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EVALUATION OF THE FRUIT MUCILAGE OF *CORDIA AFRICANA* AS TABLETBINDER IN PARACETAMOL TABLET FORMULATION: OPTIMIZATION USING RESPONSE SURFACE METHODOLOGY

BY

TEWODROS AYALEW TESSEMA (B.PHARM)

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Evaluation of the Fruit mucilage of *Cordia africana* as Tablet Binder in Paracetamol Tablet Formulation: Optimization Using Response Surface Methodology

By

Tewodros Ayalew (B.pharm)

A Thesis Submitted to School of Pharmacy, Department of Pharmaceutics and Social Pharmacy in Partial Fulfillment of the Requirements for the degree of Master of Science in Pharmaceutics.

Under the Supervision of Dr.Nisha Mary Joseph and Mr.Fantahun Molla, Department of Pharmaceutics and Social Pharmacy, Addis Ababa University

ADDIS ABABA UNIVERSITY

This is to certify that the thesis prepared by Tewodros Ayalew Tessema, entitled *"*Evaluation of the Fruit Mucilage of *Cordia africana* as Tablet Binder in Paracetamol Tablet Formulation: Optimization Study Using Response Surface Methodology" submitted in partial fulfillment of the requirements of the Degree of Master of Science in Pharmaceutics complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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ABSTRACT

Cordia africana Lam. (Amharic-wanza) (family: Boraginaceae) is a medium-sized evergreen treethat grows up to 4- 15 m with edible sticky fruits. It is native to Africa and is abundant in East Africa. The fruit mucilage of different species of cordia isfound to be an excellent binder in tablet manufacturing. However, the binding ability of the cordiana african is not yet established. Therefore, this study aimed to evaluate the binding ability of *Cordia africana* fruit mucilage in tablet formulations using paracetamol as a model drug.

The fruit mucilage of Cordia africana was extracted with maceration technique and characterizedfor different properties such as its compatibility with the model drug using the differential scanning calorimeter (DSC), the Fourier transform infrared spectroscopy (FTIR), surface morphology using scanning electron microscopy (SEM), and its crystallinity nature with X-ray Diffractometer (XRD). Furthermore, it was evaluated for loss on drying and moisture sorption studies. The mucilage was used to prepare granules using wet granulation method and finally compressed into tablet. The prepared tablets were evaluated for their hardness, disintegration time, friability, and drug release profile. Based on the preliminary study, concentration of disintegrant (starch -1500 (5-15%), mucilage concentration (3-10%), and compression force (50-100 N) were found to affect the response variables (Friability and Drug release) significantly (p value < 0.05). Therefore, the effect of these independent variables were further studied and optimized using the central composite design (CCD).

The yield of extracted Cordia mucilage powder was found to be 29 %±0.9. The FTIR and DSC studies revealed that the mucilage is compatible with the model drug. The mucilage has shown no sharp peaks with noisy signal which was due to its amorphous nature. The loss on drying and moisture sorption studies were found to be 6%±0.02 and 1.3%-6.7%, respectively. The granules exhibited a good flowability and compressibility properties. All the prepared tablets have shown hardness value of less than 100 Nand disintegration time in range from 0.55 to 10.27 minutes. The optimization study indicated that the quadratic model was the best fit model for both responses as per the model fitness summary. Furthermore, the ANOVA analysis for model adequacy testing confirmed the adequacy of the model for optimization.

Accordingly, the model provided an optimum formulation at 5.32% of mucilage concentration, 5 % of disintegrant, and 76.71 N of compression force. Under this condition, the software predicted 83.3 % drug release at 30 minutes and 0.63% of friability. The validity of this optimum formulation was confirmed experimentally. The flowability of the granule of optimized tablet was found excellent as the angle of repose was found to be $<30^{o}$ while the Carr's and Hausner ratios were determined as < 10 and < 1.11, respectively. Therefore, the results of this study suggest that the Cordia mucilage can be used as a tablet binder in tablet manufacturing.

Keywords: *Cordia Mucilage, Binder, central composite design, Response Surface Methodology, Optimization, paracetamol*

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LIST OF ACRONYMS

BP----------British Pharmacopoeia

CCD ---------- Central Composite Design

CF----------Compression Force

CM----------Cordia Mucilage

DSC ----------Differential Scanning Calorimeter

FTIR---------- Fourier Transform Infrared Spectroscopy

HCL ----------Hydrochloric Acid

HPMC---------- -Hydroxyl propyl methyl cellulose

IP----------Indian Pharmacopoeia

OT----------Optimized Tablets

REV/MIN----------Revolution per Minute

RSM---------- Response Surface Methodology

SEM ---------- Scanning Electron Microscope

ST----------Starch

TWM----------Tablet with Mucilage

TWSB---------- --Tablet with standard binder

UV/VIS ----------Ultraviolet Visible Spectroscopy

XRD---------- X-RayDiffractometer

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1. INTRODUCTION

1.1. Natural Polymers

A polymer is a large molecule (macromolecules) composed of repeating structural units that are typically connected by covalent chemical bonds. Both synthetic and natural polymers are available but the use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available and non-toxic. Moreover, the natural polymers are capableof chemical modifications, potentially biodegradable and with few exceptions, also biocompatible (John and Thomas, 2012; Kulkarni *et al*., 2012).

Natural polymers can be of plant origin such as cellulose, hemicellulose, agar, starch, pectin, Inulin, Rosin, gels plant gums or mucilage or of animal origin such as chitin, alginates, carageenans, Psyllium, xanthum gum. The specific application of plant-derived polymers in pharmaceutical formulations include their use in the manufacture of solid monolithic matrix systems, implants, films, beads, microparticles, nanoparticles, inhalable and injectable systems as well as viscous liquid formulations. These applications can be achieved through the utilization ofpolymers as binders, matrix formers, drug release modifier, film coating formers, viscosity enhancer, stabilizer, disintegrant, suspending agents, gelling agent and as bio adhesives (Saha *et al.*, 2018).

1.2. Gums and mucilage

Gums are exudates from plants following injuries or other unfavorable conditions such as drought and they are considered to be the breakdown of cell wall of the plant. On the other hand, mucilages are the normal metabolites within the cell. Acacia, tragacanth, and guar gum are examples of gums while the epidermal cells of leaves (senna), in seed coats (Cordia fruit, linseed, psyllium), roots (marshmallow), barks (slippery elm) and middle lamella (aloe) are examples of mucilage (Jani *et al*., 2009; Manchanda *et al*., 2014).

Gums and mucilages have certain similarities in that both are plant hydrocolloids. They are polymers of a monosaccharide or mixed monosaccharides and many of them are combined with uronic acids. They also have similar constituents and on hydrolysis they both yield a mixture of sugars and uronic acids. They also contain hydrophilic molecules, which can combine with waterto form viscous solutions or gels. (Jani *et al*., 2009).

Gums and mucilage exhibit good binding activity in wet granulation during the tablet formulation (Karmakar, 2016). Many studies concluded that, both show better binding activity with lesser or no toxicity over synthetic binders. (Patil *et al*., 2009; Prajapati *et al*., 2013; Choudhary and Pawar 2014; Deshmukh and Aminabhavi, 2015).

In one study, the tablet binding activity of the fruit mucilage of Solanem seratens was tested on diclofenac tablet as compared to the standard, starch. The binding activity of the fruit mucilage was found to be comparable with that of the standard (5%w/v) at 6% w/v concentration (Shankar *et al*., 2015). In addition, in another comparative study done on Paracetamol tablet, the binding activity of mucilage from Okra (Abelmoschus esculentus linn) was found to be optimal at 1%w/v as compared to the standard starch (8%w/v)(Ameena *et al*., 2010). Likewise, the study on Xyloglucan extract of Tamarind gum has also shown comparable drug release profiles at thesame concentration (10%w/v) as compared to starch (10% w/v). 82 % of the drug was released from tablets with xyloglucan while 85% of the drug was found to be released from the TWSB in 30 min. (Panchal *et al*., 2012). A mimosa plant mucilage was also tested for its binding activity in hydrochlorothiazide (HCT) tablet in comparison with polyvinyl pyrolidine (PVP). The optimalbinding was obtained at 10%w/v (Ahuja *et al*., 2013). Moreover, the drug binding activity ofgum acacia was also compared with semi-synthetic Hydroxyl propyl methyl cellulose (HPMC) on the drug, zidovudine and gum acacia was found to have good binding effect and was confirmed to have faster rate of release than the drug with standard binder, HPMC (Sankar *et al*., 2010).

Particularly, the efficacy of fruit mucilages of cordia species as binder was reported (Krishna *et al*., 2011). A research conducted on the diclofenac tablet showed that the binding effect of fruit mucilage of Cordia obliqua revealed a good binding activity at lower concentration (0.2%w/v) as compared to that of the standard binder, starch paste (5%). The mean disintegration time was found to be 6 min and 3 min for the tablet with the mucilage (TWM) and tablet with the standard binder (TWSB) respectively. The friability test has shown 0.4 and

0.21 for TWM and TWSB, respectively (Dinda and Mukharjee, 2009). Furthermore, the fruit gum of *Cordia dichotoma* was also investigated to have a good binding property for uncoated paracetamol tablets at a concentration of 10%w/v as compared to the standard starch paste (10% w/v) in Aceclofenac drug (Vidyasagar *et al*., 2010). In addition, the binding activity of fruit mucilage of *Cordia Myxa* has shown a comparable binding activity as compared to standard binder (HPMC) (Tahir *et al*., 2019).

1.3. Genus Cordia

The genus *Cordia* encompasses about 250 species; the majority are tree- or shrub-sized and native to the Americas **(**Matias *et al*., 2015**)**.Table 1.1 shows that the distribution of the cordia species in the world (Oza and Kulkarni, 2017).

Table 1.1: Distribution some species of Genus Cordia

Botanical name of the Species	Distribution
Cordia Africana	Angola, Democratic Republic of Congo, Djibouti, Eritrea, Ethiopia, South Africa, Sudan, Tanzania, and Uganda
Cordia alliodora Oken (Ruiz. and Pav.)	Tropical America (from Mexico to Argentina), Caribbean Islands, Panama, Salvador
Cordia americana L. (Gottschling & J.E. Mill.)	South America, specifically in Bolivia, Paraguay, Brazil and North Argentina
Cordia boissieri A. DC.	Southern Texas in the United States to central Mexico
Cordia chacoensis Chodat	South America, Mexico, California and West Indies
Cordia oblique Willd	Warmer part of India, Ceylon, Malacca, Java and tropical Australia
Cordia curassavica Roemand Schult	Northern and Southern America and Malaysia
Cordia ecalyculata Vell	Southern America, specifically in Brazil, Argentina and Paraguay
Cordia exaltata Lam	Brazil, Suriname, and Guyana
Cordia goetzei Gürke	Somalia, Kenya and Tanzania
Cordia latifolia Roxb	India and Pakistan

1.4. Corida africana

Cordia africana Lam. (Amharic-wanza) (family: Boraginaceae) is a medium-sized evergreen treethat grows up to 4- 15m. It has edible sticky fruits (Figure. 1.1) (Ganesan *et al*., 2015). It is umbrella-shaped, dense, and much branched. Its branches resemble twigs velvety hairy, becoming bald (Figure 1.1). The bark surface is smooth in young trees, becoming cracked or longitudinally fissured with age (Alemayehu *et al.*, 2016).

Figure 1.1: Picture of *C.africana* of (adopted from Gebreeguzuabger, 2016)

1.4.1. Distribution of Cordia africana

Cordia africana is native to Africa and majorly found in Angola, Democratic Republic of Congo, Djibouti, Eritrea, Ethiopia, South Africa, Sudan, Tanzania, Uganda, Ghana, Guinea, Kenya, Malawi, Mozambique, and Zimbabwe (Ganesan *et al*., 2015). Although *C. africana* is highly distributed in Ethiopia, it is being affected by deforestation severely. In contrast with other parts of the country, the northern part has been noted for extreme deforestation (Derero *et al*., 2011). Figure 1.2.shows the distribution of *C. africana* in Ethiopia.

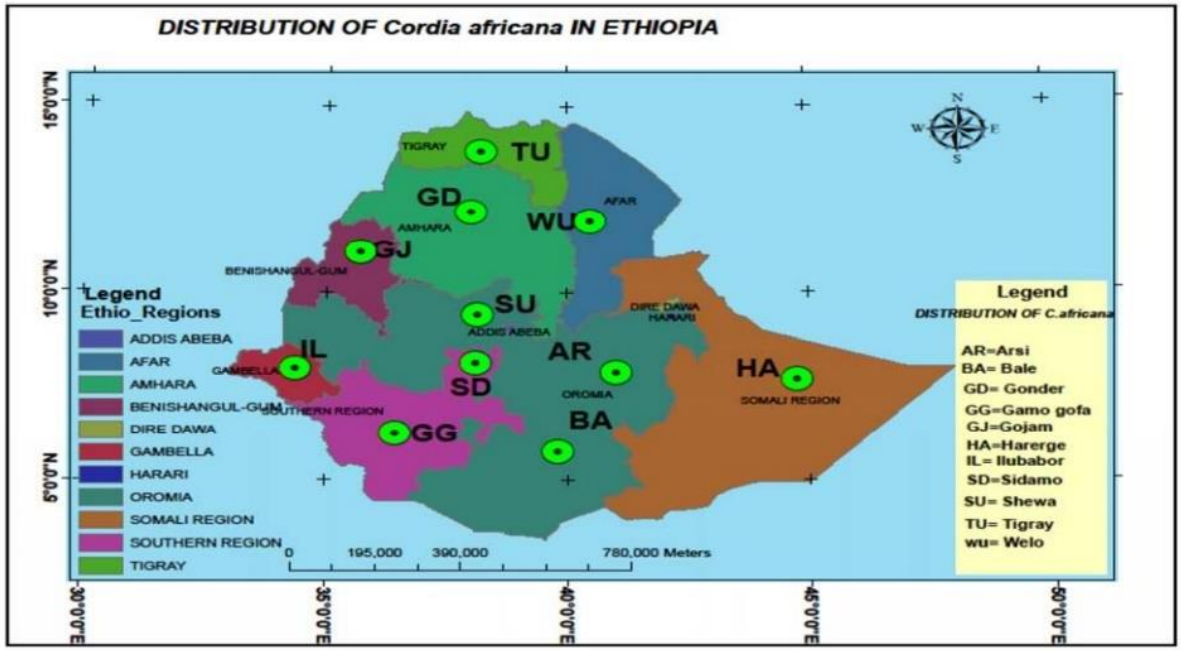


Figure 1.2: Distribution of *C.africana* in Ethiopia (Picture adopted by Alemayehu *et al*., 2016)

1.4.2. Physico-chemical properties of the fruit mucilage

1.4.2.1. Physical properties

The fruit mucilage of *C. africana* is reddish brown in color, odorless, smooth in texture and has a sweet taste. (Shankar *et al*, 2015; Pawar *et al*., 2018). The ash value was reported to be 0.7% (Benhura, and Chidewe, 2002).Generally, the fruit mucilage forms a slimy mass in water (Sharma *et al*., 2016). Its specific gravity was found to be in the range from 0.880-0.990 while itsrelative density was determined as 0.883 g/cm3. It has a refractive index of 1.468. Moreover, the moisture content was determined to be 9.4357%±2.2492 (Dagnachew *et al*., 2015).

1.4.2.2. Chemical properties

The chemical nature of the mucilage is polysaccharides or complex carbohydrates (Deshmukh and Aminabhavi, 2015). Its polysaccharides are formed by large molecules of sugars and uronic acids joined together by glycosidic links (Troncoso *et al*., 2017).

The fruit of Cordia africana contains flavonoids, tannins and triterpenes, while saponins and coumarines are present at low concentration (Alhadi *et al*., 2015). In addition, the presence of protein was reported (Hashemi *et al*., 2020). Its uronic acid content was determined to be 8.7%. The polysaccharide analysis that was done by Benhura, and Chidewe, (2002) depicted that galactose was found to be the main content (27%), followed by rhamnose (21%), mannose (17%), Xylose (11%), glucose (10%), and arabinose (9.5%) (Benhura, and Chidewe, 2002).

1.4.2.3. Toxicological property of the fruit

The cordia africana fruit has been used as a food since the time of immemorial in different forms such as juice and also in the unprocessed form. This ascertains the safety of the fruit for human use (Gebreegziabher, 2016). Figure 1.3 shows the fresh fruit of cordia before being subjected to any treatment.

Although there is no study conducted on the toxicity profile of the mucilage, the seed part (without the mucilage) was tested for acute toxicity using its crude methanolic extract with a single dose of 2000mg/kg as per the Organisation for Economic Co-operation and Development (OECD) guideline which concluded that the seed has not shown any toxicity on all of the Swiss albino mice (Yismaw *et al*., 2020).

Figure 1.3: Image of fruit of *C.africanca* (Picture taken by Tewodros A.Tessema

1.4.3. Traditional use of *Cordia africana*

Cordia africana has several uses from different parts of the whole plant. Traditionally, different parts of the plant is widely used as a medicine for different diseases such as wound, cough and toothache. Its leave is also used as fodder for animals, especially in dry seasons. In addition, its flowers are sweetly scented and used by honey bees as fodder. Moreover, ripe fruit is used as food by humans in different forms such as juice or any other form of processing. Furthermore, aswood is light, durable, moderately soft, and fungus resistant, it is highly valued to be used for high-quality furniture, doors, windows, chairs, beds, containers, cabinet-making, drums, interior construction, beehives, mortars and pestles (Alemayehu *et al*., 2016).

1.4.4. Modern use of *cordia africana*

Different parts of *C. africana* have been investigated for their pharmaceutical applications. A study conducted on the efficacy of the root and the stem bark against vancomycin-resistant enterococcus has revealed a promising result as the root extract, oleanolic acid, has shown more activity than the standard (Kamau *et al*., 2019). In another study, the anti-oxidant efficacy of the extracts of leaf and bark of *C. africana* was investigated to have positive results (Isa *et al*., 2016). Furthermore, the study conducted on the anti-diarrheal activity of the hydromethanolic extract of leaf of *C.africana* has also showen a promising result though the mechanism is not known (Ferede *et al*., 2021). Moreover, the methanolic extract of the seed was shown to have anti-ulcer activity on the study conducted using Swiss albino mice (Yismaw *et al*., 2020).

The utilization of *C.africana* fruit mucilage as a pharmaceutical excipient was also determined through one study conducted on the emulsifying property of the mucilage within the pH range of 3-13 with the highest emulsification was noted at 1% mucilage concentration and at pH of 11 (Benhura and Chidewe, 2004).Moreover, the *C. africana* was tested as a novel hydrocolloid- forming agent due to its rheological property and the result was shown to be promising (Rafe andMasood, 2014).

1.5. Pharmaceutical excipients

Most pharmaceutical formulations consist of two ingredients, the active pharmaceutical ingredient and additives (Bashir *et al*., 2016). Additives, also called excipients, are ingredients that are used to formulate the active pharmaceutical ingredient into a suitable dosage form. Binders, lubricants, glidants, and disintegrants are some of the common excipients used in tablet manufacturing. There are two general to include excipients in the formulations (1) to make the dosage form suitable for administration to the patient and (2) to enhance stability profile of the drug product (Nayak *et al*., 2015).

1.5.1. Binders

Binders are a type of excipients that are added in a tablet formulation to impart plasticity and enhance inter particulate bonding by imparting cohesiveness to the granules (Debnath *et al*., 2019). These properties of binders contribute to the mechanical properties of the tablet and drug release profile (Shailendra *et al*., 2012). This, in turn, will be essential in enhancing the strength of the tablet in processing, packaging, and handling (Vidyasagar *et al*., 2010).

The ideal binder has a high degree of surface wetting and spreadability and a high degree of wet adhesion (strong liquid bridges in the wet granules) to allow the formation of agglomerates, while also possessing plasticity in the dry state to overcome unfavorable powder flow and mechanical properties. Such a binder should yield dense, uniform granules with low friabilityand a high degree of compatibility while minimizing the amount of applied force required toform strong, dense tablets (Dürig and Karan, 2019).

Binders can be obtained from natural, synthetic or semi-synthetic origins. In recent years, naturalbinders are attracting the interest of drug formulation scientists due to their low toxicity, biodegradability, availability and low cost (Tekade and Chaudhari, 2013; Patil *et al*., 2014 ;).

1.5.1.1. Methods of incorporation of binders

Tablet uniformity is best achieved when the binding component is used in the solution as an adhesive. In solution form, the binder is well distributed in the other materials of the tablet and results in a better attachment at lower concentrations of a binder. Moreover, since powders

differ with respect to the ease with which they can be wetted, and their rate of solubilization, it is preferable to incorporate binders in the solution. Some poorly compressible tablets like paracetamol, metronidazole, and acetazolamide can be effectively tableted only when a liquid adhesive and moist granulation process is employed (Dürig and Karan, 2019).

1.5.1.1.1. Granulation

Granulation is a technique of particle enlargement by means of agglomeration. It is one of the most widespread unit operations in the production of pharmaceutical dosage forms (Hiremath *et al*., 2019). It is essential to avoid segregation, enhance the flow of powder, produce uniform mixture, produce dust-free formulation, eliminate poor content uniformity and improve compaction characteristics of mix. It is mainly classified into two types: wet granulation and dry granulation (Jannat, *et al*., 2016).

Dry granulation is a valuable technique in situations where the effective dose of a drug is too high for direct compaction and the drug is sensitive to heat, moisture or both while wet granulation is a process accomplished by adding a liquid binder or an adhesive to the powder mixture, passing the wetted mass through a screen of the desired mesh size, drying the granulation and then passing through a second screen of smaller mesh to reduce further the size of the granules (Arndt *et al*., 2018).

Generally, the ideal characteristics of granules encompass spherical form for accelerated flow, slender particle size distribution for content material uniformity and volumetric dispensing, and enough moisture and hardness to prevent breaking and dirt formation for the duration of process. Granules are mainly produced with a dimension vary of 0.2-0.5 mm to be either packed as a dosage form or be blended with different excipients earlier than pill compaction or pill filling (Parikh, 2016).

1.5.1.1.2. Factors that affect granulation properties

The quality of tablets is directly related to the granulations from which the tablets are compressed which in turn is affected by the type of formulation, processing techniques and equipment used during the process. Among these factors, the type of binder employed is

determinant to particulate size, uniformity, intergranular porosity, adequate hardness, compressibility and general quality of the granules. (Wikberg, 1991).

1.5.1.1.3. Effect of binders on granule properties

The type and concentration of binders are determinant in the type of granule produced. For example, it was found that increasing the binder concentration was followed by increases in the mean particle size, harder granules, decreased granule flowability and decrease in tapped density and hence reduction in granule porosity. The reduced flow rate of granulations produced at higher binder concentrations is associated with the increase in their average size (El-gindy, *et al*.,1988). These statements were further confirmed with another study that has been done on the effect of Neem gum on granule properties as compared to acacia. A lower flow rate wasobserved as the concentration of both neem and acacia increased. Furthermore, an increase in acacia concentration was shown to have increased the bulk density and decreased the porosity of the granules (Ogunjimi and Alebiowu, 2014).

1.5.1.1.4. Effect of processing variables on granule properties

Granule characteristics are described to be influenced by equipment employed and processing variables such as the method of granulation, the volume of granulating fluid, massing time, and method of compressing the granules to tablets (Walker *et al*., 2005). Investigations on theinfluence of various processing variables such as binder spray rate, bed temperature, atomizing pressure and fluidizing air velocity, on the granule growth behavior was examined. A direct relationship was exhibited between the granule growth rate and the amount of binder sprayed into the bed which essentially determines the speed of the aggregation process. The overall granule growth rate is observed to increase relatively with increased bed temperature for a more viscous PEG4000, while a maximum growth is seen for a lower viscosity PEG1500. The final granule size distribution was also observed to become narrower with increased bed temperature and fluidizing air velocity (Tan *et al*., 2006). Moisture content was also found to have the largest impact on granulation compressibility and tablet strength. Increasing wet massing time decreasedgranule porosity and fragmentation tendency hence increased granule strength, which led to granulation compressibility (Wikberg, 1991).

1.5.1.1.5. Granule flow

Glidants and lubricants such as talc and magnesium stearate are added to promote the flow of thetablet granulation. Glidants often possess a coefficient of friction less than that of the bulk solid and hence improve the flowability thereby decreasing interparticle friction. Adequate mixing is needed for the homogenous distribution of lubricants and satisfactory granulation flow. The percent of fines, amount and type of granulating agent, particle size distribution, and type of glidant all have measurable effects on granule flow (Pingali *et al*., 2011). Granules with a higher amount of fine indicate poor flow. The angle of repose increases with increases in the percentageof fines. Values for angles of repose $< 30^{o}$ usually indicate a free-flowing material and angles $\geq 40^{o}$ suggest a poorly flowing material (Geldart *et al*., 2006).

1.6. Tablet compression

The process of compression in pharmaceutical tableting is filling a required volume of granules in a die cavity is compressed between an upper and lower punch to densify the material into a single solid, which is subsequently ejected from the die cavity as an intact tablet. The subsequentevents that occur in the process of compression are a) transitional repacking, b) deformation at points of contact, c) fragmentation and/or deformation, d) bonding, e) deformation of the solid body, f) decompression, and finally ejection of the tablet (Santos and Sousa, 2010).

1.7. Optimization

Optimization is the process of finding the best combination of study variables in light of getting optimal results. This would be very important in avoiding random results from the random combination of the study variables as well as saving time and resources. Therefore, the essenceof optimization is unquestionable in industrial research (Beg *et al*., 2019).

Currently, the design of experiment solved many of the issues raised above such as avoiding randomity in experimental researches. It eases the way of finding the optimum variable combinations for better results. This is because the design of experiment helps to set a systematicplan ahead of the actual test conducted.

Response surface method (RSM) is one of the most commonly used optimization method in design of experiment (Kleijnen, 2015). It provides the interactions of independent variables with one or more response variables in addition to the main (individual) effects (Zhou *et al*., 2013). In this method, the effect of variables can be shown through the surface adjustment and the effect can easily be understood by observing where the surface lies over based on the graphical illustrations. This method includes the central composite design (CCD), Box-Behnken designs (BBD), Central composite rotatable design (CCRD) and face-central composite design (FCCD).

1.7.1. Central composite design (CCD)

The CCD is the most commonly used design of RSM as it mostly results in good and equal predictions from the center. Unlike other methods in RSM such as box behnken design, it needs more experimental runs due to five levels for each factor as it includes two axial points per study variable (Nigatu *et al*., 2015). Its level has 2^K points, where K is the number of factors, axial designs with $2k$ points which gives description about any curvature and the replicated center points which are important for assuring the reproducibility and model lack of fitness. The total number of needed design points (N) is determined by the formula $N = 2^K + 2k + C0$, where k is the number of factors and $C0$ is the replication number of center points (Zolgharnein *et al*.,2013).

The CCD allows the response and factor relationship to be modeled by a second-order polynomial fit and Permits navigating the interactions between variables and the quadratic terms in the fashion explained in the below equation(Nigatu *et al*., 2015).

$Y = \beta 0 + \beta 1X1 + \beta 2X2 + \beta 12X1X2 + \beta 11X1\ 2 + \beta 22X2\ 2$ where X1 and X2 are the independentvariables, β0 is the intercept, β1–β22 are the regression coefficients, and Y is the response variable.

1.8. The significant of the study

Binders are types of excipients that are added in tablet formulation to enhance mechanical properties and release profile of the tablet through inter particulate bonding (Debnath *et al*., 2019; Shailendra *et al*., 2012). They can be natural, synthetic or semisynthetic.

Synthetic and semi-synthetic pharmaceutical binders are subject to different adverse events such as cancer as they are produced following different chemical reactions. Moreover, they areexpensive, less available and nonrenewable. (Manchanda *et al*., 2014).

Research indicated that these synthetic additives are hazardous not only when taken in vivo but also for the environment (Rajeswari *et al*., 2017). On the contrary, nearly all plant binders are carbohydrates in nature and composed of repeating monosaccharide units that made them safer than synthetic ones. In addition, natural polymers remain attractive primarily because they are inexpensive, readily available, capable of a multitude of chemical modifications and potentially biodegradable and compatible due to their origin (Prajapati *et al*., 2013; Singh, 2016; Thakur *et al*., 2015; Milivojevic *et al*., 2019). Moreover, the need might be pronounced especially, when the drug is newly invented, the presence of varieties of alternative potential excipients may ease the way to its full development. (Bashir *et al*., 2016).

Paracetamol was used as a model drug in this study (figure 1.4). It is categorized as analgesic and antipyretic.Its anti-inflammatory effect is insignificant due to its low ability to inhibit prostaglandins. It is the most common drug in the alleviation of mild to moderate pain. It is an odorless white crystalline solid with a bitter taste. (NCBI, 1988). Paracetamol was chosen as a model drug totest the binding activity of the C. mucilage as it is easily accessible and cheap. Wet granulation was employed in this study as paracetamol is a poorly flowable drug (Šimek *et al*., 2017).

C. africana is a widely distributed plant in Ethiopia. It has been used as source for traditional medicine, as beverage (for example, traditionally made juice from the fruit), and even

has a great importance in furniture industry (the wood part). Therefore, The proper utilization of the native *C. africana* plant will have a big positive impact on the country's economy, by saving foreign currency, creating job opportunities and keeping the environment safe and healthy (Gebreegziabher, 2016). The fruit mucilage, as part of the plant, can effectively be usedas tablet binder and could become an alternative binder to pharmaceuticals.

Therefore; in this research, *C. africana* mucilage will be evaluated, characterized and optimized for its binding effect along with other determinant factors, the disintegrant and compression force.

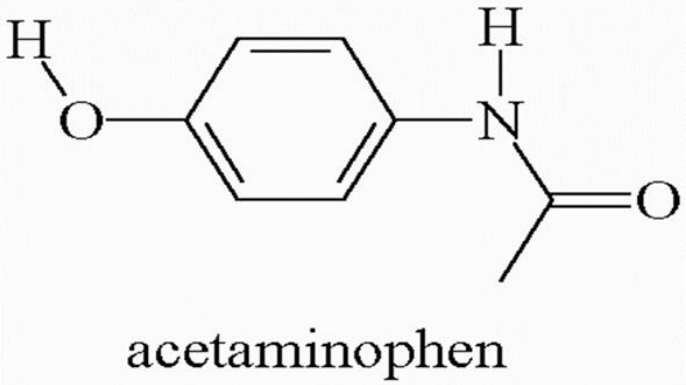


Figure 1.4: Chemical structure of paracetamol

1.9. Research questions

This study attempts to answer the following questions

1. What are the physicochemical characteristics of the C. fruit mucilage?
2. Is C.mucilage compatible with paracetamol?
3. Could the mucilage be used as a binder in tablet formulations?
4. If the answer for question number 3 is yes, what will be the optimum value of the mucilage that gives desired result?

1.10. Objectives of the study

1.10.1. General objective

To evaluate the fruit mucilage of *C.africana* as a tablet binder in paracetamol tablet formulation.

1.10.2. Specific objectives

To isolate and physicochemical characterize the fruit mucilage of *C. africana*.

To formulate tablets using the fruit mucilage of *C. africana* as a binder.

To optimize the effect of the amount of binder, concentration of disintegrant and compression force on the prepared paracetamol tablet

To evaluate the drug release, friability, disintegrant and hardness profile of theformulated or optimized tablet.

2. EXPERIMENTAL

2.1. Materials

Paracetamol IP was obtained from Cadila pharmaceuticals as a gift and other ingredients such as lactose (BDH Chemicals Ltd Poole, England), starch 1500 (Neolab Life science co., India), Talc (BDH Chemicals Ltd Poole, England), magnesium stearate (BDH Chemicals Ltd Poole, England), acetone (99%) (Riedel-de Haen, Germany), disodium hydrogen phosphate dehydrate (99.0%) (CARLO ERBA Reagents S.A.S,), potassium dihydrogen phosphate (KH_2PO_4, 99.0%) (Guangdong Guanghua Sci- Tech Co.,Ltd, China) were bought from the local market. Fruits of *C. africana* were collected from a wild source around Ayra, Gondar city, central Gondar zone.

2.2. Methods

2.2.1. Collection and authentication of *Cordia africana* fruit

The fruit of *C.africana* was collected in January 2020 from Ayra, Gondar city, Central Gondar, and Amhara regional state and authenticated by the department of Biology, Universityof Gondar.

2.2.2. Extraction of *Cordia africana* fruit mucilage

The extraction of Cordia Mucilage was done by the method described by Vidyasagar et al. as follows (Vidyasagar *et al*., 2010). The collected cordia fruit was washed to avoid any potential contaminants. Then a kilogram of the fruit was measured, peeled and macerated in distilled water by making the fruitto distilled water ratio of 1:10 and was left for 24 hours. Finally, the macerate was allowed to pass through the muslin cloth to filter the fruit and other debris materials.

2.2.2.1. Isolation of the mucilage

The filtrate which contains the mucilage was treated with acetone in the ratio of 1:3 and left to stand for 24 hours. Then, the supernatant was slowly decanted and the precipitate was transferred to the petri dishes subjected to a tray oven dryer (Kottermann® 2711, Germany) at a fixed temperature of 40^{o}c until it become dried (Vidyasagar *et al*., 2010).

2.2.2.2. Purification of the isolated mucilage

The isolated mucilage was further purified by the method explained Vidyasagar et al. as follows (Vidyasagar *etal*., 2010).The dried mucilage was powdered using mortar and pestle and passed through a sieve number 60. After this, the powdered mucilage was solubilized using distilled water. Then, the concentrated solution was precipitated using acetone and the supernatant fluid was decanted and the precipitate was dried by tray oven dryer (Kottermann® 2711, Germany) at 60 ºC until it became dried. Finally, the dried mucilage was pulverized and kept in a closed container for further use as a binder.

2.2.3. Physicochemical characterization of the dried mucilage

2.2.3.1. Loss on drying

Loss on drying was determined by the methods reported by Patil *et al*., (2009). Accordingly, five grams of mucilage was dried by tray oven dryer (Kottermann® 2711, Germany) at 105 °C for 2 hours till a constant weight was obtained. Then, the loss on drying was determined by subtracting the second weight (w2) from the original weight before being subjected to drying.

2.2.3.2. The presence of starch

A 20 ml of the mucilage was boiled then cooled and 0.1 ml iodine test solution (5% elemental iodine mixed with 10% potassium iodide) was added to check for the presence of starch or dextrin in the mucilage (Li and Liu, 2020).

2.2.3.3. Ash value determination

The ash value of cordia mucilage was done by the method mentioned below (Patil *et al*., 2009). Mucilage of 2 g was weighed, evenly distributed in the crucible, and dried at a temperature of 105 °C for one hour. Then, it was ignited in a muffle furnace (CARBOLITE,OAF 11/1, England) at 450 °C for 8 hours. The percentage ash content was calculated using Eq.2.1

$$\%\ ash\ value = \frac{CR - E}{C - E}\ x100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.2.1$$

Where E = tarred weight of crucible, CR = weight of crucible + residue, and C = weight of crucible + test portion

2.2.3.4. Swelling index

The swelling index was studied by the method mentioned by Malviya as follows (Malviya, 2011). Initially, 1 g. of the dried mucilage was added into each graduated measuring cylinders containing 25 ml distilled water, 0.1 N HCl and phosphate buffer of pH 5.8 and the volume was noted. Then, an equal amount of distilled water, HCl and phosphate buffer of pH 5.8were poured into the respective measuring cylinders and shaken vigorously which was then left for 3 hours. Finally, the second volume was noted and the swelling ratio was calculated as the ratio of the final volume to the initial volume.

2.2.3.5. Solubility study

1g of Cordia mucilage powder was weighed separately for each solvent and added to a separate volume of 10 ml of ethanol, chloroform, acetone, hot distilled water and distilled water (at room temperature). Then the solubility of the mucilage was noted after 24 hours. The solubility index was then calculated using the following formula (Eq. 2.2).

$$\%Soluble\ mass = \frac{SM}{IM} X100 \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots . Eq. 2.2$$

where SM is the soluble mass and IM is the initial mass used

2.2.3.6. Rheological study

The rheology was studied based on the method described by Keshani-Dokht *et al*., (2018). Different concentrations of *C.africana* in distilled water was prepared at 0.6%, 3%, 6.5%, 10%, and 12.4% (W/V) using a magnetic stirrer at the rate of 300 rpm for 60 minutes. Then, it was allowed to stand for 24 hours at room temperature and the viscosity was measured using a viscometer (BROOKFIELD CAP 2000+ viscometer) at room temperature with spindle number 3.

2.2.3.7. pH determination

The pH of the fruit mucilage was measured using a calibrated digital PH meter (KEDIDA CT-6021A, Shenzehen Kedida). A 1 g. of fruit mucilage was dissolved in 500 ml of distilled water and stirred by a magnetic stirrer (CIMAREC) for 30 minutes to make sure that the powder is homogeneously distributed. Then the electrode of the pH meter was inserted in the prepared solution and the reading was noted. The measurement was done in triplicate.

2.2.3.8. Moisture sorption study

The moisture sorption study was studied as per the method by Gebresamuel and Gebre-Mariam (2011). A 2 g of the predried mucilage was added to dried petridish of known weight and then transferred into different desiccators containing a relative humidity of 20%, 40%, 60%, 80% and 100% which was maintained using different saturated solutions of $KC_2H_3O_2$, K_2CO_3, KI, KCl, and K_2SO_4 respectively. The weight of each sample was measured every day until a constant weight was achieved in two successive samples. Then, the Moisture sorption was calculated as follows using Eq. 2.3.

$$\% \, Mosisture \ sorption = \frac{W1 - W2}{W1} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots . Eq\ 2.3$$

where W1 is the initial weight, and W2 is the final weight obtained

2.2.3.9. Drug-Excipient compatibility study

The drug-mucilage compatibility test was done to identify if there is any chemical shift or change while combining these two ingredients (the paracetamol and the mucilage). This was conducted using both DSC and FTIR.

2.2.3.10. Differential scanning calorimeter (DSC) analysis

The pure paracetamol, the mucilage and the combination of paracetamol and mucilage (1:1) wererun separately by DSC machine (PerkinElmer DSC 4000) with a temperature range of 30 to 450 ^{o}C. One gram of each of the above substances were weighed and sealed before subject to heat. Then, they were heated at the rate of 20k/min while maintaining the nitrogen gas flow throughout the process.

2.2.3.11. Fourier transform infrared spectroscopy (FTIR) Analysis

The pure paracetamol, the powdered form of mucilage and the combination of both paracetamol and the mucilage at a ratio of 1:1 were subjected to FTIR machine (FTIR-8400S, SHIMADZU, and Japan). A 1 g of each sample was placed on the potassium bromide face of the disk of the FTIR and the second plate was placed above. The sandwiched samples were scanned in the rangeof 4000-400cm^{-1}.

2.2.3.12. X-ray diffractometer (XRD)

The crystalline structure of the mucilage was identified by the X-ray diffractometer (XRD-7000 X-ray diffractometer MAXima, SHIMADZU Corporation, Japan at 40 KV).

2.2.3.13. Scanning electron microscope (SEM) analysis

The scanning electron microscopy assay of the dried and powdered mucilage was studied using SEM machine (TESCAN VEGA3 SEM, TESCAN ORSAY HOLDING, Czech Republic) in which the sample was coated with chromium before being subjected to the analysis.

2.2.4. Preparation and characterization of granules

2.2.4.1. Preparation of granules

The granule for the test tablet was prepared using paracetamol, cordia mucilage, starch 1500, talc, and magnesium stearate and lactose (Table 2.1). First, the dough was made with a mixing ofparacetamol, lactose (as needed), the desired mucilage concentration and only half of the desired starch by turbular mixer (Willy A. Bachofen AG, Turbula 2TF, Basel, Switzerland). Then, distilled water was added as granulating liquid and the final mass was subjected to pass through a

1.6 mm sieve. The wet mass was then transferred to petridish and dried in oven (Kottermann® 2711, Germany) at 105 ^{o}C for 30 minutes. Finally, the dried granules were mixed using Willy A. Bachofen AG, Turbula 2TF, and Basel, Switzerland with the rest of the ingredients: magnesium stearate, talc and the half of dry starch 1500 and passed through 1mm sieve.

Table 2.1: Composition of ingredients as per the CCD in paracetamol formulations

No.	Ingredients	Amount (%)
1	Paracetamol	77
2	Binder (cordia mucilage)	3-10
3	Starch (as disintegrant)	3-12
4	Magnesium stearate	1
5	Talc	1
6	Lactose	q.s to100.

2.2.4.2. Characterization of the granules

2.2.4.2.1. Bulk and tap densities

Granules of 30 g. were poured into a 250 ml measuring cylinder and the volume occupied was recorded (VO). Then, the sample in the measuring cylinder was tapped 500 times using the tapingmachine (ERWEKA SVM) and the final volume was noted (VT). Then both tap and bulk density was calculated as mass/volume (Traina *et al*., 2013).

2.2.4.2.2. Flowability and compressibility of the granule

The compressibility and flow property of the granule was determined using the Carr's index and Hausner ratio through Eq.2.5 & Eq.2.6, respectively (Traina *et al*., 2013).

$$Carr's\ index\ (\%) = \frac{\rho T - \rho B}{\rho T} \times 100 \quad \text{Eq.2.5}$$

$$Hausner's\ ratio = \frac{\rho B}{\rho T} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots .. Eq. 2.6$$

Where ρT is tapped density and ρB is bulk density

2.2.4.2.3. Angle of repose

Powder angle of repose (θ) was determined by a fixed funnel system to assess the flow property. The powder was allowed to flow freely through the funnel with an inner diameter of 10mm at the bottom and 100mm at the top, onto a flat surface from a height of 10 cm. The diameter (d), the height (h) of the powder pile and the time taken for the mucilage powders to flow through the orifice were noted. Then, the angle of repose was calculated as per Eq.2.7 (Khanam, J. and Nanda, 2005: Kalman, 2021).

$$\theta = tan^{-1} \times \frac{h}{r} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \ Eq. 2.7$$

Where h is the height of the powder pile, r is the radius of the pile

2.2.4.2.4. Flow rate determination

The flow rate was assessed by the method described by Apeji *et al.*, (2019). First, a 30 g of sample was measured and subjected to pass through the funnel fixed at height of 10 cm from the base. Then, the time took for the granules to pass through the funnel was recorded. A thrice repetition was done for each batch of the formulation and the flow rate was calculated based on Eq.2.8.

$$Flow\ rate = WG/FT \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots .. Eq. 2.8$$

Where WG is the weight of the granule and FT is the flow time for the granule

2.2.4.2.5. Granule size distribution

A sieve method as described by Kebebe *et al.*, (2010) was employed to determine the granule size distribution. Sample of 30 grams was added to a set of sieves (ERWEKA, Type AR 401, Germany) arranged with the highest mesh wire size at the top and the least size at the bottom. After shaking the sieve for 2 minutes, the granule retained in each sieve were weighed and expressed as a percentage. The procedure was repeated three times for all batches and the average value was calculated with the standard deviation.

2.2.5. Preparations and evaluation of tablet

2.2.5.1. Preparation of the tablet

The granules prepared using the formulas presented in Table 2.1 were compressed using a tablet compression machine (Shanghai Chengxiag Machinery, Co., Ltd, China) with 650mg of total weight adjustment. The numbers of batches included in the study are mentioned as in table 2.2 based on the formula 2^n +2n+6 as per the CCD for three independent variables. Variables such as the concentration of paracetamol, talc, magnesium stearate were kept constant throughout the study with values mentioned in table 2.1 while lactose was used as a filler to 650mg.

Table 2.2: The composition of independent variables per each batches of Paracetamol tablet formulation

		Factor 1	Factor 2	Factor 3
Formulation	Space Type	A:CF	B:ST	C:CM
		N	%	%
F1	Factorial	50	5	3
F2	Factorial	100	5	3
F3	Factorial	50	15	3
F4	Factorial	100	15	3
F5	Factorial	50	5	10
F6	Factorial	100	5	10
F7	Factorial	50	15	10
F8	Factorial	100	15	10
F9	Axial	32.9552	10	6.5
F10	Axial	117.045	10	6.5
F11	Axial	75	1.59104	6.5
F12	Axial	75	18.409	6.5
F13	Axial	75	10	0.613725
F14	Axial	75	10	12.3863
F15	Center	75	10	6.5
F16	Center	75	10	6.5
F17	Center	75	10	6.5
F18	Center	75	10	6.5
F19	Center	75	10	6.5
F20	Center	75	10	6.5

2.2.5.2. Evaluation of the tablet

2.2.5.2.1. Weight uniformity test

The weight of 20 tablets was measured individually from each batch using analytical balance (ADAM, AAA 160L analytical balance). The mean weight, as well as the deviation, was calculated accordingly (Vidyasagar *et al*., 2010).

2.2.5.2.2. Thickness

The mean thickness and standard deviation were determined with 10 tablets which were selected randomly from each batch and the thickness of each tablet was measured using a sliding caliper scale (Nippon Sokutei, Japan).

2.2.5.2.3. Tablet hardness test

The tablet hardness was tested using a tablet hardness tester (CALEVA Tablet hardness tester). For each batch, 10 tablets were subjected to the force exerted by the blunt tip of the machineuntil it just got broken and the force used to break the tablet was recorded accordingly (Segun *et al*., 2018)

2.2.5.2.4. Friability test

Randomly selected 20 tablets from each batch were weighed in an analytical balance. Then, transferred into the friability tester (Erweka TAR 20) and subjected to tumbling action of the instrument at 25 rpm for 4 minutes. Finally, the tablets were taken out from the friability tester, dedusted and weighed once again. The friability was then calculated using Eq. 2.9.

$$\%\ Loss(Friability) = \frac{W1 - W2}{W1} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.\ 2.9$$

Where W1 is the first weight and W2 is the second weight

2.2.5.2.5. Disintegration time test

The disintegration test was done by ERWEKA disintegration time tester. 6 tablets were used per batch and each tablet was simultaneously inserted into each cylindrical tube of a vessel filled with 900ml of distilled water which was maintained at a body temperature of 37.5^{o}c. The time in which the residue of the final tablet completely fell from the cylindrical tube to the vessel was recorded as the disintegration time of the batch (Türkmen *et al*., 2018).

2.2.6. Construction of calibration curve for Paracetamol

The calibration curve was done with 5 concentrations which were prepared from the stock concentration of 0.02%w/v (4µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml and 12 µg/ml) of paracetamol which were prepared using phosphate buffer 5.8 and the absorbance for each concentration was measured by UV-Visible spectrophotometer (UV-visible spectrophotometer, CM2203, Belarus) at □max of 267 nm. Then the linear equation for the calibration curve was noted at the end of the reading (absorbance vs. concentration).

2.2.7. In vitro drug release study

The USP type II dissolution apparatus (ERWEKA, DT600, and Germany) at a paddle rotation speed of 50 rpm was employed to study drug release from the prepared tablets. The dissolution medium was 900 mL of phosphate buffer with a pH of 5.8 maintained at a temperature of 37±0.5 °C (USP, 2019). 6 tablets were added into the dissolution medium and 5 ml of samples were taken at a prescheduled time (5, 10, 15, 30, 60, 120 minutes). Each withdrawn sample was replaced with an equal volume of fresh dissolution medium. The withdrawn samples were filtered, suitably diluted and UV absorbance was measured using UV-visible spectroscopy (UV-Visible spectrophotometer, CM2203, Belarus) at 267 nm. The concentration was calculated from the formula obtained from the calibration curve.

2.2.8. Optimization

The CCD as the most popular method in the response surface method (RSM),was used to study the effect of individual variables on the desired outcomes such as friability anddrug release. This method enables the use of five levels (including two-star points) per each factor and in addition to the main or individual effect; the interaction effect can also be navigated. (Nigatu *et al*., 2015). Providing the minimum values of independent variables as 3%,5 % and 50N and the maximum values as 10%,15% and 100N for the mucilage (binder), starch (disintegrant) and compression force respectively, the five levels per factor was generated as in Table 2.2.The friability and drug release at the 30 minutes (Drug release at t-30) were taken as response variables while the disintegrant (ST), cordia mucilage (CM) and compression forces (CF) were taken as independent variables. Therefore, the total experiment run was calculated by using the following formula as per the requirement of this design which is $2^k + 2k + n_o$, where k is numbersof factors and n numbers repetition. Therefore, the numbers of total experimental runs were summed up to be 20 substituting 3 for k and 6 for n, as the repetition for three independent variables is 6.

Table 2.3: The five levels of each independent variables in paracetamol tablet formulations

Variables	Levels				
	-α	-1	0	+1	+α
Cordia Mucilage(CM)	0.613725	3	6.5	10	12.3863
Disintegrant (ST)	1.59104	5	10	15	18.409
Compression Force(CF)	32.9552	50	75	100	117.045

2.2.9. Validation of the experimental design

The experimental design was validated through the comparison of the actual values obtained in the experiment with the predicted values given by the software and the percent relative error was calculated using Eq.2.10.

$$\% \, Relative \; error = \frac{PV - EV}{PV} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq. 2.10$$

Where PV stands for predicted values and EV stands for experimental values

2.2.10. Statistical analysis

Origin 7 Software (Origin Lab Corporation, MA, and USA) and Design expert software 13.0 (Stat-Ease Inc., Minneapolis, MN, USA) were used to statistically analyze the data. Results werecompared using one-way analysis of variance (ANOVA). P-values of < 0.05 were noted as statistically significant for a 95% confidence interval.

3. RESULTS AND DISCUSSION

3.1. The physicochemical characterization of the Cordia mucilage

The extracted *c.africana* mucilage was found to be reddish-brown in color, odorless, smooth in texture and had a sweet taste (Fig. 3.1). Moreover, starch was absent in the mucilage as confirmed by the iodine test (Pawar *et al*., 2018; Shankar *et al*, 2015). Table 3.1 summarizes the physicochemical properties of the mucilage.

Figure 3.1: The Photograph image of extracted C.africanca mucialge before subjected to drying (Picture taken by Tewodros A.Tessema)

Table 3.1: The Physicochemical properties of Cordia mucilage expressed as Mean ±SD for n=3

No.	Parameter	Results				
1	Yield	29%± 0.9				
2	Color	Reddish-Brown				
3	Loss on Drying	6% ± 0.02				
4	Total Ash	1.96%± 0.05				
5	Swelling ratio	No				
6	PH	6.8± 0.01				
7	Presence of Starch	No				
8	Solubility	% soluble mass				
		Ethanol	Acetone	Chloroform	Distilled water (hot)	Distilled water
		0	0	0	100	100

3.1.1. The swelling index

The swelling index study provides the moisture-water absorption capacity of the mucilage (Gebresamuel and Gebre-Mariam, 2011). Furthermore, it dictates the drug release mechanism. For example, the drug release retards as the swelling power increases due to the thick gel layer formed which could delay the drug release (Poosarla and Muralikrishna, 2015). In this study, the mucilage did not exhibit swelling in distilled water, HCl and phosphate buffer pH 5.8.

3.1.2. Loss on drying

The loss on drying was found to be 6% ± 0.02, which is within the pharmacopeial limit for natural gums and mucilage (≤15 %) (Kalegowda *et al*., 2017). The loss on drying was found to be less when compared to *cordia dicothoma* which have a value of 15.6% (Pawar *et al*., 2018).

3.1.3. pH determination

The pH of the *C.mucilage* was determined to be 6.8±0.01. This indicates that the mucilage has nearly a neutral pH. This result was close to the one conducted for *cordia dicothoma* which has pH of 6(Pawar *et al*., 2018).

3.1.4. Total ash determination

The ash value determines the level of impurity as well as minerals interaction in the structure of a substance. Generally, a lower ash value indicates higher purity of the substance (Kalegowda *et al*., 2017). The total ash value in this study was found to be 1.96%± 0.05, which is comparable with the impurity level of most C. mucilage species (0.7-6.86%) (Hashemi *et al*., 2020). This purity level was found to be higher than the purity level for *Cordia myxia* which has the total ash value of 5.86 %(Keshani-Dokht *et al*., 2018).

3.1.5. Solubility study

Figure 3.2 presents the solubility profile of the *C. mucilage* in different solvents. Accordingly, the mucilage was found to be completely soluble in distilled water (D &E in fig.3.2.) and it has shown no solubility in other solvents of lower polarity (ethanol, chloroform and acetone) as designated with letters A, B and C, respectively in fig.3.2. Similar finding was reported on the research conducted on *Cordia dichotoma* as it was found insoluble in non-polar solvents tested (acetone, ethanol, methanol, and ether) (Pawar *et al*., 2018).

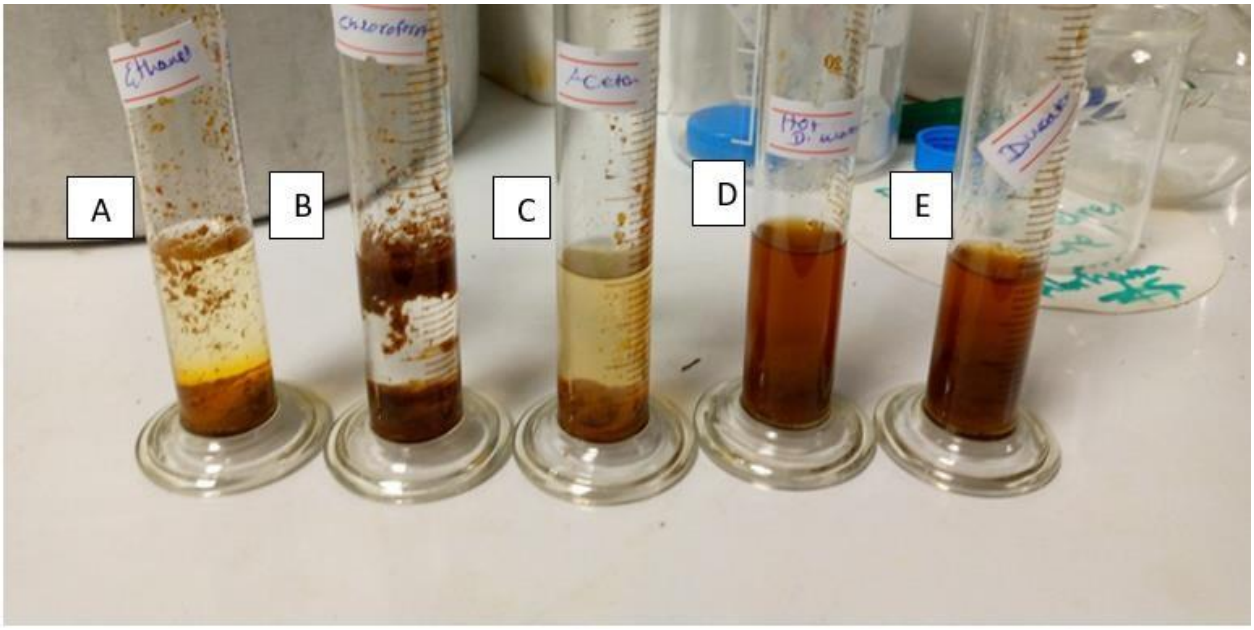


Figure 3.2: The solubility of the mucilage of *C.africana* in Ethanol [A], Chloroform [B], Acetone[C], Hot distilled water [D] and Distilled water at room temperature [E].

3.1.6. Rheological property

Viscosity is one of the important parameters to learn about the quality of the mucilage (Pawar and Lalitha, 2015). The viscosity profile of the mucilage as a function of concentration is depicted in Fig 3.3. The viscosity of the mucilage is directly proportional to its concentration due to the possible intricacy of the mucilage into the solution (Casas *et al*, 2000; Kalegowda *et al*., 2017). A similar finding was reported in the research conducted on the rheological property of *C. myxa* that showed as the concentration was determinant for its viscosity (Keshani-Dokht *et al*., 2018)

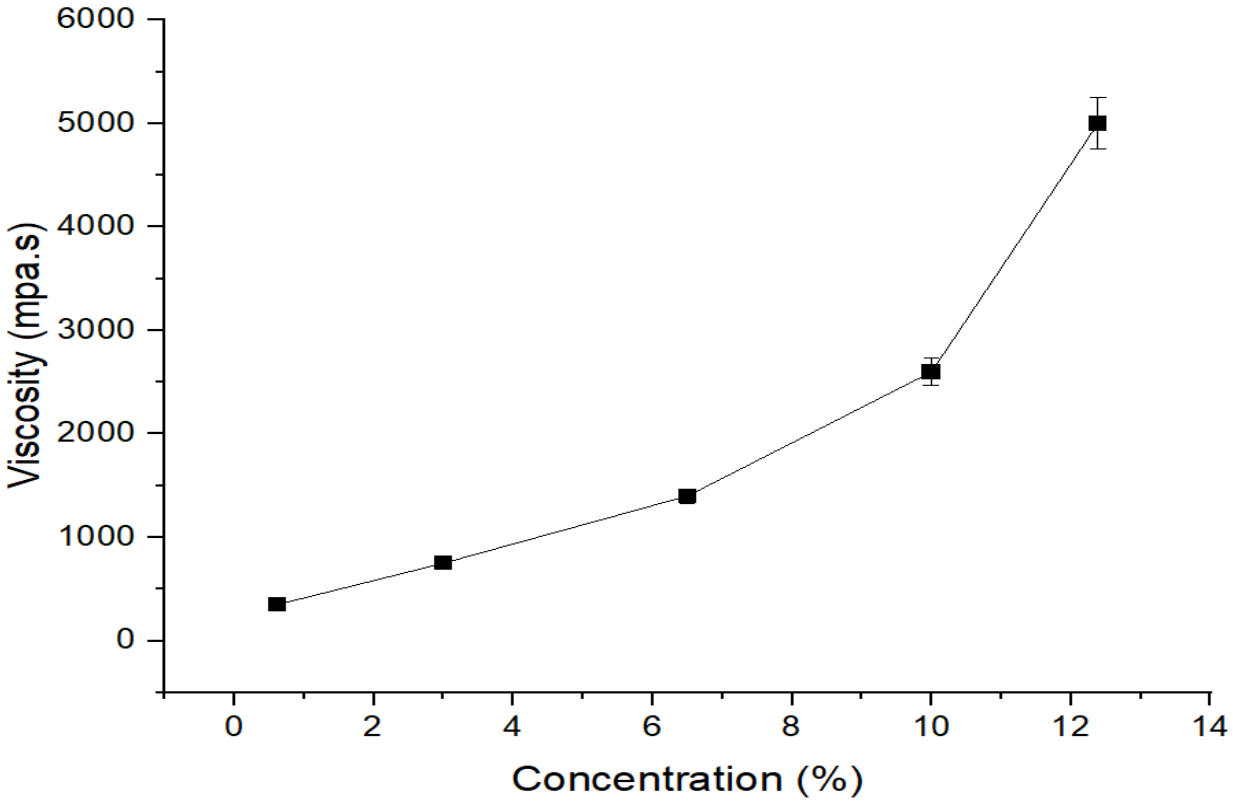


Figure 3.3: The plot of viscosity of the Cordia fruit mucilage (concentration vs. Viscosity)

3.1.7. Moisture sorption study

The moisture sorption test shows the sensitivity of material for moisture. The moisture sorptionof cordia mucilage at different relative humidity is presented in Figure 3.4. The percentage of moisture uptake was found between 1.3 and 6.7 for the range of 20-100% relative humidity, respectively, which indicates a less hygroscopic nature of the mucilage (Chu and Chow, 2000). In addition, the shape of the peak obtained in this study is similar to the characteristic peak of sugar-containing foods (J-shaped) (Isaac *et al*., 2021).

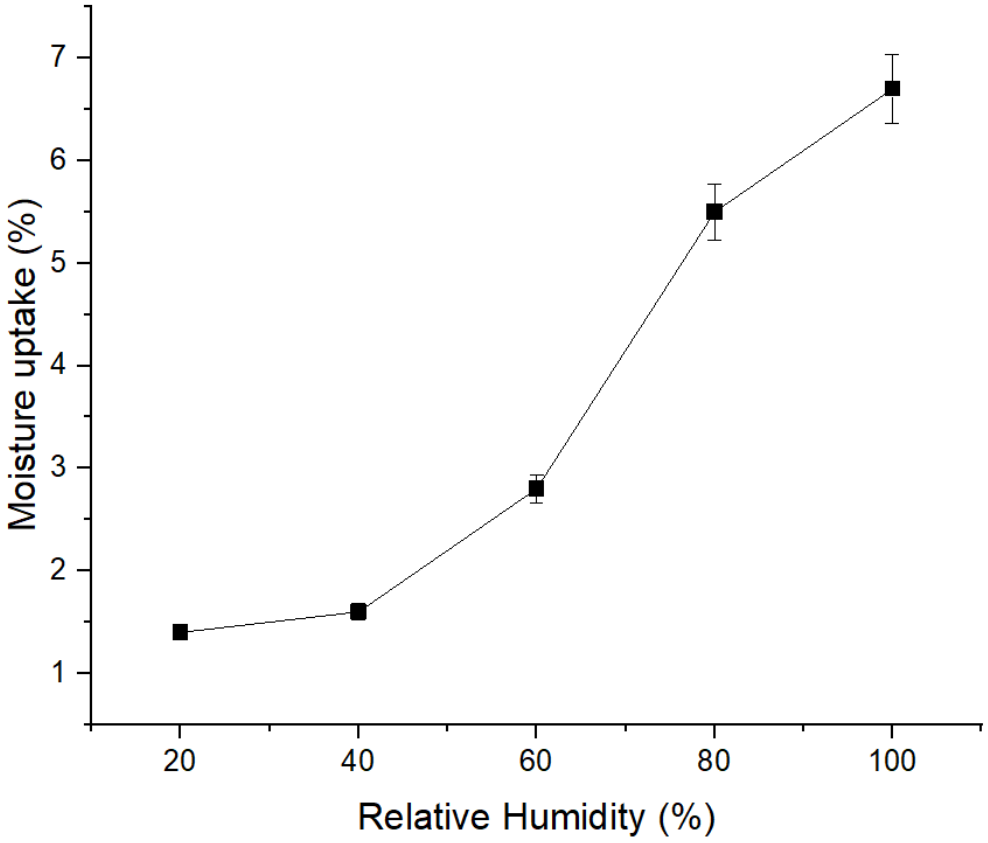
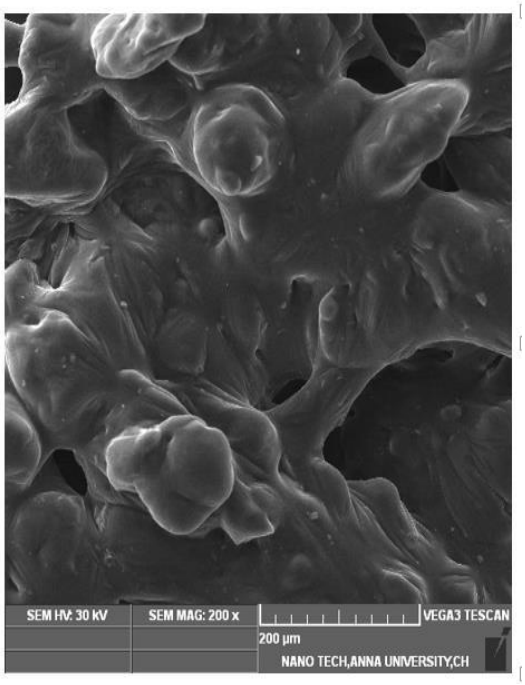


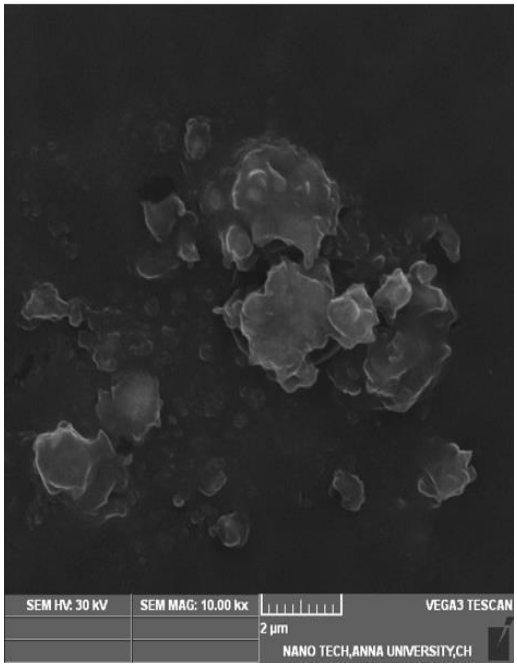
Figure 3.4: The moisture sorption of Cordia mucilage at different relative humidity

3.1.8. Scanning electron microscopy (SEM)

SEM is a tool used for substance characterization at the surface and/or near-surface morphologies (Ul-Hamid, 2018). As depicted in Figure 3.5, the size distribution of the mucilage is different with an irregular shape augmented with rough surfaces. Moreover, dimensions which are fibrous in nature, subsequently confirmed the amorphous nature of the material in addition to the supportive analysis the XRD data below in figure 3.6.

A.





B

Figure 3.5: SEM image of Cordia mucilage with magnification of 200x (A) and 10x (B)

3.1.9. X- Ray diffraction (XRD)

The XRD pattern of the mucilage was measured to get information on the crystalline structure. Due to the direct relationship between the crystallinity and stability of a substance, the determination of the nature of the mucilage as amorphous or crystalline through XRD analysis would be of great importance (Kang *et al*., 2019). As presented in figure 3.6, the mucilage has shown a noisy signal with a wide peak from 20°- 30° due to amorphous structure. This finding was similar to other findings as a peak at 20° was also observed in xanthan gum (Wang *et al*., 2021).

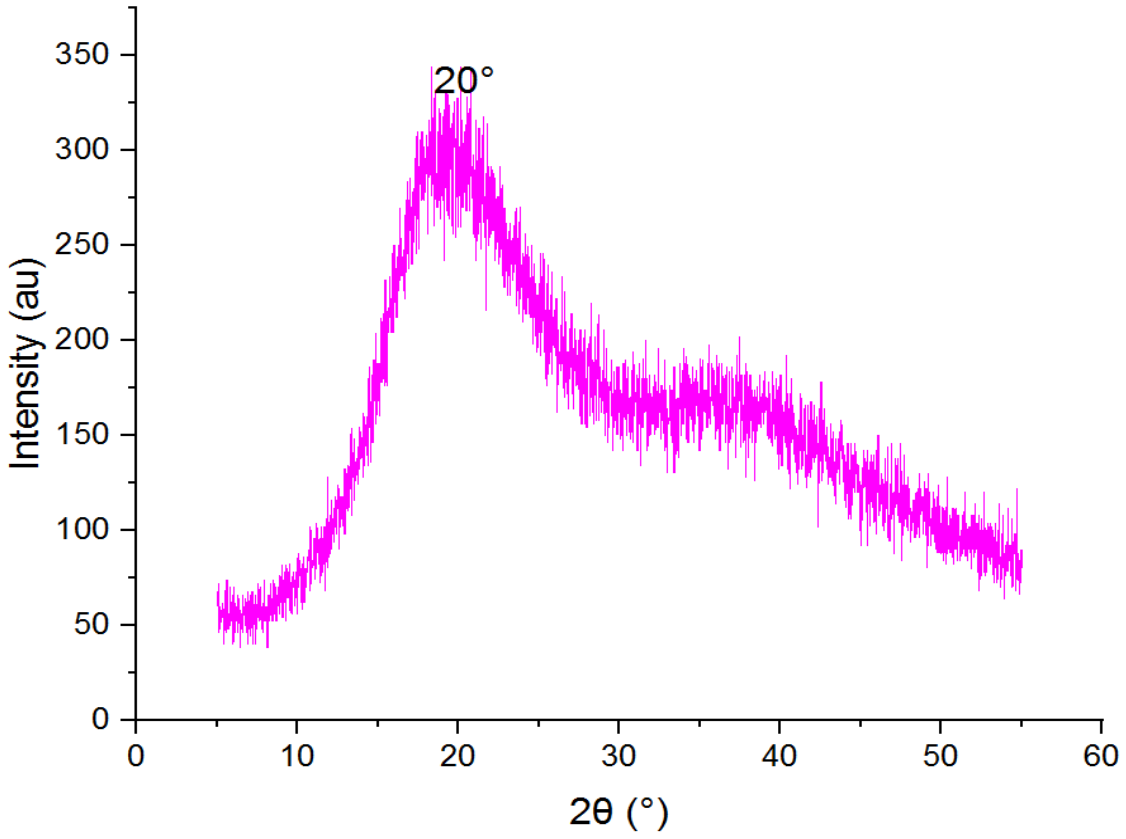


Figure 3.6: XRD pattern of the Cordia mucilage and on X-axis 2 theta and Y-axis intensity

3.1.10. Drug-excipient compatibility study

3.1.10.1. Differential scanning calorimeter (DSC)

The addition or loss of heat from a material can be tracked by differential scanning calorimeter through monitoring temperature (Hashemi *et al*., 2020). Therefore, any incompatibilities between two ingredients can be traced using DSC through changes in shape during endothermic and exothermic reactions (Nigatu *et al*., 2015). As it can be seen from Figures (3.7-3.9), all the peaks shown in the individual run are also present in the combination of the mucilage and paracetamol,which assured the compatibility of the mucilage with paracetamol. The FTIR study below also supports the current finding as it shows both substances are compatible.

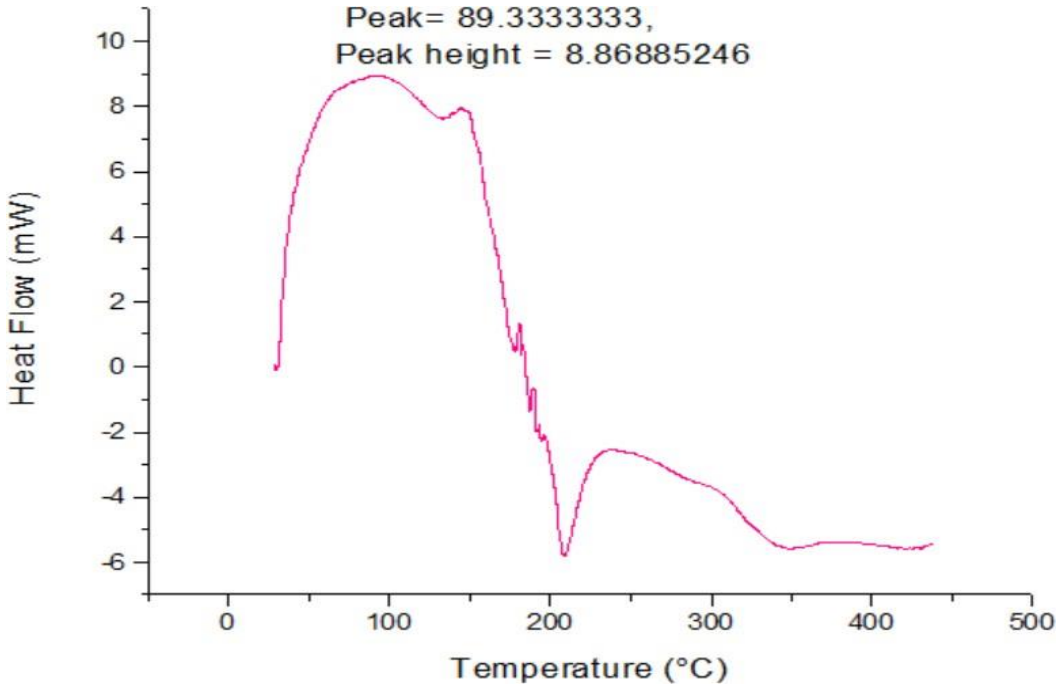


Figure 3.7: The DSC thermogram of the Cordia fruit mucilage alone

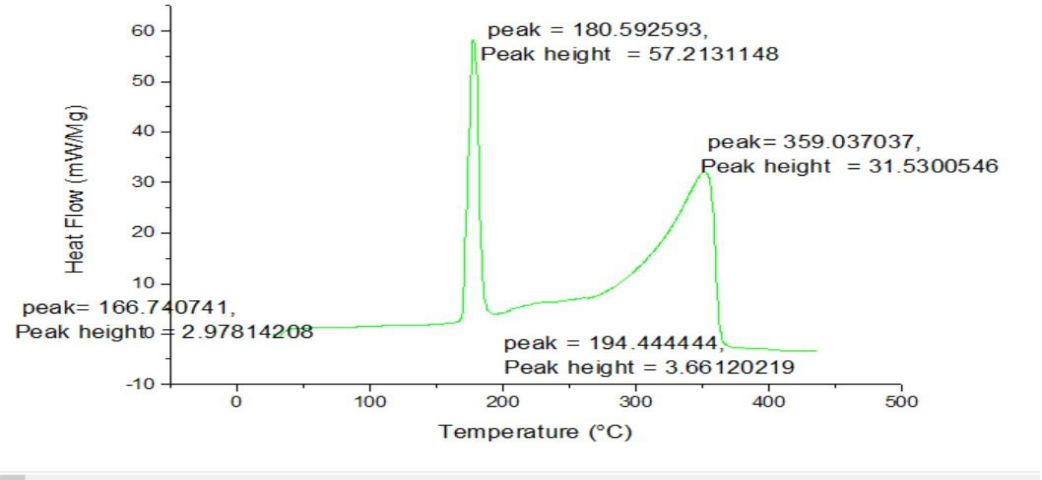


Figure 3.8: The DSC thermogram of paracetamol alone

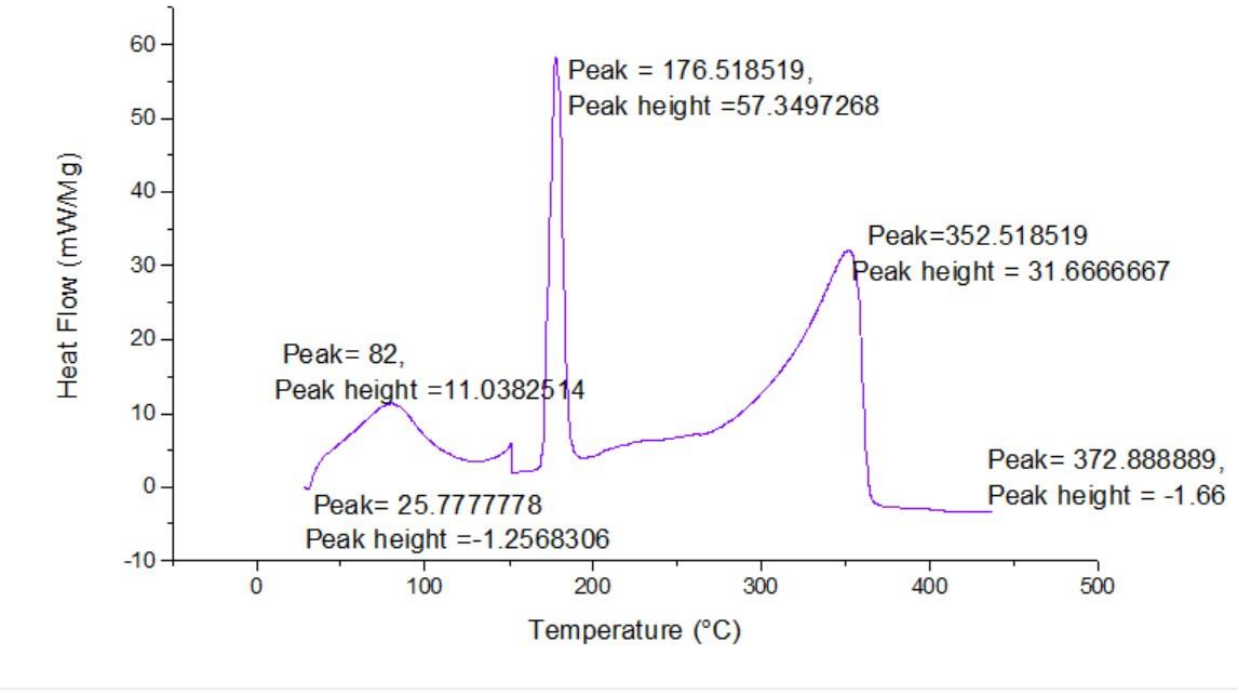


Figure 3.9: The DSC thermogram of the combination of Cordia mucilage and paracetamol at 1:1 ratio.

3.1.10.2. Fourier transform infrared spectroscopy (FTIR)

FTIR was used to show supplementary information to DSC on the compatibility of the cordia fruit mucilage with paracetamol by depicting any shift in the functional groups. The results were shown in Figures (3.10-3.13) and illustrated as follows.

The FT-IR spectrum of paracetamol showed the vibrational peaks at 3320 and 3164-3098 cm^{-1},as characteristic for to O-H and CH3 are stretching, respectively. A vibrational peak at 1653 $cm^{-1}$was due to C=O stretching while 1610 cm^{-1} attributes for and C=C stretching. Moreover, peaksat 1566, 1506, and 1442 cm^{-1} were designated to N-H bending, asymmetrical bending in C-H andC-C stretching, respectively. In addition, peaks at 1369-1328, 1260-1227, and 1170-1107 cm^{-1} were attributed to symmetrical bending in C-H bend, C-N and C-O stretching, respectively. The Vibrational peaks 966 and 837 cm^{-1} are assigned to C-N (amide) stretching and para- disubstituted aromatic ring respectively. The same result was reported in other studies (Trivedi *et al*., 2015; Nandiyanto *et al*., 2019).In the combination of the Paracetamol and Cordia mucilage all the peaks of paracetamol appeared, which confirms the compatibility of the two ingredients. The summary of the absorption of paracetamol, *C.mucilage* and the mixture of paracetamol and *C.mucialge* is given in table 3.2.

Table 3.2: The summary of IR absorption of paracetamol, Cordia mucilage, and the mixture of Paracetamol and Cordia mucilage.

Bond/Group	Absorption range(cm^{-1}	Paracetamol(cm^{-1})	Mucilage (cm^{-1}	Paracetamol and Mucilage (cm^{-1}
- OH	3500-3200	3322	3300	3322
C-H	3200-2850	3099	2933	3099
C=O	1750-1600	1608	1720	1608
C=C acetyl group	1610-1550	1561	1589	1561
C-O	1500-1200	1450	1338	1450
C-N	1300-800	1226	1027	1226
C-C	850-550	805		805

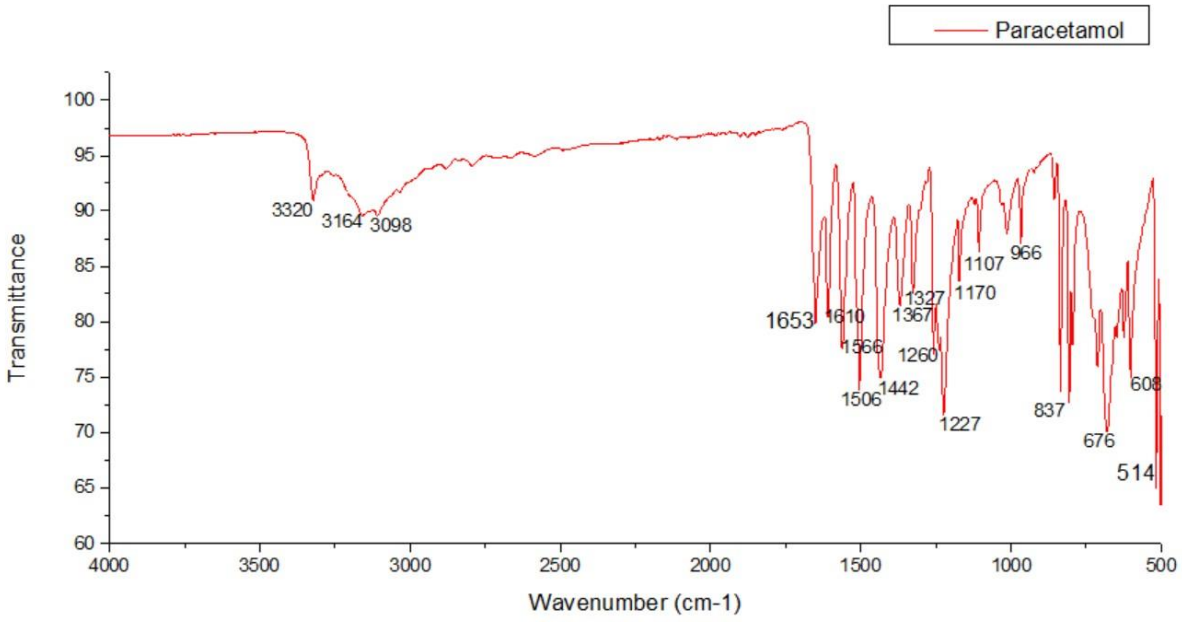


Figure 3.10: The FTIR spectra of paracetamol

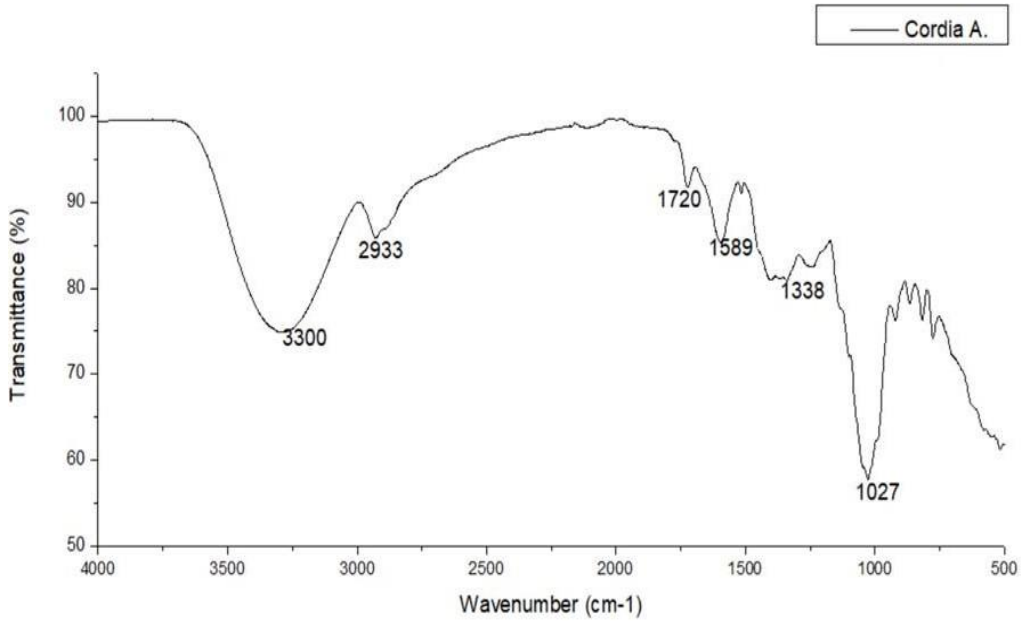


Figure 3.11: The FTIR spectra of Cordia mucilage.

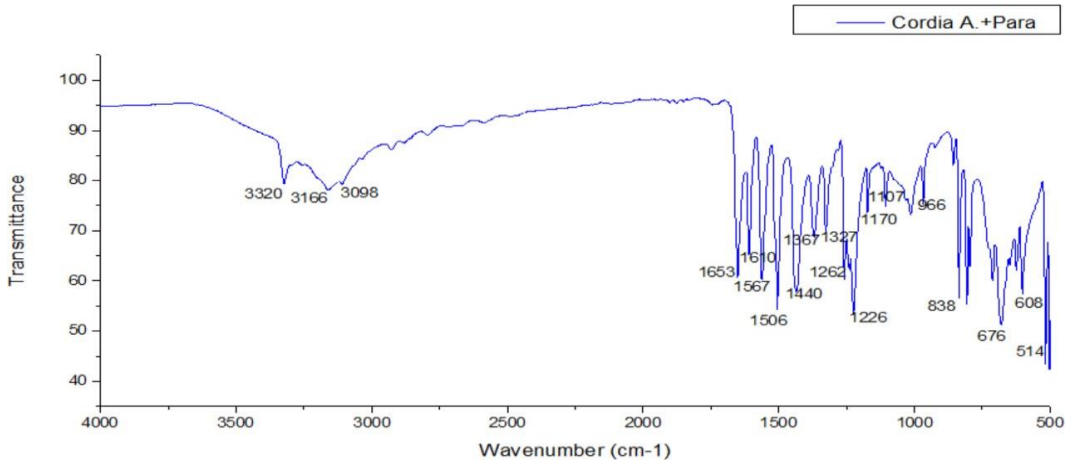


Figure 3.12: The spectra of the combination of paracetamol and Cordia mucilage at 1:1 ratio

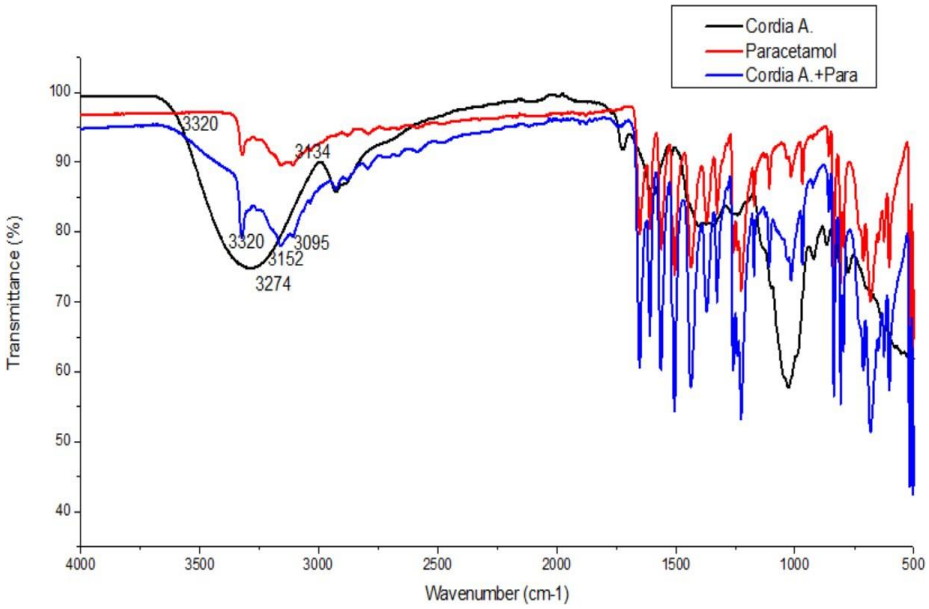


Figure 3.13: Alternative view of the spectra of Cordia mucilage and paracetamol at 1:1 ratio

3.2. Preliminary study

Optimization seeks to determine factors that are significant in the determination of the set of response variables. (Beg *et al*., 2019). In this study, three independent variables namely, compression force, binder and disintegrant, were identified from the literature and their effect against the response variables were studied (Audu-Peter and Ibrahim, 2016). The selected-response variables were drug release at time 30(Drug release at t-30(DR), friability (F), disintegration time (DIS) and tablet hardness (HD). The concentration for the independent variable to conduct the preliminary study are given in table 3.3. Providing the concentration of paracetamol, talc and magnesium stearate are kept constant (500mg, 1%, and 1% respectively). Lactose was also used as a diluent to make a total weight of 650 mg. Based on this, a total of 6 batches were formulated as shown in table 3.3.

Table 3.3: Composition of the three independent variables in paracetamol tablet formulations

Variables	Concentration/ magnitude
Cordia mucilage (binder)	3%, 6.5%, 10%
Compression force	40N, 70 N, 100N
Starch 1500 (disintegrant)	5%, 10%, 15%

3.2.1. Formation and evaluation of tablets

The different batches of tablets were formed using one factor at a time (OFAT) method in order to see the effect of individual variables on selected response variables while keeping all other variables constant with altering one variable of interest based on the composition of independent variables given in table 3.3. The total numbers of batches included in the preliminary study are described in table 3.4.The statistical analysis was conducted using One-way Anova Origin 7 Software (Origin Lab Corporation, MA, and USA). The results of the experiment are summarized as in table 3.4 and the significance of the independent variables over the determination of dependent variables are described in table 3.6. As it can be noted the table 3.6 the effect of all the three variables was found to be significant (P-value <0.05). The effect of the disintegrant was found to be directly proportional to dissolution and disintegration as shown in the result (Table 3.5). The compression force, on the other hand, has a significant retarding effect on the release as the magnitude increased and the reverse effect on friability was shown. Likewise, the binder concentration has shown a positive result on friability and hardness of the tablet while retarding effect was exhibited for the disintegration time and drug release.

Table 3.4: The independent variable composition for the formulation of preliminary tablets

Code	Compression force (N)	Disintegrant (Starch-1500) in %	Binder(Cordia mucilage) in %
P1	40	10	6.5
P2	100	10	6.5
P3	70	5	6.5
P4	70	15	6.5
P5	70	10	3
P6	70	10	10

Table 3.5: Summary of the result of the formulated tablets

Formulations	Hardness (N)	Friability (% loss)	Drug release at 30 minute (%)	Disintegration time (minute).
P1	50	1.3	93	1
P2	81	0.4	75	9
P3	77.5	0.79	74	8
P4	77	0.81	87	3
P5	69	0.9	90	2.5
P6	92.4	0.45	65	13

Table 3.6: Summary of the result for the significance of the independent variable

Variables	MeanDiff	q value	Alpha	Sig
HD-CF	65.5	7.50311E301	0.05	1
F- CF	0.85	9.73686E299	0.05	1
DR- CF	84	9.62231E301	0.05	1
DIS- CF	5	5.72756E300	0.05	1
HD-ST	77.25	8.84909E301	0.05	0
F- ST	0.8	9.1641E299	0.05	0
DR- ST	80.5	9.22138E301	0.05	1
DIS- ST	5.5	6.30032E300	0.05	1
HD-BD	80.7	9.24429E301	0.05	1
F- BD	0.675	7.73221E299	0.05	1
DR- BD	77.5	8.87773E301	0.05	1
DIS- BD	7.75	8.87773E300	0.05	1

Sig. 1 indicates the mean difference is significant at the 0.05 level Sig. 0 indicates the mean difference is insignificant at the 0.05 level

Since all the independent variables are significant in the determination of the outcome variables and some of the effects are opposite while others are synergistic, optimizing the formulation to get a better combination of independent variables in light of achieving the optimal outcome variables was sought and hence, all variables were included in the optimization study.

3.3. Preparation and evaluation of the granule

3.3.1. Preparation of the granule

The granule for each batch was prepared separately based on the data generated by the design expert software. The method used to prepare the granule was wet granulation due to the poor flowability and compressibility of paracetamol powder. The granules were prepared based on the formula indicated above in Table 2.1.

3.3.2. Evaluation of the granule

3.3.2.1. Micrometric properties

The prepared granules were evaluated for the flow property, compressibility, as well as size distribution through parameters such as angle of repose, Carr's compressibility index, Hausner's ratio, bulk density and tapped density as well as sieving. As presented in Table 3.7, the angle of repose was found to be less than 30° for all batches which depicts that the granules have a good flowability (Goh *et al*., 2018; Al-Hashemi and Al-Amoudi 2018).In a powder of good flowability, the values of bulk and tapped density would be close which in turn would lower the value of the Carr's index (Pawar and Lalitha, 2015). The Carr's index and the Hauser's ratio were found to be in the range of 5.01±0.07 to 9.53±0.39 and 1.00±0.12 to 1.10±0.02 respectively. These lower values of both the Carr's index and the Hauser's ratio below 15 and 1.25, respectively, indicate the better flowability of the granules. (Shah *et al*., 2008; Schulze, 2008).

Table 3.7: Summary results characterization of paracetamol granule (Mean ± SD).

Formulation	Bulk density(g/ml)	Tapped density(g/ml)	Flow rate (g/sec)	Angle of repose (^{o})	Carr'sindex	Hauser's ratio
F1	0.47±0.01	0.51±0.04	4.19±0.09	25.36±0.04	7.84±0.07	1.08±0.00
F2	0.45±0.06	0.49±0.01	4.11±0.23	26.66±0.34	8.16±0.12	1.07±0.09
F3	0.48±0.04	0.53±0.09	5.19±0.12	26.77±0.55	9.43±0.14	1.09±0.01
F4	0.51±0.08	0.56±0.12	4.48±0.27	28.44±0.11	8.92±0.02	1.10±0.02
F5	0.46±0.03	0.48±0.19	4.83±0.06	25.82±0.26	4.16±0.38	1.03±0.04
F6	0.49±0.07	0.52±0.06	4.17±0.11	27.78±0.72	5.76±0.29	1.06±0.12
F7	0.54±0.03	0.57±0.04	5.12±0.01	28.26±0. 09	5.26±0.46	1.04±0.02
F8	0.43±0.05	0.47±0.00	4.09±0.06	26.49±0.64	8.51±0.89	1.07±0.00
F9	0.46±0.01	0.48±0.07	4.61±0.19	26.16±0.17	4.16±0.28	1.03±0.05
F10	0.46±0.09	0.48±0.03	4.74±0.18	25.36±0.04	4.16±0.19	1.04±0.15
F11	0.48±0.09	0.50±0.01	5.22±0.19	29.19±0.18	4.01±0.58	1.04±0.12
F12	0.51±0.06	0.53±0.06	5.17±0.08	25.59±0.45	3.77±0.51	1.03±0.03
F13	0.46±0.02	0.51±0.09	4.08±0.01	25.21±0.31	9.80±0.23	1.09±0.00
F14	0.45±0.03	0.49±0.08	4.56±0.12	27.46±0.25	8.16±0.08	1.07±0.04
F15	0.50±0.05	0.53±0.05	4.88±0.09	25.26±0.02	5.66±0.39	1.06±0.08
F16	0.51±0.01	0.54±0.06	4.74±0.19	27.65±0.06	5.01±0.35	1.05±0.00
F17	0.50±0.09	0.55±0.02	4.49±0.24	29.37±0. 15	9.01±0.23	1.09±0.07

F18	0.53±0.07	0.56±0.06	5.00±0.05	28.32±0.51	5.35±0.58	1.04±0.01
F19	0.50±0.08	0.53±0.09	4.45±0.06	26.55±0. 45	5.66±0.07	1.06±0.06
F20	0.49±0.07	0.54±0.04	4.92±0.07	29.37±0. 19	9.25±0.69	1.10±0.14

3.3.2.2. Granule size distribution

The granule size distribution is very important as it has an impact on flowability, weight uniformity as well as dissolution profile of the tablet. The size analysis is also essential to ascertain the quality of the final dosage forms (Ngwuluka *et al*., 2010).Table 3.8. Presents the average granule size distribution. The granule size distribution was found to be between 416.8μm and 805.77 μm. This depicts that all batches exhibit a distribution of granules within therange required for tablets (300-1000 μm.) (Shekunov *et al*., 2007)

Table 3.8: Summary of the result of granule size distribution

Batches	**sieve pore size in Micrometer(% granule retained)**				
	1000/710 *(855)	710/315*(512 .5)	315/224*(269.5)	224/115*(169.5)	Average granule size(Micrometer)
F1	11.45(38.16)	12.35(41.16)	4.97(16.56)	1.23(4.1)	588.90
F2	12.88 (42.92)	10.21(34.03)	5.57(18.56)	1.34(4.46)	599.10
F3	10.79(35.69)	12.56(41.86)	4.98(16.6)	1.75(5.83)	576.71
F4	17.53(47.99)	12.17(40.56)	2.56(8.53)	0.87(2.9)	735.42
F5	17.66(58.83)	9.94(33.13)	2.10(7)	0.3(1.00)	693.67
F6	18.46(61.53)	9.46(31.53)	1.87(6.23)	0.21(0.7)	704.52
F7	18.19(60.63)	8.94(29.81)	2.13(7.1)	0.74(2.46)	694.45
F8	18.56(61.83)	9.39(31.30)	1.67(5.56)	0.38(1.26)	706.52
F9	22.01(73.36)	8.89(29.63)	2.34(7.8)	0.99(3.3)	805.77

F10	17.53(58.41)	7.98(26.61)	2.21(7.36)	2.28(7.6)	668.66
F11	18.87(62.81	8.38(27.93)	1.92(6.4)	0.83(2.76)	702.89
F12	18.36(61.19)	9.28(30.93)	2.34(7.81)	0.02(0.06)	702.92
F13	5.41(18.03)	5.61(12.61)	17.89(18.7)	1.09(3.63)	416.92
F14	19.87(66.23)	8.44(28.13)	1.22(4.06)	0.47(1.56)	724.09
F15	18.44(61.46)	8.72(29.06)	2.42(8.06)	0.42(1.41)	698.61
F16	19.21(64.03)	7.34(24.46)	2.51(8.36)	0.94(3.13)	700.73
F17	18.22(60.72)	6.79(22.63)	3.12(10.41)	1.87(6.23)	673.85
F18	19.28(64.26)	8.12(27.06)	2.58(8.60)	0.02(0.06)	711.48
F19	18.32(61.06)	8.54(28.46)	2.45(8.16)	0.69 (2.31)	693.91
F20	18.39(61.26)	7.34(24.46)	3.21(10.71)	1.01(3.36)	684.04

*Average sieve size

3.4. Evaluation of paracetamol tablet

The paracetamol tablets prepared with cordia mucilage as a binder were evaluated for hardness, friability, disintegration, and dissolution profile as well as weight and thickness uniformity as follows.

3.4.1. Weight uniformity and thickness evaluation

As shown in Table 3.9, all batches have shown a very good weight uniformity (648.4±2.12-653.8±1.95) since all meet the requirement to have less than ±5% weight variation (Thakur and Sharma, 2019). The thickness, on the other hand, has shown a small variation from batch to batch due to the difference in compression force used. For example, F1,F3, F5 and F7 have depicted higher thickness values (all slightly greater than 5mm) due to the low compression force used, which is 50N, whereas F9 has the highest value (5.66±0.13) due to the lowest compression force (32.9N) used. On contrary to F9, F10 showed the smallest of all thickness values (3.78±0.12) due to the maximum compression force used (117.045N). All other formulations showed thickness values between 4mm and 5 mm with good precision as the compression force is used for all of these batches is the same (75N).

Table 3.9: Summary of weight and thickness variation (Mean ±SD)

Formulation batch	**Weight variation (mg)**	**Thickness(mm)**
F1	651.08±2.52	5.15±0.18
F2	650.2±1.59	4.18±0.16
F3	651.2±2.81	5.21±0.14
F4	651.3±1.89	4.07±0.13
F5	650.6±2.31	5.12±0.12
F6	648.4±2.12	4.05±0.16
F7	651.7±1.86	5.11±0.20
F8	652.07±2.76	4.08±0.16
F9	650.1±2.47	5.66±0.13
F10	651±1.68	3.78±0.12
F11	651.6±2.65	4.50±0.11
F12	653.4±2.31	4.53±0.17
F13	653.8±1.95	4.57±0.12
F14	652.4±2.15	4.58±0.10

Continued from Table 3.8		
F15	651.65±2.31	4.60±0.11
F16	651.9±2.35	4.80±0.22
F17	652.8±1.83	4.73±0.16
F18	653.1±1.19	4.71±0.12
F19	653.2±1.93	4.54±0.16
F20	651.06±2.32	4.60±0.17

3.4.2. Tablet hardness, friability and disintegration time

In all batches, the tablet hardness has shown a directly proportional relationship with friability and an inverse proportion with disintegration time as shown in Table 3.10. Except for F1, F3, and F13, the other formulations meet the friability test limit (<1%). The reason for these three formulations to fail the friability test could be due to the fact that these formulations have the lowest binder concentration and minimum compression force was employed to compress the tablets. On the other hand, all formulations meet the hardness test, as their hardness values are below 100 N. On the other hand, all formulations meet the hardness test, as their hardness values are below 100 N. Moreover, all batches are in line with the specific pharmacopeial requirement for the disintegration time of conventional tablets (<15 minutes) (Kar *et al*., 2015).

Table 3.10: Summary of test results for Hardness, Friability, and Disintegration time

(Mean ±SD)

Formulation	**Hardness N(± SD)**	**Friability%(± SD)**	**Disintegration time (Minutes)**
F1	59.61±3.09	1.1±0.25	0.59
F2	69.21±2.54	0.7±0.18	2.51
F3	59.22±2.48	1.05±0.21	0.54
F4	71.71±3.18	0.68±0.08	2.57
F5	83.70±2.53	0.47±0.15	7.24
F6	89.11±3.96	0.33±0.12	7.12
F7	70.2±3.2	0.5±0.14	4.37
F8	84.1±3.36	0.4±0.13	7.21
F9	57.4±2.48	0.9±0.21	1.23
F10	86.3±3.69	0.39±0.20	6.39
F11	73.90±3.87	0.6±0.12	5.22
F12	78.81±1.77	0.57±0.15	0.55
F13	58.41±3.31	1.2±0.34	0.46
F14	87.03±3.63	0.31±0.14	10.27
F15	78.51±1.06	0.59±0.16	2.41
F16	76.15±3.77	0.52±0.09	2.19
F17	79.21±1.51	0.52±0.11	2.39

F18	76.31±1.39	0.55±0.08	2.51
F19	75.08±3.25	0.56±0.21	3.12
F20	75.81±3.44	0.54±0.13	2.53

3.4.3. Construction of calibration curve

Figure 3.14 depicts the calibration curve of paracetamol in phosphate buffer pH 5.8 at the wavelength of 267nm. The linear regression equation was found to be Y***=0.05402x-0.01724*** while the adjusted R square is **0. .99991.**

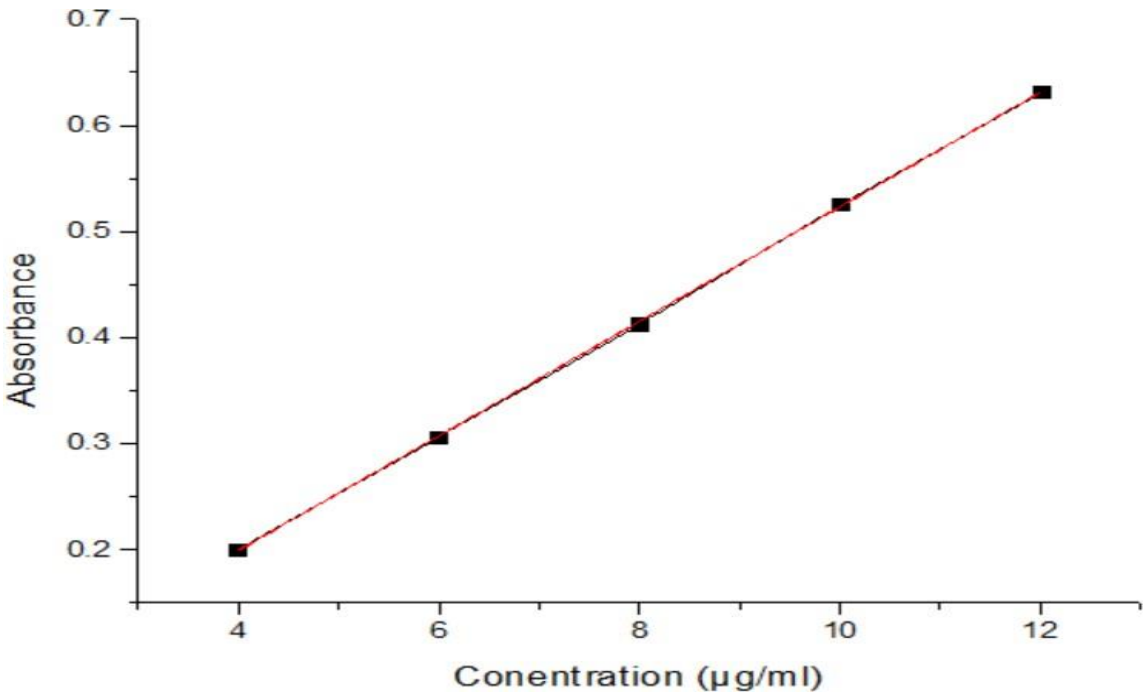


Figure 3.14: The calibration curve of paracetamol plotted at concentration against absorbance at 267nm with 95% confidence level (R2=0.99991)

3.4.4. In vitro drug release

All the batches showed a similar pattern in the release at different extents as shown in figures (3.15-3.18). This difference in the extent of their drug release is obviously due to differences in the magnitude of compression force, level of the binder and the disintegrant. For instance, F1 released its 80% content in 15 minutes while F3 and F13 released greater than 85 % of the drug before 10 minutes. This may be due to low compression force and binder concentration (50N and3% respectively) used in both F1 and F3. Although the magnitude of the Compression force is high in F13, the binder concentration used is 0.61% which might have led to the higher drug release. Moreover, the higher concentration of disintegrant used in F3 and F13 which is 15% and10%, respectively may also contribute to the higher release profile (95% at 30 minute). F14, on the other hand, has higher compression force (75N) and mucilage concentration (6.5%) but releases greater than 80% of its content at 15 minutes drug content, probably due to the highest concentration of the disintegrant (18.4%). F2, F4, F9 showed optimum drug release which is approximately 85% at 30 minute. Though F9 is composed of minimal compression force (32.95N) and higher disintegrant concentration (10%), the higher concentration of the mucilage (6.5%) balanced the release profile.

All the six central point formulations (F15-20) have shown close release profiles which are in line with their similar composition. All the releases are also recorded as approximately 85% at 30minutes which is within an optimum range according to the protocols for conventional or immediate-release tablets (FDA, 2018).

F5 to F8 showed a release profile of less than 80% of their total content within 30 minutes whichmay be due to higher binder concentration(10%). Among these formulations F7 showed marginally optimum drug release at 30 minutes (78.57%) which might be due to lower compression force (50N) and highest value of disintegrant (15%). F10 and F11 have also shown lower release value than the optimal due to the highest compression force (117.04 N) and high binder concentration (6.5%) for F10 whereas the lowest disintegrant concentration (1.59%) as well as high binder concentration (6.5%) in F11 contributed for its less release profile.

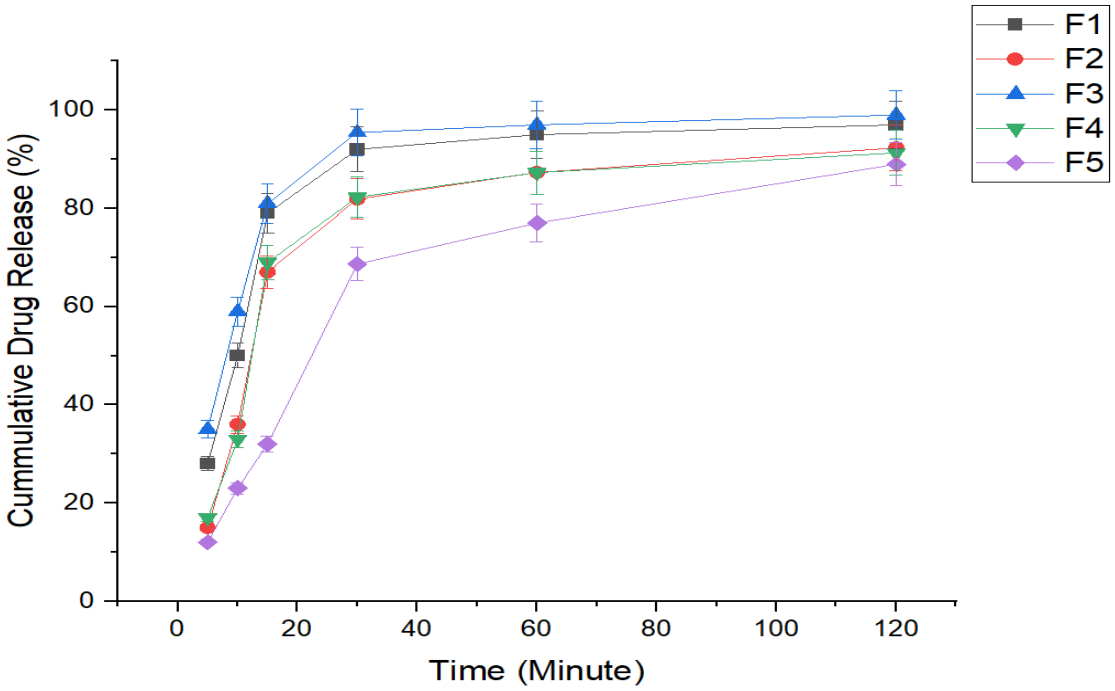


Figure 3.15: The invitro drug release profile of paracetamol formulated as per CCD (F1-F5).

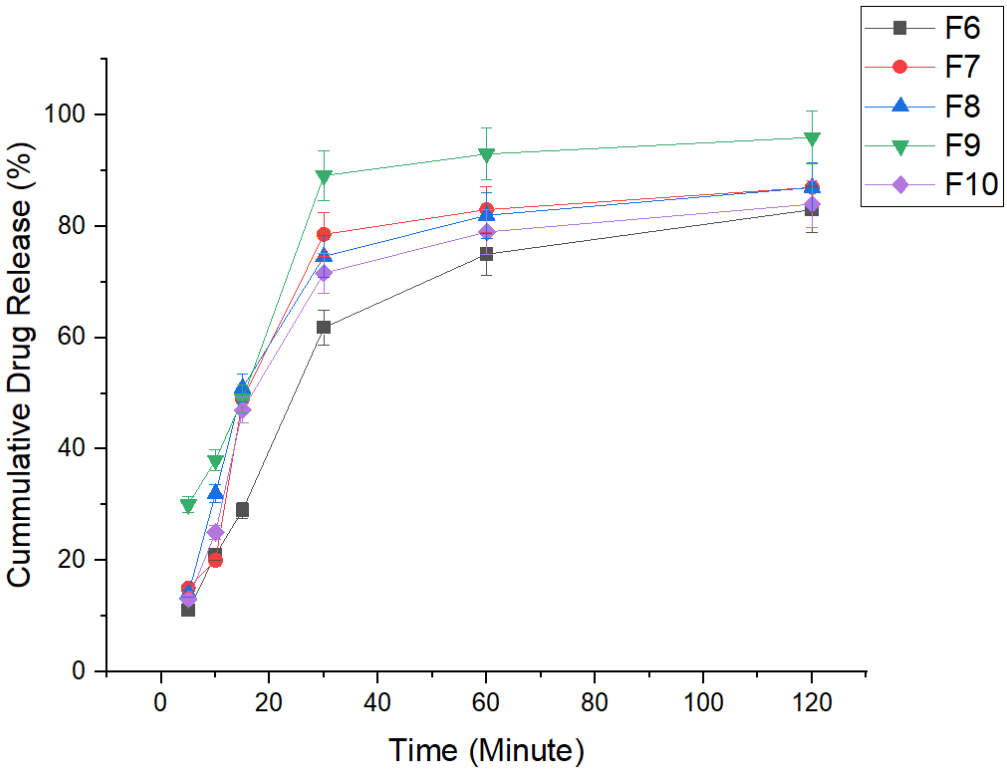


Figure 3.16: The in vitro drug release profile of paracetamol formulated as per CCD (F6-F10).

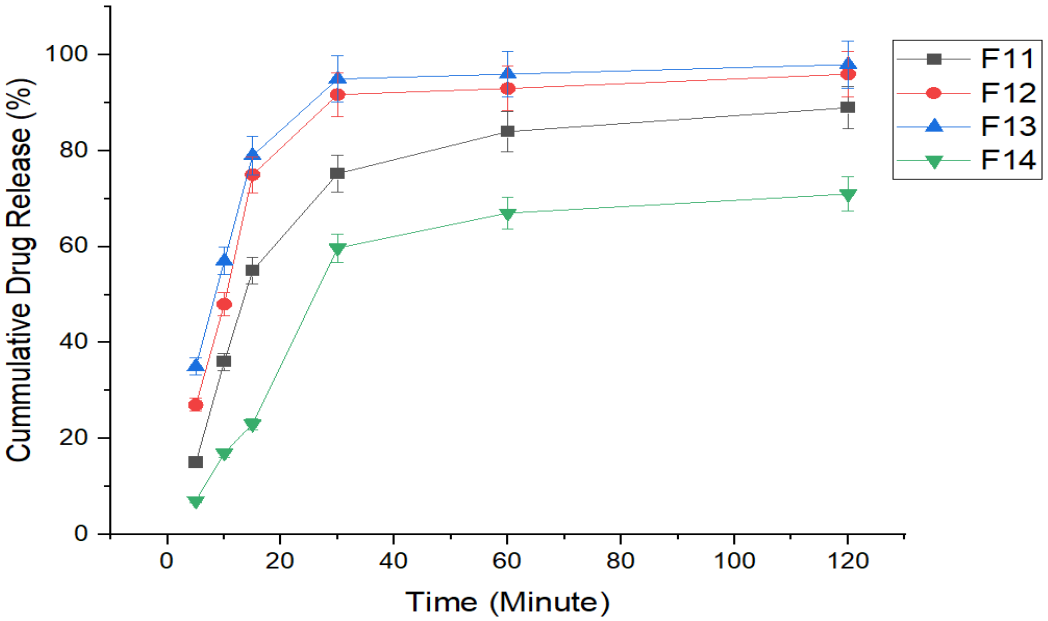


Figure 3.17: The *in vitro* drug release profile of paracetamol formulated as per the CCD (F11- F14)

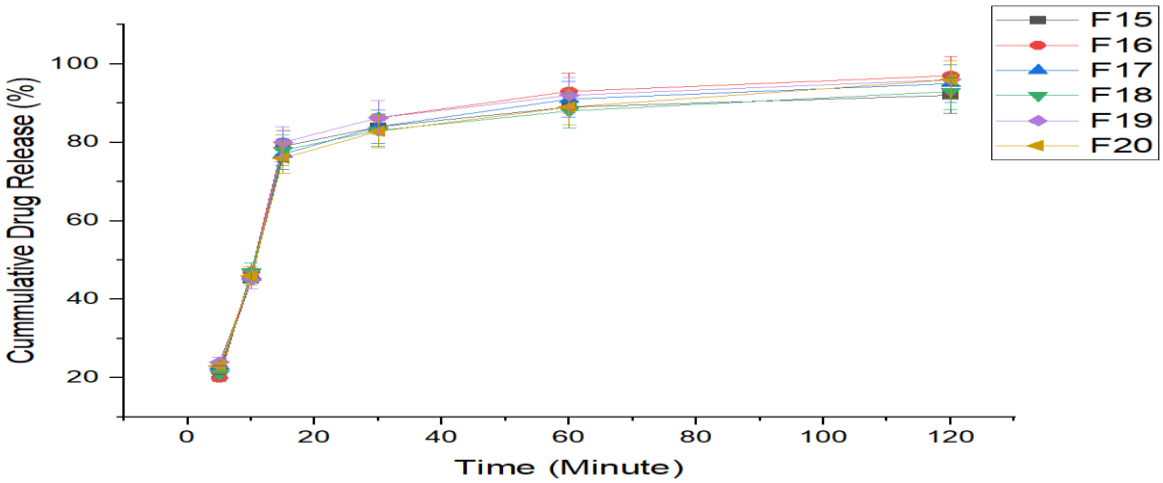


Figure 3.18: The *in vitro* drug release profile of paracetamol formulated as per the CCD (F15- F20)

3.5. Optimization of Paracetamol tablet by using Corida mucilage

The optimization was done using the CCD, one of the most widely used technique in response surface methodology (RSM). The study was conducted using the design expert software 13.0(Stat-Ease Inc., Minneapolis, MN, USA). RSM is a sequential procedure that starts from model fitness checking, the ANOVA analysis for model adequacy, diagnosis and ends with optimization and validation (Vadde *et al.*, 2006). Among RSM methods,the CCD is the widely used one as compared to its common alternatives such as, Box–Behnken which lacks augmentation with star points (Hanrahan and Lu., 2006; Almasi *et al.*,2016). The CCD includes the minimum and maximum values with repeatable central points and two additional star points per each factor. The central points are for the estimation of the pure errors while the star points are used to navigate the quadratic relationship between the study variables and the response (Azam *et al.*, 2015).

Factor screening is very important to avoid unnecessary runs which is important to save resources and time (Pramod *et al.*, 2016; Sakr *et al.*, 2021). In this study, three independent variables: the concentration of cordia mucilage (binder), the compression force and the concentration of starch-1500 powder (disintegrant) were identified as determinant while other variables such as the concentration of the drug, talc and magnesium stearate were kept constant throughout the study and lactose was used as needed to get a total weight of 650 mg.

The five levels in CCD were the two-star points (-α, +α), the minimum value (-1), the average (0) and the maximum (+1) set value. The formula, $2^n + 2n+6$ was used as per the CCD for three study variables which make the total numbers of runs 20, substituting 3 for n in the formula. Themaximum and the minimum values were determined from both the literature and the preliminary study conducted. The actual values of study variables fed to the software were 3-10%, 5-15%and 50-100N for cordia mucilage, starch-1500 and the compression force respectively. The independent variables together with the response variables are presented in Table 3.11.

Table 3.11: The summary of the results for the two response variables as per CCD

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Formulation	Space Type	A:CF	B:ST	C:CM	Drug Release at t-30	Friability
		N	%	%	%	%
F1	Factorial	50	5	3	92	1.1
F2	Factorial	100	5	3	81.89	0.7
F3	Factorial	50	15	3	95.43	1.05
F4	Factorial	100	15	3	82.281	0.68
F5	Factorial	50	5	10	68.63	0.47
F6	Factorial	100	5	10	61.809	0.33
F7	Factorial	50	15	10	78.575	0.5
F8	Factorial	100	15	10	74.608	0.4
F9	Axial	32.9552	10	6.5	89.12	0.9
F10	Axial	117.045	10	6.5	71.636	0.39
F11	Axial	75	1.59104	6.5	75.242	0.6
F12	Axial	75	18.409	6.5	91.7201	0.57
F13	Axial	75	10	0.613725	95	1.2
F14	Axial	75	10	12.3863	59.702	0.31
F15	Center	75	10	6.5	84.009	0.59
F16	Center	75	10	6.5	86.332	0.52
F17	Center	75	10	6.5	86.332	0.52
F18	Center	75	10	6.5	84	0.55
F19	Center	75	10	6.5	83.07	0.56
F20	Center	75	10	6.5	82.818	0.54

3.5.1. Mathematical model for drug release at t-30 and friability

The best mathematical model that fit the relationship between the study variables and the response was identified by using functions generated by the design expert software (Table 3.12 and 3.13) which includes the sequential p-values, lack of fit p-value, predicted residual sum of square (PRESS) and both the adjusted and predicted R^2 (Abu-Izza, *et al*., 1996;Kim, *et al*., 2007;Sharma *et al*., 2020).

Table 3.12: Model fit summary of Friability

Source	Sequential p-Value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	< 0.0001	0.0032	0.8700	0.8222	
2FI	0.1863	0.0039	0.8880	0.8336	
Quadratic	< 0.0001	0.2085	0.9823	0.9472	Suggested
Cubic	0.1564	0.3627	0.9888	0.8653	Aliased

Table 3.13: Model fit summary for Drug release at t-30

Source	**Sequential p-Value**	**Lack of Fit p-value**	**Adjusted R^2**	**Predicted R^2**	
Linear	< 0.0001	0.0146	0.8558	0.8035	
2FI	0.2303	0.0164	0.8711	0.7389	
Quadratic	**0.0024**	**0.1648**	**0.9581**	**0.8674**	**Suggested**
Cubic	0.1043	0.4236	0.9773	0.7826	**Aliased**

For both friability and drug release at 30 minutes, the design expert software suggested quadratic model for establishing mathematical relationship between the factors and response variables.

Both the adjusted and predicted R^2 which are model prediction capacity indicators, were good

enough for the model to fit. As shown in Table 3.14, the values of both the adjusted R^2 and predicted R^2 are more than 0.8which is a good suggestion that the models have a high predictionability (Pal *et al*., 2014; Ojewumi *et al*., 2019). The difference between the adjusted and predicted R^2 is also within the limit, less than 0.2 for both friability and drug release at t-30 which is a good indicator for fitness of the model in both responses (Bhasin and Ghosh, 2012; Deshmukh and Naik 2013;Zhou *et al*., 2013). The R^2 value is also an indicator of the fitness of the regression model and the closer the value to one, the higher predictability of the dependent variables (Bo *et al*., 2015). In this study, the R^2 value for both drug release at t-30 and friability were 0.9779 and 0.9907, respectively.

The other important function is the sequential p-value which states the significance of every model terms, in specific and of the mathematical model, in general (Kim *et al*., 2020). The sequential p-value must be less than 0.05 in order for the model to fit (Shishir *et al*., 2016; Eri *et al*., 2018).The results observed in this study is in line with the above stated requirement, <0.0001for friability and 0.0024 for drug release at t-30 minute. The lack of fit P value, which is acceptable if it is less than 0.1, also found to be insignificant for both response variables (Pankaj and Awasthi, 2014). Moreover, Predicted Residual Sum of Square (PRESS) value which is a model validation parameter used to assess a model's predictive ability was found to be indicative for the model fitness. Generally, the lowest the value of PRESS the higher the predictive capacity of the model. In this study lowest value is exhibited for quadratic model than other models for both responses which is a good indicator for the fit of the model (Kim *et al*, 2007; Shishir *et al*., 2016)

Table 3.14: Model summary statistics for drug release at t-30 and friability, respectively

Source	Std. Dev.	R^2	Adjusted R^2	Predicted R^2	PRESS	
Linear	3.83	0.8786	0.8558	0.8035	379.67	
2FI	3.62	0.9118	0.8711	0.7389	504.64	
Quadratic	**2.06**	**0.9779**	**0.9581**	**0.8674**	**256.36**	**Suggested**
Cubic	1.52	0.9928	0.9773	0.7826	420.13	Aliased
Friability						
Source	Std. Dev.	R^2	Adjusted R^2	Predicted R^2	PRESS	
Linear	0.0905	0.8905	0.8700	0.8222	0.2127	
2FI	0.0840	0.9234	0.8880	0.8336	0.1992	
Quadratic	**0.0334**	**0.9907**	**0.9823**	**0.9472**	**0.0631**	**Suggested**
Cubic	0.0266	0.9965	0.9888	0.8653	0.1612	Aliased

3.5.2. Model adequacy

Analysis of variance (ANOVA) is used to check the adequacy of the model by showing different functions (Hanrahan and Lu. 2006). The ANOVA for reduced quadratic model of drug release at t-30 is summarized in table 3.15 while for reduced quadratic model of Friablity is summarized in table 3.16.

The F value stands for residual error and estimates the accuracy of the model (Vadde *et al.*, 2006; Saeid *et al*., 2018). This value for both drug release at t-30 and friability is 70.09 and 194.39, respectively. The higher the F value of each term, the greater significance to cause an effect will be and the values obtained in this study satisfied the model (Xie *et al.*, 2016;Permender *et al*., 2016). Moreover, the lack of fit values for both responses are shown to be greater than 0.1 (0.2278 and 0.2116 for drug release at t-30 minutes and friability

respectively) which is a good indicator for the good fit of the model (Pankaj and Awasthi, 2014).

The measurements for signal-to-noise ratio called adequate precision were found 29.0714 and 42.981 for drug release at t-30 minutes and friability, respectively. These values are much greaterthan 4, which indicates an adequate signal to explore the design space (Adalarasan *et al*., 2015; Kaur *et al*., 2018; Bala *et al*., 2019).

The sum of squares (SEM) is obtained by dividing the main effect by the standard error of the main effect. The larger SEM value indicates the factor has a more influential effect. In both the drug release and friability analysis, the concentration of cordia mucilage was found to be more influential than other factors as shown in Table 3.15 and Table 3.16, respectively. A similar result was reported in another study (Kim *et al*., 2007).

The disintegrant (B) was found to be insignificant for the determination of friability (Table 3.16) while the interaction between the compression force (A) and the disintegrant (B) was insignificant for the determination of the drug release at t-30 minutes. Therefore, these factors were avoided using a backward model reduction approach to improve the model prediction ability (Said *et al*., 2015; Reddy *et al*., 2020).The model terms, A, B, C, AC, BC, A^2, and C^2 were significant for drug release at t-30 minutes and A, C, AC, A^2, and C^2 for friability as the p- values were found to be less than 0.05 for every model terms mentioned above.

Table 3.15: ANOVA for reduced quadratic model of drug release at t-30

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1886.48	7	269.50	70.09	< 0.0001	significant
A-CF	294.80	1	294.80	76.67	< 0.0001	
B-ST	215.72	1	215.72	56.10	< 0.0001	
C-CM	1187.41	1	1187.41	308.79	< 0.0001	
AC	19.44	1	19.44	5.06	0.0441	
BC	44.76	1	44.76	11.64	0.0052	
A^2	34.61	1	34.61	9.00	0.0111	
C^2	99.32	1	99.32	25.83	0.0003	
Residual	46.14	12	3.85			
Lack of Fit	34.10	7	4.87	2.02	0.2278	not significant
Pure Error	12.05	5	2.41			
Cor Total	1932.63	19				

Table 3.16: ANOVA for reduced quadratic model of Friability

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.18	5	0.2360	194.39	< 0.0001	Significant
A-CF	0.2554	1	0.2554	210.41	< 0.0001	
C-CM	0.8104	1	0.8104	667.57	< 0.0001	
AC	0.0351	1	0.0351	28.92	< 0.0001	
A^2	0.0136	1	0.0136	11.22	0.0048	
C^2	0.0703	1	0.0703	57.88	< 0.0001	
Residual	0.0170	14	0.0012			
Lack of Fit	0.0135	9	0.0015	2.12	0.2116	not significant
Pure Error	0.0035	5	0.0007			
Cor Total	1.20	19				

3.5.3. Model diagnosis

In addition to the ANOVA analysis, the diagnostic plots, which are determinant for model adequacy are presented below. Figures 3.19-3.26 have shown are all the diagnosis conducted are within their limit, indicating the predictability of the model. Donghui *et al*., 2014).

Externally studentized residuals are more sensitive in finding outliers than internally studentized residuals (Ranganai, 2016; Abdel-Raoof et al., 2020) .Therefore, the design of expert software was adjusted at externally studentized residuals for the whole process of the diagnosis.

3.5.3.1. Normal plot of residuals

The normal plots of residuals are shown to be closer to the straight line in case of both responses as shown in figure 3.19. This depicts that the prediction could satisfy the analysis (Bunny *et al*., 2015)

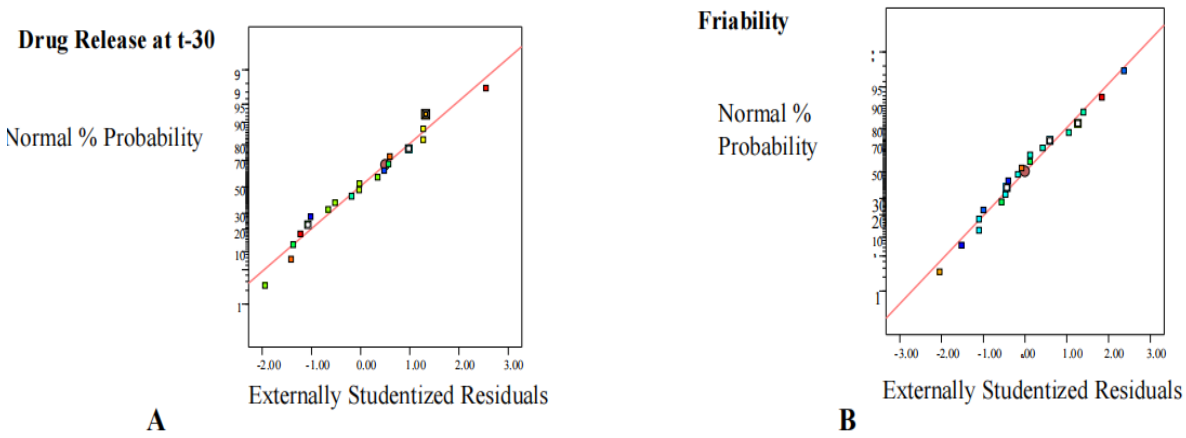


Figure 3.19: The normal plot of residuals for drug release at t-30 (A) and friability (B)

3.5.3.2. Residual vs. Predicted

Residual vs. predicted graphs assess the assumption of constant variance (Singh *et al*., 2011). The plots should scatter randomly within the limit (Bhusari *et al*., 2020)**.** The plots for both responses in this study are scattered within the limit which shows better model predictability Figure 3.20.

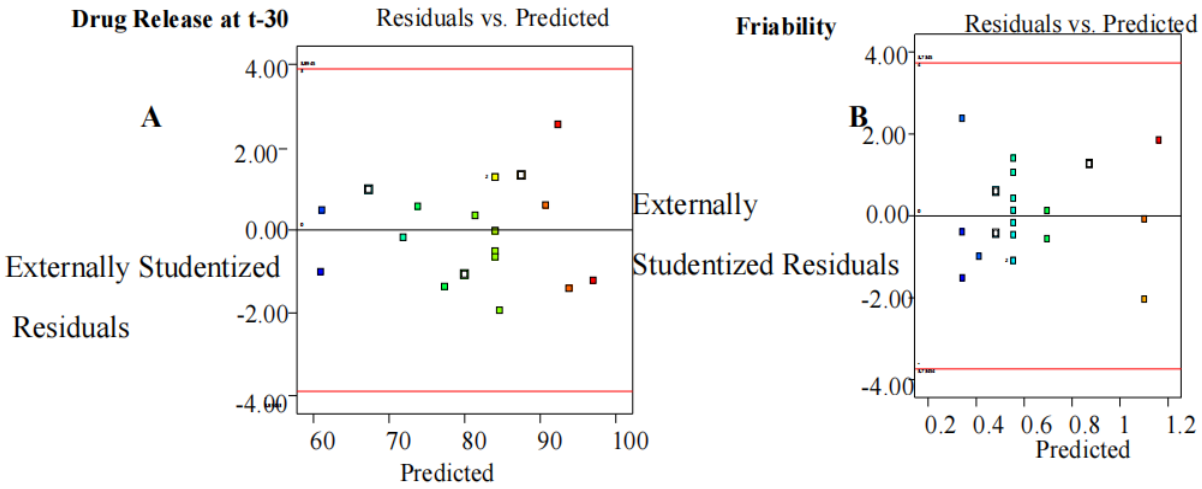


Figure 3.20: Residuals vs. Predicted plots for release at t-30 (A) and Friability (B)

3.5.3.3. Residuals vs. Run

This is the plot of residuals against the actual run and points should be randomly scattered tosatisfy the model (Dao *et al*., 2019).Figure 3.21 depicts randomly scattered plots.

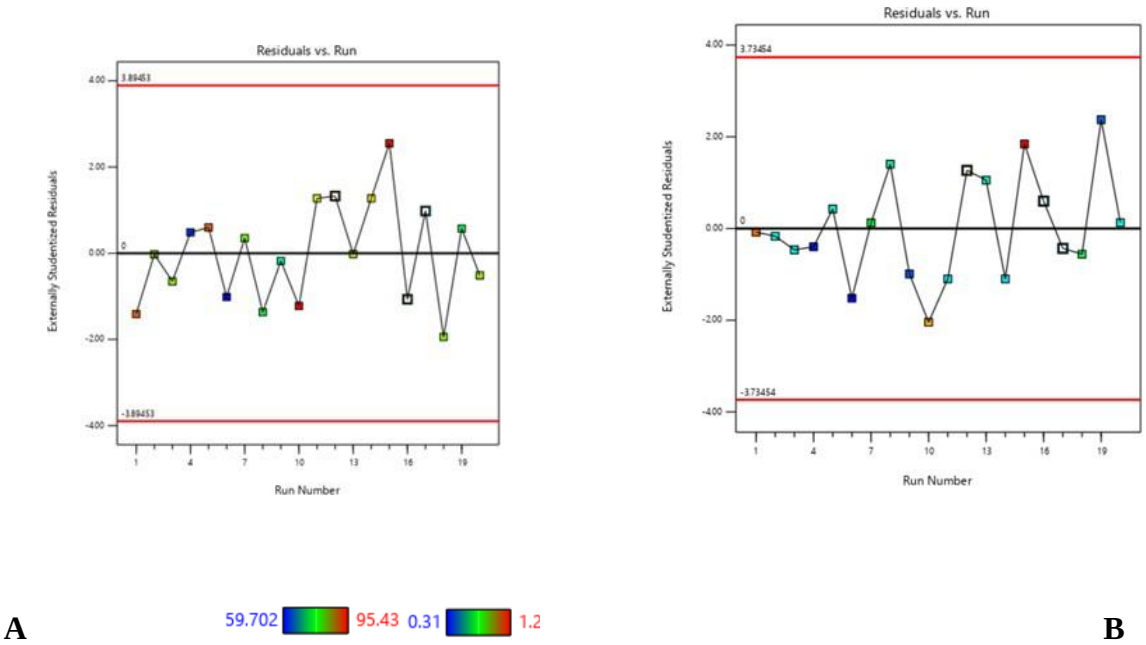


Figure 3.21: The residuals vs. run plots for drug release at t-30 min (A) and Friability (B)

3.5.3.4. Predicted vs. Actual

The predicted vs. actual plot is drawn to see how close the prediction is to the actual values obtained during the experiment and the perfect straight line provided by the software (Iloamaeke *et al*., 2020).The plots in this study showed good predictability for both responses as the experimental and the predicted data are in good agreement with each other and the perfect line asshown in figure 3.22(Sabbagh *et al*., 2018).

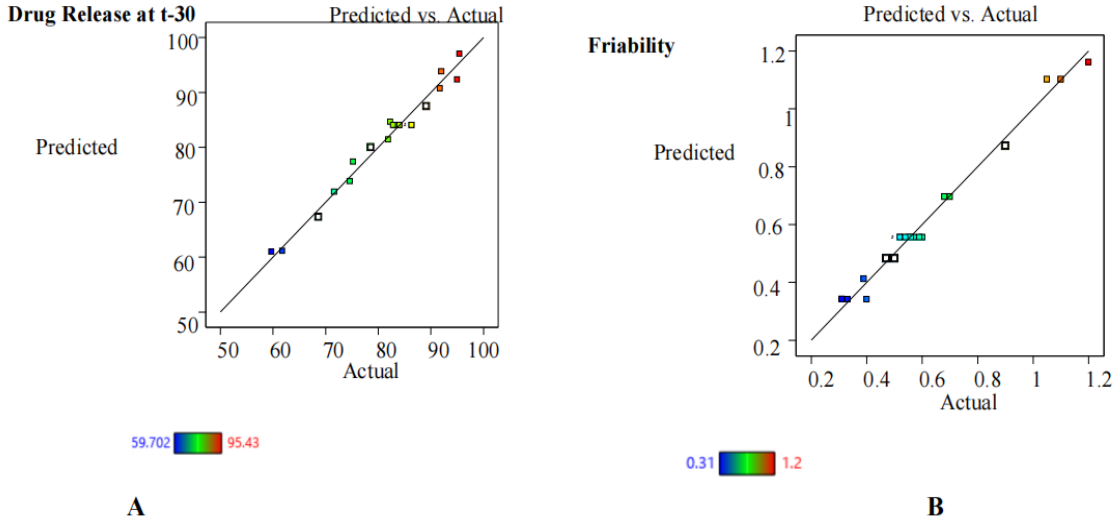


Figure 3.22: Predicted vs. Actual plots for drug release at t-30 (A) and Friability (B)

3.5.3.5. The Box-Cox plot

The box-cox plot dictates the power law of transformation. This means that it is a test to convert the non-normal distribution of dependent variables to normal. The distribution of the dependent variables is normal if the 95 % confidence interval is around lambda of 1.Therefore, transformation for both responses is not recommended as shown in figure 3.23(Singh *et al*., 2011).

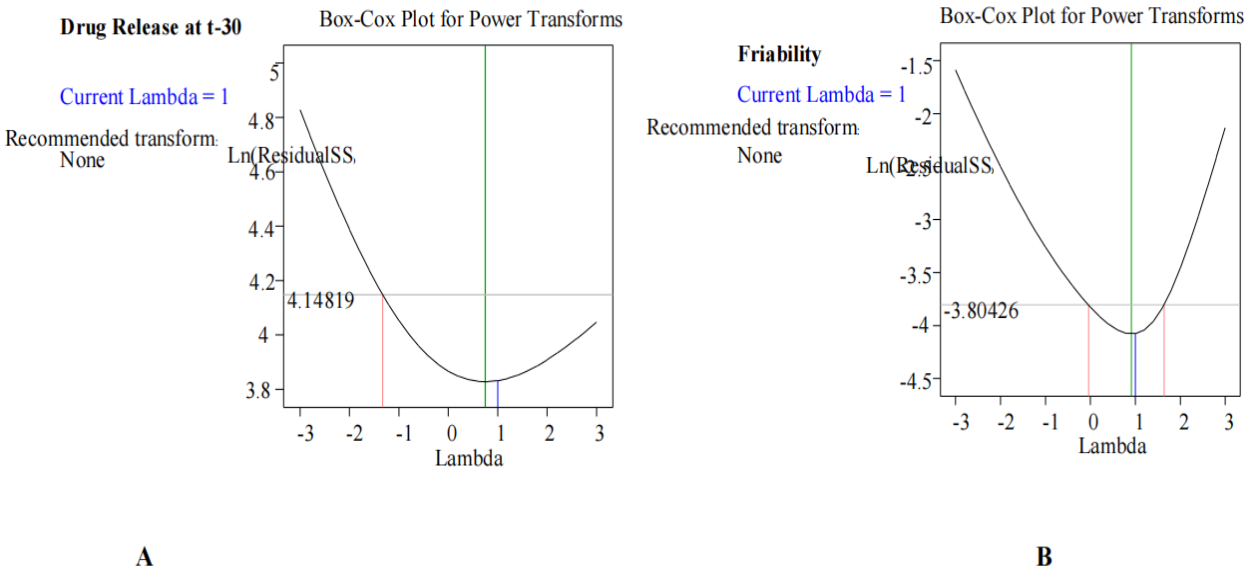


Figure 3.23: The box-cox plots for drug release at t-30 (A) and friability (B)

3.5.3.6. Cook's distance

The cook's distance shows any alteration that could be made by the quadratic model in the case of omission of data points (Abdel-Raoof *et al*., 2020).The cook's distance of less than 1 is desirable as it implies that omission of any data points is unlikely in changing the prediction of regression coefficients(Jaswir *et al*., 2019). The results in this study are in good agreement with the above requirement as shown in figure 3.24.

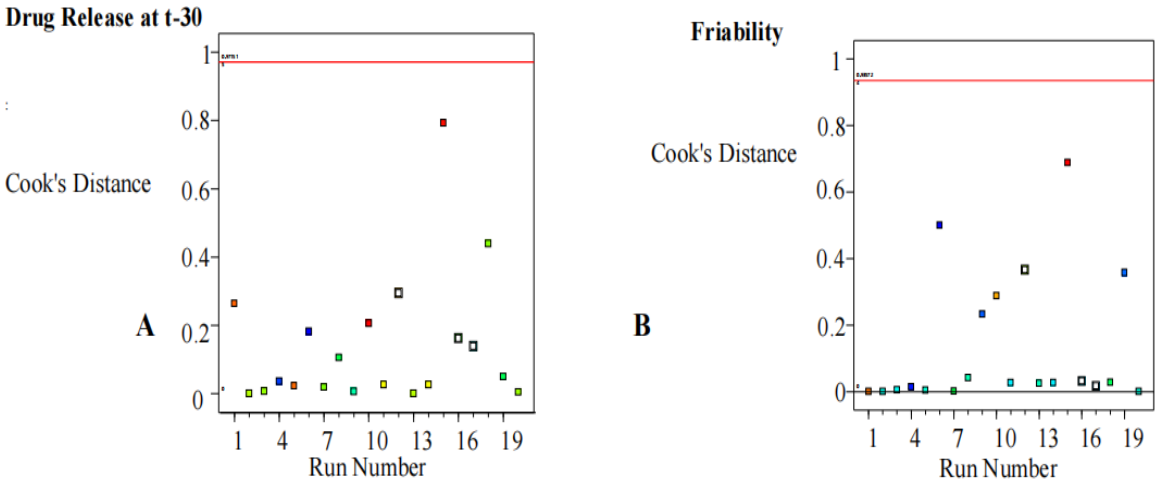


Figure 3.24: Cook's distance plots for drug release at t-30 (A) and Friability (B).

3.5.3.7. Leverage vs. Run

The leverage plot depicts the extent of the influence of the points on the model. If the leverage is one or nearly one means, it will control the model and hence, it would be reduced by adding replicates (Jain *et al*., 2019).Figure 3.25 shows the leverage vs. Run is good as it is far from one.

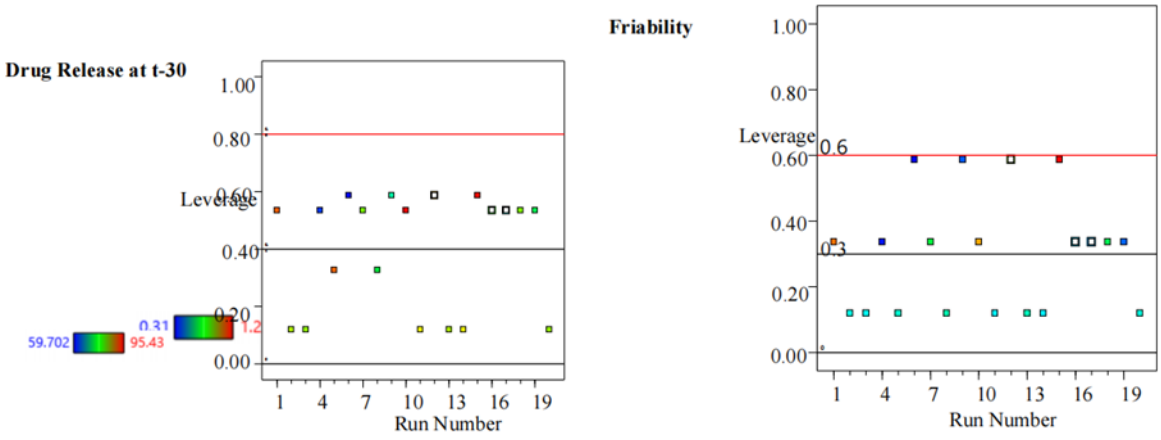
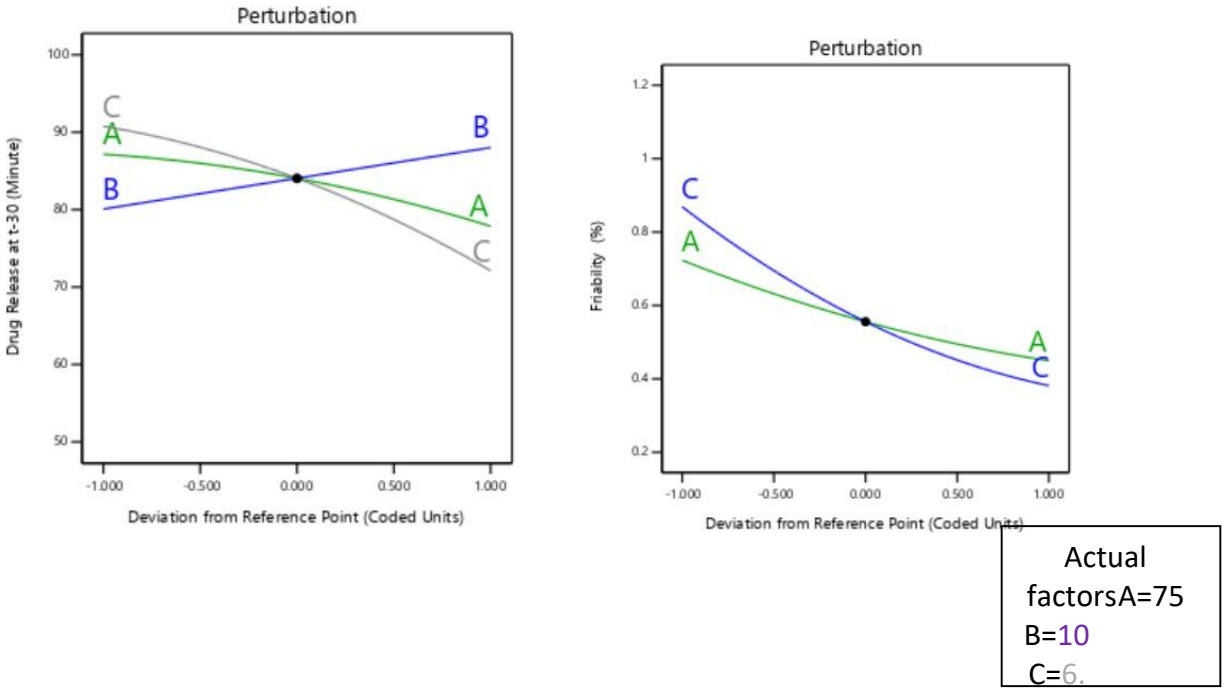


Figure 3.25: Leverage vs. run plots for drug release at t-30 (Left) and Friability (Right).

3.5.3.8. Perturbation

The perturbation plot is important in showing the impact of factors (study variables) on the response variables while all are at the center point and the curve with higher change is perceived to be the one with a big impact on the response than others (Mukherjee *et al.*, 2014;Shahabipour and Bohlooli, 2019). Figure 3.26 shows the factor C (the binder) highest impact on both responses than other factors whereas factor B (the disintegrant) is found to have the least or insignificant effect on responses.



A B

Figure 3.26: Perturbation curve of drug release at t-30 (A) and Friability (B)

3.5.4. Model equation

The equation was generated in terms of coded factors as actual factors cannot be used to show the relative impact of factors based on their coefficient. This is because in the case of the actual factors, the coefficients are scaled based on the unit of each factor and the intercept cannot show the mid-point in the design space (Shende *et al*., 2014; Ohale *et al*., 2017). However, the actual equation is important in predicting the dependent variables based on the level of each factor. The negative coefficient in the equations shows retarding or decreasing effect while the positive signsare for the agonist impact of the factors on the response (Iloamaeke *et al*., 2020). The equations generated are after model reduction and some of the model terms are not mentioned as they were not significant. As it can be seen from equations 3.1 and 3.2, both the compression force and concentration of cordia mucilage have a retarding effect on the drug release while the disintegrant enhances the drug release. The equation for friability showed that both the compression force and the cordia mucilage have reducing effect which is noted as negative coefficients. The factors' effect can also be seen from the contour and 3D plot

clearly (from Figure 3.27 to Figure 3.28). Moreover, the effect of disintegrant was insignificant for friability (Figure 3.29). The same interaction was also found in another study in which the disintegrant lacks a determinant effect on the friability. This probably could be logical as the effect of most disintegrants are through swelling after being immersed in a medium (Akin-Ajani *et al*., 2016).on the other hand, the effect for the cordia mucilage on friability was almost doubled as compared to the compression force as shown in equation 3.2. The effect can also be seen on the response surface graphs (figure and contour plots (figure). The same report was given byAdeleye *et al*. (2010) while observing the effect of cissus gum on the release of paracetamol tablets. The possible reason could be strengthening inter particulate bonding by mucilage adhesion.

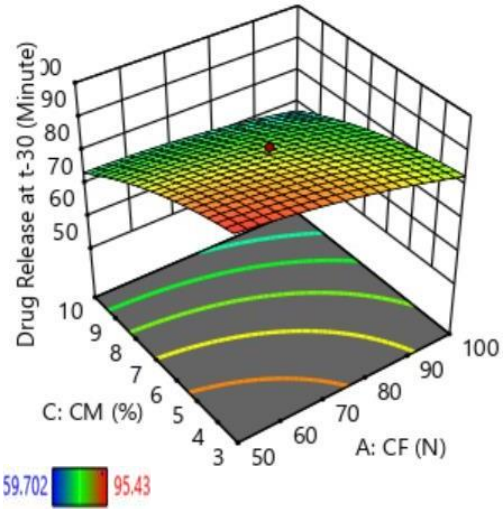
$$Drug\ Release\ at\ 30\ minute = 84.0469 - 4.64613 \times A + 3.9744 \times B - 9.32447 \times C + 1.55888 \times AC + 2.36538 \times BC - 1.54205 \times A2 - 2.61225 \times C^2 \quad \text{Eq. 3.1}$$

$$\text{Friability} = 0.555668 - 0.13676 \times A - 0.243599 \times C + 0.06625 \times AC + 0.0305897 \times A2 + 0.0694806 \times C^2 \quad \text{Eq.3.2}$$

3.5.5. Contour and 3D Plots

The graphical presentation of the interaction of variables is displayed using both the contour and the 3D graph as shown in Figure. The change in the response surface was observed as two factors interact at different settings while maintaining the third variable at the center (average) (Jaswir *et al*., 2019). The 3D graphical presentations indicate the effect of different factors on response and show how sensitive the response surface is to the change of every factor (Huiduan and Jianzhong, 2016). The discussion above is further supported with both the contour and the 3D graphs below. As the concentration of cordia mucilage and the compression force decrease, the drug release improves (Figure 3.27) while the concentration of disintegration is directly proportional to the drug release (Figure 3.28). Both the concentration of cordia mucilage and compression force were found to have inversely proportional relationship with friability while the effect of disintegrant was insignificant for friability (Figure 3.29)

A



B

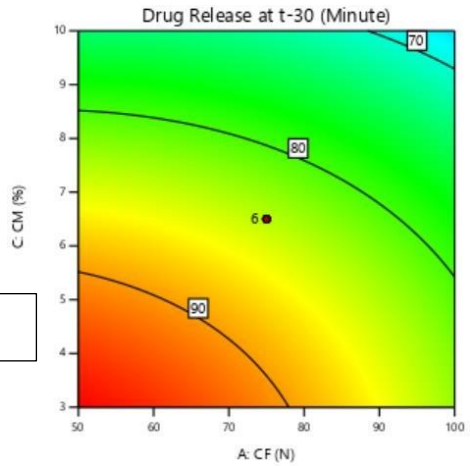
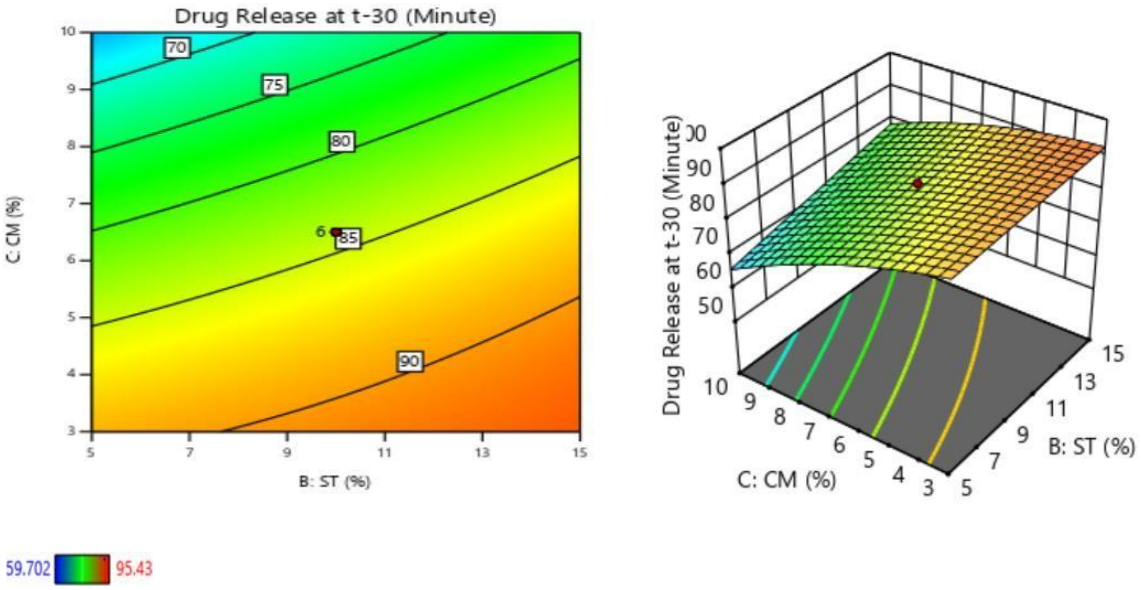


Figure 3.27:3D surface plot (A) and Contour (B) and of the Compression Force against the Cordia mucilage on drug release at t-30 while factor B (disintegrant) is kept at the center point (10%).



A B

Figure 3.28: Contour (A) and 3D surface plot (B) of the disintegrant against the Cordia mucilage on drug release at t-30 while factor A (compression force) is kept at the center point (75N).

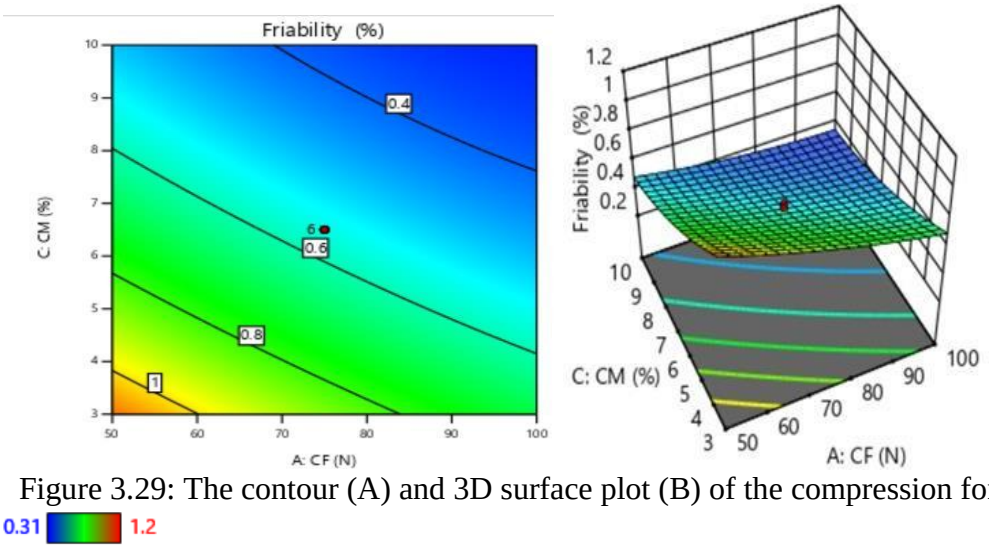


Figure 3.29: The contour (A) and 3D surface plot (B) of the compression force (CF)

against the binder (CM) to show the combined effect on Friability.

3.5.6. Optimization of independent factors

Both numerical and graphical optimization techniques of design expert software were used tofind the optimal point (Elhawi *et al*., 2020). The criteria were set as: minimum for cordia mucilage, starch-1500 (disintegrant), and friability whereas maximum criterion was selected for drug release and the criterion for compression was left to be in range as shown in table 3.17. Among the solution generated by the software, the point with a desirability value of 1 was selected. Desirability is a mathematical measure that ranges between 0 and 1, and tells how different combinations of factors satisfy the goal in response variables and the higher the value isthe more desirable the combinations are for the target responses (Nigatu *et al*., 2015). The optimum response variables based on the criteria were selected with desirability of 1 and the Ramps graph was generated to show the combinations as in fig. 3.30. The desirability function is indicated separately in Figures 3.31 and 3.32.

Table 3.17: Criteria set for numerical optimization while the importance is set at medium level for all variables (+++)

Variables	Criteria	Goal
Compression Force	50-100N	in range
Disintegrant (Starch-1500)	5-15%	Minimum
Binder(Cordia Mucilage)	3-10%	Minimum
Friability	0-1%	Minimum
Drug Release	80-100%	Maximum

3.5.7. Ramps graph

Ramps graph is used to show the numerically optimized factor settings in accordance with their optimum responses. Figure 3.30 depicts that the optimum response values of 83.33%

and 0.634% was noted for drug release at 30 minutes and friability, respectively (shown in blue dots) for the criteria set for each factor (shown in red dots) which are 76.7134N, 5% and 5.328% for compression force, disintegrant and binder (cordia mucilage), respectively.

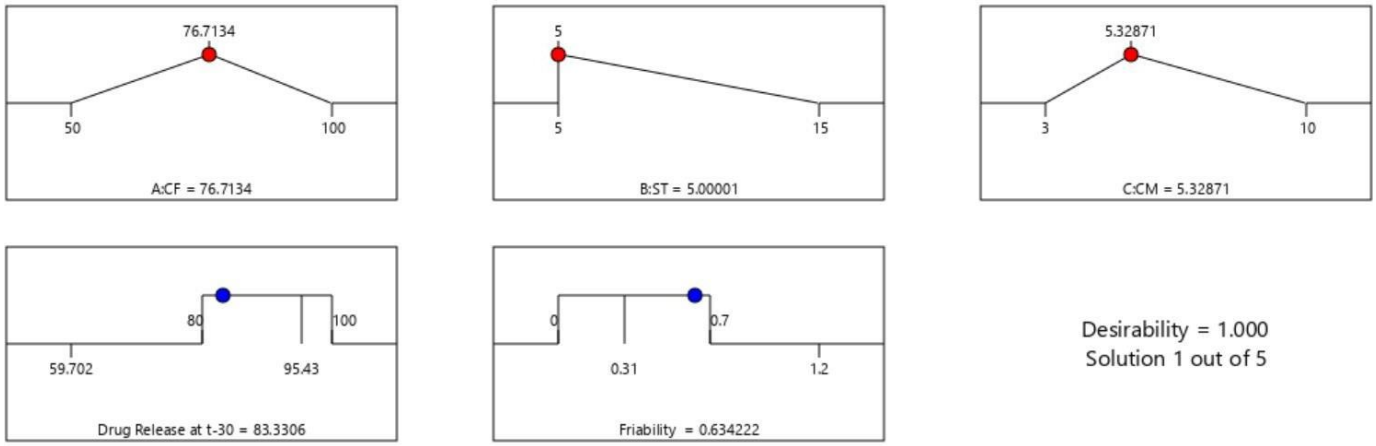


Figure 3.30: Ramps graph with desirability of 1 for the numerical optimization.

3.5.8. Desirability plots

Desirability is a relative function that is between zero, and one. The Design of Expert software looks for the function for maximum response, which approaches one. The finding of the best maximum response starts at several points in the design space and becomes narrower as it approaches to one (Sadhukhan *et al*.,2016). Figures 3.31 and 3.32 show the best combination andthe maximum response for this study having the desirability value of one.

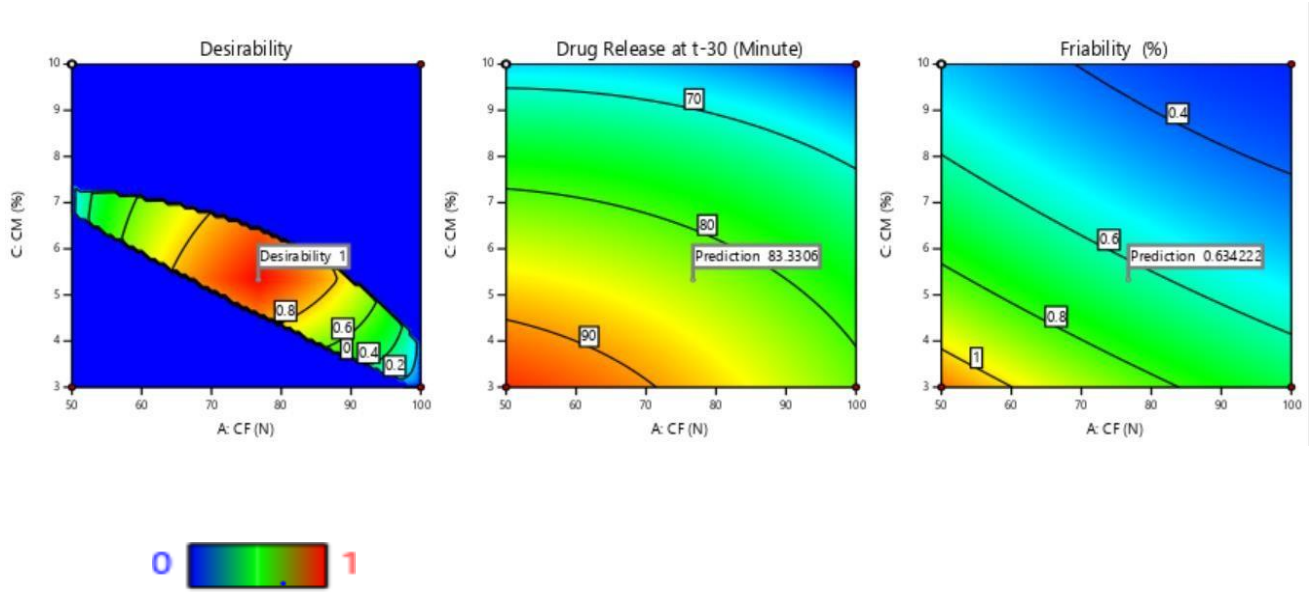


Figure 3.31: Desirability graph for the response variables plotted compression force against Cordia mucilage while maintaining factor B (disintegrant) at 5%.

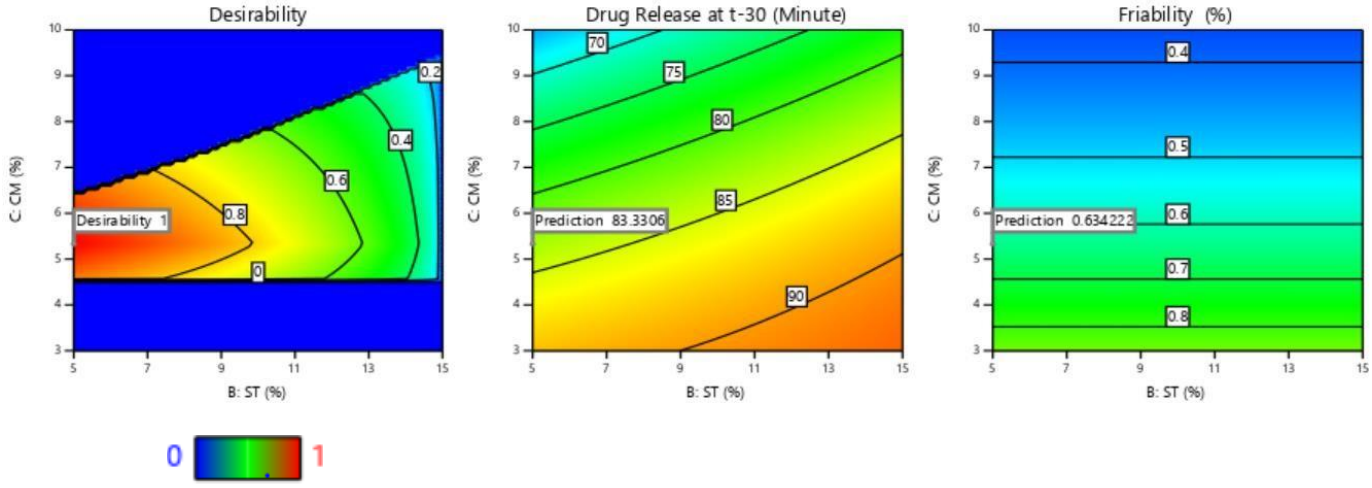


Figure 3.32: Desirability graph of the response variables plotted as disintegrant against binder (Cordia mucilage) while maintaining CF at 76.713

3.5.9. Overlay plots

Overlay plots are superimposed contour plots that depict the acceptable region that satisfies the condition required (Singh *et al*., 2011). In this study, the yellow shaded region in Figures 3.33, 3.34, and 3.35 indicates the area which satisfies the imposed criteria. Accordingly, the optimum condition which was obtained in the numerical optimization techniques also indicated in the overlay plots: compression force of 76.7134 N, concentration of starch 1500 (5%), and concentration of corida mucilage (5.32871%). Under these conditions, the software predicts 83.333133% drug release at t-30 and 0.634242% friability.

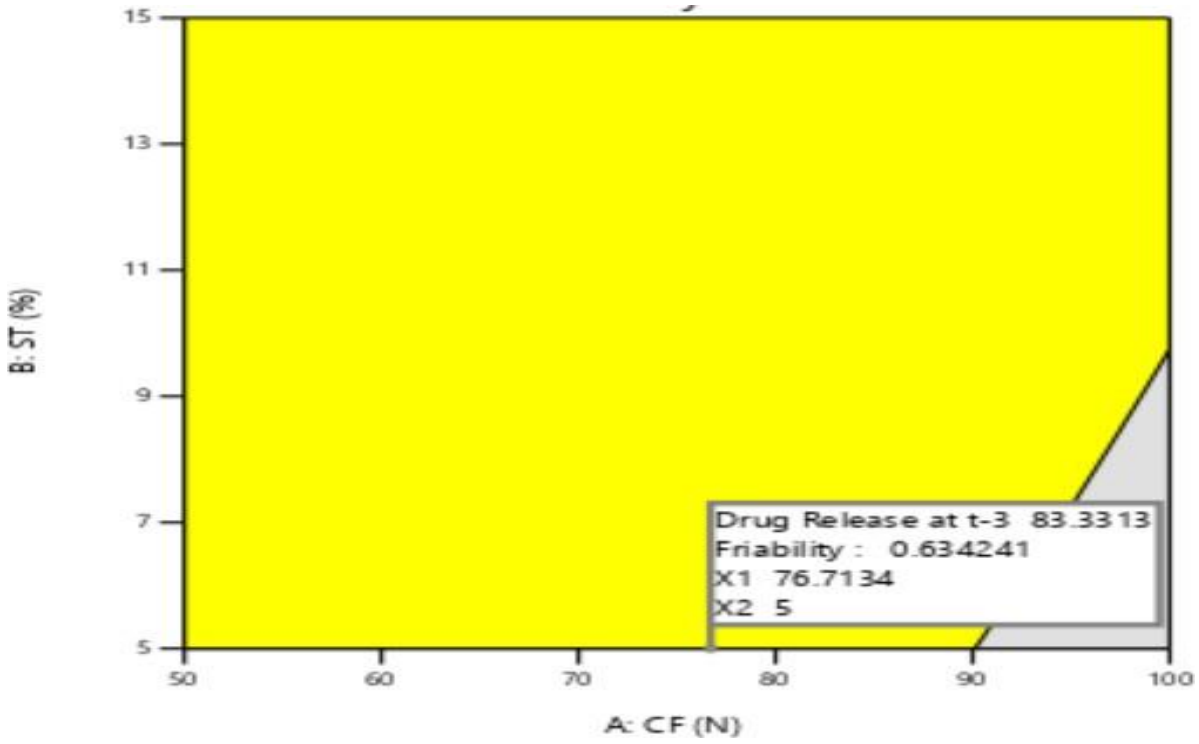


Figure 3.33: An overlay plot of response variables with ST and CF while keeping factor C (CM) at 5.32871%

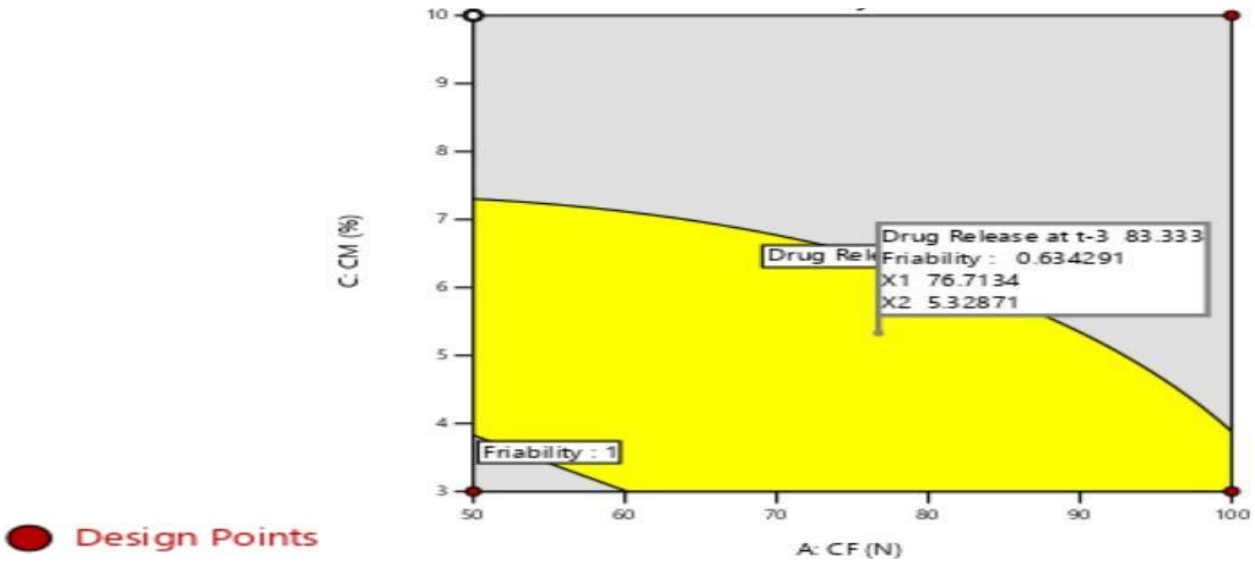


Figure 3.34: An overlay plot of response variables with CM and CF while keeping factor B (ST) at 5%

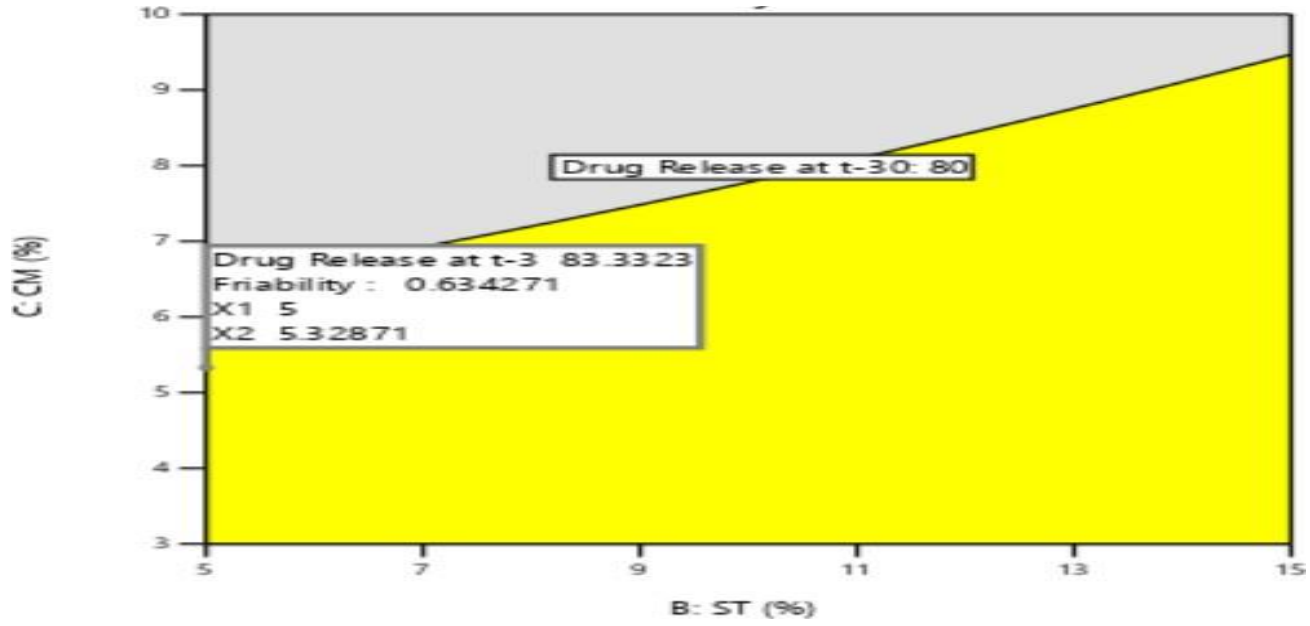


Figure 3.35: An overlay plot of response variables with ST and CM while keeping factor A (CF) at 76.7134

3.5.10. Validation of the optimized formulation

Once the optimum conditions were identified, some confirmation runs are needed to see if the prediction can be used in the real situation (Arvindekar and Laddha, 2016; Beg *et al*., 2019). The factor setting of the optimum solution in the design space was used as a confirmation location. When conducting the confirmation runs every setting was adjusted in the same fashion as wasfor the original experiment (Liyana-Pathirana and Shahidi, 2005; Al-Gheethi *et al*., 2019).Normally, a confirmation run shouldn't be too small as the chance of getting the difference in themean and variability is difficult in such cases. In most cases, a confirmation run of 5-10 is highlyrecommended (Jensen, 2016). Five checkpoints were evaluated for response variables and the relative error (% RE) was calculated. Table 3.18 shows all the calculated relative errors are within 5% variations. All values are found between -3.17% and 4.02%, which ensures the validity of the model. Therefore, the optimization technique was found to be successful in finding the optimum binding effect of the fruit mucilage of *C. africana* along with other independent variables.

Table 3.18: Model validation using five check points

Code	Optimized formulation composition	Response variable	Experimental value (%)	Predicated value (%)	%RE
OT-1	CF=76.713N	Friability	0.65	0.634	-2.5
	ST=5%	Drug release at t-30	84.221	83.331	-1.06
	CM=5.329%				
OT-2	CF=76.710 N	Friability	0.65	0.63	-3.17
	ST= 5%	Drug release at t-30	83.11	83.2	0.1
	CM=5.375%				
OT-3	CF=76.713N	Friability	0.61	0.634	3.78
	ST=5.257%	Drug release at t-30	82	83.494	1.78
	CM=5.329%				
OT-4	CF=74.894 N	Friability	0.62	0.646	4.02
	ST=5.007%	Drug release at t-30	84.56	83.719	-1
	CM= 5.329%				
OT-5	CF=71.978N	Friability	0.67	0.665	-0.751
	ST=5%	Drug releaseat t-30	85.34	84.294	-1.24
	CM=5.329%				

3.5.11. Evaluation of the granule of the optimized tablet (mean ±SD).

Table 3.18 shows the granule characterization of the five batches of the optimized tablet formulation. All are found to be within the acceptable ranges for angle of repose (<30$^{o)}$, Carr's compressibility index (within 5-15%), Hauser's ratio (<1.1).

Table 3.19: Summary of the Evaluation of Granules of the optimized tablet

Formulation	**Bulk density**	**Tapped density**	**Flow rate (g/sec)**	**Angle of repose (^{o})**	**Carr's index**	**Hausners ratio**
OT-1	0.48±0.01	0.52±0.04	4.54±0.19	26.55±0.06	7.69±0.85	1.08±0.01
OT-2	0.53±0.08	0.57±0.01	4.49±0.24	27.37±0. 15	7.17±0.13	1.08±0.07
OT-3	0.52±0.07	0.56±0.06	4.52±0.05	25.72±51	7.14±0.28	1.07±0.00
OT-4	0.51±0.06	0.56±0.03	4.45±0.06	26.93±0. 45	8.92±0.07	1.09±0.07
OT-5	0.49±0.07	0.52±0.02	4.62±0.07	26.46±0. 19	5.77±0.12	1.06±0.14

3.5.12. Evaluation of optimized tablet

Figure 3.36 illustrates the release pattern of the optimized formulation. Accordingly, similar release pattern was exhibited among all batches as compared to the predicted values seen from the software. As it can be seen from the figure all batches have shown to release 80% of their content in 30 minutes. The friability variation is given in figure 3.37. All values have shown a friability at an acceptable range which is between 0.61% and 0.67%.

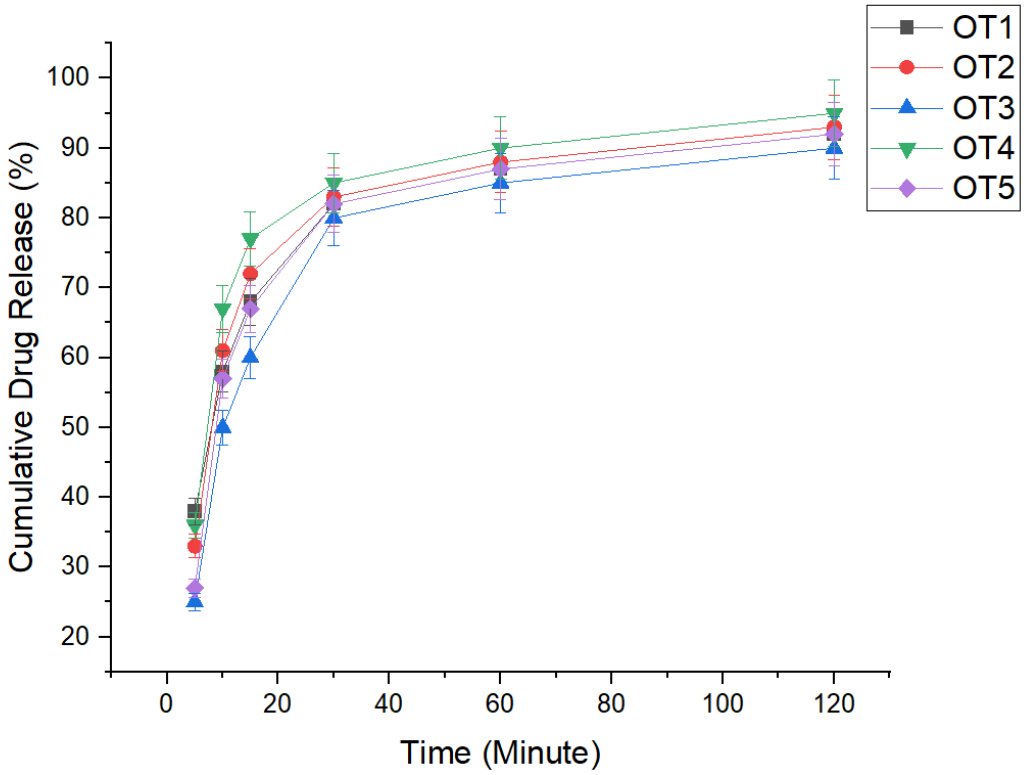


Figure 3.36: The release pattern of the 5 formulations of the optimized tablet.

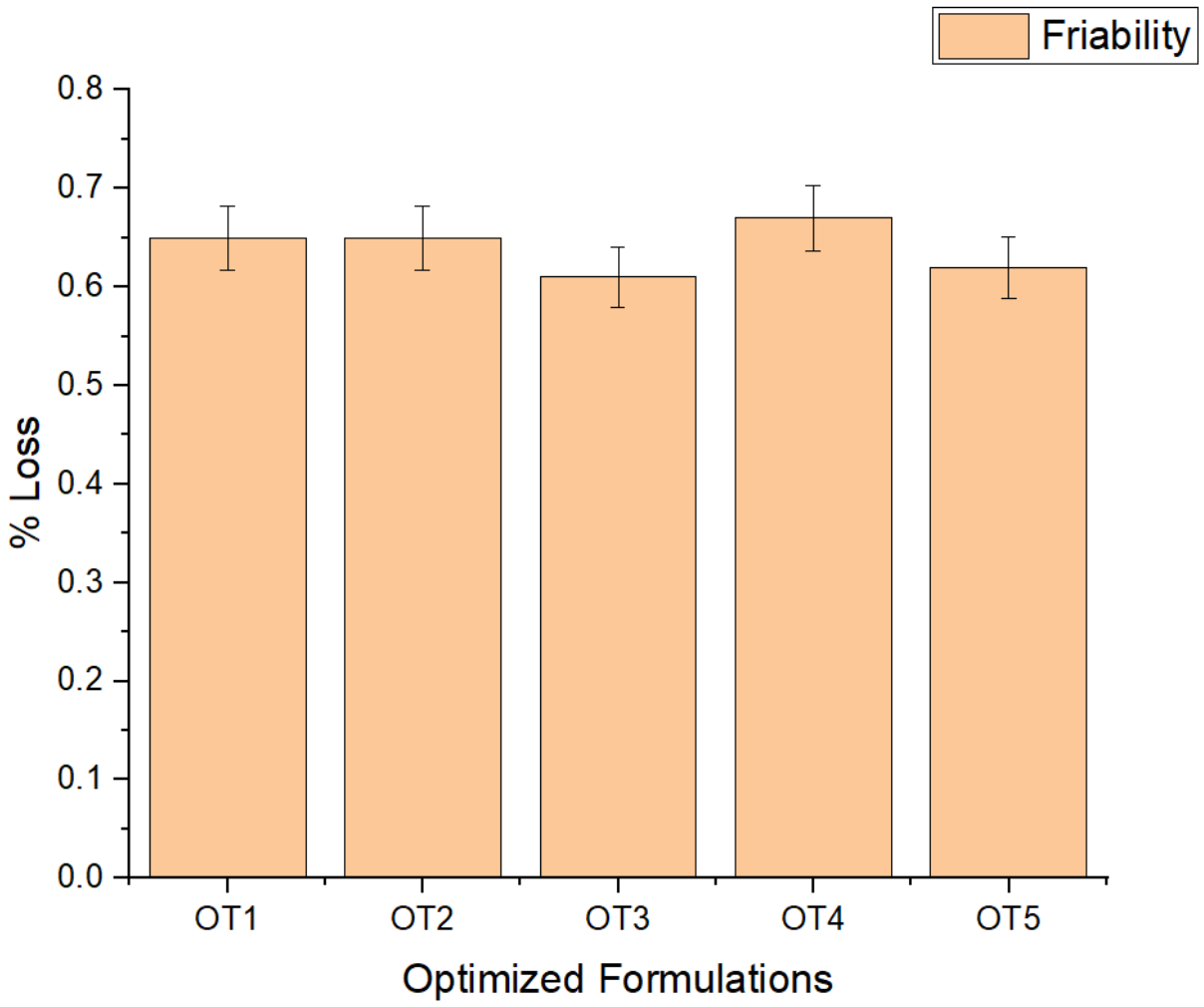


Figure 3.37: The release pattern of the 5 formulations of the optimized tablet.

4. CONCLUSION

In this study the cordia mucilage was extracted from cordiana a fricana fruit and characterized as well as evaluated as a tablet binder in paracetamol tablet preparation.

The FTIR and DSC tests revealed that the fruit mucilage with paracetamol was found to be compatible. Prior to the actual study, significant factors for the determination of drug release, disintegrant, friability and hardness were screened through a preliminary study. The preliminary study showed that all the three factors namely, the disintegrant (ST), binder (CM) and compression force (CF) were found to be significant and hence, were included in the actualstudy.

In the actual study, the use *c.africana* as a binder (CM) was optimized along with other determinant factors using CCD. The result of the optimization experiment depicted that the role of the disintegrant concentration was negligible on friability while all the three factors (CF, CM, and SD) were found to be determinants for the drug release.

The optimization study showed that the optimal drug release at 30 minutes was 83.33% while thefriability was found to be 0.63% for factor combinations of 76.7N, 5.32 % and 5% for the compression force, the mucilage and the disintegrant respectively. The confirmatory run also has shown that all results are within 5% of the relative error which made sure that the predictions made by the design expert software are realistic and reputable.

In conclusion, the Cordiamucilage can be used as an alternative binder for tablets and the optimization model was proven to be effective for identifying the optimum concentration of the Cordia Mucilage along with other determinant factors.

5. SUGGESTION FOR FURTHER WORK

Further investigations are applicable for the following points

1, Evaluation of the Cordia Mucialge as sustaining agent for tablets.

2, Stability test for the tablets formulated with the Cordia Mucilage.

3, Toxicological study of the fruit mucilage

4, Chemical analysis of the fruit mucilage

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