ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF PHARMACY

DEPARTMENT OF PHARMACEUTICS AND SOCIAL PHARMACY

Formulation, *In-vitro* Evaluation and Optimization of Directly Compressible Glibenclamide Orodispersible Tablets

By

Solomon Bayu (B. Pharm)

December, 2016

Addis Ababa, Ethiopia

Formulation, *In-vitro* Evaluation and Optimization of Directly Compressible Glibenclamide Orodispersible Tablets

A thesis submitted to the School of Graduate Studies of Addis Ababa University in partial fulfilment of the requirements for the Degree of Master of Science in Pharmaceutics

By

Solomon Bayu (B. Pharm)

Under the supervisionof Prof.TsigeGebre-Mariam and Dr.AntenehBelete, Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University

Addis Ababa UniversitySchool of Graduate studies

This is to certify that the thesis prepared by Solomon Bayu, entitled"formulation, *in-vitro*evaluation and optimization of directly compressible glibenclamide orodispersible tablets" and submitted in partial fulfilment of the requirements for the Degree of Master of Science in pharmaceutics complies with the regulations of the University and meets the accepted standards with respect tooriginality and quality.

Signed by the Examining Committee:

Name	Signature	Date
1. Dr. Kaleab Asres (Examiner)	_____	_____
2. Dr. Nisha Mary Joseph (Examiner)	_____	_____
3. Prof. Tsige Gebre-Mariam (Advisor)	_____	_____
4. Dr. Anteneh Belete (Advisor)	_____	_____

_----------

Head, Department of Pharmaceutics and Social Pharmacy, SOP, AAU

TABLE OF CONTENT

Acknowledgements

I extend my reverence to Almighty God and His mother Virgin Saint Mary who gave me the strength and courage to complete this thesis work, and the opportunity to thank those people who upkeep me for the accomplishment of the study.

A sincere and whole-hearted thank you to my advisors, Prof. Tsige Gebre-Mariam and Dr.Anteneh Belete whose meticulous guidance, valuable suggestions,polite approach,strong commitmentand motivational speechesduring the course of the study and enabled me to complete this thesis work. I have benefited tremendously from working with you and am thankful for the opportunity you gave for me.

I would like to acknowledge Cadila Pharmaceutical Manufacturing Sh. Co., for their generous gift of glibenclamide raw material and Ethiopian Pharmaceutical Manufacturing Sh. Co., for providing laboratory space, chemicals, apparatus and raw materials.

I would also like to thankEthiopian pharmaceutical Manufacturing Sh.Co., for sponsoring my postgraduate study and Addis Ababa University for sponsoring my research.

Finally, I'd like to thank my beloved family and ever supportive friends. I love you all and I couldn't have achieved this study without your unwavering support. Thank you, Mom, Nets, Napi and Mati for always believing and supporting me.

LIST OF TABLES

List of Figures

Abstract

Glibenclamide (GLM) is an orally active hypoglycaemic agent which belongs to sulphonylurea group. It controls blood glucose level primarily acting on beta cells, which are the insulin-producing cells of pancreatic islet tissue to increase their sensitivity to glucose and to stimulate the production and release of more insulin. It is used for the treatment of noninsulin dependent diabetes mellitus (NIDDM). It shows poor absorption and low bioavailability from a conventional tablet, which is attributed to its poor water solubility. In this study crospovidone and sodium bicarbonateas disintegration agent and dissolution enhancer, respectively, were used to formulate and optimize orodispersible tablets (ODT) of GLM in order to minimize absorption lag time, hasten the onset of action, improve bioavailability and compliance. Tablets were prepared by direct compression technique at different levels of compression force and evaluated for physicochemical properties. Those formulations of tablets which showed better performance were optimized using central composite design. The optimized tablets were compared for their release propertieswith marketed products.

The results showed simultaneous optimization of the dependent variables offered the most desirable representative optimum formulation, within the common optimum section, with hardness of 5.75 Kg/cm2, friability of 0.2%, wetting time of 16.5 sec, disintegration time of 9.4 sec and cumulative drug release of 98.0%in 30min at concentration of 9.73mg crospovidone, 30.33mg sodium bicarbonate and 16.3KN compression force. The validity of obtained optimal point was confirmed by the low magnitude of percent prediction errors of the response variables. Comparative study of the cumulative drug release of GLM within 60 min between marketed conventional tablet of GLM (Daonil®) and the optimized ODT with the model independent method revealed that there was a significant difference between the two formulations with a dissimilarity factor $f_1$value of 73.25% and similarity factor $f_2$value of 9.01%.Thus, the results of this study showed ODT of GLM possess significantly rapid disintegration and enhanced dissolution profiles.

Keywords:*Glibenclamide, Orodispersible tablets, crospovidone, Sodium bicarbonate, Direct compression, central composite design, Optimization.*

A**cronyms**

BCS	Biopharmaceutics Classification System
BD	Bulk Density
BP	British Pharmacopoeia
CCD	Central Composite Design
DC	Direct Compression
FDA	Food and Drug Administration
FDT	Fast Dissolving Tablet
FT-IR	Fourier Transformed Infra-Red
GLM	Glibenclamide
ICH	International Conference on Harmonization
IR	Infra-Red
MCC	Microcrystalline Cellulose
MDT	Mouth Dissolving Tablet
NIDDM	Non-Insulin Dependent Diabetes Mellitus
ODT	Oro-dispersible Tablet
RSM	Response Surface Methodology
TD	Tapped Density
USP	United State Pharmacopoeia
UV	Ultra-Violet
WA	Weight of Average
WHO	World Health Organization
WI	Weight of Individual
2FI	Two factor Interaction

1. Introduction

Oral drug delivery has been known for decades as the most widely utilized route of drug administration for the systemic delivery of different dosage forms of various pharmaceutical products (Desai *et al*., 2016).Among solid oral dosage forms, tablets and capsules have the high capacity for production and convenience for the delivery of a number of drugs and have been developed into a wide range of formulations. Especially tablets are the most useful and important dosage forms, which are highly preferred for systemic effects, and account for 70% of dispensed medicines (Rajan and Sanjay, 2001).This is mainly due to several advantages tablets have, like the ease of administration, good chemical and microbiological stability, low cost, better dose precision, ease of self-medication and manufacturing (Debruyn *et al.*, 2011).

However, many patients especially children and elderly have difficulty in swallowing tablets and hard capsules, resulting in high incidence of non-compliance and ineffective therapy. For such problems, currently, ODTs have emerged as alternative dosage forms, which disintegrate instantly in the mouth before swallowing (Garud *et al*., 2014;Brniak*et al*., 2015).Moreover, the current popularity and acceptability of ODTs are related with the rapid disintegration of the tablets from the patient tongue or buccal mucosa without water, which results in a quick dissolution of the drug and fast drug absorption(Aguilar-Diaz *et al*., 2012**).** Another feature which attracts pharmaceutical companies to consider ODT as an option to conventional tablets is the potential of improving the delivery of insoluble drugs by enhancing the problem of dissolution to maximize drug absorption for quick onset of drug action and also minimizepossibility of first pass metabolism (Divate*et al*., 2011; Mohanachandran*et al*., 2011)**.**

1.1. Orodispersible Tablets

ODTs are patient friendly solid dosage forms, which disintegrate in the mouth within 3 min before swallowing, according to European Pharmacopeia (EU). ODTs dissolve or disintegrate in the absence of water for easy administration of active pharmaceuticals following the introduction of a tablet into the mouth and undergo absorption from the mouth, pharynx, and oesophagus as the saliva passes down into the stomach (Elkhodairy*et al*., 2014).Currently, this delivery system is popular and extensively produced by pharmaceutical companies as a preferred alternative to conventional tablets and hard capsules, due to their ability to

improvepatient compliance,enhancedissolution and improve the bioavailability of pharmaceuticals (Schlemeier and Schmidt, 2002; Swamy*et al*., 2007).

ODTs have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industryand importance as a convenient and potentially safer alternative to address many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for paediatrics, geriatrics and psychiatric patients with dysphagia. ODTsimprove drug dissolution, drug absorption, and onset of clinical effect, as compared toconventional tablets(Rahman *et al.*, 2010**;** Panigrahi*et al*., 2012).ODTs undergo pre-gastric absorption and bypass first pass metabolism to reducethe total dose required and to improveclinical performance by reducing the side effect of a drug (Shu *et al.*, 2002). Other advantages of ODT includeeasyadministration to geriatric and paediatric patients (Slavkova and Breitkreutz, 2015), rapid drug therapy interventionand convenient for disabled, bedridden, travellers and busy people, who haveno access to water and its simplicity to manufacture at low cost as a conventional tablet *(Fu et al*., 2004).

The characteristics of ODTs are attributable to fast and quick ingress of water into the tablet resulting in rapid disintegration. Approaches for formulating such product include maximizing the porous structure of the tablet matrix, using highly water soluble excipients and incorporating suitable disintegrants at an appropriate concentration.

1.2. Methods of manufacturingoro-dispersible tablets

ODTs are formulated by using several processes, which differ in their methodologies and the formed tablet properties such as mechanical strength, taste and mouth feel, swallowability, wetting, disintegration, dissolution, bioavailability, and stability of the tablet (Kaushik *et al*., 2004). Currently the various technologies, which are used by pharmaceutical companies to produce ODT include: freeze drying, moulding, direct compression, sublimation, spray-drying, mass extrusion, cotton candy, melt granulation and fast dissolving films (Parakh and Gothoskar, 2003).

1.2.1. Tablet moulding

The two types of moulding aresolvent and heat methods.The solvent method involves moistening the powder blend with a hydroalcoholic solvent followed by compression at low pressures in moulded plates to form a wetted mass (compression moulding). The solvent is

then removed by air-drying (Fu*et al.*, 2005). The heat moulding process involves preparation of a suspension that contains a drug, agar, and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a gel and drying at 30^0C under vacuum.Since the strength of moulded tablet is a great concern, binding agents, which increase the mechanical strength of the tablets are mandatory to include each formulation (Bircan and Comoglu, 2012).

1.2.2. Freeze drying (Lyophilization)

A typical procedure involved in the manufacturing of ODTs using freeze drying includes dissolving/dispersing the active drug in an aqueous solution of a carrier. The mixture is prepared by weighing and pouring on the walls of the preformed blister packs and the trays holding the blister packs are passed through a liquid nitrogen freezing tunnel to freeze the drug solution or dispersion, then the frozen blister packs are placed in refrigerated cabinetsfor freeze drying at low temperature and pressure (Sreenivas*et al*., 2005). Freeze drying forms rapidly dissolvedtablets thanother methods. This imparts glossy amorphous structure to the bulking agent and sometimes to the drug (Bhasin*et al*., 2011).

1.2.3. Spray drying

Typical formulations contain hydrolyzed and non-hydrolyzedgelatin as a supporting agent for the matrix, mannitol as a bulking agent and modified starch as adisintegrant and also effervescent agents to further enhance disintegration and dissolution. Due to the formation of porous powder by spray drying,in this method, most of the time, disintegration time less than 20 sec is estimatedin aqueous media(Mishra*et al*., 2006).

1.2.4. Sublimation

In this method, a subliming material like camphor and ammonium chloride are removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where the sublimating agent particles previously occupied in the compressed mannitol tablets prior to sublimation(Badgujar and Mundada, 2011). This gives high porosity (approximately 30%), rapid disintegration and dissolution in saliva (Youron*et al*., 2004).

1.2.5. Direct compression method

Direct compression (DC) is the easiest method to manufacture ODTs. The main advantages of DC are its low manufacturing cost, useof common excipients and improving their availabilityto media, useof conventional tablet equipment's and minimized unit operations(Chang*et al*., 2011). In most of the ODTs formulationsin DC method, the use of superdisintegrants is common to improve disintegration and dissolutionof tablets at the optimum concentration. In general, the disintegration and dissolution of directly compressible rapidly disintegrating tablets rely on the effect of superdisintegrants, water soluble excipients and effervescentagents with the advantage of easy exposure of excipients to saliva(Bircan and Comoglu, 2012).

i) Superdisintegrants

The incorporation of superdisintegrants in tablet formulation causestabletsand granulesto disintegrate, which facilitatesdissolution(Chellan and Sekar, 2008). A disintegrating agent can be added either prior to granulation (intragranular) or prior to compression (extragranular) or at both processing steps. Extragranular component facilitates breakup of tablets to granules and the intragranularcomponent produces further erosion of the granules to fine particles.Sodium starch glycolate is one of the commonly used modified starches and its mechanism of disintegration is rapid and extensive swelling with minimum gellingcharacteristics. And, its optimum concentration is 4-6%. If it goes beyond its limit, it becomes viscous and gelatinous mass, which increases the disintegration time by resisting the breakup of the tablet. It is highly efficient at low concentration because of its greater swelling capacity.The other common modified cross-linked cellulose disintegrant issodium carboxymethylcellulose carmellosesodium, whichhas highly internal cross-linked structure and due to cross-linkage insoluble in water. However,the cross-linking is important to cause4-8 times rapid swelling of the cellulose, when contact with water to improve disintegration. Pharmaceutical formulators are also usingcross-linked polyvinylpyrrolidine(crospovidone), which is freely flowable and has thecapacity to give a more porous surface to a tablet Crospovidoneis water insoluble and spongy in nature, swells very little, and returns to its original size. The disintegration mechanism of crospovidone is capillary action and wicking action(Kundu and Sahoo, 2008).These features of crospovidone and suitability in direct compression haveattracted formulators forits use in ODTs.

ii) Effervescent agents

The effervescent system is composed of dry acid and dry base which, when reacted with each other in the presence of water or saliva, initiate an effervescent reaction. The effervescent reaction accelerates the disintegration of tablet through the evolution of carbon dioxide gas. Moreover, due to the evolution of carbon dioxide gas, the bitter taste of the drug is also masked and a pleasant mouth feels is felt (Seager, 1998).

iii) Sugar based excipients

The sugar-based excipients which are commonly used for pharmaceutical bulking agents (like dextrose, fructose, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate,polydextrose andxylitol)display high aqueous solubility and sweetness, and hence impart taste masking property and provide pleasing mouth feel(Bircan and Comoglu, 2012).

1.2.6. Cotton candy process

Another technology for manufacturing of ODT is the cotton candy process, also known as candy floss process, which involves centrifugation to produce a floss-like crystalline structure. In this technology, the matrix is formed from saccharides or polysaccharides processed into an amorphous floss through a shear foam process. The matrix is cured and milled to make flowable, compactible, and highly soluble filler. Because of the formation of porous three-dimensional structures with the active ingredients encased in the pores, the resulting surface area is high. Therefore, dispersion and dissolution occur quickly when the product is placed in the mouth (Kuchekar*et al*., 2003).

1.2.7. Mass extrusion

This technology involves softening the active blend with the solvent mixture of water soluble polyethylene glycol by methanol and expulsion of softened mass through the extruder to get a cylinder of the product which is cut into even segments using heated blade to form tablets (Hirani*et al*.,2009).

1.2.8. Melt granulation

It is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no

water or organic solvents are needed. Because there is no drying step, the process is less time consuming and uses less energy. It is a useful technique to enhance the dissolution rate of poorly water soluble drugs. This approach to preparing ODT with sufficient mechanical integrity involves the use of a hydrophilic waxy binder (Superpolystate, PEG-6-stearat, e etc.). So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilizes rapidly leaving no residues(Shukla*et al*., 2009).

1.2.9. Fast dissolving films

It is a newer developing front that provides a very convenient means of taking medications and supplements. In this technique, water soluble film forming polymer (pullulan, CMC, HPMC etc.), drug and other taste masking ingredients are dissolved in a non-aqueous solvent to prepare a non-aqueous solution, which on evaporation of the solvent forms a film. Resin adsorbate or coated microparticles of the drug can be incorporated into the film if the drug is bitter. This film when placed in mouth melts or dissolves rapidly and releases the drug in solution or suspension form. This system forms the thinfilms of size less than 2x2 inches which dissolve within 5 sec with instant drug delivery and flavored taste(Bi *et al*., 1996).

1.3. Glibenclamide

Glibenclamide (GLM) is an orally active white crystallinehypoglycaemic agent with no objectionable taste and odour, which frequently used for the treatment of Type II non-insulin-dependent diabetes mellitus (NIDDM). It is a poorly water-soluble drug and can be classified as a class II drug according to the Biopharmaceutical Classification System (BCS). It belongs to the second generation sulphonylurea to control blood glucose level primarily acting on directly beta cells, which are the insulin-producing cells of pancreatic islet tissue to increase their sensitivity to glucose and to stimulate the cells to produce and release more insulin (Wei and Lobenberg., 2006).

GLM (Fig. 1.1) shows variability in absorption and bioavailability from gastrointestinal tract administration and also shows poor compliance from conventional immediate release tablet, which is attributed to its poor water solubility and long-term use of the drug to control blood glucose level (Wei and Lobenberg, 2006; Gianotto*et al*., 2007). The drug is started at a dose of 2.5 mg/day or less and continued with a maintenance dose of not more than 20 mg/day. It has apKa of 5.3, itis practically insoluble in water. Hence its absorption is dissolution limited,

but in a soluble form, it is nearly (84 ± 9%) absorbed from gastrointestinal tract. The peak serum concentration reaches in 2-6 hours and falls within 24 hours (Schwinghammer*et al*., 2010). The elimination half-life of GLM is 2 to 5 hrs after oral administrationand extensively metabolized by liver microsomal enzymes to active metabolite form (Groop*et al*., 1985).

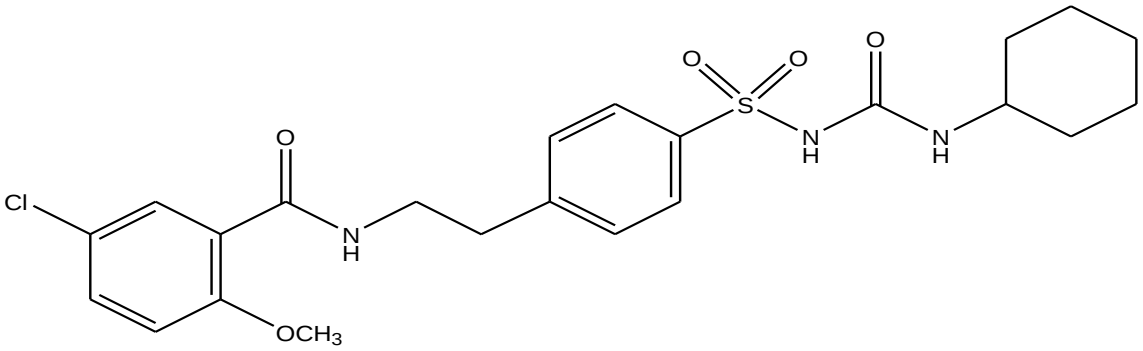


Fig.1.1. Chemical structure of GLM(USP30-NF25, 2007).

1.4. The present study

Poor solubility of drugs in biological media presents a great challenge for pharmaceutical industries and researchers developing new products. Thus, pharmaceutical researchers are endeavouring to develop a formulation of such drugs having improved dissolution and bioavailability. The drug GLM is Class II hypoglycaemic agent (Bassam *et al*., 2004). GLM is a low dose drug with poor aqueous solubility in gastric media with possible dissolution rate limited bioavailability. Studies by different researchers have shown that the absorption of GLM is limited by its dissolution rate following poor water solubility in oral administration (Tashtouch*et al*., 2004).This leads to incomplete and erratic absorption that ultimately affects necessary drug plasma concentration and limitation of drug clinical efficacy (Zerrouk*et al., 2006*). Consequently, such an erratic absorption causes increasedthe occurrence of adverse drug reactions and/or poor patient compliance (Virally*et al*., 2007).

There are various techniques used to improve the solubility of poorly soluble drugs. Direct compressible ODT is a new and promising method to enhance the dissolution of poorly soluble drugs with the advantage of improving the availability of excipients for dissolution media, hence rapid wetting and disintegration to maximize surface area for drug dissolution and absorption.

Therefore, in this study, it is aimed to develop GLM ODT containing superdistegrant and effervescent agent prepared by DC technique.It is anticipated that such an approach will allow fast, reproducible and complete drug dissolution with maximum bioavailability, ultimately improving GLM clinical efficacy and minimizing possible occurrence of adverse drug reaction by decreasing erratic drug absorption, hence it reduces eventually the initial dose required for complete management. Furthermore, since the drug is intended to be dispersed and absorbed in the mouth and other pre-gastric sites of the gut, the possible occurrence of hypoglycaemic shock due to GLM active metabolites are expected to be reduced with the new formulation. Besides, easy and comfortable administration of ODT without water will also contribute to maximize treatment outcome of GLM by improving compliance of patients, who use the drug as a lifelong treatment.

1.5. Objectives of the study

1.5.1. General objective

- To formulate, characterize and optimize directly compressible formulation of glibenclamideODTs.

1.5.2. Specific objectives

- To formulate glibenclamideODT formulation;
- To characterize glibenclamideODTformulations;
- To characterizethe physico-chemical properties of glibenclamideODTs;
- To optimize the formulation and process variables of glibenclamideODTs;
- To study the *in vitro* drug release profile of optimized glibenclamideODTs; and
- Tocompare the release profiles of the optimized glibenclamideODT with locally marketed reference immediate releasetablet.

2. Materials and Methods

2.1. Materials

Micronized Glibenclamide (Cadila Pharmaceuticals Ltd., Gujrat, India)was obtained as a gift sample from CadilaPharmaceutical Manufacturing PLC, Ethiopia. Microcrystalline cellulose (MCC), magnesium stearate and Talc (Shandong Head Co., Ltd. China), crospovidone (BASF, Germany),Sodium bicarbonate, Citric acid and Aspartame(China Associate Co., Ltd. China),monobasic potassium phosphate(Fisher Scientific LTD., UK), methanol (Carlo Erba Reagents, Italy) & distilled water were from Ethiopian Pharmaceutical Manufacturing PLC (EPHARM), Daonil®5mg (Sanofi, France).All chemicals and solvents used in the study were of analytical grade.

2.2. Methods

2.2.1. Construction of calibration curve

i) Calibration curve of GLM in pH 6.8 and 7.4 phosphate buffer

A Stock solution containing 1 mg/ml of GLMwas prepared by dissolving an amount equivalent to 25mg pure GLM in 25ml of absolute methanol. From the stock solution, 5ml samplewas transferred to each of the first and the second 100ml volumetric flasks and diluted up to volume with pH 6.8 and 7.4 phosphate buffer, respectively. From each diluted solution aliquots of 1, 2, 3, 4, 5, 6 and 7 ml portion were transferredto a series of the first seven and the second seven50ml volumetric flasks and dilutedtovolume with pH 6.8 and 7.4 phosphate buffer to getthe first and the second seven(1, 2, 3, 4, 5, 6 and 7µg/ml) seriesof concentrations, and their absorbance were read using a UV/Visible spectrophotometer (UV-1800, Shimadzu, Kyoto, Japan) at 300 nm(BP, 2009). After filtered with 0.45µm Whatmanfilter paper, using the dissolution media pH 6.8 and 7.4 phosphate buffer as blank, respectively. Finally, calibration curves and the corresponding correlation coefficients and equations describing the relationship between concentration and absorbance in each dissolution media were generated following Beer-Lambert's law.

2.2.2. Preparation and compression of orodispersible tablet

Based on preliminary and experimental design, DC formulations were proposed as shown in Table2.1 and Table 2.2, respectively,effervescent agents (citric acid and sodium bicarbonate)

were pre-heated at a temperature of 80ºC for 2 hrsin an ovenand otheringredients were passed throughsieve size 224µm separately, then the drug and other excipients, except the effervescent agents were thoroughly mixed by adding appropriate portion of each ingredient and GLM at a time and blended it to get a uniform mixture. Finally,pre-heated effervescent agents were thoroughly mixed and added to the premixed physical blend prior to compression. Compression of sixteen preliminaryand twenty experimental design formulationblend was performed with 10/32 normal concave punches using 45 stations fully automatic rotary tablet press machine (Legacy6100, India) at a three level of compression force with the average weight 200 mg and stored in a stability chamber at 25ºC and 25 % RH. Finally, the compressed tablets were subjected to post-compression parameter characterization.

2.2.3. Characterization ofpowder

i) Angle of Repose

The angle of reposewasdetermined by funnel method. The funnel was adjusted to a height of 10 cm. After the powder blend was passed through 224 µm sieve. Accurately weighed 30g blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone and height of powder heap were measured and angle of repose was calculated according toEquation 2.1.

$\theta = \tan^{-1}(h/r)$……...……..Eq. 2.1

Whereh is height,r is radius of the powder cone, and θis angle of repose

ii) Bulk density (BD)

Accurately weighed and sieved 30g of the blend was transferred to 250 ml graduated cylinder, carefully leveled without compacting, and the apparent bulk volume was read. Bulk density in g/ml was calculated using Equation 2.2.

Bulk density = Weight of powder/ Bulk volume…….....Eq. 2.2

iii) Tapped density (TD)

Accurately weighed and sieved 30 g of the blend was transferred to 250 ml graduated cylinder. Then, the cylinder was tapped using a tap densitometer (STAV 2003, Gemini BV,

Apeldoorn, Netherlands), at a fixed tap of 14 ± 2 mm and at a nominal rate of 300 taps per min, until no further change in the volume was noted (500 times) and the tapped volume was read. Finally, the tapped density in g /ml was calculated using Equation 2.3.

Tapped density = Weight of powder / Tapped volume ……..……...…….Eq. 2.3

iv) Carr's Index

Compressibility index of the powderswas determined by Carr's compressibility index according to Equation 2.4.

Carr's index (%) = [(TD-BD)/ TD *100] ……..…….Eq. 2.4

v) Hausner's Ratio

Hausner's ratio is a number that was correlated with the flowability of the powdersusing TD and BD in Equation 2.5.

Hausner's Ratio = TD / BD …….Eq. 2.5

Table 2.1: Preliminary formulations of GLM ODTs.

	Ingredients (mg)							
FormulationCode	Glibenclamide	Crospovidone	Sodium Bicarbonate	Citric Acid	Aspartame	Talc	Magnesium stearate	Avicel-pH-102
Fp1	5	2.5	-	35	1	6	2	148.5
Fp2	5	2.5	-	35	1	6	2	148.5
Fp3	5	10	-	35	1	6	2	141.0
Fp4	5	10	-	35	1	6	2	141.0
Fp5	5	-	10	35	1	6	2	141.0
Fp6	5	-	10	35	1	6	2	141.0
Fp7	5	-	40	35	1	6	2	111.0
Fp8	5	-	40	35	1	6	2	111.0
Fp9	5	2.5	10	35	1	6	2	138.5
Fp10	5	2.5	10	35	1	6	2	138.5
Fp11	5	10	40	35	1	6	2	101.0
Fp12	5	10	40	35	1	6	2	101.0
Fp13	5	2.5	40	35	1	6	2	108.5
Fp14	5	2.5	40	35	1	6	2	108.5
Fp15	5	10	10	35	1	6	2	131.0
Fp16	5	10	10	35	1	6	2	131.0

2.2.4. Drug-Excipients Interaction Study

Drug-excipient interactions were checked by using Fourier transformed infrared spectroscopy (FT-IR)(Model SHIMADZU FT-IR-8400S, Japan) in transmittance mode, with a sample of pure GLM alone and 1:1 sample of pure GLM with each excipient that were included in the formulations. The spectra of each sample were recorded at a resolution of 4 cm^{-1} and wave number ranging between 4000 and 400 cm^{-1}using potassium bromide plate with infra-red solution software.

2.2.5. Post compression evaluation

i) Weight variation test

Individual weights (WI) of 20 tablets from each formulation were weighed using an analytical balance (ae ADAM®, Danbury, USA). Their average weight (WA) was calculated. Percent weight variation was calculated usingEquation 2.6.

% Weight variation = (WA–WI) / WA x 100……...……..…….Eq. 2.6

ii) Drug content determination

Ten tablets from each batch were randomly selected and crushed in mortar and pestle. A sample of the powder equivalent to 5mg GLM was extracted with absolute methanol, filtered using cellulose acetate filter having a pore size of 0.45µm and assayed spectrophotometrically (UV-1800, Shimadzu, Kyoto, Japan) at 300 nm(BP, 2009). After appropriate dilutionwith phosphate buffer pH 6.8.The drug content was determined using the standard calibration curve and check with the requirement90% and 110% according to USP30-NF25, (2007).

iii) Hardness

The crushing strengths of ten tablets were measured using a hardness tester (ERWEKA GmbH, Heusenstamm, Germany) and the average values and standard deviation were calculated.

iv) **Thickness**

Twenty tablets from the representative batch were randomly taken and individual tablet thickness was measured by using thickness tester (ERWEKA GmbH, Heusenstamm, Germany). Average thickness and standard deviation were calculated.

v) Friability test

From each formulation, twenty tablets were accurately weighed and placed in the friability tester apparatus (ERWEKA GmbH, Heusenstamm, Germany). The apparatus was operated at 25 rpm for 4 min. After 100 rotations tablets were dedusted and reweighed. The friability was calculated as the percentage weight loss using Equation 2.7.

% Friability = (W1 – W2) /W1x 100…….……...Eq. 2.7W1 = Initial weight of the 20 tablets, W2 = Final weight of the 20 tablets after friability

vi) Disintegration test

The test was carried out on 6 tablets using the apparatus specified in USP(ZT304, ERWEKA GmbH, Heusenstamm, Germany), in 900 ml distilled water at 37 ±2ºc as a disintegration mediumand the time taken for complete disintegration of the tablet with no particulate matter remaining in the mesh was recorded in sec (BP, 2009).

vii) Wetting time

A piece of tissue paper folded twice was placed in a small Petri dish containing 10ml of coloured water. A tablet was placed on the paper, and the time for complete wetting was measured for each three trials and mean and standard deviation was determined.

viii) *In vitro* dissolution studies

Dissolution of GLMfrom the formulated tablets were studied in phosphate buffer of pH 6.8 (900 ml) using a USP dissolution apparatus II(ERWEKA D-63150 GmbH, Germany) (USP 30/NF25, <711>, 2007) with a rotating paddle stirrer at 50 rpm and at 37 ± 0.5°Cand the test was performed on six tablets.A sample of GLM ODTs equivalent to 5mg of the active ingredient was used in each test from each formulation. Starting from min 5 with a 5 mintime interval 10ml of dissolution fluid was withdrawn from the apparatus and passed through cellulose acetate filter (0.45 μm) pore size and the same volume of withdrawn aliquot was

replacedinto the dissolution mediumwith fresh medium. Each sample was assayed at 300 nm for GLM using a UV/visible spectrophotometer (UV-1800, Shimadzu, Kyoto, Japan) and the amount of drug present in the samples were calculated from the calibration curve. The procedure was done three times for each formulation up to 30 min.

2.2.6. Optimization method

Optimization was conducted using CCD for estimating the effect of independent variables (concentration of crospovidone, concentration of sodium bicarbonate and level of compression force) on the dependent variables (hardness, friability, wetting time, disintegration time and in vitro cumulative drug release at 30min) using Design-Expert ® software (Version 6.0.8, Stat-Ease Inc., Minneapolis, MN, USA). The experiments were conducted in three blocks with the default setting of rotatable design with the axial (star) points set at 1.68179 ($\alpha = 2k/4$) coded units from the center. Block one (6 runs): composed of 4 factorial points, plus 2 center points, block two (6 runs): composed of 4 factorial points, plus 2 center points and block three (8 runs): composed of 6 axial points, plus 2 center points. In this full CCD, each numeric factor was varied over five levels: plus and minus alpha (axial points), plus and minus 1 (factorial points) and the center point (Giordano *et al.*, 2010). As shown in (Table 2.2), the star points were let to exceed the operating limits. The responses of the 20 experiments were analysed numerically by fitting linear, two-factor interaction (2FI), and quadratic polynomial models to the responses. The highest order polynomial was selected where the additional term is significant ($P < 0.05$), has insignificant lack of fit, exhibits low standard deviation, high "R-Squared" values, and a low "PRESS.". The general formula of the model is represented as in Equation 2.8.

$$Y = ß_o + ß_1A + ß_2B + ß_3C + ß_4AB + ß_5AC + ß_6BC + ß_7A^2 + ß_8B^2 + ß_9C^2 \quad \text{Eq. 2.8}$$

Table 2.2: Experimental Levels of independent variables for optimization of GLB ODTs.

Variables	**Levels**				
	- α	**-1**	**0**	**+1**	**+ α**
Crospovidone (mg)	–(0.06)	2.5	6.25	10	12.56
Sodium Bicarbonate (mg)	–(0.23)	10	25	40	50.23
Compression force (KN)	9.27	12	16	20	22.73

Where ßo, the intercept, is the arithmetic average of all quantitative outcomes of twenty experiments, ß1 to ß9 are the coefficient computed from the observed experimental values of Y, and A, B, and C, are the coded levels of the independent variable(s). The terms AB, AC, BC,and A^2, B^2, and C^2 are the interaction and polynomial terms, respectively. The main effects (A, B, and C) postulate the average result of changing one factor at a time from its low to high value. The interaction terms (AB, AC, and BC) show how the response changes when two factors are changed accordingly. The polynomial terms (A^2, B^2, and C^2) symbolize nonlinearity.

2.2.7. Experimental Design

Initially, before the experimental design for optimization was worked out, preliminary studies were conducted, in order to identify the most critical independent variables having potentially significant effects on the response variables, according to the literature. Based on the preliminary study, factors, such as the concentration of superdisintegrant (crospovidone), the concentration of effervescent agent ($NaHCO_3$) and level of compression force were found to be critical, which affect the various responses. The response variables evaluated were the disintegration time, wetting time, tablet hardness, friability and cumulative drug release at 30 min. CCD was employed to give 20 possible combinations of the 3 factors evaluated at 3 levels using $2k + 2^k + 6$, in which two were conventional, three were with crospovidone alone, three were with effervescent agent alone and the remaining twelve formulations were a combination of crospovidone and effervescent agent as shown in Table 2.3.

The responses were analysedwith ANOVA using Design-Expert version 6.0.8 Software and mathematical equations were generated for each(Hardness, Friability, Wetting time, Disintegration time and cumulative drug release at 30min.) and tested for significance. The response surface and contour plots were generated to study eachresponse (Singh *et al.,* 2010; Pabari and Ramtoola, 2012).

Table 2.3: GLM ODT experimental design formulations

Formulation Code	Ingredients (mg)							
	Glibenclamide	Crospovidone	Sodium - Bicarbonate	Citric Acid	Aspartame	Talc	Magnesium-Stearate	Avicel-pH-102
F1	5	6.25	50.23	35	1	6	2	94.52
F2	5	-	25	35	1	6	2	126.00
F3	5	10	40	35	1	6	2	101.00
F4	5	10	40	35	1	6	2	101.00
F5	5	6.25	25	35	1	6	2	119.75
F6	5	2.50	40	35	1	6	2	108.50
F7	5	6.25	25	35	1	6	2	119.75
F8	5	6.25	25	35	1	6	2	119.75
F9	5	2.50	40	35	1	6	2	108.50
F10	5	2.50	10	35	1	6	2	138.50
F11	5	6.25	25	35	1	6	2	119.75
F12	5	12.56	25	35	1	6	2	113.44
F13	5	2.50	10	35	1	6	2	138.50
F14	5	10	10	35	1	6	2	131.00
F15	5	10	10	35	1	6	2	131.00
F16	5	6.25	-	35	1	6	2	144.75
F17	5	6.25	25	35	1	6	2	119.75
F18	5	6.25	25	35	1	6	2	119.75
F19	5	6.25	25	35	1	6	2	119.75
F20	5	6.25	25	35	1	6	2	119.75

2.2.8. Comparison of release profiles

Comparison of the *in vitro* drug release profile of the optimized ODTs with conventional uncoated GLM5mg tablet(Daonil®) marketed in Ethiopia was done using pH 7.4phosphate bufferas dissolution media within 60 min.The release profile comparison was carried out with a model independent method using a dissimilarityfactor (f_1) and a similarity factor (f_2). The factor (f_1) was used to calculatethe (%) difference between the two curves at each time point and is a measure of therelative error between the two curves (Eq. 2.9).

$$f_1 = \{[\Sigma_{t=1}^{n} | R_t - T_t|]/ [\Sigma_{t=1}^{n} R_t]\} \times 100 \quad \text{Eq. 2.9}$$

Where*n* is the number of time points, R and T are the release values of the reference and the testformulations respectively at time t. The factor (f_2) is a logarithmic reciprocal square root transformation of the sum ofsquared error and was used to measure the similarity in (%) release between the two curves (Eq. 2.10).

$$f_2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\} \quad \text{Eq. 2.10}$$

According to Food and Drug Administration (FDA)curves whose f_1 values are close to 0 and $f_2$values close to 100 are considered similar.Generally,$f_1$values up to 15 (0-15) and$f_2$values greater than 50 (50-100) ensure similarity of release profiles(Moore and Flanner, 1996).

2.2.9. Statistical Analysis

Each test was conducted in triplicate and the results were reported as mean and SD. Analysis of the resultswas done by one-way analysis of variance (ANOVA) on computer software Origin 7.0 for windows (Partner Software, Originatr1 Lab Corporation, USA).To demonstrate graphically the influence of each factor on responses and to indicate the optimum level of factors, the contour and response surface plots were generated using Design-Expert software version 6.0.8(Stat-ease, Corp. Australia). $P < 0.05$ was considered significant.

3. Results and Discussion

3.1. Calibration curves of glibenclamide

The standard calibration curves for GLM at pH = 6.8 and pH = 7.4 phosphate buffers are shown in Fig. 3.1. The generated equations describing the relationshipbetween concentration and absorbance at pH 6.8 phosphate buffer and at pH 7.4 phosphate buffer, were A= 0.04945C + 0.0370 and A = 0.0481C + 0.0103 with correlation coefficient (R^2) valuesof 0.9998 and 0.9999, respectively atabsorption maxima (λmax) of 300 nm(BP, 2009).The linear regression equations generated were used for calculation of the concentration of GLM in the buffered media.

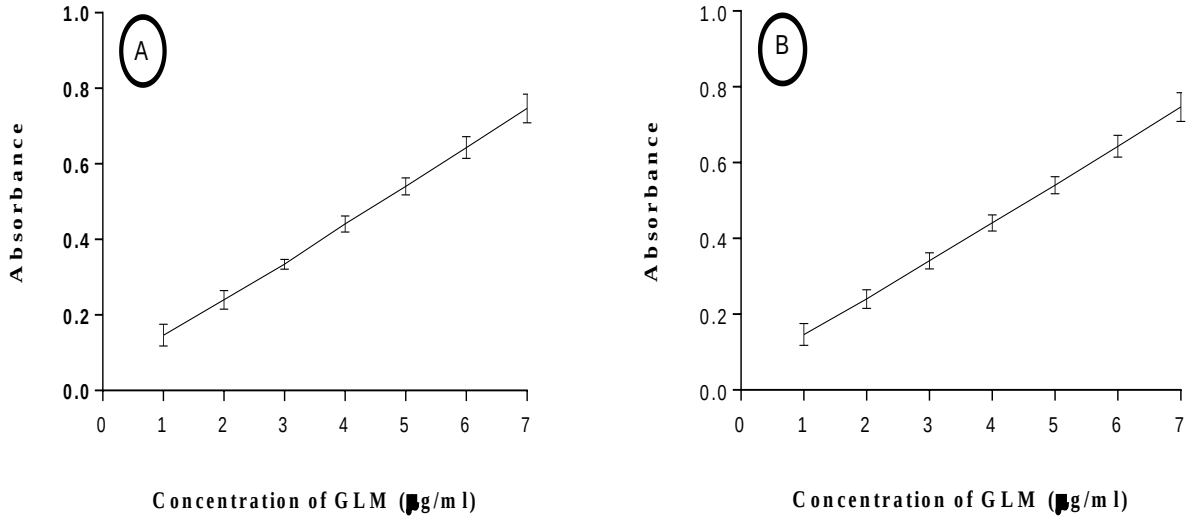
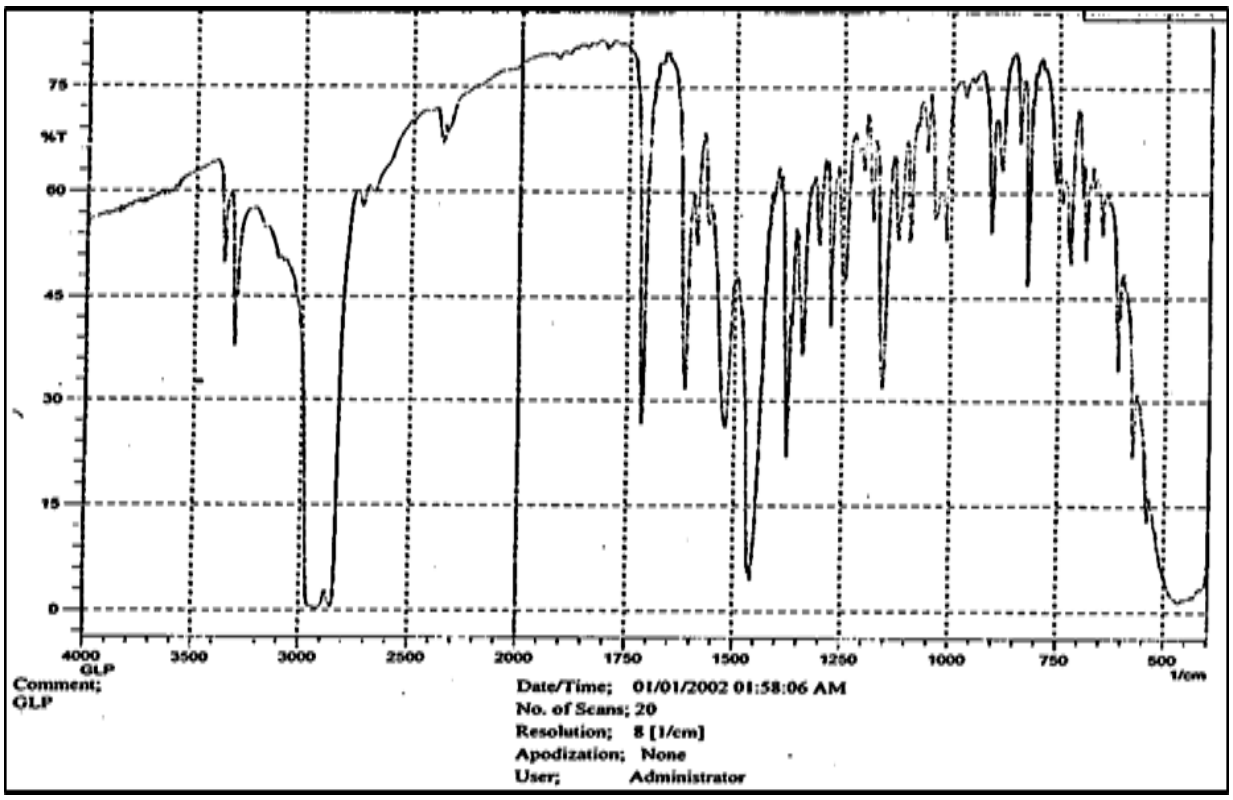


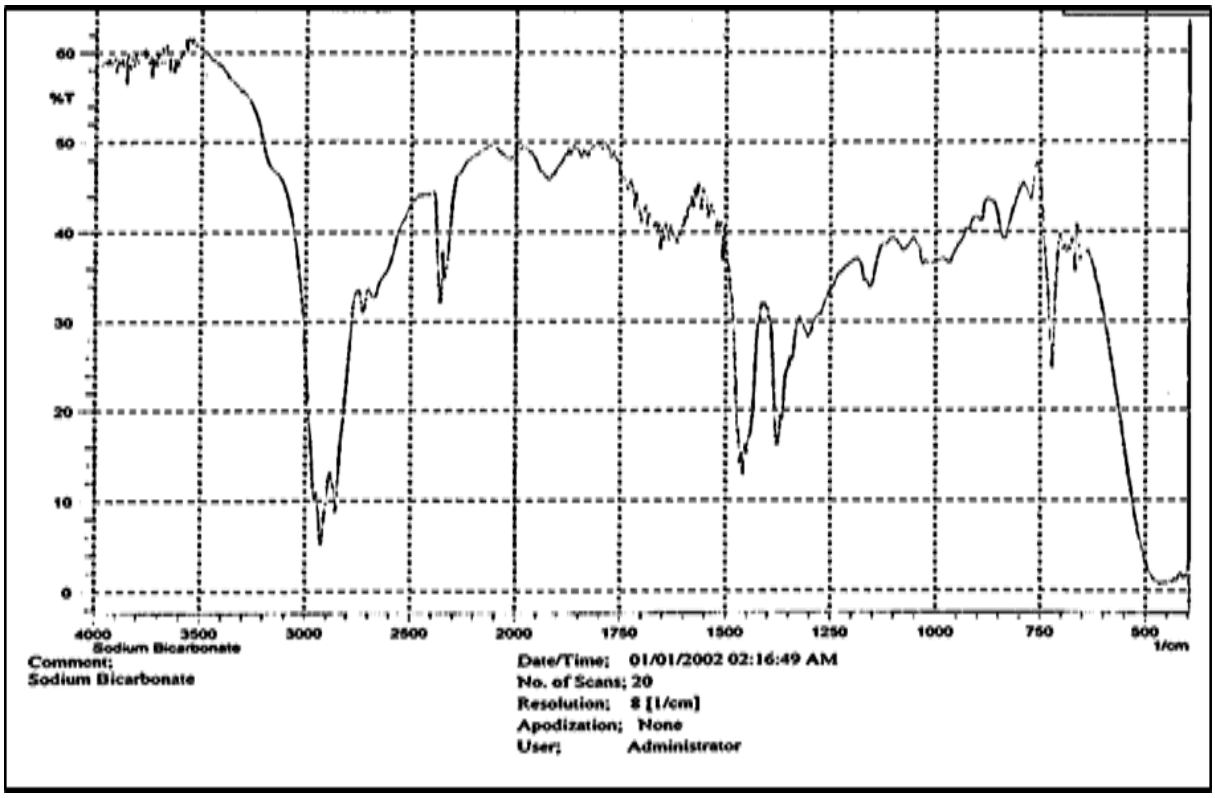
Fig3.1: UV absorption calibration curve for glibenclamide reference standard in pH = 6.8 phosphate buffer (A) and in pH = 7.4 phosphate buffer (B).

3.2. Compatibility study

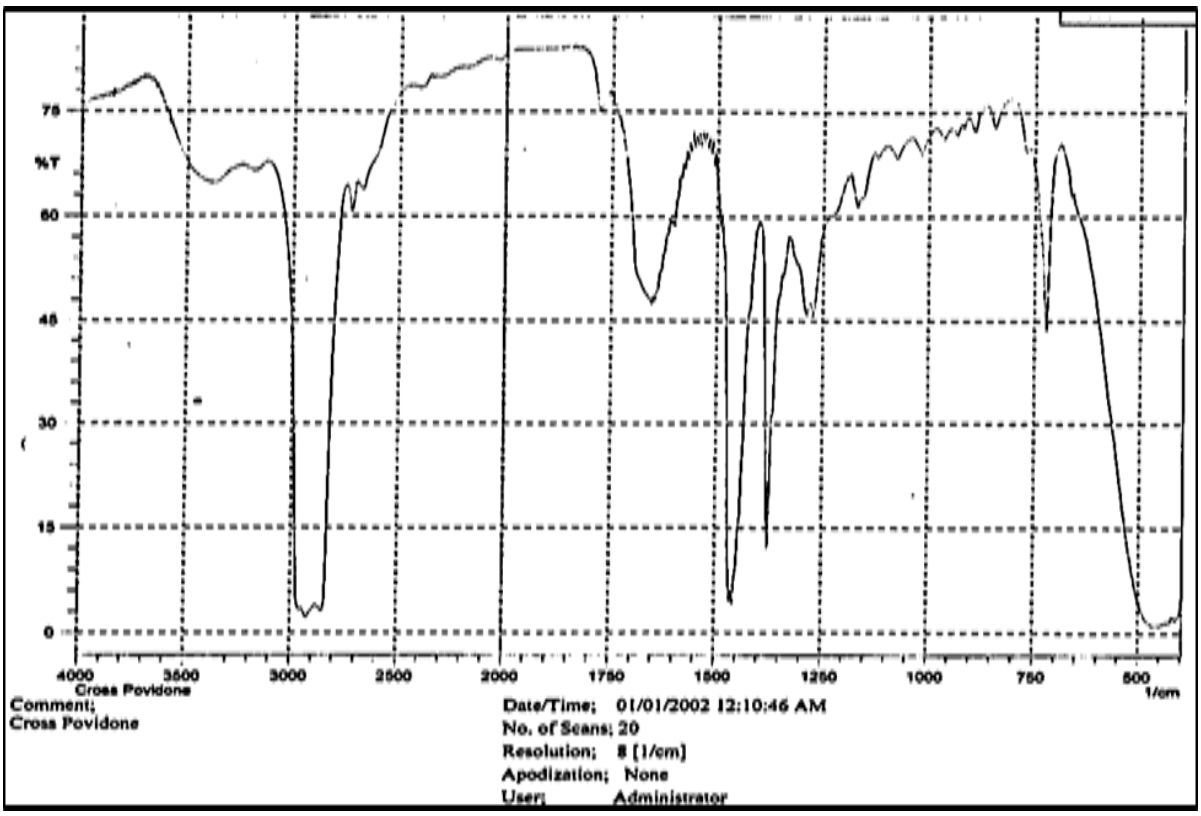
The FTIR spectrum of pure GLM is shown in Fig. 3.2 A. As it can be seen, it exhibits characteristic amide peaks at 3365.55 cm^{-1}, 3313.48cm^{-1} and 1714.60 cm^{-1}, C-H stretching at 2950.89 $cm^{-1}$and 2852.52$cm^{-1}$and urea carbonyl stretching (urea NH stretching) vibration at 1616.24$cm^{-1}$and 1521.73 cm^{-1}. Accordingly, the FTIR studies revealed that all characteristic peaks for GLM appeared in the mixture and hence there is no incompatibility of the drug substances with any of the excipients used in the formulation.


%T
75
60
45
30
15
0
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
1/cm
GLP
Comment;
GLP
Date/Time; 01/01/2002 01:58:06 AM
No. of Scans; 20
Resolution; 8 [1/cm]
Apodization; None
User; Administrator

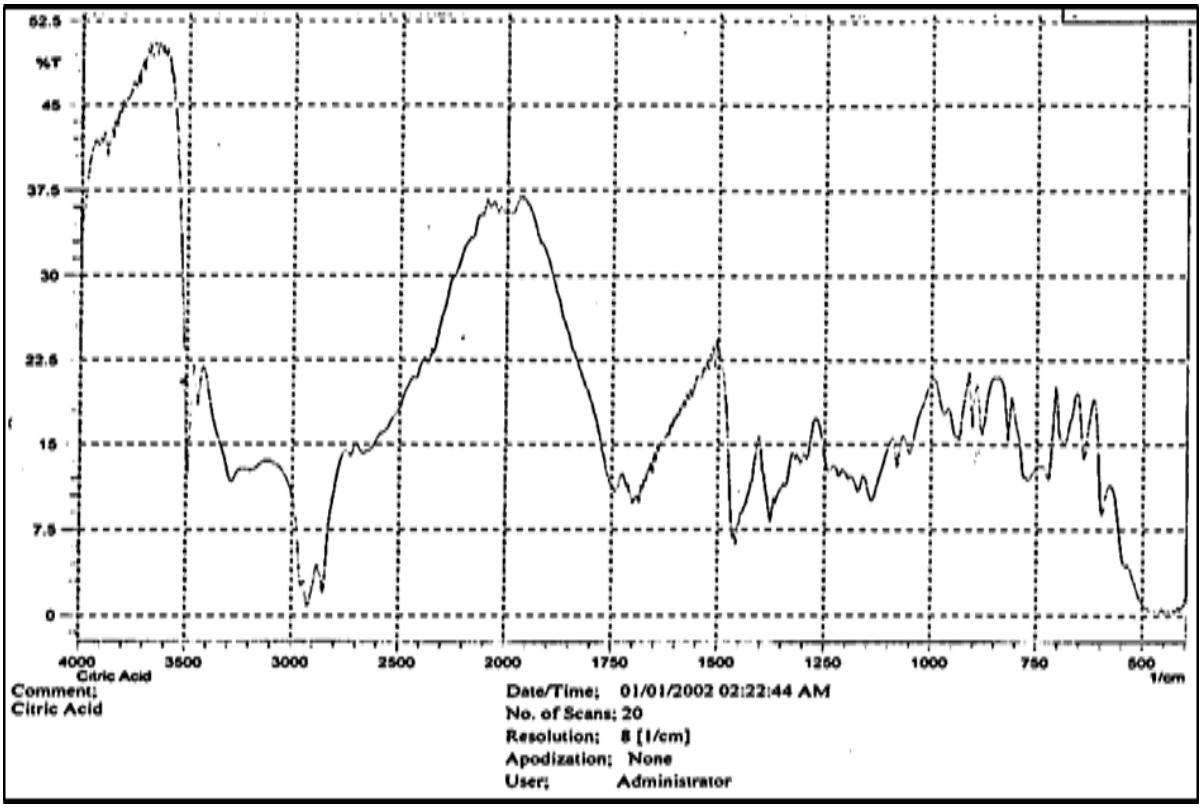
A.


%T
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
1/cm
Sodium Bicarbonate
Comment;
Sodium Bicarbonate
Date/Time; 01/01/2002 02:16:49 AM
No. of Scans; 20
Resolution; 8 [1/cm]
Apodization; None
User; Administrator

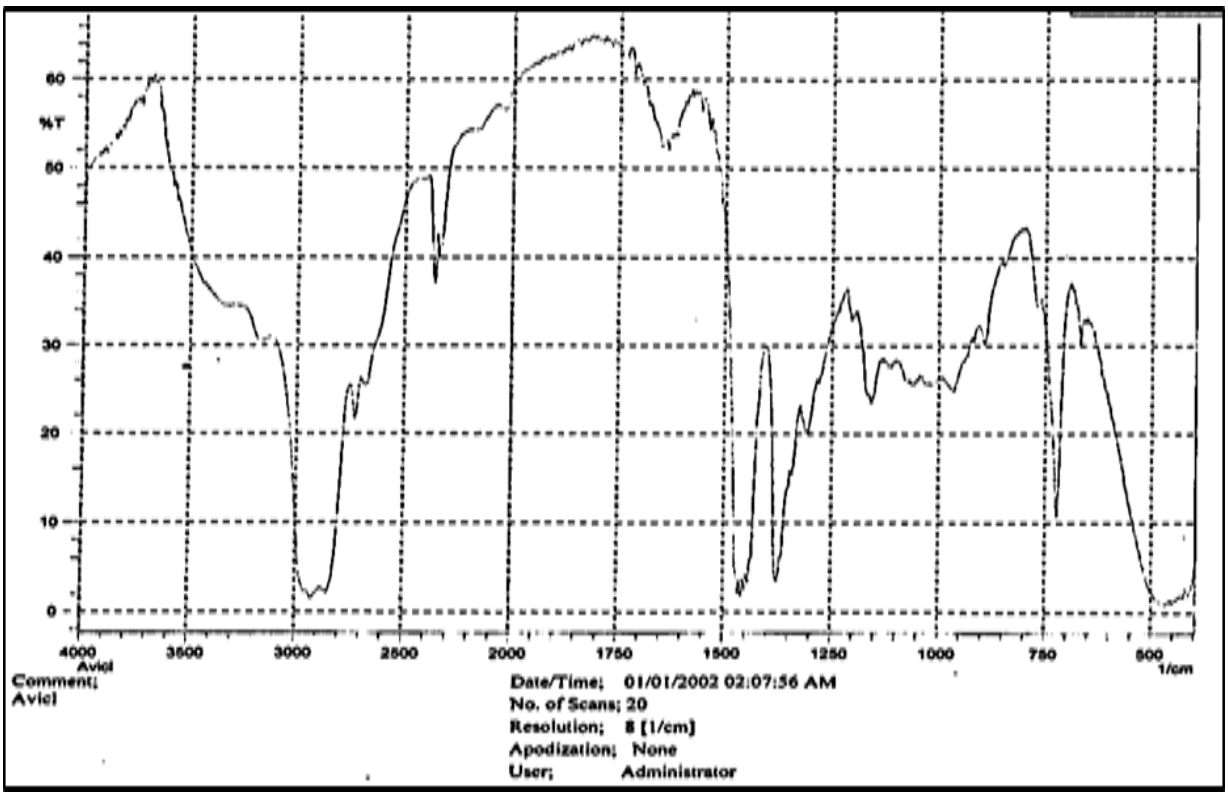
B.


75
%T
60
45
30
15
0
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
1/cm
Cross Povidone
Comment;
Cross Povidone
Date/Time; 01/01/2002 12:10:46 AM
No. of Scans; 20
Resolution; 8 [1/cm]
Apodization; None
User; Administrator

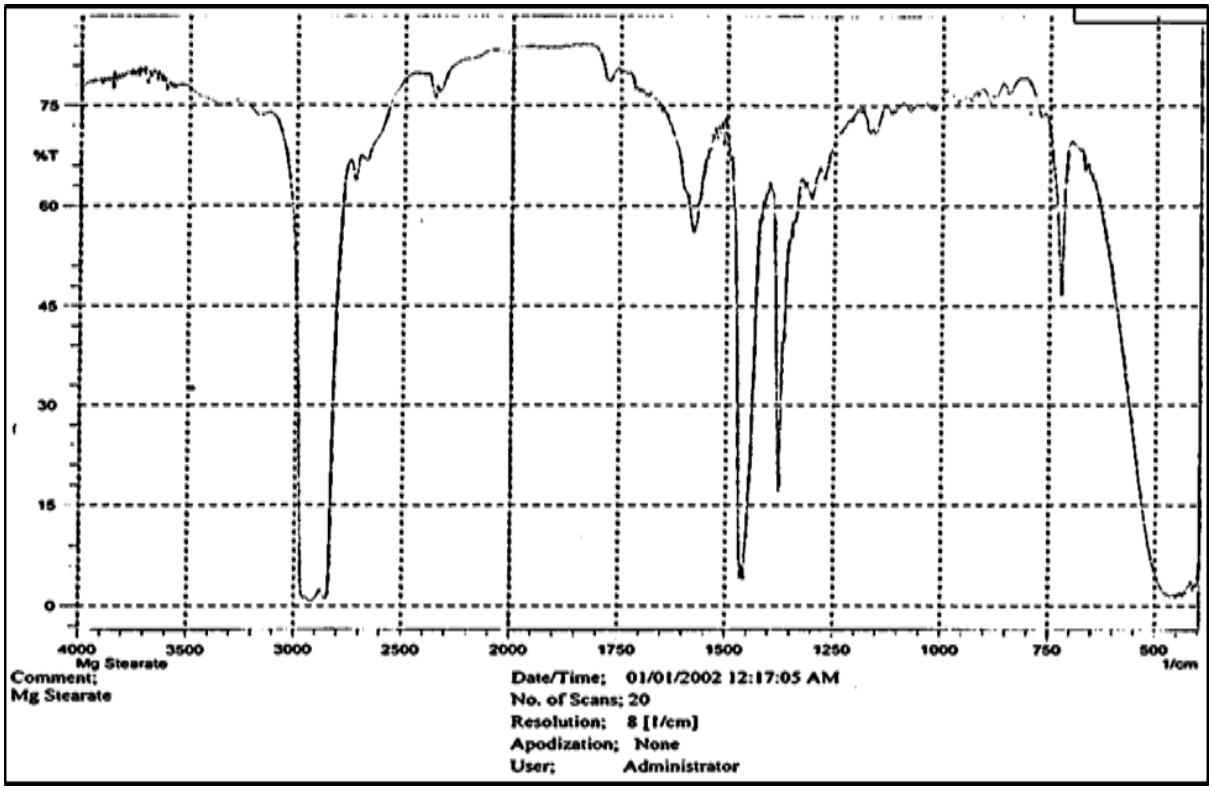
C.


52.5
%T
45
37.5
30
22.5
15
7.5
0
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
1/cm
Citric Acid
Comment;
Citric Acid
Date/Time; 01/01/2002 02:22:44 AM
No. of Scans; 20
Resolution; 8 [1/cm]
Apodization; None
User; Administrator

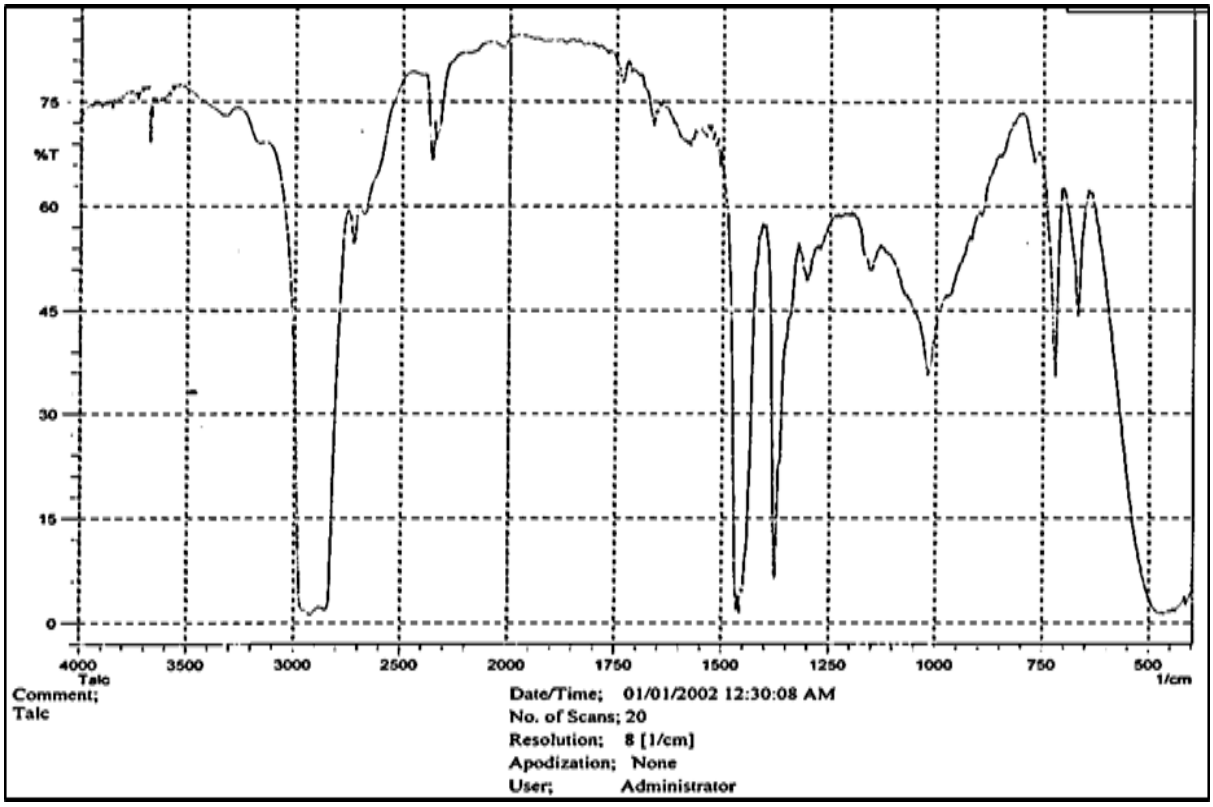
D.


%T
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
1/cm
Avicl
Comment;
Avicl
Date/Time; 01/01/2002 02:07:56 AM
No. of Scans; 20
Resolution; 8 [1/cm]
Apodization; None
User; Administrator

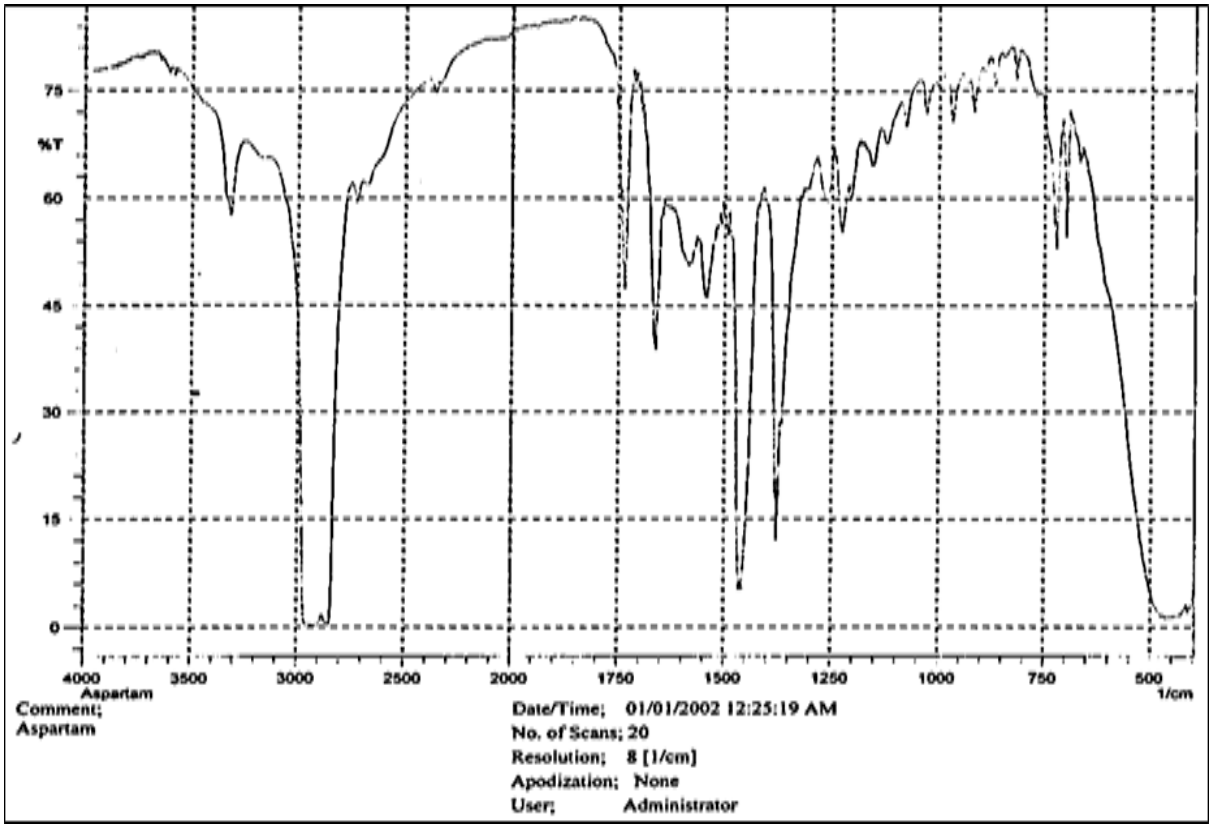
E.


%T
75
60
45
30
15
0
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
1/cm
Mg Stearate
Comment;
Mg Stearate
Date/Time; 01/01/2002 12:17:05 AM
No. of Scans; 20
Resolution; 8 [1/cm]
Apodization; None
User; Administrator

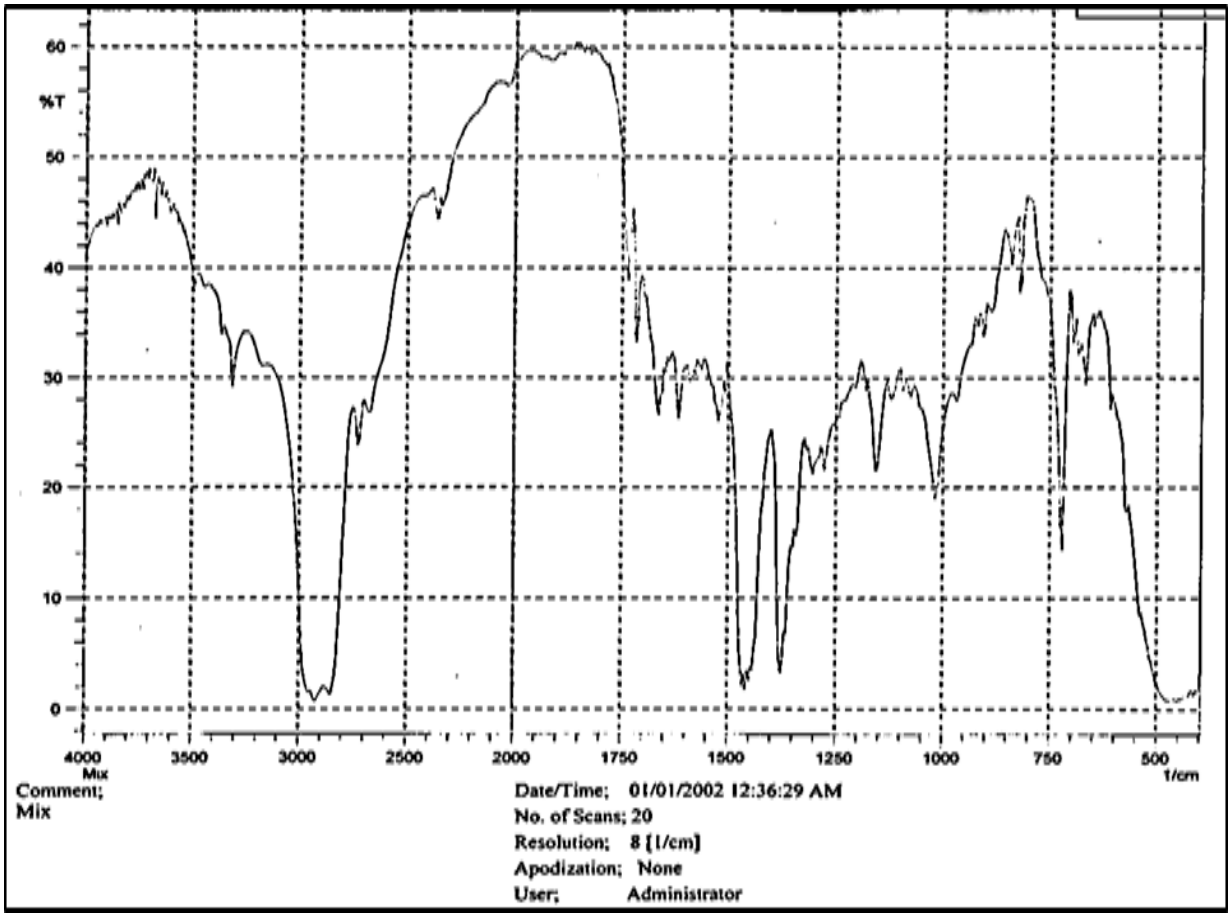
F.


75
%T
60
45
30
15
0
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
1/cm
Talc
Comment;
Talc
Date/Time; 01/01/2002 12:30:08 AM
No. of Scans; 20
Resolution; 8 [1/cm]
Apodization; None
User; Administrator

G.


75
%T
60
45
30
15
0
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
1/cm
Aspartam
Comment;
Aspartam
Date/Time; 01/01/2002 12:25:19 AM
No. of Scans; 20
Resolution; 8 [1/cm]
Apodization; None
User; Administrator

H.



I.

Fig 3.2. FTIR spectra of A). GLM pure, B). Sodium bicarbonate, C). Crospovidone, D). Citric acid, E). Avicel, F). Magnesium stearate, G). Talc, H). Aspartame and I). Mixture of all

3.3. Preliminary studies

Preliminary studies wereperformed in order to identify the most critical factors that could significantly affect the response. These include two formulation variables, i.e., the concentration of superdisintegrant&effervescent agent and one process variable i.e., the level of compression force. The response variables considered in thepreliminary study were cumulative drug release at 30min, disintegration time, wetting time, friability and hardness of tablets.

In the preliminary study, 1.25% - 5% crospovidoneand 5% - 20% sodium bicarbonate ranges of concentration were used in the formulations. To investigate the responses of combined formulations, both crospovidoneand sodium bicarbonate were used at low level, high level and low to high level, and in order to give sufficient strength for the tablets, all the above physical blends were compressed at two levels of compression force of 12KNand 20KN.

3.3.1. Evaluation of physical blends

The physical properties of the preliminary formulations are shown in Table 3.1. As can be seen in the table, the bulk density was in the range of 0.39 ± 0.0 - 0.53 ± 0.0 g/cm^3 and the tapped density between 0.47 ± 0.0 - 0.64 ± 0.0g/cm^3. Besides, almost all formulations had Hausner‘s ratio less than or equal to 1.30 indicating good flow property (USP 30/NF25, <711>, 2007). The compressibility index rangedfrom 14.8 ± 1.2to 21.2 ± 2.6, again indicating an acceptable flow of the blend. This was further demonstrated by the values of angle of repose which was in the range of 23.6 ± 1.4 - 29.67 ± 1.1^0, indicating good flow characteristics of the granule. However, one-way ANOVA showed that both crospovidone and sodium bicarbonate had no significant effect on the flow and compressibility of the granules($p = 0.021$). This might be due to the fact that the effect of crospovidone and effervescent agents on the flow and compressibility of the granules were overcome by the presence of highly flowable and compressible microcrystalline cellulose in each formulation (Gohel, 2005,Zgoda*et al*., 2009).

Table 3.1: Pre and post compression characterization of preliminary formulations

Formulation Code	Angle of Repose(°) ± SD	Bulk Density(g/cm^3)± SD	Tapped Density (g/cm^3)± SD	Carr's Index (%) ± SD	Hausner's Ratio ± SD	Hardness (kg/cm^2) ± SD	Friability (%) ± SD	Wetting time (sec) ± SD	Disintegration time(sec) ± SD	% release in 30 min ± SD
Fp1	25.41 ± 2.3	0.48 ± 0.0	0.56 ± 0.0	17.20 ± 3.3	1.21 ± 0.0	4.10 ± 0.1	0.24 ± 0.0	44.00 ± 2.5	33.00 ± 1.5	84.10 ± 1.6
Fp2	29.55 ± 3.5	0.39 ± 0.0	0.47 ± 0.0	17.00 ± 2.8	1.21 ± 0.0	9.10 ± 0.2	0.20 ± 0.0	59.00 ± 3.3	39.00 ± 2.0	80.10 ± 1.5
Fp3	24.10 ± 1.7	0.52 ± 0.0	0.63 ± 0.0	17.50 ± 3.3	1.30 ± 0.0	4.80 ± 0.3	0.20 ± 0.0	26.00 ± 1.3	18.00 ± 1.0	89.50 ± 1.1
Fp4	23.60 ± 1.4	0.51 ± 0.0	0.61 ± 0.0	18.00 ± 3.1	1.22 ± 0.0	9.60 ± 0.8	0.17 ± 0.0	38.00 ± 1.5	21.00 ± 1.0	86.50 ± 1.3
Fp5	29.02 ± 0.7	0.51 ± 0.0	0.64 ± 0.0	20.30 ± 2.4	1.25 ± 0.0	3.70 ± 0.3	0.45 ± 0.0	28.00 ± 1.0	17.00 ± 1.0	87.90 ± 1.7
Fp6	28.73 ± 0.6	0.52 ± 0.0	0.63 ± 0.0	17.50 ± 2.2	1.21 ± 0.0	8.50 ± 0.4	0.31 ± 0.0	37.00 ± 1.0	23.00 ± 1.5	85.10 ± 1.7
Fp7	26.40 ± 2.5	0.41 ± 0.1	0.53 ± 0.1	21.20 ± 2.6	1.26 ± 0.0	3.20 ± 0.2	0.65 ± 0.0	21.00 ± 2.0	15.00 ± 1.0	90.30 ± 1.4
Fp8	29.50 ± 1.1	0.50 ± 0.0	0.62 ± 0.0	19.35 ± 1.3	1.24 ± 0.0	6.60 ± 0.2	0.41 ± 0.0	45.00 ± 1.0	32.00 ± 2.o	88.80 ± 1.1
Fp9	29.67 ± 1.1	0.50 ± 0.0	0.61 ± 0.3	17.30 ± 1.3	1.30 ± 0.0	4.20 ± 0.3	0.36 ± 0.0	16.00 ± 1.0	7.00 ± 1.0	95.30 ± 1.3
Fp10	26.40 ± 2.3	0.43 ± 0.0	0.53 ± 0.0	18.80 ± 3.1	1.23 ± 0.0	8.40 ± 1.9	0.20 ± 0.0	21.00 ± 1.0	14.00 ± 1.0	92.80 ± 1.7
Fp11	27.65 ± 1.1	0.52 ± 0.0	0.61 ± 0.0	14.80 ± 1.2	1.20 ± 0.0	3.30 ± 0.7	0.65 ± 0.0	13.00 ± 1.0	8.00 ± 1.0	99.80 ± 1.5
Fp12	24.15 ± 1.3	0.52 ± 0.0	0.61 ± 0.0	14.90 ± 2.4	1.20 ± 0.0	5.60 ± 0.1	0.61 ± 0.0	23.00 ± 1.0	15.00 ± 1.0	99.50 ± 1.2
Fp13	25.70 ± 1.4	0.53 ± 0.0	0.63 ± 0.0	15.90 ± 3.3	1.20 ± 0.0	3.10 ± 0.6	0.67 ± 0.0	16.00 ± 1.9	11.00 ± 1.6	98.80 ± 1.9
Fp14	25.60 ± 1.4	0.52 ± 0.0	0.62 ± 0.0	16.10 ± 3.1	1.20 ± 0.1	5.50 ± 0.4	0.61 ± 0.0	17.00 ± 1.4	11.00 ± 1.2	92.80 ± 1.3
Fp15	28.50 ± 1.5	0.52 ± 0.0	0.62 ± 0.0	16.10 ± 1.6	1.20 ± 0.0	4.10 ± 0.2	0.42 ± 0.0	17.00 ± 1.1	10.00 ± 1.3	98.80 ± 1.1
Fp16	28.90 ± 1.2	0.49 ± 0.0	0.62 ± 0.0	20.90 ± 1.5	1.26 ± 0.0	7.80 ± 0.2	0.38 ± 0.0	19.00 ± 1.1	13.00 ± 1.1	97.90 ± 1.1

3.3.2. Effect of crospovidone

Crospovidoneis cross-linked polyvinyl pyrrolidonesuperdisintegrant, which rely principally on the combination of swelling and wicking mechanisms. Crospovidone particles are found to be granular and highly porous which facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. In order to study the effect of crospovidone concentration on tablet properties, various formulations containing 1.25% and 5% were prepared (Table 2.1). As can be seen in Table 3.1, as the concentration of crospovidone increases from 1.25% to 5%, the disintegration time and wetting time of the tablets decreases significantly($p = 0.003$), at a constant concentration of sodium bicarbonate and compression force level. This effect is due to the wetting and disintegrating action of crospovidone through itsporosity and capillary action, which provides and facilitates pathways for the penetration of fluid into the tablet cores(Zhao and Augsburger, 2005).The liquid is drawn up or "wicked" into these pathways through capillary action and ruptures the interparticulate bonds causing fast ingress of water and break up of tablets.A similar result was observed by Parthiban*et al*(2011).On the other hand,an increase ina concentration of crospovidonesignificantly ($p = 0.0014$) enhanced cumulative drug release of the tablets at 30min as shown in Table 3.1 and Fig. 3.3.This effect might be due to enhanced wetting and disintegration of the tablets with increasing crospovidone concentration. A similar finding was observed by Shirsand*et al* (2009).Thus, the levels ofcrospovidone for further studies were kept at 1.25%, 3.125%, and 5%.

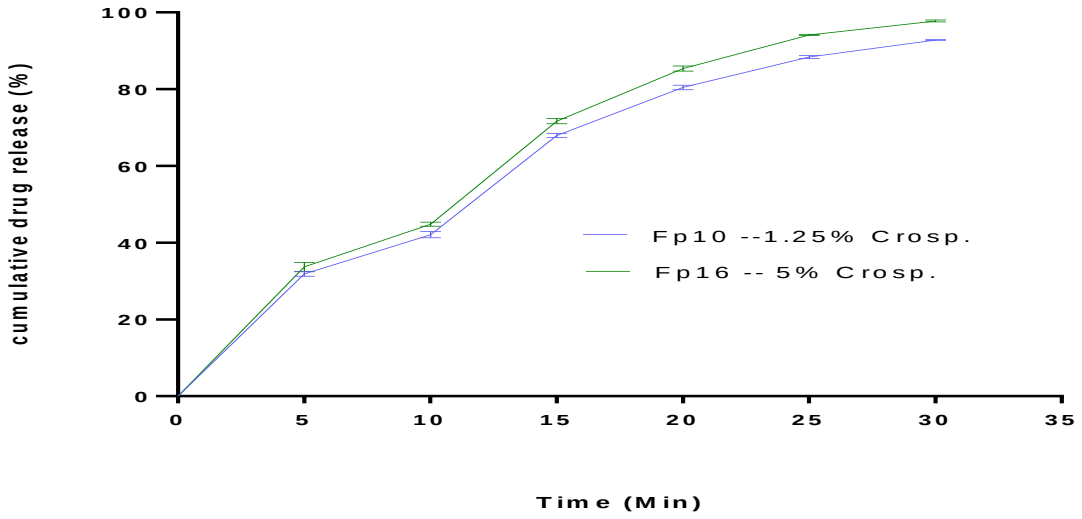


Fig3.3: The effect of crospovidoneon cumulative drug release of GLM ODT

3.3.3. Effect of effervescent agent

Effervescent agents evolve gas by means of chemical reactions that take place upon exposure to water and/or to saliva. The most common reaction for pharmaceutical purpose is the acid-base reaction. The reaction starts in the presence of water, even with a small amount as catalyzing agent, and because water is one of the reaction products, it will cascade further the rate of reaction to produce gas and more water for complete wetting and disintegration of the tablets*(Fu et al*., 2004).The effect of an effervescent agent on the characteristics of ODTs is presented in Table 3.1. As can be seen in the table, there was a significant decrease (p = 0.0011) in the disintegration as well as wetting time as the concentration of sodium bicarbonate increases from 5% to 20%. Both disintegration and wetting time were shorter in those formulations that contain high concentration of sodium bicarbonate. This might be due to the fact that disintegration and wetting time were facilitated by the rapid availability of the base for effervescent reaction to generatecarbon dioxide gas which further facilitatedrapid disintegration and wetting of the tablets by the bursting action of the evolved gas. This is in agreement with the reports ofSwamy*et al*(2009). This suggests that an increase in effervescent agent leads to a significant decrease in tablet disintegration and wetting time.

On the contrary, those formulations with a higher concentration of sodium bicarbonate in table 3.1showed a significant decrease (p = 0.0002) in hardness and a significant increase in friability of tablet. This might be due to poor compressibility nature of sodium bicarbonate which decreases the physical integrity of the tablets. This study is in agreement with the report of Sallam (1998), which suggests that an increase in a concentration of sodium bicarbonate leads to a significant decrease in hardness and increased in friability of tablet.

The effect of an effervescent agent on the release of ODTs in30 min is presented in Table 3.1 and Fig.3.4.Theresults show that an increase in the concentrationof sodium bicarbonatesignificantly (p = 0.012) enhanced the cumulative drug release of the tablet in30 min.These effects might be due to the fact that the rapid reaction of the effervescent agent'scauses to generate carbon dioxide gas which rapidly disintegrates the tablets by bursting action of evolved gas and due to the rapid breakage of the tablet and porous surface formation which increase surface area for dissolution. In addition, the effervescent reaction potentially increasesthe microenvironment pH around the granules and saliva(Shirsand*et al*, 2009), which is suitable to improve the solubility of weak acid drug GLM (pka=5.3), since the solubility of weaklyacidic drugsimproved by adjusting the pH to more alkaline. This is

inagreement with the reports of Jacob*et al*(2009), which suggest that an increase in the amount of an effervescent agent contributes to drug release enhancement due toa porous surface formation and increase microenvironment pH.Thus, the levels of sodium bicarbonate for further studies were kept at 5%, 12.5%, and 20%.

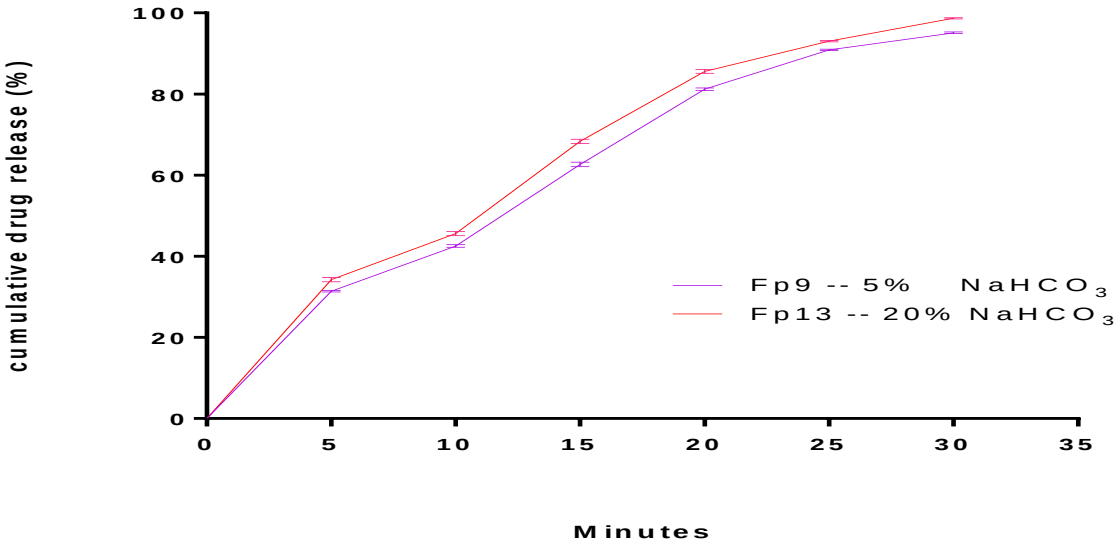


Fig3.4: The effect of an effervescent agent on cumulative drug release of GLM ODT.

3.3.4. Effect of compression force

ODT requires highlywettable excipient, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression force, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength. In addition, low compression pressure causes fast dissolving dosage forms to be soft, friable, and unsuitable for packaging. So a strategy to increase tablet mechanical strength without forgoingtablet porosity or requiring a special packaging to handle fragile tablets should be providedfor ODTs.

In order to investigate the effect of compression force, various tablet formulations were compressed at 12KN and 20KNwhile keeping other factors constant. As shown in Table 3.1, increasing compression force resulted in a significant decrease in friability($p = 0.001$),

significant increase in disintegration time (p = 0.0022) and significant increase in wetting time(p = 0.0011). These effects might be due to an increase in compression force which causes to decrease the porosity of a tablet and minimize the free ingress of water for wetting and disintegration of tablets. This effect is in agreement with the study ofGoel*et al* (2008) which revealed that an increase in compression force causes to increase disintegration time and wetting time of ODTs.An increase in compression forcedecreasesfriability and increases tablet compactness leading to a significant increase in hardness orphysical integrity of tablets.

Some studies shown that compression force have very minimal effect on the release of a drug from a tablet(Ibrahim*et al*., 1991; Santos *et al*., 2010). While others shown that it has effect on the release properties (Khan and Rhodes, 1976).In this study, as shown in Table 3.1 and Fig.3.5, the effect of compression force had not pronounced (p= 0.0728) on the cumulative drug release of the tablet in 30 min.Rather at this stage of drug release, the dissolution of ODT is depends on other formulation factors that directly affect wetting and disintegration of the tablet. Thisstudy is in agreement with the study of Adeleye*et al* (2015), which showed that compression force had minimal effect, on the release of drug from tablet core,thus, the levels of compression force for further studies were keptat 12KN, 16KN, and 20KN.

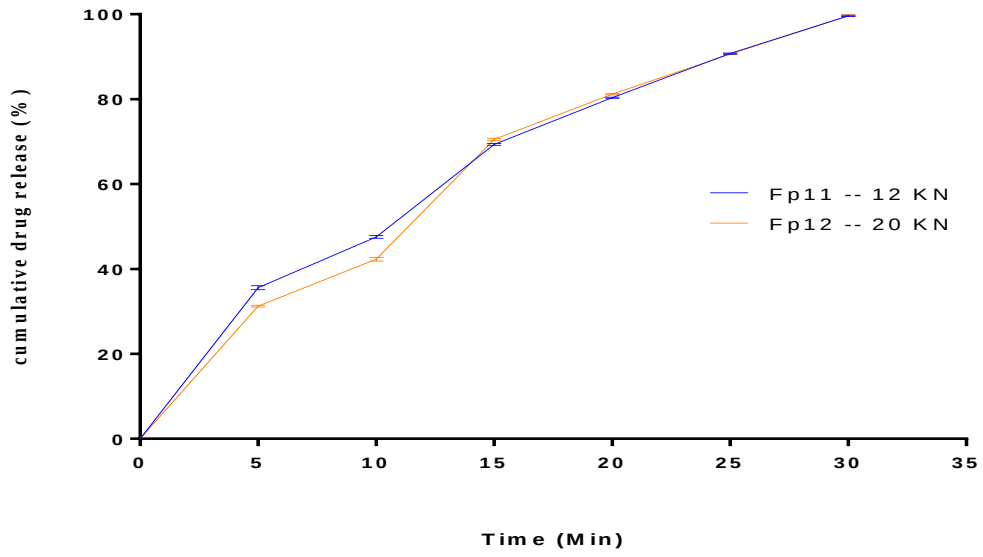


Fig3.5: The effect of compression force on cumulative drug release of GLM ODT.

3.4. Experimental design formulations

3.4.1. Pre-compression evaluation

Blend ready for compression containing GLM and various excipient mixtures shown in Table 2.2 were subjected to analysis. The results showed thatangle of repose were in the range of 24.9 ± 1.6 to 30.0 ± 1.2º which indicated good flow property. Other indirect measuresof the flow of a powder, which primarily depends on particle size distribution, particle shape, and the tendency of the particles to adhere to one another include bulk density, tapped density and Hausner'sratio, which were the range of 0.31 ± 0.01 to 0.55 ± 0.02g/cm^3, 0.39 ± 0.02 to 0.67 ± 0.04g/cm^3 and 1.20 ± 0.0 to 1.26± 0.10g/ml,respectively.The three measures indicate that,all formulations have acceptable powder flow.The results revealed that the level of crospovidone and sodium bicarbonate had no significant effect on the flow of the blend(P = 0.016). This may be due to the fact that the effect ofcrospovidoneand sodium bicarbonate were overwhelmed by the presence of the highly compressible and flowable MCC in each formulation (El-Sakhawy & Hassan, 2007). Carr's indexes of all the formulations were found to be the range of 16± 2.0 to 20.5± 3.5%. This result further confirmed the good flow and compressibility index of the blend.

Table 3.2: Pre-compression parameters of glibenclamide experimental design formulations.

Formulations Code	Angle Repose (°) ± SD	Bulk Density (g/cm^3)± SD	Tapped Density (g/cm^3)± SD	Car's Index (%) ± SD	Hausner's Ratio± SD
F1	29.2 ± 1.6	0.52 ± 0.01	0.63 ± 0.01	17.5 ± 1.0	1.21 ± 0.0
F2	30.0 ± 0.9	0.55 ± 0.01	0.66 ± 0.01	16.7 ± 2.5	1.20 ± 0.0
F3	27.7 ± 1.2	0.54 ± 0.01	0.65 ± 0.02	16.9 ± 1.6	1.20 ± 0.0
F4	24.9 ± 1.6	0.55 ± 0.02	0.67 ± 0.04	17.9 ± 3.0	1.22 ± 0.1
F5	28.4 ± 1.5	0.51 ± 0.01	0.63 ± 0.01	19.0 ± 1.6	1.23 ± 0.0
F6	30.0 ± 1.2	0.52 ± 0.01	0.63 ± 0.02	17.5 ± 1.6	1.21 ± 0.0
F7	29.8 ± 1.3	0.51 ± 0.01	0.62 ± 0.03	17.8 ± 1.4	1.21 ± 0.0
F8	26. ± 82.9	0.47 ± 0.02	0.58 ± 0.03	18.0 ± 3.4	1.20 ± 0.1
F9	27.2 ± 2.6	0.46 ± 0.01	0.55 ± 0.04	16.4 ± 3.0	1.20 ± 0.1
F10	29.8 ± 3.6	0.39 ± 0.01	0.48 ± 0.05	18.7 ± 4.5	1.23 ± 0.1
F11	30.0 ± 1.2	0.53 ± 0.01	0.64 ± 0.01	17.1 ± 1.5	1.21 ± 0.0
F12	29.1 ± 1.7	0.53 ± 0.01	0.64 ± 0.02	17.0 ± 1.7	1.20 ± 0.0
F13	29.8 ± 2.5	0.37 ± 0.02	0.45 ± 0.04	17.8 ± 3.8	1. 21 ± 0.1
F14	25.1 ± 1.9	0.52 ± 0.01	0.63 ± 0.04	17.5 ± 3.5	1.21 ± 0.1
F15	26.6 ± 1.8	0.52 ± 0.01	0.64 ± 0.03	18.8 ± 3.8	1.23 ± 0.1
F16	26.5 ± 2.7	0.31 ± 0.01	0.39 ± 0.02	20.5 ± 3.5	1.26 ± 0.1
F17	28.0 ± 1.3	0.54 ± 0.00	0.65 ± 0.02	17.0 ± 2.2	1.20 ± 0.0
F18	26.3 ± 1.3	0.52 ± 0.00	0.62 ± 0.01	16.0 ± 2.0	1.20 ± 0.0
F19	29.3 ± 1.6	0.51 ± 0.00	0.63 ± 0.01	19.0 ± 2.3	1.23 ± 0.0
F20	28.0 ± 1.2	0.52 ± 0.00	0.63 ± 0.01	17.5 ± 1.5	1.21 ± 0.0

3.4.2. Tablet Characterization

Tablets from the 20 formulations were tested for drug content, weight variation, thickness, hardness, and friability. As shown in Table 3.3, the mean tablet weight variation, drug content and thickness had values ranging from 194 ± 2.1mg to 204 ± 2.5mg, 95.90 ± 0.5 % to 101.30 ± 0.5 % and 2.80 ± 0.0 mm to 4.40 ± 0.0 mm, respectively. The mean tablet weight variation and the content of GLM were within the acceptable limits of 7.5% and 90 - 110%, respectively,according to USP30-NF25, (2007).

Tablets must be able to withstand mechanical damage during handling and transportation experienced in the manufacturing environment. As can be seen in Table 3.3, the crushing strengthof the tabletsrangedfrom 2.9 ± 0.52 to 10.10 ± 0.14 kg/cm^2. The other measure of tablet strength is friability. As seen in Table 3.3friability was in the range of 0.05 to 0.60%, which is within the accepted pharmacopeia limit <1% (USP30-NF25, 2007).

Wetting time of ODTsis another important parameter which needs to be assessed to give an insight into the disintegration properties of tablets; a lower wetting time implies quicker disintegration time of a tablet. The results of wetting time for the twenty ODT batches are shown in Table 3.3(11 ± 0.5 and 58 ± 2.0sec).The result clearly indicates that formulationF3containing a higher percentage of an effervescent agent (20%), and higher percentage of superdistegrants (5%) at minimum compression force (12KN) showed the minimum wetting time whereas,formulation F16 containing 3.125% crospovidone only at 16KN compression force hadlonger wetting time.

Disintegration is the first important step for drug absorption from solid dosage forms after oral administration. Tablet disintegration isaffected by the particle size, the degree of substitution, the extent of cross-linking,and tablet hardness and/or the compaction force used in making the tablet.ForODTs, disintegration time is considered to be one of the important criteria in selecting the best formulation. As shown in Table 3.3, the *in vitro* disintegration time is in the range of 7 ± 1.0 – 47 ± 1.5 sec. F3 andF7 which contain 5% and 3.125% crospovidone, 20% and 12.5% effervescent agent and compressed at 12KN and 9.27KN respectively, showed the shortest disintegration time of 7 ± 1.0 sec whereas F16 which contains only 3.125% crospovidoneand compressed at 16KN exhibited the longest disintegration time of (47 ± 1.5) sec. It is interesting to see here that there is a good correlation between the wetting and disintegration time of the ODTs.

Table 3.3: Post compression parameters of glibenclamideexperimental design ODT.

Formulations Code	Hardness (kg/cm^2) ± SD	Thickness (mm) ± SD	Friability (%) ± SD	Weight Variation (mg) ± SD	Content Uniformity (%)± SD	Wetting time (sec) ± SD	Disintegration time (sec) ± SD
F1	3.5 ± 0.2	3.4 ± 0.0	0.4 ± 0.0	201 ± 1.5	99.8 ± 0.5	19.0 ± 3.0	16.0 ± 2.1
F2	3.3 ± 0.5	3.9 ± 0.0	0.5 ± 0.0	199 ± 2.5	98.1 ± 0.7	41.1 ± 1.0	30.0 ± 1.5
F3	3.5 ± 0.6	4.0 ± 0.0	0.3 ± 0.0	198 ± 1.6	96.1 ± 1.0	11.0 ± 0.5	8.0 ± 1.7
F4	6.7 ± 0.1	3.1 ± 0.0	0.3 ± 0.0	199 ± 2.0	96.9 ± 1.8	20.0 ± 1.6	15.0 ± 1.2
F5	5.6 ± 0.6	3.4 ± 0.0	0.2 ± 0.01	199 ± 1.8	96.7 ± 0.9	27.0 ± 1.4	18.0 ± 2.2
F6	6.4 ± 0.1	3.4 ± 0.0	0.2 ± 0.0	201 ± 1.7	100.2 ± 0.5	34.0 ± 1.2	26.0 ± 2.1
F7	2.9 ± 0.5	4.4 ± 0.0	0.4 ± 0.0	197 ± 1.4	99.2 ± 1.6	12.0 ± 2.0	7.0 ± 1.0
F8	6.0 ± 0.2	3.4 ± 0.0	0.2 ± 0.0	200 ± 2.3	100.1 ± 1.2	23.0 ± 2.5	14.0 ± 1.0
F9	3.5 ± 0.2	3.9 ± 0.1	0.6 ± 0.0	198 ± 2.1	99.8 ± 2.1	18.0 ± 2.1	14.0 ± 1.5
F10	4.5 ± 0.2	2.9 ± 0.0	0.3 ± 0.0	200 ± 1.5	97.9 ± 1.6	40.0 ± 3.1	35.0 ± 2.8
F11	5.9 ± 0.2	3.4 ± 0.0	0.2 ± 0.0	198 ± 1.5	98.2 ± 1.4	26.0 ± 1.2	16.0 ± 1.8
F12	8.5 ± 0.1	3.0 ± 0.0	0.1 ± 0.0	199 ± 1.7	98.2 ± 1.8	15.0 ± 1.7	8.0 ± 1.9
F13	7.0 ± 0.1	3.2 ± 0.0	0.2 ± 0.0	194 ± 2.1	95.9 ± 0.5	48.0 ± 5.0	36.0 ± 4.0
F14	4.0 ± 0.6	3.3 ± 0.0	0.2 ± 0.0	196 ± 2.8	98.4 ± 0.7	18.0 ± 1.9	11.0 ± 1.6
F15	6.5 ± 0.3	3.7 ± 0.0	0.1 ± 0.0	199 ± 1.8	96.8 ± 1 .6	42.0 ± 4.0	32.0 ± 5.0
F16	10.1 ± 0.1	2.8 ± 0.0	0.08 ± 0.0	198 ± 1.6	96.9 ± 1.7	58.0 ± 2.0	47.0 ± 1.5
F17	6.1 ± 0.2	3.4 ± 0.0	0.2 ± 0.0	198 ± 1.1	97.8 ± 0.8	25.0 ± 1.7	16.0 ± 1.8
F18	9.4 ± 0.2	3.1 ± 0.0	0.05 ± 0.0	204 ± 2.5	101.3 ± 0.5	39.0 ± 3.2	27.0 ± 2.0
F19	5.80 ±.1.0	3.4 ± 0.0	0.2 ± 0.0	201 ± 1.3	99.8 ± 1.6	27.0 ± 1.5	14.0 ± 1.7
F20	6. 6.0 ± 0.1	3.2 ± 0.0	0.2 ± 0.0	203 ± 1.2	101.1 ± 0.4	26.0 ± 1.2	15.0 ± 1.6

(n=3, Mean ± SD).

3.4.3. In vitro drug release

Several independent factors affect the release of drug in oral dosage forms. In many ODT technologies based on direct compression, the addition of superdisintegrantspredominantly affects the rate of disintegration and the dissolution of soluble and insoluble drugs. The presence of other formulation ingredients such as water soluble excipients and effervescent agents also further hastens the process ofdisintegration and dissolution. The primary change in a release from such types of formulations are due to differences in the particle size generated, since breaking tablets into finer fragments createsa much larger surface area to dissolution and decrease absorption lag time. In general, the dissolution process of tablet depends on wetting followed by disintegration. Hence, both wetting and disintegration time may be used as confirmation tests for the evaluation of ODT dissolution.

The *in vitro*drug release behaviours of different formulations are shown in Fig.3.6A and B. USP specification for the release of GLM from tablets states that not less than 75% of the labelled claim of GLM should be dissolved in 45 min (USP30-NF25, 2007).As can be seen in the Figure, all of the twenty ODT formulations released more than 75% of the labelled claim within 25 min. Thus, all the formulations passed the USP requirement. It is interesting to note thatthe percentage of superdisintegrant and effervescent agent appear to influence drug release patternsremarkably, whereas the change in compression force had minimaleffect on the cumulative drug release at later release periods. For instance,F16 showed minimum cumulative drug release at 30min (84 ±1.60 %)due to the lower percentage of crospovidone(3.125%) and absence of effervescent agent. Except for formulation F2 and F16, all the other formulations having crospovidone and effervescent agent, showed much more drug release profile over a period of 30 min. The complete drug release from F3, F4 and F12, were due to higher percentage of crospovidone and sodium bicarbonate.

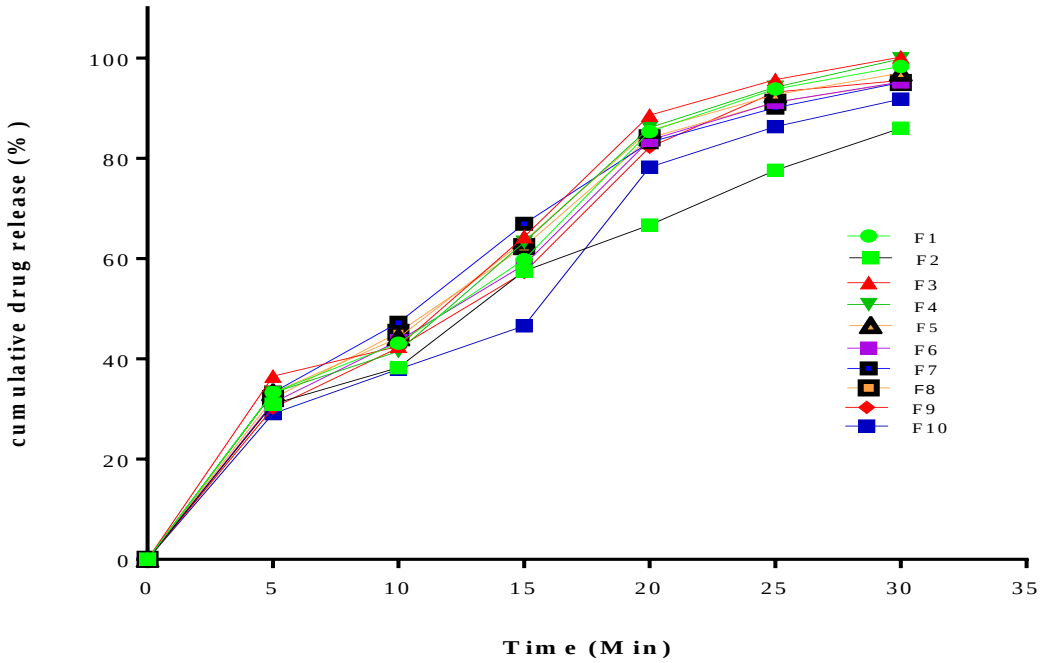


Fig3.6A.Drug release profile of GLM ODT for optimization.

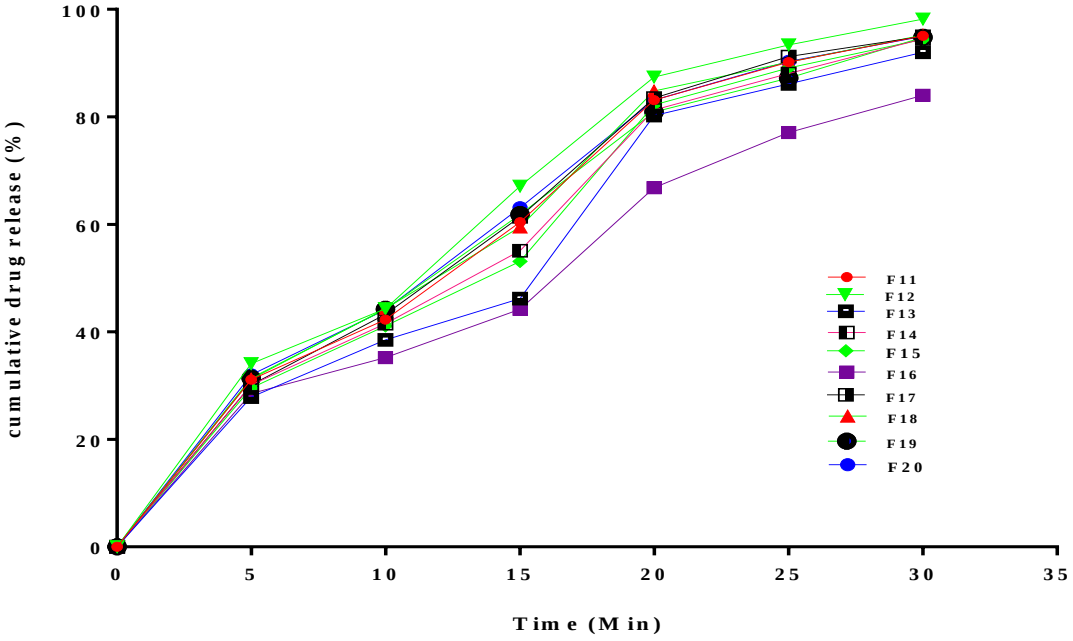


Fig. 3.6B:Drug release profile of GLM ODT for optimization.

3.4.4. Mathematical model selection

The responses of the twenty experiments were used to fit an equation and predict the properties of all possible formulations for composite design. Appropriate response models for the responses were selected based on the response fit summary. The software fits linear, two-factor interaction, quadratic and cubic polynomials to the dependent variables and suggests a model based on the least sum of square in the fit summary table.

In the fit summaries for the responses the "Sequential Model Sum of Squares" summary table shows how terms of increasing complexity contribute to the total model. For each source of terms, the probability ("PROB > F") which falls below 0.05, was selected. For wetting and disintegration time, the quadratic model was suggested by the software with R-square of 0.9232 and 0.9366, respectively (Table 3.5)and for hardness, friability and cumulative drug release at 30 min linear model was chosen with R-square of 0.6799, 0.8082 and 0.7467, respectively (Table 3.4& 3.6). In the meantime the software chosen models which exhibit low standard deviation, high "R-Square" values and a low "PRESS" (predicted residual sum of squares) for each response. Modelestimates each point using all of the design points of p-value, lack of fit F-values and R-square values, as stated in Table 3.4 and 3.6 for linear model for hardness, friability and drug release at 30 min with ($p = 0.0003$ and lack of fit $F = 73.27$), ($p < 0.000$ and lack of fit $F = 393.50$) and ($p < 0.0011$, lack of fit $F = 125.23$), respectively and asshown in Table 3.5 for wetting time and disintegration time, quadratic model is suggested ($p = 0.0290$ and lack of fit $F = 1.13$) and ($p = 0.0018$ and lack of fit $F = 3.04$), respectively. Therefore, with evidence of the fit summary tables, linear model for hardness, friability and drug release at 30 min and quadratic model for wetting time and disintegration time were selected as best fit models by the software analysis.

The model was also used to generate the response surface plots, three-dimensional displays of the response surface, and predicted response(s) for any set of factor and the adequacy of model equations to represent the relationship between the responses and the measured components were statistically validated using ANOVA provision in the software.ANOVA is the most important tool for the evaluation of significance and goodness of fit of a regression model and significance of individual model coefficients (Kusic*et al.*, 2010). Hence, in the design ANOVA was applied to test the significance of the selected models and model coefficients for the responses by considering p-value,significantif the p-value is less than 0.05andinsignificant if greater than 0.05.

Table 3.4: Fit summary statistics for the selection of models for hardness and friability.

Response	Source	R Squared	Adj.R Squared	Pred.R Squared	PRESS	P-value	Lack of fit F-value	Remark
Hardness	Linear	0.6799	0.6198	0.4137	45.41	0.0003	73.27	suggested
	2FI	0.9642	0.9354	0.8129	105.77	0.9768	99.21	
	Quadratic	0.7321	0.4911	−1.0239	176.18	0.9240	151.6	
	Cubic	0.9431	0.8198	−11.2091	769.31	0.0134	114.1	Aliased
Friability	Linear	0.8082	0.7722	0.6663	0.13	< 0.0001	393.5	suggested
	2FI	0.8711	0.8116	0.4089	0.1475	0.14750	41.17	
	Quadratic	0.9221	0.8520	0.3625	0.1534	0.15340	175.0	
	Cubic	0.9989	0.9966	0.8128	0.070	< 0.0001	19.27	Aliased

Table 3.5: Fit summary statistics for selection of models for wetting and disintegration time.

Response	Source	R Squared	Adj. R Squared	Pred. R Squared	PRESS	P-value	Lack of fit F. value	Remark
Wetting time	Linear	0.8109	0.7755	0.7044	904.56	0.8543	1.93	
	2FI	0.8178	0.7337	0.5384	1506.27	0.9193	2.54	
	Quadratic	0.9232	0.8541	0.6767	1283.29	0.0290	1.13	suggested
	Cubic	0.9591	0.8541	0.7091	1214.64	0.3621	0.63	Aliased
Disintegration time	Linear	0.7142	0.6606	0.5376	1087.17	0.0001	7.84	
	2FI	0.7331	0.6099	0.2496	0.8203	0.8203	10.02	
	Quadratic	0.9366	0.8796	0.7629	0.0018	0.0018	3.04	suggested
	Cubic	0.9834	0.9474	0.7661	0.0580	0.0580	0.31	Aliased

Table 3.6: Fit summary statistics for selection of models for cumulative drug release at 30 min.

Response	Source	R Squared	Adj.R Squared	Pred.R Squared	PRESS	P-value	Lack of fit F.value	Remark
Cumulative drug release at 30 min	Linear	0.7467	0.6993	0.5408	134.54	<0.0001	125.23	suggested
	2FI	0.7526	0.6385	0.1706	243	0.9568	1.68.18	
	Quadratic	0.8189	0.6560	–0.3668	400.46	0.3523	196.68	
	Cubic	0.9019	0.6892	–20.432	6278.99	0.3780	530.74	Aliased

As shown in summaries of the ANOVA results, for hardnessin Table 3.7, for friability in Table 3.8 and for drug release at 30 min Table 3.11, linear model of the responses were significant for hardness (p=0.0003),friability (p<0.0001) and for drug release at 30min(p=0.0001). ANOVA results in the Table 3.7 revealed that the main effects,B (sodium bicarbonate) (p=0.0122)and C (compression force) (p=0.0002), were significant model terms for hardness, whereas A (conc. of crospovidone) (p=0.0995), wasinsignificant model term.For friability, ANOVA results in Table 3.8 indicated that the main effects A (Conc. of crospovidone P =0.0008), B (Conc. of sodium bicarbonate P =0.0001) and C (compression force P =0.0001)were significant model terms for the linear model.ANOVA results of cumulative drug release at 30 min in Table 3.11indicated that the main effects, A (concentration of crospovidone) (p=0.0007) and B (conc.of sodium bicarbonate) (p<0.0001) were significant model terms. However, the level of compression force (p=0.8118) was insignificant model term for the linear model of drug release at 30min. Hence, backward elimination procedure was applied to reduce the insignificant terms to improve model prediction quality of hardness, friability, and release.

Table 3.7: Summary of ANOVA for surface response linear model of hardness.

Source	Sumof square	Df	Mean of square	F-value	p-value	Remark
Model	52.66	3	17.55	11.33	0.0003	significant
A-CP	4.74	1	4.74	3.06	0.0995	insignificant
B-NaHCO3	12.37	1	12.37	7.98	0.0122	significant
C-CF	35.54	1	35.54	22.93	0.0002	significant
Residual	24.80	16	1.55			
Cor total	77.45	19				

Table 3.8: Summary of ANOVA for response surface linear model of friability.

Source	Sum of square	Df	Mean of square	F-value	p-value	Remark
Model	0.30	3	0.10	22.47	< 0.0001	significant
A-CP	0.077	1	0.077	16.95	0.0008	significant
B-NaHCO3	0.11	1	0.11	24.87	0.0001	significant
C-CF	0.12	1	0.12	25.59	0.0001	significant
Residual	0.072	16	4.514E−003			
Cor total	0.38	19				

For wetting and disintegration time, the selected model was quadratic with (p-value of 0.0002 for wetting time) and(p-value of <0.0001 for disintegration time),as shown in Table 3.9 and Table 3.10, respectively. ANOVA results for wetting time in Table 3.9 revealed that the main effectsA (Conc. of crospovidone P =0.0005), B (Conc. of sodium bicarbonate p<0.0001), C (compression force p=0.0002) and the effect B^2(sodium bicarbonate^2) (p=0.0043) were significant model terms and ANOVA results of disintegration time in Table 3.10 revealed that

the main effects A (Conc. of crospovidone, p=0.0002), B (Conc. of sodium bicarbonate P<0.0001), C (compression force p=0.0004) and the effect B^2 (sodium bicarbonate^2) (p=0.0002) were significant model terms, whereas other effects like A^2, C^2, interaction effect (AB, BC & AC) were insignificant, So that, backward elimination procedure was applied for insignificant terms to improve the model prediction efficiency of wetting and disintegration time.

Table 3.9: Summary of ANOVA for response surface quadratic model of wetting time

Source	**Sumof square**	**df**	**Mean of square**	**F-value**	**p-value**	**Remark**
Model	3012.62	9	334.74	13.36	0.0002	significant
A-CP	629.59	1	629.59	25.13	0.0005	significant
B-NaHCO3	1248.73	1	1248.73	49.83	<0.0001	significant
C-CF	767.93	1	767.93	30.65	0.0002	significant
A^2	18.12	1	18.12	0.72	0.4151	insignificant
B^2	336.68	1	336.68	13.44	0.0043	significant
C^2	0.81	1	0.81	0.032	0.8608	insignificant
AB	6.13	1	6.13	0.24	0.6317	insignificant
AC	10.13	1	10.13	0.40	0.5393	insignificant
BC	6.13	1	6.13	0.24	0.6317	insignificant
Residual	250.58	10	25.06			
Cor total	3263.20	19				

Table3.10: Summary of ANOVA for response surface quadratic model of disintegration time.

Source	Sum of square	df	Mean of square	F-value	p-value	Remark
Model	2201.97	9	244.66	16.42	< 0.0001	significant
A-CP	492.35	1	492.35	33.05	0.0002	significant
B-NaHCO3	778.87	1	778.87	52.28	< 0.0001	significant
C-CF	407.89	1	407.89	27.38	0.0004	significant
A^2	24.20	1	24.20	1.62	0.2313	insignificant
B^2	470.74	1	470.74	31.60	0.0002	significant
C^2	5.00	1	5.00	0.34	0.5754	insignificant
AB	15.13	1	15.13	1.02	0.3374	insignificant
AC	28.13	1	28.13	1.89	0.1995	insignificant
BC	1.13	1	1.13	0.076	0.7891	insignificant
Residual	148.98	10	14.90			
Cor total	2350.95	19				

Table 3.11: Summary of ANOVA for response surface linear model of cumulative drugrelease at 30min

Source	Sum of square	df	Mean of square	F-value	p-value	Remark
Model	218.78	3	72.93	15.73	< 0.0001	significant
A-CP	81.77	1	81.77	17.63	0.0007	significant
B-NaHCO3	136.74	1	136.74	29.49	<0.0001	significant
C-CF	0.27	1	0.27	0.059	0.8113	insignificant
Residual	74.20	16	4.64			
Cor total	292.98	19				

For all the five dependent variables (response) significant mathematical regression models were generatedin terms of coded factors and using model term coefficients, as shown in Eq. 3.1 for a hardness of a tablet, Eq. 3.2 for friability of a tablet, Eq. 3.3 for wetting time, Eq. 3.4 for disintegration time and Eq. 3.5 for drug release at 30 min of ODT.

Hardness (H) = +5.75 + 0.59*A - 0.95*B +1.61*C……..……Eq. 3.1

Friability (F) = +0.25 - 0.075*A + 0.091*B - 0.092*C……...…….Eq. 3.2

Wetting time (WT) = +23.57 - 6.79*A - 9.56*B + 7.50*C + 4.83*B^2…….Eq. 3.3

Disintegration time (DT) = +14.86 - 6.00*A - 7.55*B + 5.47*C + 5.72*B……...……..Eq. 3.4

Release at 30min (R %) = +94.60 + 2.45*A + 3.16*B…….……Eq. 3.5

The polynomial equation was used to draw conclusion after considering the intensity ofcoefficient and the mathematical sign it carries, that is, positive or negative (Chakraborty *et al.,* 2013, Takayama *et al.,* 2003).The sign of model coefficients have meanings on the response variables, that a coefficient implies the change in response, whenever that term is changed by one unit leaving the other terms constant. The magnitude implies the strength, whereas the sign indicates the direction factor varies the response. A positive sign indicates a positive effect where as a negative sign indicates a negative effect on the response.Based on Eq. 3.1 linear mathematical model for hardness of tablet, the two independent factors (concentration of crospovidone (A) and compression force (C) significantly affect the hardness of a tablet positively, whereas concentration of sodium bicarbonate (B) affects hardness negatively. The effect of compression force was the strongest with higher coefficient (+1.61) than concentration of crospovidone and sodium bicarbonate. From Eq. 3.2 linear model of friability, the concentration of crospovidone (A) and compression force (C) showed significant negative effect on tablet friability. However, concentration of sodium bicarbonate (B) has positive significant effect on friability. The effect of compression force(C)(-0.092) and the effect of sodium bicarbonate(B)(+0.091) were found to be the more determinant factorsthan the effect of crospovidone (A) (-0.075).

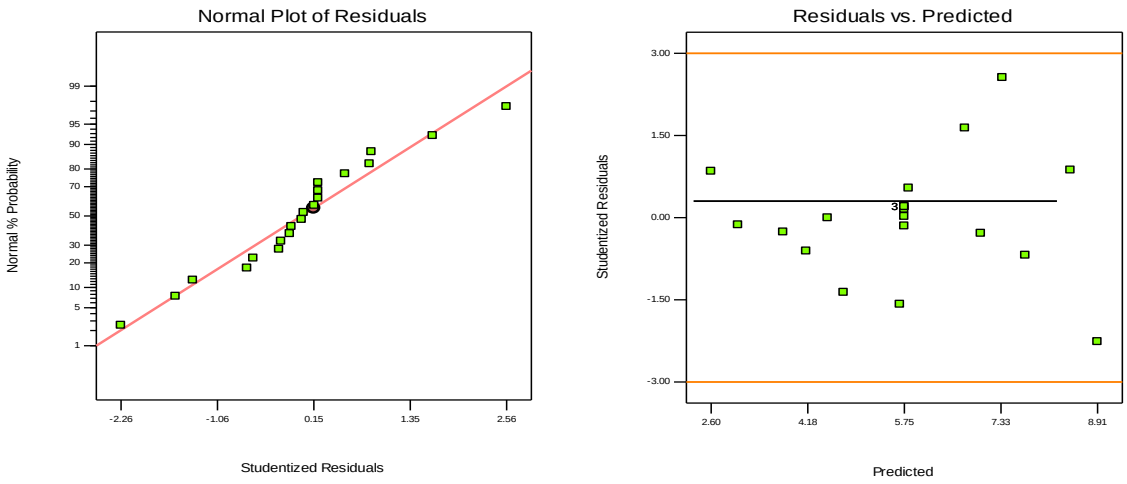
Quadratic models of wetting and disintegration time in Eq. 3.3 and Eq. 3.4,respectively, indicate thatconcentration of crospovidone (A) and concentration ofsodium bicarbonate (B), have a significant negative effect on tablet wetting and disintegration time. Therefore,

increasing these factors result in a decrease in tablet wetting and disintegration time. Again in these cases, the effect of sodium bicarbonate was found to be more determinant than the other factors on bothwetting and disintegration time of ODT with a higher coefficient,(-9.56 in wetting time and -7.55 in disintegration time). Similarly, as observed from Eq. 3.3 and Eq. 3.4 compression force (C) and the effect of sodium bicarbonate^2 (B^2) had a significant effect on tablet wetting and disintegration time.

Linear regression model of cumulative drug release at 30min in Eq. 3.5 showedonly concentration of crospovidone (A) and concentration of sodium bicarbonate (B), have positive significant effects on cumulative drug release of a tablet at 30 min. However, the effectof Compression force (C) was not significant; this is because the late stage of drug releasewhich might occur after a complete wetting and disintegration of the tablet earlydue to the presence of superdisintegrant and effervescent agents which cause the tablet to lose its physical integrity in the late stage and result in wetting and disintegration of a tablet early for ready dissolution without being affected by applied compression force. In the study,the effect of sodium bicarbonate was found to be more significant than crospovidone on release with higher coefficient of + 3.16.

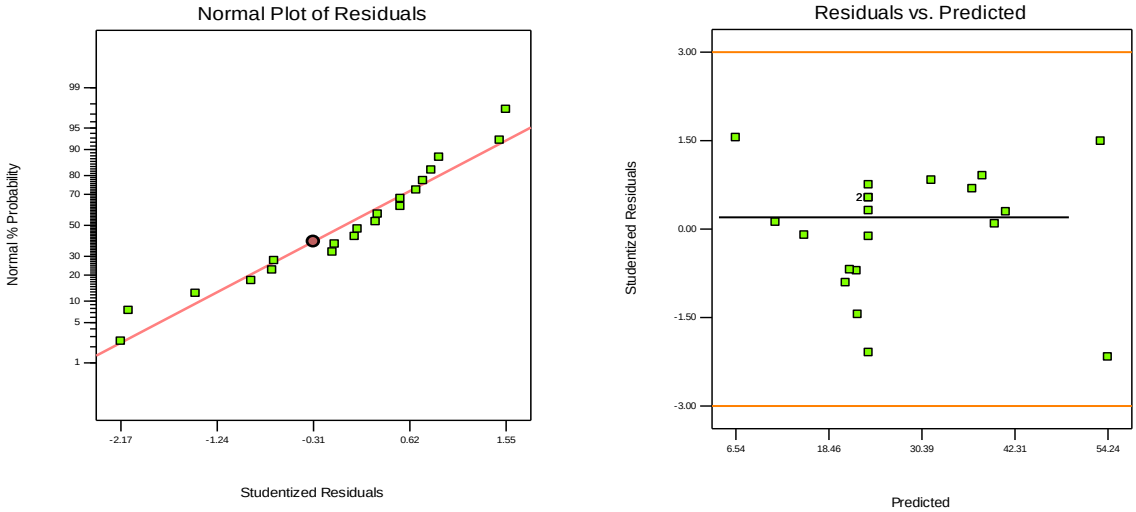
3.4.5. Model adequacy checking

In order to check the adequacy of models in this study, the normal probability plots of the residuals and the plots of the residuals versus predicted valuesfor the selected responses of hardness, friability, wetting time, disintegration time and cumulative drug release within 30 min were plotted and these are presented in Figures 3.7 –3.11.The useful data on the model efficiency is summarized in residuals providing a clear understanding of any variation in fit to the model. The two plots related to residuals are the normal probability plot of residuals and the plot of internally studentizedresiduals versus predicted values, which are considered as additional tests of model adequacy checking tools(Bari*et al*., 2010).Acheck on normal probability plot of residuals in Fig. 3.7 A, 3.8 A, 3.9 A, 3.10 A and 3.11 A were based on the points or point clusters, which placed closely to the diagonal line, inferring that the errors were distributed normally for all responses.On the other hand the plot of internallystudentized residuals versus predicted values in Figures 3.7 B, 3.8 B, 3.9 B, 3.10 B and 3.11 B, indicated that the points are randomly scattered, with no apparent pattern or structure, and all values lie within the recommended range of −3 and +3 outlier detection limits.



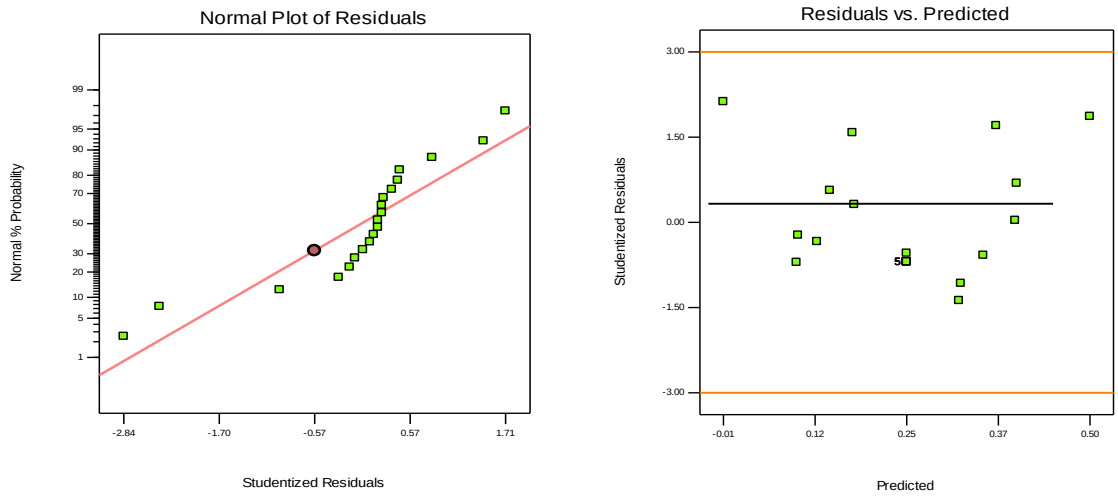
A) **B)**

Fig 3.7: Normal probability plot of residuals for hardness (A), and Plots of the residuals versus predicted response for hardness (B).



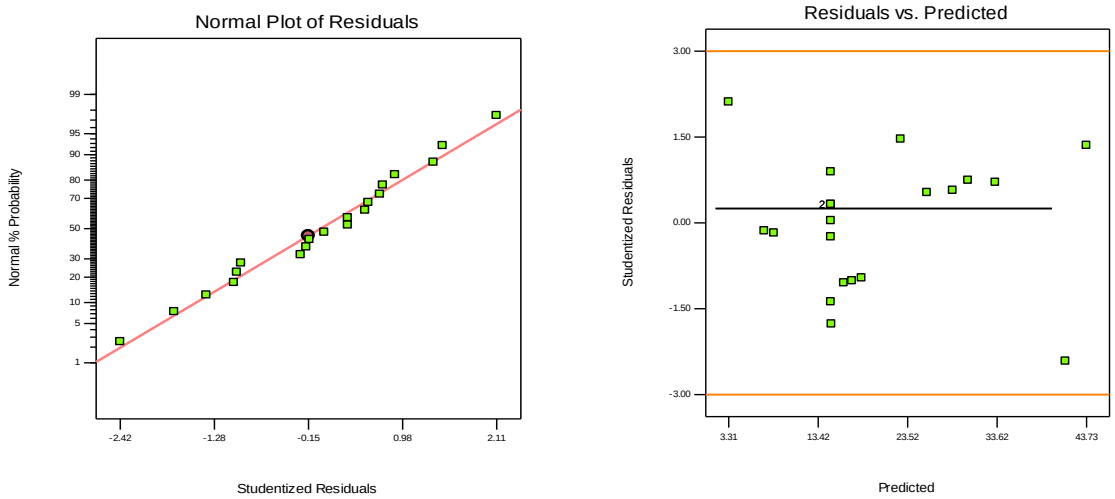
A) **B)**

Fig 3.8: Normal probability plot of residuals for friability (A), and Plots of the residuals versus predicted response for friability (B).



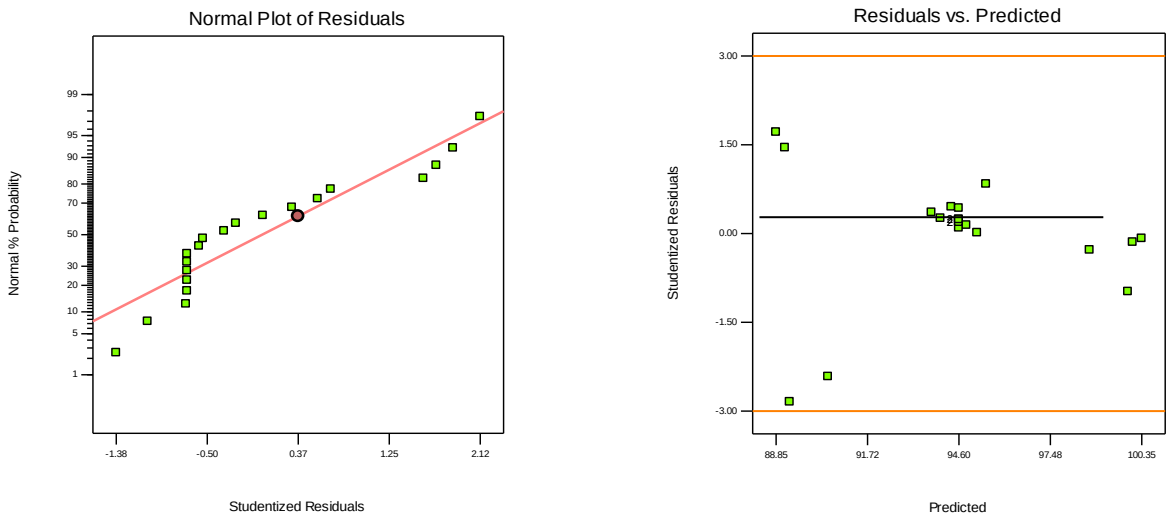
A) B)

Fig 3.9: Normal probability plot of residuals for wetting time (A), Plots of the residuals versus predicted response for wetting time (B).



A) **B)**

Fig 3.10: A: Normal probability plot of residuals for disintegration time (A), and Plotsof the residuals versus predicted response for disintegration time (B).



A) **B)**

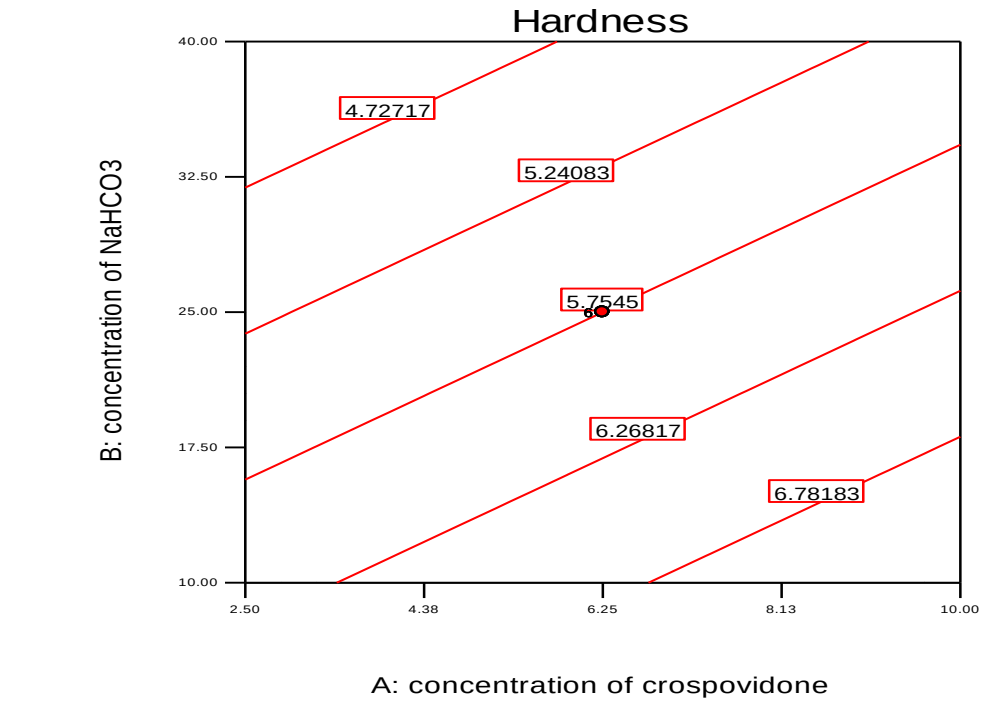
Fig 3.11: Normal probability plot of residuals for cumulative drug release at 30min (A), and Plots of the residuals versus predicted response for cumulative drug release at 30min (B).

Based on the data analysis of the two plots related to residuals, the models were found adequate and therefore, the models were used for further analysis.

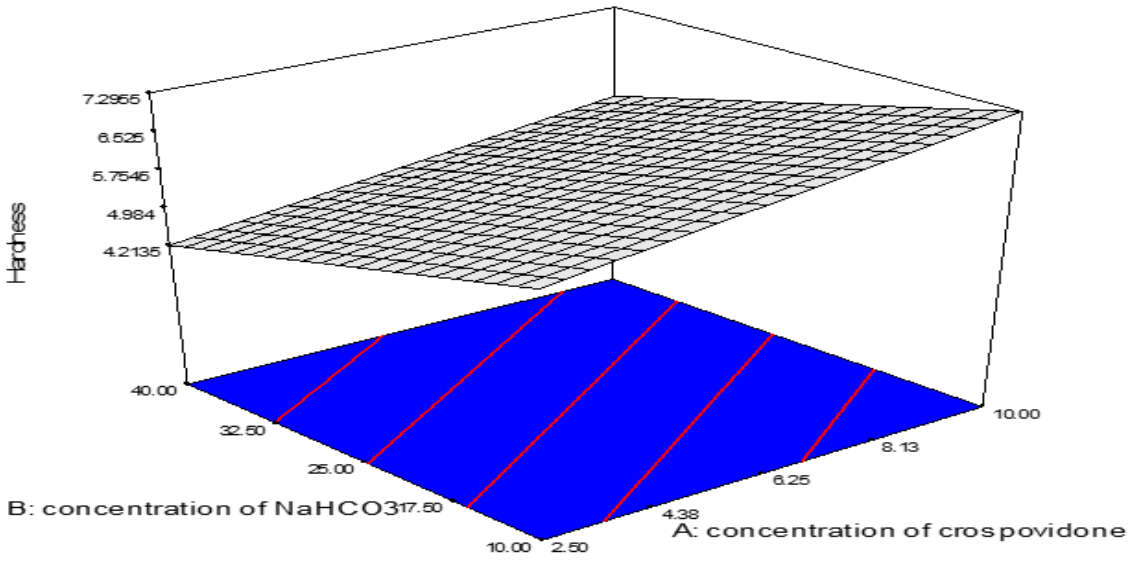
3.4.6. Contour and surface response analysis

In order to studythe main and the interaction effect of factors, three-dimensional response surface plots, as a function of two factors at a time by maintaining all other factors constant, is commonly used(Madgulkar*et al*., 2009). Equivalent to that, contour plots, denoted by the projection of the response surfaces in the x–y plane, provide a direct determination of the effects of the independent variables on responses (Liu*et al*., 2010). In the analysis,figures were selectedbased on significant factors that were specified in the mathematical models. Figures 3.12 A and B show the combined effect of crospovidone, sodium bicarbonate and compression forceon tablet hardness. Both surface response plot and contour plot indicate thatcrospovidone, sodium bicarbonate and compression force play very significant roles in impactingtablet hardness, although the effect of compression force seemed to be slightly higher as compared to the effect ofcrospovidone and sodium bicarbonate. Moreover, a straight diagonal parallel lines on the contour plots show, there is no synergistic effect rather

only main effect of the independent factors on hardness of a tablet. This is also confirmed by the coefficients of linear mathematical model of hardness(Eq.3.1).

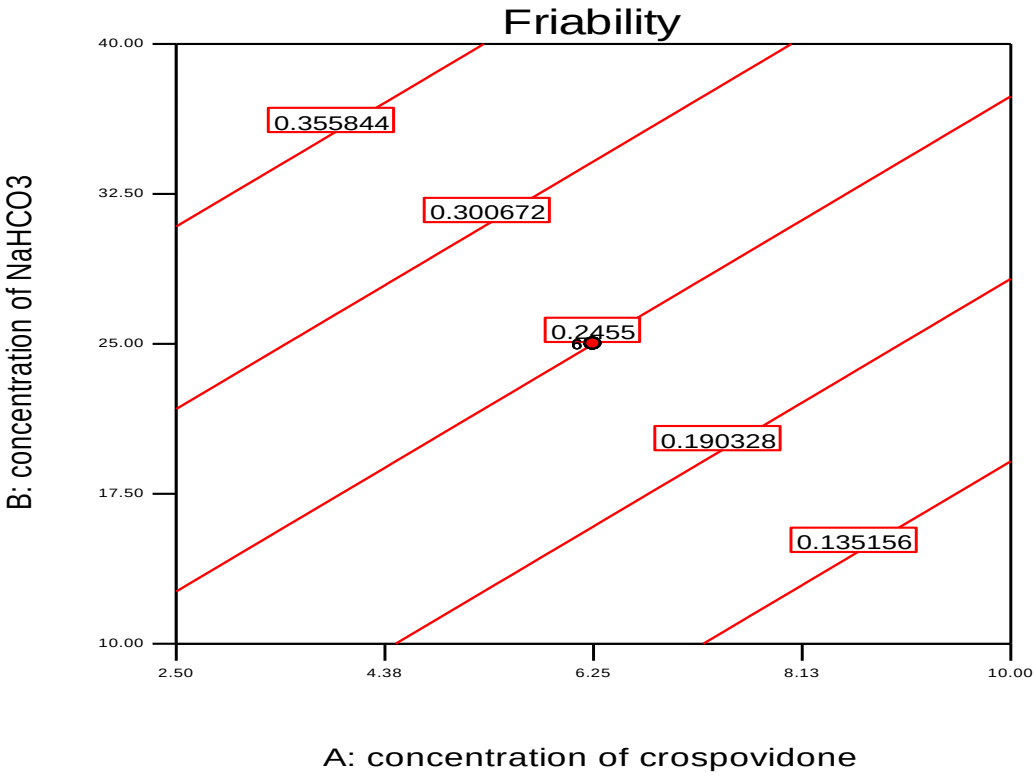


A)

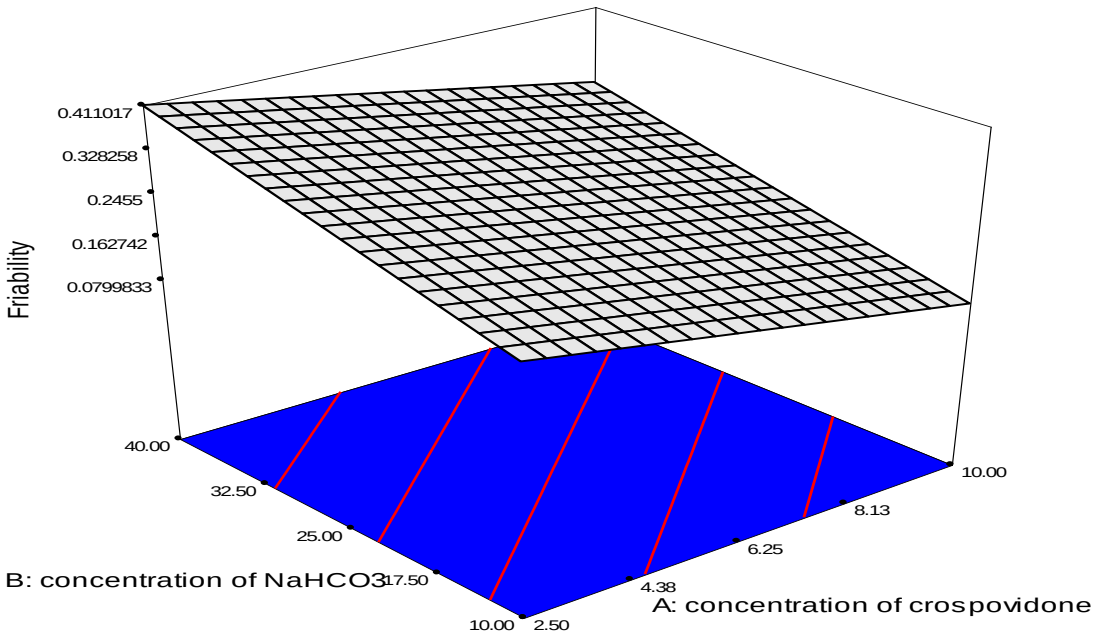


B)

Fig 3.12: Contour plot (A) and Surface response plot (B) of hardness as a function of crospovidone and sodium bicarbonate.



A)

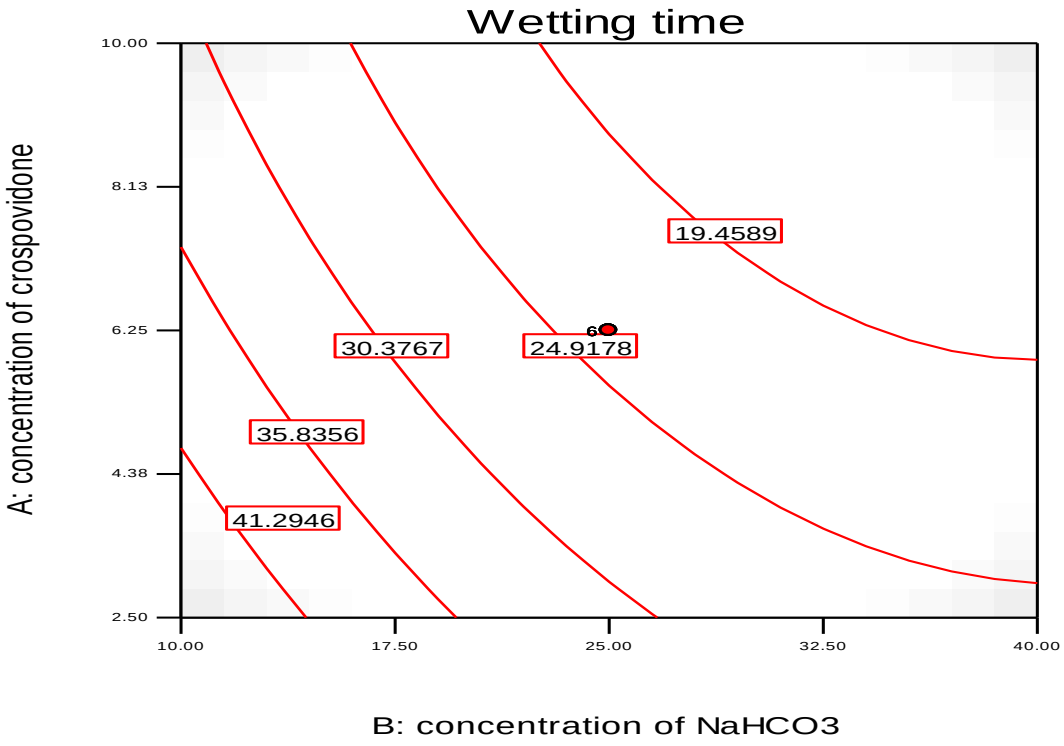


B)

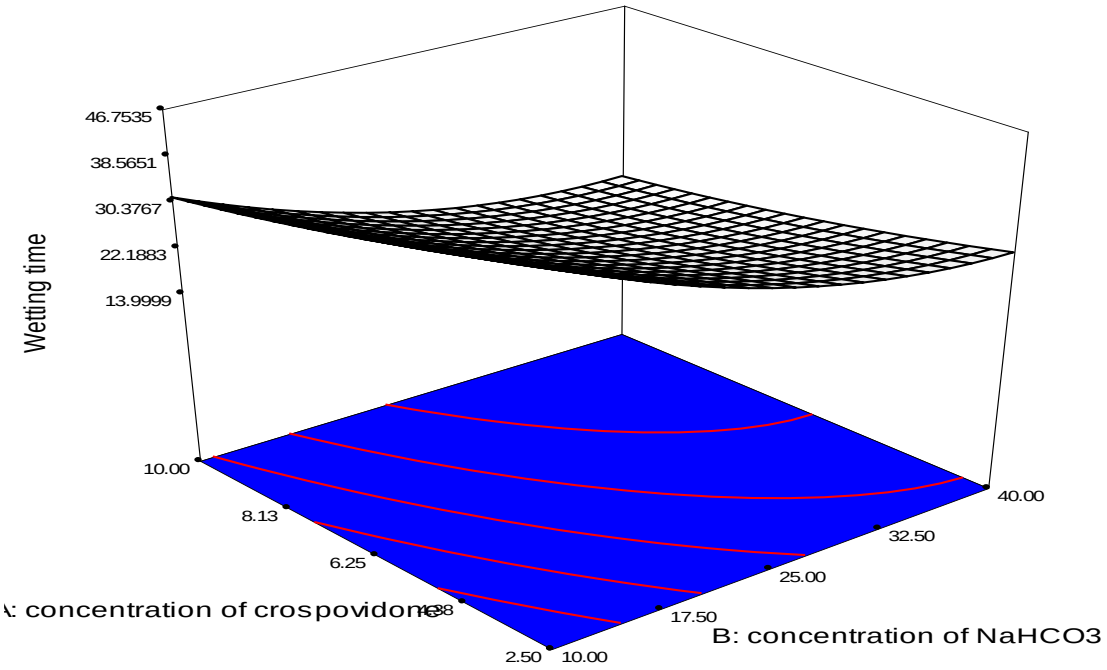
Fig3.13: Contour plot (A) and Surface response plot (B) of friability as a function of crospovidone and sodium bicarbonate

Figures 3.13 A and B depict the combined effects of crospovidone, sodium bicarbonate and compression force on tablet friability.Both surface response plot and contour plot indicate, crospovidone, sodium bicarbonate and compression force imparts a very significant role in influencingtablet friability. However, the effect of compression force and sodium bicarbonate were more significanton tablet friability than crospovidone, Moreover, a straight parallel diagonal lines on the contour plot indicate, there is no synergistic effect of factors on tablet friability, which is alsoconfirmed by the coefficients of linear mathematical model of friability(Eq.3.2).

The contour and response surface plots shown in Figures 3.14A and B depict the significant effect of the combination of crospovidone and sodium bicarbonate, and quadratic effect of sodium bicarbonateon the time required to wet tablets.In comparison, the effect of sodium bicarbonate appeared to be more pronounced than the effect ofthe other variables, besides, the slightly curved diagonal lines on the contour plot and slightly twisted response surface plots shown in the figures were due to a slightly quadratic effect of effervescent agents on tablet wetting time.These analysis were also confirmed by the coefficients of quadratic model for wetting time in (Eq.3.3).

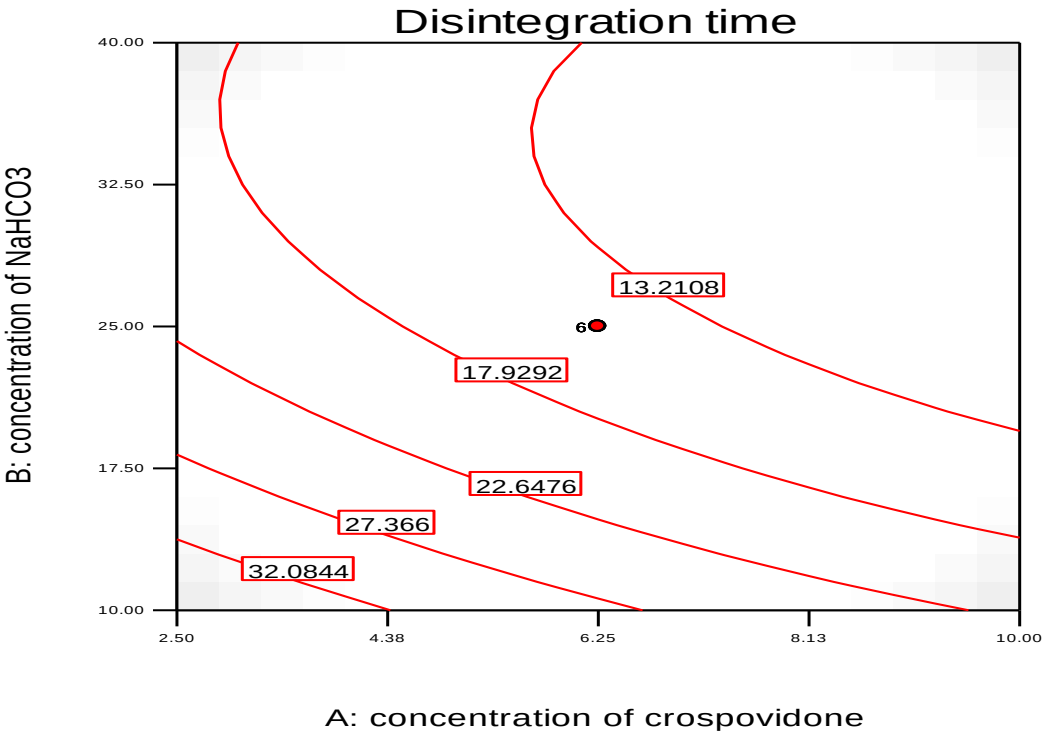


A)

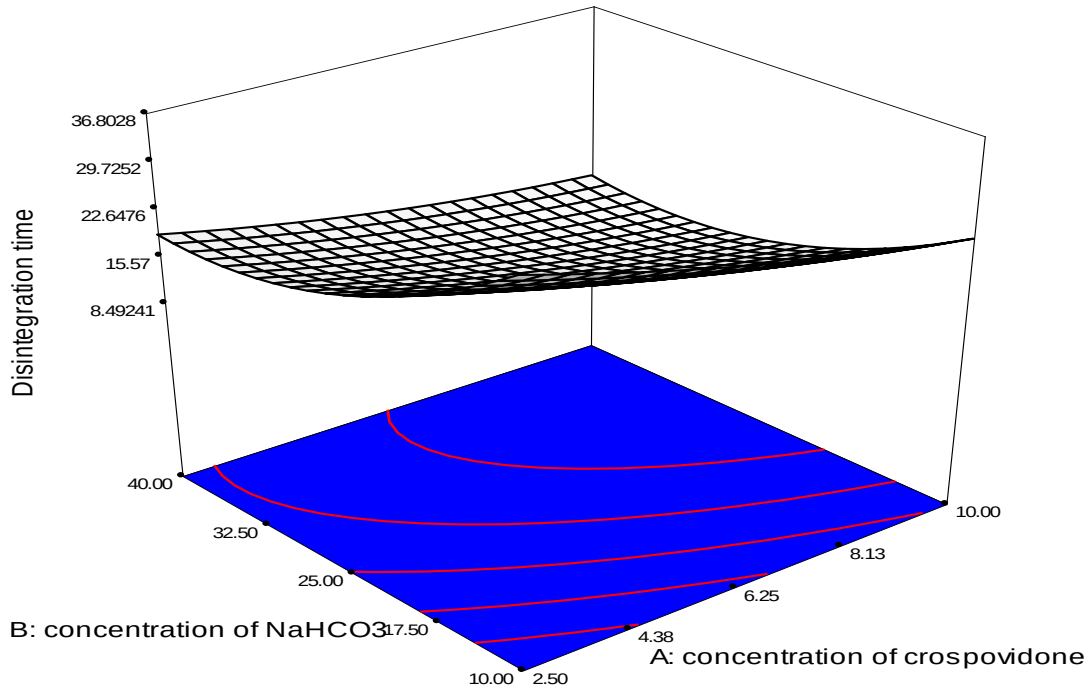


B)

Fig3.14: Contour plot (A) and Surface response plot (B) of wetting time as a function of crospovidone and sodium bicarbonate



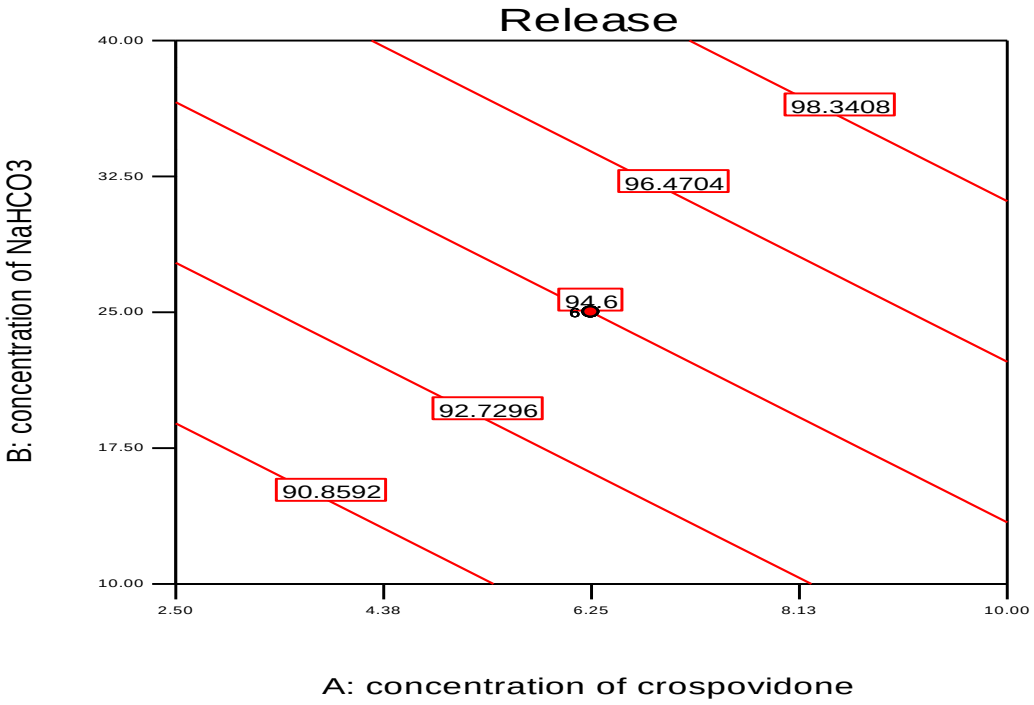
A)



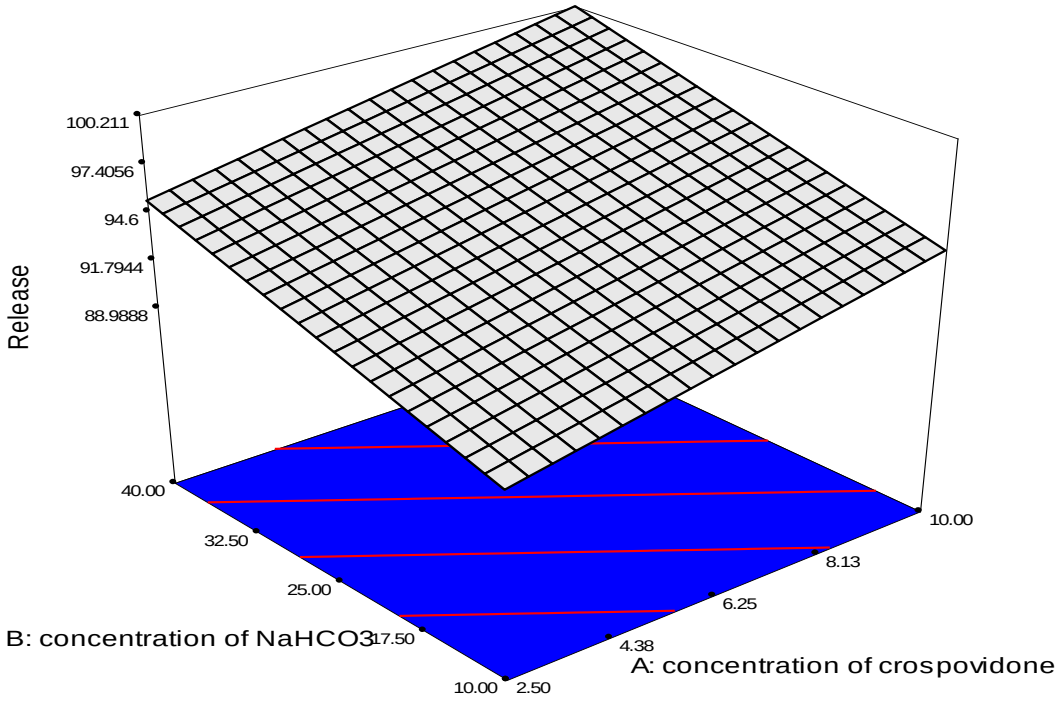
B)

Fig3.15: Contour plot (A) and Surface response plot (B) of disintegration time as a function of crospovidone and sodium bicarbonate.

The contour and response surface plots in Fig.3.15A and B show that combination of crospovidone and sodium bicarbonate,and quadratic effect of sodium bicarbonate play very significant roles on tablet disintegration time. The effect of sodium bicarbonate appeared to be more pronounced than the effect of the other significant factors. The slightly curved diagonal lines on the contour plot and slightly twisted response surface plots in Fig 3.15 was due to a slight quadratic effect of an effervescent agent on the disintegration time of a tablet. This analysis was also confirmed by the coefficients of quadratic mathematical models for tablet disintegration time inEq.3.4.

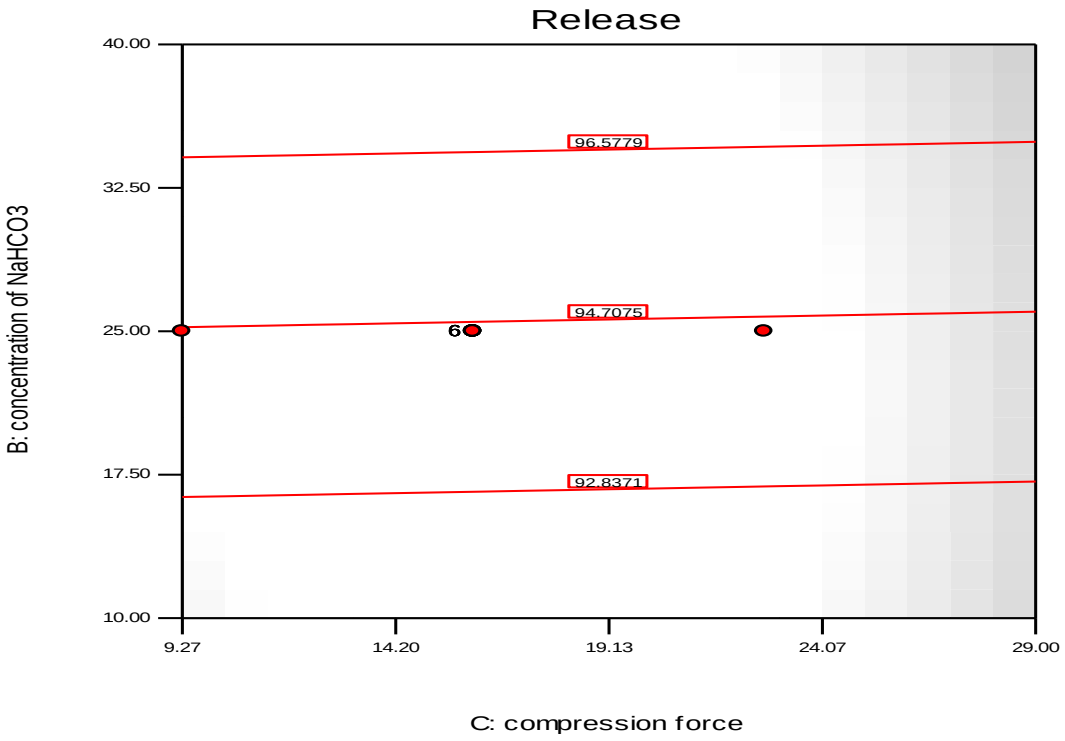


A)

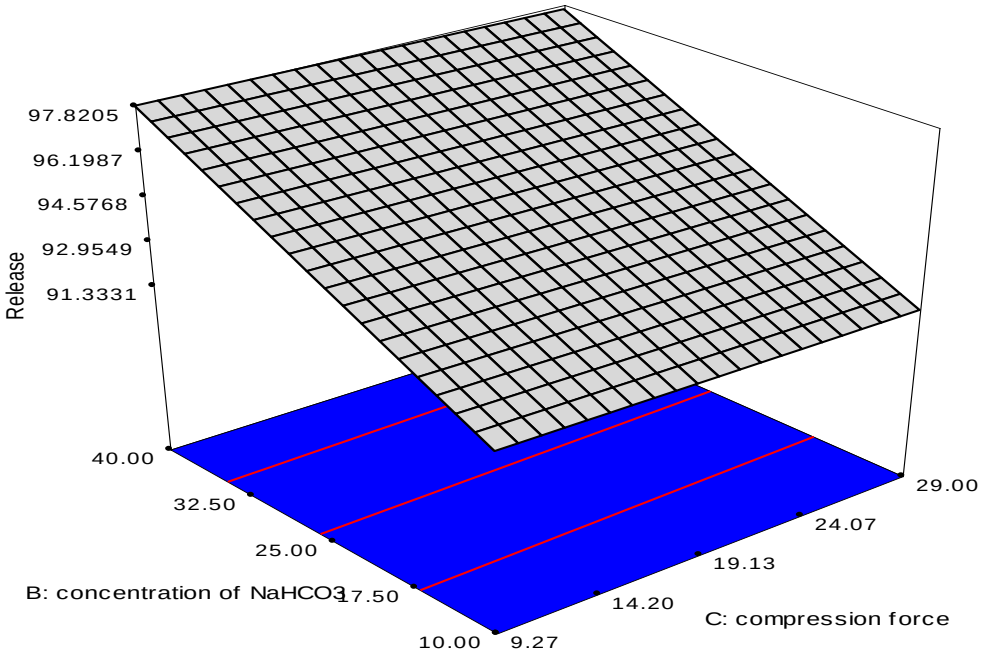


B)

Fig3.16: Contour plot (A) and Surface response plot (B) of cumulative drug release at 30 min as a function of crospovidone and sodium bicarbonate.



A)



B)

Fig3.17: Contour plot (A) and Surface response plot (B) of cumulative drug releaseat 30min as a function of compression force and sodium bicarbonate.

The effect of crospovidone and sodium bicarbonate play a very pronounced role on the cumulative release of drug within 30 min, as shown in Fig. 3.16(A and B), contour plot and response surface plots, respectively. The effect of sodium bicarbonate appeared to be more significant than the effect ofcrospovidone. Accordingly, the straight parallel diagonal lines on the contour and non-twisted response surface plots suggest that, there is no interaction effect of variables on the release of the drug at 30min,revealing the effect is only from the main effect of crospovidone and sodium bicarbonate. However, contour plot and response surface plot in Fig. 3.17 A and B show a series of horizontal parallel straight lines and non-twisted response surface plots, which reveal that compression forcedoesn´t, have significant effect on cumulative release of drug within 30 min. Thus, the two factors which significantly affect % drug release after 30 min were crospovidone and sodium bicarbonate.This analysis was also confirmed by the equation of linear mathematical model for ODT cumulative drug release within 30 min(Eq.3.5).

3.5. Simultaneous Optimization

Following formulation, evaluation and establishing of mathematical regression models for the experimental design formulations, to relate the independent variables with the selected responses, formulation optimization was done, which allowed to simultaneously find a formulation that demonstrates desired properties of responses, by setting factor ranges to the actual levels and the "target" at maximum values for hardness, friability, wetting time, disintegration time and cumulative drug release at 30min. The lower limit and the upper limit were set as in (Table 3.12) to get the desirability equation. Equal emphasis to upper or lower bounds were given for each response with a weight of 1 where desirability (di) was varied from 0 to 1 in linear fashion and all responses were given medium setting of importance level as compared to one another (Khayet *et al*., 2010). The final optimal experimental parameters were obtained by using both numerical and graphical optimization techniques of Design-Expert® 8.0.6 software.

3.5.1. Numerical optimization

A numerical optimization technique, focusing on the desirability approach, was used to create the optimum settings for the desired formulation. The design of the process was done to optimize the five desired dependent variables. For that purpose, the new optimized

formulation dependent variable limits and the range of three independent factors areshown in Table 3.12.

Table 3.12**:** Criterion setting of factors and responses for the optimization of GLM ODTs.

Variables	**Goal**	**Lower limit**	**Upper limit**	**Lower weight**	**Upper weight**	**Importance**
Crospovidone(mg)	Range	2.5	10	1	1	3
Sodium Bicarbonate(mg)	Range	10	40	1	1	3
Compression force(KN)	Range	12	20	1	1	3
Hardness(kg/cm^2)	Range	5	8	1	1	3
Friability (%)	Range	0	0.5	1	1	3
Wetting time (sec)	Range	0	20	1	1	3
Disintegration time (sec)	Range	0	10	1	1	3
Cumulative drug release at 30min (%)	Range	90	100	1	1	3

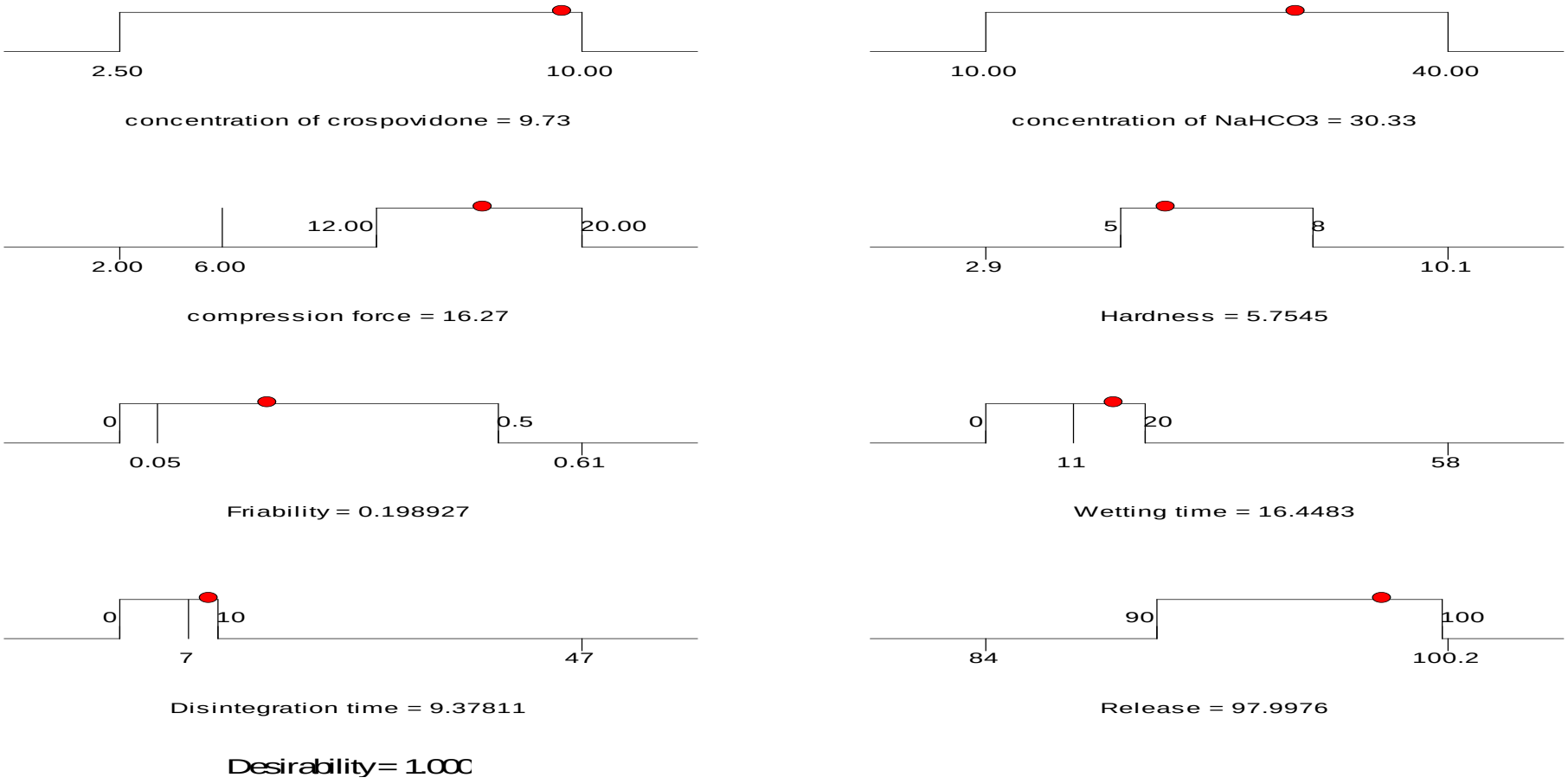


Fig3.18: Desirability ramp for numerical optimization of eight goals: concentration of crospovidone, concentration of sodiumbicarbonate, compression force, hardness, friability, wetting time, disintegration time &cumulative release within 30 min.

In optimization of multiple responses by using desirability approach, individual desirability functions indicate measures of how well the goals for each response are fulfilled, whereas overall desirability function is a measure of how well the combined goals for all responses are satisfied. Desirability function ranges from 0 to 1, with a value near to 1 representing a higher satisfaction of response goals (Yang *et al*., 2008, Ranjan*et al*., 2012). In this study, the values of individual desirability functions of hardness, friability,wetting time, disintegration time and cumulative drug release within 30 min were found to be 1.00 for all responses from the Design-Expert solver, as calculated from the optimal point obtained (H = 5.75, F = 0.199, WT = 16.45, DT = 9.37 and R% = 97.99), respectively. Therefore, fully desired responses were realized for all responses. The overall desirability function (D) was then obtained from the individual desirability functions and found to be 1.00 from the software solver calculated based on Equation 3.6.

$$D=[d_1^{p1}\, d_2^{p2}\, d_3^{p3}\ldots di^{pi}]^{1/\sum pi} \quad \text{Eq.3.6}$$

Where i is the number of responses, di the individual desirability functions and pi is the relative importance of i^{th} response as compared to the others. Importance (pi) varies from 1 to 5, from least to most important, respectively. Fig. 3.19and Fig.3.20, show contour view and 3D plot of the overall desirability function ‘’D’’ for the (concentration of crospovidone (A) and concentration of sodium bicarbonate (B).

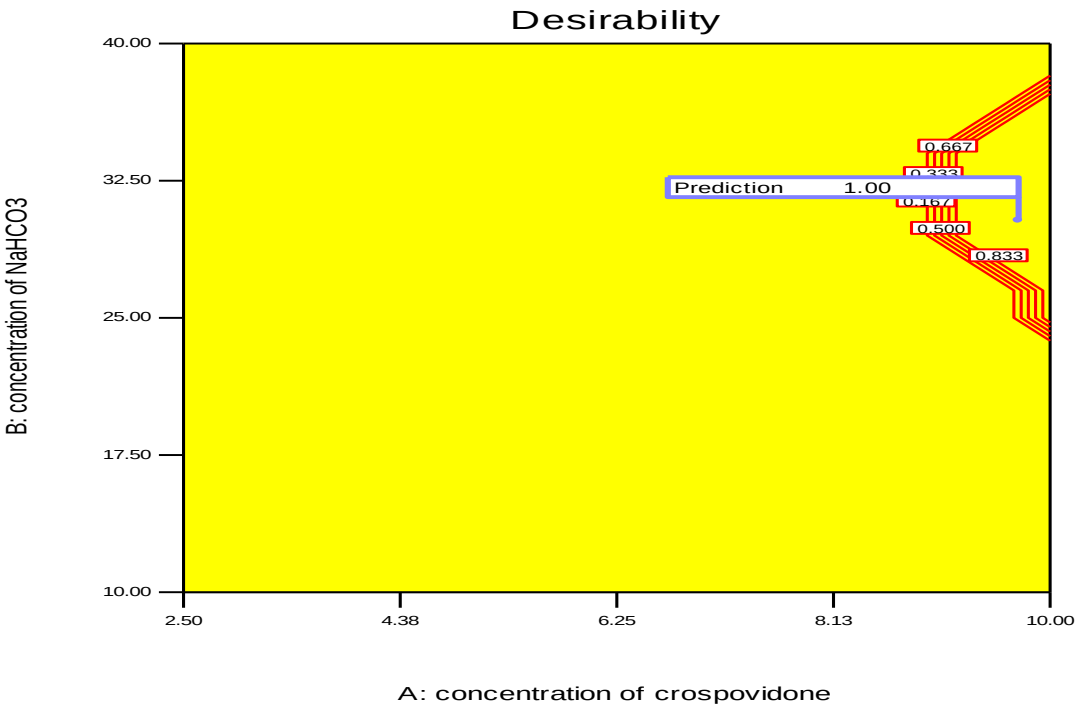


Fig 3.19: Contour view of the most desirable operating conditions for crospovidone and Sodium bicarbonate.

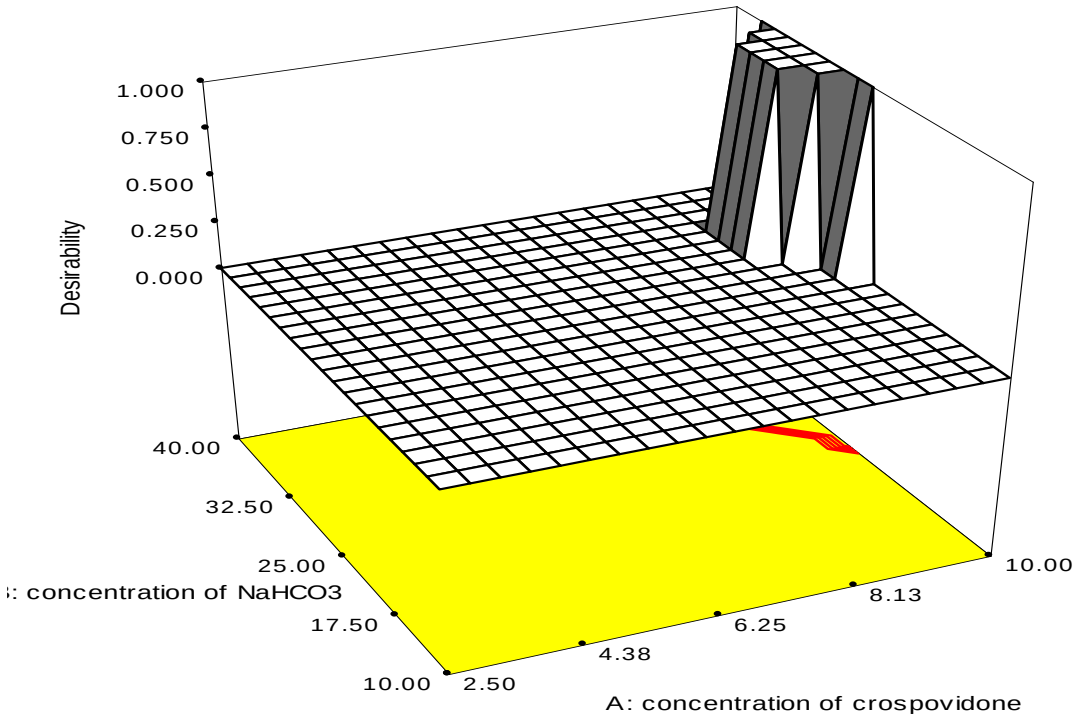


Fig3.20: 3Dview of the most desirable operating conditions for crospovidone and sodium bicarbonate.

3.5.2. Graphical Optimization

The software was also used to optimize the process graphically to see a broader operating window, with the same requirements as in the numerical optimization. It produced the "overlay" plot of response and contours for each response shaded out regions not meeting the specifications, leaving an operating window or "sweet spot" (coloured) where the factors were set to satisfy the requirements on all the five responses. Fig.3.21 shows the overlay plot in which the yellow area represents the area complying the imposed criteria, which was plotted using concentration of crospovidone and sodium bicarbonate. The area identified by yellow colour was preferred as representative of the optimized area corresponding to 9.73 mg of crospovidone, 30.33 mg of sodium bicarbonate and 16.27 KN compression force. With these conditions, the model predicts 5.75kg/cm^{2}hardness, 0.199% friability, 16.45 sec wetting time, 9.37sec disintegration time and 97.99% cumulative drug release in 30 min.

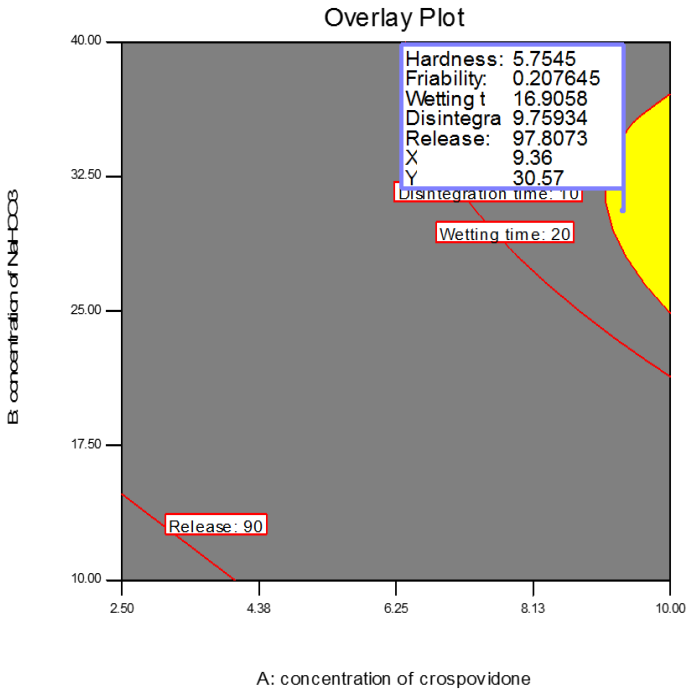


Fig 3.21: Optimum region identified by overlaying plots of the five responses asafunctionof crospovidone and sodium bicarbonate

3.5.3. Confirmation test

Confirmation experiments were conducted in a triplicate at the optimal combinations of the independent factors (A= 9.73mg, B = 30.33mg and C = 16.27KN) to confirm the validity of achieved optimal points during optimization. ODT of GLMwas prepared based on the optimization formulation and the compressed tablets were evaluated for hardness, friability, wetting time, disintegration time and cumulative drug release at 30 min. As shown in Table 3.13, the predicted values and experimental results were in agreement and the percentage error values obtained at optimal levels of the factors were within 5%, confirming that the experimental values of the optimized formulations agreed with the predicted values.

Table 3.13: The value of optimized formulation predicted responses, experimental responses and percentage error.

Response	**Predicted value**	**Experimental value**	**% Error**
Hardness (kg/cm^2)	5.75	5.51	4.35
Friability (%)	0.199	0.207	3.86
Wetting time (sec)	16.45	16.00	2.81
Disintegration time (sec)	9.37	9.00	4.11
Cumulative drug release at 30min (%)	97.99	99.60	1.62

3.6. Characterization of optimized formulation physical blend

AspresentedinTable 3.14, the optimized formulation's granule showed the angleofrepose of 26.60 ± 1.40°,Hausner ratio of 1.20 ± 0.10 andcompressibilityindex of 16.67 ± 1.13%.The bulkdensityandtappeddensityofthepreparedgranuleswere0.50 ± 0.01g/cm^3 and0.60 ± 0.02g/cm^3, respectively.Theresultsofthe angleofreposeindicateexcellentflowpropertyofthegranule andthevaluesofcompressibilityindex and Hausner ratiofurthersupportsexcellentflowproperty of direct compressible optimized ODT.

Table 3.14: characterization of DC optimized ODT formulation granules

Parameters	**Experimental values ± SD**
Bulk density (g/cm^3)	0.50 ± 0.01
Tapped density (g/cm^3)	0.60 ± 0.02
Angle of repose(^{0})	26.60 ± 1.40
Car's index (%)	16.67 ± 1.13
Hausner ratio	1.20 ± 0.10

3.7. Comparative studyof drug release profile

Comparison of the *in vitro*drug release profile of the optimized GLM ODT and conventional GLM (Daonil®)5mg tablets were studied for their similarity and difference factors. Fig.3.22 showsthe 60 min drug release profile of optimized ODT and marketed immediate release tabletof GLM (Daonil®) using dissolution media pH 7.4 phosphate buffer, where significant difference in the release profile with a difference factor (f_1) and similarity factor (f_2) value of 73.25% and 9.01%, respectively, was observed. The results of the 60 min releasestudy of GLMfrom the optimized GLM ODT formulationreveal muchhigher release than the marketed GLM(Daonil®).

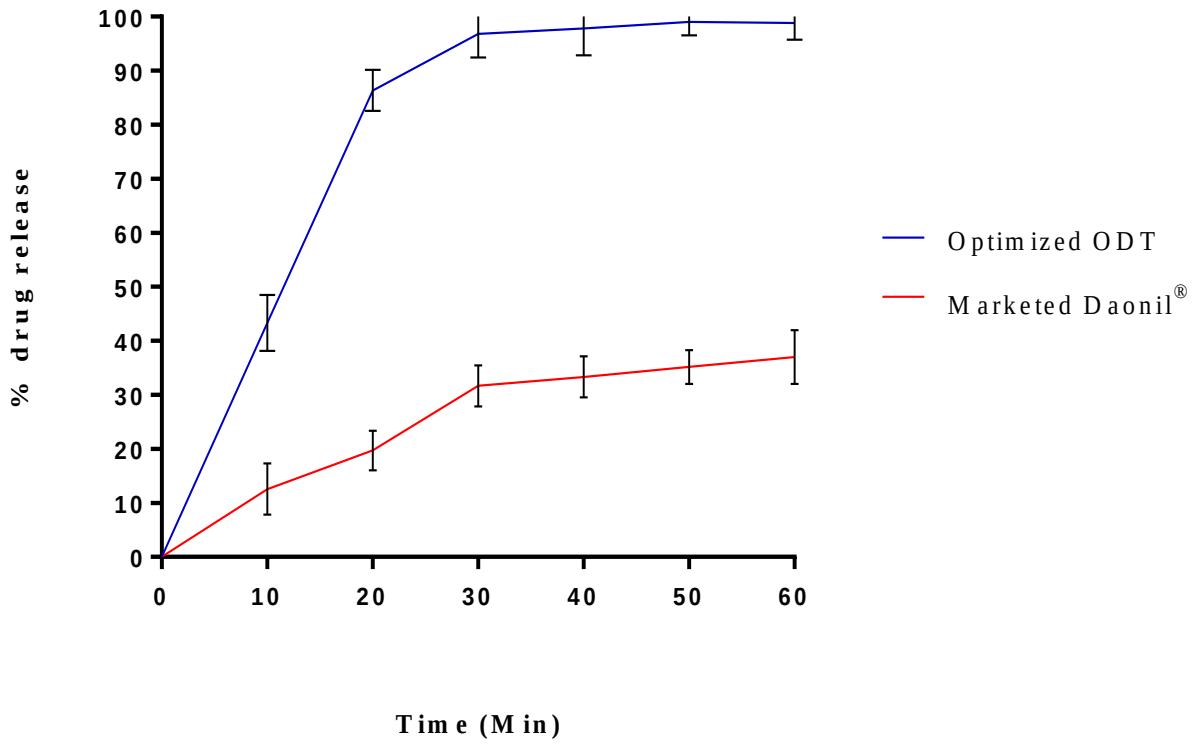


Fig3.22: Drug release profile of optimized GLM ODTs compared with Daonil® tablet 5mg

4. Conclusion

ODT of GLM has beenprepared by DC method using crospovidone and effervescent agent and evaluated for the release profile. The resultsindicated that both formulation variables (concentration of crospovidone and effervescent agent) have significant impacton the responses of the ODT, such as hardness, friability, wetting time, disintegration time and cumulative drug release at 30min.However, the cumulative drug release of glibenclamide orodispersible tablet at 30 min was not significantly influenced with an increase in compression force. CCD of the RSM was employed to find an optimum formulation with acceptable hardness and friability, rapid wetting time, and rapid disintegration time and enhanced cumulative drug release. The desired optimum condition was obtained at 9.73 mg crospovidone, 30.33 mg sodium bicarbonate and at 16.27KN compression force. With these optimum conditions, the experimental results of hardness, friability, wetting time,and disintegration time and percentage cumulative drug release at 30minwere 5.51 Kg/cm^2, 0.207%, 16 sec, 9 sec and 99.60%, respectively. The experimental responses were found to be in close agreement with the predicted values and validity of the optimized formulation was confirmed by less than 5% prediction errors. Comparison of drug release between the optimized ODT and conventional marketed tablet Daonil® showed drug release from ODT was higher than Daonil®. In conclusion, the results showed that GLM ODTs having an adequate crushing strength and exhibiting faster disintegration and enhanced dissolution can be successfully prepared by using a combination of a superdisintegrant and effervescent agentthrough the application of CCD in optimizing formulation variables.

5. Suggestions for further work

In order to scale-up and ultimately produce GLM ODTs in large scale it is suggested that the following additional investigations be conducted.

- *In vivo* drug bioavailability studies;
- *In vivo* and *in vitro* correlation of drug release; and
- Accelerated and real time stability studies,

6. References

Adeleye, O.A., Femi-Oyewo, M.N. and Odeniyi M.A. (2015). Effect of compression pressure on mechanical and release properties of tramadol matrix tablets. Curr. Issues Pharm. Med. Sci. 28, 120-125

Aguilar-Díaz, J. E., García-Montoya, E., Sune-Negre, J. M., Pérez-Lozano, P., Miñarro, M. and Tico, J. (2012). Predicting orally disintegrating tablets formulations of ibuprophen tablets: application of the new sedem-ODT expert system. Eur. J. Pharm. Biopharm. 80, 638-648.

Badgujar, B. P. and Mundada, A.S. (2011). The technologies used for developing orally disintegrating tablets: A review. Acta Pharm. 61, 117-139.

Bari, N., Alam, Z., Muyibi, S.A., Jamal, P. & Abdullah-Al-Mamun (2010). Statistical optimization of process parameters for the production of citric acid from oil palm empty fruit bunches. *Afr. J. Biotechnol* 9**,** 554-563.

Bassam M., Zubaida S. and Al-Qashi. (2004). In vitro and in vivo evaluation of glibenclamide in solid dispersion system. Drug Dev &Ind Pharm. 30, 601-607

Bircan, Y. and Comoglu, T. (2012). Formulation technologies of orally fast disintegrating tablets, Marmara Pharm J. 16, 77- 81

Bi, Y., Sunada H., Yonezawa Y., Danjo K. and Iida K. (1996). Preparation and evaluation of compressed tablets rapidly disintegrating in the oral cavity. Chem Pharm Bull . 44, 2121-2127.

Brniak, W., Maślak, E. and Jachowicz, R. (2015). Orodispersible films and tablets with prednisolone microparticles Original Research Article, Eur J Pharm Sci 75, 81-90.

BP (2009). British Pharmacopoeia: The Pharmaceutical Press, her Majesty's stationery office, London, vol. I−VI.

Chakraborty, P., Dey, S., Parcha, V., Bhattacharya, S.S. and Ghosh, A. (2013). Design expert supported mathematical optimization and predictability study of buccoadhesive pharmaceutical wafers of loratadine. BioMed Res Int, doi

:10.1155/2013/197398.
Available at http://www.ncbi.nlm.nih.gov/pubmed/23781498.

Chang R.K., Guo X., Burnside B.A. and Couch R.A. (2000). Fast dissolving tablets Pharm Tech. 24, 52 - 58.

Chellan, V.R. and Sekar, V. (2008). Immediate release tablets of telmisartan using superdisintegrant formulation, evaluation and stability studies. Chem Pharm Bull. 56, 575 - 577

Debruyne, F., Gittelman, M., Sperling, H., Börner, M. and Beneke, M. (2011). Time to onset of action of vardenafil: a retrospective analysis of the pivotal trials for the orodispersible and film-coated tablet formulations. J. Sex Med 8, 2912-2923.

Desai, S., Poddar, A. and Sawant, K. (2016). Formulation of cyclodextrin inclusion complex-based orally disintegrating tablet of eslicarbazepine acetate for improved oral bioavailability. Mater Sci Eng C. 58, 826-834.

Divate, S., Kavitha, K. and Sockan, G. (2011). Fast disintegrating tablets an emerging trend. Int J Pharm Sci Rev Res. 6, 18–22.

Elkhodairy, K. A., Hassan, M. A. and Afifi, S. A. (2014). Formulation and optimization of orodispersible tablets of flutamide. Saudi Pharm J. 22, 53-61.

El-Sakhawy, M., & Hassan, M. L. (2007). Physical and mechanical properties of micro-crystalline cellulose prepared from agricultural residues. Carbohydrate Polymers, 67, 1–10.

Fu, Y., Jeong, S. H. and Park, K. (2005). Fast-melting tablets based on highly plastic granules. J Control Release. 109, 203-210.

Fu, Y., Yang, S., Jeong, S.H., Kimura, S. and Park, K. (2004). Orally fast disintegrating tablets: Developments, technologies, taste masking and clinical studies. Crit Rev Ther Drug Carrier Syst. 21, 433 – 476.

Garud, S., Derle, D., Valavi, A., Shaikh, S. and Derle, N. (2014). A review on: orodispersible tablet technology a novel approach to develop the supergenerics. Int J Pharm Sci Rev Res. 40, 231–236.

Gianotto, E., Arantes, R., Lara-Filho, M., Saraiva, A., Filho, C. and Fregonezi-Nery, M. (2007). Dissolution test for glibenclamide tablets. Quim Nova. 30, 1218–1221.

Giordano, P., Martínez, H., Iglesias, A., Beccaria, A. and Goicoechea, H. (2010). Application of response surface methodology and artificial neural networks for optimization of recombinant oryzasativa non-symbiotic hemoglobin production by escherichia coli in medium containing by product glycerol. Bio resource Technol. 101, 7537 - 7544.

Goel, H., Vora, N. and Rana, V. (2008). A novel approach to optimize and formulate fast disintegrating tablets for nausea and vomiting. AAPS Pharm Sci Tech, 9, 774-781.

Gohel, M. C. (2005). A review of co-processed directly compressible excipients. J Pharm Pharmaceut Sci. 8, 76-93.

Gohel, M. C., Parikh, R. K., Brahmbhatt. B. K. and Shah A. R. (2007). Preparation and assessment of novel coprocessed superdisintegrant consisting of crospovidone and sodium starch glycolate. AAPS Pharm Sci Tech. 8, Article 9.

Groop L., Wahlin B., E,Totterman K.J., Melander A., Tolppanen E.M. and Fyhrqvist F. (1985). Pharmacokinetics and metabolic effects of glibenclamide and glipizide in type 2 diabetes. Eur J Clin Pharmacol. 28, 697 - 704.

Hirani, J.J., Rathod, D.A. and Vadalia K.R. (2009). Orally disintegrating tablets: A review. Tropical J Pharma Res. 8, 161-172

Ibrahim, H., Rai, P.P. and Bangudu, A. B. (1991). Evaluation of mucilage from thestem bark of cissus populnea. Afri. J. of Pharm. Sci. 22, 35

Jacob, S., Shirwaikarb, A. and Nairc, A. (2009). Preparation and evaluation of fast disintegrating effervescent tablets of glibenclamide. Drug Dev. Ind. Pharm. 35, 321-328.

Kaushik, D., Dureja, H. and Saini, T. R. (2004). Formulation and evaluation of olanzapine mouth dissolving tablets by effervescent formulation approach. Indian Drugs. 41, 410-412.

Khan, K.A. and Rhodes, C. (1976). Effect of variation in compaction force on properties of six direct compression tablet formulations. J. Pharm. Sci.65, 1835–1837

Khayet, M., Seman, M. and Hilal, N. (2010). Response surface modeling and optimization of Compositenanofiltration modified membranes. J. Membrane Sci. 349, 113 - 122.

Kuchekar B., Atul S., Badhan C. and Mahajan, H.S. (2003). Mouth Dissolving Tablets: A novel drug Delivery system, Int. J App. Bio.Pharma Tech. 35, 7 - 9

Kundu,S. and Sahoo, P.K. (2008). Recent trends in the developments of orally disintegrating tablet technology. Pharma Times. 40, 11- 15.

Kusic, H., Jovic, M., Kos, N., Koprivanac, N. and Marin, V. (2010). The comparison of photooxidation processes for the minimization of organic load of colored waste water applying the response surface methodology. *J. Hazard. Mater.*183**:** 189 - 202.

Liu, Y., Zheng, Y. and Wang, A. (2010). Response surface methodology for optimizing adsorption process parameters for methylene blue removal by a hydrogel composite. Adso. Sci. Tec. 28, 913-922.

Madgulkar, A.R., Bhalekar, M.R. and Padalkar, R.R. (2009). Formulation design and optimization of novel taste masked mouth dissolving tablets of tramadol having adequate mechanical strength. AAPS Pharm Sci Tech. 10, 574-581.

Mishra, D.N., Bimodal, M., Singh, S.K. and Vijaya Kumar, S.G. (2006). Spray dried excipient base: a novel technique for the formulation of orally disintegrating tablets. *Chem Pharm Bull* 54, 99 -102.

Mohanachandran, P., Sindhumol, P. and Kiran, T. (2011). Superdisintegrants: An overview. Int. J. Pharm. Sci. Rev. Res. 6, 105–109.

Moore, J.W. and Flanner, H.H. (1996). Mathematical comparison of dissolution profiles. Pharm. Technol. 20, 64 - 74.

Pabari, R. M. and Ramtoola, Z. (2012). Application of face centred central composite design to optimise compression force and tablet diameter for the formulation of

mechanically strong and fast disintegrating orodispersible tablets. Int J Pharm. 430, 18-25.

Parakh S.R. and Gothoskar A.V. (2003). A review of mouth dissolving tablet technologies. *Pharm Tech* 27, 92 - 98.

Parthiban, K.G., Nagarjun, K. and Kumar N. (2011). Study of the impact of mode of incorporation of superdisintegrants in the dissolution of oral dosage forms. Int. J. Pharm. Res. Dev. 5, 70 - 76.

Rahman, Z., Zidan, A. S. and Khan, M. A. (2010). Risperidone solid dispersion for orally disintegrating tablet: Its formulation design and non-destructive methods of evaluation. Int J Pharm. 400, 49-58.

Ranjan, A. P., Mukerjee, A., Helson, L. and Vishwanatha, J. K. (2012). Scale up,optimization and stability analysis of Curcumin C3 complex-loaded nanoparticles for cancer therapy. J. Nano. biotech. 10, 1-18.

Rajan, K.V. and Sanjay, G. (2001). Current status of drug delivery technologies & future directions. Pharmaceutical technology online. 25, 1-14.

Sallam, E., Ibrahim, H., Abu, D. R., Shubair, M. and Khalil, E. (1998). Evaluation of fast disintegrants in terfenadine tablets containing a gas evolving disintegrant. Drug Dev Ind Pharm. 24, 501-507.

Santos, J.V., Batista, A.E. and Pina, M.E. (2010). The influence of the compressionforce on zidovudinerelease from matrix tablets. AAPSPharmSci. Tech. 11, 1442.

Schiermeier, S. and Schmidt, P. C. (2002). Fast dispersible ibuprofen tablets. Eur. J. Pharm. Sci. 15, 295-305.

Schwinghammer ,T.L., Antal, E.J., Kubacka, R.T., Hackimer, M.E. and Johnston J.M. (1991). Pharmacokinetics and pharmacodynamics of glyburide in young and elderly nondiabetic adults. Clin Pharm.10, 532-538

Seager, H. (1998). Drug delivery products and the zydis fast dissolving dosage forms. J Pharm Pharmacol. 50, 375-382.

Shirsand, S. B., Suresh, S., Para, M. S. and Swamy, P. V. (2009). Design of fast disintegrating tablets of prochlorperazine maleate by effervescence method, Indian J Pharm Sci. 71, 447–451.

Shukla, D., Chakraborty, S., Singh S., Mishra, B. (2009). Mouth dissolving tablets I: An overview of formulation technology. *Sci Pharm.* 77, 309–26.

Shu, T., Suzuki, H., Hironaka, K., Ito, K. (2002). Studies of rapidly disintegrating tablets in the oral cavity using co-grinding mixtures of mannitol with crospovidone. Chem. Pharm. Bull. 50, 193-198.

Singh, K., Gupta, S., Singh, A. and Sinha, S. (2010). Experimental design and response surface modeling for optimization of rhodamine B removal from water by magnetic nanocomposite. Chem. Eng. J. 165, 151-160.

Slavkova, M. and Breitkreutz J. (2015). Orodispersible drug formulations for children and elderly. Review Article. Eur. J. Pharm Sci. 75, 2-9.

Sreenivas, S. A, Dandagi, P. M., Gadad, A. P., Godbole, A. M., Hiremath, S. P. and Mastiholimath, V. S. (2005). Orodispersible tablets: New-fangled drug delivery system A review. Indian J Pharma Edu Res. 39, 177-181.

Swamy P.A., Areefulla S.H., Shrisand S.B., Gandra S. and Prashanth B. (2007). Orodispersible tablets of meloxicam using superdisitegrant blends for improved efficiency, Ind J Pharm Sci. 69, 836 - 840.

Swamy, P. V., Divate, S. P., Shirsand, S. B. and Rajendra, P. (2009). Preparation and evaluation of orodispersible tablets of pheniramine maleate by effervescent method. Indian J Pharm Sci. 71, 151-154.

Takayama, K., Fujikawa, M., Obata, Y. and Morishita M. (2003). Neural network based optimization of drug formulations. Adv Drug Deliver. 55, 1217 - 1231.

Tashtouch, B.M., Al-Qashi, Z.S. and Najib, N.M. (2004). In vitro and in vivo evaluation of glibenclamide in solid dispersion systems. Drug Dev. Ind. Pharm. 30, 601–607.

Virally, M., Blicklé, J.F., Girard, J., Halimi, S., Simon, D. and Guillausseau, P.J. (2007). Review Type 2 diabetes mellitus: epidemiology, pathophysiology, unmet needs and therapeutical perspectives. Diabetes & Metabolism .33, 231– 244

Wei, H. and Lobenberg, R. L. (2006). Bio relevant dissolution media as a predictive tool for glyburide: a class II drug. Eur J Pharm Sci. 19, 45-62.

Yang, K. and El-Haik, B. (2008). Design for Six Sigma: a Roadmap for Product Development. 2nd ed. McGraw-Hill Co. Inc., New York. Pp. 611 - 642.

Yourong, F,u., Shicheng Y., Seong H.J., Susumu, K. and Kinam P. (2004). Orally fast disintegrating tablets: developments, technologies, Taste masking and clinical studies. Crit Rev Ther Drug Carrier Syst. 21, 433 – 475

Zerrouk, N., Corti, G., Ancillotti, S., Maestrelli, F., Cirri, M. and Mura P. (2006). Influence of cyclodextrins and chitosan, separately or incombination, on glyburide solubility and permeability. Eur J Pharm Biopharm. 62, 241-246.

Zgoda M. M., Nachajski, M. J. and Kołodziejczyk M. K. (2009). Microcrystalline cellulose and their flow morphological properties modifications as an effective excipients in tablet formulation technology containing lattice established API and also dry plant extract. Polim Med. 39, 17-30.

Zhao, N. and Augsburger, L. L. (2005). The influence of swelling capacity of superdisintegrants in different pH media on the dissolution of hydrochlorothiazide from directly compressed tablets. AAPS Pharm. Sci. Tech. 6, E120-E126

Declaration

I, the undersigned, declare that this is my original work and has not been presented for a degree in any university

Name: Solomon Bayu

Signature: _____

This thesis has been submitted for examination with our approval as a university advisor.

Prof. Tsige Gebre-Mariam

Signature: _____

Dr. Anteneh Belete

Signature: _____

Place and date of submission: Addis Ababa, Ethiopia, December. 2016