INVESTIGATION OF THE DISINTEGRATION BEHAVIOUR AND DISSOLUTION PROFILE OF OMEPRAZOLE IN DIFFERENT BEVERAGES

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CERTIFICATION

This is to certify that the project work "INVESTIGATION OF THE DISINTEGRATION BEHAVIOUR AND DISSOLUTION PROFILE OF OMEPRAZOLE IN DIFFERENT BEVERAGES" was carried out by Philip Ogochukwu Nweke in the Department of Pharmaceutics and Pharmaceutical Technology, University of Benin, Benin City.

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ABSTRACT

Variable drug release from solid dosage forms has been a major cause of bioavailability problems. The two main processes by which they release drugs are disintegration and dissolution.

The objective of the present study was to assess the disintegration and dissolution of Omeprazole in different beverages like Coca-Cola, Chivita juice, Hollandia yoghurt and Malta Guinness. The test was carried out per the US Pharmacopoeia standard for delayed-release drugs. A hybrid medium of different beverages and pH 6.8 phosphate buffer (250ml) was prepared to mimic *in-vivo* conditions. The result showed that the disintegration time increased in Hollandia yoghurt, while it decreased in Coca-Cola, Malta Guinness and Chivita juice. As the viscosity of fluid increases, the disintegration time was also increased. Coco-cola which contains Carbon Dioxide is implicated in reducing the disintegration time of omeprazole. Since the dissolution profile phase of the study, the results reflected that the drug release was retarded in Hollandia yoghurt and it was sufficiently released in Coca-Cola, Malta Guinness and Chivita juice. From the above study, it can be concluded that there is variation in the disintegration time and dissolution profile of the studied drug in different beverages. Hollandia yoghurt had poor disintegration and dissolution quality compared to other dissolution media used.

Keywords: Disintegration, Dissolution, Beverages

Contents

CHAPTER ONE

1.0 INTRODUCTION

A rate-limiting stage in the dispersion of pharmaceuticals is the breaking down of a compressed tablet or capsule into granules or individual particles. As a result, a quick breakdown is necessary for high bioavailability.

The initial phase in dissolving pharmaceuticals is called disintegration, it is the simple breaking up of solid compounds in a fluid medium (M. Almukainzi et al., 2014). Because the contents of oral solid dosage forms can only break down and be assimilated to be accessible if they disintegrate, disintegration directly influences the therapeutic activity of the medicine (Eraga et al., 2015; Zuo et al., 2013).

For both solid dosage forms, the disintegration assay is a helpful method for figuring out whether the medicine dissolves well within the given time (disintegration time) under particular experiments. (USP, 2020); (Almukainzi *et al*. 2010)

Furthermore, this test is the best quality-by-design (QbD) performance test for predicting drug release in particular situations, such as with highly soluble medicines and biopharmaceutical categorization system (BCS) class 1 pharmaceuticals (Almukainzi et al., 2019; Grube et al., 2019; Zuo et al., 2013a). Disintegration is most typically investigated in

water for the most immediate release (IR) or in a simulated gastric medium for the delayed release. (USP 2020).

It can be presumed that any available beverage, such as pop, juices, and alcoholic beverages, may be used to administer dietary supplement dose forms since no specific beverage (such as water) is mentioned.

Recent advances in pharmaceutical technologies, polymer sciences, and analytical tools have enabled the design of smarter drug delivery systems. For medications intended as smart dosage forms, a variety of formulation strategies are used to maximize therapeutic effectiveness and/or minimize side effects. Many patents have been issued for extended-release, programmed-release, or targeted-release techniques. They not only offer the manufacturers an edge over their competitors but often offer obvious advantages to the patients as well, due to the reduced dose, frequency, and total dose consumption, as well as the minimal exposure of the non-target tissues to pharmacological effects. Traditionally, most patients take their medications with one or more beverages, including health drinks with complex compositions. It is a known fact that there is a great variation in the quantity and regimen followed for the consumption of these beverages. Here are the possibilities of probable interactions between any of the components of these beverages and the formulation ingredient, including the drug candidate. Such interactions have so far been neglected, and only a few, like those with grapefruit juice, have been reported.

A few reports also cite the dramatic alterations in the release profiles of commonly used OTC-type drugs due to concomitant consumption of alcoholic beverages. Unlike the drug-

drug or food-drug interactions, however, the data available on probable drug–beverage interactions are very limited.

A variety of excipients are usually employed by different manufacturers to ensure a final drug product with optimum physicochemical properties.

In the end, these excipients will have an impact on how the drug products disintegrate, resulting in various solid drug products having varied disintegration behaviours. This may lead to differences in the bioavailability of the active ingredients, (Zuo J. *et al,* 2004).

According to numerous studies, food in the stomach slows down or stops medications from disintegrating (Abrahamsson et al., 2004). (Radwan et al, 2012).

When four dietary supplements and three painkiller tablets were investigated by Zuo et al. and Sreelesh et al. to see how they affected the disintegration time, they found that the beverages, in some cases rather drastically, delayed the timings at which the tablets began to dissolve.

From a scientific perspective, it is obvious that the solid dosage forms' contents can only dissolve and become bioavailable after being destroyed. Disintegration is the first and most fundamental stage in ensuring bioavailability.

Instead of any other beverage, medications should be consumed with a full glass of water. Many patients do not, however, heed this advice. Instead, when they swallow their pills, they frequently ingest any nearby beverages, such as juices, coffee, and soft drinks. Drug-beverage interactions can have a variety of negative effects, some of which can affect metabolism or excretion (Farkas Greenblatt, 2008; Jaruratanasirikul & Kleepkaew, 1997).

Others involve modifying drug dissolution and absorption by drug breakdown and dissolution (Eraga et al., 2015; Priya Patel and Hina Bagada, 2013; Rana et al., 2017; Zuo et al., 2013a).

Several studies that have been published have shown the impacts of various drinks, especially beer and wine (Zuo *et al*., 2013a). When 40% ethanol was used as a disintegration medium instead of water, a significant delay in disintegration was seen (Bisharat *et al., 2019*). Additionally, some drinks, primarily cola drinks, showed extended stomach emptying, which may have an impact on the rate and depth of medication absorption (Kondal & Garg, *2003;* Nomani *et al., 2019*).

This study aimed to investigate the impact of beverages on the disintegration and dissolution of a commercially available drug, Omeprazole.

1.1 Solid dosage disintegration theory and their mechanisms

In general, when tablets are swallowed, they disintegrate upon entering the stomach, and even those that are to be dispersed in water before administration must overcome the cohesive strength caused by compression and any binder present. It is therefore customary to insert a disintegrant, which will bring about this process. As previously stated, the term "disintegration" refers to the penetration of the tablets by an aqueous medium, disruption of internal bonds, and subsequent breakdown of the tablet.

In theory, a pressure difference is required to cause a liquid to flow with a deal or death velocity in a horizontal pore of hydraulic radius (m) at a time (t) when its meniscus moves a distance (L) along the pore, as shown below:

$dl/dt = pm^2/k_o ήL$…….1.1

P = pressure

m = hydraulic radius

k_0 = pore shape factor

THE viscosity of the liquid

L = distance moved by the liquid

The pressure differential derived from the drop in pressure of the meniscus is

$P = (YCos\Theta)/m$..... (1.2)

Where,

Y = surface tension of the liquid

Θ = constant angle to the pore wall

Substituting equation (1.2) into (1.1) we have

$dl/dt = [(YCos\Theta/m + (m^2/k_0L)]$

$dl/dt = (YCos\Theta m/ k_o \acute{\eta} L)$……..….(1.3)

If L = 0, and t = 0; on integration,

$dl/dt = mYCos\Theta/k_o \acute{\eta} t$…….(1.4)

When the pore is compact throughout the volume of liquid in the pores, (V) is proportional to (L), and at a time (t)

$V^2 = kL$……. (1.5)

k = coefficient representing the properties of the liquid in the pore network within the compact.

1.2 Proposed mechanisms of disintegration

1.2.1 ***Swelling theory***:

Swelling is among the most well-known mechanisms of disintegration. The swelling is the omnidirectional expansion of the particle population, which increases pressure, pushes apart nearby particles, exerts pressure on the system as a whole, and ultimately breaks up the tablet. Even though the dissolution fluid in it exerts a force in the tablet pores, this force could not be adequate on its own, particularly if the solid particle attachments are strong. However, when a disintegrant is present, the fluid exerts forces strong enough to disintegrate the compact. According to this idea, the disintegrant particles enlarge as they come into contact

with the aqueous fluid that is dissolving, exerting mechanical forces that lead to the tablet's rupture or disintegration into smaller pieces. Examples of such disintegrants, sometimes known as "busters," include cellulose derivatives and action-modified starches.

Based on the recognised increase in the dimension of starch exposed to aqueous fluids, the swelling action is known as "bursting." It is crucial to maximising the concentration present because one common issue with this group is that many disintegrants form sticky or gelatinous material upon swelling, which makes it difficult to break up the tablets.

1.2.2 ***Water uptake***

Tablet and capsule disintegration has been linked to water uptake as a mechanism of action. When Khan and Rhodes (1975) examined the explicit absorption characteristics of several disintegrants, they concluded that water-attracting particles were necessary for a tablet to properly disintegrate. These assertions were reinforced by (Mitreveg and Hollenbeck, 1982). A sophisticated technique for calculating water intake was created by (Van Kemp et al. 1986). Their research lends credence to the idea that at least in part, the disintegrant action is caused by the rate of wetness.

1.2.3 ***Deformation***

It has long been known that the process of tabletting can result in plastic deformation. Photomicrographs were used by (Hess, 1978) to provide proof that disintegrant particles deform during tablet compression.

It was demonstrated that when exposed to water, the distorted particles assumed their original shape. When potato starch granules are significantly distorted during compression,

research shows that the granules return to their previous size and, in certain situations, their swelling capacity increases (Fuher, 1964).

1.2.4 *Heat of wetting*

The idea that the heat of soaking disintegrant particles could constitute an action mechanism was initially put forth by Matsumaru in 1959. He noticed that starch particles have mild exothermic characteristics when they are moist, and he claimed that this is what causes the localised stress brought on by capillary air expansion. This idea cannot, however, fully explain how the majority of contemporary disintegrating agents function and is limited to a narrow subset of disintegrants. In their investigation of these phenomena, List and Muazzam (1979) found disintegrants with significant heat of wetting but no corresponding shortening of the disintegration time.

1.2.5 *Particle size of disintegrants*

There is a correlation between the physical properties of disintegrants, such as particle size, and modes of action, such as swelling and water uptake. The relative efficiency of disintegrants has been attempted to be related to the particle size of the disintegrants.

Smallenbrock and associates (1981) looked into how starch grain size affected tablet breakdown. They discovered that starches with larger particle sizes were more efficient disintegrants than those with coarser grains. These authors postulated that this behaviour was brought on by more edoema. The impact of cross-linked polyvinyl pyrrolidine (PVP) on disintegrant effectiveness was studied by Rudnic et al. in 1982. Additionally, they discovered that the coarser PVP grades were more effective disintegrants than the finer grades.

In a different investigation, Rudnic et al. (1982) noted that larger particles, which swelled to a greater extent and at a faster rate than the finer particles, were responsible for both the rate and the occurrence of sodium starch glycolate's intrinsic swelling. They hypothesised that particle size has a significant impact on the overall effectiveness of a commercial brand of sodium starch glycolates since they discovered a striking association between the rates of swelling and the water uptake for this disintegrant.

1.2.*6 Strain recovery*

The strain within the tablet or capsule is the consequence of forcing macromolecules into a metastable configuration, either due to the interlocking of the polymer chains or as a result of spontaneous crystallisation during the compaction of a tablet. The stored energy can be released as heat immediately following the compaction, or if this is not or only partially the case, when the polymer comes in contact with a fluid, i.e., a disintegration medium or physiological fluids. Hydration of the polymer gives rise to sufficient mobility for entropy recovery to take place, and, with that, recovery of the original shape.

of the polymer molecules Therefore, strain recovery can be regarded as the reversible viscoelastic process of deformation. It is unidirectional and in the opposite direction of the applied compression force.

1.3 Molecular structure

In an attempt to identify the mechanism(s) of action of tablet disintegrants (the action of the structure of the disintegrants). Fukuoka *et al.* (1981) published one of the first such reports in which they examined the two corn starch fractions, amylose and amylopectin content, to

solve disintegrant and dissolution problems encountered in tablet formulations. Starches (maize, potato, rice, and corn) are used in indirect compression. Other disintegrants used similarly are cellulose derivatives (5–10%), sodium alginate (2–5%), clays (5–10%), alginate (5–10%), PVP (1–5%), modified cellulose gum (0.25–5%), bond cation exchange resin, etc.

1.4 factors affecting the disintegration of capsules

The following are established factors that affect the disintegration time of capsules, they include:

1. The percentage of the disintegrant present
2. The type of disintegrant used
3. Types of other excipients present in the capsule
4. Presence of surfactants
5. The nature of the drug substance

1.5 Dissolution test

Dissolution analysis of pharmaceutical solids has become an essential test in drug product development and production, as well as in regulatory bodies' evaluation of product quality. Dissolution testing can assess the effects of drug substances' biopharmaceutical properties and formulation principles on the release of the drug product as well as give information regarding the rate and extent of drug absorption in the body.

1.5.1 ***Significance of dissolution in drug absorption***

Before a medicine is absorbed, it often goes through a few different steps if it has a systemic effect. First, intestinal transit flow and stomach emptying carry the medication to the site of absorption. Dissolution typically occurs in the stomach or small intestine during the second step.

The third phase involves the drug's penetration after it was dissolved in the gastrointestinal membrane. The medicine subsequently undergoes first-pass hepatic metabolism before entering circulation. The following procedures are crucial for medication absorption. When a drug's rate of dissolution is slowed down by poor solubility, dissolution becomes the rate-limiting phase. Drug dissolution, therefore, influences the extent and rate of disintegration.

There have been numerous ways proposed, and those listed in the official texts are classified as forced convention and sink approaches. Three techniques—the revolving basket, the paddle, and the oscillating method—are suggested by British Pharmacopoeia (1988).

The theoretical expression most often used to describe the dissolution rate is the Noyes-Whitney equation (Noyes and Whitney, 1897).

$$dm/dt = A.\left(\frac{D}{h}\right) * (Cs - C) \quad \text{.....1.6}$$

Where,

D is the diffusion coefficient of the drug substance in a stagnant layer of dissolution medium around each drug particle with thickness h,

A = drug particle surface area,

C_s = the saturation solubility

C = drug concentration in the bulk solution.

1.6 Concept of dissolution

The process by which solid materials enter a solvent to produce a solution is known as dissolution. Dissolution, put simply, is the process through which a solid material dissolves. Fundamentally, it is governed by the solvent's and solids' attraction to one another.

The amount of medication that moves from the solid state to the solvent phase per unit of time is represented by a kinetic parameter known as "dissolution."

Following oral delivery, the medicine must dissolve in the gastrointestinal juices to be absorbed. The dissolution of medicinal products is also influenced by formulation-dependent factors (Dressman et al., 1998). In vivo, continuous drug removal from the intestine due to intestinal wall absorption often ensures that the concentration in the bulk solution is minimal in comparison to saturation solubility (Ungell and Abrahamsson, 2000). This condition,

known as the "sink condition," is strongly advised for all in vitro dissolution studies to obtain physiologically accurate dissolution data (USP 31, 2008; FDA, 1997).

1.7 Dissolution of solid substances

The main area for dissolution rate studies during the early phases of drug development is the evaluation of different solid forms of a drug (e.g., salts, solvates and hydrates, polymorphs, amorphous forms), or the effects of particle size. This section focuses on the solid phase and the importance of solid-state properties on the dissolution rate of APIs.

1.8 Classification of solid substances

Drug molecules are held together in a crystal by weak forces such as hydrogen bonds, forces of attraction between polarisable units, or van der Waals forces (Brittain and Byrn, 1999; Grant, 1999). In the crystalline state, the atoms, ions, or molecules are grouped in unit cells, which are repeated in a regular pattern to form crystal lattices, in a periodic, three-dimensional (3D) pattern. A compound can exist in solid crystalline phases called polymorphs when it has at least two distinct molecular configurations in the solid state (Grant, 1999; Bernstein, 2002). The solid is known as a "solvate" when solvent molecules are incorporated, while the term "hydrate" is used when water is the incorporated solvent (Morris, 1999). Non-crystalline materials with an unclear long-range organisation are known as amorphous forms (Hancock and Zografi, 1997). The phrase "crystal habit" refers to the exterior shape (morphology) that results from a change in the crystal structure, which can occur either frequently or seldom.

Different physicochemical features (thermodynamic, spectroscopic, kinetic, surface, and mechanical) arise from variations in packing properties, lattice energies, and between the solid forms. These variations may have a significant impact on how well an active pharmaceutical component functions. (1969; Haleblian and McCrone). For the pharmaceutical sector, these characteristics are crucial since variations in, say, flowability or tabletting characteristics, may make manufacturing procedures challenging. On the other side, the solid form may affect the physical and occasionally chemical stability (Byrn et al., 2001). But a fundamental problem is that varying degrees of bioavailability for different drug entities may result in variable dissolution rates, which could result in therapeutic failure (Haleblian and McCrone, 1969; Vippagunta et al., 2001). Examples of traditional APIs are ritonavir and carbamazepine (Meyer et al., 1992). (Chemburkar et al., 2000). Regulations mandate that the pharmaceutical industry characterise the physicochemical characteristics of APIs and assess how they affect dissolving behaviour (Byrn et al., 1995).

1.9 STABILITY RELATIONSHIPS BETWEEN SOLID PHASES - IMPLICATIONS FOR SOLUBILITY AND DISSOLUTION

Thermodynamically, only one solid form is stable at constant temperature and pressure. All the other forms tend to transform into a stable, solid form. The Gibbs free energy of a polymorph is defined as:

$G = H - TS$……(1.7)

Where,

H is the enthalpy,

T is the absolute temperature

S is the entropy.

The Gibbs free energy of the stable solid form is the lowest. If a reversible transition takes place below the melting point of either polymorphic form at a specific transition temperature (Tt), then two polymorphs are categorised as being enantiomers. The Gibbs free energy of the two phases is identical at the transition temperature, indicating that the two phases are in equilibrium. Each enantiomer has a range of stability. Metoclopramide, tolbutamide, and carbamazepine are a few examples of enantiotropic APIs. Only one polymorph is stable at all temperatures in a monotropic system (i.e., has the lowest Gibbs free energy). There have been reports of a monotropic system, such as chloramphenicol palmitate (Giron, 1995). Metastable solids are those that, despite being thermodynamically unstable, can exhibit kinetically stable behaviour for a while under specific circumstances. Above the glass transition temperature (Tg), a solid's amorphous form, which lacks long-range order, is the form that is most energetic and has the propensity to crystallise into a crystalline form.

Different lattice-free energies also give rise to differences in solubility between the solid forms. The solid having higher lattice-free energy *(i.e.,* the less stable form) dissolves faster because the release of a higher amount of stored lattice-free energy will increase its solubility and, hence, the driving force for dissolution. Hydrates are very common among pharmaceutical APIs; about one-third are capable of hydrate formation (Griesser, 2006).

The hydrates are usually more stable and less soluble than their anhydrous counterparts at the temperatures regularly used in solubility and dissolution testing (25–37 °C) (Shefter and Higuchi, 1963; Yalkowsky, 1981). The stability of hydrate crystal structures is related to the

hydrogen bonding ability of water molecules, which contributes to stabilising the crystal lattices (Gillon et al., 2003; Morris, 1999). The general rule that lower dissolution and absorption rates are obtained with hydrate forms has been found to hold *e.g.,* theophylline (de Smidt *et al.*, 1986; Zhu *et al.*, 1996), ampicillin (Zhu and Grant, 1996), and glutethimide (Khankari and Grant, 1995), but opposite observations also exist, for example in the case of erythromycin (Allen, 1978). Amorphous forms of pharmaceuticals are much more soluble than their crystalline counterparts (Hancock and Parks, 2000). The determination of meaningful experimental solubilities for amorphous materials is difficult, however, because of their tendency to rapidly revert to the crystalline state upon exposure to small quantities of solvent.

1.10 Phase transformations & dissolution

Because of the improved biopharmaceutical qualities they exhibit as a result of their higher solubilities and faster-dissolving rates, the pharmaceutical creation of metastable forms with increased thermodynamic activity is occasionally desired. For example, during processing (such as wet granulation, drying, or milling) (Aaltonen et al., 2007), storage (Byrn et al., 1995), or perhaps most importantly, during dissolution in the aqueous environment of the GI tract, metastable forms become thermodynamically more stable and are therefore unacceptable (Kahela et al., 1983; Meyer et al., 1992). The bioavailability and therapeutic efficacy may be compromised as a result of these transformations, as the crystallisation of a stable form may interfere with the dissolution kinetics and reduce the drug concentration that is available for absorption. There is an urgent need for novel applications since the experimental interpretation of the *in vitro* solubility or dissolution of pharmaceuticals capable of hydrate formation is a difficult issue (Shefter and Higuchi, 1963; Zhu et al., 1996;

Tian et al., 2007). Although solid-solid transformations of pharmaceutical APIs are also feasible, the focus of this section is on solvent-mediated transformations.

1.11 Quality control of capsules

The pharmacopoeia formularies have certain standards to which capsules must conform. The standards are aimed at guaranteeing the quality of capsules on a batch-to-batch basis. Below is a list of official and unofficial specifications (BP, 1988):

1. Uniformity of capsule weight
2. Uniformity of content
3. Disintegration time
4. Dissolution test

1.11.1 Uniformity of weight

Ten hard gelatin capsules are usually weighed individually and the contents are removed. The emptied shells are individually weighed, and the net weight of the contents is calculated by subtracting the weight of the shell from the respective gross weight. The content of active ingredients in each capsule may be determined by calculation based on the percent drug content in the formulation.

1.11.2 Uniformity of content

According to the monograph, the amount of drug substance determined by assay falls within the range of 85.0% to 115.0% of the label claim for nine (9) of ten (10) dosage units tested, with no unit falling outside the range of 75.0% to 125.0% of the labelled drug content.

1.11.3 Disintegration time

The amount of drug substance determined by assay falls within the range of 85.0% to 115.0% of the label claim for nine (9) of the ten (10) dosage units tested, with no unit falling outside the range of 75.0% to 125.0% of the labelled drug content, according to the monograph.

1.12 Physicochemical properties of the drug being studied

1.12.1 Omeprazole

Omeprazole is a proton pump inhibitor (PPI) and potent inhibitor of gastric acidity that is widely used in the therapy of gastroesophageal reflux disease and peptic ulcer disease.

Omeprazole is a benzimidazole with selective and irreversible proton pump inhibitory activity. Omeprazole forms a stable disulfide bond with the sulfhydryl group of the hydrogen-potassium (H+-K+) ATPase found on the secretory surface of parietal cells,

thereby inhibiting the final transport of hydrogen ions (via exchange with potassium ions) into the gastric lumen and suppressing gastric acid secretion. This agent exhibits no anticholinergic activity and does not antagonise histamine H2 receptors**.**

It is free in ethanol and methanol, slightly soluble in acetone and isopropanol, and only very slightly soluble in water. It has a melting point of 155°C.

1.12.2 Coca-Cola

Coca-Cola is a dark-coloured, watery beverage that is composed of water, purified carbon dioxide, which gives it "fizz," phosphoric acid, citric acid, and carbonic acid, which gives it its tartness and caffeine. Coca-Cola has a pH of 2.8.

1.12.3 Malta Guinness

Malta Guinness has a pH of 4.4 and contains a vitamin A content of 49.51 mg/dl and a vitamin C content of 9.48 mg/dl. It also contains a low amount of calcium and sodium, as well as a negligible amount of iron, zinc, cadmium, copper, manganese, and nickel. (Ukalina Obuzor Gloria, Emmmanuel Ajaezi Nneka*, 2010)*

1.12.4 Hollandia yoghurt drink

Hollandia drink has a pH of 4.2 and contains approximately 2.4% of protein, 1.61% of fat, 0.03% of crude fibre, 0.28% of ash, and a moisture content of 79.16.

(Matela KS*, et al,* 2019)

1.12.5 Chivita juice drink

Chivita juice drink has a pH of 3.2 and contains total solids of 6.1%, ash content of 4.5%, vitamin C content of 27 mg, and a protein content of 0.4 (Nwachukwu I. N. *et al., 2015).*

1.13 Objectives of the study

This study was carried out to investigate the effect of commonly consumed beverages on the disintegration of omeprazole capsules. This study is aimed at evaluating the effect of commonly consumed beverages on the disintegration of capsules serving as a preliminary to dissolution.

This effect will be evaluated by comparing the disintegration time of omeprazole capsules in these beverages to the disintegration time of water in these same capsules.

1.14.1 Specific objectives

The objectives of this project are:

1. to investigate the impact of different beverages on the disintegration time and dissolution profile of commercially available Omeprazole samples.
2. to compare the disintegration phenomena of the drug samples with those obtained with water at room temperature.
3. to compare the dissolution profile of the drug samples with that obtained with the blank.
4. From the above, we can ascertain the influence of these beverages on drug bioavailability and therapeutic efficacy.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 Materials

Omeprazole capsules of 20 mg (Prilosec), sodium hydroxide (NaOH), hydrochloric acid, Coca-Cola (Coca-Cola), Chivita 100% orange juice (Chi LTD), Malta Guinness (Guinness breweries) Yogurt Hollandia (Chi LTD)

Instruments used include electric weighing balances (B154, Mettler-Tolledo, Switzerland); disintegration test apparatus (MK4 disintegration test unit, Manesty); UV spectrophotometer (UNICOTM 2011; UK); laboratory sieves of 710 m (Endicotts Limited, England); station dissolution apparatus (ST7, G.B. Caleva Ltd., England); pH meter; dropper pipette; measuring glass; spatula; and thermometer.

2.2 Methods

2.2.1 *Weight variation test*

It was carried out as per the method in the US Pharmacopoeia. Twenty capsules of the drug were selected randomly and were individually weighed using the electronic weighing balance. The average weight and percentage variation of weight were calculated.

2.2.2 ***Disintegration media***

Disintegration testing was performed in 4 test beverages, including Malta Guinness, Coca-Cola®, Chivita mango juice, and Hollandia yoghurt drink. Compared with 0.1N HCl, which is the USP reference medium for gastric-coated capsules, when the disintegration of the capsule is not attainable with HCl, the phosphate buffer pH 6.8 is used. The tests were performed in 800 ml of each different medium.

All experiments were conducted at a normal human body temperature of 37.5%C.

2.2.3 Disintegration time test

The disintegration test was performed using the USP general chapter on disintegration (701>) for delayed-release (enteric-coated) capsules and tablets.

Six capsules of omeprazole were subjected to the USP disintegration test in a disintegration test apparatus. In each cylinder, one capsule was placed and allowed to oscillate vertically in a beaker containing 1 L of disintegration medium kept at 37 2 °C. The time taken for each capsule to disintegrate completely was recorded, and then a calculation was done for the mean disintegration time.

2.2.4 ***Dissolution test***

The dissolution study was done with the USP Standard Dissolution apparatus, with the capsule exposed to 500 ml of 0.1 N HCl for 2 hours in the acid stage and 900 ml of phosphate buffer, pH 6.8, for 1 hour in the buffer stage at 37± 0.5 C and 90 rpm. Omeprazole (20 mg) was introduced into each beaker. Aliquots of 5 ml samples were withdrawn periodically at 30 min, 60 min, 90 min, and 120 min interval marks at the acid stage; at the buffer stage, samples were similarly withdrawn at 10 min, 20 min, 30 min, 40 min, 50 min, and 60 min and replaced with the same volume of media that was maintained as the blank medium. The samples were analysed after suitable dilution using a UV spectrophotometer at 304 nm. The above process was performed separately for each beverage, viz., Coca-Cola carbonated drink, yoghurt, Chivita mango juice, and Malta Guinness. Each time, 250 ml of beverage was added to 650 ml of phosphate buffer (pH 7.6), which was used as a dissolution medium. The temperature of the beverages was kept at 37 0.5 degrees Celsius while they were added to the media.

2.3 Preparation of calibration standard

100 mg of pure omeprazole was weighed into a 100-ml beaker using the electronic balance. 20 ml of 0.1 N NaOH was measured into the beaker, and the solution was stirred until the sample dissolved completely. The solution was made up to volume (100 mL) with 0.1 N NaOH to achieve a concentration of 1 mg/mL. With the aid of a 5 ml pipette, 1 ml of the solution was collected and placed into the 10 ml sample bottle and diluted up to the 10 ml mark to obtain a concentration of 100 ug/ml. This solution was then diluted serially to obtain solutions of 20, 40, 60, 80, and 100 g/mL of omeprazole. Each solution was analysed at a wavelength of 304 nm in the UV spectrophotometer.

The calibration curve was plotted as a graph of absorbance against concentration.

CHAPTER 3

3.0 RESULTS AND DISCUSSIONS

3.1 Weight variation test

The capsule had a mean weight of 221±0.11 mg. The result of this test shows that the capsule passed the weight variation test according to the US Pharmacopoeia.

3.2 Disintegration test

There was no evidence of disintegration of the capsule after 1 hour in 0.1N HCl, so the samples were transferred into a 6.8 pH phosphate buffer.

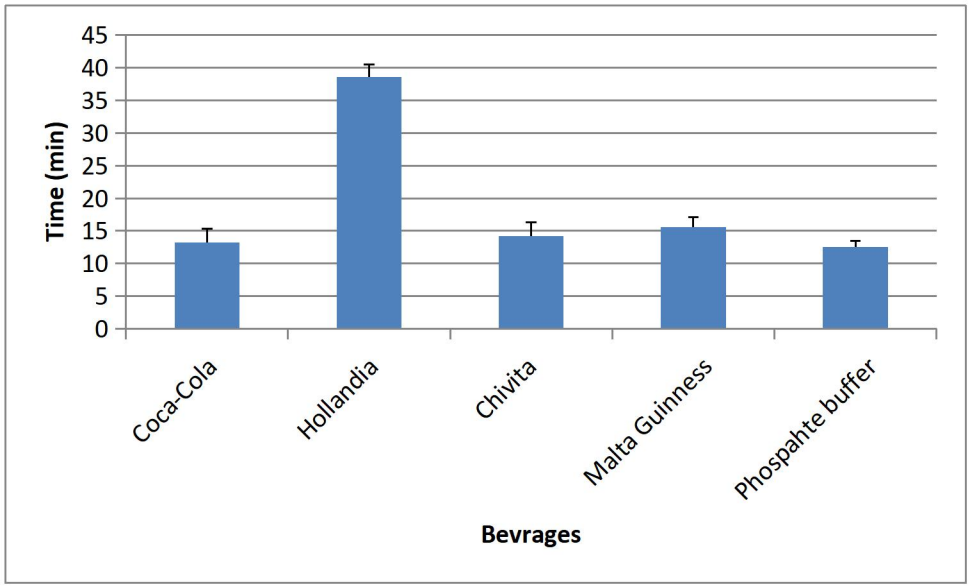

FIG 1: Disintegration time of Omeprazole in different beverages

The disintegration time for omeprazole in different test media was studied and shown in Table 1. The control used was distilled water.

The drug disintegrated fastest in Coca-Cola, with a disintegration time of 13.2±2 min. It may be suggested that this could be due to the pressure exerted by the carbon dioxide (CO2) gas in Coca-Cola.

The disintegration times for Malta Guinness and Chivita juice were 15.6±1.50 and 14.2±2 min, respectively; when compared to the disintegration time for water, which served as the control, there was no significant difference.

The most significant result was for Hollandia yoghurt, which had a disintegration time of 38.62 min. The prolonged disintegration of Hollandia yoghurt may be attributed to the increased viscosity of the drink in comparison to water. Mechanistically, the first step of the disintegration process is water uptake. A good correlation between the penetration rate of a fluid into a tablet and the disintegration time results from viscosity, contact angle, and surface tension (Anwar *et al.,* 2005). This relationship can be explained by the Washburn equation (Washburn, 1921) below:

Where v is the volume of liquid penetrating at time t, γ is the surface tension, θ is the contact angle, η is the viscosity, and r is the capillary radius.

Increased media viscosity has been shown to cause a profound delay in drug disintegration time. For example, it has been shown that disintegration is delayed in milk (Anwar *et al.*, 2005). This is because the penetration rates for milk are slow, which may be a reflection of its relatively high viscosity and low surface tension (Stellrecht, 1999).

3.3 Dissolution Test

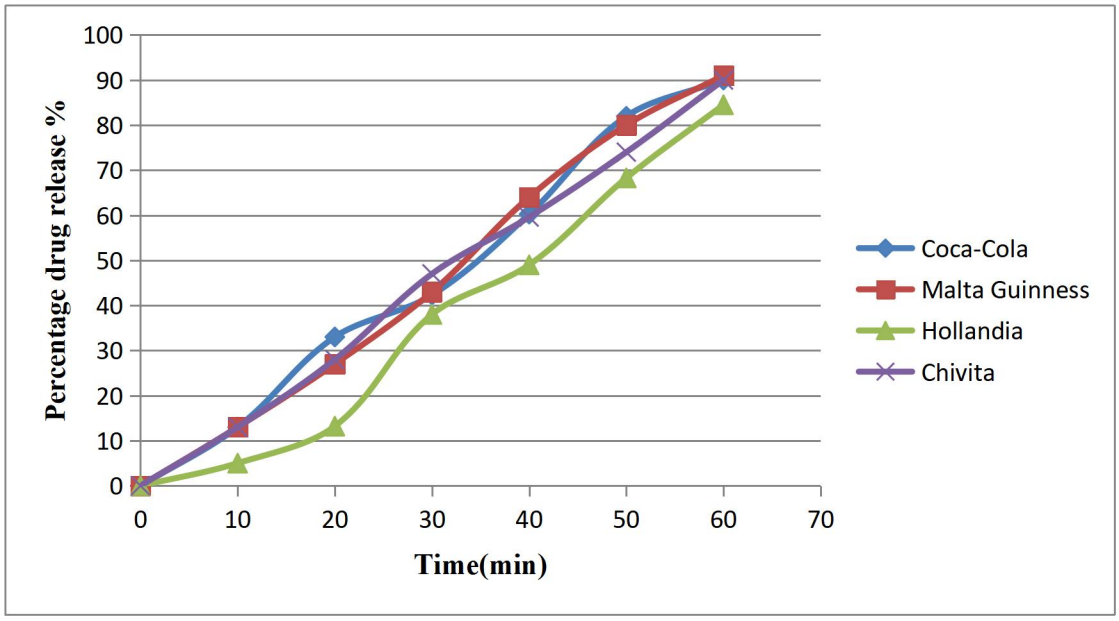

FIGURE 2: Dug release profile of Omeprazole capsules in different beverages

The solution medium with phosphate buffer stabilises pH and osmolarity in a way that mimics the isotonic nature of the human body (Raffaella *et al., 2016),* creating a favourable environment to dissolve omeprazole. The drug release of Omeprazole in Coca-Cola was 90±0.15 % after 60 minutes.

Cola Drink Medium is a carbonated beverage rich in sodium citrate and phosphoric acid, with a little quantity of sodium benzoate, as well as sweeteners, e.g., aspartame. The highly acidic nature of this medium enhances its organoleptic properties. Carbonation influences pH (2.3–2.6), resulting in carbonic acid, which gives acid media (Cochrane *et al.*, 2009). Some excipients in Omeprazole include lactose monohydrate, sodium starch glycolate, sodium stearate, and sodium lauryl sulfate; they are susceptible to erosion in an acidic environment. This might explain why Cola was able to release the drug to a sufficient degree.

The drug release in the Hollandia drink was 86.5±0.54 % after 60 minutes, which was below the standard as per the US pharmacopoeia. This result could be attributed to the presence of protein (casein) and fat, which can form a film around the tablets that cause significant rigidity and slow down the water penetration into the tablet, causing slow disintegration (Abrahamsson *et al.,* 2004), which could ultimately lead to the insufficient release of the drug.

The drug release was 92±0.16 % and 91±0.15 % in Chivita and Malta Guinness, respectively, after 60 minutes. The constituents of these beverages did not retard the release rate of the drug. According to the US Pharmacopoeia, the dissolution of the drug was within the normal range.

A factor that could play a role in the result obtained is the pH of the dissolution medium. For weak acids, the dissolution rate increases with an increase in pH, whereas for weak bases, it increases with a decrease in pH. Omeprazole is a weak base. All the dissolution mediums used for the experiment had low pH, and this could be why their rate of dissolution was within the normal range except for Hollandia yoghurt.

The level of dissolved gases present in the dissolution medium can affect the release profile of a dosage form. The presence of dissolved gases can cause changes in the performance of the dissolution medium by forming bubbles on the dosage form or altering the interaction of the medium. The dissolved gas could coat the tablets or other dosage forms. This is most likely to happen as the medium is heated to the test temperature (37°C). The coating can affect the drug release by altering the dissolution and disintegration or dissolution of the tablet. Coca-Cola and Malta Guinness both contain dissolved CO2, but their dissolution rates weren't retarded based on the results obtained.

CHAPTER 4

4.0 CONCLUSION

The study examined the influence of different beverages on the disintegration and dissolution of omeprazole. The study proposed the use of hybrids, which would better simulate *in vivo* conditions.

Except for Hollandia, none of the beverages used in the studies slowed the disintegration of Omeprazole.

Hollandia-modified in vitro dissolution media altered dissolution.

characteristic of omeprazole. Other beverages did not alter the dissolution of the drug. Further studies are needed to assess these claims in vivo.

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APPENDIX

TABLE 2: DISSOLUTION PROFILE OF OMEPRAZOLE IN 0.1N HCl + BEVERAGES

Time(hrs)	Coca-Cola	Malta Guinness	Hollandia Yoghurt	Chivita Juice
2	0.38±0.07	0.39±0.07	0.19±0.06	0.31±0.03

TABLE 3: DISSOLUTION PROFILE OF OMEPRAZOLE IN pH 6.8 PHOSPHATE BUFFER + BEVERAGES

CUMULATIVE % OF DRUG DISSOLVED

Time(min)	Coca-Cola	Malta Guinness	Hollandia	Chivita Juice
0	0	0	0	0
10	13±0.17	13±0.11	5.13±0.19	13 ± 0.19
20	33±0.14	27±0.18	13.22±0.17	28 ± 0.17
30	42.3±0.18	43±0.16	38±0.13	47 ± 0.13
40	60.26±0.13	64±0.14	49±0.14	59.62 ± 0.14
50	81.95±0.16	80±0.12	68.28±0.27	74.34 ± 0.17
60	90.13±0.15	91±0.15	84.51±0.54	90 ± 0.16

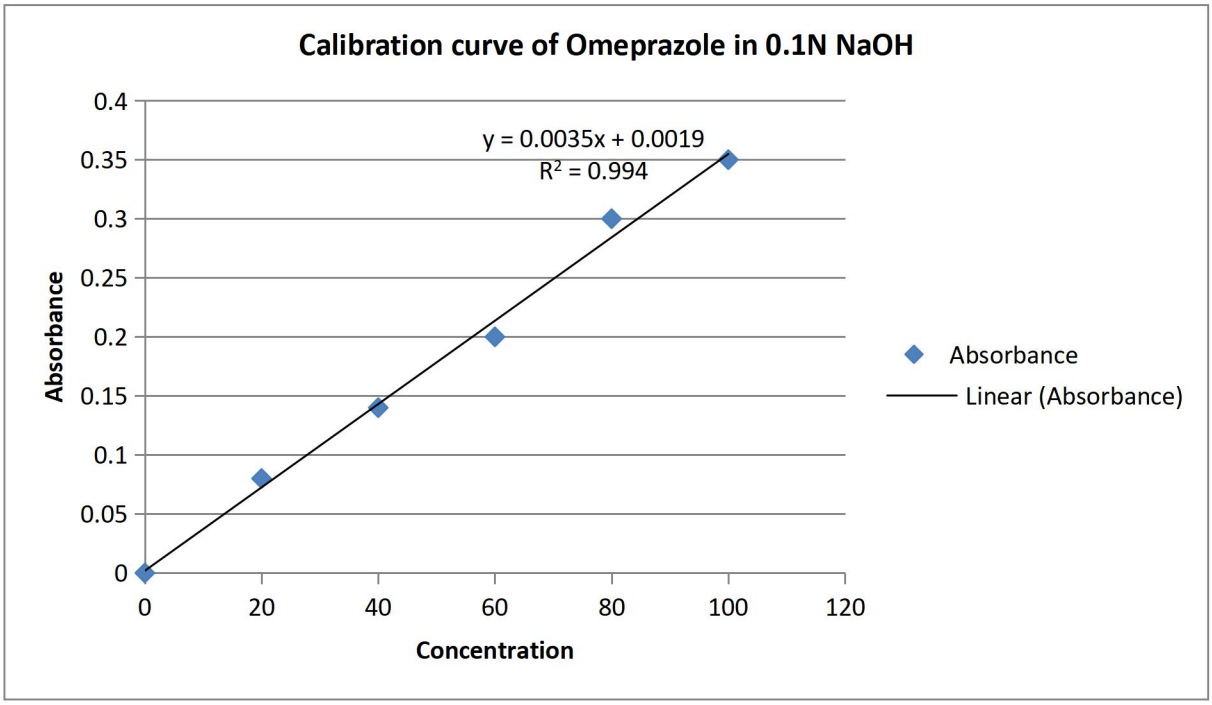

TABLE 1: DISINTEGRATION VALUES OF OMEPRAZOLE IN VARIOUS BEVERAGES

Beverages	**Disintegration time (min)**
Coca-Cola	13.2±2.16
Hollandia yoghurt	38.6±2
Chivita Juice	14.2±2
Malta Guinness	15.6±1.50
Phosphate buffer	12.5±1