

THE BINDER EFFECT OF POVIDONE ON
THE MECHANICAL PROPERTIES OF
PARACETAMOL CONTAINING TABLETS

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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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DECLARATION

This proposal is my original work and has not been presented for a degree in any other university.

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DEDICATION

To the memory of Nelly Wawira Koech

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I am grateful to my project supervisors Dr. Shital Maru and Dr. Lucy Tirop for their guidance throughout this study.

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ABBREVIATIONS AND ACRONYMS

BP	British Pharmacopoeia
BFI	Brittle Fracture Index
C.I	Compressibility Index
CSFR	Crushing Strength Friability ratio index
CSFR: DT	Crushing Strength Friability ratio to disintegration time index
h	Height of heap
H.R	Hausner's ratio
K30	kollidon 30
K90	Kollidon 90
r	radius of heap
R	Flow rate
V _B	Bulk volume
V _T	Tapped volume
V _o	Unsettled apparent volume
V _f	Final tapped volume
ρ _B	Bulk density
ρ _T	Tapped density

DEFINITION OF TERMS

Dry tableting mixture: refers to the dry ungranulated mix of paracetamol, potassium Sorbate and corn starch.

ABSTRACT

BACKGROUND. Binders are excipients added either dry or in solution form to drug-filler mixtures to provide cohesiveness. This ensures the intactness of the tablet after compression. Materials with low or no cohesive qualities of their own will require a stronger binder. Powder compression is the reduction in the volume of a powder due to the application of a force.(Aulton M.E, 2013). The process of tablet making involves optimization of input variables. Prior to compression, the tableting mixture is characterized by particle size distribution analysis, measurement of the true, bulk and tapped densities and evaluation of the flow properties. The mechanical properties of the tablet are measured by resistance to crushing, friability and disintegration tests

.PROBLEM STATEMENT. Elastic deformation is a reversible phenomenon hindering tablet formation, whereas plastic deformation and brittle fracture of particles are irreversible and promote tablet formation. Paracetamol mainly exhibits particle fragmentation and high elastic deformation leading to tablet capping. Choice of binder is a critical process in paracetamol tablet formulation.

OBJECTIVE. To study the effect of the binders povidone K90 and Povidone K30 on the mechanical properties of paracetamol containing tablets.

METHOD. Granules containing a varying ratio of the binders povidone K90 and povidone K30 were formulated. The flow properties of the granules were determined. The mechanical properties of the tablets formed were studied. Descriptive analysis was by bar charts and inferential analysis was by R statistical software version 3.2.0.

RESULTS. Paracetamol containing tablets with 100% povidone K90 exhibits the highest mechanical strength as measured by the crushing strength friability ratio (CSFR). Paracetamol containing tablets with a binary mixture of povidone K90 and povidone K30 in the ratio of 1:3 have the best mechanical properties as measured by the crushing strength friability ratio: disintegration time (CSFR : DT).

CONCLUSION. A binary binder mixture of povidone K90 and povidone K30 in the ratio of 1:3 produces paracetamol containing tablets with the best mechanical properties and tablets with 100% povidone K90 have the highest mechanical strength.

CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

Binders are agents used to impart cohesiveness to a powdered material. Immobile liquid binders affect the type of granules produced not only in the mechanism of agglomeration but also by their distribution within the agglomerate (Pandeya, 2009). One important characteristic of a tablet binder is its ability to be effectively and evenly distributed through the interparticulate voids in a compound tablet. (Mattsson, 2000). Material with low or no cohesiveness will require a stronger binder than materials with high cohesiveness. Powder compression is the reduction in the volume of a powder due to the application of a force. (Aulton M.E, 2013) The compression takes place in a die by the action of the upper and lower punch by which the compressive force is applied. Increased proximity of particle surfaces accomplished during compression leads to the formation of bonds which provide coherence to the particles. Compaction is the formation of a solid specimen of defined geometry by powder compression. Resistance to deformation of bulk material is related to the ultimate yield strength of the materials undergoing compression. (Patel S, 2006). The process of tablet making involves optimization of input variables. Compression of the tableting mixtures can be direct, as dry granules or as wet granules. Characterization of the tableting mixtures is by particle size distribution analysis, measurement of the true, bulk and tapped densities and evaluation of the flow properties. The mechanical properties of the tablets are analyzed by performing the resistance to crushing, friability and disintegration tests.

1.2 PROBLEM STATEMENT

Paracetamol crystallizes in three polymorphic forms, monoclinic form I (stable), Orthorhombic form II (metastable) which is the most wanted form in industry, and unstable form III. (Srinivasan .K, 2014). The monoclinic paracetamol form I is the thermodynamically stable form (Bashpa .P, 2014) and is commonly used in the manufacture of tablets. Form I cannot be compressed directly due to poor densification properties. Paracetamol tablets have usually to be produced through a wet granulation process. Elastic deformation is a reversible phenomenon hindering tablet formation, whereas plastic deformation and brittle fracture of particles are irreversible and promote tablet formation. Paracetamol mainly exhibits particle fragmentation and high elastic deformation leading to tablet capping.

1.3 OBJECTIVES

1.3.1 GENERAL OBJECTIVE

To study the effect of varying povidone binder ratios on the mechanical properties of paracetamol containing tablets.

1.3.2 SPECIFIC OBJECTIVE

To formulate and evaluate the flow properties of paracetamol containing granules at different binder ratios of povidone K90 and povidone K30

To determine the mechanical properties of the tablets with varying ratios of povidone K90 and povidone K30.

1.4 JUSTIFICATION OF THE STUDY

Anecdotal evidence from production staff at lab and allied ltd. Kenya suggests that formulation of paracetamol containing tablets is problematic. The paracetamol tablet batches in production often present with tablet defects of chipping, capping and laminating. The choice of binder in the formulation of paracetamol containing tablets is therefore critical.

1.5 SIGNIFICANCE OF THE STUDY

The study will suggest the best binder ratio of povidone K90 to povidone K30 that results in paracetamol containing tablets with good mechanical properties.

CHAPTER TWO: LITERATURE REVIEW

2.1 POVIDONE (Rowe, 2009)

2.1.1 NON-PROPRIETARY NAMES

BP: Povidone

JP: Povidone

PhEur: Povidone

USP: Povidone

2.1.2 SYNONYMS

Polyvinylpyrrolidone; povidonum; povipharm; PVP; 1-vinyl-2-pyrrolidinone polymer.

2.1.3 EMPIRICAL FORMULA AND MOLECULAR WEIGHT

$(C_6H_9NO)_n$ 2 500 – 3 000 000

The USP 32 describes povidone as a synthetic polymer consisting of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K value in the range 10-120.

Approximate molecular weights for the different grades of Povidone.

K-Value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

2.1.4 DESCRIPTION

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with k- values equal to or lower than 30 are manufactured by spray drying and occur as spheres. Povidone k-90 and higher k- value povidones are manufactured by drum drying and occur as plates.

2.1.5 TYPICAL PROPERTIES

Acidity/alkalinity PH=3.0-7.0 (5% w/v aqueous solution)

Bulk density 0.29- 0.39g/cm³

Tapped density 0.39- 0.54g/cm³

Flowability 16- 20g/s

Particle size distribution;

Kollidon K 25/30: 90% > 50µm, 50%> 100µm, 5%> 200µm

Kollidon K 90: 90%> 200µm, 95%> 250µm

Solubility; freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water;

Practically insoluble in ether, hydrocarbons and mineral oil. In water, the

Concentration of a solution is limited only by the viscosity of the resulting solution,

Which is a function of the k- value.

2.1.6 APPLICATION IN PHARMACEUTICAL FORMULATION

In tableting, povidone solutions are used as binders in wet granulation. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol or hydroalcoholic solutions. Povidone k-30 has better binding properties than starch(P. nagadivya et al., 2012). Povidone is used as a solubilizer in oral and parenteral drug forms and has been shown to improve dissolution in solid dosage forms. Povidone solutions may also be used as coating agents or binders when coating active pharmaceutical ingredients on a support such as sugar beads. Povidone has additionally been used as a suspending, stabilizing and viscosity increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble drugs may be increased by mixing with povidone.

USES OF POVIDONE

USE	CONCENTRATION (%)
Carrier for drugs	10-25
Dispersing agent	up to 5
Eye drops	2-5
Suspending agent	up to 5
Tablet binder, coating agent	0.5-5

2.1.7 STABILITY AND STORAGE CONDITIONS

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure of around 110- 130°C. Steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives. Since it is hygroscopic, povidone powder should be stored in an airtight container in a cool, dry place.

2.1.8 INCOMPATIBILITIES

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulphathiazole,

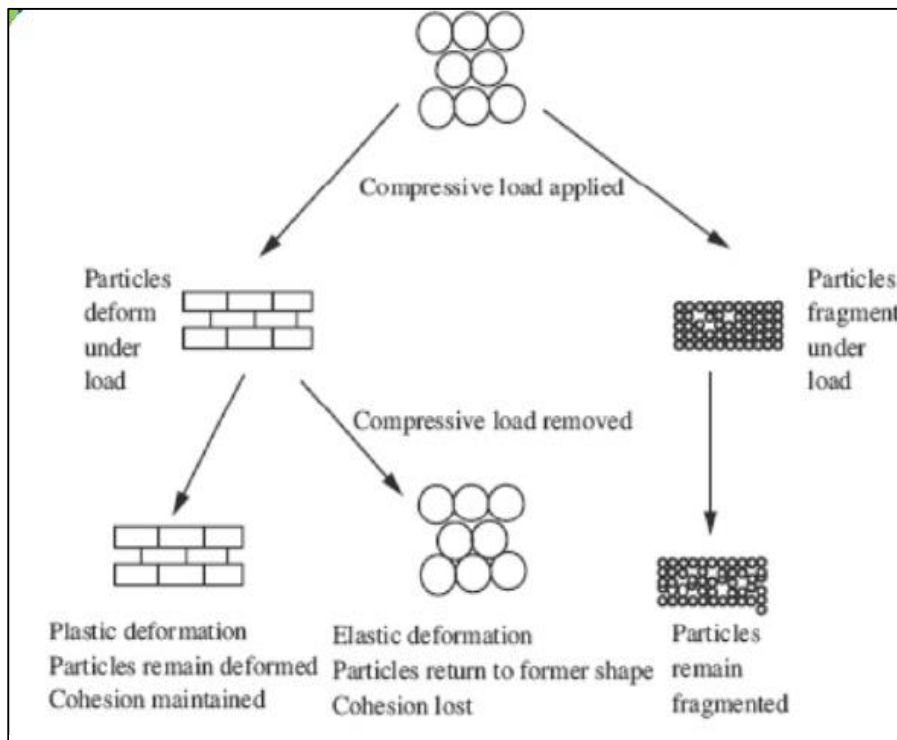
sodium salicylate, salicylic acid, phenobarbital, tannin and other compounds. The efficacy of the preservative thimerosal may be affected by the formation of complexes with povidone.

2.1.9 SAFETY

Povidone is widely used as an excipient, particularly in oral tablets and solutions. It is nontoxic when consumed orally and is not absorbed from the gastrointestinal tract. Evidence shows that povidone may accumulate in body organs following intramuscular injection. The World Health Organization (WHO) has set a daily maximum intake for povidone at 25mg/Kg body weight.

2.2 COMPRESSION OF PARTICLES AND GRANULES

The compressibility of a powder is its propensity, when held within a confined space, to reduce in volume while loaded. A sequence of processes occurs during compression. Initially the particles in the die are rearranged resulting in a closer packing structure and reduced porosity. Subsequent reduction of tablet volume is associated with changes in the dimensions of the particles. Particles can change their shape temporarily by elastic deformation and permanently by plastic deformation (Figure 1). Particles can also fracture into a number of smaller, discrete particles. The particle fragments can then find new positions, which will further decrease the volume of the powder bed. When the applied pressure is further increased, the smaller particles formed could again undergo deformation. One single particle may undergo this cycle of events several times during one compression. Following compression, particle surfaces are brought into close proximity to each other and particle-particle bonds can be formed. Elastic deformation can be described as a densification of the particle due to a small movement of the cluster of molecules or ions that forms the particle. Plastic deformation is considered to occur by the sliding of molecules along slip planes within the particles. Elastic and plastic deformations of particles are time independent processes. Deformation can also be time dependent, this is called viscoelastic and viscous deformation of a material. Many pharmaceutical substances have a viscous character and the properties of tablets are thus dependent on the punch displacement-time relationship of the compression process (Aulton M.E, 2013).



(Aulton M.E, 2013)

Figure 1 Illustration of particle deformation during compression

The majority of powders handled in pharmaceutical production consists not of porous primary particles but rather granules. The processes involved in the compression of granules are the physical changes in the granules and the physical changes in the primary particles from which the granules are formed. At low compression forces, the reduction in volume of the bed of granules can occur by rearrangement within the die. With increasing loading, a further reduction in bed volume changes the structure of the granules. The granules can deform, both elastically and permanently, but reduce their intra-granular porosity (densify). Deformation and densification of granules have been suggested to occur by the repositioning of primary particles within the granules. Table 1 shows the dominating compression mechanisms for dense particles and granules.

Table 1 Mechanism of compression of dense particles and granules

Dense particles	Granules
Repositioning of particles	Repositioning of granules
Elastic particle deformation	Permanent granule deformation
Plastic particle deformation	Granule densification
Viscoelastic particle deformation	Granule fragmentation
Particle fragmentation	Deformation of primary particles

2.3 CONSOLIDATION OF PARTICLES

When the surfaces of two particles approach each other closely enough at a separation of less than 50nm, their free surface energies result in a strong attractive force, a process known as cold welding. This hypothesis is favored as a major reason for the increasing mechanical strength of a bed of powders subjected to increasing compressive forces. On the macro-scale, any load applied to the powder bed must be transmitted through the points of particle contact. Under appreciable forces, these transmission may result in the generation of considerable frictional heat. If this heat is not dissipated, the local rise in temperature may cause melting of the contact areas of the particles. Solidification of the melt results into fusion bonding which in turn raises the mechanical strength of the mass. In both cold and fusion welding, the process is influenced by factors like the chemical nature of the materials, the extent of the available surface, the presence of surface contaminants and the intersurface distances. If large, clean surfaces are brought into intimate contact, then bonding should occur. Brittle fracture and plastic deformation generate clean surfaces, which the compressional force ensure are kept in close proximity (Lachman L, et al., 1987).

2.4 POWDER FLOW (BP 2012 APPENDIX XVII N)

The four commonly used methods for testing powder flow are: angle of repose, compressibility index, hausner ratio, flow rate through an orifice and shear cell.

2.4.1 ANGLE OF REPOSE

Angle of repose is a characteristic related to interparticulate friction, or resistance to movement between particles. The angle of repose is the constant, three- dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material. The common methods for determining the static angle of repose are based on two important experimental variables: the height of the funnel through which the powder passes may be fixed relative to the base or the height may be varied as the pile forms,

the base upon which the pile forms may be of fixed diameter or the diameter of the powder cone may be allowed to vary as the pile forms.

Table 2 Flow properties and corresponding angles of repose

Flow property	Angle of repose (degrees)
Excellent	25 – 30
Good	31 – 35
Fair	36 – 40
Passable	41 – 45
Poor	46 – 55
Very poor	56 – 65
Very, very poor	> 66

The funnel height should be maintained at approximately 2 – 4cm from the top of the powder pile as it is being formed in order to minimize the impact of the falling powder on the tip of the cone. If a symmetrical cone of powder cannot be successfully or reproducibly prepared, this method is not appropriate. The angle of repose is calculated from the following equation:

$$\text{Tan } \Theta = \frac{\text{Height}}{\text{radius}} \quad \text{Equation 1}$$

2.4.2 COMPRESSIBILITY INDEX AND HAUSNER RATIO

The basic procedure in determining the compressibility index and hausner ratio is to measure the unsettled apparent volume, V_o , and the final tapped volume, V_f , of the powder after tapping the material until no further volume changes occur. The compressibility index and the hausner ratio are calculated as follows:

$$\text{Compressibility index} = \frac{V_o - V_f}{V_o} \times 100 \quad \text{Equation 2}$$

$$\text{Hausner ratio} = \frac{V_o}{V_f} \quad \text{Equation 3}$$

Alternatively, the compressibility index and hausner ratio may be calculated using measured values of bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows:

$$\text{Compressibility index} = \frac{\rho_{\text{bulk}} - \rho_{\text{tapped}}}{\rho_{\text{bulk}}} \times 100 \quad \text{Equation 4}$$

$$\text{Hausner ratio} = \frac{\rho_{\text{bulk}}}{\rho_{\text{tapped}}} \quad \text{Equation 5}$$

Table 3 Scale of flowability

Compressibility Index (per cent)	Flow character	Hausner ratio
1 – 10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59

Compressibility index and hausner ratio are not intrinsic properties of the powder and are therefore dependent on the methodology used. The unsettled apparent volume, V_o , the final tapped volume, V_f , the bulk density, ρ_{bulk} , and the tapped density, ρ_{tapped} , will be affected by the diameter of the cylinder used, the number of times the powder is tapped to achieve tapped density, the mass of the material used in the test and the rotation of the sample during tapping.

2.4.3 FLOW THROUGH AN ORIFICE

Determining flow rate through an orifice is useful only with free-flowing materials. The flow rate through an orifice is measured as the mass per time flowing from any of a number of containers (cylinders, funnels, hoppers). Measurement of flow rate can be in discrete increments or continuous.

The methods used in determining flow rate are based on three important variables: the type of containers used to contain the powder. Common containers are cylinders, funnels and hoppers from production equipment. The second variable is the size and shape of the orifice used. The last variable is the method of measuring flow rate. Flow rate can be measured continuously using an electronic balance with some sort of recording device (strip chart recorder, computer). It can also be measured in discrete samples. For example the time it takes for 100g of powder to pass through an orifice to the nearest tenth of a second. Continuous measurement using an electronic balance can more effectively detect momentary flow rate variations.

Flow rate through an orifice is not an intrinsic property of the powder. It is very much dependent on the size and shape of the orifice, the type of container material (metal, glass or plastic) and the diameter and height of the powder bed.

The dimensions for the cylinder should be such that the diameter of the opening is greater than six times the diameter of the particles and the diameter of the cylinder should be greater than twice the diameter of the opening.

It is not advisable to use a funnel, particularly one with a stem, because flow rate will be determined by the size and length of the stem as well as the friction between the stem and the powder.

2.4.4 SHEAR CELL METHODS

A wide variety of parameters can be obtained from shear cell methods including the yield loci representing the shear stress – shear strain relationship, the angle of internal friction, the unconfined yield strength, the tensile strength, and a variety of derived parameters such as the flow factor, Flowability indices and critical hopper and bin parameters.

Shear cell designs are cylindrical, annular and the plate type. A significant advantage of this methodology is the greater degree of experimental control. It is however time consuming and requires a well-trained operator.

2.5 EVALUATION OF COMPRESSION BEHAVIOUR

In research and development, evaluating the compression behavior of particles and mechanisms of compression involved in the volume reduction process involves characterization of the ejected tablets and characterization of the compression and

decompression events. Characterization of the ejected tablets involves inspection and the determination of the pore structure of the tablet, in terms of mean pore size, pore size distribution and specific surface area. Characterization of the compression and decompression events is based on relationships between parameters that can be derived from the compaction process.

2.5.1 INSPECTION OF TABLETS

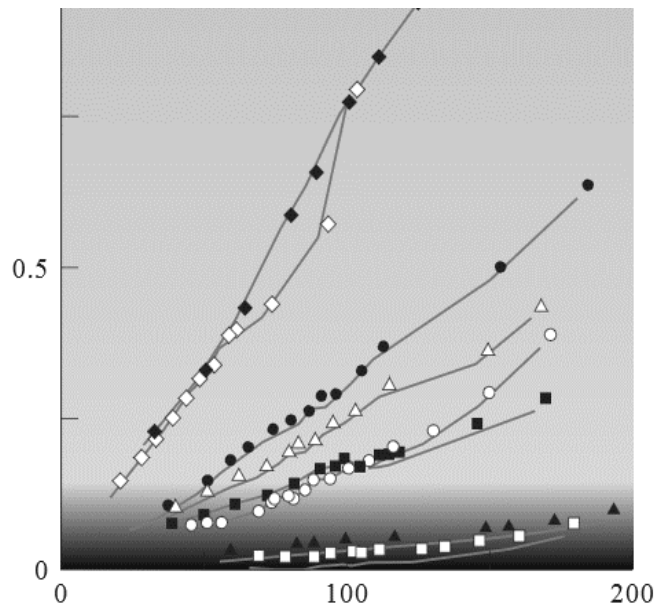
Inspection of intact tablets by scanning electron microscopy and profilometry studies the changes in the physical properties of particles during compression. Such changes include fragmentation into smaller particles, permanent shape changes due to deformation and the formation of cracks within the particles. Information about the relative positions of the particles within the tablet and hence the inter-particulate pore structure is also given. The fracture path during strength testing can be estimated from inspection of the tablet fracture surface.

2.5.2 PORE STRUCTURE AND SPECIFIC SURFACE AREA

Measurement of the characteristics of the pore structure of tablets is an important way to study the evolution of tablet structure during compression. Information on pore size distribution can be obtained by mercury intrusion measurements and by gas adsorption-desorption. Fragmentation is a size reduction process and so can be assessed by measuring the specific surface area of a particulate solid before and after compaction, or measuring changes in tablet surface area with compaction pressure. The surface area of tablets can be determined by gas adsorption, mercury intrusion and air permeametry. The slope of the relationship between tablet surface area and applied pressure represents the degree of fragmentation and can be used to classify materials with respect to their fragmentation propensity (Figure 2). (Aulton M.E, 2013).

2.5.3 FORCE DISPLACEMENT PROFILES

Force displacement profile is the relationship between upper punch force and upper punch displacement during compression. This has been used to derive information on the compression behavior of a powder and to make predictions on its tablet forming ability. The area under a force-displacement curve represents the work or energy involved in the compression process. The force displacement curve can be divided into different regions, denoted E1, E2 and E3. (Figure 3). The areas of E1 and E3 should be as small as possible for a powder to perform well in a tableting operation and give tablets of a high mechanical strength. Force displacement curves can be used to monitor the compression behavior of a substance in order to document and evaluate reproducibility between batches. The energy applied to the powder can be calculated from the area under the force-displacement curve. This compaction energy is used to overcome friction between particles, deform particles and create new particle surfaces by fragmentation.



(Aulton M.E, 2013)

Figure 2 Tablet surface area as a function of compaction pressure

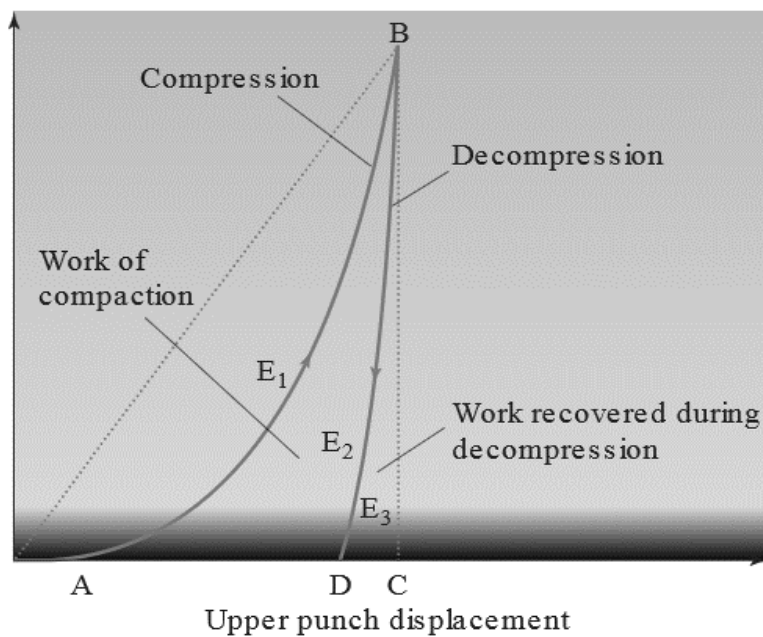


Figure 3 The relationship between upper punch force and upper punch displacement during compression and decompression of a powder (Aulton M.E, 2013).

2.5.4 TABLET VOLUME-APPLIED PRESSURE PROFILES

There exists a number of tablet volume-applied pressure relationships. These expressions in addition to having tablet volume and applied pressure parameters also contain constants which often are defined in physical terms. The most recognized of these expressions is the tablet porosity-applied pressure function according to Heckel.

Heckel analysis: The compression of a powder can be described in terms of a first-order reaction where the pores are the reactant and the densification the product. Based on this assumption, the following expression was derived:

$$\ln (1/e) = KP + A \quad \text{Equation 6} \quad (\text{Aulton M.E, 2013})$$

Which can also be written as

$$\ln (1/1-D) = KP + A \quad \text{Equation 7} \quad (\text{Santil M, 2012})$$

Where e is the tablet porosity, D is the relative density of the compact, P the applied pressure, A is a constant that reflects particle rearrangement and fragmentation, K is the slope of the linear part of the relationship and reflects particle deformation during compression. The reciprocal of K represents yield stress or yield pressure (P_y) for the particles. K is assumed to be one third of the yield stress of plastic particles. (Lum, 1999).

$$\ln (1/e) = P/P_y + A \quad \text{Equation 8} \quad (\text{Aulton M.E, 2013})$$

Constant A gives densification of the powder due to initial particle rearrangement, (D_a). (Patel S, 2006). A being the sum of two densification terms.

$$A = \ln [1/1-D_0] + B \quad \text{Equation 9}$$

Where $\ln [1/1-D_0]$ is related to the initial die filling and B gives densification due to slippage and rearrangement of primary and fragmented particles, (D_b). D_0 is defined as the densification due to die filling or initial powder packing.

$$D_a = 1 - e^{-A} \quad \text{Equation 10}$$

$$D_b = D_a - D_0 \quad \text{Equation 11}$$

Heckel plots can identify the predominant form of deformation in a given sample. Figure 4 (a) shows a heckel plot for a comparatively soft materials that undergoes plastic deformation retaining different degrees of porosity depending on the initial packing of the die. For example sodium chloride. Figure 4 (b) shows harder materials with higher yield pressure values that undergo compression by fragmentation first to provide a denser packing. For example lactose. Type 4 (a) heckel plots have a higher final slope than type 4 (b) therefore, as expected, they have a lower yield pressure value. Hard, brittle materials are more difficult to compress than soft, yielding ones. The crushing strength of tablets can be correlated with the value of K . High values of K usually indicate hard tablets. This information can be used as a means of binder selection when designing tablet formulations. In addition to the predictive capability, establishing behavioral patterns for a given formulation (fingerprinting) can provide important diagnostic information in case of batch failure.

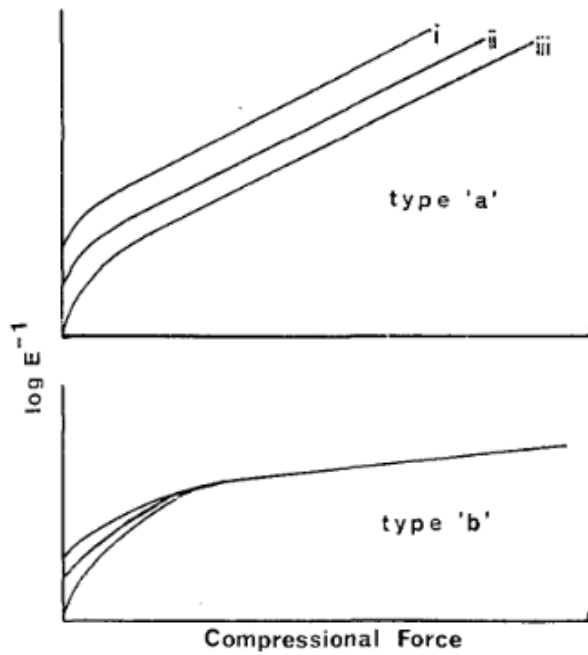


Figure 4 Example of heckel plots (Lachman L, et al., 1987).

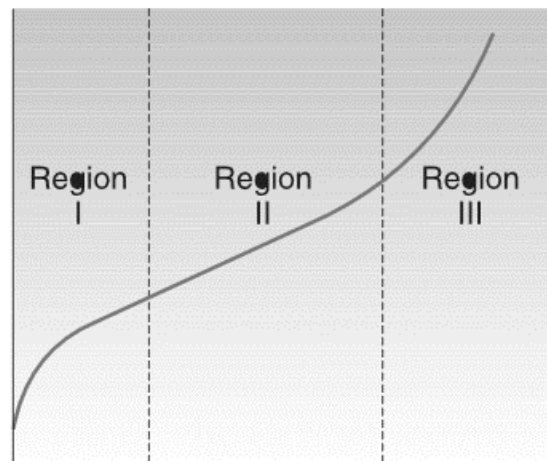


Figure 5 A heckel profile indicating the three regions of powder compression(Aulton M.E, 2013).

Figure 5 shows a typical heckel profile. The initial curvature in region 1 is associated with particle fragmentation and repositioning. Thereafter in region II, the relationship is linear over a substantial range of applied pressure. In this linear region, particle deformation controls the compression process and from the gradient of this linear

part, the yield pressure can be calculated. In region III, the profile deviates from the linear relationship and this curvature reflects the elastic deformation of the whole tablet.

Kawakita analysis: The kawakita equation describes the relationship between the volume reduction of powder column and the applied pressure.(Autamashih et al., 2011a).

$$P/C = (1/ab) + (P/a) \quad \text{Equation 12}$$

Where p is applied pressure, C the degree of volume reduction and a and b are constants.(Aulton M.E, 2013) The degree of volume reduction relates the initial height of the powder column (h_0) to the height of the powder column (the compact) at an applied pressure P (h_p) as follows

$$C = (h_0 - h_p)/h_0 \quad \text{Equation 13}$$

The equation is applied primarily to powders of solid particles.

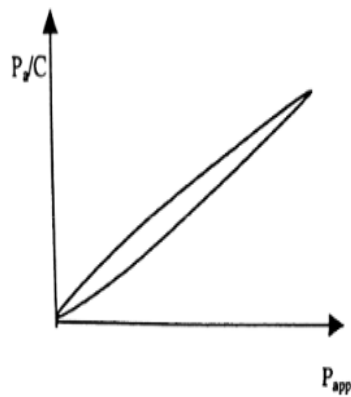


Figure 6 A kawakita compression profile (Comoglu, 2007).

Figure 6 shows a typical example a kawakita profile during compression of powder. A plot of P/C against P gives a straight line from which the constants a and b can be derived. The value a is equal to the initial porosity and b has the value of the reciprocal of stress but a good correlation has not been found between its value and any mechanical property of the particles used. (Comoglu, 2007) . In 1983, Kawakita applied another equation in describing the volume reduction on tapping and vibrating processes, where the pressure P is replaced by the tapping number N (Autamashih et al., 2011a).

$$N/C = (1/ab) + N/a \quad \text{Equation 14}$$

Where N is the tapping number, C is the volume reduction and a and b are constants.

C is given by

$$C = (V_0 - V_N) / V_0 \quad \text{Equation 15}$$

Where V_0 is the initial volume and V_N is the volume at tapping number N . The constant a describes the compressibility and $1/b$ the cohesive property of the powder.

Walker and Bal'shin equation: The walker equation was proposed in 1923.

$$V = a - K \ln P \quad \text{Equation 16}$$

Where V is the powder volume, P is the applied pressure and a and K are constants. K values were found to be high for plastically deforming particles compared to hard, brittle ones. In 1938, walker republished the equation as

$$\log P = -K \cdot V_{\text{app}} + C \quad \text{Equation 17}$$

Where V_{app} is the apparent specific volume. However the walker equation is of little use in modern time.

The cooper-Eaton model: This is based on the assumption that compression of powder takes place in two stages, filling of the voids in stage one and fragmentation and deformation of the particles in stage two.

$$(V_i - V_p) / (V_i - V_t) = C_3 \exp(-K_3/P_a) + C_4 \exp(-K_4/P_a) \quad \text{Equation 18}$$

Where C_3 , C_4 , K_3 and K_4 are constants.

The terms on the right side of the equation are related to the slippage of particles at early stages of the compaction and to the subsequent elastic deformation. The equation had the limitation of assignment of some physical significance to the constant parameters in the equation and applicability to a single-component system. Van der Zwan and Siskens proposed simplification of the Cooper-Eaton equation as

$$(V_i - V_p)(V_i - V_t) = C_5 \exp(-K_5/P_a) \quad \text{Equation 19}$$

Where C_5 is equal to the sum of C_3 and C_4 and K_5 is a new constant. These workers then reported that the Kawakita's constant b equals approximately to the reciprocal of K_5 in the simplified Cooper-Eaton model.

2.5.5 EVALUATION OF DIE WALL FRICTION DURING COMPRESSION.

Methods have been developed to assess the serious problem of friction during tableting. These methods are based on the use of force signals during powder compression or tablet ejection. In a single-punch press with a movable upper punch and a stationary lower punch, a force is applied by the upper punch and transmitted axially to the lower punch and also laterally to the die. The ejection of the tablet involves the application of an ejection force by the lower punch. Typical force profiles during compression in a single punch press are shown in Figure 7. When the descending punch establishes contact with the powder bed in the die, the force increases with compression time. The applied force rises to a maximum value and thereafter decreases during the decompression phase to zero. Force traces from the lower punch and the die wall will also be obtained. The force transmitted from the upper punch to the lower depends on a number of factors which can be summarized in the following expression

$$F_a = F_b e^{KL/D} \quad \text{Equation 20} \quad (\text{Aulton M.E, 2013})$$

Where F_a and F_b are applied and transmitted forces, L and D are the length and diameter of the powder column within the cylindrical die (figure 8) and K is a constant.

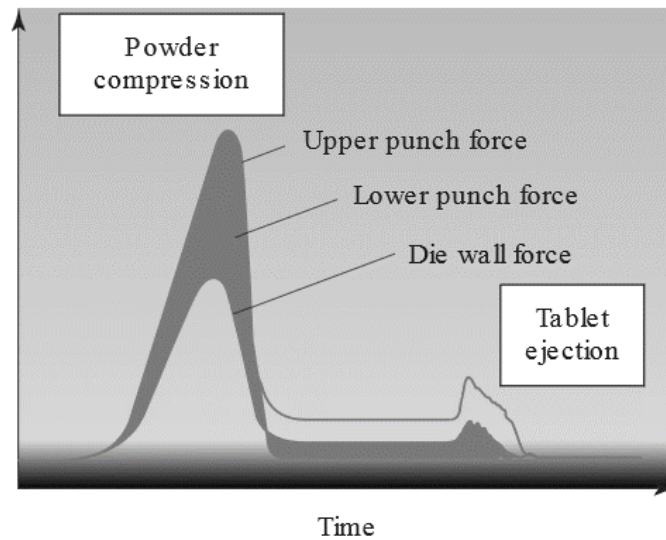


Figure 7 Force time signals during uniaxial powder compression (Aulton M.E, 2013).

The constant K is a function of the friction coefficient between particles and the die wall. Both the difference in transmitted force (upper punch force- lower punch force) and the ratio between the upper punch and lower punch force (denoted the R value) are used as measures of die wall friction. For a well lubricated powder, the force transmission corresponds to $R > 0.9$. Most tablets are created by uniaxially compressing powder within a die to a given displacement curve.(Stephens, J.D et al., 2012).

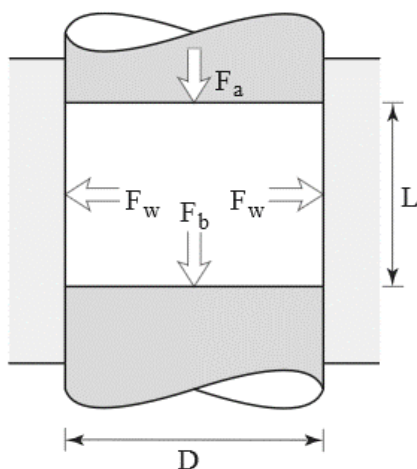


Figure 8 Punch and die wall Forces (Aulton M.E, 2013).

Ejection of the tablet results in an increased force signal from the lower punch, called the ejection force, which is a function of the lateral die wall force and the friction between the tablet and die wall. The friction coefficient (μ) is the ratio between the ejection force (F_e) and the die wall force (F_w) at the beginning of the ejection phase

$$\mu = F_e/F_w \quad \text{Equation 21}$$

Therefore to derive the measures of friction between powder or tablet and the die wall from force signals during tableting in a single-punch the procedure uses; force difference between upper and lower punch, force ratio between lower and upper punch, maximum ejection force and the friction coefficient during ejection.

2.6 POST COMPRESSION TESTS ON TABLETS

2.6.1 FRIABILITY TEST FOR UNCOATED TABLET (BP 2012 Appendix XVIII G)

A drum with an internal diameter between 283-291mm, a depth of between 36-40mm, of transparent, synthetic polymer with polished internal surfaces subject to minimum static build up is used. One side of the drum is used. The tablets are tumbled at each turn of the drum by a curved projection with an inside radius of 75.5-85.5 mm that extends from the middle of the drum to the outer wall. The outer diameter of the central ring is between 24.5-25.5mm. The drum is attached to the horizontal axis of a device that rotates at 25 ± 1 r/min. Thus at each turn the tablets roll or slide and fall onto the drum wall or onto each other. For tablets with a unit mass equal to or less than 650mg the sample taken should correspond as near as possible to 6.5g. For tablets with a unit weight of more than 650mg, take a sample of 10 whole tablets. The tablets are carefully dedusted prior to testing. The tablet sample is accurately weighed and placed in the drum. The drum is rotated 100 times and the tablets removed. Any loose particles from the tablets is removed and the tablets accurately weighed. If cracked, cleaved or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If the results are difficult to interpret or if the weight loss is

greater than the targeted value, the test is repeated twice and the mean of the 3 tests determined. A maximum loss of mass (obtained from a single test or from a mean of the 3 tests) not greater than one per cent is considered acceptable for most products.

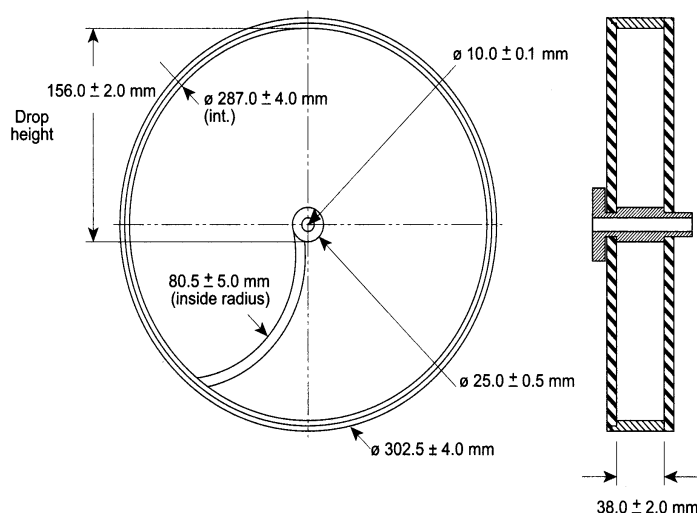


Figure 9 Friability testing machine (BP 2012 Appendix XVIII G)

2.6.2 DISINTEGRATION TEST FOR TABLETS (BP 2012 APPENDIX XII A)

This test is provided to determine whether tablets disintegrate within the prescribed time when placed in a liquid medium. Complete disintegration is that state in which any residue of the dosage unit remaining on the screen of the dosage apparatus, is a soft mass having no palpably firm core.

The apparatus consists of a basket-rack assembly, a 1 litre, low form beaker, 149 ± 11 mm in height and having an inside diameter of 106 ± 9 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35°C and 39°C and a device for raising and lowering the basket in the immersion fluid at a constant frequency between 29 and 32 cycles per minute, through a distance of 55 ± 2 mm.

The basket rack assembly consists of 6 open-ended transparent tubes, each 77.5 ± 2.5 mm long and having an inside diameter of 21.85 ± 1.15 mm and a wall 1.9 ± 0.9 mm thick; the tubes are held in a vertical position by 2 plates, each 90 ± 2 mm in diameter and 6.75 ± 1.75 mm in thickness, with 6 holes, each 24 ± 2 mm in diameter equidistant from the centre of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a woven stainless steel wire cloth, which has a plain square weave with 2.0 ± 0.2 mm mesh apertures and with a wire diameter of 0.615 ± 0.045 mm. The parts of the apparatus are assembled and rigidly held by means of 3 bolts passing through the 2 plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid, and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged. The time required for the upward stroke is equal to the time required for the downward

stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket rack moves vertically along its axis. There is no appreciable horizontal movement or motion of the axis from the vertical.

The procedure involves placing one dosage unit in each of the 6 tubes of the basket, and if prescribed, adding a disc. The apparatus is operated using the specified medium, maintained at $37 \pm 2^\circ\text{C}$. At the end of the specified time the basket is lifted from the fluid and the dosage units observed. All of the dosage units should have completely disintegrated. If 1 of 2 dosage units fail to disintegrate, the test is repeated on 12 additional dosage units. The requirements of the test are met if not less than 16 of the 18 dosage units tested have disintegrated.

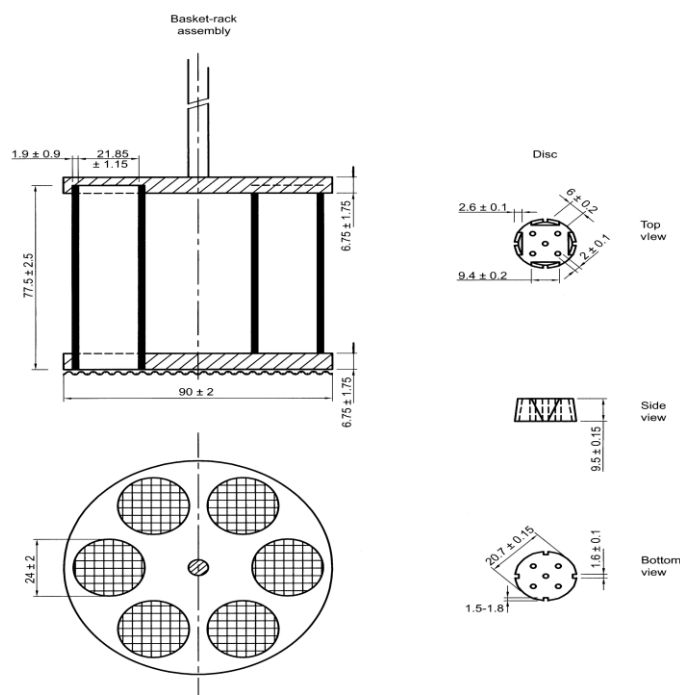


Figure 10 Disintegration test apparatus (BP 2012 Appendix XIA)

2.6.3 RESISTANCE TO CRUSHING OF TABLETS (BP APPENDIX XVIII)

This test is intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing.

The apparatus consists of two jaws facing each other, one of which moves towards the other. The flat surfaces of the jaws are perpendicular to the direction of movement. The crushing surfaces of the jaws are flat and larger than the zone of contact with the tablet. The apparatus is calibrated using a system with a precision of 1 newton.

The operating procedure involves placing the tablet between the jaws, taking into account, where applicable, the shape, the break-mark and the inscription; for each measurement the tablet is oriented in the same way with respect to the direction of application of the force.

The results are expressed as the mean, minimum and maximum values of the forces measured. The type of apparatus used is indicated and, where applicable, the orientation of the tablets.

2.6.4 BRITTLE FRACTURE INDEX

Brittle fracture refers to capping and lamination of tablets, which occurs at the point of ejection of the tablets from the machine dies. The problem is attributable to the presence of entrapped air or low density regions in the tablet. Sudden elastic recovery following tablet ejection from the die has been implicated as a possible cause of brittle fracture. Voids and low density regions constitute weak points in the tablet from which cracks emanate and propagate when the tablet is subjected to diametrical stress (Okor, 2005). Elastic materials are more prone to brittle fracture than plastic materials. Plastic materials ameliorate brittle fracture because they deform readily under stress to relieve the stress that would have concentrated at the edge of the void. Binders act to ameliorate capping and lamination by decreasing the plastoelasticity of pharmaceutical powders (Okoye et al., 2012). Brittle fracture index (BFI) is a measure of the tablet tendency to laminate or cap during manufacture (Uhumwangho et al., 2006). It is given by the equation developed by Hiestand et al.

$$\text{BFI} = 0.5 \left[\frac{T}{T_0} - 1 \right] \qquad \text{Equation 22}$$

Where T and T₀ are the tensile strengths of the tablets with and without the centre hole. The centre hole ($\leq 0.6\text{mm}$) is a built-in model defect to simulate actual void formed in the tablet during compression. The BFI value has a range of 0 (no fracture tendency) to 1 (Maximal fracture tendency). Tablet samples with BFI ≥ 0.5 display a high fracture tendency during tableting.

2.6.5 CRUSHING STRENGTH FRIABILITY RATIO

The crushing strength-friability ratio (CSFR) can be used to measure the mechanical strength of tablets (J. Muazu et al., 2009). CSFR is a quotient of crushing strength to the friability. High CSFR values are indicative of tablets with greater mechanical strength relative to the tablets with low CSFR values.

2.6.6 CRUSHING STRENGTH FRIABILITY/DISINTEGRATION TIME RATIO

The Crushing Strength friability/Disintegration time ratio (CSFR/DT ratio) has been suggested as a better index for measuring tablet strength (crushing) and weakness (friability), it simultaneously evaluates the negative effects of these parameters on disintegration time. A higher value of CSFR/DT ratio shows a better balance between binding and disintegration properties. Generally the higher the CSFR/DT ratio the better the disintegration of the tablet (Alebiowu and Adeagbo, 2009).

CHAPTER THREE: METHODOLOGY

3.1 STUDY DESIGN

This research project was an experimental study.

3.2 STUDY LOCATION

This study was carried out at the pharmaceuticals laboratories of the department of pharmaceuticals and pharmacy practice, school of pharmacy, college of health sciences, University of Nairobi, Kenya.

3.3 MATERIALS

Paracetamol powder BP (Changushu haugang pharmaceutical Co. Ltd. Yuaiang Yetang Changshu City Siangsu province, China), white corn starch BP (BDH chemicals Ltd. Poole England), Magnesium stearate BP (Sigma Aldrich Co. 3050 Spruce street, St. Louis MO 63103 U.S.A), Potassium Sorbate BP (Rugao chingjiang food company ltd. Tonggang road, changjiang town, Rugao city 226532 Jinangsu, China), Povidone K90 (BASF SE Carl – Bosch – street 38 67 056 Ludwigshafen Germany), Povidone K30 (BASF SE Carl – Bosch – street 38 67 056 Ludwigshafen Germany). The Potassium Sorbate BP was gifted by lab and allied company, Kenya.

3.4 EQUIPMENT

Porcelain mortar and pestle, Mesh sieves (710 μ m, 355 μ m, 180 μ m), planetary mixer, Tablet press (Erweka, electric type, Germany), Disintegration test machine (Erweka 2T3, GmbH Heusentamm, Germany), Friability tester Machine (Erweka, Heusentamm type TA3R, Germany), Hardness tester machine (Schleuniger mod 2E/205 Switzerland), Electronic digital caliper (Wezu).

3.5 METHOD

3.5.1 PREPARATION OF DRY TABLETING MIXTURE

A 300g batch formulation of paracetamol (85%w/w), corn starch (13%w/w) and potassium sorbate (2%w/w) was dry mixed.

3.5.2 PREPARATION OF GRANULES

The wet granulation method of massing and screening was used. The 300g batch formulation of paracetamol (85%w/w), corn starch (13%w/w) and potassium sorbate (2%w/w) was split into five batches. A 5% w/w binder concentration made of binary mixtures of povidone k90 and povidone k30 in the ratios of 0:1, 1:3, 1:1, 3:1 and 1:0 was added and mixed in dry form to the five batches. The batches were massed with the appropriate amount of distilled water for 5 minutes. The wet mass was forced through a 710 μ m mesh sieve and dried in a hot air oven at 50°C for 70 minutes. The dried granules were passed through a series of sieves of sizes 710 μ m, 355 μ m and 180 μ m. 20% of the fines were reintroduced into the sieved granules. The sieved granules were lubricated with 1% magnesium stearate and stored in airtight plastic containers for evaluation of flow properties.

3.5.3 EVALUATION OF FLOW PROPERTIES

3.5.3.1 BULK AND TAPPED DENSITIES.

The bulk volume (V_B) was measured by determining the volume occupied by a 50g sample introduced in a 100ml measuring cylinder. The bulk density (ρ_B) was determined from the equation:

$$\rho_B = \frac{W}{V_B} \text{ g/ml} \quad \text{Equation 23}$$

The tapped volume (V_T) was determined by tapping the cylinder from a fixed height on a soft base until there was no further reduction in volume. The tapped density (ρ_T) was calculated from the equation:

$$\rho_T = \frac{W}{V_T} \text{ g/ml} \quad \text{Equation 24}$$

3.5.3.2 COMPRESSIBILITY INDEX AND HAUSNER RATIO

The compressibility index (C.I) and hausners ratio (H.R) were determined from the bulk density (ρ_B) and tapped density (ρ_T) using the following equations:

$$\text{C.I} = \frac{\rho_T - \rho_B}{\rho_T} * 100 \quad \text{Equation 25}$$

$$\text{H.R} = \frac{\rho_T}{\rho_B} \quad \text{Equation 26}$$

3.5.3.3 ANGLE OF REPOSE

A 50g sample was allowed to fall through a funnel from a fixed height to form a cone. The height of the heap (h) was determined. The base of the heap was traced out using a pencil and its radius (r) determined. The angle of repose was determined from the equation:

$$\text{Tan } \Theta = \frac{h}{r} \quad \text{Equation 27}$$

3.5.3.4 FLOW RATE

A funnel was firmly secured to a retort stand. A 50g (W) sample was allowed to fall freely under gravity and the time of flow (t) in seconds noted. The flow rate (R) was calculated from the expression:

$$\text{R} = \frac{W}{t} \text{ g/s} \quad \text{Equation 28}$$

Each experiment was conducted three times. The mean value and standard deviation was determined.

3.5.4 COMPRESSION OF GRANULES

Granules of size fraction 710 μ m - 180 μ m were used to prepare 375mg \pm 15mg tablets using a single, electric tablet press iEP-1 (Erweka Germany) fitted with 10mm flat punch and die set. A fixed compression load was used after the pretrials.

Table 4 Tablet formula

No.	Material	B1	B2	B3	B4	B5
1	Paracetamol	80.00 (300mg)	80.00 (300mg)	80.00 (300mg)	80.00 (300mg)	80.00 (300mg)
2	Corn starch (disintegrant)	13.00 (48.75mg)	13.00 (48.75mg)	13.00 (48.75mg)	13.00 (48.75mg)	13.00 (48.75mg)
3	Potassium Sorbate (preservative)	1.00 (3.75mg)	1.00 (3.75mg)	1.00 (3.75mg)	1.00 (3.75mg)	1.00 (3.75mg)
4	PVP K-30 (binder)	0.00 (0.00mg)	1.25 (4.69mg)	2.50 (9.37mg)	3.75 (14.06mg)	5.00 (18.75mg)
5	PVP K-90 (binder)	5.00 (18.75mg)	3.75 (14.06mg)	2.50 (9.37mg)	1.25 (4.69mg)	0.00 (0.00mg)
6	Magnesium stearate (lubricant)	1.00 (3.75mg)	1.00 (3.75mg)	1.00 (3.75mg)	1.00 (3.75mg)	1.00 (3.75mg)
7	Total	100 (375mg)	100 (375mg)	100 (375mg)	100 (375mg)	100 (375mg)

3.5.5 POST-COMPRESSION TESTS OF TABLETS.

The tablets were tested for uniformity of weight, disintegration time, crushing strength and friability.

3.5.5.1 UNIFORMITY OF WEIGHT

Twenty tablets were picked at random and individually weighed. The percentage deviation of individual weight from the average weight was determined.

3.5.5.2 DISINTEGRATION TEST

The disintegration test was determined in distilled water at $37 \pm 0.5^{\circ}\text{C}$ in a six unit disintegration unit (Erweka 2T3, GmbH Heustentamm, Germany). Tablets were placed on the wire mesh just above the surface of the distilled water in the tube. The time taken for each of the tablet to disintegrate and all the granules to go through the mesh was recorded.

3.5.5.3 CRUSHING STRENGTH TEST

A Schleuniger hardness tester (mod 2E/205, Switzerland) was used to determine the load required to diametrically break the tablet into two halves. The mean of five readings was taken.

3.5.5.4 FRIABILITY TEST

The friability of the tablets was determined by a friability test machine (Erweka, Heustentamm type TA3R, Germany) operated at 25 revolutions per minute for 4

minutes. 20 tablets were selected at random and their weights taken before and after friabilation. The percentage weight loss and friability was determined.

CHAPTER FOUR: RESULTS AND DISCUSSION

4.1 FORMULATION OF GRANULES

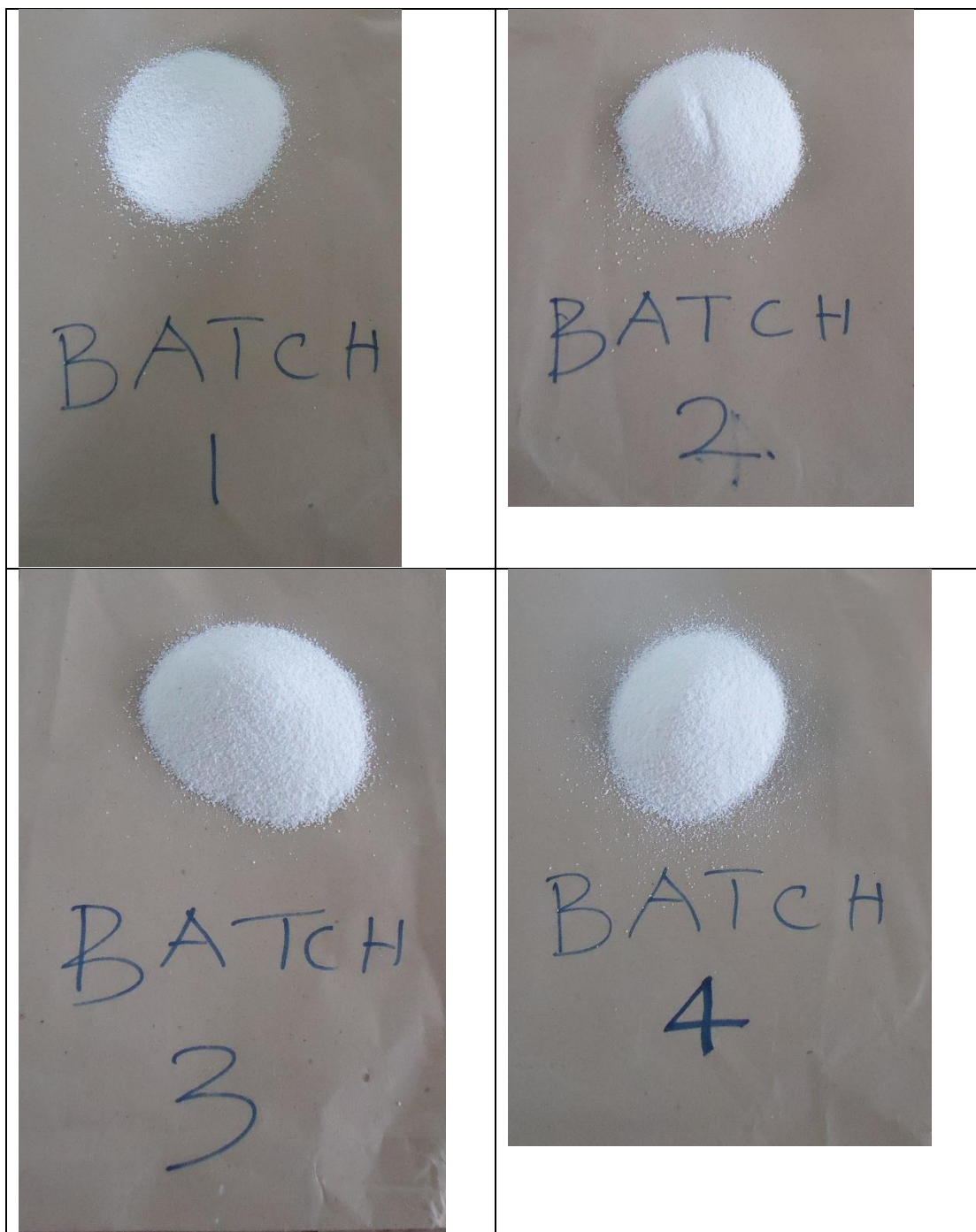


Figure 11 Batch 1, Batch 2, Batch 3 and Batch 4 granules

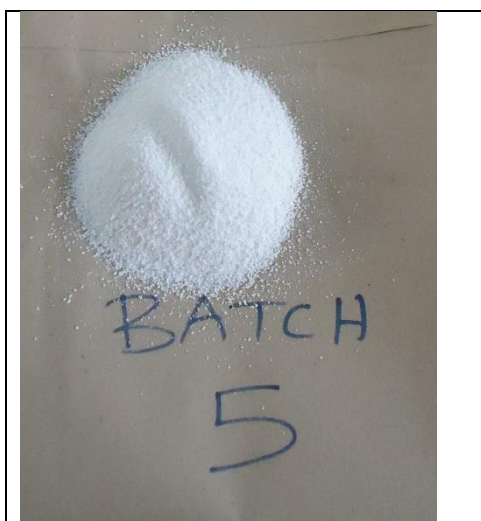


Figure 12 Batch 5 granules

4.2 GRANULE PROPERTIES

Table 5 Table of granule densities and flow properties

PARAMETER	BATCH 1	BATCH 2	BATCH 3	BATCH 4	BATCH 5
5%w/w binder ratio K90:K30	1:0	3:1	1:1	1:3	0:1
Bulk Density (g/ml)	0.50	0.48	0.48	0.48	0.48
Tapped Density(g/ml)	0.59	0.56	0.59	0.59	0.63
Compressibility Index(%) n=3	14.77±0.84	13.77±0.90	19.10±0.79	19.55±0.79	23.93±0.23
Hausner's Ratio n=3	1.17±0.01	1.16±0.01	1.24±0.01	1.24±0.01	1.31±0.01
Angle of Repose(°) n=3	23.77±0.92	28.77±0.58	23.47±0.92	27.93±0.11	24.13±0.23
Flow rate (g/s) n=3	2.46±0.07	2.59±0.08	2.08±0.09	2.38±0.11	1.97±0.05

Figures 9 and 10 show pictures of batches 1,2,3,4 and 5 of the granules formulated with binary mixtures of a 5% w/w Povidone K90 and Povidone K30 in the ratio of 1:0, 3:1, 1:1, 1:3 and 1:0 respectively.

Table 3 shows granule properties of bulk density, tapped density, compressibility index, hausner's ratio, angle of repose and flow rate.

Batch 2 had the lowest compressibility index and hausner's ratio of 13.77 % and 1.16 while batch 5 had the highest compressibility index and hausner's ratio of 23.93 % and 1.31. Batch 3 had the lowest angle of repose of 23.47°. Batch 2 had the highest flow rate of 2.59 g/s and batch 5 had the lowest flow rate of 1.97 g/s.

For Passable flow of granules, the flow parameters specified are compressibility index of < 25 , Hausner's ratio < 1.34 and angle of repose $< 45^\circ$. Based on these specifications all the batches had granules with passable flow properties.

4.3 TABLET PROPERTIES AND EVALUATION

4.3.1 APPEARANCE

The tablets were circular, smooth, shiny and white.

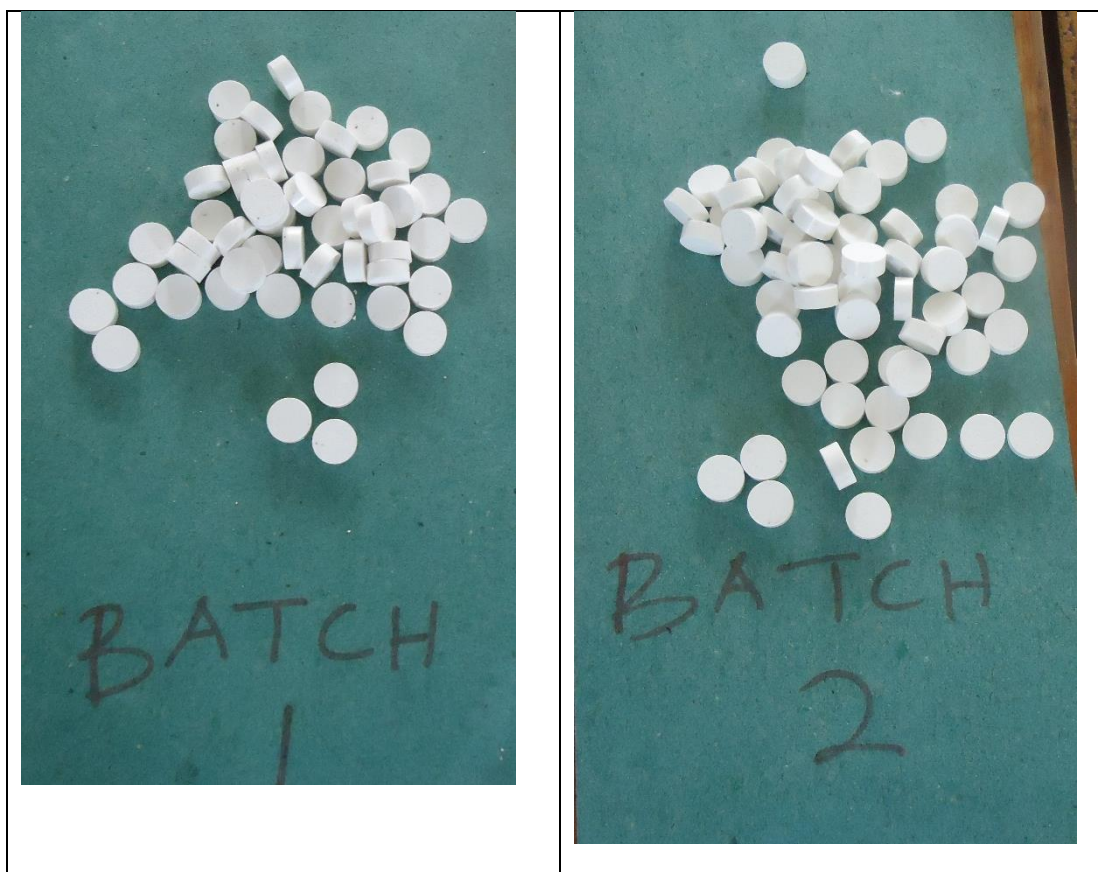


Table 6 Batch 1 and Batch 2 Tablets

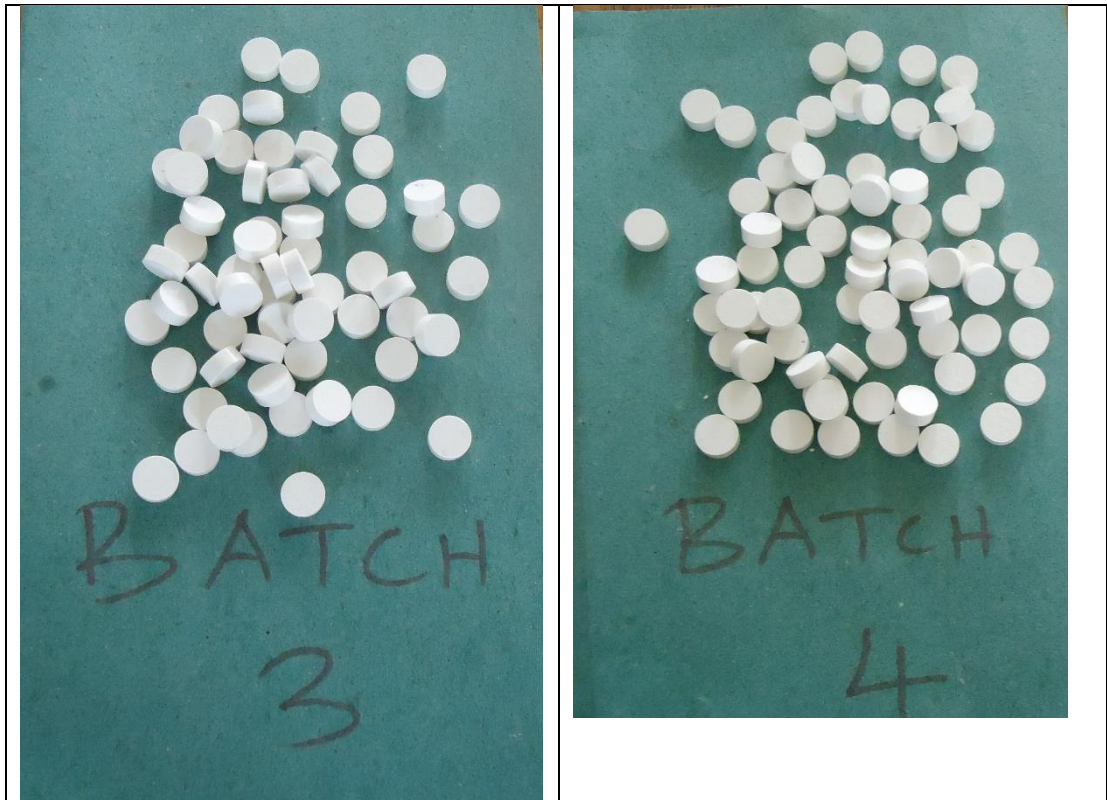


Figure 13 Batch 3 and Batch 4 tablets



Figure 14 Batch 5 tablets

4.3.2 POST COMPRESSION TESTS ON TABLETS

Table 7 Table on post compression tests on tablets

PARAMETER	BATCH 1	BATCH 2	BATCH 3	BATCH 4	BATCH 5
5%w/w binder ratio K90: K30	1:0	3:1	1:1	1:3	0:1
Tablet thickness(mm) ±SD n=3	4.11±0.05	4.10±0.07	3.95±0.04	3.90±0.08	4.00±0.10
Tablet diameter(mm) ±SD n=3	9.93±0.01	9.92±0.01	9.94±0.03	9.92±0.02	9.95±0.01
Uniformity of weight(mg) ±SD	390±0.01	380±0.01	380±0.01	370±0.01	380±0.01
Crushing strength (kgf) ±SD	9.08±0.81	9.12±1.27	12.88±0.94	11.36±0.82	13.00±0.14
Friability (%) ±SD n=3	0.34±0.14	0.88±0.08	0.69±0.08	0.91±0.08	1.05±0.14
Crushing strength/Friability Ratio (CSFR)	26.71	10.36	18.67	12.48	12.38
Disintegration Time(min) ±SD n=3	99.55±16.56	30.74±18.20	14.97±5.81	2.51±0.77	4.10±1.22
Crushing strength friability ratio: Disintegration time (CSFR:DT)	0.26	0.33	1.24	4.97	3.01

Tablet thickness should be controlled within a $\pm 5\%$ variation of a standard value (B. Samyutharini et al., 2013). Batch 1 and 3 had tablet thickness that was within $\pm 5\%$ variation of a standard value. Batch 2, 4 and 5 had tablet thickness that was outside the $\pm 5\%$ variation of a standard value.

Crushing strength is not an official test. Different limit ranges of crushing strength have been stated. 4Kgf - 7Kgf (H Musa et al., 2010), 4Kgf – 10Kgf (Bendari et al., 2015), 4Kgf – 15Kgf (Autamashih et al., 2011). All the batches had their crushing strength values between 4Kgf and 15Kgf.

All the tablet batches were within the targeted $375\text{mg} \pm 15\text{mg}$ tablet weight. BP (2012) Appendix XIIC specifies that the percentage mass deviation of uncoated tablets with an average mass of more than 250mg should not be more than 5%. Within each batch, none of the individual weights deviated from the average weight by $\pm 5\%$. The tablets thus complied with the BP (2012) specifications for uniformity of weight. Batch 1 tablets had the highest average weight of 390mg and batch 4 tablets had the lowest average weight of 370mg.

Crushing strength/friability ratio (CSFR) has been used as an index of the mechanical strength of tablets (Autamashih et al., 2011). High CSFR values indicate stronger tablets. Batch 1 tablets with 100% povidone K90 presented the highest CSFR of 26.71. Batch 5 containing 100% povidone K30 showed a CSFR OF 12.38. This shows that povidone K90 produced stronger tablets and had a higher binding power than povidone K30. Binders increase the cohesiveness of the particles and impart mechanical strength to the tablets.

Crushing strength friability ratio /disintegration time ratio (CSFR/DT) has been suggested as a better index than CSFR in measuring tablet quality. In addition to measuring tablet strength (crushing) and weakness (friability), it also evaluates the negative effects of these parameters on disintegration time. Higher CSFR/DT values indicate a better balance between binding and disintegration properties (Femi-Oyewo et al., 2015). Batch 4 had the highest CSFR/ DT ratio of 4.97. The order of CSFR: DT in ranking was batch4>batch5>batch 3>batch2>batch1.

Based on the BP (2012) specifications for disintegration time for uncoated tablets (< 15 minutes), batches 3, 4 and 5 complied.

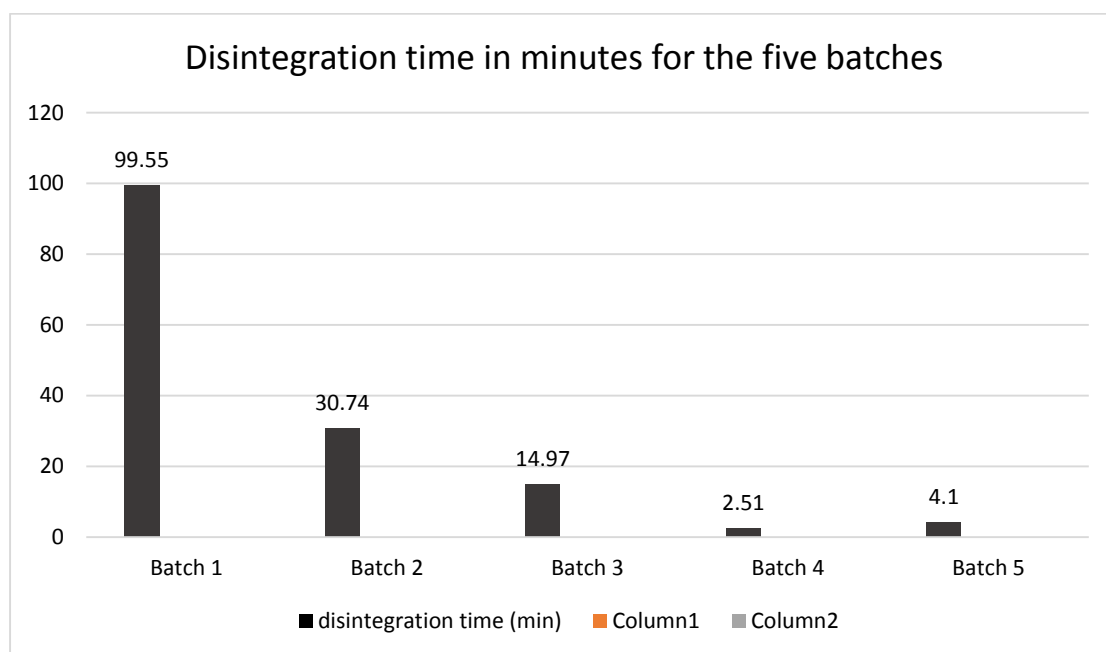


Figure 15 Disintegration time for the five batches

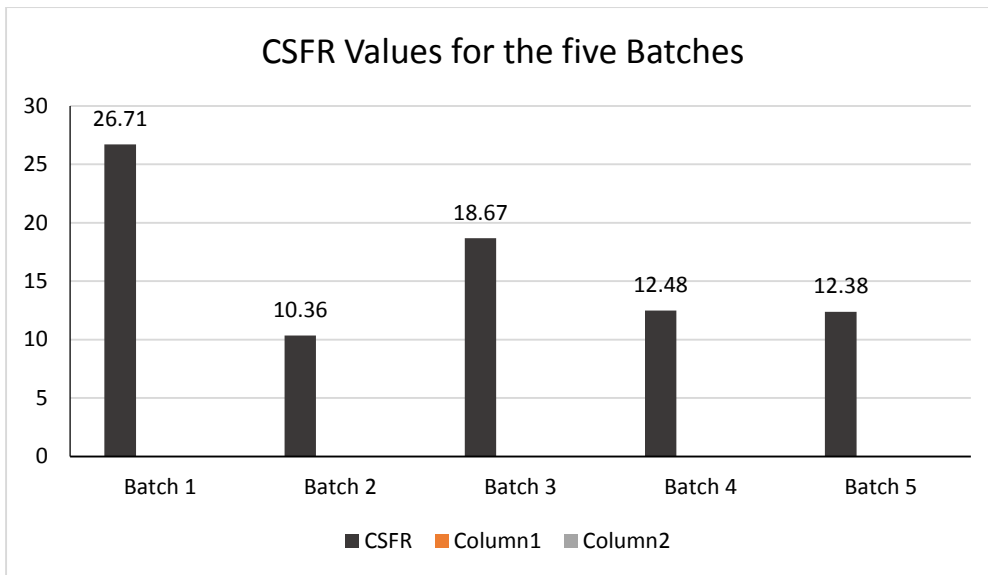


Figure 16 CSFR Values for the five batches

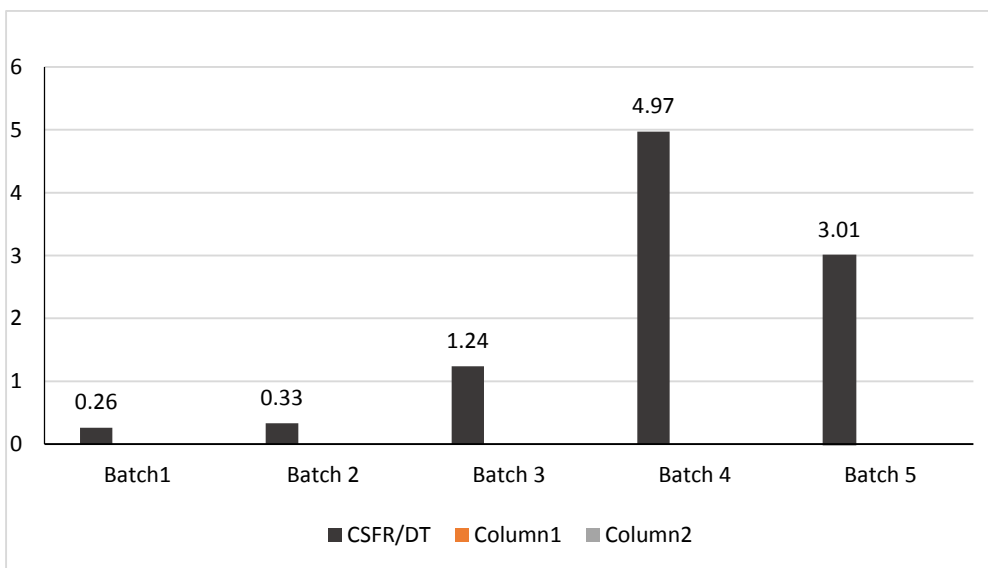


Figure 17 CSFR/DT Values for the five batches

Statistical analysis involved modelling for crushing strength friability ratio (CSFR) and crushing strength friability ratio: disintegration time (CSFR:DT) using R statistical software version 3.2.0

Table 8 Table of modelling for crushing strength friability ratio (CSFR)

FORMULATION/MODELS	Coefficients	Standard error	t value	Pr (> t)
BATCH 1	26.7059	0.6456	41.366	P<0.0005
BATCH 2	-16.3422	0.9130	-17.899	P<0.0005
BATCH 3	-8.0392	0.9130	-8.805	P<0.0005
BATCH 4	-14.2224	0.9130	-15.577	P<0.0005
BATCH 5	-14.3249	0.9130	-15.690	P<0.0005

R²=0.955 Adjusted R²=0.9466, F=107.3, 95%, P<0.005

Interpretation:

The above model shows that batch1 had the highest crushing strength friability ratio (highest coefficient=26.7 and t=41.37 P<0.0005).

The model was fitted and it was statistically significant (adjusted R²=0.9466, P<0.0005). The residuals were normally distributed with a mean of zero and a constant variance.

The line graph re-emphasizes the regression model findings:

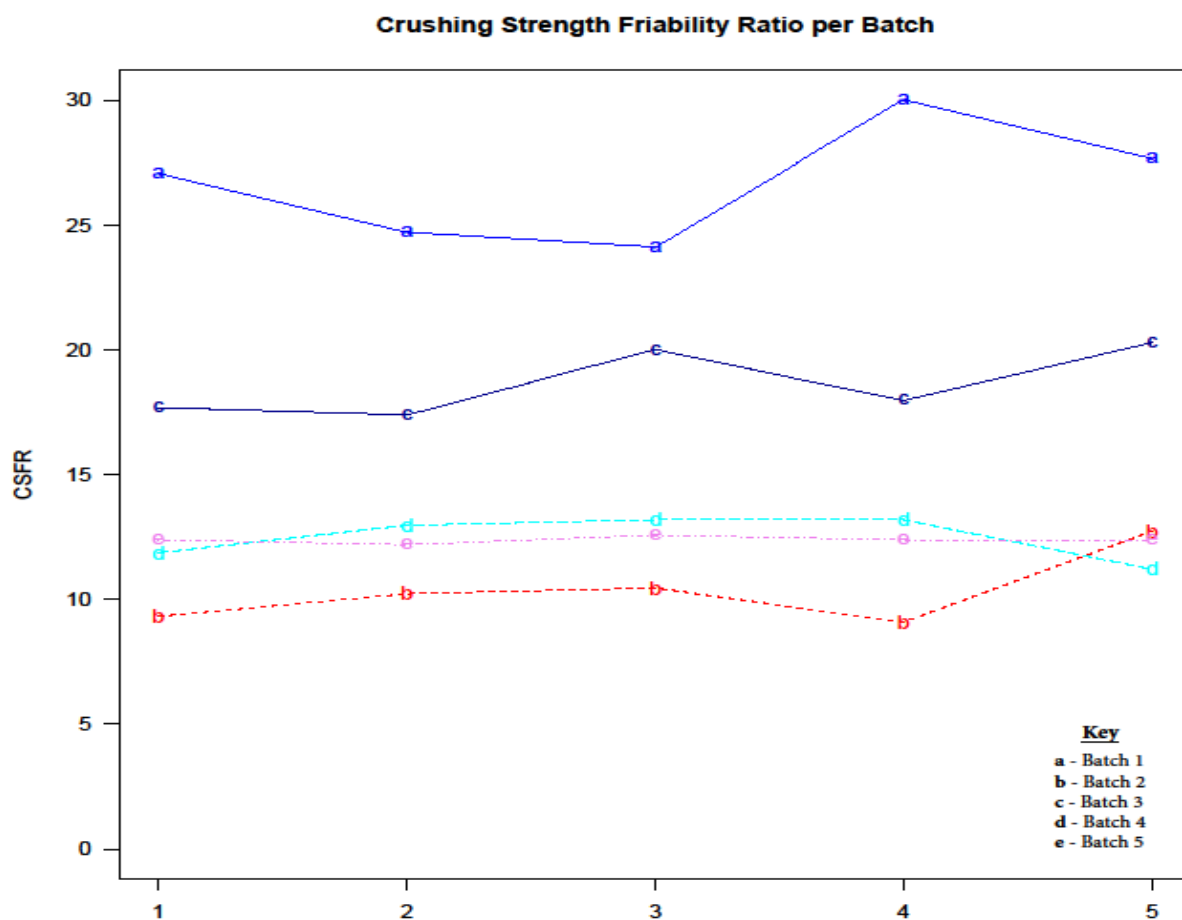


Figure 18 line graph on the model fittings for crushing strength Friability Ratio (CSFR)

Table 9 Table of Modelling for crushing Strength Friability Ratio/Disintegration time (CSFR/DT)

FORMULATION/MODELS	Coefficients	Standard error	t value	Pr (> t)
BATCH 1	0.2505	0.4059	0.617	P=0.5442
BATCH 2	0.2518	0.5741	0.439	P=0.6657
BATCH 3	1.3138	0.5741	2.289	P=0.0331
BATCH 4	5.5200	0.5741	9.615	P<0.0005
BATCH 5	3.2505	0.5741	5.662	P<0.0005

R²=0.8669 Adjusted R²=0.8402, F=32.56, 95%, P<0.0005

Interpretation:

The model on crushing strength friability ratio: disintegration time indicated that batch 4 had the best mechanical property since it had the highest regression coefficient 5.52, t=9.615 and P<0.0005. Batch 1 had the lowest coefficient of 0.2505, the p value of 0.5442

was not statistically significant therefore the conclusion of bath 1 having the worst mechanical strength cannot be made.

The model was fitted and was statistically significant (adjusted $R^2=0.8402$, $P<0.0005$) and all the residual were normally distributed with a mean of zero and a constant variance.

The graph below can also be used to emphasize the regression model findings:

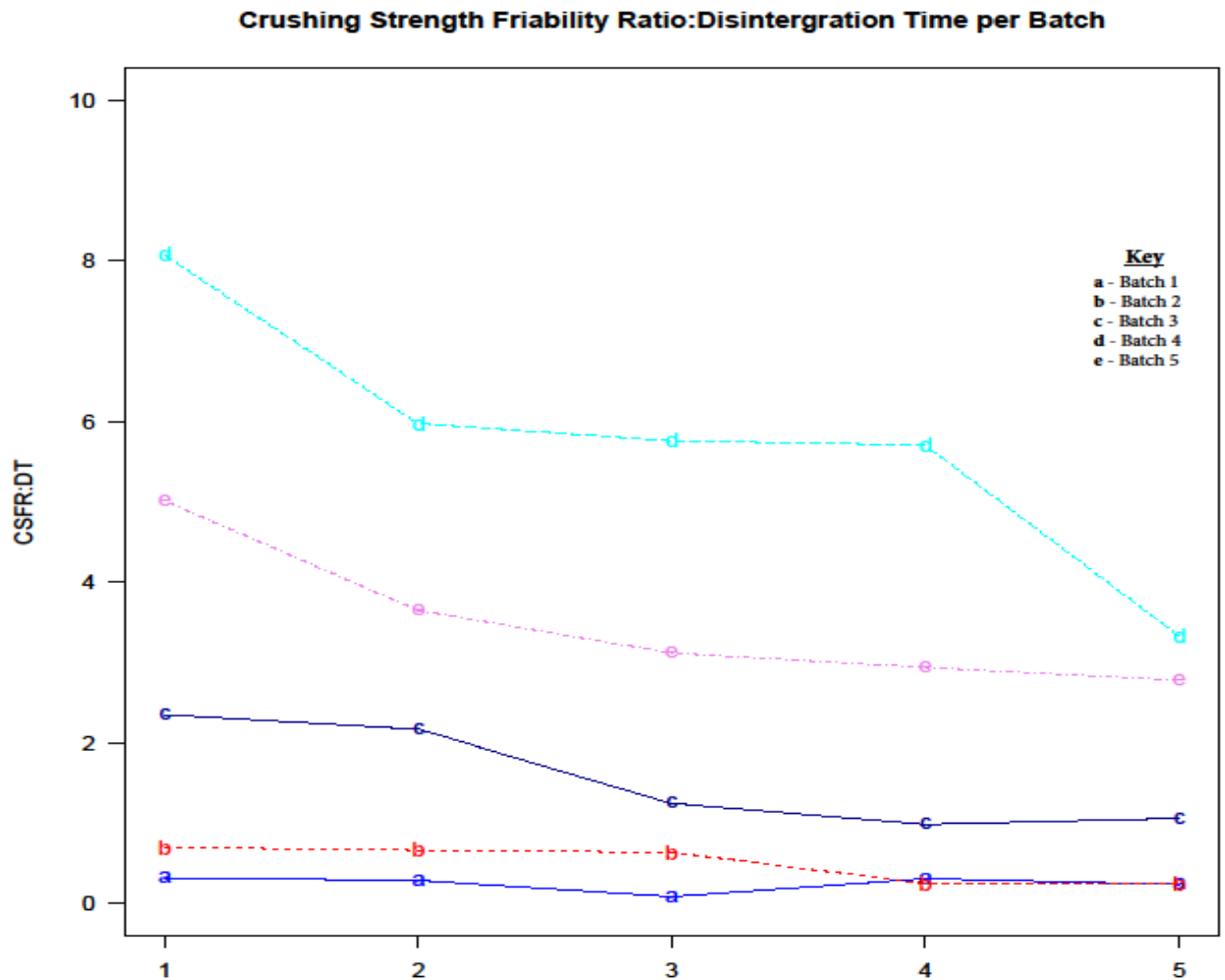


Figure 19 Line graph on the model fittings for crushing strength friability ratio/disintegration time (CSFR/DT)

CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS

Batch 1 tablets (povidone K90: Povidone K30 of 1:0) have the highest mechanical strength ($p < 0.005$) due to the highest coefficients in the modelling for crushing strength friability. This means that povidone K90 has the highest binding power. Batch 4 tablets with a kollidon K90: Kollidon K30 binder ratio of 1:3 have the best mechanical property ($p < 0.0005$) due to their highest coefficients in the modelling for crushing strength friability ratio to disintegration time (CSFR: DT).

The results suggest that a binary binder mixture of Kollidon 90 and Kollidon K30 in the ratio of 1:3 results in Paracetamol tablets with the best mechanical properties.

Further studies on the effect of kollidon K90 and kollidon K30 on the compressibility profile of the Paracetamol containing properties is recommended.

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