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FORMULATION, OPTIMIZATION AND *IN VITRO* EVALUATION OF FAST DISINTEGRATING TABLETS OF SALBUTAMOL SULPHATE

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A thesis submitted to Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in partial fulfillment of the requirements for the Degree of Masters of Science in Pharmaceutics

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This is to certify that the thesis prepared by Fikadu Ejeta, entitled "*Formulation, Optimization and In Vitro Evaluation of Fast Disintegrating Tablets of Salbutamol Sulphate"* and submitted in partial fulfillment 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 to originality and quality.

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List of acronyms

BP:	British Pharmacopoeia
CCD:	Central Composite Design
CI:	Compressibilty Index
COPD:	Chronic Obstructive Pulmonary Disease
FDTs:	Fast Disintegrating Tablets
FEF:	Forced Expiratory Flow
FEV:	Forced Expiratory Volume
FT-IR:	Fourier Transform Infrared Spectroscopy
FVC:	Forced Vital Capacity
HR:	Hausner's Ratio
JP:	Japan Pharmacopoeia
MCC:	Microcrystalline Cellulose
MNTL:	Mannitol
ODTs:	Orodispersible Tablets
PXRD:	Powder X-Ray Diffraction
Rpm:	Rotations Per Minute
SBS:	Salbutamol Sulphate
USP/NF:	United States Pharmacopoeia / National Formulary
WHO:	World Health Organization

Abstract

Obstructive respiratory disorders include asthma and chronic obstructive pulmonary disorders characterized by airflow limitation. Salbutamol sulphate is widely used drug for the treatment of chronic obstructive airway diseases. Oral administration of SBS is complicated due to sore throat conditions, the patient experiences difficulty in swallowing a conventional tablet dosage form and more difficult to use inhalation devices effectively owing to advanced age and the presence of other comorbidities. Moreover, aerosol drug delivery needs inhalation technique and difficulty of swallowing conventional tablet dosage forms decreases patient compliance. This study provides FDTs of SBS formulation with lower disintegration times and good mechanical strength for an immediate release with rapid onset of action and better patient acceptance.

Formulation factors affecting the response variables (ammonium bicarbonate, crospovidone and microcrystalline cellulose to mannitol ratio (MCC/MNTL) were selected based on literature review and preliminary studies. Consequently, the levels of ammonium bicarbonate (subliming agent), levels of crospovidone (superdisintegrant) and MCC/MNTL (direct compression diluents) were considered. Ammonium bicarbonate level was fixed at 5% because of its esthetic impacts on tablets physical appearance. Central composite design was employed as study design to study and optimize the effect of formulation variables (concentration of crospovidone and MCC/MNTL) on tablet disintegration time, friability, hardness and wetting time. Accordingly, FDTs of SBS were prepared by sublimation technique with incorporation of superdisintegrant; and characterized for different tablet properties. Formulation (F6) containing 9.24% crospovidone, 1.25:1 MCC/MNTL and 5% ammonium bicarbonate showed the shortest disintegration time (12 ± 1.53 sec) and lowest wetting time (11 ± 1.00 sec) and; formulation (F8) containing 5% crospovidone, 2.31 : 1 MCC/MNTL and 5% ammonium bicarbonate had the largest crushing strength (7.88kg/cm^2) and lowest friability (0.17%). These properties could be due to the disintegrant and binding properties of crospovidone and MCC respectively. All of the formulations released 75% of the label claim within 20 min.

Accordingly, ANOVA and lack of fit test obtained by Design-Expert illustrated that selected independent variables had significant effect on the response variables and excellent correlation were observed between actual and predicted values. Simultaneous optimization of the responses with desired attributes indicated disintegration time 14.2 sec, hardness 7kg/cm^2 , friability 0.30

and wetting time 13.2 sec at 7.82% crospovidone and 1.56: 1 MCC/MNTL (at 70%) as optimum formulation. The validity of an optimum formulation was further confirmed by the low magnitude of percent prediction error.

The optimized formulation was characterized for powder properties, tablets physicochemical properties and tablets morphology. The study showed that free flowing powder, robust prediction (between the actual and predicted values) and porous tablets. FDTs of SBS with lower DTs and good mechanical strength which is suitable for patients with obstructive respiratory disorders was successfully developed.

Key words: salbutamol sulphate, sublimation technique, superdisintegrant, fast disintegrating tablets, optimization, central composite design

1. Introduction

1.1. Obstructive Respiratory disorders

Obstructive respiratory disorders are characterized by airflow limitation (Harrison, 2005; Dipro, 2011; & Nakpheng *et al*., 2016). Airflow obstruction is induced by multiple mechanisms including airway inflammations, airway epithelial dysfunction, and disturbance of the autonomic nervous system (; Matsumoto *et al*., 2013). The obstructive respiratory pattern is the hallmark decrease in expiratory flow rates. With fully established disease, the ratio of forced expiratory volume in 1s (FEV1)/ forced vital capacity (FVC) is decreased, as is the forced expiratory flow by (FEF) 25–75%. These obstructive respiratory disorders include Asthma and Chronic obstructive pulmonary disease (Harrison, 2005). Chronic inflammatory disorder is correlated with allergy, airway inflammation, increased airflow resistance, and airway hyper-responsiveness which lead to airflow limitation (Wang *et al*., 2015). Chronic obstructive pulmonary disease (COPD) a disease state characterized by airflow limitation that is not fully reversible (Macintyre, 2006).

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The inflammation also causes an associated increase in the existing bronchial hyper-responsiveness to a variety of stimuli (Pawankar *et al*., 2011). Asthma is a serious public health problem throughout the world, affecting people of all ages (Wang *et al*., 2015). According to World Health Organization (WHO) estimates, 235 million people in the world currently suffer from asthma, with over 50% of the adult cases and over 80 % of the infant cases caused by house dust mite (WHO, 2007). Approximately 250,000 people die prematurely each year from asthma; almost all these deaths are avoidable (Pawankar *et al*., 2011).

Chronic obstructive pulmonary disease (COPD) includes emphysema, which is characterized by destruction and enlargement of the lung alveoli; chronic bronchitis, a clinically defined condition with chronic cough and phlegm; and small airways disease, a condition in which small bronchioles are narrowed (Harrison, 2005). COPD is also a disease of increasing public health importance around the world (Wang *et al*., 2015). The natural history of COPD depends heavily upon the continued exposure to tobacco smoke. Specifically, in COPD patients who continue to smoke, the rate of decline in forced expiratory volume in the first second (FEV1) is several times faster than in those who quit smoking and those without COPD (Macintyre, 2006). According to

Global Initiative for COPD estimate, COPD will rise from the sixth to the third most common cause of death worldwide by 2020 (Pauwels, 2001). There are no medications that reverse COPD, and COPD therapy is generally aimed at alleviating symptoms, improving function, and reducing exacerbations and hospitalizations (Macintyre, 2006).

Obstructive respiratory disorders are common and have significant worldwide health impact (Harrison, 2005). While there is no cure, with combined efforts in environmental controls to minimize exposure to allergens and irritants, appropriate pharmacologic therapy, and patient and healthcare provider education, the disease can be successfully managed to reduce morbidity, mortality, and financial costs (Viegi, 2010). The preferred treatment is symptomatic therapy such as salbutamol which is efficacious and cost effective. They are the mainstay of the control strategy launched by World Health Organization (WHO). The WHO has identified salbutamol as an essential drug, based upon its clinical efficacy and low cost (Lindenberg *et al*., 2004). Multiple dosing of various conventional dosage forms in a day with repeated administration leads to tolerance to its bronchodilator effect (Malakar *et al*., 2014).

With regard to the appropriateness of a solid oral dosage form, age-dependency of swallowability has to be taken into account. Before 5 months of age, an extrusion reflex enables the infants to swallow only liquids. However, at the age of 6 months, they can physiologically and anatomically swallow multiparticulates in soft food or beverages, depending on size, shape and hardness of the particles (Bowles *et al*., 2010). Fear of risk of aspiration and choking when administering solids in children younger than 7 years old; and unable to swallow solids are among the reasons that limit the use of marketed solid dosage forms in children. The type of formulation, as well as the requirement of chewing or not, has an impact on the age at which children are able to swallow. FDTs are accepted to younger children than dosage forms having to be directly swallowed, i.e. tablets and capsules (Walch *et al*., 2016). Hence, a dosage form, which disintegrates rapidly and smoothly in the oral cavity within a small amount of saliva, might be a suitable dosage form even for infants and toddlers (Stoltenberg and Breitkreutz, 2011).

Conventional oral solid dosage forms are not ideal for patients with dysphagia. Many studies estimated that 35% of the general population, 30 - 40% of elderly nursing home patients and elderly institutionalized patients, 18 - 22% of all persons in long-term care facilities and 25- 50%

of patients hospitalized for acute neuromuscular disorders and head injuries, have dysphagia (ElMeshad and Hagrasy, 2011). In general, it can be more difficult for patients with COPD to use inhalation devices effectively compared with other populations owing to advanced age and the presence of other comorbidities (Harrison, 2005). Due to sore throat conditions, the patient experiences difficulty in swallowing a conventional tablet dosage form.

Manufacturers have developed liquid formulations for commonly used pediatric products and for patients in acute setting or adherence problems. They are not free of problems and often unstable and have short expiration dates. Accurate measurement and administration of prescribed dose is also a problem (Florence and Seipman, 2009; Perioli *et al*., 2011).

Regarding aerosol dosage forms (aerosol inhaler, nebulizers and powder for inhalation); only 10 to 20% of the dose reaches the lungs to act directly on smooth muscle, the remainder stays in the mouth, stomach or on the apparatus. Besides children younger than 5 years of age receive a lower lung dose and adults dosed on a weight basis demonstrate excessive cardiac stimulation; so fixed maximal dose is required (Harrison, 2005). The international ban on the production and use of chlorofluorocarbons (major component of such dosage form) has resulted in the ongoing development of new delivery method for active medication. Appropriate inhalation technique is essential to achieve optimal drug delivery and therapeutic effect. Dry powder for inhalations once exhaled causes loss of dose and moistening of the dry powder, causes aggregation into larger particles (Dipro, 2011). These types of dosage forms need skills and provision of written action plans as an essential component of care (National Asthma Education and Prevention Program guideline, 1997). Tolerance to both the bronchoprotective effect and bronchodilator activity occurs with all inhaled β_2-agonists (Cazzola *et al*., 2013).

SBS exhibits site-specific absorption in the stomach and upper parts of the small intestine (Swarbrick, 2007). Drug absorption requires molecules be in solution at the absorption site (Lachmann *et al*., 1990). Conventional tablets may pass the site of absorption until disintegration and dissolution takes place which results in reduced bioavailability. FDTs may increase the opportunity to be absorbed because they appear as a solution at the site of absorption. This can lead to improved bioavailability of drugs, especially those with limited absorption sites in the small intestine (Shargel, 2004; Swarbrick, 2007).

Even though the oral administration of salbutamol and other short acting ß$_2$ agonists have been used in the past to provide a more prolonged duration of action; this approach is being supplanted by the use of ß$_2$ agonists that have long duration of action when administered by inhalation. The initial therapy for COPD patients who experience symptoms intermittently are short-acting bronchodilators (Dipro, 2011). As salbutamol is subjected to 1st pass hepatic biotransformation (Nakpheng *et al*., 2016), saturation of the enzyme occurs when the drug concentration is high. As a result, the rate process then becomes a zero-order process. This could improve bioavailability of the drug as all the enzyme molecules become complexed with drug, free drug could escape metabolism (Shargel, 2005). The bioavailability of drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first-pass metabolism is reduced as compared to conventional tablet (Tagaro *et al*., 2004).

For these reasons the developments of FDTs have recently interested not only the pharmaceutical industry, but also academia. Actually FDTs are preferred by an increasing number of patients especially children and elderly, but also adult consumers who like to have their medication readily available at any time. Patients appreciate the convenience and the discreteness of these products which can be taken without water and which guarantee a rapid onset of action (Abdelbary *et al*., 2004). As long as dispersion is rapid, bioavailability of drug can be significantly greater than those observed from conventional tablet dosage forms (Teran and Flament, 2016).

Preliminary experiments indicated that variables such as concentration of ammonium bicarbonate, concentration of Crospovidone and MCC/MNTL were factors which affect the various responses such as disintegration time, friability and tablet hardness.

Disintegration and solubilisation of directly compressed tablets depend on single or combined action of disintegrants and water-soluble excipients. The pH is unlikely to affect crospovidone functionality, as it is a nonionic polymer. Consequently, crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–8% concentration in tablets prepared by direct-compression methods (Rowe *et al*., 2009). Crospovidone is the disintegrant of choice for fastest disintegration, shortest wetting time, enhanced rate of drug dissolution and robust tablets

(Schiermeier and Schmidt, 2002). Crospovdone swells without forming gels that can slow tablet disintegration or dissolution. But, other superdisintegrants form gels when fully hydrated, particularly at high use concentrations required in some formulations to achieve desired tablet disintegration or drug dissolution (Mizumoto *et al*., 2005; Abed *et al.*, 2010; USP 36/ NF 31, 2013).

Ammonium bicarbonate is chemically inert and, when subjected to high temperature and low pressure, sublime due to its' volatile nature resulting in highly porous structure in the tablets. It is used as porous forming agent at 2.5-20% concentration in tablets. The superiority of ammonium bicarbonate is attributed to its solid, crystalline nature. The residual fractions of liquid volatile materials in tablets after sublimation undergo solidification and contribute as binders, while ammonium bicarbonate in residual concentration does not undergo such change and therefore does not have any significant impact on the mechanical properties of tablets (Mishra and Rohera, 2016).

High porosity is the main factor controlling fast disintegration of FDTs while excipient compactability being the factor responsible for mechanical strength. Binder/disintegrant systems which offer dual advantages have partly addressed both the requirements. MNTL has pleasant mouth feel and sweetening characteristics. Conversely, MCC provides better mechanical properties for FDTs than mannitol. The development of FDTs requires more than just good binding properties in an excipient (Al-khattawi & Mohammed, 2015). Amalgamation of cellulose and polyol-based excipients such as MNTL are required for developing FDTs (Al-khattawi & Mohammed, 2013).

Aspartame (artificial sweetener) is non-carcinogenic and can be consumed by diabetic patients. It is much more intense sweetener compared to other sweetening agents; with acceptable daily intake of 50mg/kg. Vanillin flavor is natural flavor which supplement and complement the sweetening agent (Walsh *et al*., 2014).

Colloidal silicon dioxide and magnesium stearate were employed as flow promoter and lubricant, respectively. Maize starch was used as filler.

1.2. Salbutamol sulphate

Salbutamol is β-Phenylethylamine, the parent compound of the sympathomimetic amines, consists of a benzene ring and an ethylamine side chain. In the salt, It exists as Bis [(1*RS*)-2-[(1,1-dimethylethyl) amino]-1-[4-hydroxy-3- (hydroxymethyl) phenyl] ethanol] sulfate (BP, 2013). SBS, a β_2-selective agonist, has a substituent at position 3 (Goodman and Gilmann, 2006). It relaxes airway smooth muscle and inhibits release of bronchoconstricting mediators from mast cells (Matsumoto *et al*., 2013). It may also inhibit microvascular leakage and increase mucociliary transport by increasing ciliary activity (Katzung, 2006).

1.2.1. Physicochemical properties of SBS

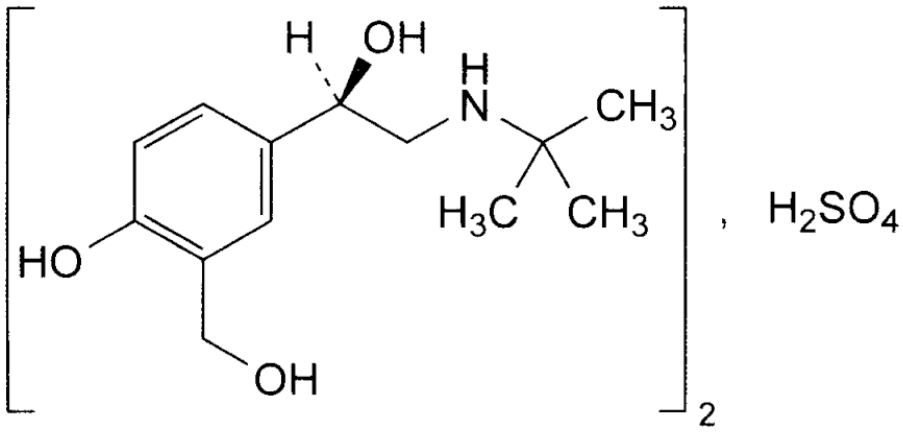


Figure 1.1: Structural formula of SBS

SBS has a molecular weight of 576.7 with a structural formula $C_{13}H_{21}NO_3.½\ H_2SO_4$. It is a white, odorless powder, slightly bitter in taste with a melting point of 150 ^{0}C; soluble in four parts of water; slightly soluble in ethanol 96%, chloroform and ether; contains not less than 90% and not more than 110% of $C_{13}H_{21}NO_3.½\ H_2SO_4$ calculated with reference to the dried substance (USP 36-NF31, 2013; BP, 2013).

Normally, salbutamol is used in the form of its racemate in a 1:1 ratio. The (R) - salbutamol is the active enantiomer, while the (S)-salbutamol causes airway hypersensitivity that leads to bronchoconstriction in animal models studies (Nakpheng *et al*., 2016). However, evidence that this occurs consistently in humans or is clinically relevant is lacking (Dipro, 2011). It is found in syrup, aerosol, injection, and tablet dosage forms (Katzung, 2006).

1.2.2. Pharmacodynamic properties

SBS is short-acting β_2 adrenergic receptor agonist. It is one of the widely used drugs for the treatment of bronchial asthma, chronic bronchitis and obstructive airway diseases (Katzung, 2006). It primarily binds to $ß_2$- receptors at the synapse with very little binding to $ß_1$-receptors. Salbutamol has an advantage of minimizing side effects associated β_1 receptor stimulation (Goodmann and Gilmann, 2006). Stimulation of β_2-adrenergic receptor activates cytoplasmic G proteins, which, in turn, activate adenylyl cyclase to produce cyclic adenosine monophosphate (cAMP), generally thought to be responsible for the bulk of activity through activation of various proteins by cAMP-dependent protein kinase A. This activation, in turn, decreases unbound intracellular calcium, producing smooth muscle relaxation, mast cell membrane stabilization, and skeletal muscle stimulation (Matsumoto *et al*., 2013). It is first line recommended therapy as initial management of Asthma (both intermittent and persistent) and COPD alone or in combination in the form of tablet, 2-4 mg 2-4 times a day which causes poor patient compliance (Harrison, 2005; Dipro, 2011).

1.2.3. Pharmacokinetic properties

When administered orally salbutamol is absorbed and distributed by blood circulation with a bioavailability of about 50% (Morgan *et al*., 1982; Nakpheng*et al*., 2016). Peak plasma concentrations of salbutamol occur at 1.0-4.0 h after the dose with negligible plasma protein binding (Morgan *et al*., 1982). Its bronchodilation effect lasts for 4-8 h with bronchoprotection (prevention of bronchoconstriction induced by exercise or nonspecific bronchial challenges) for 2-4 h (Dipro, 2011).

The oral dosage form faces the problem of 1st pass hepatic biotransformation which decreases bioavailability of the drug. Biotransformation of salbutamol occurs in the liver by the phenylsulfotransferase enzyme. When salbutamol is conjugated with the sulfatase enzyme, 4'-O-sulfate salbutamol is produced and this has higher water solubility. Salbutamol is also actively eliminated by renal excretion in both its conjugated and parent forms (Morgan *et al*., 1982; Nakpheng*et al*., 2016). The elimination half-life of salbutamol is within 4-6 h (Malakar *et al*., 2014) with relatively high apparent volume of distribution indicating extensive extravascular distribution as salbutamol belongs to biopharmaceutics classification systems class I i.e. high solubility and high permeability (Morgan *et al*., 1982; Lindenberg *et al*., 2004).

1.3. Fast disintegrating tablets

Enormous and increasing costs, with estimates from $150 million to $900 million, are involved in the research and development of a single new drug that reaches the market. Because of the economic investment required and the need to efficiently access multiple technologies, it is efficient (significant clinical as well as financial value) to optimize the existing drugs for reasons of potency, selectivity, drug metabolism, and dosing convenience before the drug reaches the market (Katzung, 2006) led to the emergence of FDTs.

Fast dissolving drug delivery system is novel drug delivery system and a patient-oriented pharmaceutical preparation which aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form which disintegrate or dissolve in a few seconds after placement in the mouth (Watanabe *et al.*, 1999, Ibrahim and El-Setouhy, 2010). FDTs are uncoated tablets which disperse rapidly before being swallowed. FDTs have gained popularity among the wide population; because they are easily administered to the geriatrics, pediatrics, patients with poor physiological (patients suffering from mental disorders) and physical abilities (patients suffering from dysphagia); and traveling patients that may not have ready access to water; where swallowing conventional solid oral-dosage forms presents difficulties. As drug dissolves in saliva, it bypasses enterohepatic circulation and prevents first-pass metabolism by undergoing pre-gastric absorption. This improves bioavailability of the drug and reduces dosing frequency and dose-related untoward effects (Rahman *et al.*, 2013).

1.4. Technologies and Formulation Processes for Making FDTs

The FDTs can be prepared using various techniques such as lyophilization, molding and compaction (granulation methods (wet granulation, dry granulation and spray drying), direct compaction (by using super disntegrants) and compaction with subsequent treatments (sublimation)) (Fu *et al*., 2004; Gad, 2008). There are several technologies that produce commercially available FDTs. Zydis® (Cardinal Health, Dublin, Ohio), Orasolv®/Durasolv® (Cima labs, Eden praire, Minnesota) and WOWTAB® (Yamanouchi Pharma technologies, Norman, Ocklahoma) are well known technologies. Although these technologies meet the special requirements for FDTs to some extent, none has all the desired properties. As a result combinations of methods are preferred. Some of the marketed products are Claritin®RediTabs®

(Loratidine), Feldene Melt® (Piroxicam) & Pepsid®ODT® (Famotidine) by Zeydis technology (Lyophilisation process); Propulsid ®QuickSolv® (Cisapride Monohydrate) by QuickSolv® technology (Lyophilisation process); and Benadryl®Fastmelt® (Diphenhydramine citrate), Nasea OD (Ramosetoron HCl) & Gaster D (Famotidine) by WOWTAB® technology (direct compression processes by combinations low and high moldability saccharides) (Fu *et al.*, 2004).

1.4.1. Freeze-drying

Freeze-drying (lyophilization) is a process of removing water from a substance at lower temperatures under controlled conditions through sublimation (Stoltenberg and Breitkreutz, 2011). This technique provides the advantage of processing pharmaceutical substances at lower temperatures, therefore eliminating sensitivity to adverse thermal effects, and allows the solid to be stored in a dry place with relatively fewer stability problems. Lyophilization produces products which disintegrate more rapidly when compared to other available solid dosage forms since the resultant structures are very porous. Additionally, the freeze-drying process results in a glassy amorphous structure of the bulking agents in a formulation, therefore improving its disintegration properties. FDTs manufactured by this method possess poor mechanical strength and need special packaging (Ahmed *et al*., 2013).

1.4.2. Sublimation

This technique involves incorporation of volatile materials such as ammonium bicarbonate, urea, naphthlene and camphor to the other tablet ingredients which are compressed to produce FDTs. The volatile material entrapped within the compressed tablets is removed by a process of sublimation, which results in formation of pores within the formulation (Koizumi *et al*., 1997; Oh *et al*., 2013 and Mishra & Rohera, 2016).

A high porosity while used for the enhancing disintegration rate of FDTs is undesirable for tablet mechanical strength (Fukami *et al*., 2006). Many FDTs are highly porous, and if the formulation parameters are not optimized, the tablets can exhibit higher friability, irrespective of any hardness changes. Thus, in order to produce mechanically hard FDTs without compromising the disintegration time, processed excipients are recommended to be used (Moqbel *et al*., 2016).

1.4.3. Spray drying

Spray drying can be used to prepare FDTs (Corrigan *et al*., 2014). This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredients and compressed into tablets. The formulations are incorporated by hydrolyzed and non-hydrolyzed gelatins as supporting agents, bulking agent, superdisintegrant and an acidic material (e.g., citric acid) and/or alkali material (e.g., sodium bicarbonate) to enhance disintegration and dissolution (Fu *et al*., 2004).

1.4.4. Molding

This technique produces FDTs which are solid dispersions. Moulded tablets are usually prepared from soluble ingredients such as xylitol, lactose, glucose, sorbitol, sucrose and mannitol. The powder blend is moistened with a hydroalcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air drying. Molded tablets are very less compact than compressed tablets. They possess porous structure that enhances dissolution. Unfortunately, moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablets often occurs during tablet handling and when blister pockets are opened with possible limitations in stability (Fu *et al*., 2005).

Moreover, to show some studies done on this area; Suresh *et al* (2007) prepared FDTs of SBS by wet granulation process using sublimeable components viz. camphor and ammonium bicarbonate. These FDTs showed DT of 5 to 40 sec, hardness of 3.4 to 3.8kg/cm^2 and friability of 0.3 to 0.8%. Dineshmohan *et al* (2010) formulated FDTs of SBS using Primojel (sodium starch glycolate), L-Hydroxy propyl cellulose and Kollidon CL as superdisintegrants separately by direct compression method. These FDTs showed DT of 8.85 to 8.93sec, hardness 2.03 to 2.34kg/cm^2, and friability of 0.1130.193%. Rasheed *et al* (2011) developed FDTs of SBS using Indium 414, Croscarmelose and sodium starch glycolate as superdisintegants separately by direct compression. These FDTs showed DT of 26-08 secs, friability 0.86-0.32% and hardness 2.1 to 2.8 kg/cm^2. Nanjawade *et al* (2011) developed FDTs of SBS by wet granulation meyhod using croscarmellose, sodium starch glycolate L-hyroxy propyl cellulose and crospovidone XL-10. These FDTs showed DT 7 to 18 sec, hardness of 4.2 to 4.8 kg/cm2 and friability 0.56 to 0.84%.

Sharma (2013) formulated FDTs of SBS using sodium starch glycolate as superdisintegant by direct compression. These FDTs showed DT 45 sec, friability 0.5 % and hardness 1.5 kg/cm^2. Prasanth *et al* (2013) formulated FDT of SBS using croscarmellose and sodium starch glycolate separately as superdisintegrant by direct compression method. These FDTs showed DT of 22 to 54 sec, hardness 3.09 to 3.55 kg/cm2 and friability 0.31 to 0.698%. Sharma *et al* (2015) formulated FDTs of SBS and citrizine hydrochloride in combined pharmaceutical dosage form by direct compression method using sodium starch glycolate as superdisintegrant. These FDTs showed DT of 45sec, hardness of 1.8kg/cm^{2,} wetting time of 28 sec and friability of 0.3%. Sallam *et al* (2017) developed FDTs of SBS using Acidisol and polyplasdone XL as superdisintegrant separately by direct compression method. These FDTs showed DT of 13 sec.

Thus a combination of sublimation and superdisintegrant was chosen to prepare FDTs of good mechanical strength and lower disintegration times without affecting its attractiveness.

1.5. The present study

The present work attempts to develop and optimize FDTs with lower DTs and good mechanical strength, which releases SBS in the stomach and upper gastrointestinal tract for an immediate release with rapid onset of action that will increase its bioavailability and improves patient compliance.

2. Objectives of the study

2.1. General objective

- To formulate, optimize, and evaluate fast disintegrating tablets of salbutamol sulphate

2.2. Specific objectives

- To formulate and develop FDTs of SBS with lower DTs and good mechanical strength
- To characterize and evaluate the physicochemical properties of FDTs of SBS; and
- To study and optimize the formulation variables of FDTs of SBS.

3. Materials and methods

3.1. Materials

MCC (Avicel® MicrocelluloseWeissenborn GmbH + KG, Weissenborn, Germany), bromophenol blue (BDH Chemicals Ltd. Poole England), crospovidone (China Associate Co. Ltd, Shenzhen, China), colloidal silicon dioxide (Aerosil®) (Evonik Industries AG, Germany), magnesium stearate (China Associate Co. Ltd, Shenzhen, China), MNTL (China Associate Co. Ltd, Shenzhen, China), hydrochloric acid (BDH Ltd., Poole, England) and maize starch(China Associate Co. Ltd, Shenzhen, China) were all kindly donated by the Ethiopian Pharmaceuticals Manufacturing S.C. (Ethiopia). Vannillin (Lonza Guangzhou Ltd, China) and Aspartame (China Associate Co. Ltd, Shenzhen, China) were donated by the Cadilla Pharmaceuticals P.L.C (Ethiopia). SBS (Supriya Life Science Ltd., India) were donated by the Julphar Pharmaceuticals P.L.C. (Ethiopia). Ammonium bicarbonate (VWR international Ltd. Poole, England) was purchased from local suppliers and used as received.

3.2. Methods

3.2.1. Calibration curves of SBS

A. Calibration curve of SBS in 0.1 N HCl

A stock solution of SBS was prepared by accurately weighing and transferring 4.8 mg of SBS (equivalent to 4 mg of salbutamol) into screw capped glass. Then, it was made up to 50 mL volume with 0.1N HCl to make final concentration of 96 µg/mL (USP 36-NF31, 2013) and the contents of the flask were mixed on laboratory orbitary shaker for 5 min to ensure complete dissolution.

The stock solution (96 µg/mL) was further diluted with 0.1N HCl separately to prepare series of concentrations from 4-16 µg/mL. Then, the diluted samples were filtered and absorbance was measured in triplicate using UV-VIS spectrophotometer (UV-1800, SHIMADZU, Japan) at 276 nm using 0.1N HCl as blank. Finally, calibration curve was plotted, concentration against absorbance.

B. Calibration curve of SBS in distilled water

SBS 4.8 mg (equivalent to 4 mg of salbutamol) accurately weighed and transferred in to screw capped glass. It was then dissolved in 100 mL distilled water to make final concentration of 48

µg/mL and the contents of the flask were mixed on laboratory orbitary shaker for 5 min to ensure complete mixing.

The stock solution (48 µg/mL) was further diluted with distilled water separately to prepare series of concentrations from 3-10 µg/mL. Then, the diluted samples were filtered and absorbance was measured in triplicate using UV-VIS spectrophotometer (UV-1800, SHIMADZU, Japan) at 276 nm using distilled water as blank. Finally, calibration curve was plotted, concentration against absorbance. (BP, 2013).

C. Calibration curve of SBS in phosphate (pH 6.8)

Stock solution was prepared by dissolving 4.8 mg of SBS (equivalent to 4 mg of salbutamol) working standard in 100 mL phosphate buffer (pH 6.8) and mixed on laboratory orbitary shaker for 5 min to ensure complete mixing. From this stock solution, seven different working standard solutions of final concentration of 1, 2, 3, 4, 5, 6, and 7 µg/mL were prepared. The UV absorbance readings of these solutions were measured at 276 nm using UV/Visible spectrophotometer (UV-1800, SHIMADZU, Japan). Phosphate buffer (pH 6.8) was used as a blank. Finally, calibration curve was plotted, concentration against absorbance.

3.2.2. Drug - excipients interaction study

The compatibility between the drug and excipients used in the formulation was studied using Fourier transform infrared spectroscopy (FT-IR) (Shimadzu FTIR-8400S spectrometer, Japan) at room temperature. Samples of SBS, crospovidone and physical mixture of SBS and crospovidone were ground and mixed thoroughly with KBr at a 1:5 sample/KBr ratio. The KBr discs were prepared by compressing the powders at a pressure of 49 KN for 5 min in a hydraulic press. Each IR spectrum was collected with 20 scans and spectral resolution of 4 cm^{-1}. Scanning was performed between wave numbers 4000 - 400 cm^{-1}. Background spectrum was collected before running each sample. IR Solution Software was used for data treatment.

3.2.3. Morphological study

Morphology details of the specimens were determined by using a Scanning Fluorescent optical microscope (LEITZ WETZLAR, Germany). The tablets were placed over the platform of the microscope and images were taken. Microphotographs were taken on magnification at 10X for surface profiling.

3.2.4. Measurement of micrometric properties

Micrometric properties like bulk density, tapped density, HR and CI and angle of repose of each formulation powder were studied as follows.

I. Bulk density and tapped density

Accurately weighed 30 g of powder blend of each formulation powder was carefully introduced into a 250 mL graduated cylinder and the bulk volume of the powder was noted. After 500 times tapping using a tap densitometer (stav2003, J. Engelsmann Ag, Germany), the tapped volume was noted. Finally, bulk density and tapped density of each formulation were obtained by using the following equation;

$$\rho b = \frac{m}{vb} \qquad \text{Eqn. 3.1}$$

Where, ρ_b is bulk density (g/mL), m is weight of sample (g), and v_b is bulk volume (mL); and

$$\rho t = \frac{m}{Vt} \qquad \text{Eqn. 3.2}$$

Where, ρ_t is tapped density (g/mL) and v_t is tapped volume (mL).

II. Compressibility index and Hausner ratio

The CI and HR of each formulation was calculated from the bulk and tapped densities.

$$CI = [(\rho t - \rho b/\rho t)] * 100 \qquad \text{Eqn. 3.3}$$

$$HR = \rho t/\rho b \qquad \text{Eqn. 3.4}$$

III. Angle of repose

Angle of repose was determined by using a fixed funnel method. Accordingly, 30 g of a sample was allowed to flow from 10 cm height through a glass funnel orifice with an inner diameter of 15 mm. The duration of flow was recorded and used to calculate the flow rate. Then, the radius (R) and the height (H) of the pile were determined and the angle of repose (θ) was calculated as follows.

$$\text{Angle of repose } (\theta) = \tan - 1(H/R) \qquad \text{Eqn. 3.5}$$

3.2.4. Preparation of FDTs of SBS

Thirteen FDT formulations of SBS were prepared by sublimation technique and addition of superdisintegrant. During the preparation, all the ingredients were passed through a 224 μm (No:

60) sieve separately and incorporated geometrically and all the ingredients except magnesium stearate and colloidal silicone dioxide, were mixed in a Turbula mixer (Willy A. Bachofen AG, Turbula®2TF, Basel, Switzerland) at a speed of 49 rpm for 10 min. Magnesium stearate and colloidal silicone dioxide were then added and mixed for further 5 min. Finally, the blend obtained was directly compressed using a single punch tablet press (Manesty Machines Ltd, England) with 7.1 mm punch, adjusting the hardness to be between 6 kg/cm^2 and 7 kg/cm^2. The tablets were kept in tray dryer oven at 50 °C for 8 h to facilitate complete volatilization of ammonium bicarbonate (Koizumi *et al*., 1997; Oh *et al*., 2014).

Table 3.1: Preliminary formulations of FDTs (150 mg) of SBS at different formulation factors

Form	**Ingridients (%W/W)**								
	SBS	AB	Crosp.	MCC	MNTL	Vanilin	Aspartame	Mg staerate	Coll. Sio2
PF1	3.2	15	6	38.5	19.23	1	1	1	1
PF2	3.2	10	4	34.1	34.11	1	1	1	1
PF3	3.2	5	2	26.23	52.46	1	1	1	1
PF4	3.2	0	6	53.46	26.73	1	1	1	1
PF5	3.2	15	0	44.46	22.23	1	1	1	1

*SBS = salbutamol sulphate, AB = ammonium bicarbonate, Crosp.= crospovidone, MCC = microcrystalline cellulose, MNTL = mannitol

The drug and excipients were mixed with different concentration of independent variables (crospovidone and MCC/MNTL) in order to select and optimize the concentration of the independent variables to get the formulation having the optimum disintegration time, hardness, friability and wetting time.

Table 3.2: Study formulations of FDTs (150 mg) of SBS at different levels of Ammonium bicarbonate

Study form.	Ingredients (%w/w)								
	SBS	AB	Crosp	MCC/ MNTL	Maize starch	Vannilin	Aspar tame	Mg Staerate	Aerosil
SF1	3.2	0	6	35/35	16.80	1	1	1	1
SF2	3.2	2.5	6	35/35	14.30	1	1	1	1
SF3	3.2	5	6	35/35	11.80	1	1	1	1
SF4	3.2	7.5	6	35/35	9.30	1	1	1	1

Table 3.3: Compositions of FDTs (150 mg) of SBS formulations used in optimization study

For m	Point type	Composition (%)								
		*SBS	*AB	Crospo vidone	*MCC/ MNTL	Aspar tame	vani llin	Mg stearate	Aer osil	Maize starch
F1	Factorial	3.2	5	2.00	2.00	1	1	1	1	15.8
F2	factorial	3.2	5	8.00	0.50	1	1	1	1	9.8
F3	factorial	3.2	5	8.00	2.00	1	1	1	1	9.8
F4	factorial	3.2	5	2.00	0.50	1	1	1	1	15.8
F5	axial	3.2	5	0.76	1.25	1	1	1	1	17.04
F6	axial	3.2	5	9.24	1.25	1	1	1	1	8.56
F7	axial	3.2	5	5.00	0.19	1	1	1	1	12.8
F8	axial	3.2	5	5.00	2.31	1	1	1	1	12.8
F9	center point	3.2	5	5.00	1.25	1	1	1	1	12.8
F10	center point	3.2	5	5.00	1.25	1	1	1	1	12.8
F11	center point	3.2	5	5.00	1.25	1	1	1	1	12.8
F12	center point	3.2	5	5.00	1.25	1	1	1	1	12.8
F13	center point	3.2	5	5.00	1.25	1	1	1	1	12.8

3.2.5. Evaluation of formulated tablets

The tablets were evaluated according to the available standards for disintegration time, drug content, hardness, friability, *in vitro* dissolution rate, wetting time and weight variation.

I. Disintegration test

The disintegration time was carried out according to USP36/NF31, 2013. Six tablets from each formulation were randomly selected and placed in a disintegration apparatus filled with 900 mL of distilled water kept at 37 ± 2 ^{0}C. The time required for complete disintegration of the tablets with no palpable mass remaining in the apparatus was recorded as the disintegration time.

II. Drug content assay

Twenty tablets were weighed and taken in mortar and crushed to make powder. A quantity of powder weighing 4.8 mg of salbutamol sulfate was taken in 100 ml (0.048% w/v salbutamol sulfate BP) volumetric flask containing distilled water (BP, 2013). It was shaken by automatic shaker for 30 min and; sonicated for 10 min and allowed to cool at room temperature. The solution was filtered by Whatman filter paper No.1. The salbutamol absorbance was determined at 276 nm using a UV-VIS spectrophotometer. Three samples of each formulation were used to determine the content.

III. Hardness test

Ten tablets were randomly taken from each formulation and tablet hardness was measured by using hardness tester. The hardness was measured in terms of kg/cm^2. The mean value and standard deviation of the ten tablets were recorded.

IV. Friability test

Tablet friability was determined by taking previously weighed 10 tablets in friablator and rotated at 25 rpm for 4 min. Then, the tablets were taken out, dusted and reweighed. The percentage friability of the tablets was calculated by the formula:

$$\text{Friability (\%)} = \left[\frac{\text{initial weight} - \text{final weight}}{\text{initial weight}}\right] \times 100 \qquad \text{Eqn. 3.6}$$

V. *In vitro* dissolution study

In vitro dissolution study was carried out using USP apparatus type II (paddle method). An automated dissolution tester (ERWEKA, Germany) at 50 rpm and a dissolution media of 500 mL HCl and phosphate buffer (pH 6.8) as dissolution medium maintained at 37 ± 0.5 °C (USP36/NF31, 2013). Fast disintegrating tablet of desired formulations was taken and placed in the vessels of dissolution apparatus. Samples of 5 mL were collected from the vessels at specified time intervals (5, 10, 15, 20, 25 and 30 min) and replaced by blank medium; filtered by using Whatman filter paper and salbutamol contents of the tablets were determined by UV-Visible spectroscopy at 276 nm. Blank experiments were also performed at the same wavelength for correction. Drug concentration was calculated and expressed as percent drug release.

VI. Wetting time

The wetting time of the tablets was evaluated using six tablets of each formulation. A Whatman filter paper folded once diametrically was placed in a Petri dish of 8.5 cm in diameter. A small volume (8 mL) of water containing water soluble dye, bromophenol blue, was added to the Petri dish. A tablet was carefully placed on the Whatman filter paper at t = 0 and the time for complete wetting of the tablet were determined. The appearance of the dye on the surface of the tablet was taken as a sign for complete wetting.

VII. Weight variation

Twenty tablets of each formulation were selected at random and weighed individually. The weight of each individual tablet was noted. Average weight for each formulation was calculated.

3.2.6. Experimental design

Central composite design (CCD), one of the response surface method designs and which is a powerful statistical approach to model and optimize the response of interest influenced by several independent variables was used in this study. CCD was chosen as it can detect any non-linearity in factor-response relationship (Pabari *et al*., 2012). So, it was adopted to statistically optimize the responses that factors like concentration of crospovidone and MCC/MNTL may have on the tablets.

According to the CCD matrix for two independent variables (n =2), the total number of experiments (N) is determined as: $N = (2^n + 2n + nc) = 2^2 + 2 \times 2 + 5 = 13$. The 13 experimental

runs of the CCD matrix were carried out and the observations were analyzed using Design-Expert ® Software to find the optimum area, at which the desired responses are achieved, and to construct the response surface plots and contour plots for the fitted polynomial equations of the responses.

The selected formulation variables with their limits, units and notations are given in the Table 3.4 below.

Table 3.4: Independent variables and their limits used for the optimization study

	Limits				
Variables	-α	-1	0	+1	+α
Crospovidone (%)	0.76	2	5	8	9.24
MCC:MNTL (W/W)	0.19	0.5	1.25	2	2.31

α = 1.414

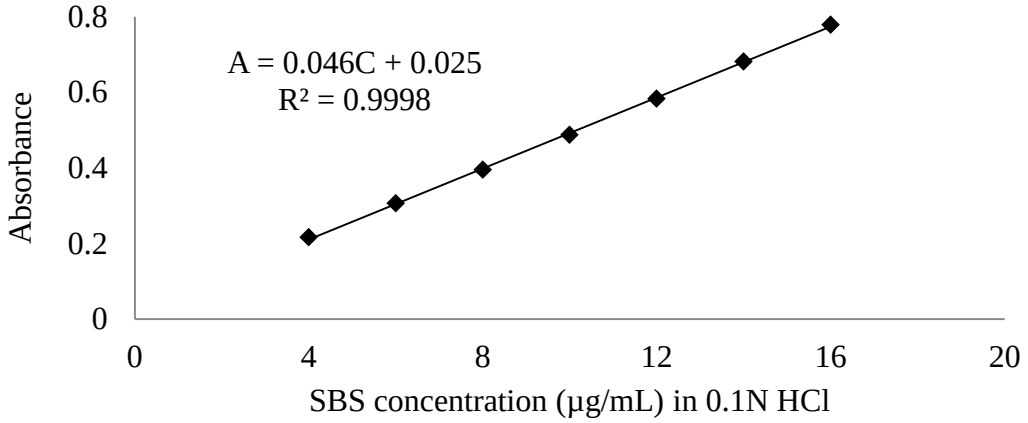
3.2.7. Statistical analysis

The statistical analysis of all batches was performed with Microsoft Excel software and the results were expressed as a mean ± standard deviation. The *in vitro* dissolution study and drug content assay were conducted in triplicate. One way analysis of variance (ANOVA) was applied for comparison of all results. 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 6.0.8 software (Stat-ease, Corp. Australia). A *P* value of less than 0.05 was considered as statistically significant.

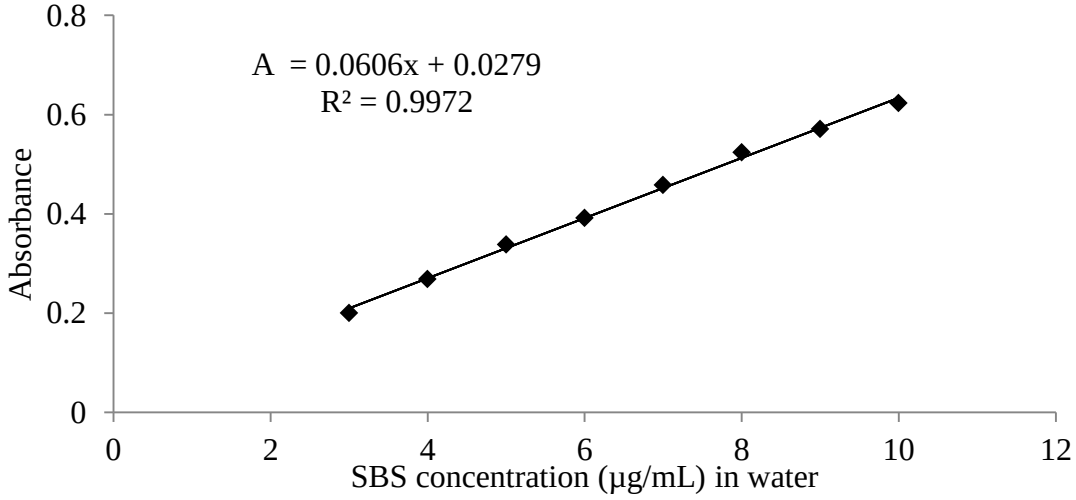
4. Results and Discussion

4.1. Calibration curves of SBS

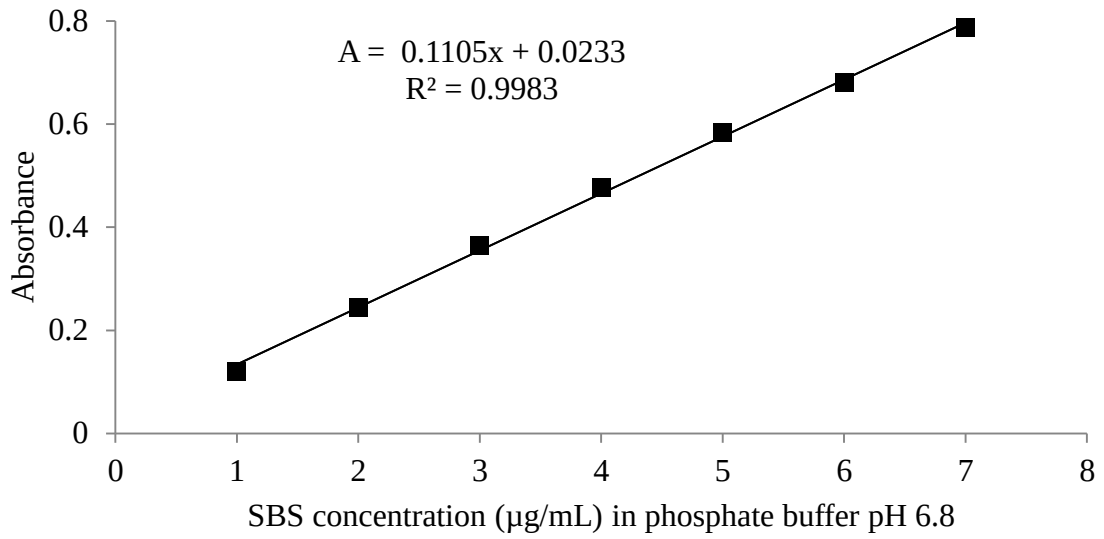
UV-VIS spectrophotometer method is a simple, rapid, accurate and precise method and can be used for the determination of salbutamol content in pure form and in pharmaceutical dosage forms (Corrigan *et al*., 2006; Malakar *et al*., 2014; Samir *et al*., 2014; JP, 2015). Hence salbutamol calibration curve was prepared by using 0.1N HCl, distilled water and phosphate buffer (pH 6.8) as solvent and the UV-VIS spectrophotometer method. The UV absorbance calibration curve of pure SBS at 276 nm in 0.1N HCl, distilled water and Phosphate buffer (pH 6.8) are shown in Figure 4.1A, B and C respectively.



(A)



(B)



(C)

Figure 4.1: Calibration curve of Salbutamol using 0.1N HCl (A), distilled water (B) and Phosphate buffer pH 6.8 (C) at 276 nm

UV-Visible absorbance studies of salbutamol at 276 nm showed linearity in the chosen concentration range. The Beer's Lambert calibration curve (Figure 4.1A, B and C) yielded a correlation coefficient (R^2) of 0.9998, 0.9972 & 0.9983 in 0.1 N HCl, distilled water and phosphate buffer pH 6.8 respectively which indicates linear absorbance in the chosen concentration range.

4.2. Preliminary study

Before applying the experimental design for optimization, preliminary studies were conducted in order to identify the most critical formulation variables. Factors that could possibly have significant effects on the response variables, according to literature, were considered in the preliminary studies. These include Crospovidone, Ammonium bicarbonate and MCC/MNTL.

Preliminary formulations containing both ammonium bicarbonate and crospovidone (PF1-PF3) showed less disintegration times. Formulations containing high amount of ammonium bicarbonate showed higher friability and lower hardness (PF1 and PF5). Formulations containing only crospovidone (PF4) and only ammonium bicarbonate (PF5) showed higher disintegration times when compared to formulations containing combination of crospovidone and ammonium bicarbonate.

Table 4.1: physicochemical attributes of preliminary formulation study of FDTs of SBS

Preliminary Form.	DT (sec) ± SD	Friability (%)	Hardness (Kg/cm^2) ± SD
PF1	9 ± 1.41	1.10	2.85 ± 0.60
PF2	13.5 ± 1.29	0.80	4.58 ± 0.50
PF3	28.5 ± 1.29	0.69	5.6 ± 0.5
PF4	41 ± 1.82	0.50	6.11 ± 1.0
PF5	48.25 ± 1.70	0.90	4.79 ± 1.2

The development of FDTs requires more than just good binding properties in an excipient (Al-khattawi et al., 2015). Based on the preliminary studies, the concentration of MCC and Mannitol were set to 70% in order to investigate their effect (Bi *et al*., 1999; Schiermeier and Schmidt 2002; Rahul *et al*,. 2009). Besides Crospovidone was kept at 6% (Mishra and Rohera, 2016), MCC and MNTL 70% at 1:1 ratio (Westerhuis *et al*, 1996) to study the effect Ammonium bicarbonate. The binding properties of MCC increase the tablets' mechanical strength and the pore forming agent decreases the DTs. As a result the combination of crospovidone and ammonium bicarbonate selected for this study.

4.2.1. Effect of Ammonium bicarbonate on tablet properties

Formulations containing higher amount of ammonium bicarbonate showed decreased disintegration time and hardness with an increase in tablet friability as shown in Table 4.2. However, these tablets were more friable as well as not esthetically appealing due to pores formed in the tablets. The crushing strength of the produced tablets was low as the formed pores were detrimental to the structural integrity of tablets (Koizumi *et al*., 1997). As a result, a concentration of ammonium bicarbonate was fixed at a constant level with desired responses for further studies. To study the effect of sublimation of Ammonium bicarbonate on tablet properties and fix the level of ammonium bicarbonate for further studies all other factors were kept constant.

Crushing strength is an important material property that should be considered in order to design high quality tablet products. In the present study, increasing concentration of ammonium bicarbonate from 0% to 7.5% caused decrease in crushing strength from 4.5 to 3.37 kg/cm^2. This

is because of the reduction of the number of contact points between particles due to increase in interparticulate void as a result of sublimation of ammonium bicarbonate which decreases the crushing strength of tablets. These findings are in agreement with the studies of Juppo*et al* (1996) and Mishra & Rohera (2016).

One of the major problems associated with the formulation of FDTs is the fragile nature of the tablets owing to their softness that is essential for fast disintegration. According to USP/NF, 2013, tablets with friability <1% is considered as mechanically strong enough to resist abrasion during transportation and handling. In the present study, tablet friability varied between 0.15% and 0.41%. Concentration of volatile material, i.e., ammonium bicarbonate, showed that it had positive effect; thus an increase in its concentration increased the friability. These findings are in agreement with the studies such of Bi *et al* (1999).

The disintegration time decreased from 45.17secs to 29 secs. Concentration of ammonium bicarbonate had negative effect on the disintegration time as 7.5-fold increase in its concentration (0 to 7.5%) causes decrease in disintegration time of FDTs from 45.17 sec to 29 sec. Hence water uptake capacity of tablet increases causing faster disintegration of tablets. These findings are in agreement with the studies of Koizumi *et al* (1997).

Therefore, concentration of ammonium bicarbonate was adjusted at 5% for further studies as a compromise between its positive and negative attributes. At 5% concentration the pores formed were considered to have acceptable esthetic impacts.

Table 4.2: physicochemical attributes of study formulations of FDTs of SBS

Study Form.	Tablet properties					
	Diameter (mm) ± SD	weight (mm) ±SD	Thickness (mm) ±SD	Hardness (Kg/cm^2) ±SD	Friability (%)	DT (sec) ±SD
SF1	7.09 ± 0.001	150 ± 1.0	3.34±0.21	4.50 ± 1.77	0.15	45.17 ± 0.75
SF2	7.07 ± 0.01	146 ± 1.2	3.30±0.20	4.42 ± 0.82	0.22	39.83 ± 1.17
SF3	7.08 ± 0.003	142 ± 0.9	3.31±0.23	4.15 ± 0.61	0.32	35 ± 1.41
SF4	7.08 ±0.004	138 ± 0.5	3.32±0.18	3.37 ± 0.38	0.41	29 ± 1.26

4.3. Micromeritic properties of powder blend of SBS formulations

The widespread use of powders in the pharmaceutical industry has generated a variety of methods for characterizing powder flow which is crucial in handling and processing operations such as flow from hoppers, mixing and compression to ensure uniform tablet weight and drug content.

Table 4.3: Micromeritic properties of powder blends of FDTs of SBS

Form.	ρbulk (g/mL) ±SD	ρtapped (g/mL) ± SD	HR ± SD	CI (%) ± SD	Flow rate (g/s)	Angle of rep. (degree) ±SD
F1	0.42 ± 0.01	0.48 ± 0.00	1.16 ± 0.02	13.71 ± 1.42	5.00 ± 1.00	30.71 ± 0.32
F2	0.42 ± 0.01	0.49 ± 0.00	1.17 ± 0.02	14.83 ± 1.16	3.50 ± 1.00	32.28 ± 0.33
F3	0.41 ± 0.01	0.48 ± 0.00	1.14 ± 0.05	12.71 ± 3.86	3.53 ± 0.50	33.93 ± 0.31
F4	0.45 ± 0.00	0.52 ± 0.00	1.16 ± 0.01	14.36 ± 0.44	4.25 ± 0.25	31.61 ± 0.39
F5	0.44 ± 0.00	0.50 ± 0.00	1.14 ± 0.00	12.00 ± 0.00	5.50 ± 0.50	30.33 ± 0.58
F6	0.39 ± 0.00	0.45 ± 0.00	1.15 ± 0.00	13.33 ± 0.00	4.50 ± 0.50	31.37 ± 0.49
F7	0.45 ± 0.00	0.51 ± 0.00	1.13 ± 0.00	11.76 ± 0.00	4.17 ± 0.28	30.28 ± 0.52
F8	0.39 ± 0.00	0.44 ± 0.00	1.13 ± 0.00	11.36 ± 0.00	4.17 ± 0.28	30.28 ± 0.52
F9	0.42 ± 0.01	0.49 ± 0.00	1.16 ± 0.02	13.71 ± 1.42	3.66 ± 0.14	33.54 ± 0.38
F10	0.42 ± 0.00	0.49 ± 0.00	1.17 ± 0.00	14.28 ± 0.00	3.66 ± 0.14	33.50 ± 0.33
F11	0.42 ± 0.00	0.48 ± 0.00	1.17 ± 0.00	14.28 ± 0.00	3.66 ± 0.14	33.54 ± 0.38
F12	0.42 ± 0.01	0.48 ± 0.00	1.16 ± 0.02	13.71 ± 1.42	3.66 ± 0.14	33.54 ± 0.38
F13	0.42 ± 0.00	0.49 ± 0.00	1.17 ± 0.00	14.28 ± 0.00	3.66 ± 0.14	33.50 ± 0.33

HR, CI and angle of repose have become simple, fast and popular for predicting powder flow characteristics (USP36/NF31, 2013). Accordingly, the bulk density, tapped density, HR and CI of the formulations were determined as shown in Table 4.3.

Powder handling and processing operations are dependent on the physicochemical properties of powder materials (Shah *et al*., 2017).

The results of the present study showed angle repose ranging from 30.33 ± 0.58 to 33.93 ± 0.31, HR 1.13 ± 0.00 to 1.17 ± 0.02 and CI 11.36 ± 0.00 to 14.83 ± 1.16 indicating that all the blends have good flow properties The bulk and tapped densities were closer in value resulting in lower

HR and CI values which indicate free flowing powder with good compressibility (USP36/ NF31, 2013).

Alternatively, the HR and CI are measures of the propensity of a powder to be compressed as a measure of powder compressibility. As such, they are measures of the powder's ability to settle, and they permit an assessment of the relative importance of interparticulate interactions (frictional force interaction and the adhesion force interaction between particles or between particles and contacting surface) (Shah et al., 2017).

4.4. Compatibility study: Fourier transform infrared spectroscopy (FT - IR)

FT-IR analysis was performed to detect the possible interactions between the drug and crospovidone. As shown in Annexes (Annex I, Annex II & Annex III), the characteristic peaks of SBS observed were: C-O stretching of primary alcohol at 1112 cm^{-1}, C-O vibrations of phenol at 1207 cm^{-1}, C= C stretch of phenol at 1614 cm^{-1} and C-H stretching at 2852 cm^{-1}, =C-H stretch of phenol at 2952 cm^{-1}, O-H stretching at 3149 cm^{-1} and N-H stretching at 3469 cm^{-1} . The characteristic peaks of crospovidone were observed: C-N stretching at 1456, C=O stretching at 1633 cm^{-1} and; a pair of N-H stretching at 3361 cm^{-1} & 3267 cm^{-1}. The absence of major shift in the peak positions and retention of characteristic peaks for SBS and crospovidone physical mixture suggest the absence of apparent interactions in the solid state between the drug and crospovidone.

4.5. Evaluation of FDTs

The various physicochemical properties of the FDTs formulations are shown in Table 4.4. FDTs of SBS were prepared using crospovidone and MCC/MNTL and then evaluated for various parameters like disintegration time, friability, hardness, *in vitro* drug release and wetting time to select the optimum combination.

According to literature, the oral disintegration time of FDTs is preferably about 30 s or less (Kuno *et al*., 2005). Disintegration depends on the effect of disintegrants and water soluble excipients in the formula (Mizumoto *et al*., 2005). As shown in Table 4.4, the *in vitro* disintegration time ranged from 12 ± 1.67 to 38 ± 1.41sec.

The hardness of FDT is usually preferable between 4 and 8 kg in order to withstand handling during manufacturing, packaging and transportation (Shoukri *et al*., 2009). The hardness values for all tested tablets were within (4.40 ± 0.56) and (7.88 ± 1.14). It was clear from the results that the increase of the MCC/MNTL led to an increase in the FDT's hardness.

Friability values for all the formulations were found to be in the range of 0.17 to 0.58 (<1%); indicating sufficient mechanical integrity and strength for the prepared tablets (USP36/ NF31, 2013).

Wetting time is an important parameter for disintegration properties of the tablets. The WT ranged from 11 ± 1.00 – 37 ± 1.00.

Table 4.4: Physicochemical properties of FDTs (150 mg) SBS

Form.	DT (sec)	Hardness (kg/cm^2)	Friability (%)	Wetting time (sec)	Weight variation (mg)	Content uniformity (%)
F1	20 ± 0.89	6.80 ± 0.95	0.23	18 ± 1.23	141.10 ± 1.02	96.34 ± 0.27
F2	20 ± 1.79	5.35 ± 0.65	0.51	18 ± 0.71	143.00 ± 0.72	98.87 ± 0.40
F3	12 ± 1.67	7.80 ± 0.49	0.21	11 ± 1.41	141.65 ± 0.99	102.26 ± 0.53
F4	38 ± 1.41	4.55 ± 0.45	0.53	37 ± 1.00	144.50 ± 1.15	95.47 ± 0.39
F5	32 ± 0.63	5.78 ± 0.69	0.36	31 ± 1.58	139.55 ± 1.28	103.39 ± 0.26
F6	12 ± 1.53	6.60 ± 0.78	0.38	11 ± 1.00	147.20 ± 0.95	94.61 ± 0.54
F7	30 ± 1.27	4.40 ± 0.56	0.58	29 ± 1.87	145.33 ± 0.49	96.61 ± 0.52
F8	13 ± 1.55	7.88 ± 1.14	0.17	12 ± 0.71	139.05 ± 1.05	98.69 ± 0.26
F9	22 ± 1.09	6.16 ± 1.13	0.373	21 ± 1.58	145.95 ± 0.83	102.61 ± 0.27
F10	22.67 ± 1.03	6.12 ± 0.93	0.374	21 ± 1.42	148.45 ± 1.23	101.22 ± 0.40
F11	22.33 ± 1.03	6.14 ± 1.05	0.375	21 ± 1.22	145.15 ± 0.81	101.21 ± 0.55
F12	22.00 ± 1.37	6.15 ± 0.97	0.371	21.4 ± 1.14	143.15 ± 0.93	100.43 ± 0.40
F13	22.33 ± 1.21	6.15 ± 1.01	0.372	21.2 ± 1.01	139.25 ± 0.85	100.26 ± 0.52

The weight of different FDTs ranged from 139.05 ± 1.05 to 148.45 ± 1.23. All formulations were within the pharmaceutical specification for weight variation according to the USP with an acceptable limit of ± 7.5% (USP36/NF25, 2013).

The average drug content of each formulation ranged from 94.61 ± 0.54 to 103.39 ± 0.26 of the label claim. Thus, all formulations complied with the pharmacopoeial limits as per BP requirement with an acceptable limit of 92.5-107.5% (BP, 2013).

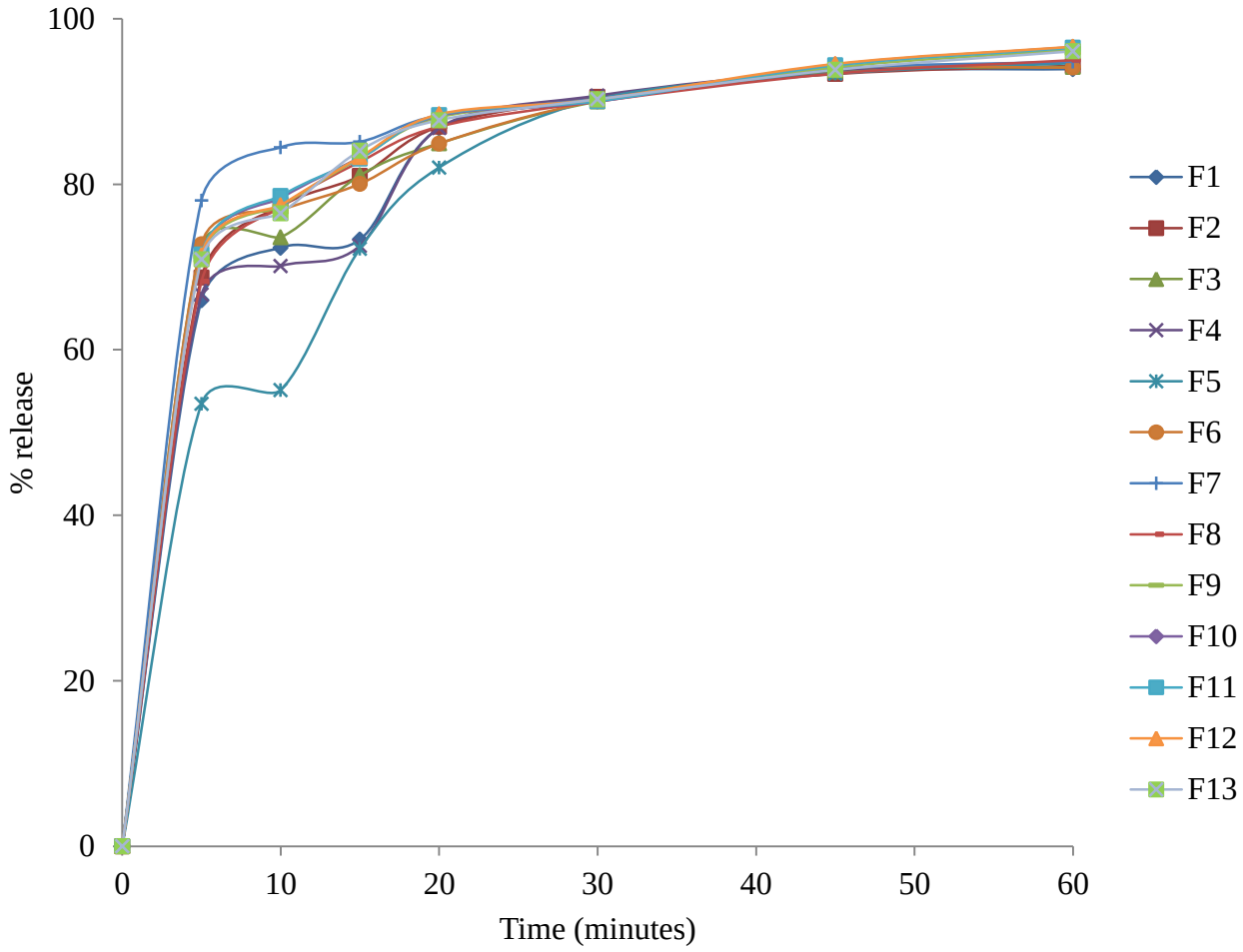


Figure 4.2: *In vitro* dissolution profiles of FDT of SBS formulations in 0.1N HCl

The amount of drug released in a predetermined time was used to characterize drug release from the tablets in 0.1 N HCl and phosphate buffer (pH 6.8) (Zarmpi *et al*., 2017; Guhmann *et al*., 2015). The USP specification for the release of salbutamol from tablets of SBS states that "not

less than 80% of the label claim of salbutamol should be dissolved in 30 min" (USP36/NF31, 2013).

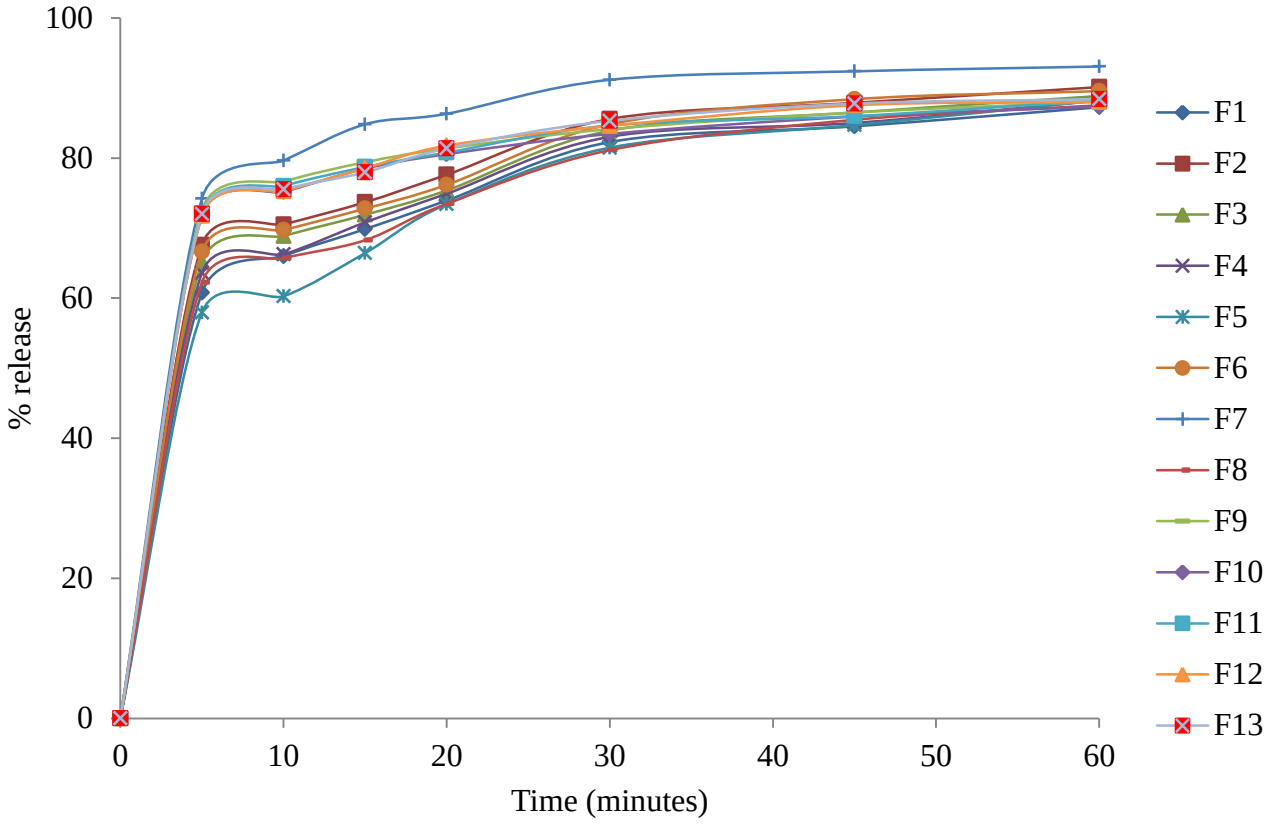


Figure 4.3: *In vitro* dissolution profiles of FDT of SBS formulations in Phosphate buffer (pH 6.8)

All the formulations released more than 80% of the label claim within 15 min except for formulations with minimum amount of superdisintegrant and higher amount of MCC in acidic medium. The release was higher in acidic medium because SBS is salt of weak base which highly dissociate in the medium.

Thus, all the FDT formulations passed the USP requirement for dissolution within 20 min in acidic medium and 30 min in phosphate buffer (pH 6.8) as shown in Figure 4.2 & Figure 4.3 respectively.

4.5.1. Effect of crospovidone concentration

It was observed that, increasing level of crospovidone had significant effect on DT ($p<0.0001$), wetting time ($p<0.0001$) and hardness ($p<0.0001$). The superior disintegrant capability of crospovidone can be attributed to its rapid capillary action, faster hydration rate, and little tendency for gel formation and due to its high and fast water absorption ability. It creates large wicking forces, further swelling and disintegrating the tablet into finer particles due to its porous particle morphology. The effect on crushing strength of tablets can be attributed to its plastic nature and binding capacity apart from being an excellent disintegrating agent; it acts as highly compressible material in dry state, and therefore an increase in its concentration from 2% to 8% increased the crushing strength of tablets significantly. These findings are in agreement with the studies of Bi *et al* (1999); Kuno *et al* (2005) and Mishra and Rohera (2016).

4.5.2. Effect of MCC/MNTL

It can be seen that MCC/MNTL had significant effect on disintegration time ($p<0.0001$), wetting time ($p<0.0001$) and friability ($p<0.0001$). Effect on disintegration time and wetting time might be due to rapid disintegration of MCC due to rapid passage of water by means of capillary pores; MCC is almost completely fibrous. Additionally, MCC contains free hydroxyl groups and thus the interaction force in a contact point is stronger which leads to the breakage of hydrogen bonds and subsequent widening of tablet pores. Effect on friability and hardness ($p<0.0001$) might be due to the fact that, the MCC had better compression properties and binding effect compared to MNTL. These findings are in agreement with the studies of Westerhuis *et al* (1996); Mostafa *et al* (2013) and Moqbel *et al* (2016).

4.6. Formulation of FDTs

According to preliminary investigations, the percentage of superdisintegrant namely cropovidone (A) and MCC/MNTL (B) were selected as the independent variables. Both independent variables (A and B) had significant effects on the disintegration time, hardness, friability and wetting time. Even though, ammonium bicarbonate decreased disintegration time, it was kept constant at 5%.

4.7. Optimization study

The aim of the optimization of pharmaceutical dosage formulations is generally to determine the levels of variables from which a robust product with high quality characteristics may be produced (Ahmed *et al*., 2013). The optimization of responses was conducted with Design-Expert® 6.0.8 *S*oftware. It was used to construct the response surface and contour plots for the fitted equations and to find the optimum area at which the desired responses could be achieved.

4.7.1. Selection and checking adequacy of mathematical models

Models selection was by the best fit method to describe the responses of interest with the help correlation coefficient (R^2) which suggest a high degree of correlation between the experimental and predicted responses. In addition, the predicted R^2 values are in good agreement with the adjusted R^2 values indicating reliable models. It is necessary to check the fitted model to ensure that it provides an adequate approximation of the real system by using ‘‘lack of fit’’ test and residual. The lack of fit test denotes whether the selected model is adequate to describe the observed data or a more complicated model is required to be used. The selected model needs to have insignificant lack of fit test. The residuals are the differences between the empirical and predicted values of the responses which are used to estimate experimental errors. If the model fit the data well, the residual would appear as a random error and indicate good model for that response along with significant lack of fit. As a result, model summary statistics for the selected significant models are shown in the Table 4.5.

Table 4.5: Numerical test results for selection of response models of disintegration time, hardness, friability and wetting time

Responses	Source	R^2	Adjusted R^2	Predicted R^2	Adequate precision
DT	2FI	0.9960	0.995	0.987	83.1
Hardness	linear	0.9940	0.993	0.987	82.3
Friability	linear	0.9960	0.995	0.991	104
WT	2FI	0.9970	0.9970	0.9920	105

It can be observed that R^2 is high for all responses (disintegration time, hardness, friability and wetting time) which suggest a high degree of correlation between the experimental and predicted responses. The predicted R^2 values are in good agreement with the adjusted R^2 values indicating the models are reliable.

ANOVA results were used to summarize the test for significance of regression model as well as for individual model coefficient. The larger the value of F and the smaller the value of p, the more significant is the corresponding coefficient term. The value of *p* was less than 0.05 indicating that models were statistically significant. ANOVA of the responses indicated that response surface models developed for all responses were significant and adequate.

The best fitting mathematical model was selected based on the comparisons of several statistical parameters including correlation coefficients (R^2), adjusted R^2 and Adeq Precision.

The model selected for DT is 2FI and its R^2 value indicates that 99.60% of the variability in the response could be explained and only 0.40% of the total variation cannot be explained by the model. The Pred R-Squared of 0.987 is in reasonable agreement with the Adjusted R^2 of 0.995 which indicate that the 2FI model provides an excellent explanation for the relationship between the independent variables and the corresponding response. This was further confirmed by the coefficients in the mathematical model generated for DT. The model F-value of 736 implies the model is significant as shown in Table 4.6.

Table 4.6: Summary of ANOVA results of response surface model for Disintegration time

Source	Sum of squares	df	Mean square	p-value	F-value	Remark
Model	706	3	235	0.0001	736	significant
A	368	1	368	0.0001	1.15E+003	significant
B	313	1	313	0.0001	978	significant
AB	25	1	25	0.0001	78.1	significant
Residual	2.88	9	0.32			
Lack of fit	2.57	5	0.514	0.046	6.56	significant
Cor Total	709	12				

The selected model for hardness is linear. The goodness of fit of the model was checked by determination coefficient (R^2) of 0.9940. The Model F-value of 856 implies the model is significant as shown in Table 4.7.

Table 4.7: Summary of ANOVA results of response surface model for hardness

Source	Sum of squares	df	Mean square	p-value	F-value	Remark
Model	12.7	2	6.33	0.0001	856	significant
A	1.09	1	1.09	0.0001	148	significant
B	11.6	1	11.6	0.0001	1.56E+003	significant
Residual	0.074	10	0.074			
Lack of fit	0.073	6	0.012	0.0009	53	significant
Cor Total	12.7	12				

The selected model for friability is linear. The goodness of fit of the model was checked by determination coefficient (R^2) of 0.9960. The Model F-value of 1.26E+003 implies the model is significant. Besides, predicted R^2 of 0.9910 is in reasonable agreement with the adjusted R^2 of 0.9950. For this response, B is the significant model term while A term is not significant as shown in Table 4.8.

Table 4.8: Summary of ANOVA results of response surface model for friability

Source	Sum of squares	df	Mean square	p-value	F-value	Remark
Model	0.174	2	0.87	0.0001	1.26E+003	significant
A	1.72E-005	1	1.72E-005	0.629	0.248	Not significant
B	0.174	1	0.174	0.0001	2.52E+003	significant
Residual	0.00691	10	6.91E-005			
Lack of fit	0.0006	6	0.0001	0.0001	143	significant
Cor Total	0.175	12				

For wetting time, the selected model is 2FI with F-value of 1.18E+003 and p-value of 0.0001, which implies the model, is significant as shown in Table 4.9.

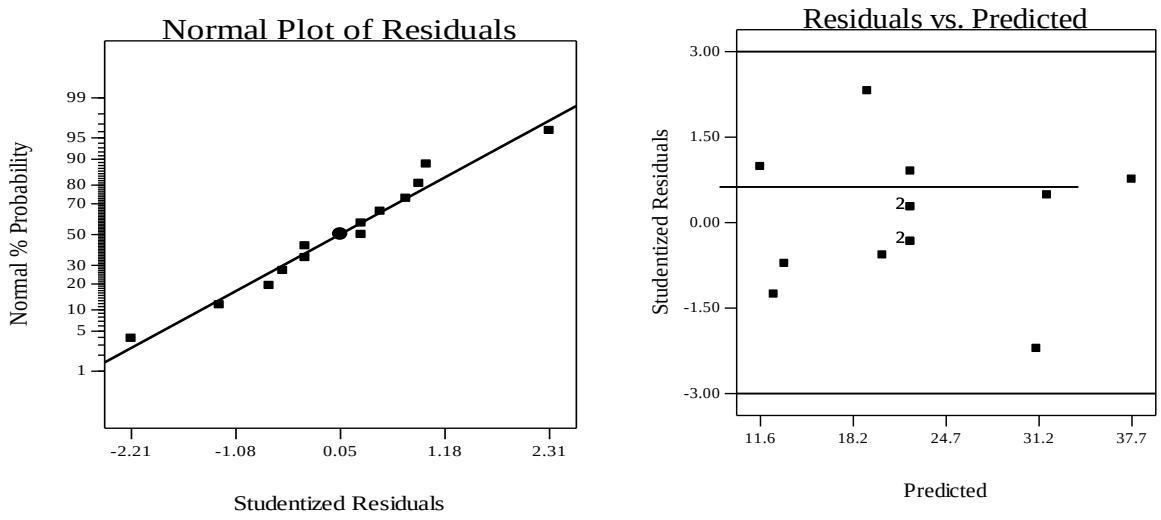
Table 4.9: Summary of ANOVA results of response surface model for wetting time

Source	Sum of squares	df	Mean square	p-value	F-value	Remark
Model	717	3	239	0.0001	1.18E+003	significant
A	368	1	368	0.0001	1.82E+003	significant
B	313	1	313	0.0001	*1.55E+003*	significant
AB	36	1	36	0.0001	178	significant
Residual	1.82	9	0.202			
Lack of fit	1.69	5	0.338	0.02	10.6	significant
Cor Total	719	12				

Usually, it is important to confirm if the selected model provides adequate approximation of the real system. By applying the diagnostic plots provided by the Design-Expert Software, such as normal probability plots of the studentized residuals, as well as the predicted versus actual value plots, the model adequacy can be checked (Pabari and Ratoola, 2012).

The normal probability plots of the residuals and the plots of the residuals versus the predicted response for DT, hardness, friability and wetting time are shown in Figures 4.4 to 4.7. The important information on the model performance is summarized in residuals (i.e. difference between observed and predicted values) providing a clear view for any discrepancy in fit to the model.

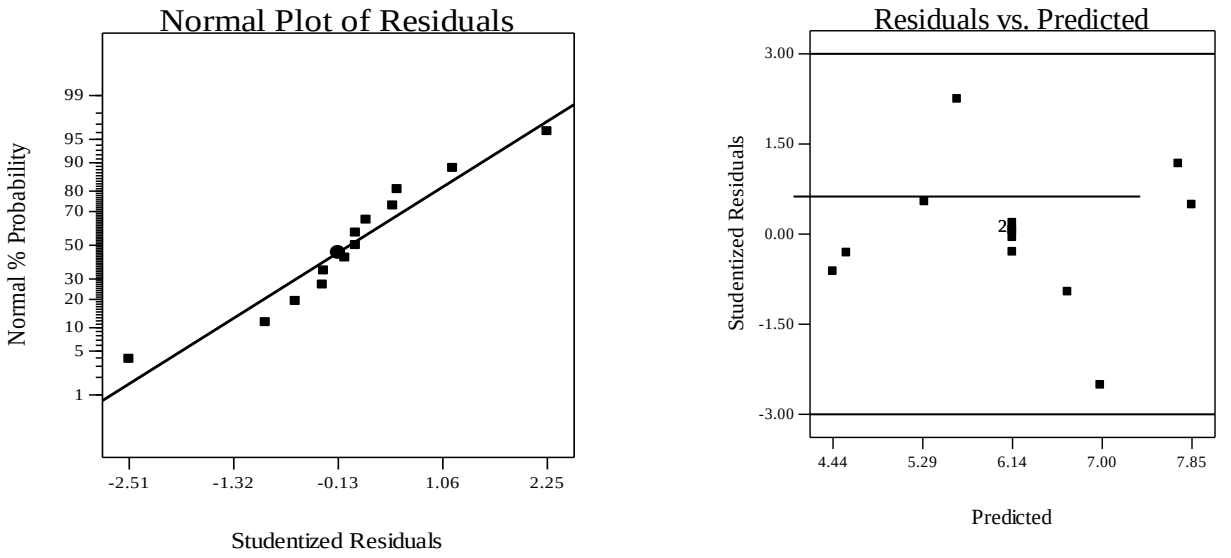
Hence, two plots related to residuals: the normal probability plot of residuals and the plot of internally studentized residuals versus predicted values are considered as additional tests of model adequacy checking tools



A B

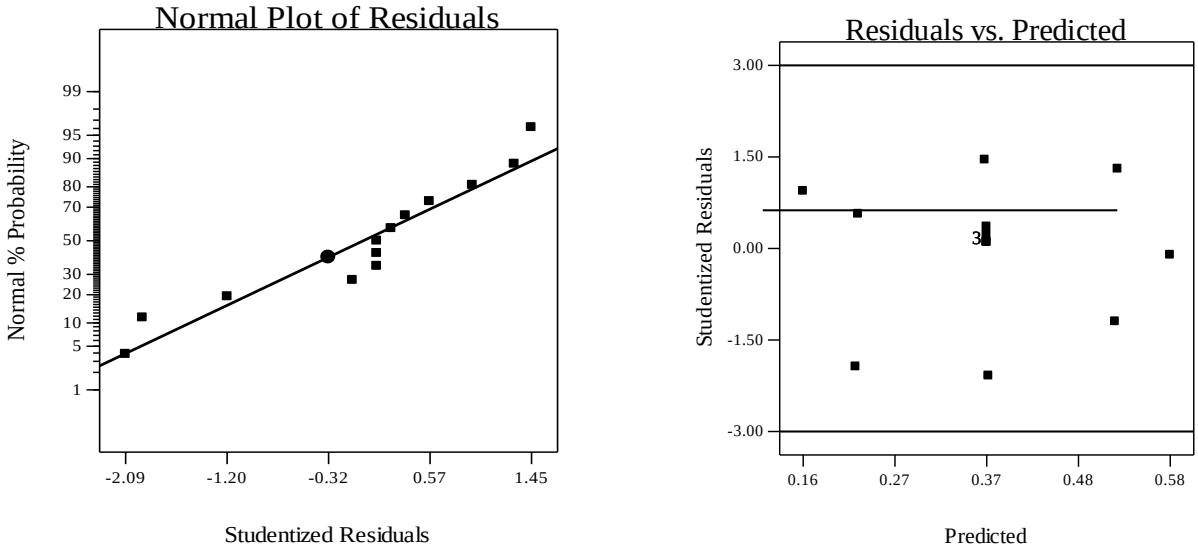
Figure 4.4: Normal probability plot of residuals (A) and plots of the residuals against predicted response (B) for DT

Figures of normal probability plot of residuals for the selected responses showed that points or point clusters are placed closely to the diagonal line implying that the errors are distributed normally for all responses. Plots of the residuals against predicted response for selected responses indicate that the points are randomly scattered with no obvious pattern or structure, and all values lie within the recommended range of −3 and +3 outlier detection limits.



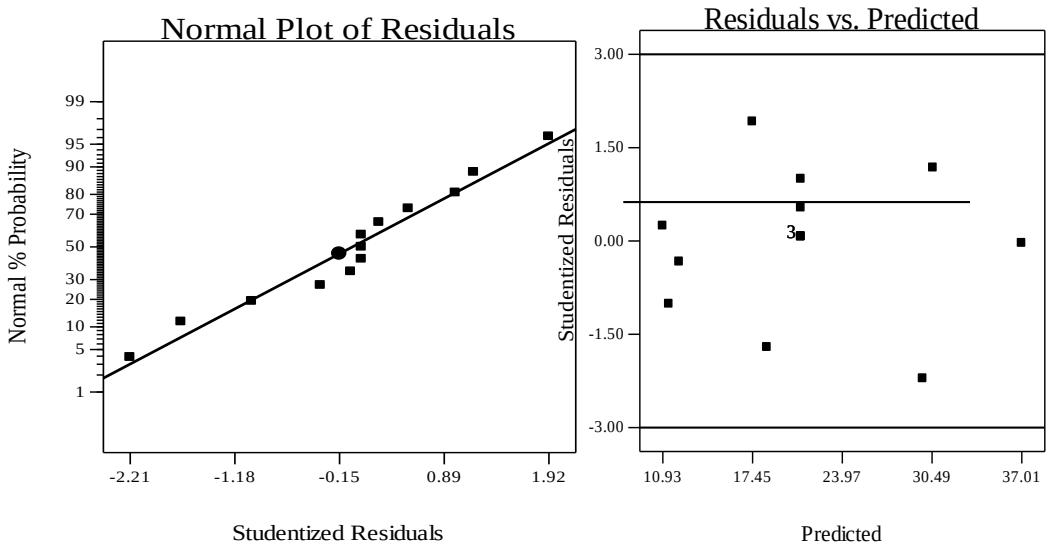
A B

Figure 4.5: Normal probability plot of residuals (A) and plots of the residuals against predicted response (B) for hardness



A B

Figure 4.6: Normal probability plot of residuals (A) and plots of the residuals against predicted response (B) for friability



A B

Figure 4.7: Normal probability plot of residuals (A) and plots of the residuals against predicted response (B) for WT

Figures 4.4 to 4.7 indicated a constant variation. The equal scatters of the residual data above and below the x-axis indicate that the variances were independent of the value of the responses which again support the assumptions of the model. It can be concluded from these analyses that the proposed models are adequate and there is no reason to infer any violation of the independence or constant variance assumption. Therefore, the models were used for further analysis.

4.7.2. Mathematical regression models

The final mathematical regression models in terms of coded factors

$$\text{Disintegration time} = 22.2 - 6.79A - 6.26B + 2.5AB \quad \text{Eqn. 4.1}$$

$$\text{Hardness} = 6.14 + 0.37A + 1.2B \quad \text{Eqn. 4.2}$$

$$\textit{F}\text{riability} = 0.372 - 0.00146A - 0.147B \quad \text{Eqn. 4.3}$$

$$\text{Wetting time} = 21 - 6.79A - 6.26B + 3AB \quad \text{Eqn. 4.4}$$

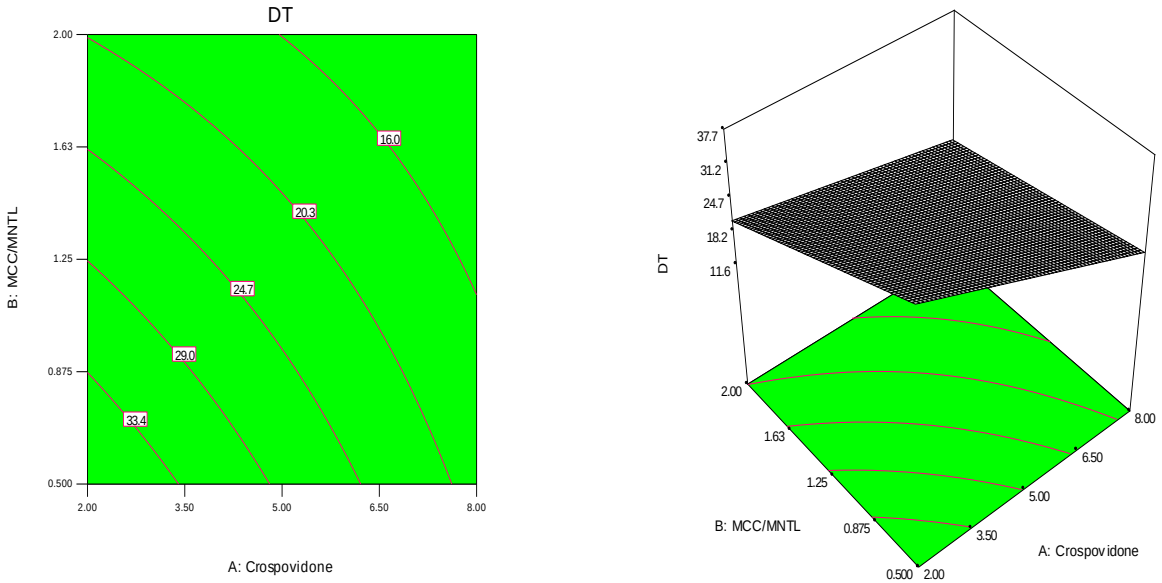
Where, A is crospovidone concentration and B is MCC/MNTL

As it can be seen from the above equations, the magnitude of the coefficients shows strength and the sign indicates the effects on the response whereas the positive sign indicates the increment

and the negative sign indicates the decrement on the response variables. Accordingly increasing crospovidone level decreased DT, friability and WT; and increased the hardness of tablets. On the other hand, increasing MCC/MNTL decreased DT, friability and WT; and increased the hardness of tablets.

4.7.3. Contour plot and surface response analysis

The 2-D contour plots, represented by the projection of the response surfaces in the x–y plane, provide a straightforward determination of the effects of the independent variables on the dependent variables. The corresponding 3-D response surface plots, graphical representation of the regression, show the effect of independent variables on the selected response variables (Solaiman *et al.*, 2016). The regression models developed can help to understand the interaction among variables and to determine the optimum level of each variable for maximum response (Huang *et al.*, 2009).

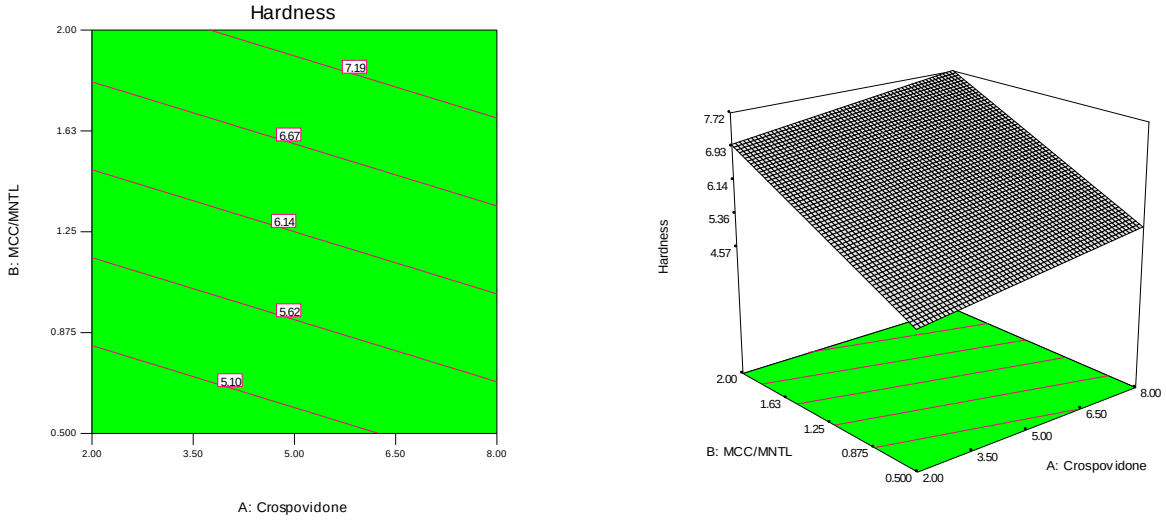


A B

Figure 4.8: Contour plot (A) and surface response plot (B) of DT as a function of concentration of crospovidone and MCC/MNTL

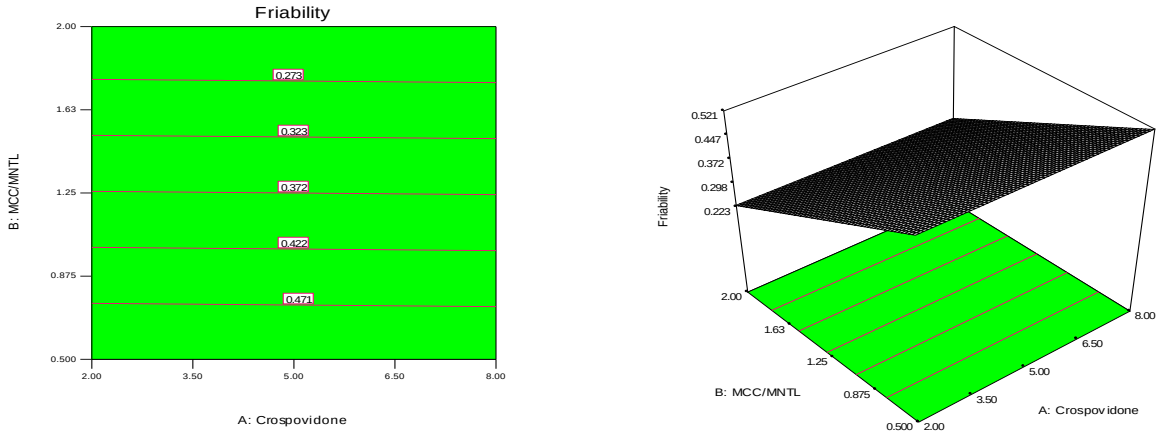
Figure 4.8 depicts the combined effects of concentration of crospovidone and MCC/MNTL on the tablet disintegration time. The contour plot indicates that both concentration of crospovidone

and MCC/MNTL play very significant role in influencing tablet disintegration time. However, the effect of crospovidone appeared to be more pronounced as compared to the MCC/MNTL. This was confirmed from the coefficients in the mathematical model generated for disintegration time.



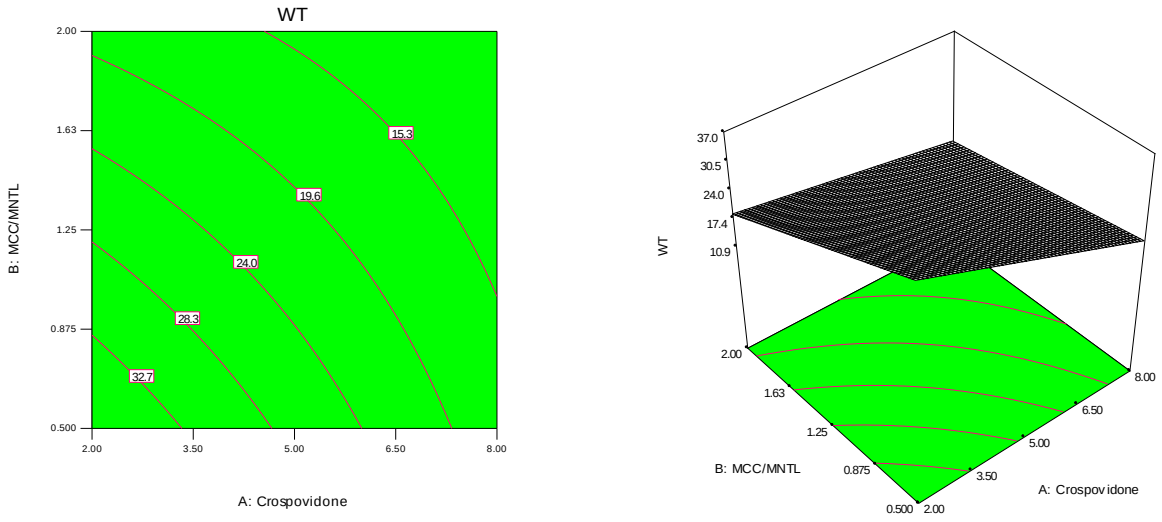
A B

Figure 4.9: Contour plot (A) and surface response plot (B) of hardness as a function of concentration of crospovidone and MCC/MNTL



A B

Figure 4.10: Contour plot (A) and surface response plot (B) of friability as a function of concentration of crospovidone and MCC/MNTL



A B

Figure 4.12: Contour plot (A) and surface response plot (B) of wetting time as a function of concentration of crospovidone and MCC/MNTL

The contour and response surface plots shown in Figure. 4.9, respectively, indicate the combined effects of crospovidone concentration and MCC/MNTL on hardness. The parallel straight line of the contour plot and the non- twisted response surface indicate that there is no interaction effect of the two parameters on the hardness. Additionally, the plots show that the model components individually affect the hardness significantly, with comparatively more significant effect of MCC/MNTL than the concentration of crospovidone.

The contour and response surface plots shown in Figure. 4.10, respectively, indicate the combined effects of crospovidone concentration and MCC/MNTL on friability. The parallel straight line of the contour plot and the non- twisted response surface indicate that there was no interaction effect of the two parameters on the friability. Additionally, the plots showed that MCC/MNTL affects friability significantly. But the effect of crospovidone on the friability is not significant relative to MCC/MNTL.

The combined effect of crospovidone and MCC/MNTL on wetting time of the FDTs is shown in Figure 4.11. The plots indicate that concentration of crospovidone and MCC/MNTL play a very significant role in influencing the response wetting time. However, the effect of crospovidone

appeared to be more pronounced as compared to the MCC/MNTL. Moreover, as the curvilinear contours of Figures 4.11 indicate, the interactive effect of the two variables was significant.

4.7.4. Simultaneous optimization of the response variables

The key aim of the optimization process was to simultaneously obtain lower DT, friability & wetting time; and higher hardness at lowest possible combination of formulation variables. Hence, both numerical and graphical optimization techniques were used for simultaneous optimization.

A. Numerical optimization

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. The optimization was done with constraints for dependent variables as the goals to locate the optimum setting of independent variables in the new formulation as shown in the following Table 4:10.

Table 4.10: Criterion settings of factors and responses for optimization

Constraint name	Goal	Lower limit	Upper limit	Importance
Crospovidone	is in range	2.0	8.0	3
MCC/MNTL	is in range	0.50	2.0	3
DT	is in range	1.0	15.0	3
Hardness	is in range	5.0	7.0	3
Friability	is in range	0.10	0.35	3
WT	is in range	1.0	15.0	3

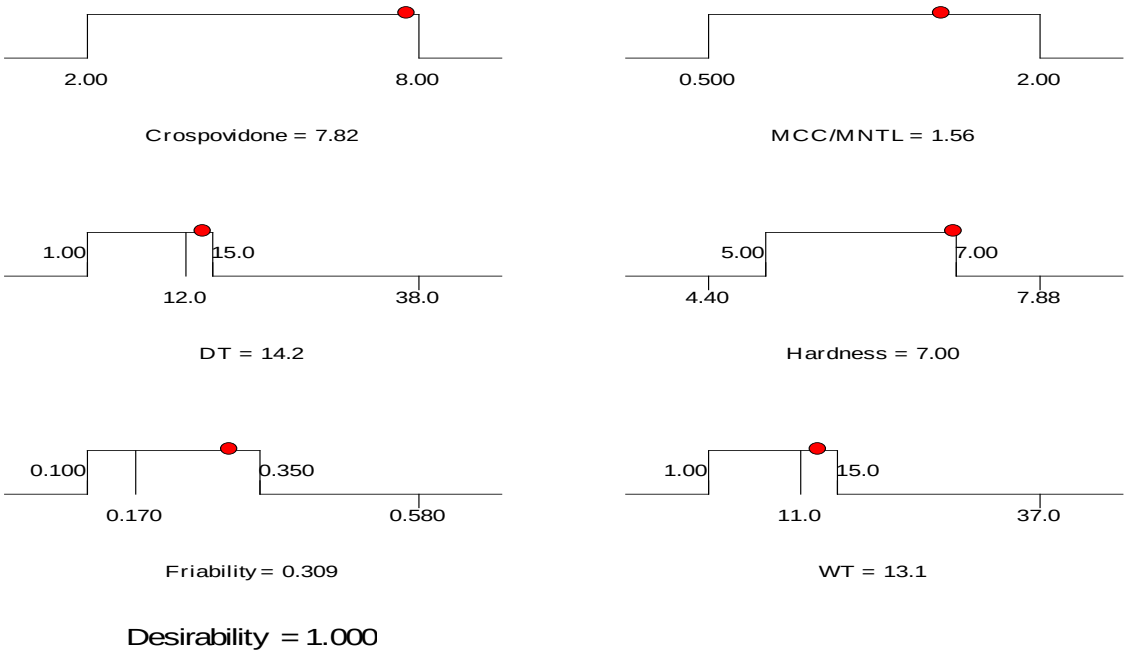


Figure 4.12: Desirability ramp for numerical optimization

The desirability function approach is one of the most widely used methods for optimization of multiple response processes. This function searches for a combination of factor levels that jointly optimize a set of responses by satisfying the requirements for each response in the design. Figure 4.12 shows the predicted optimum values and the corresponding levels of parameters according to the set goals. The dot indicates the best solutions found by the Design-Expert ®Software.

In multiple response optimizations, using desirability approach, individual desirability functions indicate measures of how well the goals for each response are satisfied; whereas overall desirability function is a measure of how well the combined goals for all responses are satisfied. The scale of the desirability function ranges between d = 0, for a completely undesirable response, and d = 1 for a fully desired response above which further improvements would have no importance. In this case, the overall desirability of d= 1 was obtained as shown in the Figure 4.12.

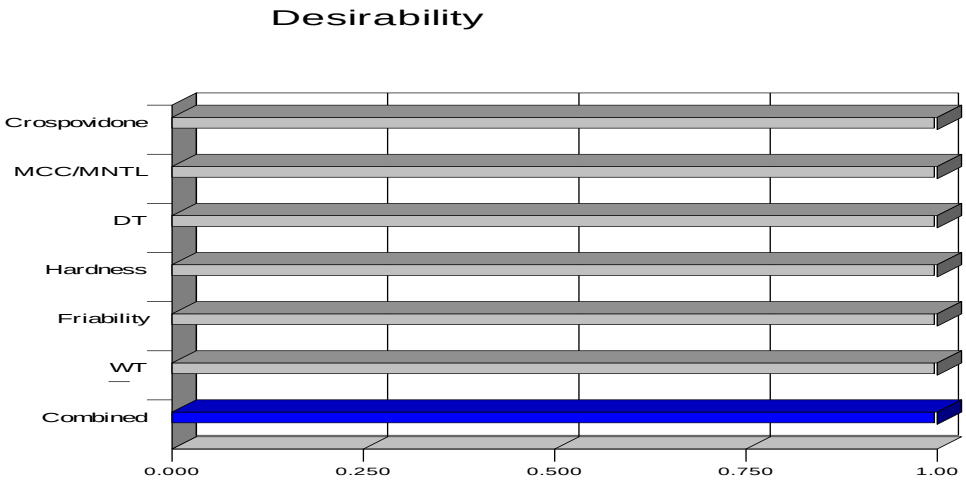


Figure 4.13: Desirability Histogram for numerical optimization

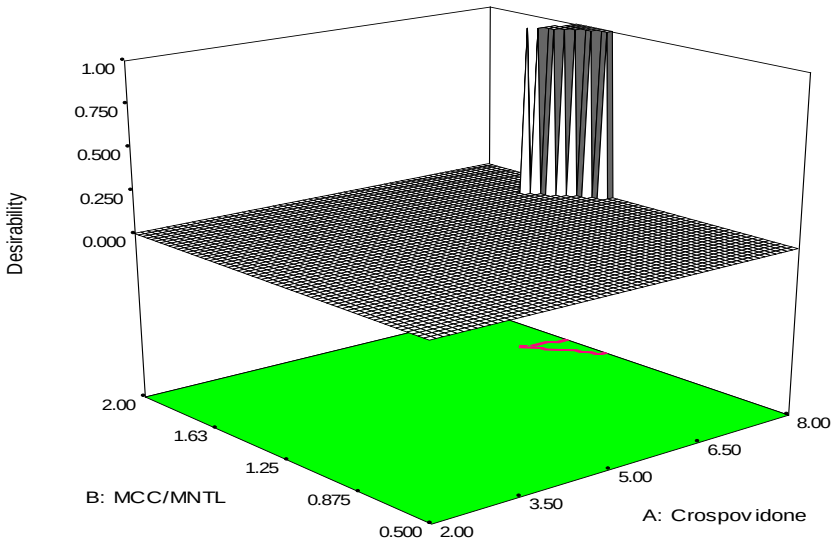


Figure 4.14: Three dimensional (3D) view of most desirable operating conditions

B. Graphical optimization

The graphical optimization allows visual selection of the optimum conditions according to certain criteria. The results of the graphical optimization are the overlay plots. For each response, the lower and upper limits have been chosen according to the numerical optimization results. The same criteria proposed in the numerical optimization have been introduced in the graphical optimization.

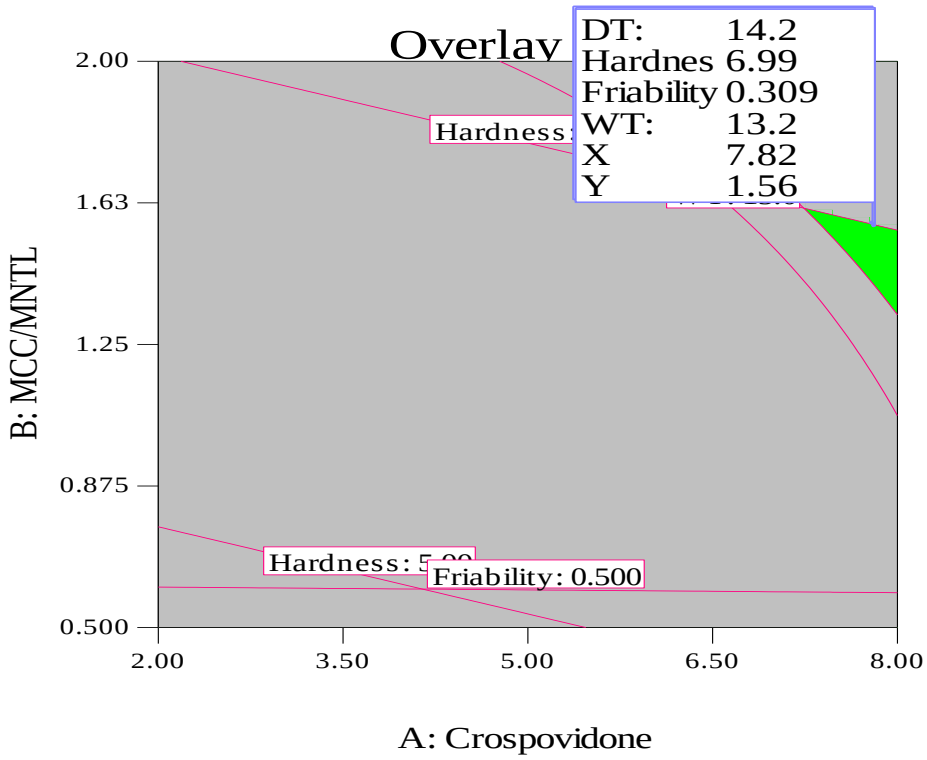


Figure 4.15: Optimum region identified by overlaying plots of the responses as functions of crospovidone concentration and MCC/MNTL

Figure 4.15 shows the overlay plot in which the green area represents the area satisfying the imposed criteria. The point identified by the flag was chosen in the graph as representative of the optimized area corresponding to crospovidone concentration of 7.82%, and MCC/MNTL of 1.56:1. Under these conditions the model predicts were disintegration time of 14.2 sec, hardness of 7 kg/cm^2, friability of 0.31% and wetting time of 13.1 sec.

4.8. Optimized formulation

To experimentally confirm the validity of the obtained optimal point, confirmatory experiments were carried out at the optimal combinations of the factors (A = 7.82%, and B = 1.56:1).

4.8.1. Characteristics of the optimized FDTs of SBS

The powder blend of optimized formulation was evaluated for powder flow. Characterization of the powder blend showed that the powder blend of the optimized formulation has good flow and compressibility properties.

Table 4.11: Physicochemical characteristics of the optimized SBS formulation powder blend

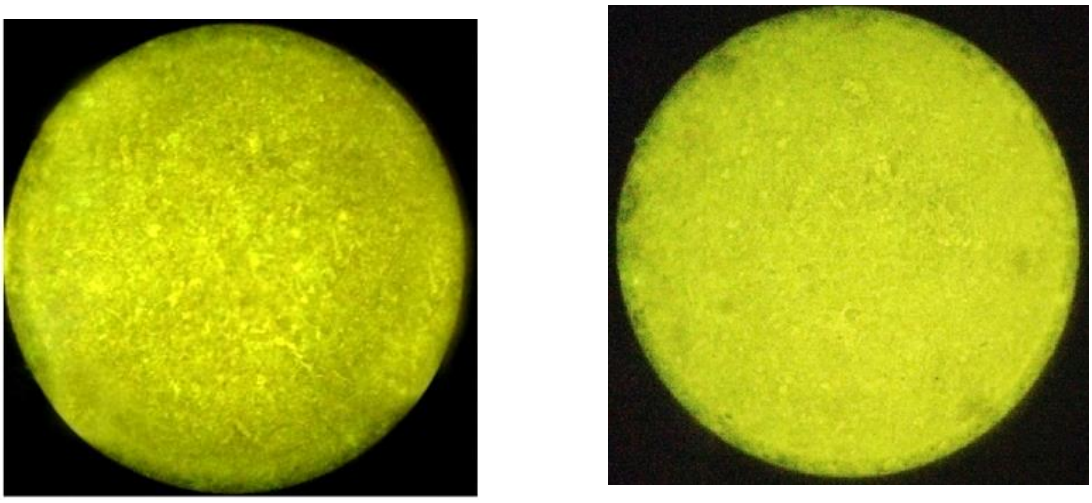
Parameters	Results ± SD
Bulk density (g/mL)	0.41 ± 0.01
Tapped density (g/mL)	0.48 ± 0.00
CI (%)	1.14 ± 0.05
HR	12.71 ± 3.86
Angle of repose (degree)	33.93 ± 0.31
Flow rate (g/s)	3.53 ± 0.50

The optimized formulation was evaluated for tablet properties. The results are presented in the Table 4.12. The values of percentage errors were below 5%, confirming that the experimental values of the optimized formulations agree well with the predicted values. The close resemblance between the observed and predicted response values indicate the robustness of the predictions; as well as the validity of the generated model.

Table 4.12: Percentage error of actual optimum formulation against the predicted responses

Responses	Predicted values	Actual values± SD	% Error
DT (sec)	14.2	14.57±0.53	2.53
Hardness (kg/cm^2)	7.00	7.17±0.82	2.37
Friability (%)	0.31	0.31±0.01	0.32
WT(sec)	13.1	13.14±0.69	0.30

4.8.2. Microscopic study for surface profiling



(A) **(B)**

Figure 4.16: Optical microphotograph of optimized FDTs of SBS before (A) and after (B) sublimation

The surface morphology before and after sublimation of optimized formulation illustrate the smooth surface of tablets before heat treatment and some small pores were formed on the surface of the latter, arising due to sublimation of ammonium bicarbonate during the temperature treatment of the tablets. Even though, the interparticular voids formed on the surfaces of the tablet are important for disintegration; highly porous tablets became esthetically unattractive (Mishra and Rohera , 2016).

5. Conclusion

In the present study, FDTs of SBS were formulated and characterized for different tablet properties as per different available standards. Factors such as level of crospovidone and MCC/MNTL were assessed for their effect on dependent factors such as disintegration time, hardness, friability and wetting time. By employing central composite design as the study design, optimization was performed for selected response factors to find the optimum level of formulation study factors. Accordingly, the desired optimum condition was obtained at 7.82% crospovidone and 1.56:1 MCC/MNTL. Under these conditions, the disintegration time, hardness, friability and wetting time were 14.57 ± 0.53, 7.17 ± 0.82 kg/cm^2, 0.311% and 13.14 ± 0.69 sec respectively. The experimentally observed responses were found to be in close agreement with the predicted values for the optimized formulations. Moreover, the validity of the obtained optimal point was confirmed by the low magnitude of percent prediction error (<5%). FDTs of SBS with lower DTs and good mechanical strength was successfully developed.

Suggestions for further work

Further investigations are suggested in the following points:

- Investigate the *in vivo* performance of the optimized formulation; and
- Conduct stability studies of the optimized.

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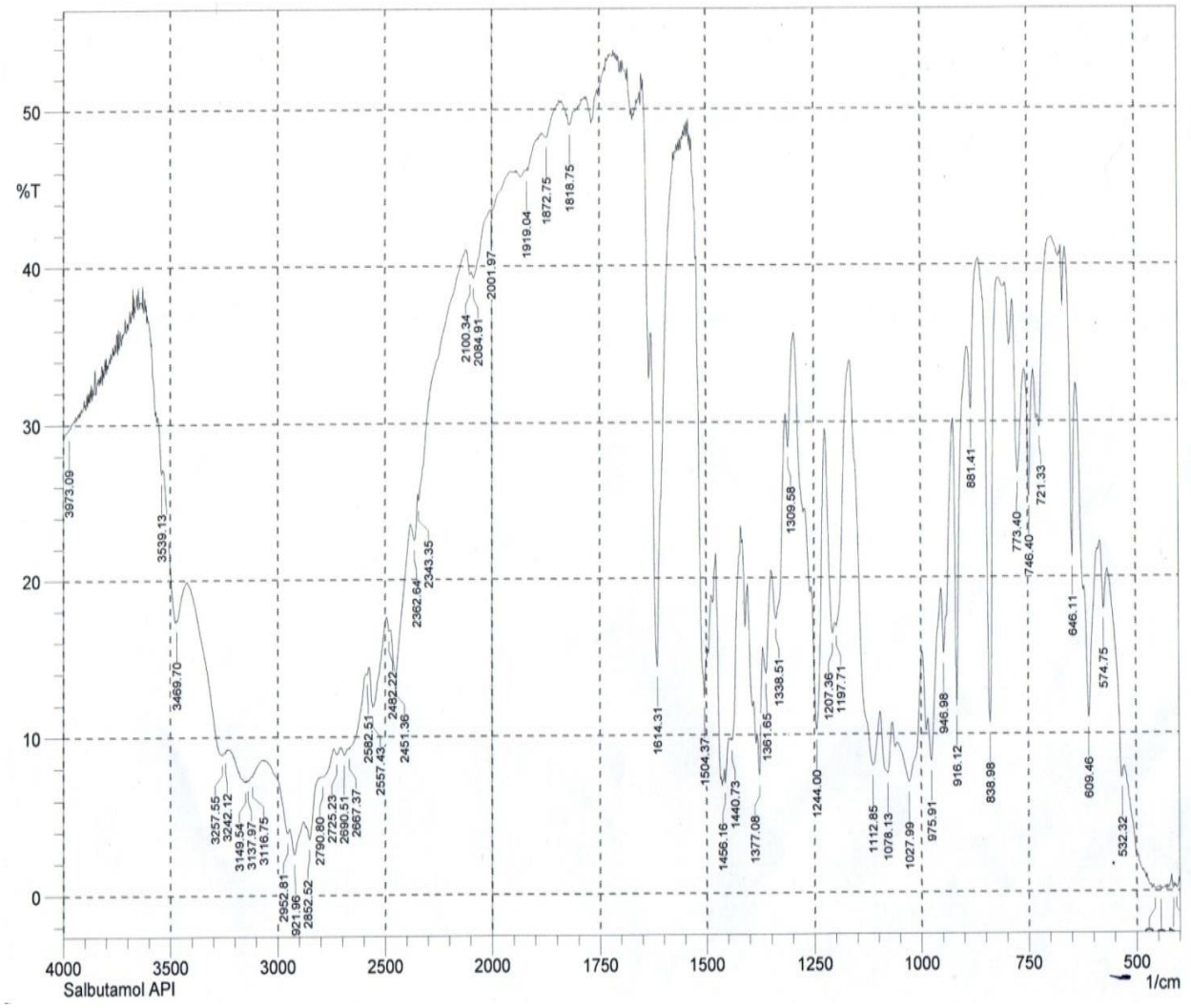
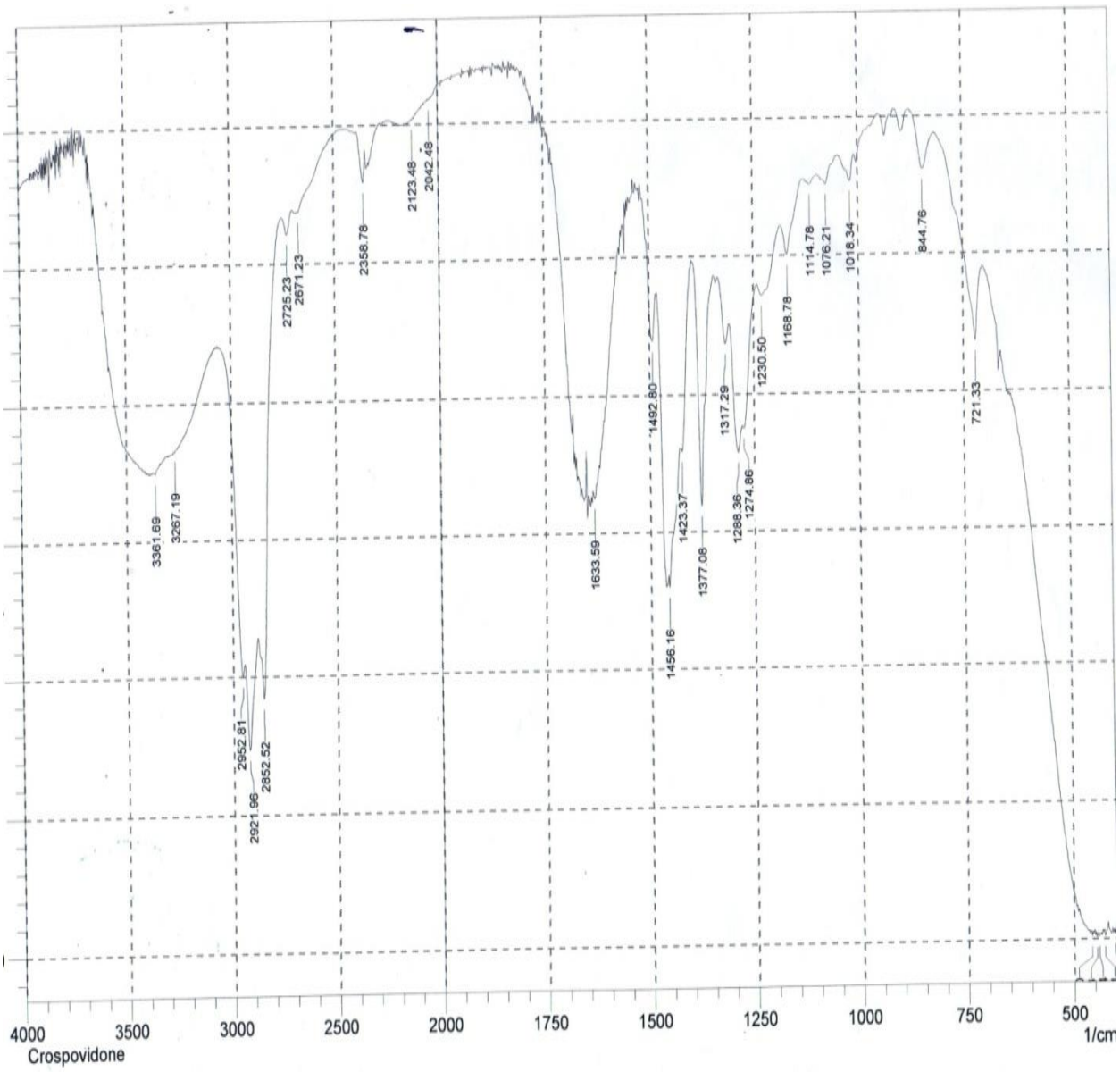
Annexes

Annex I: FT-IR Spectra of SBS



Annex II: FT-IR Spectra of Crospovidone



Annex III: FT-IR Spectra of SBS and crospovidone physical mixture (1:1) ratio