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FORMULATION AND OPTIMIZATION OF TASTE-MASKED ORODISPERSIBLE TABLETS OF STYRENE- DIVINYL BENZENE COPOLYMER COMPLEXED METOCLOPRAMIDE BY SUBLIMATION TECHNIQUE

GIDEON OLANI (B. PHARM., MBA)

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FORMULATION AND OPTIMIZATION OF TASTE-MASKED ORODISPERSIBLE TABLETS OF STYRENE- DIVINYL BENZENE COPOLYMER COMPLEXED METOCLOPRAMIDE BY SUBLIMATION TECHNIQUE

A thesis submitted to the School of Graduate Studies, 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 Master of Science in Pharmaceutics

Gideon Olani (B.Pharm., MBA)

Under the supervision of Prof. Tsige Gebre-Mariam and Dr. Anteneh Belete, Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University

Addis Ababa University

School of Graduate studies

This is to certify that the thesis prepared by Gideon Olani, entitled "*Formulation and Optimization of Taste-masked Orodispersible Tablets of Styrene- Divinyl Benzene Copolymer Complexed Metoclopramide by Sublimation Technique"* 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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Ato Alemu Tekewe	_____	_____
(External Examiner)		
Dr. Nisha Mary Joseph	_____	_____
(Internal Examiner)		
Prof. Tsige Gebre-Mariam	_____	_____
(Advisor)		
Dr. Anteneh Belete	_____	_____
(Advisor)		

_____

Dean, School of Pharmacy, AAU

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ABSTRACT

Metoclopramide (MCP) is used to treat gastroparesis, by stimulating stomach activity to empty the stomach. The matter that complicates oral administration of MCP is the fact that patients with gastroparesis often have symptoms such as vomiting and nausea as well as fullness and bloating, each of which can lead to patient discomfort with or unwillingness to swallow the available oral tablet and associated water. If vomiting takes place, the amount of MCP that remains in the stomach is unknown, and the result of treatment is even less predictable. This study provides a rapidly dissolving oral MCP formulation and administration of MCP for immediate release formulation to abate the rapid onset of gastroparesis.

Conventional taste masking techniques such as use of sweeteners, amino acids, flavoring agent are often unsuccessful in masking the taste of highly bitter drugs since they are overpowered by the taste of the medicine. MCP is an intensely bitter drug; hence, if it is incorporated directly into an orodispersible tablet (ODT), the main objective behind formulation of such a dosage form will definitely become futile. Hence, ion exchange resin (IER) has been used as drug carrier to mask its taste after the drug is loaded into an IER by an exchanging reaction, with the formation of drug–resin complex.

Screening experiments for parameters such as: drug to resin ratio, swelling time and stirring (complexation) time were optimized to 1:3, 30 min and 1 h, respectively, for maximum drug loading. The effect of temperature was found to be not significant on maximum amount of drug loading. During preparation of drug resin complex (resinate), the other variables were kept constant. The effect of formulation variables (concentration of ammonium bicarbonate as subliming agent, concentration of crospovidone as superdisintegrant and amount of microcrystalline cellulose (MCC)) and a process variable (compression force) on tablet hardness, disintegration time, and friability was optimized using 2^4 randomized full factorial design.

Accordingly, the various models describing the relationship of the selected variables were obtained using Design-Expert 8.0.7.1 software and the models were analyzed. The corresponding surface response and contour plots were also obtained and the optimum area was determined and, then validated. Simultaneous optimization of the responses gave the most desirable representative optimum formulation, within the common optimum region, with a disintegration time of 17.82 s,

hardness of 75.49 N and friability 0.40% at ammonium carbonate 14.20%, crospovidone 6.14%, MCC 51.31% and compression force 10.15 KN. The validity of obtained optimal point was confirmed by the low magnitude of percent prediction error. With that a stable, taste-masked MCP ODTs, which is suitable for patients with gastroparesis was developed.

The prepared optimized formulations were characterized for powder properties, tablets morphology, *in vitro* drug release behavior, taste-masking and stability. The study showed that a porous, taste-masked, and stable MCP ODTs with superior *in-vitro* drug release profile as compared to available marketed products, which is suitable for patients with gastroparesis was developed.

Key words: metoclopramide, ion exchange resin, resinate, orally disintegrating tablets, taste-masking, sublimation technique, optimization, full factorial design

ACRONYMS

ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
CINV	Chemotherapy-Induced Nausea and Vomiting
CKD	Chronic Kidney Disease
CTZ	Chemoreceptor Trigger Zone
3D	3- Dimension
DLE	Drug Loading Efficiency
DRC	Drug Resin Complex
DT	Disintegration Time
DVB	Divinyl Benzene
EPHARM	Ethiopian Pharmaceuticals Manufacturing Share Company
FTIR	Fourier Transform Infrared Spectrophotometer
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonization
IER	Ion Exchange Resin
MCC	Micro Crystalline Cellulose
MCP	Metoclopramide
NF	National Formulary
ODT	Orodispersible Tablet
qs	Quantity Sufficient
rpm	Revolution per Minute
RS	Reference Standard
USP	United States Pharmacopoeia
UV	Ultra Violet

1. INTRODUCTION

1.1 Orally disintegrating (or dissolving) tablets (ODTs)

Tablets are the most widely used dosage form because of their convenience in terms of self-administration, compactness and ease in manufacturing. However, dysphasia is a common problem encountered in all age groups in concern to solid dosage forms, which results in high incidence of noncompliance and ineffective therapy during administration of solid dosage forms. In more recent years, increasing attention has been paid to formulate not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating (or dissolving) tablets (ODTs) that are intended to dissolve and/or disintegrate rapidly in the mouth. (Abed *et al*., 2010).

ODTs are solid dosage forms that are placed in the mouth, rapidly disintegrate and/or dissolve when in contact with the saliva and then easily swallowed without the need for water. Over the last decades, the demand for development of ODTs has enormously increased, as it has significant impact on the patient compliance (Hirani *et al*., 2009). ODTs offer an advantage for populations who have difficulty in swallowing. A study showed that dysphagia is common among all age groups of people, but it is more specific in pediatric and geriatric population (Prajapati and Patel, 2010).

ODTs are also called orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and repimelts. However, of all the above terms, the United States Pharmacopoeia (USP 30/NF25, <711>, 2007) approved these dosage forms as ODTs. The European Pharmacopoeia (Ph. Eur., 2005) uses the term ‘‘Orodispersible tablet’’ for tablets that disperse readily within 3 min in the mouth before swallowing. United States Food and Drug Administration (FDA) defined ODT as ‘‘A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within matter of seconds when placed upon the tongue’’ (Fu *et al*., 2004). The main attribute of this drug delivery is administration without water.

Target groups for ODTs are wide ranging as people of all ages can experience difficulty in swallowing conventional tablets and capsules. This includes children and the elderly who either experience difficulty and cannot swallow or have not learnt to swallow the conventional solid dosage forms. In addition, institutionalized psychiatric patients as well as hospitalized or bedridden patients suffering from a variety of disorders such as stroke, Parkinson's disease, multiple sclerosis and cerebral palsy also find difficulty in swallowing and require ODTs because of their physical condition (Chandrasekhar *et al.*, 2009; Peera *et al*., 2013). The convenience and ease of using ODTs is also important to patients, with some adults preferring these dosage forms as they are easy to handle and swallow, can be taken without water and have a rapid onset of action. For example, patients with a limited access to water would also find such ODTs extremely beneficial.

ODTs provide several advantages as they combine the properties of both liquid and conventional tablet formulations, and also offer advantages over both traditional dosage forms. ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients; no risk of obstruction of gastrointestinal tract by the dosage form, which is beneficial for traveling patients who do not have access to water, easy administration of inpatients (specially for mentally retarded and psychiatric patients); the rapid disintegration of the tablet results a quick dissolution of the drug and fast absorption that provide rapid onset of action. Besides, improving the acceptability and compliance of patients, ODTs have been investigated for their potential to increase the bioavailability through the enhancement of the dissolution rate. Fast dissolving formulation has become popular as novel drug delivery system (NDDS) because it is safest, most convenient and an economical method of drug delivery having the highest patient compliance (Ciper and Bodmeier, 2006).

1.2 Manufacturing of ODTs

Design of an ODT requires enough porosity inside the tablet for fast dissolving or fast melting while maintaining the mechanical strength of the tablet (Fu *et al*., 2004). There are several technologies that produce ODTs. The technologies are usually grouped according to the method used in making ODTs: freeze drying method, molding method, and

compression method. ODT preparation methods also include sublimation, spray-drying, phase transition and mass extrusion.

1.2.1 Freeze drying

Freeze drying (lyophilization) is a process in which solvent is removed from a frozen drug solution or a suspension containing structure-forming excipients. First of all, the material is frozen to bring it below its eutectic point. Then, drying is carried out to reduce the bound moisture to the required level. Due to lyophilization, bulking agent and sometimes drug acquire glossy amorphous structure and thus dissolution is enhanced. It normally consists three steps. First, material is frozen to bring it below the eutectic point. Then, primary drying to reduce the moisture around 4% (w/w) of dry product. Finally, secondary drying to reduce the bound moisture up to required final volume. Entire process is carried out at non-elevated temperature; therefore, nullifying adverse thermal effects that may affect drug stability during processing (Roy, 2016).

1.2.2 Direct compression

Direct compression is one of the most popular techniques for preparation of ODTs. The advantages of this method include easy implementation, use of conventional equipments along with commonly available excipients, limited number of processing steps, cost effectiveness and also accommodate higher dose in comparison to the other methods. The basic principle involved in the development of these dosage forms using this technique is addition of superdisintegrant in optimum concentrations so as to achieve rapid disintegration along with pleasant mouth feel. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration (Shukla *et al*., 2009). The disintegration and dissolution of directly compressed tablets depends on single or combined effect of disintegrant, water soluble excipients and effervescent agents. Disintegrant efficacy is strongly affected by tablet size and hardness. Sugar-based excipients have been widely used as bulking agents because of their high aqueous solubility and sweetness, pleasant

mouth-feel and good taste-masking capacity. Nearly all formulations for ODTs incorporate some sugar materials in their formulations (Sharma *et al*., 2008).

1.2.3 Molding

In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression (Badgujar and Mundada, 2011). The solvent is then removed by air drying. Molded tablets are very less compact than compressed tablets. They possess porous structure that enhances dissolution (Fu *et al.*, 2005).

1.2.4 Sublimation

The basic principle involved in this technique is addition of volatile salts (e.g., ammonium bicarbonate) to other tablet excipients and the mixture is then compressed into tablets. Entrapped volatile material is then removed via sublimation. A high porosity is achieved due to the formation of many pores where volatile material particles previously existed in the compressed tablets prior to sublimation, which help in achieving rapid disintegration when the tablet comes in contact with saliva (Dali *et al*., 2009). Mouth dissolving tablets with highly porous structure and good mechanical strength can be developed by this method (Amidon, 2012).

1.2.5 Spray drying

Spray drying provides a fast and economical way of removing solvents and producing highly porous fine powders that dissolve rapidly. Because processing solvent is evaporated rapidly, spray drying can produce highly porous, fine powder. Spray drying can be used to prepare rapidly disintegrating tablets. 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 (Allen and Wang, 2001). The formulations are incorporated by hydrolyzed and non-hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as

disintegrating 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).

1.3 Taste-masking in ODTs

The taste-masking of unpleasant taste drugs is a major challenge especially for the development of ODTs in pharmaceutical industry. Taste of a pharmaceutical product is an important parameter for patient compliance. Thus, taste-masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment, especially in pediatrics. There are a number of factors that are taken into consideration during the taste-masking formulation like, extent of the bitter taste of the active component, total dose of the drug, drug particulate shape and size distribution, solubility and ionic characteristics of drug, formulation characteristics in terms of disintegration and dissolution rate, desired release rate and bioavailability and type of dosage form (Sohi *et al.*, 2004).

Though the use of flavors and/or sweeteners is very much a non-platform technology, an overview of different approaches and pharmaceutical platform technologies that may be utilized for the taste masking of active pharmaceutical ingredients (APIs) in oral dosage forms as explained by Walsh *et al*. (2014) as elaborated in Fig. 1.1 below.

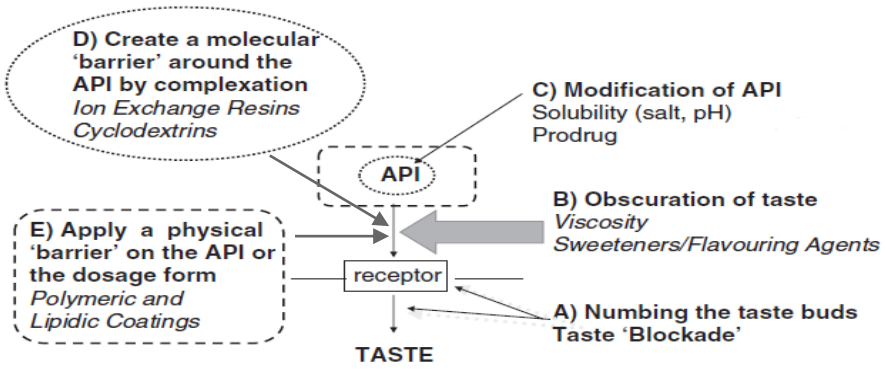


Figure 1.1: Overview of taste masking methods. (Adopted from Walsh *et al*. (2014))

Two approaches are commonly utilized to mask unpleasant taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility

and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste buds (Helmy *et al*., 2011).

Several methods are available to achieve the approaches stated above. The first is to mask the distasteful sensation by the addition of flavors, sweeteners and effervescent agents. The second method involves the use of complexing agents (cylcodextrins, ion exchange resins) through the formation of inclusion complexes or resinates. The third is to avoid the bitter drugs coming into direct contact with patients' taste buds by coating or granulation. The flavor is often overpowered by the taste of the medicine and the use of effervescent agents is not always convenient. Moreover, the coatings and the granulation of the active ingredient as well as microencapsules may often rupture during compressing and chewing of the tablet, as well as contribute to a gritty feel. Among the numerous available taste-masking methods, ion exchange resins are inexpensive and can be used to develop a simple, rapid and cost-effective method of taste masking (Helmy *et al*., 2011).

1.4 Ion-exchange resins

IERs are cross-linked synthetic high molecular weight solid water insoluble usually white or yellowish, fabricated from organic polymer (polyelectrolyte) having ionizable functional group (Sivaneswari *et al*., 2015). An IER can be described as an assembly of polymers that contain ionizable groups distributed along the polymer backbone. The ionizable groups of the polymer backbone are associated with ions. When the polymer is combined with a solution of counter ions, the counter ions in the solution exchange with the ions of the polymer and the counter ions are physically removed from the solution. Therefore, counter ions (e.g., drug ion) in solution can exchange with the ions of the IER (e.g., polymer) through an ionic interaction, as opposed to a covalent interaction. The pharmacologically active drug ions can then be eluted from the IER to treat the subject (Bhise *et al*. 2008).

1.4.1 Types of IER

There are two major classes of ion-exchange polymers: cation and anion exchange resins. Cation exchange resins contain covalently bound negatively charged functional groups and

exchanges positively charged ions whereas anion exchange resins have positively charged functional groups and exchanges negatively charged ions. Cation exchange resins can be further classified into strong acid cation exchange resins and weak acid cation exchange resins. In a weak acid resin the ionizable group is a carboxylic acid (COOH) as opposed to the sulfonic acid group (SO_3H) used in strong acid resins. Anion exchange resins can be further classified strong base anion exchange resins and weak base anion exchange resin. In strong basic anion exchange resin the ionizable group is quaternary ammonium and in weakly basic anion exchange resin the ionizable group is polyalkylamine (Sivaneswari *et al*., 2015).

Table 1.1: Common ion exchange resins

Type	Exchange Resins species	Polymer backbone	Commercial
Strong cation	$-SO_3H$	Polystyrene DVB	Amberlite IR 120, Dowex 50, Indion 244, Purolite C100HMR, Kyron -T-154
	$-SO_3Na$	Sodium Polystyrene	Tulsion T-344, Amberlite IRP 69, Indion 254
Weak cation	-COOH		Amberlite IRC 50, Indion 204, Purolite C102DR, Kyron-T-104, Kyron-T-114, Doshion P544(R), Tulsion T-335
	$-COO-K^+$	Methacrylic acid DVB	Tulsion T-339, Amberlite IRP88, Indion 234, Kyron-T-134
Strong anion	N^+R_3	Polystyrene DVB	Amberlite IR 400, Dowex 1, Indion 454, Duolite AP 143
Weak anion	N^+R_2	Polystyrene DVB	Amberlite IR 4B, Dowex 2

1.4.2 Use for drug complexation

Pharmaceutical applications of resins were recognized in the early 1950s when Amberlite IRC-50 (a weak cation exchange resin) was used in the successful purification of streptomycin. Over the succeeding five decades, IER have found use as taste masking of

bitter tasting drugs. As palatability relies on the substance being dissolved (or partially dissolved) to elicit the taste sensation, it follows that the formation of a high molecular weight complex will adversely affect the solubility of the compound. This minimizes undesirable organoleptic properties, such as taste or odor, by ensuring that the drug is present below the taste threshold (Elder, 2005).

Thus, IERs can be used in drug formulations to stabilize the sensitive components, sustain release of drug, disintegrate tablets and mask taste. The resin form insoluble adsorbate or resinates through weak ionic bonding with oppositely charged drugs so that dissociation of drug resin complex (DRC) does not occur under the salivary pH conditions (Pattarakan, 2011). Bitter cationic drugs can get adsorbed onto the strong cation exchange resin of sulfonic acid functionality to form the complex which is non bitter (Borodkin, 1991). Similarly bitter anionic drugs can get adsorbed onto the strong anion exchange resin of quaternary ammonium functionality to form the complex which is non bitter.

The selection of IER for drug delivery applications is primarily governed by the functional-group properties of the IER. However, the following points need to be considered during selection: capacity of the IER; degree of cross linking in the resin matrix; particle size of resin, nature of drug and site of drug delivery. It is also important to evaluate the resin in the pH- and ionic-strength environment, simulating the *in vivo* situation; swelling ratio; biocompatibility and biodegradability; regulatory status of the IER (Bhattacharjee and Dass, 2013).

1.4.3 Advantages of IER

The polymeric (physical) and ionic (chemical) properties of IER will release the drug more uniformly than that of simple matrices (because of physical properties only) (Chaudhary, 1956). Moreover, IER imparts flexibility in designing a variety of delivery systems, such as liquids (Sprockel and Price, 1989), beads (Motycka, 1985), microparticles (Ichikawa, 2001) and simple matrices (Sanghavi, 1988). Due to the versatile utility of IERs, they are being used for various drug delivery and therapeutic applications. IERs are physical stable,

high molecular weight water insoluble polymers. They are not absorbed by the body and therefore are inert (Singh *et al*., 2007).

IERs have been used to overcome various pharmaceutical formulation problems including bitter taste, poor stability, deliquescence, and poor dissolution of drugs (Singh *et al*., 2007). Puttewar *et al*. (2010) indicated that saliva, with an average pH of 6.7 and a cation concentration of 40 meq/L, would only elute a few percent of drug from resin adsorbate. Jeong and Park (2008b) reported that the kinetics of drug release from drug/resin complexes are dependent upon the amine moieties of the drugs used, such as NH_2, –NH–, –N–, and $–N^+–$; and the order of decreasing complex strength among the amine drugs follows: –N– >–NH–>NH_2- .

1.4.4 Dowex Marathon C®

Dowex Marathon C® is a strong acid cation exchange resin based on a cross-linked acrylic-copolymer, styrene- divinyl benzene (DVB) matrix containing sulfonic acid (-SO_3H) functional groups. Degree of resin crosslinkage is the percentage of DVB in the resin copolymer. It contains 8% DVB and total swelling of 8%. It combines with high capacity; it is insoluble in all common solvents, having excellent physical and chemical stability and operating characteristics (Dow Chemical Company, 2002a). The -SO_3H functional group strongly ionizes to -SO_3^-. The degree of cross linking is controlled by the percent of DVB used in the copolymerization. A conventional gel type, styrenic ion exchanger is built on a matrix prepared by co-polymerizing styrene and DVB as elaborated in Figures 1.2 and 1.3 (Dow Chemical Company, 2000). Maximum operating temperature and pH range for Dowex Marathon C® are 120 ºC and 0–14, respectively (Dow Chemical Company, 2002b).

The most commonly used polymer backbone for strong cation exchange resin is based on polystyrene. DVB is included in the copolymerization for cross linking the polymer chains (Mastropietro *et al*., 2015). The resin characteristics are altered with degree of sulfonation, providing that differently sulfonated resins could be prepared (Sivaneswari *et al*., 2015). Copolymers based on vinyl, DVB and polystyrene having extensive charged

functional sites have extensive binding sites leading to very high drug-loading capacity (Rehman and Khan., 2012).

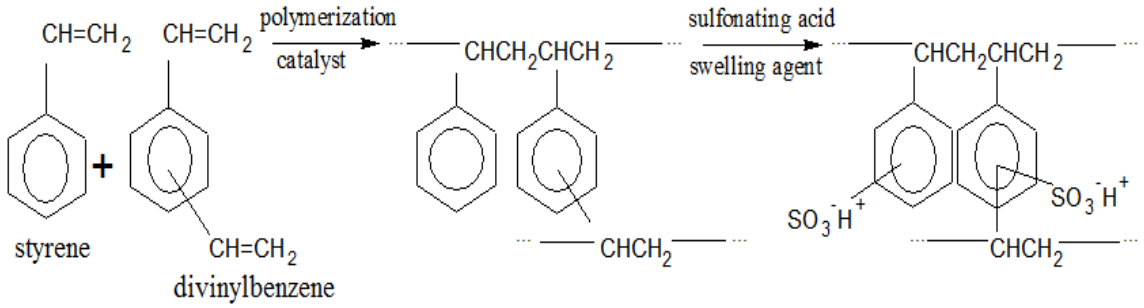


Figure 1.2: Resin structure and manufacture

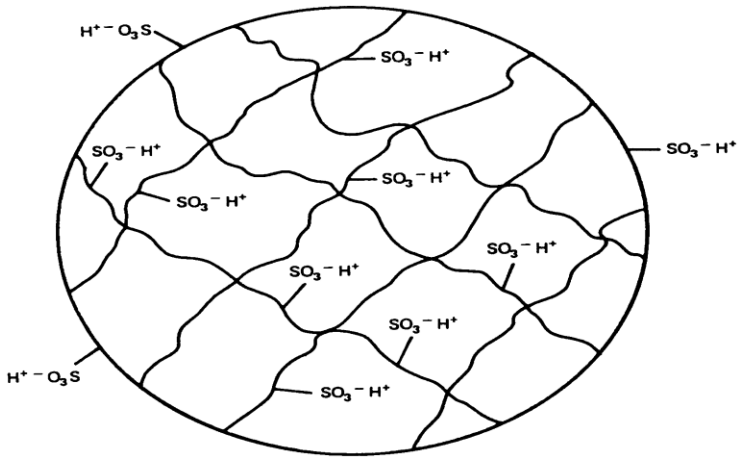


Figure 1.3: Cation exchange resin schematic showing negatively charged matrix and exchangeable positive ions

1.5 Metoclopramide HCl

1.5.1 Physicochemical properties

Metoclopramide (MCP), 4-Amino-5-chloro-N-(2-(diethyl amino) ethyl)-2-methoxy benzamide (Fig. 1.4), which is characterized as a weak base, is a dopamine-receptor antagonist used for its antiemetic and prokinetic properties. It is a bitter, white or almost white crystalline powder and it is odorless. At 25 °C, 1 g MCP is soluble in 0.7 g of water, 3 g of ethanol (96%) and 55 g of chloroform, though it is practically insoluble in ether. It

is soluble in dilute hydrochloric acid. It shows two ionization constants; pK1 = 0.42 and pK2 = 9.71 (Ghonim, 2014).

MCP is available as *10 mg tablet, 5mg/5 mL Syrup, 0.2 mg/drop pediatric oral Drop, and 5 mg/ mL Injection in 2 mL ampoule* as MCP HCl.

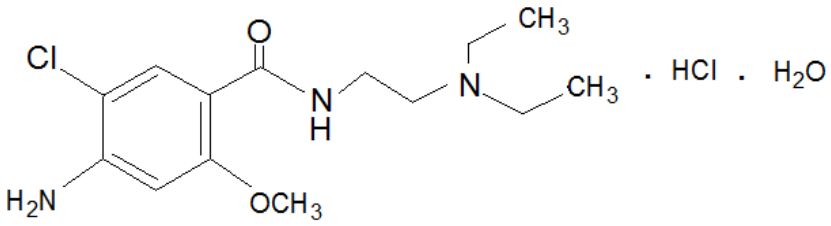


Figure 1.4: Chemical structure of MCP

1.5.2 Pharmacokinetic and pharmacodynamic properties

Bioavailability following oral administration of MCP is rapid and almost complete. Peak plasma concentration is usually attained at 1-2 hours. Onset of action following oral administration is 30-60 min for effects on GI tract. Duration is for 1-2 hours. Distribution extent in mice indicate that MCP is distributed into most body tissues and fluids; high concentrations attained in GI mucosa, liver, biliary tract, and salivary glands, with lower concentrations in brain, heart, thymus, adrenals, adipose tissue, and bone marrow. It is distributed into milk in humans; milk concentrations are higher than plasma concentrations 2 hours after oral administration. 13-30% of MCP is bound to plasma proteins, principally albumin. It is minimally metabolized (about 10%). Whether major metabolite found in urine and feces is active is not known yet. It is excreted in urine (85%) as unchanged drug and metabolites and also in feces (about 5%). The rest is removed by hemodialysis or peritoneal dialysis. The average elimination half-life in individuals with normal renal function is 5 to 6 h (McEvoy *et al.*, 2011).

MCP is useful to treat gastro-intestinal symptoms associated with chronic kidney disease (CKD). MCP is a more specific agent to treat drug-associated emesis, including chemotherapy-induced nausea and vomiting (CINV) and it supersedes in many situations the phenothiazines and butyrophenones. This is because at lower doses, MCP acts as a selective D2 antagonist at the chemoreceptor trigger zone (CTZ) and its effects mirror those

of the phenothiazines and butyrophenones. However, it also exerts peripheral D2 antagonism at these doses, and stimulates cholinergic receptors in gastric smooth muscle, thus stimulating gastric emptying. It may, therefore, be more effective than phenothiazines and butyrophenones when nausea is related to gastrointestinal or biliary diseases. The prokinetic dopamine (D2) antagonist MCP should also be used for patients with nausea and vomiting associated with functional gastric or intestinal stasis (Walker and Whittlesea, 2012). MCP is also used in diabetic gastric stasis, postsurgical gastric stasis, prevention of postoperative nausea and vomiting, prevention of cancer chemotherapy-induced emesis, intubation of the small intestine, radiographic examination of the upper GI tract and gastroesophageal reflux (McEvoy *et al.*, 2011).

1.6 Optimization methods

Pharmaceutical formulators often face the challenge of finding the right combination of formulation variables that will produce a product with optimum properties. One of the difficulties in the quantitative approach for formulation design is due to difficulty in understanding the real relationship between causal factors and individual pharmaceutical responses. Optimization becomes more important for particular delivery systems.

It is desirable to develop an acceptable pharmaceutical formulation in the shortest possible time using minimum number of man-hours and raw materials. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions (Collins *et al*., 2009). The number of experiments required for these studies is dependent on the number of independent variables and its levels selected. The traditional ‘one variable at a time method’ requires many experiments and there is no guarantee that an optimal formulation can be achieved. Moreover, the interaction between different factors, which can influence the target responses, may not be detected (Bezerra *et al*., 2008). Systematic optimization technique can be successfully employed for the design and development of ODTs. These studies usually involve the use of response surface methodology (RSM), which has proven to be a useful tool in the development of solid dosage forms. Factorial design is a type of RSM, where all the factors are studied in all possible combination. Factorial design is an

efficient technique in estimating the influence of individual variables (main effects) and their interactions using minimum experimentation (Collins *et al*., 2009).

But, statistical experimental design provides an economical means to obtain desirable information about an experimental method by just performing a few numbers of experimental runs; they also help to determine any type of interactions among study variables and also used to predict the chances of experimental errors. Therefore, the use of an experimental design is quite helpful in the optimization of pharmaceutical formulations (Ranjan *et al*., 2012).

1.6 The present study

Dysphagia is common among all age groups of people, although pediatric and geriatric patients are the most affected ones. Formulation of orally disintegrating MCP tablets could help to improve patient compliance and therapeutic effect. ODTs do not need water for swallowing and they are very convenient for patients who are travelling or do not have immediate access to water, as well as ease of administration to geriatric, pediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.

MCP, a derivative of para-aminobenzoic acid, is a commonly prescribed drug used for the management of gastrointestinal disorders such as gastric stasis, gastroesophageal reflux and for the prevention of cancer chemotherapy- induced emesis. The matter that complicates oral administration of MCP is the fact that patients with gastroparesis often have symptoms such as vomiting and nausea as well as fullness and bloating, each of which can lead to patient discomfort with or unwillingness to swallow the available oral tablet and associated water. If vomiting takes place, the amount of MCP that remains in the stomach is unknown, and the result of treatment is even less predictable. Emesis is often preceded with nausea making administration of MCP with a glass of water more difficult; hence it is beneficial to administer MCP as ODTs. MCP is an intensely bitter drug. If MCP is incorporated directly into an ODT, an acceptable degree of palatability and the desired therapeutic effect will not achieved.

Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Conventional taste masking techniques such as the use of sweeteners, amino acids, flavoring agents are often unsuccessful in masking the taste of highly bitter drugs as explained by Szakonyi, (2014) and Malladi, *et al.* (2010) as the flavor is often overpowered by the taste of the medicine and the use of effervescent agents is not always convenient. A suitable solution here is to use IER. IERs can be used as the drug carriers to mask its taste by forming drug-resin complex formation.

Thus, in the present study an attempt has been made to mask the taste of MCP and to formulate ODTs with good mouth feel so as to prepare a "patient-friendly dosage form"

1.7 Objectives of the study

1.7.1 General objective

- To formulate, optimize and evaluate orodispersible taste-masked tablets of MCP complexed with styrene-DVB copolymer using sublimation technique.

1.7.2 Specific objectives

- To prepare and characterize taste-masked MCP-styrene DVB copolymer resinate;
- To formulate taste-masked MCP resinate orodispersible tablets using sublimation technique;
- To evaluate the taste-masked MCP orodispersible tablets;
- To optimize the process and formulation parameters of taste-masked orodispersible tablets of MCP resinate; and
- To evaluate an optimized formulation of taste-masked MCP orodispersible tablets.

2. MATERIALS AND METHODS

2.1 Materials

MCP HCl (Benzochem Lifesciences (P) Ltd, India), styrene-DVB gel matrix (DOWEX MARATHON C® Dow Chemical Company, USA), microcrystalline cellulose (Avicel®) Microcellulose Weissenborn GmbH + KG, Weissenborn, Germany), ammonium carbonate (BDH Laboratory Supplies Poole, BH15 1TD, England), crospovidone (China Associate Co. Ltd, Shenzhen, China), colloidal silicon dioxide (Aerosil®) (Evonik Industries AG, Germany), purified talc powder (Gangotri Inorganic (P) Ltd, India), magnesium stearate (China Associate Co. Ltd, Shenzhen, China), mannitol (China Associate Co. Ltd, Shenzhen, China), hydrochloric acid and sodium hydroxide (BDH Ltd., Poole, England), disodium hydrogen orthophosphate and potassium dihydrogen orthophosphate (VWR international Ltd. Poole, England) were all kindly donated by the Ethiopian Pharmaceuticals Manufacturing S.C., and used as received. MCP HCl 10 mg oral tablets PREMOSAN® (batch number 0009; Exp. Date 07/2018 Julphar, U.A.E.) and Regurg® (batch number T-684; Exp. Date 04/2017 Leben Laboratories PVT. Ltd., India) were purchased from local market in Addis Ababa.

2.2. Methods

2.2.1 Characterization of Dowex Marathon C®

*2.2.1.1 **Total exchange capacity** (Total new volume capacity)*

Three milliliters of conditioned (washed repeatedly with distilled water to remove minerals, chemicals and contaminants), undried resin gel was transferred to a 5 mL graduated cylinder, and water was filled in it. Air bubbles from the resin bed was removed by stirring with a stainless steel wire. The resin was then allowed to settle to its minimum volume by gently tapping the graduated cylinder and the volume of the resin was recorded.

The resin was transferred to a 250 mL conical flask with 100 mL of water. Then, 2 mL of 0.1 N sulfuric acid was added, heated to 70 ^{0}C to 80 ^{0}C, and held at that temperature for 5 min with occasional stirring. After the mixture was cooled to room temperature, 2.5 mL of

50% (v/v) nitric acid, 2 mL of ferric ammonium sulfate, and 0.2 mL of 0.1 N ammonium thiocyanate solutions were added. The resulting solution was titrated with 0.1 N silver nitrate volumetric solution until it turned colorless, and about 5 mL of excess silver nitrate was added. The mixture was heated to boiling to coagulate the silver chloride precipitate and cooled to room temperature. Finally, 10 mL of nitrobenzene was added, stirred vigorously and the excess silver nitrate was titrated with 0.1 N ammonium thiocyanate.

The total capacity is determined as:

(net mL $AgNO_3$ × N) / (mL of resin) = Eq / L

2.2.1.2 pH of resin

The resin gel (25 mL) of was soaked in 20 mL of 10% (w/v) neutral brine solution for 15 min. The pH of the resin solution was measured with calibrated pH meter (SevenCompact™ pH/Ion S220, China) three times.

2.2.1.3 Density measurement

Fully hydrated resin (25 mL) was placed in to a graduated plastic measuring cylinder and suspended with 50 mL of purified water. After the resin was completely settled down, the water was decanted. The mass of the resin sediment was weighed and the density was calculated from the mass and volume of the resin obtained. The measurement was repeated three times.

2.2.1.4 Moisture content

Ten milliliters of the resin (as received) was transferred to a flask, and it was converted completely to the hydrogen form by stirring with 150 mL of 4 N HCl for 30 minutes. The acid was decanted, and the resin was washed in the same manner with water until the wash water is neutral pH.

Five milliliters of the regenerated resin was transferred to a glass filtering crucible, and the excess surface water only was removed by very careful suction filtration. The conditioned resin was transferred to a tarred weighing bottle, and weighed. Then, it was made to dry in

a vacuum oven at a pressure of 50 mm of mercury at 100°C for 16 hours. Finally, it was transferred from the vacuum oven to a Desiccator, and cooled to room temperature and again weighed.

2.2.2 Activation of the cation exchange resin

HCl (4 N, 200 mL) was added to the resin gel (100 g). The mixture was stirred continuously for 30 min (Blackburn *et al*., 1979). Then, it was washed repeatedly with distilled water until the pH of supernatant is the same as pH of the distilled water used. Finally the resin gel was dried.

2.2.3 Construction of calibration curve

Calibration curve of MCP HCl in 0.1 N HCl

Stock solution of MCP HCl was prepared by dissolving 100 mg of MCP HCl working standard to 100 mL in a volumetric flask with 0.1 N HCl. Ten milliliters of the stock solution was further diluted to 100 mL with 0.1 N HCl to prepare working standard solution. From this working standard solution, six different standard solutions of final concentrations of 4, 6, 8, 10, 12 and 14 µg/ mL were prepared. The UV absorbances of the solutions were measured in triplicate at 273 nm with UV/Visible spectrophotometer (UV-1800, SHIMADZU, Japan) using 0.1 N HCl as a blank. Absorbances were plotted against concentrations of solutions to obtain the calibration curve.

Calibration curve of MCP HCl in phosphate buffer (pH 6.8)

Standard stock solution of MCP HCl working standard was prepared by dissolving 100 mg of MCP HCl working standard in 100 mL phosphate buffer (pH = 6.8). Ten milliliters of the stock solution, was diluted to 100 mL phosphate buffer (pH = 6.8) to prepare working standard solutions. Six different standard solutions of final concentrations of 4, 6, 8, 10, 12 and 14 µg/ mL were prepared. The UV absorbance readings of the solutions were measured at 273 nm using UV/Visible spectrophotometer (UV-1800, SHIMADZU, Japan).

Phosphate buffer (pH 6.8) was used as a blank. The absorbance versus concentration of solutions were plotted to obtain the calibration curve.

2.2.4 Preparation of MCP resinate

Drug-resin complexes (also called "resinates") were prepared by the batch method described by Walsh *et al*. (2014). Briefly, an activated resin (3 g) was added in a 500 mL beaker containing 250 mL of distilled water and allowed to *swell* for 30 min. One gram of MCP HCl was added (*ratio* of drug to resin of 1:3) and *stirred* for 60 min in a water bath at 37 ^{0}C. Then, resinate was separated by filtration. The formed resinate was washed with copious amount of distilled water, filtered, and then dried overnight in the oven at 60 ^{0}C. Finally, dried resinate beads were grinded using kneading machine (FRITSCH pulverisette 2, Germany) and sieved with sieve of 18 mesh.

2.2.5 Drug loading efficiency

Drug loading efficiency (DLE) was determined using the method described by Helmy *et al*., (2011) as shown below in Equations. 2.1 and 2.2. The filtrate was collected and assayed spectrophotometrically at a wavelength of 273 nm to determine the DLE using a UV-Visible spectrophotometer (UV-1800, SHIMADZU, Japan).

$$Total\ amount\ of\ bound\ drug = Total\ amount\ of\ used\ drug - Amount\ of\ unbound\ drug \quad (2.1)$$

Where absorbance of working standard is total amount of used drug and absorbance of filtrate is amount of unbound drug.

$$DLE = \frac{Total\ amount\ of\ bound\ drug}{Total\ amount\ of\ drug\ used} \times 100 \quad (2.2)$$

The effects of swelling time, drug:resin ratio, temperature and stirring (complexation) time were investigated.

2.2.6 Characterization of resinates

Particle size and size distribution

The particle size and size distribution of the resinates were determined by laser light Diffractometry (Malvern Mastersizer S (long), Model; AWM2000, UK). Five grams of resinates prepared in 1:3 ratio of drug to resin were weighed and dispersed in a sample unit after cleaning the sample dispersion unit three times. Filtered water was used as a dispersant. Data presentation on the mastersizer window for resinate size distribution was analyzed.

Drug-resin complexation study

Drug-resin complexation study was carried out using FT-IR spectroscopy. FT-IR spectra of MCP HCl, Dowex Marathon C®, and 1:3 drug-resin complex (DRC) of MCP and Dowex Marathon C® were recorded at room temperature using an FT-IR spectrophotometer (FTIR-8400S, Shimadzu, Japan) in transmittance mode. The sample (8 mg) was ground and mixed with liquid paraffin in a mortar and pestle. The mixture was placed onto the face of a potassium bromide (KBr) plate and a second window was placed on top of the first salt plate to form a thin film of the mull by compression between the two plates. The plate was placed in the IR spectrometer and the spectra were recorded three times. Each IR spectrum was collected with spectral resolution of 4.0 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 analysis.

2.2.7 Physicochemical characterization of powder blends for tablet compression

The physicochemical properties of various powder blends, such as bulk and tapped density, compressibility index, angle of repose and Hausner ratio were determined using the methods described below.

Bulk density

For each formulation, 50 g of powder blend was carefully introduced into a 250 mL graduated cylinder and the volume of resinate was noted. The bulk density of each formulation was then obtained by dividing the weight of samples by the respective volumes using Eq. 2.3.

$$D_b = \frac{M}{V_b} \tag{2.3}$$

Where, D_b is bulk density (g/cm^3), M is weight of sample (g), and V_b is volume of resinate (cm^3).

Tapped density

A sample of 50 g of powder blend of each formulation was carefully introduced into a 250 mL graduated cylinder and was tapped 500 times using a tap densitometer (ERWEKA, SVM 20, Germany). The tapped volume was then noted and the tapped density of each formulation was calculated using Eq. 2.4.

$$D_t = \frac{M}{V_t} \tag{2.4}$$

Where D_t is tapped density (g/cm^3) and V_t is final tapped volume of powder (cm^3).

Compressibility index

The Carr's index (which indicates degree of compressibility) of each formulation was calculated from bulk and tapped densities using Eq. 2.5.

$$Carr's \quad index\,(\%) \quad = \frac{(D_t - D_b)}{D_t} \times 100 \tag{2.5}$$

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. The radius (R) and the height (H) of the pile were determined and the angle of repose (θ, degree) was calculated using Eq. 2.6.

$$Angle\ \ of\ \ repose\ \ \ (\theta) = \tan^{-1}\left(\frac{H}{R}\right) \tag{2.6}$$

2.2.8 Preparation of taste-masked orodispersible MCP tablets

Taste-masked formulations of MCP tablets were prepared by direct compression method. All ingredients of the formulations were passed through a 224 μm sieve separately and incorporated geometrically. All of the ingredients, except the lubricant, were mixed in a TURBULA® Mixer (Willy A. Bachofen AG, Turbula®2TF, Basel, Switzerland) at a speed of 49 rpm for 10 min. The lubricant was added and mixed for further 5 min. The blend obtained was directly compressed using an instrumented single punch tablet press (KORSCH XP1, Berlin, Germany), with 10 mm punch at 10 and 20 KN compression forces and 300 mg tablet weight. The tablets were subjected to evaporation at 50 °C for 8 h until constant weight was achieved to ensure complete sublimation of ammonium bicarbonate (Singh *et al*., 2008).

Table 2.1: Preliminary formulation study of taste-masked MCP ODTs at different formulation factors

Formulation	Formulation condition	Conc. of $(NH_4)_2CO_3$ (%)	Conc. of Crospovidone (%)	Amount of MCC (%)	Mannitol	Talc	Aerosil	Mg stearate
SF 1	Low Crospovidone, low MCC, in the absence of $(NH_4)_2CO_3$	0	1	40	55	2.0	1.0	1.0
SF 2	High Crospovidone, low MCC, in the absence of $(NH_4)_2CO_3$	0	7.5	50	38.5	2.0	1.0	1.0
SF 3	Low Crospovidone, High MCC, in the absence of $(NH_4)_2CO_3$	0	1	53.5	41.5	2.0	1.0	1.0
SF 4	Low Crospovidone, high MCC, in the presence of $(NH_4)_2CO_3$	15	1	53.5	26.5	2.0	1.0	1.0

SF- Study Formulation

2.2.9 Characterization of taste-masked orodispersible MCP tablets

Crushing strength

Ten tablets were randomly taken and the crushing strength of each tablet was determined using a hardness tester (CALEVA, Model; THT2, Frankfurt Germany) 24 h after compression. The mean value and standard deviation of the ten tablets were recorded.

Friability

Ten tablets were randomly selected from each lot, weighed and placed in a friability tester (ERWEKA, Model; TAR 20, Germany). The tablets were made to rotate in the chamber at a speed of 25 rpm for 4 min. The tablets were de-dusted using a 2 mm sieve and reweighed. The percentage weight loss was calculated as percentage friability using Eq. 2.7.

$$\text{Percentage Friability} = \frac{(W1 - W2)}{W1} \times 100 \qquad (2.7)$$

Where, W1 = Initial weight of the 10 tablets, W2 = Final weight of the 10 tablets after testing.

Disintegration test

Disintegration time was carried out according to USP30-NF25. Six tablets from each formulation were randomly selected and placed in a disintegration apparatus (GB Caleva Ltd., Model; DIST2, England) filled with 800 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.

Wetting time

A piece of tissue paper folded twice was placed in a Petridish containing simulated saliva using 6.8 pH phosphate buffer (BP, 2000). Time required for complete wetting was recorded as wetting time. Tablets from each formulation were selected and the average time taken for the tablets to wet completely, when placed gently on the tissue paper in a

Petridish was noted. Six tablets from each formulation were randomly selected, and the mean value and standard deviation were calculated.

Morphological property

Morphology details of the specimens were determined by using an inverted optical microscope, Model LEITZ WETZLAR 512731, Germany. The tablets were placed over platform of the microscope and images were taken. Microphotographs were taken on magnification at 10X for surface profiling.

***In vitro* dissolution studies**

In vitro dissolution studies were carried out using USP apparatus type I (basket method). An automated dissolution tester (LABINDIA DS 8000, INDIA) at 50 rpm, and a dissolution media of 900 mL 0.1 N HCl and phosphate buffer pH 6.8 maintained at 37 ± 0.5 °C were used. To each of the six flasks, a tablet was placed and the equipment was allowed to run. Five milliliters aliquots of dissolution media were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min intervals. The volume withdrawn at each time point was replaced with equal volumes of fresh dissolution medium maintained at 37 ^{0}C $\pm$ 0.5 ^{0}C. Each sample was filtered through a Whatmann filter paper No.1. The content of MCP HCl was spectrophotometrically analyzed at 273 nm. Cumulative percent of MCP HCl released was calculated and plotted against time.

Drug content and content uniformity test

The content of MCP HCl was determined according to BP (2000). Twenty tablets were powdered and 50 mL of 0.1 N HCl was added to powder containing the equivalent of 10 mg of anhydrous MCP HCl. Sufficient amount of water was added to produce 100 mL and filtered. Ten milliliters of 2 M NaOH was added to 20 mL of the filtrate. Extracted with 90 mL quantities of chloroform, an extract was filtered through anhydrous sodium sulphate supported on adsorbent cotton previously moistened with chloroform and the filter was washed with 5 mL chloroform. Sufficient chloroform was added to the extracts and washings to produce 100 mL and the absorbance of the resulting solution was measured at

273 nm using UV/Visible spectrophotometer (Model SHIMADZU UV-1800, Japan). The amount of MCP was analyzed spectrophotometrically and the drug content was determined from the standard calibration curve.

2.2.10 Taste masking evaluation

Ethical clearance

For the *in vivo* bitterness threshold concentration determination and taste masking evaluations, ethical clearance was requested and acquired from the ethical review committee of the School of Pharmacy, College of Health Sciences, Addis Ababa University.

Determination of bitterness threshold concentration of MCP

The bitter taste threshold value of MCP was determined using the method described below. A series of MCP HCl standard solutions of different concentrations (10, 20, 30, 40, 50, and 60 μg/ mL) were prepared in phosphate buffer pH 6.8. Starting with the lowest concentration, twelve volunteers from whom prior informed consent was obtained were instructed to place 1 mL of the standard solution on the center of their tongues. The solution was retained in the mouth for 30 s and then spit out. The mouth was thoroughly rinsed with distilled water. The next higher concentration was then tasted after 10 min and the volunteers were asked about the taste they felt. The threshold value was selected from standard solution of MCP HCl as the lowest concentration solution that had produced bitter taste in the volunteers.

In vivo taste-masking evaluation of taste masked ODTs

Panel evaluation of taste was made as per the method described by (Pein, 2013). The panel testing is a psychophysical rating of the gustatory stimuli. In this study, a group of human volunteers (twelve members) were trained for taste evaluation by using determined threshold of bitterness value. Subsequently, test solution was tasted and rated on the same scale to assess its bitterness. If the majority of the volunteers found the taste-masked MCP

ODTs to be tasteless and agreeable, taste evaluation in volunteers confirmed that the taste of drug was masked by complexing with Dowex Marathon C® resin.

In vitro taste-masking evaluation of taste masked ODTs

Taste-masking evaluation of resinates was determined *in vitro* using the UV method. Resinates containing equivalent to 10 mg of MCP were placed in a volumetric flask with 25 mL of phosphate buffer pH 6.8 and stirred for 5 min. The mixture was filtered, and then the concentration of the drug in the filtrate was analyzed spectrophotometrically and compared with the threshold value determined *in vivo*.

2.2.11 Stability studies

The short term stability studies of the optimized formulation was carried out by storing the tablets (in amber colored and rubber stoppered bottles) at accelerated conditions (40 °C ± 2 °C/75% RH ± 5% RH) as per international conference on harmonization guideline for a period of 3 months. At the intervals of 1 month, 2 month and 3 months, the tablets were visually examined for any physical changes, drug content, hardness, disintegration time, friability and wetting time (ICH, 2003).

2.3 Experimental design

Preliminary experiments indicated that variables such as concentration of ammonium bicarbonate (A), concentration of Crospovidone (B), MCC concentration (C) and compression force (D) were critical factors which affect the various responses. The response variables investigated were tablet hardness, disintegration time (DT) and friability. A 2^4 randomized full factorial design was adopted to optimize the variables. In this design, four factors were evaluated, each at 2 levels, and experimental trials were performed at all 16 possible combinations (i.e. $2^4 = 16$). A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

$$Y = ß_0 + ß_1X_1 + ß_2X_2 + ß_3X_3 + ß_4X_4 + ß_{12}X_1X_2 + ß_{13}X_1X_3 + ß_{14}X_1X_4 + ß_{23}X_2X_3 + ß_{24}X_2X_4 + ß_{34}X_3X_4 + Ɛ \quad (2.8)$$

Where Y is the dependent variable, $ß_0$ is the arithmetic mean response of the 16 runs, and $ß_i$ is the estimated coefficient for the factor X_i. The main effect (X_1, X_2, X_3 and X_4) represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2, X_1X_3, X_1X_4, X_2X_3, X_2X_4 *and* X_3X_4) shows how the response changes when two factors are change simultaneously. The polynomial term (X_1X_2, X_1X_3, X_1X_4, X_2X_3, X_2X_4 *and* X_3X_4) are included to investigate nonlinearity.

The results of the optimization experiments were analyzed using Design-Expert 8.0.7.1 software where the optimum area at which the desired responses, and the response surface plots and contour plots for the fitted polynomial equations of the responses were obtained. The selected formulation and process variables with their limits, units and notations are given in Table 2.2 and the composition of the 16 formulation of ODT of MCP are summarized in Table 2.3.

Table 2.2: Independent variables and their levels used in the factorial design.

Variables	Levels	
	-1	+1
Concentration of ammonium bicarbonate, A (%)	5	15
Concentration of Crospovidone, B (%)	1	7.5
Amount of MCC, C (%)	40	55
Compression force, D (KN)	10	20

Table 2.3: Levels of full factorial design and compositions of different taste masked MCP ODTs prepared with drug-resin complex of 1:3 ratio.

Formulation	Compositions of ingredients (% W/W)								Compression force, D (KN)
	DRC	$(NH_4)CO$	Crospovidone	MCC	Mannitol	Talc	Aerosil	Mg stearate	
OF 1	13.8	5.00 (-1)	1.00 (-1)	40.00 (-1)	36.12	2.0	1.0	1.0	10.00 (-1)
OF 2	13.8	15.00	1.00 (-1)	40.00 (-1)	26.12	2.0	1.0	1.0	10.00 (-1)
OF 3	13.8	5.00 (-1)	7.50 (+1)	40.00 (-1)	29.62	2.0	1.0	1.0	10.00 (-1)
OF 4	13.8	15.00	7.50 (+1)	40.00 (-1)	19.62	2.0	1.0	1.0	10.00 (-1)
OF 5	13.8	5.00 (-1)	1.00 (-1)	55.00 (+1)	21.12	2.0	1.0	1.0	10.00 (-1)
OF 6	13.8	15.00	1.00 (-1)	55.00 (+1)	11.12	2.0	1.0	1.0	10.00 (-1)
OF 7	13.8	5.00 (-1)	7.50 (+1)	55.00 (+1)	14.62	2.0	1.0	1.0	10.00 (-1)
OF 8	13.8	15.00	7.50 (+1)	55.00 (+1)	4.62	2.0	1.0	1.0	10.00 (-1)
OF 9	13.8	5.00 (-1)	1.00 (-1)	40.00 (-1)	36.12	2.0	1.0	1.0	20.00 (+1)
OF 10	13.8	15.00	1.00 (-1)	40.00 (-1)	26.12	2.0	1.0	1.0	20.00 (+1)
OF 11	13.8	5.00 (-1)	7.50 (+1)	40.00 (-1)	29.62	2.0	1.0	1.0	20.00 (+1)
OF 12	13.8	15.00	7.50 (+1)	40.00 (-1)	19.62	2.0	1.0	1.0	20.00 (+1)
OF 13	13.8	5.00 (-1)	1.00 (-1)	55.00 (+1)	21.12	2.0	1.0	1.0	20.00 (+1)
OF 14	13.8	15.00	1.00 (-1)	55.00 (+1)	11.12	2.0	1.0	1.0	20.00 (+1)
OF 15	13.8	5.00 (-1)	7.50 (+1)	55.00 (+1)	14.62	2.0	1.0	1.0	20.00 (+1)
OF 16	13.8	15.00	7.50 (+1)	55.00 (+1)	4.62	2.0	1.0	1.0	20.00 (+1)

OF- Optimization Formulation

2.4 Statistical analysis

Unless and otherwise stated, each test was conducted in triplicate and the results are reported as mean and standard deviation. The results were treated statistically using Origin 7 software (OriginLab Corporation, MA, and USA). One way analysis of variance (ANOVA) was applied for comparison of optimization results. A statistically significant difference was considered when $P < 0.05$.

3. RESULTS AND DISCUSSION

3.1 Characteristics of Dowex Marathon C® resin

Total exchange capacity (Total new volume capacity)

The total exchange capacity of the regenerated, wet resin for the triplicate sample was equal to 2.00 eq per L, or 43.6 kg/ft^3 as $CaCO_3$. (To convert meq/ mL to a more recognizable unit multiply meq/ mL by 21.8 and the result will equal Kg/cu.ft.)

Total exchange capacity is a measurement of the resin's theoretical capacity i.e., a measure of all the ion exchange sites on a resin, also called *the salt splitting capacity of a resin.* In other words, the total capacity is the maximum theoretical quantity of ions that the resin can load. For example, the resin's capacity of 2.00 equivalent/L, mean that one liter of resin contains 2.00 equivalents of exchange sites. Typical capacity values for strong acid cation exchanging resin described by Dardel (2015) are 1.7 to 2.2 eq/L. So the result obtained lies in the range.

pH, density and moisture content of resin

The pH, density and moisture content of the triplicate sample were found to be 7.22 $\pm$ 0.05, 1.16 $\pm$ 0.02 g/ mL and 52 $\pm$ 1.2 %, respectively.

3.2 Calibration curves of MCP

The UV absorbance calibration curves of pure MCP HCl at 273 nm in 0.1N HCl and phosphate buffer pH 6.8 are shown in Fig. 3.1 and 3.2, respectively.

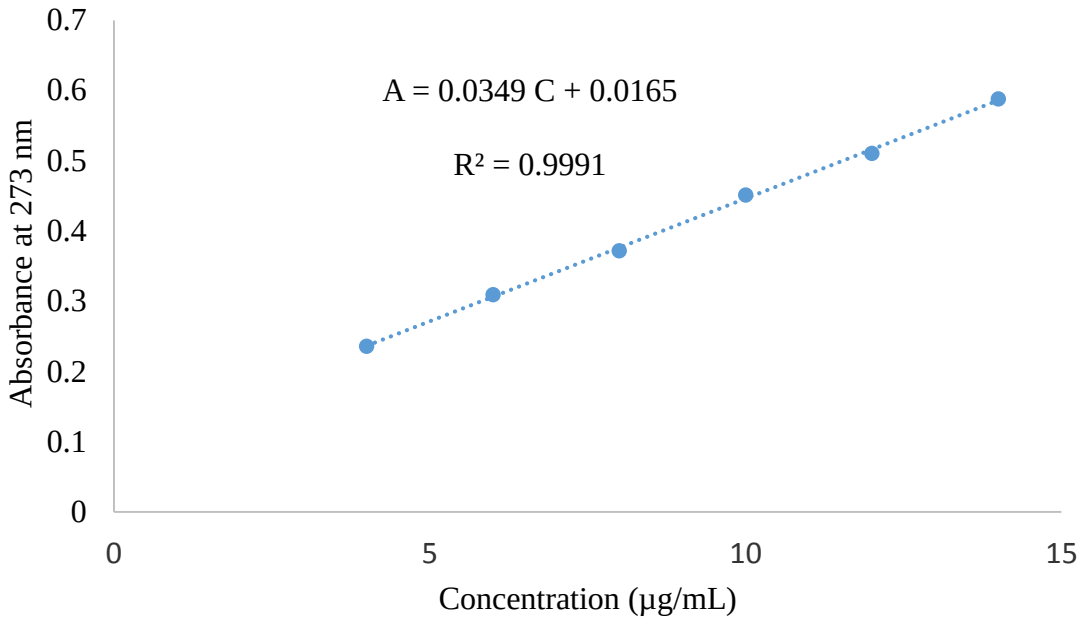


Figure 3.1: UV absorption calibration curve of MCP in 0.1N HCl at 273 nm with 95% confidence interval

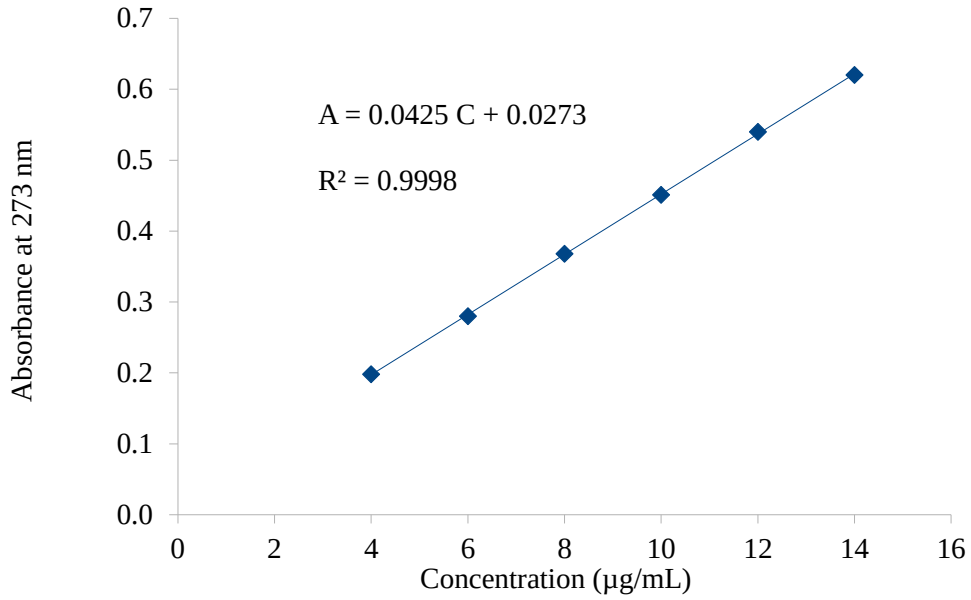


Figure 3.2: UV absorption calibration curve of MCP in phosphate buffer pH 6.8 at 273 nm with 95% confidence interval

The Beer's Lambert calibration curve in 0.1 N HCl yielded a linear regression equation of A = 0.0349 C + 0.0165 with a coefficient of determination (R^2) of 0.9991, p <0.0001 and the calibration curve in pH 6.8 phosphate buffer yielded a regression equation of A = 0.0425 C + 0.0273 with R^2 = 0.9998, p<0.0001 (where, A is absorbance and C is the concentration in µg/ mL).

3.3 Drug loading efficiency

After activation with acid treatment, the exchangeable ion on the resin is H^+. Relative selectivity of H^+ is least than other ionic forms and therefore it increases the percent complexation (Sivaneswari *et al*., 2015).

For the efficient drug loading, it is important to know the time it takes to reach equilibrium and how much drug will be loaded into the resin, which depend on the resin-type and loading method. The time to reach equilibrium and drug loading are dependent on many variables, such as the molecular weight and charge density of both the drug and resin, degree of cross linking and particle size of the resin, nature of the solvent and mixing conditions. If the molecules diffusing into ion-exchange particles are large or if the polymers in the resin are highly cross-linked, it will take more time to reach the equilibrium condition. Particle size is another important factor, which can influence the time required to establish equilibrium conditions. Fine particles have more surface area and less internal volume for ions to diffuse, and so less time might be required to reach equilibrium (Jeong and Park, 2008b). Drug loading, is highly dependent on the pH of the medium and can be applied for taste masking without affecting the dosage form characteristics (Sahu *et al*., 2013).

First of all, in order to be loaded in the ion-exchange resin, a drug needs to have charged groups. Generally, the loading is accomplished using two well-known methods. One is the batch method, and the other is a column method. In the batch method, a specific amount of resin is added to a drug solution and mixed until equilibrium is obtained. In the column method, a concentrated drug solution is passed through a resin-packed column until the effluent concentration is the same as the eluent concentration (Jeong and Park, 2008b).

Jeong and Park (2008b) recommended the batch method for drug loading into the ion-exchange resin because using a column method requires frequent measurement of changes in the pH of the reaction medium which in turn could monitor drug loading, because as complex formation reaches completion, the pH returns to the initial pH of the eluent. Yu *et al*. (2012) also explained that batch method is easy to operate. Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. Moreover, as the reaction is an equilibrium phenomenon, maximum efficiency was best achieved in the batch process. Equilibrium time was shorter due to thinner barrier for diffusion of ions, as it is a continuous motion. Higher swelling efficiency in the batch process resulted in more surface area for ion exchange.

As shown in Table 3.1, 3.2, 3.3 and 3.4, screening experiments for parameters such as drug to resin ratio, swelling time, temperature and stirring (or complexation) time were conducted to optimize maximum drug loading. During preparation of resinate, the other variables were kept constant while varying the variable of interest.

The equilibrium profiles of drug loading into the ion exchange resins depends on type and number of functional groups of resin's exchanging site. The strong acid had a higher affinity for ionic drugs, and this increased the amount of drug in the resulting complex.

Table 3.2 shows the effect of soaking time on drug loading. The results reveal that a 30 min swelling time of Dowex® in demineralized water gave the maximum MCP loading of 97.05%. This may be the result of maximum swelling and hydrating properties of Dowex® that affect the rate of ion exchange. Less drug-loading efficiency may be observed in unswollen resin matrix. In unswollen resin matrix, the exchangeable groups are latent and coiled toward the backbone, hence less drug-loading efficiency (Remington, 2002).

Increased temperature during complexation increases the ionization of drug and resin. The effect is more pronounced for poorly water soluble and unionized drugs. Higher temperatures tend to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. It was reported that cation exchangers are not affected as significantly by temperature changes as anion exchange resins (Remington, 2002). As MCP

is water soluble drug and ionizable drug temperature does not show any significant effect on drug adsorption and also cation exchange resins are not significantly affected by temperature changes as shown in Table 3.3. Table 3.4 depicts equilibrium ion exchange in solution occurs stoichiometrically and hence it is affected by complexation (or stirring) time.

Table 3.1: Effect of resin concentration (drug: resin) on drug loading at swelling time of 30 min, 37 ^{0}C and stirring time of 60 min.

Drug : resin	% Drug loading
1:1	62.18 ± 1.12
1:2	80.78 ± 1.25
1:3	96.69 ± 1.14
1:4	96.84 ± 1.34

Table 3.2: Effect of swelling time of resin on drug loading at 1:3 ratio of drug to resin, 37 ^{0}C and stirring time of 60 min.

Swelling time (min)	% Drug loading
10	83.22 $\pm$ 1.86
20	88.45 $\pm$ 1.54
30	97.05 $\pm$ 1.07
60	97.13 $\pm$ 1.02

Table 3.3: Effect of Temperature on drug loading at 1:3 ratio of drug to resin, swelling time of 30 min and stirring time of 60 min.

Temperature (^{O}C)	% Drug loading
25	95.16 ± 0.50
30	95.55 ± 0.64
40	95.31 ± 0.71
50	95.48 ± 1.13
60	95.85 ± 0.83

Table 3.4: Effect of complexation time on drug loading at 1:3 ratio of drug to resin, swelling time of 30 min and 37 ^{0}C.

Complexation time (min)	% Drug loading
15	54.24 ± 1.58
30	67.35 ± 1.54
45	83.37 ± 1.74
60	96.67 ± 1.36
120	96.35 ± 1.26

3.4 Characteristics of taste-masked MCP resinate

Taste is an important parameter in administering drugs orally and is a critical factor to be considered while formulating ODTs and other formulations which come in contact with the taste buds. Although there are different methods of taste masking, the entrapment of bitter drug substances in polymer based resins via complexation has become an increasingly attractive strategy for taste-masking by creating a physical barrier around the bitter drug to keep them from coming in direct contact with the patients' taste buds. In addition, these DRC must remain intact without undergoing significant ionization during administration in the patient's mouth.

Most of the bitter drugs have amine as a functional group, which is the cause of their obnoxious taste. If the functional groups are blocked by complex formation the bitterness of the drug reduces drastically. A DRC is made from the bitter drugs and ion-exchange resins (Karaman, 2014).

Hence, in the current study, resinates with different polymer to drug ratios at different swelling times and complexation (stirring) times were prepared and characterized.

3.4.1 Particle size distribution

The particle size distribution curve is shown in Fig. 3.3.

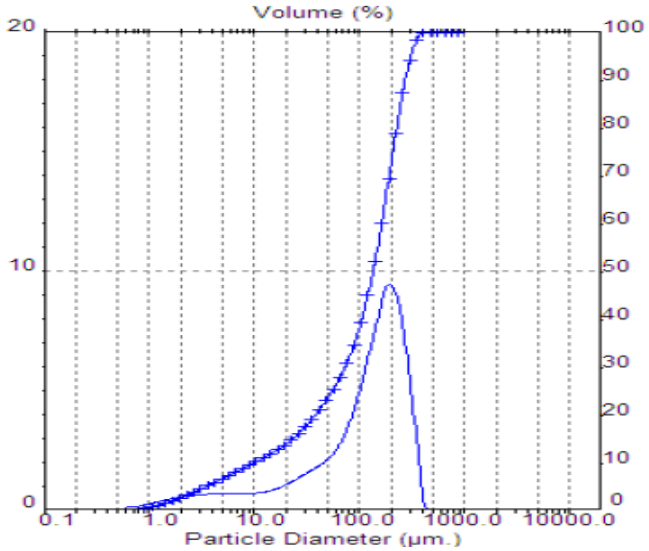


Figure 3.3: Particle size distribution curve of resinate sample.

The micromeritic properties of MCP resinate is shown in Table 3.5.

Table 3.5: Micromeritic properties of MCP resinate

S/N	Attribute	Value
1	D (v, 0.5)	134.57 µm
2	D (v, 0.1)	9.85 µm
3	D (v, 0.9)	273.37 µm
4	D [4, 3]	139.42 µm
5	D[3,2]	19.06 µm
6	Span	1.958
7	Obscuration	13.9%
8	Specific surface area	0.2098 m^2/g

D (v, 0.5) is the size of particle at which 50% of the sample is smaller and 50% is larger than this size. D (v, 0.1) is the size of particle for which 10% of the sample is below this size. D (v, 0.9) is the size of particle for which 90% of the sample is below this size. D [4, 3] is the volume mean diameter. D [3, 2] is the surface area mean diameter and also called the Sauter mean. Span is measure of the width of the distribution. The smaller the value the narrower the distribution. Obscuration is measure of the amount of laser light lost due to the introduction of sample within the analyzer beam and the result obtained for this value lies within an ideal range of between 10 and 30%.

Properties of pharmaceutical grade ion exchange resins include fine free flowing powders, particle size of 25-150 µm, contain functional groups capable of exchanging ionic groups, insoluble in all solvents and all pH's, not absorbed from the GIT, can be ground to smaller size or agglomerated to larger size (Hughes, 2008). The resin used in this study fulfils the aforementioned characteristics.

Forms of ion exchange resins can include spherical and non-spherical particles. The non-spherical particles are frequently manufactured by grinding of the spherical particles. Products made in this way typically have particle size in the range 1 µm to 200 µm. The spherical particles are frequently known as 'Whole Bead.' The non-spherical particles are frequently known as 'Powders' (Hughes and Ziarno , 2004).

This enhancement of volume reduction by grinding has several reasons. First, the shape of the ground resin is much rougher and not ideally round compared to bead resins. This property improves the compaction significantly because the single particles can adhere together whereas round beads do not. This leads to a solid block when compacting ground resins. Bead resins do not form a solid block after compaction. Secondly, the particle size distribution is optimized for compaction. The different particle sizes in a mixture lead to a more dense packing, because the void space in between the bigger particles is filled with finer resin material, whereas bead resins have a narrow particle size distribution and thus the voids are filled with air. Thirdly, it also improves heat transfer in the drying process due to the reduced particle size and increase in particle surface (Fehrmann and Aign, 2013).

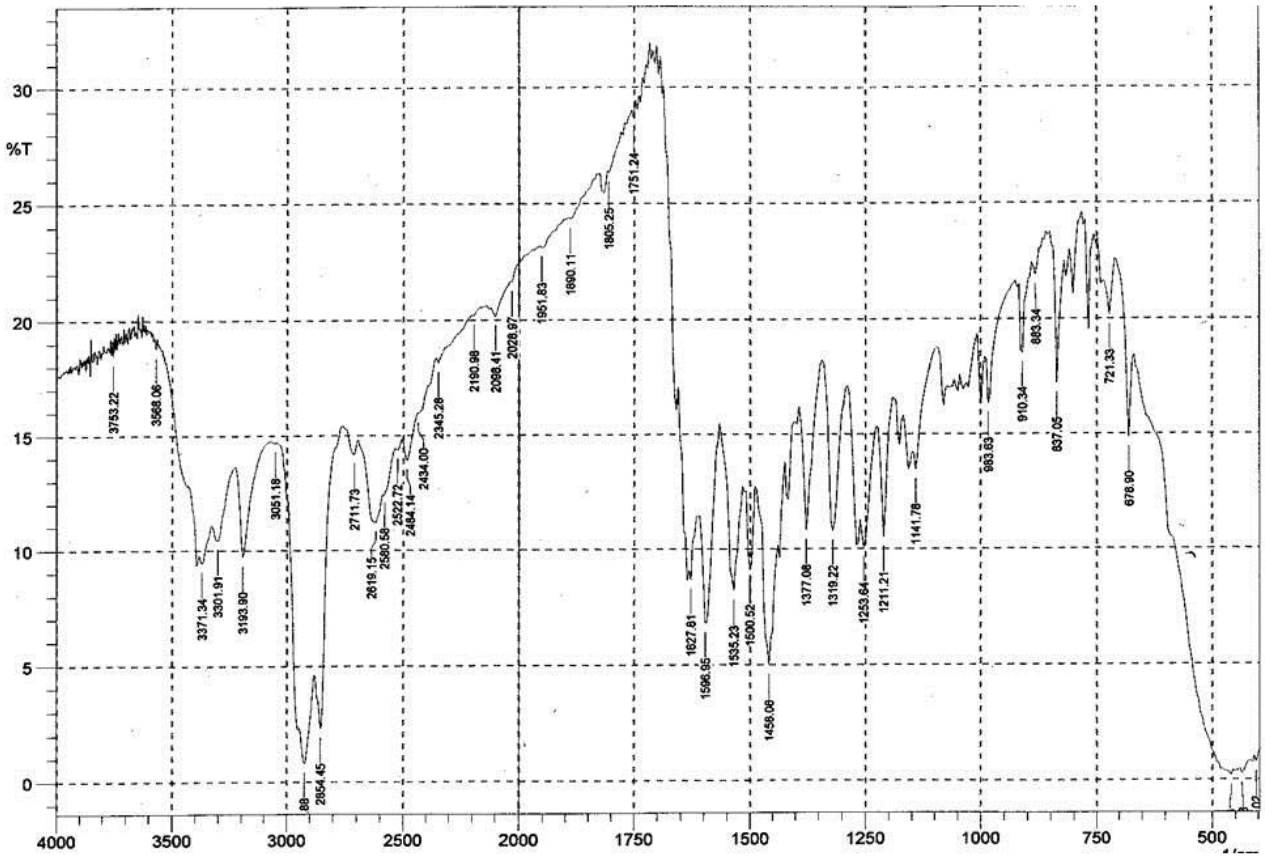
In an ion exchange kinetics, one of the major factors controlling the ion exchange reaction is the diffusion time required for the equilibrium of ions between liquid phase and solid phase. The transfer of ions is diffusion controlled and described by Fick's equation. There are three basic steps to consider: initially, ion transfer from the bulk of the solution to the static boundary layer (film) surrounding the resin bead occurs. This process is independent of the size of the resin beads. Then, ion transfer through the film to the bead surface takes place; the rate of this film diffusion process is a function of 1/r (where r is the bead radius). During loading, the ion presentation rate to the resin bead is faster than the ion diffusion rate through the surface film. With smaller resin beads, the surface area is larger and the film diffusion rate is increased. Finally, ion transfer within the bead occurs; and here the rate of particle diffusion process is a function of $1/r^2$. In the release phase, the increased ion concentration in the solution increases the diffusion rate through the film, and particle diffusion then becomes the limiting factor. Smaller resin beads have a shorter path within the solid phase and the particle diffusion rate is increased (Dow Chemical Company, 2006). The consequence of reducing the bead size, therefore, is to improve the resin kinetics in both the loading and release of drug from the DRC.

3.4.2 FT-IR spectra of MCP, Dowex Marathon C® and resinate

FT-IR spectra of MCP, Dowex Marathon C® and 1:3 DRC, respectively, are depicted in Figs 3.4 A to C.

The FT-IR spectrum of pure MCP in the 4000 - 450 cm^{-1} region showed prominent peaks at 3305.76 cm^{-1}, 3396.41 cm^{-1}, 1596.95 cm^{-1}, 693 cm^{-1} corresponding to the -NH stretching, -OH stretching, C=O and C-Cl stretching, respectively (Patel, 2009). The bands at 2923 and 2876 cm^{-1} of the FT-IR spectrum of fresh resin DOWEX MARATHON C® are due to the aliphatic C-H stretching absorbance of methyl group in the main chain and in aromatic rings and of methylene group respectively. SO_2 asymmetric stretching appears at 1382 cm^{-1}. Strong band at 1652 cm^{-1} indicates aromatic C=C bond. The peaks at 1500 - 1600 cm^{-1} are due to deformation and skeletal vibrations of C-H in DVB. Bands appear at 2366 cm^{-1} which may be assigned to O-H stretching vibration originating from the polymer (Oliveira *et al*., 2005). The FT-IR spectrum of the drug: resin complex spectrum shows absence of

peaks at 3305.76 cm^{-1} corresponding to –NH stretching and peak absorption of 1382 cm^{-1} for SO_2 group (Figure 3.4 C) suggesting that interaction of amine group of drug with the resin backbone has occurred. In addition, the FT-IR spectrum of the DRC showed no significant shift or reduction in intensity of the characteristic peaks of MCP at 3396.41 cm^{-1}, 1596.95 cm^{-1}, 693 cm^{-1} corresponding to the -OH stretching, C=O and C-Cl stretching (Figure 3.4 A and C). Besides, there is no additional peak observed on the resinate spectrum. Hence, the FT-IR spectroscopic study suggests that the drug is complexed with the resin.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%T
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25
20
15
10
5
0
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
3753.22
3568.06
3371.34
3301.91
3193.90
3051.19
2854.45
2711.73
2619.15
2580.58
2522.72
2484.14
2434.00
2345.28
2190.98
2098.41
2028.97
1951.83
1690.11
1805.25
1751.24
1627.61
1596.95
1535.23
1500.52
1458.06
1377.08
1319.22
1253.64
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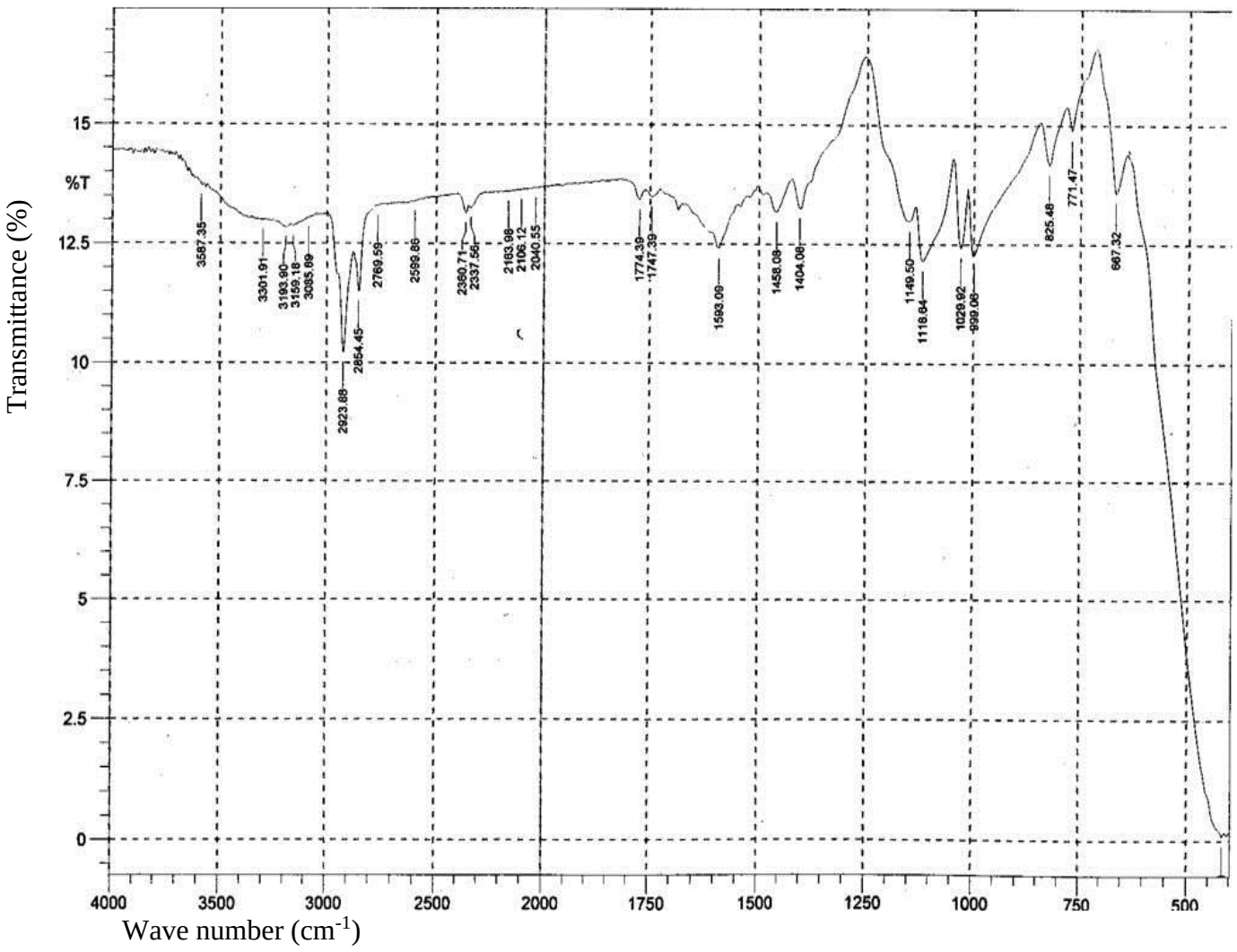
Wave number (cm-1)

(A)


Transmittance (%)
%T
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12.5
10
7.5
5
2.5
0
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3301.91
3193.90
3159.18
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2923.88
2854.45
2769.59
2599.86
2360.71
2337.56
2183.98
2106.12
2040.55
1774.39
1747.39
1593.09
1458.08
1404.08
1149.50
1118.64
1029.92
999.06
825.48
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1250
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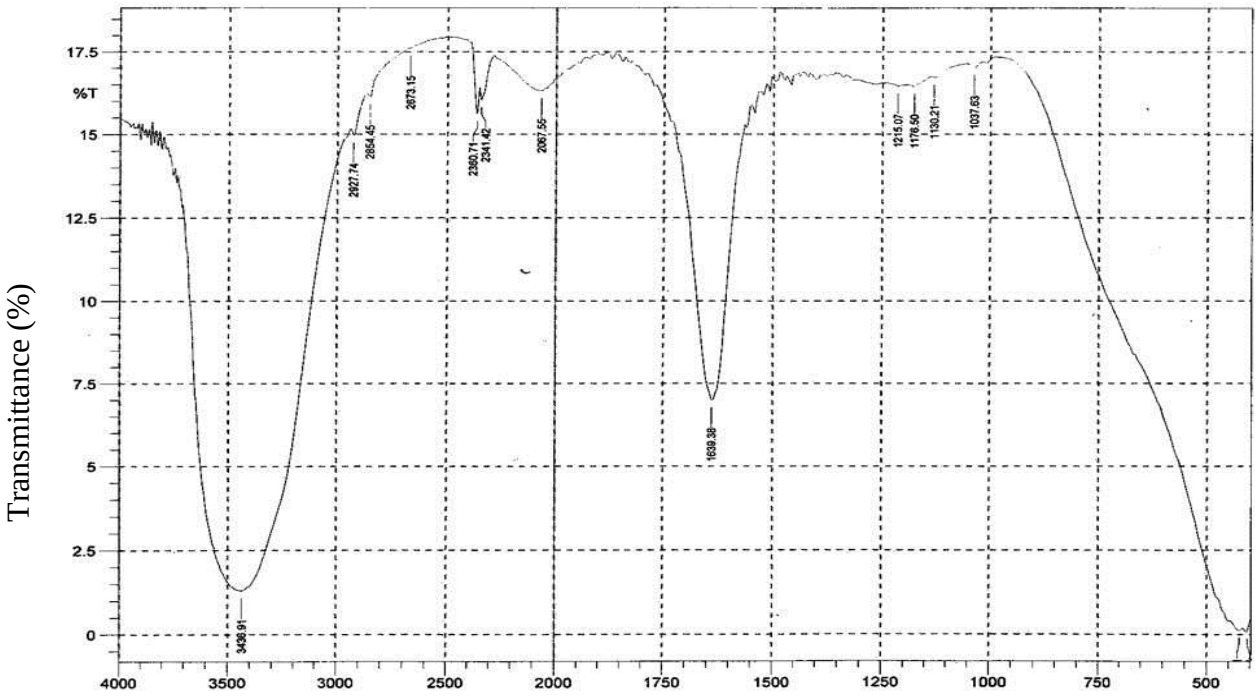
Wave number (cm-1)

(B)



(C)

Figure 3.4: FT-IR spectra of MCP (A) Dowex Marathon C® (B) and 1:3 MCP and Dowex Marathon C® complex (C).

3.5 Tablet formulation study

In the formulation of the ODTs, common glidiants i.e., talc and colloidal silicon dioxide and lubricant i.e., magnesium stearate were used. Of the common tablet diluents, careful consideration was made to select the appropriate diluent. First of all as MCP is an amine drug and lactose is incompatible with amines, it was excluded. In addition, since starch is poorly compressible and not well suited for direct compression, it was also excluded. However, mannitol has a soothing effect which is desirable feature for ODTs. The compressibility index of mannitol was also checked with those of lactose and starch and found to have comparable value (Amidon, 2012). Hence, mannitol was selected as the diluent of choice.

Disintegration and solublization of directly compressed tablets depend on single or combined action of disintegrants and water-soluble excipients. Most commercial ODTs have been developed using mannitol as the bulk excipient. It is overwhelmingly preferred over lactose because of its extremely low hygroscopicity, excellent chemical and physical compatibility, good compressibility and better sweetness (Gad, 2008).

The plasticity of MCC together with its relatively low bulk density, high surface area and high hygroscopicity explains its unique binding properties. When compared to brittle excipients, MCC is more cohesive (Thoorens *et al.*, 2014).

MCC is widely used in pharmaceutical formulations, primarily as a solid binder in tablets. It also has some lubricant and disintegrant properties that makes it useful in tableting. It performs as a binder because it undergoes significant plastic deformation during compression bringing the extremely large surface area into closed contact and facilitating hydrogen bond formation between the plastically deformed, adjacent cellulose particles. In addition, the existence of moisture within the porous structure of MCC acts as an internal lubricant. This facilitates slippage and flow within the individual microcrystals during plastic deformation, which enforces the formation of hydrogen bond bridges and gives MCC a very good hardness (Yousuf *et al*., 2005). For the reasons, MCC was employed as a binder in the study.

In addition, inert subliming agent ammonium carbonate was included to the other tablet excipients, compressed into tablets to generate a porous structure when the volatile material is removed via sublimation (Fu *et al*., 2004). Obviously a highly porous tablet exhibits an excellent disintegration.

MCC being a diluent increases the mechanical strength of the tablet and crospovidone is also known to produce mechanically strong tablets (Guy, 2009). Crospovidone is the strongest among other superdisintegrants, which results in the fastest *in vivo* disintegration time (Abed *et al*., 2010). Unlike other superdisintegrants which are either poorly compressible or non-compressible, crospovidone is highly compressible material as a result of its unique particle morphology (ISP, 2009). Anionic superdisintegrants, such as croscarmellose sodium and sodium starch glycolate, can interact with cationic APIs and retard dissolution. Thus, the nonionic superdisintegrant, crospovidone is preferred when working with cationic APIs (Fitzpatrick, 2011).

In contrast to other superdisintegrants like sodium starch glycolate and croscarmellose sodium, crospovidone exhibits virtually no tendency toward gel formation, even at high ratio. Disintegrants that result with gel formation are not appreciable in ODTs and chewable products (Shah and Augsburger, 2001). It has been investigated ISP (2009) that crospovidone particles appear granular and highly porous. This unique, porous particle morphology facilitates wicking of liquid into the tablet and particles to generate rapid disintegration.

3.5.1 Effect of crospovidone concentration

In order to investigate the effect of crospovidone concentration on tablet properties, formulations at low (1% (w/w)) and high concentration (7.5 % (w/w)) were prepared. As the concentration of crospovidone increased, the disintegration time decreased significantly (SF2 Vs SF3) (Table 3.6). Increasing the crospovidone also increased tablet hardness and decreased friability. Based on these results, the levels of crospovidone for further optimization studies were set at 1 and 7.5%.

3.5.2 Effect of MCC concentration

The effect of the amount of MCC on the characteristics of ODT is presented in Table 3.6. Formulations containing higher amount of MCC showed good tablet integrity with an increase in tablet hardness and a decrease in friability (SF1 Vs SF3). On the contrary, there was an increase in disintegration time as the amount of MCC increased. As a result, MCC concentration from 40% to 55% were selected for further studies.

3.5.3 Effect of subliming agent

Formulations containing higher amount of ammonium carbonate showed decreased disintegration time and hardness with an increase in tablet friability (SF3 Vs SF4). As a result, concentration of ammonium carbonate in the range of 5% to 15% were selected for further studies

3.5.4 Effect of compression force

In order to investigate the effect of compression force on various tablet characteristics, tablets were compressed at 10 KN, 15 KN and 20 KN while keeping other factors constant. As can be expected, increasing compression force resulted in a decrease in friability and increase in disintegration time. Thus, the levels of compression force for further studies were kept at 10 to 20 KN.

Table 3.6: Physicochemical properties of tablets prepared for formulation study of taste masked MCP ODTs

Formulation	Thickness (mm ± SD)	Diameter (mm ± SD)	Disintegration time (s ± SD)	Friability (% ± SD)	Hardness (N ± SD)
SF 1	3.42 ± 0.22	9.47± 0.01	21 ± 1.00	0.74 ± 0.02	53.00± 0.03
SF 2	3.25 ± 0.42	9.48 ± 0.01	30 ± 1.32	0.20 ± 0.01	127.00± 0.01
SF 3	3.10 ± 1.02	9.48 ± 0.01	47 ± 1.84	0.31± 0.02	100.40± 0.60
SF 4	3.41 ± 0.20	9.47± 0.03	27± 1.02	0.58± 0.02	71.20± 1.61

3.6 Formulation optimization

Screening the important factors, among a wider set of possible controllable factors, is the first exercise during optimization study by RSM. In the optimization of the ODTs, various factors including concentration of subliming agent, concentration of superdisintegrant, amount of direct compression diluent, MCC and compression force were considered which affect the various response variables, viz., considered- hardness, disintegration time and friability. Besides choosing optimum levels of factors affecting the process of drug-resin complex formation to achieve maximum drug loading (i.e. 1:3 ratio of drug to resin, swelling time of 30 min and stirring time of 60 min), those four factors were further optimized.

3.6.1 Characteristics of resinate containing powder blend

Powder flow properties are crucial in the processing of tableting operations such as flow from hoppers, mixing and compression. A uniform flow from the hopper into the die cavity ensures uniform tablet weight and drug content. Table 3.7 shows, the bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose of the optimization formulations. The results of bulk and tapped densities ranged from 0.50 to 0.51 and 0.55 to 0.62, respectively with the Carr's index and Hausner ratio of all the formulations below 18.18 and 1.22, respectively, indicating that all the blends have good flow properties (USP, 2007). The angle of repose values of all the formulations were also in the range of 28.61 to 34.82, which also shows the good flowing nature of the blends.

Table 3.7: Flow properties of resinate containing powder blends of the optimization formulations of taste-masked MCP ODTs.

Formulation	Flow rate (g/s) ± SD	Angle of repose (degree) ± SD	Bulk density (g/ mL) ± SD	Tapped density (g/ mL) ± SD	Hausner ratio ±SD	Compressibility (Carr's) Index (%) ± SD
OF 1/ OF 9	4.85± 0.23	30.80± 1.29	0.50± 0.02	0.58± 0.03	1.16± 0.02	14.01±0.29
OF 2/ OF 10	4.60± 0.39	31.12± 2.01	0.50± 0.41	0.59± 0.02	1.17± 0.04	15.10±0.29
OF 3/ OF 11	5.82± 0.22	28.61 ± 2.30	0.50± 0.03	0.55± 0.01	1.11± 0.04	10.01±0.41
OF 4/ OF 12	4.20± 0.40	31.60± 1.13	0.51± 0.03	0.60± 0.05	1.18± 0.05	15.30±0.40
OF 5/ OF 13	2.89± 0.52	34.82± 2.16	0.51± 0.05	0.62± 0.05	1.22± 0.02	18.18±0.63
OF 6/ OF 14	3.01± 0.29	33.97± 1.09	0.51± 0.03	0.62± 0.04	1.21± 0.01	17.34±0.29
OF 7/ OF 15	3.61± 0.61	33.13± 2.42	0.51± 0.04	0.61± 0.02	1.20± 0.05	16.32±0.47
OF 8/ OF 16	5.21± 0.24	29.40± 2.32	0.50± 0.02	0.57± 0.02	1.13± 0.01	12.93±0.24

3.6.2 Evaluation of tablet properties

The various physicochemical properties of the tablets of the optimization formulations are shown in Table 3.8. Tablets require a certain amount of strength or hardness to withstand the mechanical shocks of handling during manufacturing, packaging as well as shipping. Besides, tablet hardness is closely linked to disintegration time. For conventional compressed tablets, a hardness of 50 N is the minimum requirement for satisfactory tablet product. As shown in the Table 3.8, the hardness of the tablets ranged from 45.00 ± 0.12 N to 145.00 ± 0.13 N. All the tablets have acceptable hardness except those tablets obtained from OF2. Another measure of tablet strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. The percentage friability for all the formulations was below 1%, indicating that the friability is within the acceptable limit of USP30/NF25.

For ODTs, disintegration time is considered to be one of the important criteria in selecting the best formulation. As shown in Table 3.9, the *in vitro* disintegration time ranged from 11±0.22 to 67±0.15 s. Formulation OF4 had the shortest disintegration time (11± 0.22 s). Whereas, formulation OF13 exhibited the longest disintegration time (67.00± 0.15 s).

Table 3.8: Hardness, friability and disintegration times of taste-masked MCP ODTs prepared for optimization

Formulation	Hardness (N) ± SD	Friability (%) ± SD	Disintegration time (s) ± SD
OF1	52.00± 0.22	0.55± 0.11	17.00± 0.13
OF 2	45.00± 0.12	0.62± 0.13	15.00± 0.11
OF 3	64.00± 0.11	0.46± 0.22	13.00± 0.12
OF 4	58.00± 0.13	0.5± 0.12	11.00± 0.22
OF 5	75.00± 0.13	0.38± 0.12	29.00± 0.17
OF 6	70.00± 0.22	0.43± 0.22	24.00± 0.13
OF 7	89.00± 0.12	0.31± 0.13	21.00± 0.11
OF 8	84.00± 0.22	0.34± 0.12	19.00± 0.14
OF 9	104.00± 0.11	0.26± 0.13	48.00± 0.22
OF 10	98.00± 0.12	0.3± 0.22	42.00± 0.13
OF 11	115.00± 0.22	0.2± 0.14	38.00± 0.12
OF 12	111.00± 0.13	0.23± 0.13	34.00± 0.22
OF 13	123.00± 0.11	0.11± 0.22	67.00± 0.15
OF 14	116.00± 0.22	0.17± 0.15	64.00± 0.13
OF 15	145.00± 0.13	0.04± 0.13	59.00± 0.22
OF 16	134.00± 0.14	0.07± 0.22	53.00± 0.13

3.6.3 Selection and checking adequacy of mathematical models

Model summary statistics for the selected significant models are shown in Table 3.9. It can be observed that R^2 is high for all responses (hardness, friability and disintegration times), 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, suggesting reliable models. It is necessary to check the fitted model to ensure that it provides an adequate approximation to the real system. ANOVA table has been 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 lower than 0.05, indicating that the model may be considered to be statistically significant. ANOVA of the responses indicated that response surface models developed for all responses were significant and adequate. The influence of formulation variables and process variable on the responses is shown in Tables 3.10-3.12.

Table 3.9: Numerical test results for selection of response models of hardness, friability and disintegration time

Response	Source	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS
Hardness	RMain effects	0.995519	0.99389	0.99052	72.32884
Friability	RMain effects	0.995676	0.994103	0.990851	76.18766
Disintegration time	R2FI	0.994428	0.991642	0.985735	54.44722

The best fitting mathematical model was selected based on the comparisons of several statistical parameters, including multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) , and the predicted residual sum of square (PRESS) provided by Design-Expert®8.0.7.1 Software. Consequently, the selected model for drug disintegration time is reduced 2FI. The goodness of fit of the model was checked by determination coefficient (R^2) of 0.9944. In this case, the R^2 value indicates that 99.44% of the variability in response could be explained and only 0.56% of the total variation cannot be explained by the model. The "Pred R-Squared" of 0.9857 is in reasonable agreement with the "Adjusted R-Squared" of 0.9916. The aforementioned results indicate that the reduced 2FI model provided an excellent explanation for the relationship between the independent variables and the corresponding response.

However, the selected model for friability and hardness is reduced main effects, i.e., after selecting the significant model terms only main effects were chosen. The determination coefficient (R^2) for hardness and friability are 0.9955 and 0.9956, respectively. So, R^2

values of both responses are closer to 1, which indicates a better prediction of the models, for a good fit of a model.

As shown in Table 3.10, the reduced 2FI model is statistically significant for disintegration time ($P < 0.05$), which is desirable as it indicates that the terms in the model have significant effect on the response. Table 3.10 also depicts A (concentration of ammonium bicarbonate), B (concentration of crospovidone), C (amount of MCC) and D (compression force), are significant model terms as well as CD (interaction effect of amount of MCC and compression force) is also significant model term. The Model F-value of 356.92 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Table 3.10: Summary of ANOVA results of response surface model for disintegration time.

Source	Sum of Squares	df	Mean square	F-value	*p*-value	Remark
Model	5353.75	5	1070.75	356.9167	< 0.0001	significant
A-Ammonium bicarbonate concentration	56.25	1	56.25	18.75	0.0015	significant
B-Crospovidone concentration	210.25	1	210.25	70.08333	< 0.0001	significant
C-MCC concentration	870.25	1	870.25	290.0833	< 0.0001	significant
D-Compression force	4096	1	4096	1365.333	< 0.0001	significant
CD	121	1	121	40.33333	< 0.0001	significant
Residual	30	10	3			
Cor Total	5383.75	15				

For hardness and friability, the selected model is reduced main effects as explained above with F-value of 610.99 and 633.16, respectively and a *p*-value of <0.0001 as shown in Table 3.11 and 3.12, which imply the models are significant. The greater the F-value is

from unity, the more certain it is that the factors explain adequately the variation in the data about its mean, and the estimated factor effects are real. There is only a 0.01% chance that a "model F-value" this large could occur due to noise. The *p*-values less than 0.05 indicate model terms are significant. In this case, A (concentration of subliming agent, ammonium bicarbonate), B (concentration of superdisintegrant, crospovidone), C (amount of MCC) and D (compression force) are significant model terms.

Table 3.11: Summary of ANOVA results of response surface model for hardness.

Source	Sum of Squares	df	Mean square	F-value	*p*-value	Remark
Model	13705.75	4	3426.438	610.9959	< 0.0001	significant
A-Ammonium bicarbonate concentration	162.5625	1	162.5625	28.98784	0.0002	significant
B-Crospovidone concentration	855.5625	1	855.5625	152.5623	< 0.0001	significant
C-MCC concentration	2232.563	1	2232.563	398.1064	< 0.0001	significant
D-Compression force	10455.06	1	10455.06	1864.327	< 0.0001	significant
Residual	61.6875	11	5.607955			
Cor Total	13767.44	15				

Table 3.12: Summary of ANOVA results of surface response model for friability.

Source	Sum of Squares	df	Mean square	F-value	*p*-value	Remark
Model	0.441775	4	0.110444	633.1629	< 0.0001	significant
A-Ammonium bicarbonate concentration	0.007656	1	0.007656	43.89251	< 0.0001	significant
B-Crospovidone concentration	0.028056	1	0.028056	160.8436	< 0.0001	significant
C-MCC concentration	0.100806	1	0.100806	577.9121	< 0.0001	significant
D-Compression force	0.305256	1	0.305256	1750.003	< 0.0001	significant
Residual	0.001919	11	0.000174			
Cor Total	0.443694	15				

The normal probability plots of the residuals and the plots of the residuals versus the predicted response for hardness, disintegration time and friability are shown in Figures 3.5-3.10. 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. Figure 3.5, 3.6 and 3.7 show that points or point clusters are placed closely to the diagonal line implying that the errors are distributed normally for all responses. Figures 3.8, 3.9 and 3.10 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.

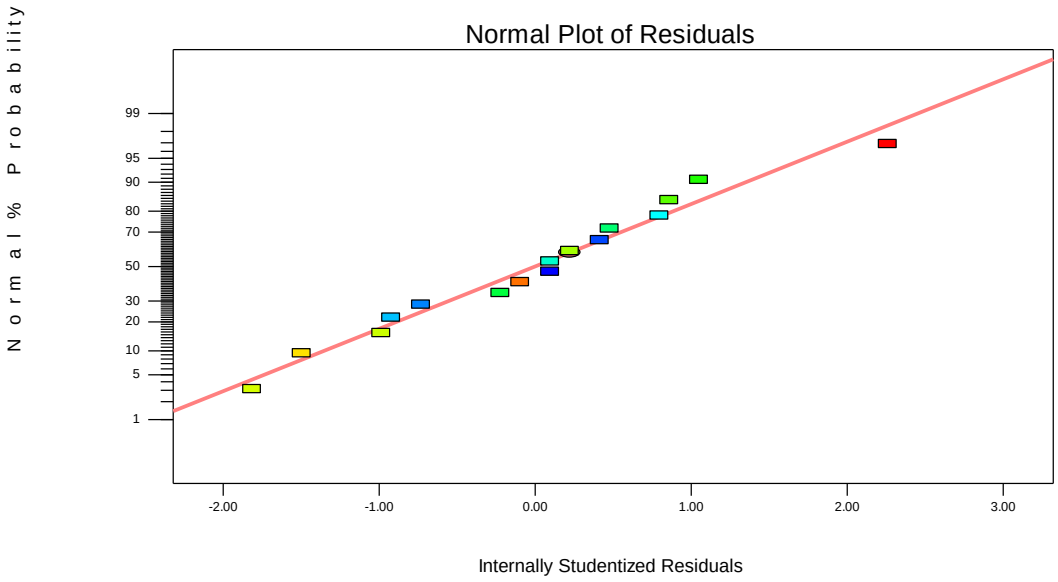


Figure 3.5: Normal probability plot of residuals for hardness.

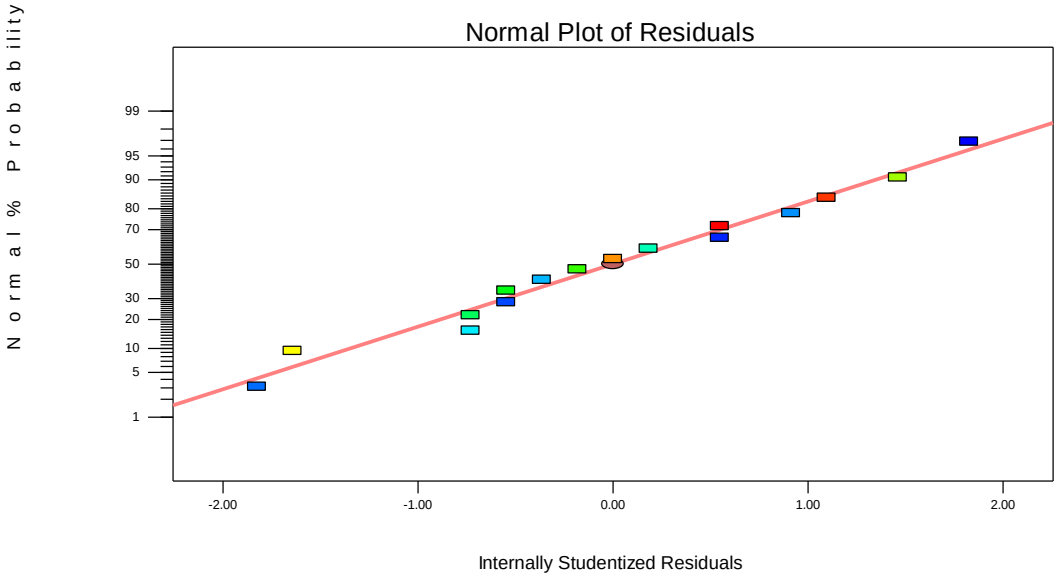


Figure 3.6: Normal probability plot of residuals for disintegration time.

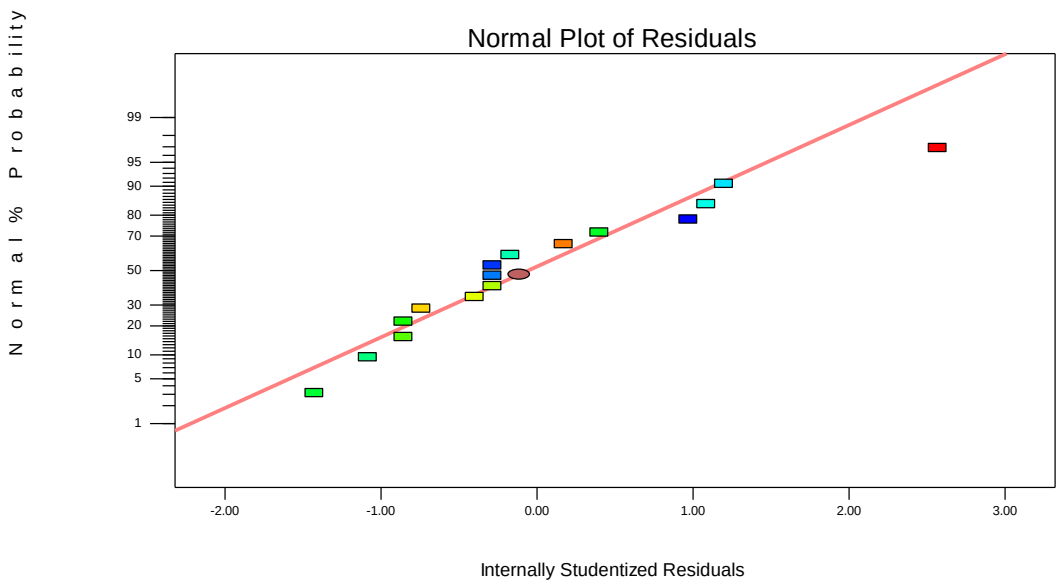


Figure 3.7: Normal probability plot of residuals for friability.

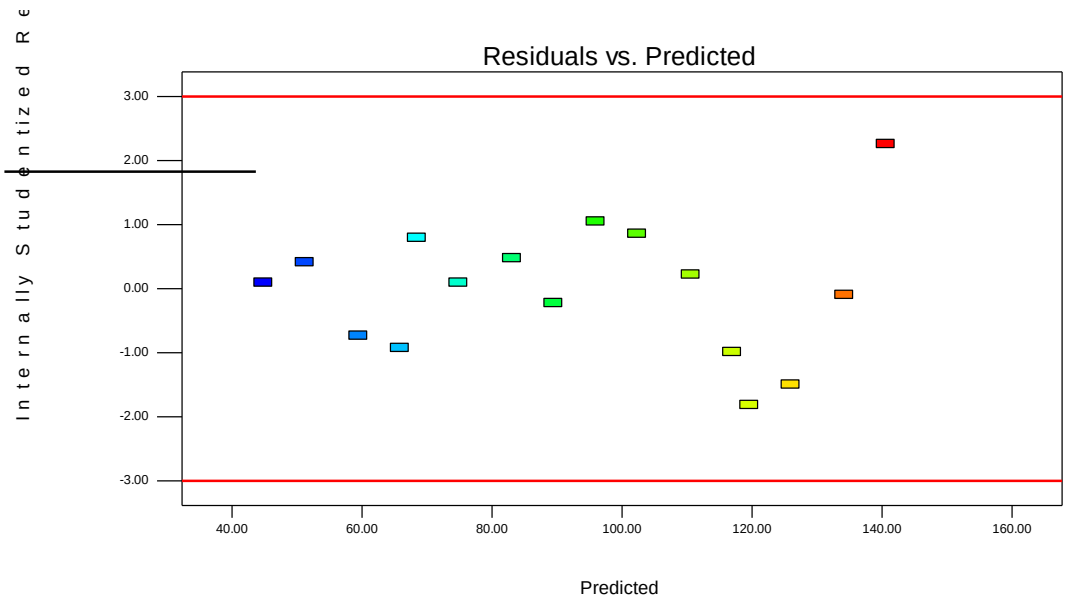


Figure 3. 8: Plots of the residuals against predicted response for hardness.

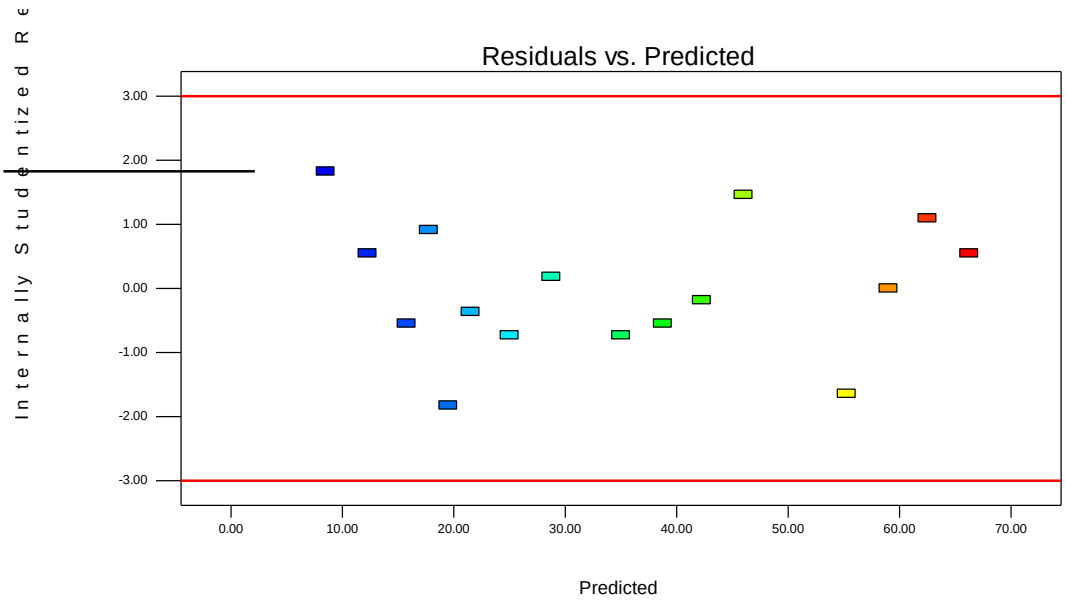


Figure 3. 9: Plots of the residuals against predicted response for disintegration time.

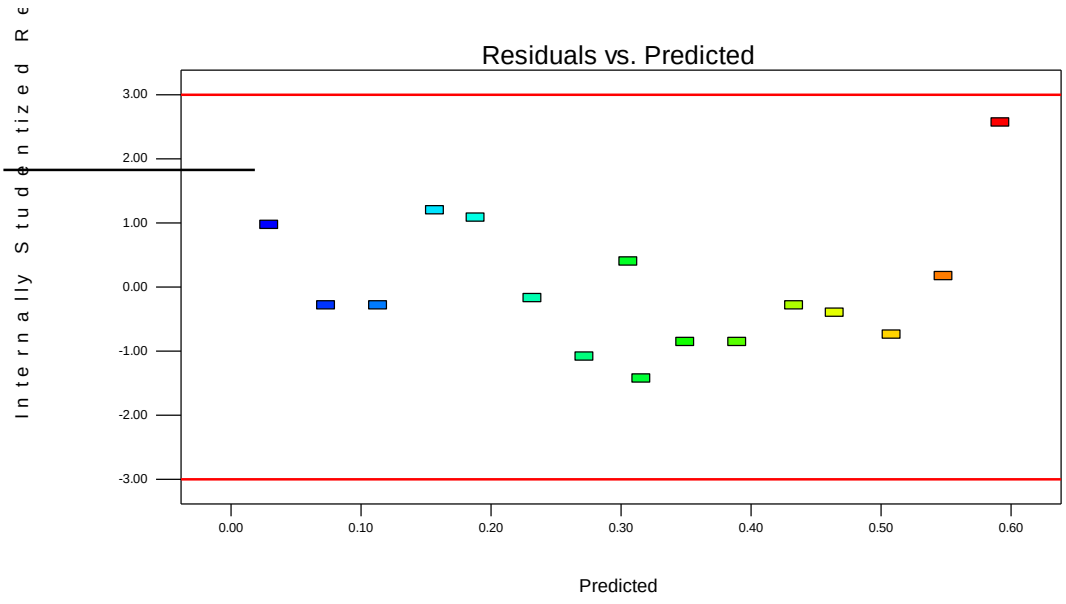


Figure 3.10: Plots of the residuals against predicted response for friability.

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.

3.6.4 The mathematical regression models

The mathematical regression models in terms of coded factors developed from the model terms in Table 3.13 show the regression coefficients of the model terms in their respective models for each response.

Table 3.13: Estimated model term regression coefficients for the selected models for each response for taste-masked MCP ODTs.

	Coded Coefficients			Actual Coefficients		
	Hardness	**Disintegration time**	**Friability**	**Hardness**	**Disintegration time**	**Friability**
Intercept	92.6875	34.625	0.310625	-62.00	+0.65705	+1.23872
Main effect						
A-Ammonium bicarbonate concentration	-3.1875	-1.875	0.021875	-0.63750	-0.37500	+4.375E-003
B-Crospovidone concentration	7.3125	-3.625	-0.04188	+2.25000	-1.11538	-0.012885
C-MCC concentration	11.8125	7.375	-0.07938	+1.57500	-0.11667	-0.010583
D-Compression force	25.5625	16	-0.13813	+5.11250	-0.28333	-0.027625
Interaction effect						
CD	--	2.75	--	--	+0.073333	--

The final mathematical regression models in terms of coded factors (Eq. 3.1 to Eq. 3.3) were developed using model term coefficients.

$$\text{Hardness (Y1)} = -3.19A + 7.31B + 11.81C + 25.56D + 92.69 \quad (3.1)$$

$$\text{Disintegration time (Y2)} = -1.88A - 3.63B + 7.38C + 16D + 2.75*C*D + 34.63 \quad (3.2)$$

$$\text{Friability (Y3)} = 0.022A - 0.042B - 0.079C - 0.14D + 0.31 \quad (3.3)$$

Where, A is concentration of subliming agent, ammonium bicarbonate, B is concentration of superdisintegrant, crospovidone, C is amount of MCC, and D is compression force.

Coefficients of the developed models have physical meanings on the response variables. A coefficient is the amount the response changes when that term is changed by one unit, while holding the other terms constant. Both the magnitude and sign of coefficients are important: the magnitude implies the strength, whereas, the sign indicates the direction of that factor variable on the corresponding response variable. A positive sign indicates a positive effect whereas a negative sign indicates a negative effect on the response.

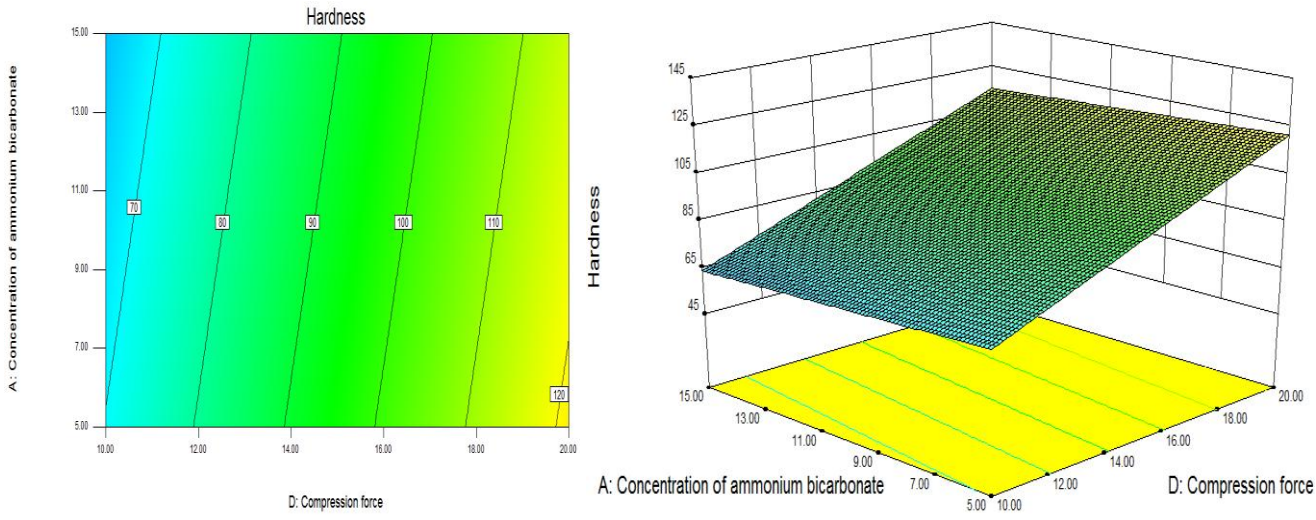
As Eq. 3.1 and 3.3 show, three factors i.e., concentration of crospovidone (B), amount of MCC (C) and compression force (D) significantly affect hardness positively while concentration of ammonium bicarbonate (A) significantly affect hardness negatively and the converse is true in the case of friability. The effect of compression force on the hardness was the strongest with largest coefficient (+25.56) than the other variables investigated.

The concentration of ammonium bicarbonate (A) and concentration of crospovidone (B) significantly affect disintegration time negatively, whereas the amount of MCC (C), compression force (D) as well as interaction factor C and D significantly affect disintegration time positively (Eq. 3.2); however, the effect of compression force was again found to be the more determinant than the other variables on disintegration time as it has largest coefficient (+16).

3.6.5 Contour plot and surface response analysis

The three-dimensional response surface plots, obtained as a function of two factors maintaining all other factors constant, are helpful in understanding the effects of each factor as well as their interaction. The corresponding contour plots, represented by the projection of the response surfaces in the x–y plane, provides a straight forward determination of the effects of the independent variables on the dependent variables. In all the presented figures, two factors were selected according to their significance and the third and fourth factors were kept at level zero (that is mid-point).

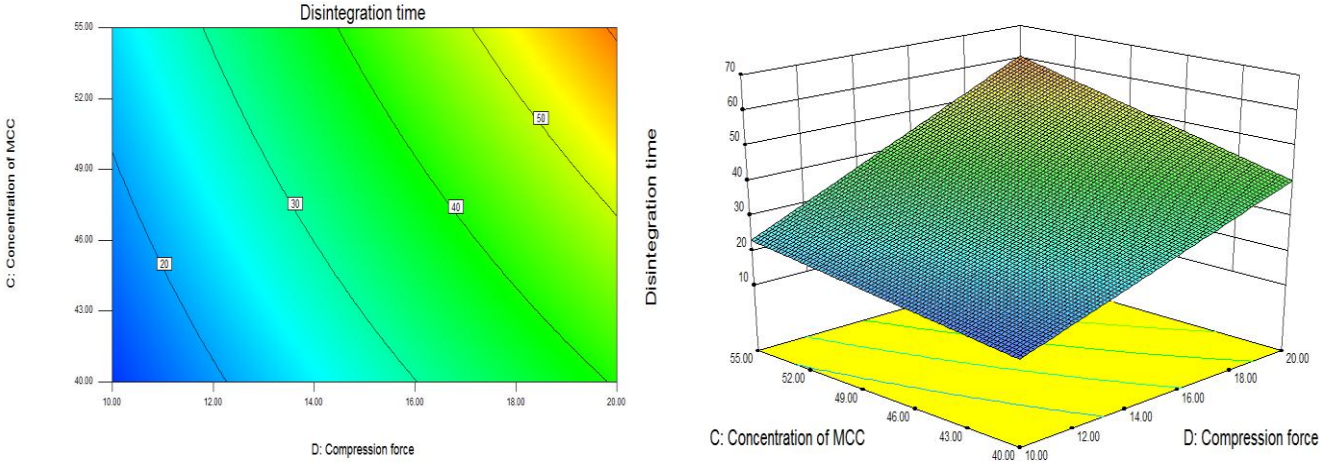
The contour and response surface plots shown in Fig. 3.11 A and B, respectively, indicate the combined effects of compression force and concentration of ammonium bicarbonate on hardness. The diagonal parallel straight lines of the contour plot and the non-twisted response surface indicate that there was no interaction effect of the two parameters on the hardness. However, the plots show that the linear model components individually affect the hardness significantly, with comparatively more significant effect of compression force than the concentration of subliming agent, ammonium bicarbonate.



A B

Figure 3.11: Contour plot (A) and surface response plot (B) of hardness as a function of concentration of ammonium bicarbonate and compression force.

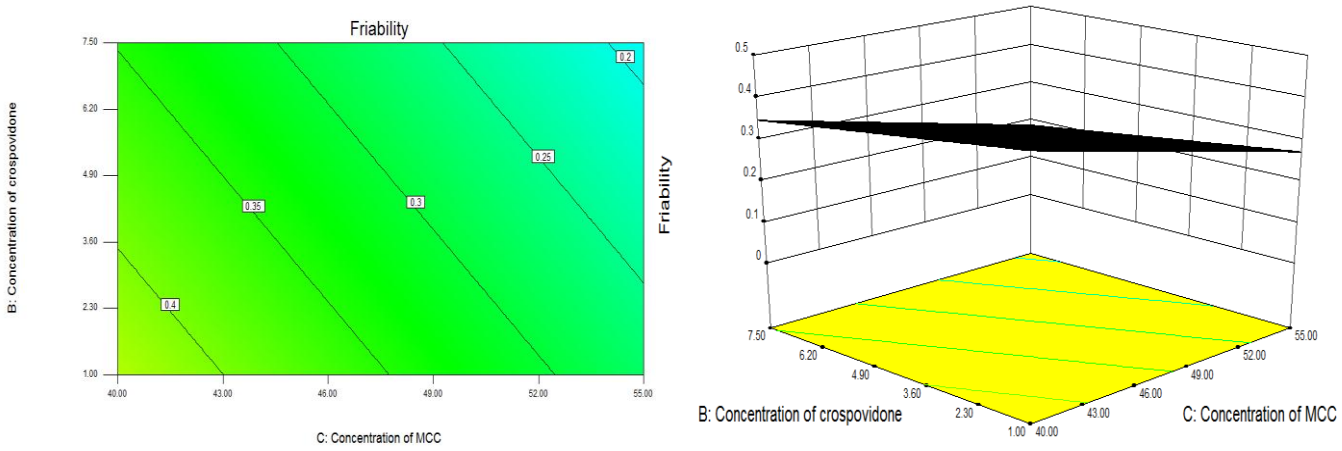
Fig. 3.12 A and B depict the combined effects of amount of MCC and compression force on tablet disintegration time. The contour plot indicates that both amount of MCC and compression force play a very significant role in influencing tablet disintegration time. In addition, the effect of compression force appeared to be slightly higher as compared to the amount of MCC. Besides, the slightly curved diagonal lines on the contour plot show the minor synergistic effect of the variables on the response. This was further confirmed by the coefficients in the mathematical model generated for hardness (Eq. 3.2).



A **B**

Figure 3.12: Contour plot (A) and surface response plot (B) of disintegration time as a function of amount of MCC and compression force.

The combined effects of concentration of crospovidone and amount of MCC on tablet friability of the orally disintegrating tablet are shown in Fig. 3.13 A and B. The plots indicate that both concentration of crospovidone and amount of MCC play a very significant role in influencing the response friability. However, the effect of the amount of MCC appeared to be more pronounced as compared to the concentration of crospovidone. This was confirmed from the coefficients in the mathematical model generated for friability (Eq. 3.3).



A B

Figure 3.13: Contour plot (A) and surface response plot (B) of friability as a function of concentration of crospovidone and amount of MCC.

3.6.6 Simultaneous optimization of the response variables

After generating the model polynomial equations to relate the dependent and independent variables, the formulation was optimized for the three responses simultaneously. The final optimal experimental parameters were obtained using both numerical and graphical optimization techniques of Design-Expert® 8.0.7.1 software, which allows the compromise among various responses and searches for a combination of factor levels that jointly optimize a set of responses by satisfying the requirements for each response in the set.

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 hardness in the range of 70-80 N, disintegration time in the range of 0-30 s and friability in the range of 0-0.5% as the goals to locate the optimum setting of independent variables in the new formulation as shown in Table 3.14.

Table 3.14: Criterion settings of factors and responses for optimization of taste-masked MCP ODTs.

Variable	Goal	Lower limit	Upper limit	Lower weight	Upper weight	Importance
Ammonium bicarbonate (%)	Range	5	15	1	1	-
Crospovidone (%)	Range	1	7.5	1	1	-
MCC (%)	Range	40	55	1	1	-
CF (KN)	Range	10	20	1	1	-
Hardness (N)	Range	70	80	1	1	5
Disintegration time (s)	Range	0	30	1	1	3
Friability (%)	Range	0	0.5	1	1	5

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. Fig. 3.14 shows the predicted optimum values and the corresponding levels of parameters according to the set goals. The dot indicates the best solution found by the Design-Expert solver.

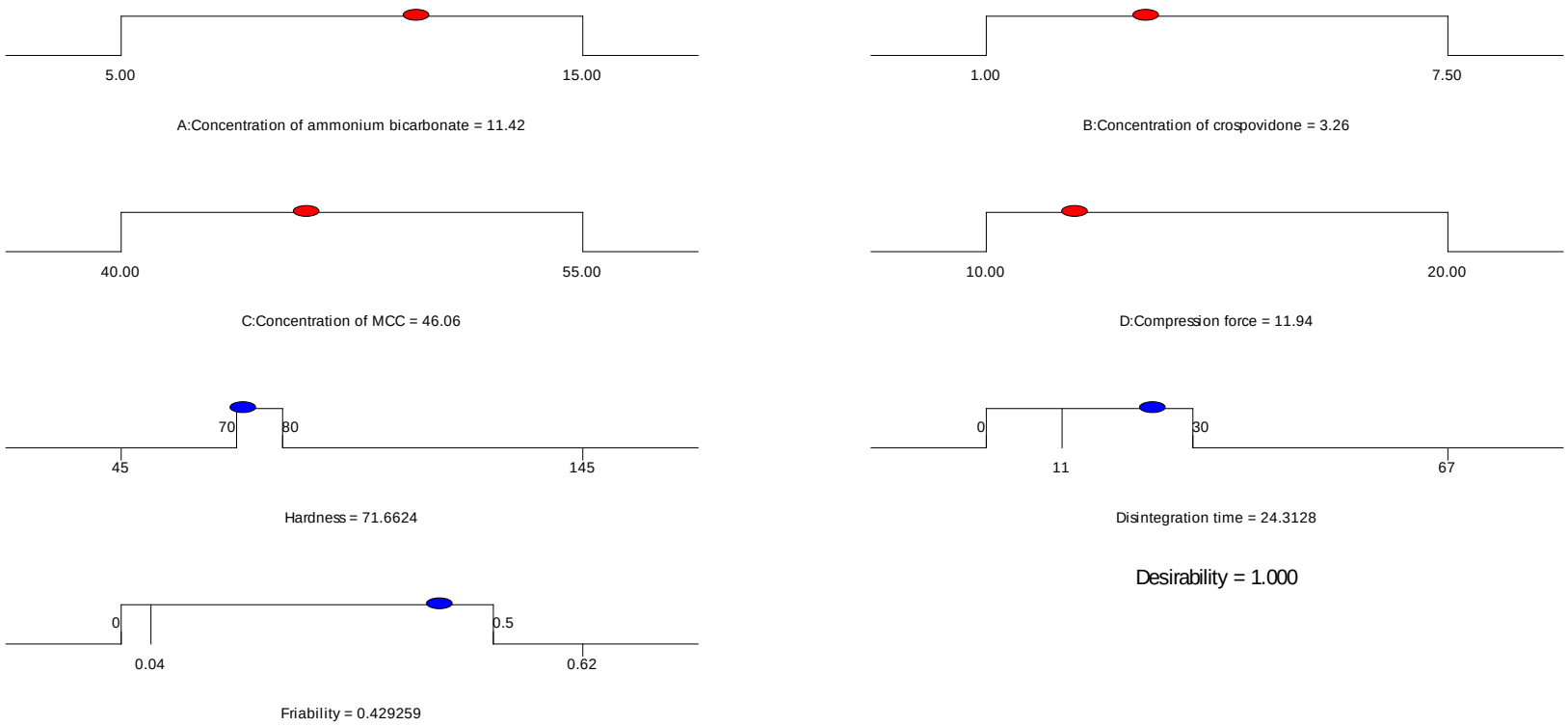


Figure 3.14: Desirability ramp for numerical optimization of seven goals, namely: concentration of ammonium bicarbonate, concentration of crospovidone, MCC concentration, compression force, hardness, disintegration time and friability.

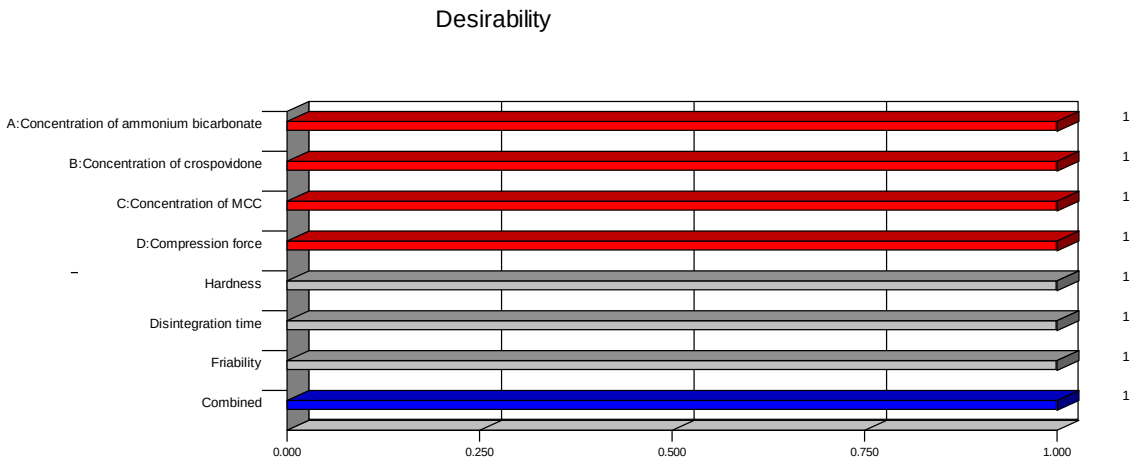


Figure 3.15: Desirability bar graph for numerical optimization of seven goals, namely: concentration of ammonium bicarbonate, concentration of crospovidone, MCC concentration, compression force, hardness, disintegration time and friability.

In multiple response optimization using desirability approach, individual desirability functions d_i 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. Desirability function ranges from 0 to 1, with value closer to one indicating a higher satisfaction of response goal(s). In this study, the values of individual desirability functions d_i of hardness, disintegration time and friability were obtained from the Design-Expert solver to be 1.00 for all responses, as calculated from the optimal point obtained ($Y_1 = 71.66$, $Y_2 = 24.31$ $Y_3 = 0.43$). This indicates that, fully desired responses were achieved for all responses. The overall desirability function (D) was then obtained from the individual desirability functions to be 1.00 from the software solver calculated based on Equation 3.6.

$$D = \left[d_1^{p_1} d_2^{p_2} d_3^{p_3} \ldots d_i^{p_i} \right]^{1/\sum p_i} \qquad (3.4)$$

Where i is the number of responses, d_i the individual desirability functions and p_i is the relative importance of ith response as compared to the others. Importance (p_i) varies from 1 to 3, from least to most important, respectively. Figure 3.16 shows a 3D plot of the overall desirability function D for the (A: concentration of ammonium bicarbonate and C: amount of MCC) plane.

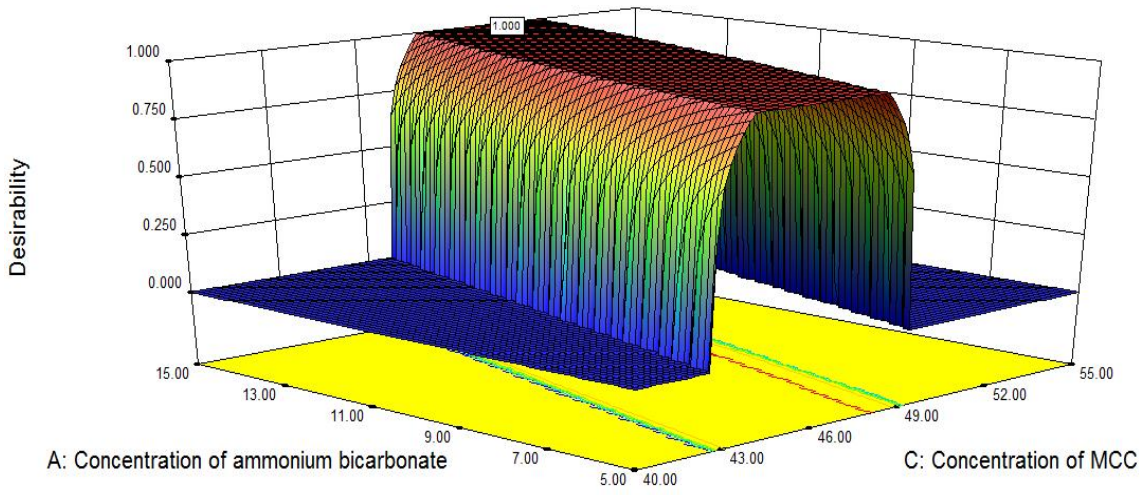


Figure 3.16: 3D view of most desirable operating conditions.

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/or 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.

Fig. 3.17 shows the overlay plot in which the yellow 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 concentration of ammonium bicarbonate of 14.20%, concentration of crospovidone of 6.14%, amount of MCC of 51.31% and compression force 10.15 KN. Under these conditions the model predicts hardness of 75.49, disintegration time of 17.82 s. and friability of 0.40 %.

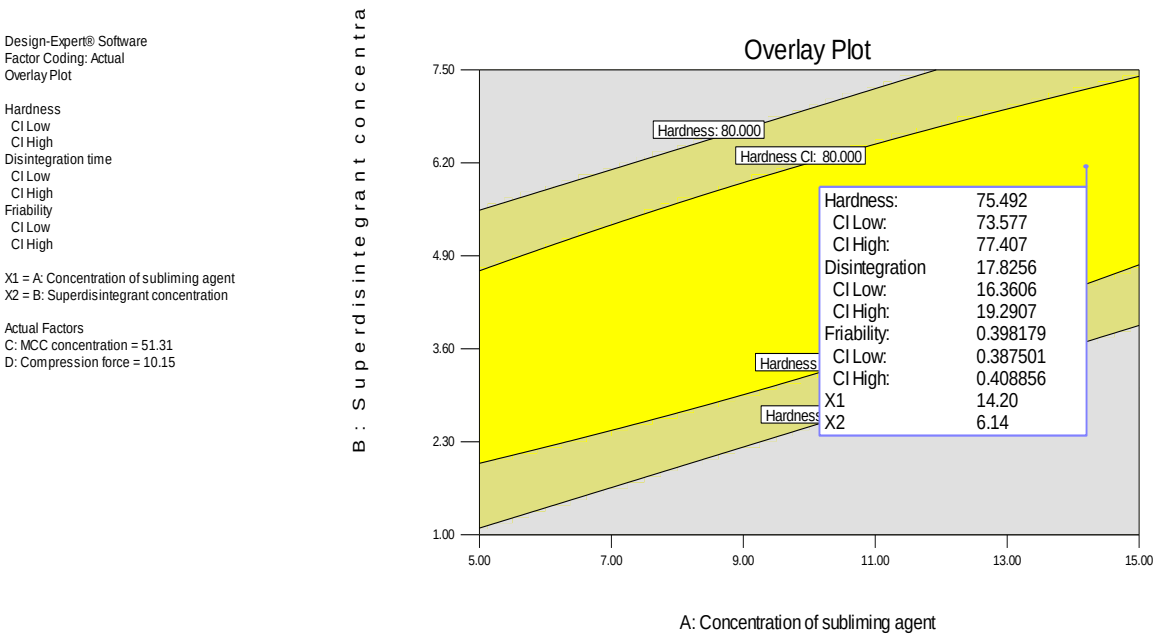


Figure 3.17: Optimum region identified by overlaying plots of the three responses as functions concentration of ammonium bicarbonate and crospovidone.

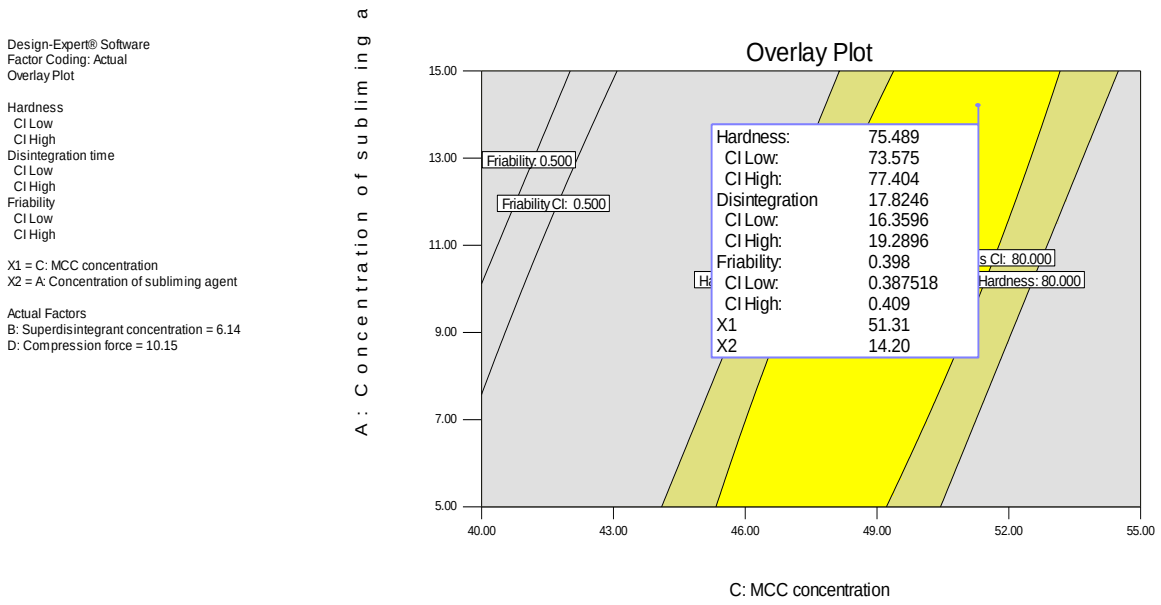


Figure 3.18: Optimum region identified by overlaying plots of the three responses as functions of amount of MCC and concentration of ammonium bicarbonate.

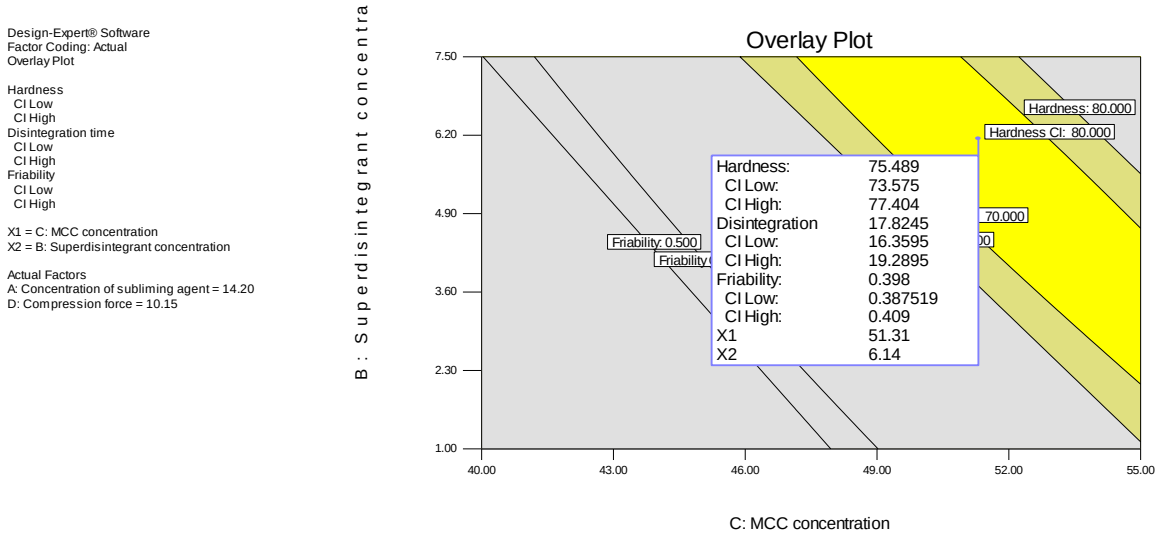


Figure 3.19: Optimum region identified by overlaying plots of the three responses as functions of amount of MCC and concentration of crospovidone.

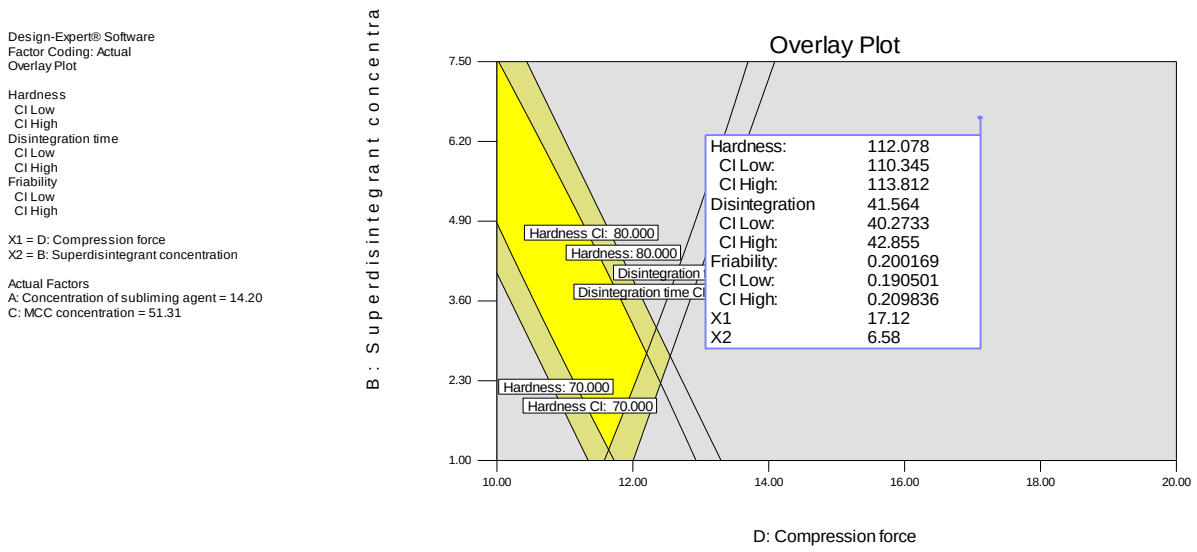


Figure 3.20: Optimum region identified by overlaying plots of the three responses as functions of compression force and concentration of crospovidone.

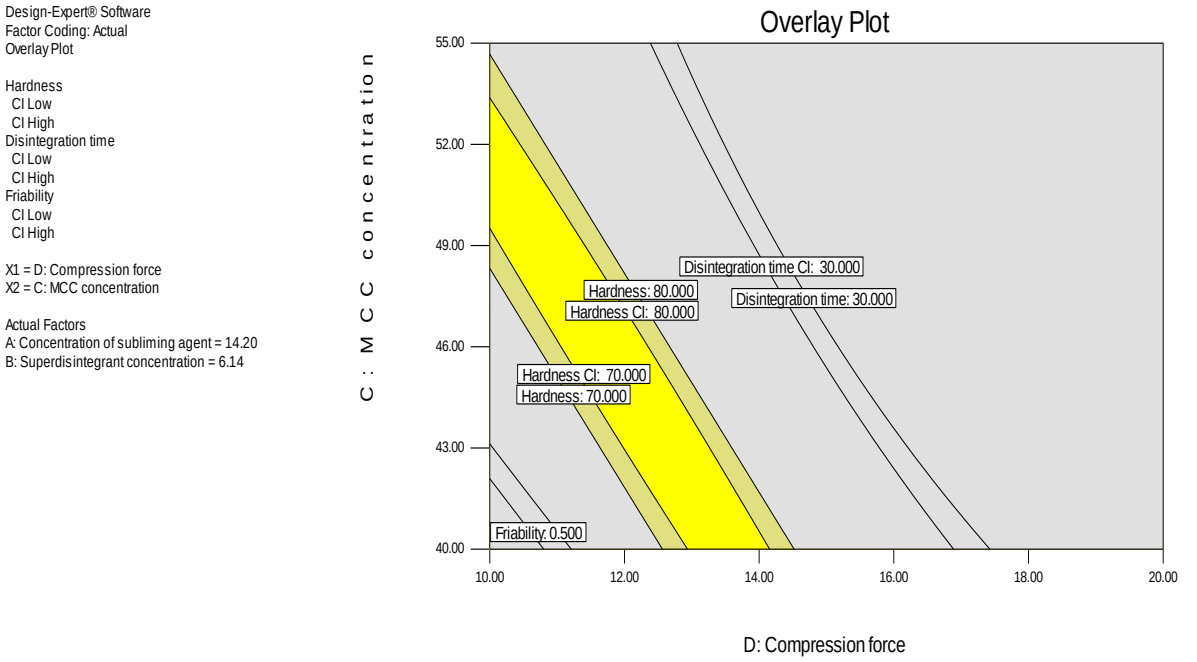


Figure 3.21: Optimum region identified by overlaying plots of the three responses as functions of compression force and amount of MCC.

Confirmation test

To experimentally confirm the validity of the obtained optimal point, confirmatory experiments were carried out at the optimal combinations of the factors (A= 14.20, B= 6.14, C=51.31 and D=10.15). Resinate formulation containing resin to drug ratio of 1:3 were prepared by swelling resin for 30 min at stirring time of 60 min and at room temperature. Three batches of taste masked ODTs were prepared according to the optimized formulation and powder and tablet properties were characterized as shown in Tables 3.15 and 16, respectively.

The resinate blend was prepared by mixing MCP loaded resins with all the ingredients. Characterization of the powder blend also showed that the powder blend of the optimized formulation has a very good flow and compressibility properties (Table 3.15).

Table 3.15: Physicochemical characteristics of the optimized MCP DRC powder blend (mean ± SD, n=3).

Parameters	Experimental values DRC powder blend
Bulk density (g/cm3)	0.50 ± 0.02
Tapped density (g/cm3)	0.57 ± 0.03
Angle of repose (^{o})	29.40 ± 2.34
Carr's Index (%)	12.92 ± 0.25
Hauser ratio	1.13 ± 0.01

Table 3.16 presents the predicted values, experimental results and the percentage error values obtained at optimal levels of the factors.

Table 3.16: Formulations prepared based on the predicted and the experimental values of the various responses (n = 3).

Responses	**Predicted value**	**Experimental value**	**Percentage error**
Hardness	75.49179	76.00 $\pm$ 1.32	0.67
Disintegration time	17.8255	18.00 $\pm$ 1.54	1.01
Friability	0.39818	0.39 $\pm$ 0.07	2.01

According to the results in Table 3.16, there exists a good correlation between predicted and experimental values after optimization (error of less than 5%). Thus, the method was quite useful for optimizing the parameters and hence a comparison made was useful for the full experimentation and comparison purpose. Furthermore, 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.

3.7 Characterization of the optimized taste masked MCP ODTs

3.7.1 Advanced microscopic study for surface profiling

From the formulated batches of resinate, the optimized formulation was examined for surface morphology and shape using inverted optical microscope (Fig. 3.22). The surface morphology before and after sublimation of optimized formulation illustrate the smooth surface of tablets before heat treatment and some small pores and cavities were formed on the surface of the later, arising due to sublimation of ammonium carbonate during the temperature treatment of the tablets.

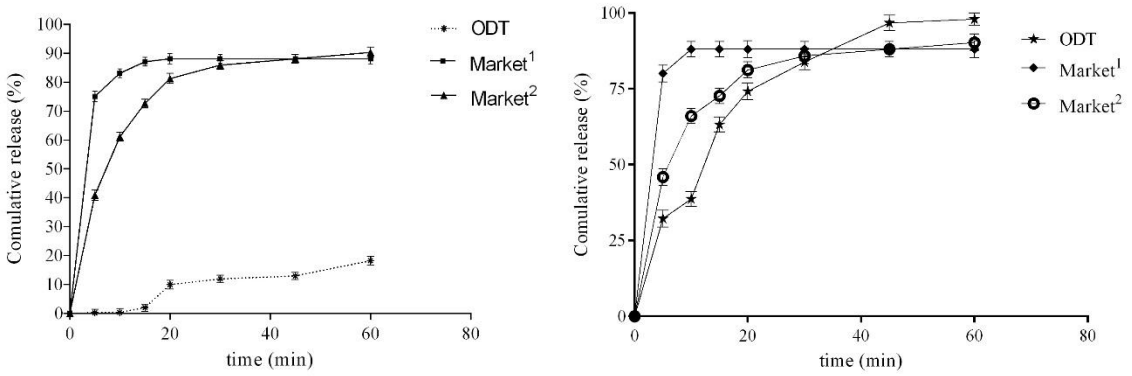
(a) **(b)**

Figure 3.22: Inverted optical microphotograph of optimized taste masked MCP orodispersible tablet before (a) and after (b) sublimation at 10X magnification.

3.7.2 *In vitro* drug release behaviors

The *in vitro* drug release behaviors of the optimized formulations in phosphate buffer (pH 6.8) and 0.1 N HCl media were shown in Figures 3.23. In phosphate buffer (pH 6.8), only 0.25% was released in 5 min and 10% was released in 20 min for the optimized formulation whereas Premosan® released 75.1% and Regurg® released 40.94%. The USP30/NF25 specification for the release of MCP from tablets of MCP is that "not less than 75% (Q) of the label claim of MCP should be dissolved in 30 min in 0.1 N HCl media". As shown in the Figure 3.23, the optimized formulations released more than 75% of the label claim within 20 min, meeting the USP requirement.

Moreover, the complete release profile of the optimized formulation for all the three batches taken was determined (Fig. 3.23) and was compared with conventional MCP tablet found on the market. The results showed that the optimized taste masked ODTs showed superior *in-vitro* cumulative drug release.



(a) (b)

Figure 3.23: *In vitro* release profile from optimized taste-masked ODTs in phosphate buffer (pH 6.8) (a) and 0.1 N HCl (b) compared with marketed products (n = 6, Mean ± SD).

The uniformity of dosage units can be demonstrated by either of the two methods, weight variation test or content uniformity test. For tablets of high dose drugs (which contain 25 mg or more of an active ingredient comprising 25% or more, by weight, of the dosage form

unit), weight variation test is recommended by the USP30/NF25, as an effective means of assuring uniform potency. But for tablets of low dose drugs (tablet formulations containing less than 25 mg of an active ingredient comprising less than 25% by weight of the dosage form), excipients make up the bulk of the tablets' weight. Therefore, content uniformity test was performed for the 10 mg MCP orodispersible tablets.

The British Pharmacopoeia states that MCP tablets must contain not less than 90.0% and not more than 110.0% of the amount of MCP of the label claim (BP, 2000). The assay result for the optimized MCP tablets was 98.00 ± 1.25%, indicating that the tablets comply with the BP specification.

3.7.3 Taste-masking efficiency

Bitterness threshold concentration of MCP

The bitterness threshold concentration of MCP ODTs was determined *in vivo* on twelve healthy human volunteers with series of MCP standard solutions of different concentrations (10, 20, 30, 40, 50, and 60 μg/mL). No subject felt bitterness up to concentration of 30 μg / mL. Nine out of twelve volunteers felt the bitterness, after 30 s at the concentration of 40 μg / mL and only three of the volunteers did not feel the bitterness at 40 μg / mL. Therefore, it was concluded that the threshold concentration of MCP that triggered the sensation for bitterness, was 40 μg/ mL.

In vivo taste-masking evaluation

Taste evaluation in volunteers confirmed that the taste of drug was masked by complexing with Dowex Marathon C® resin. All of the twelve volunteers found the taste masked MCP ODTs to be tasteless and agreeable.

The panel testing is a psychophysical rating of the gustatory stimuli. In this method, a group of human volunteers are trained for taste evaluation by using the determined threshold bitterness value. Subsequently, test material is tasted and rated on the same scale to assess its bitterness. The ease of the method combined with the accuracy of human perception of taste against any other gustatory evaluation technique makes panel testing the most commonly used technique (Pein, 2013).

In vitro taste-masking

The word 'medicine' for a child is synonymous with bad taste. Oral pharmaceuticals have been continually adapted for making their *"bitter taste better"*, especially to the pediatric and the geriatric consumers. Taste masking is a viable strategy to improve the patient compliance, especially for bitter drugs, whereby, a gamut of methodologies may be adopted to deliver a palatable formulation. Taste masked products developed from innovative pharmaceutical technologies not only increase the commercial profits, but also create brand value for a company. Such intellectual wealth acts as an impetus for emergence of the innovative low cost commercially viable taste masking technologies (Sohi *et al.*, 2004).

IERs have been used as drug carriers in pharmaceutical dosage forms for taste masking. IERs are cross linked water-insoluble polymers carrying ionizable functional groups. Drugs can be loaded into an IER by an exchanging reaction, and hence a DRC is formed. Drug is released from resinate by exchanging with ions in the gastro-intestinal fluid, followed by drug diffusion. There are literature reports on the interaction of amine drugs with polysulfonic acid ion- exchanged resin that indicated these resins might be very useful in the taste masking (Anand *et al.*, 2001).

The taste-masking efficiency of the MCP resinate was determined by spectrophotometric analysis based on the amount of drug released at 5 min from the taste-masked resinate in a phosphate buffer (pH 6.8) (Fig. 3.23). As shown in the figure 3.23, the optimized formulation released a maximum of 25 μg/ mL drug in 5 min. This value is less than the threshold bitterness concentration of 40 μg/ mL and might be attributed to the poor ionization of the API from the DRC in phosphate buffer (pH 6.8) media with near to neutral pH.

Evaluation of taste-masking can be carried out using gold standard (i.e. human taste panel) and analytical evaluation methods (i.e. UV probe or electronic tongues) (Pein, 2013)**.** A research done by Kim *et al*. (2013) on taste-masking efficiency of drug loaded resin evaluated by electronic tongue and *in vivo* panel test by human volunteers showed a good

correlation between *in vitro* and *in vivo* tests. Hence, DRC-loaded ODT according to the *in vitro* and *in vivo* correlation of bitter taste-masking could provide platforms in ODT dosage formulations. The DRC is absolutely tasteless with no after taste and at the same time, its bioavailability is not affected (Jeong and Park, 2008a).

3.7.4 Accelerated stability study

As illustrated in Table 3.17, the short term stability studies on the optimized formulation did not show any major changes in evaluation parameters that could affect the tablet properties.

Table 3.17: Accelerated stability data for the optimized MCP ODTs formulation

S/N	Evaluation	0 month	1 month	2 month	3 month
1	Hardness (N)	76.00 ± 1.32	75.15 ± 1.25	75.00 ± 1.40	74.00 ± 1.38
2	Disintegration time (s)	18.00 ± 1.54	17.00 ± 1.40	17.00 ± 1.35	16.00 ± 1.55
3	Friability (%)	0.39 ± 0.07	0.40 ± 0.03	0.42 ± 0.06	0.47 ± 0.08
4	Content uniformity (mg)	98.00 ± 1.25	96.50 ± 1.55	96.45 ± 1.10	95.30 ± 1.10
5	Wetting time (s)	28.00 ± 1.20	26.00 ± 1.45	26.00 ± 1.40	25.00 ± 1.60

Disintegration time, friability and drug content uniformity were within the monograph specification as well as the other parameters including hardness and wetting time were also in an acceptable range in the three successive months. Disintegration time was less than 20 min. Friability was less than 0.5% and as much as 95.3% of a drug content was observed till the third month. The hardness of the tablet was not less than 70 N whereas the wetting time was not more than 30 min. Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients (Shankarrao *et al.*, 2010). This method duplicates the *in vivo* disintegration as the tablets are motionless on the tongue. Less is the wetting time, the more porous are the tablets (Sahu *et al*., 2013). The assays of the tablets were also within the pharmacopeia range of 90% to 110%. Therefore the results showed that the formulation was stable.

4 CONCLUSION

Taste-masked resinate of MCP was prepared and characterized. The effects of drug:resin ratio, swelling time, stirring rate and temperature on the various physicochemical properties of the resinate were studied and optimized. FT-IR spectra of MCP, resin, and MCP and resin complex (resinate) showed complexation between the drug and resin.

Orodispersible tablet of the resinate powder blend was prepared using sublimation technique. Formulation study was conducted to assess formulation factors and consequently, formulation variables (concentration of subliming agent- ammonium bicarbonate, concentration of superdisintegrant- crospovidone and amount of MCC) and a process variable (compression force) significantly affected the various responses, such as tablet hardness, disintegration time, and friability of the prepared taste-masked MCP ODTs. The RSM based on 2^4 full factorial experimental design was employed to obtain an optimum formulation with acceptable hardness, rapid disintegration time and friability. Accordingly, the desired optimum condition was obtained at 14.2% ammonium bicarbonate, 6.14% crospovidone, 51.31% MCC and 10.15 KN compression force. Under these conditions, the hardness, disintegration time and friability were 75.49 ± 1.32 N, 17.82 ± 1.54 s and 0.398 ± 0.07%, respectively. The 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. A dissolution study of the taste-masked MCP ODTs showed that the release of drug from the DRC was retarded in phosphate (pH 6.8) media and, therefore, the amount of drug released from the taste-masked MCP ODTs was found to be below the bitterness threshold of MCP, which was determined *in vivo*. On the contrary, the optimized formulation released more than 75% of claimed label of drug in 20 min, fulfilling compendial requirement.

From the foregoing, it can be concluded that a stable, taste-masked MCP ODTs was successfully developed.

5. RECOMMENDATIONS FOR FURTHER RESEARCH

Further investigations are suggested in the following points:

- Investigate the *in vivo* performance of the optimized formulation;
- Determine the long term stability of the formulation;
- As the formulations are all lab scale, perform optimized pilot scale and commercial scale in order to attain successful batch scale up;
- Carryout a production process validation to establish documented evidence that the manufacturing process of 10 mg MCP ODT will consistently produce a product that is safe, effective and will meet all the quality specifications according to the manufacturing formula; and
- Study resin kinetics to define its drug loading and release patterns.

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