thickness (mm)	**18.40-19.50**	**17.40-17.50**	**16.50-17.50**	**18.50-19.00**	**18.50-19.10**
Hardness (kpa)	**8.50-9.00**	**6.50-9.00**	**8.90-10.00**	**6.50-9.00**	**8.50-10.00**
Friability (%)	**2.75**	**1.82**	**1.59**	**1.36**	**2.20**
Disintegration time (mins)	**0.50-0.72**	**0.50-0.51**	**0.50-0.71**	**1.00-6.00**	**2.17-10.00**

3.2.1 Friability of tablets

The value for friability obtained from this study were between 1.36-2.75. Values above 2 were usually considered high except in direct compression cases, as applicable here

3.2.2 Tablet weight uniformity and tablet dimension

The mean diameter of the tablets range from 9.09-10.06mm and the thickness range from 16.5-19.1mm which is within acceptable range of diameter and thickness respectively.

3.2.3 TABLET CRUSHING STRENGTH

From table 3.2 above, the hardness ranges from 6.5-10 which is within the optimum range for tablet hardness. Values below this will produce tablets too soft, frail and will easily break. While values of hardness on the other extremity would produce tablets which does not disintegrate fast.

3.2.4 TABLET DISINTEGRATION

The dissolution medium used here was water and the disintegration time for the batches above was from 30 seconds to 600 seconds (10 minutes). Batches A, B and C demonstrated excellent disintegration properties while batches C and D had fair disintegration characteristics. The fair disintegration characteristics demonstrated only proved that the ratio at which the batches were formulated were not optimum and for the sake of further studies, the ratio used in batches A, B and C should be further elucidated.

Although, all the tablets disintegrated below the 15 minutes specification for uncoated tablets, the fast disintegrating properties of batches A, B and C can be preferentially harnessed.

3.2.5 TABLET DISSOLUTION

To carry out a dissolution test, a standard calibration curve of the active ingredient (Glimepiride) was obtained and is shown below:

CHAPTER FOUR

4.0 CONCLUSION

From the study carried out, the co-processing of excipients which comprises HPMC, Sodium starch and cassava starch co-processed with glimepiride

improved the physical properties of the final tablets because the tablets were sufficiently hard, had good disintegration time and withstood mechanical stress.

The tablet produced from the co-processed excipients can serve as a means for direct compressing of a tablet with poor compressibility like glimepiride.

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