Optimization and Evaluation of Aqueous Coating of Famotidine

By

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Praise is due to ALLAH whose worth cannot be described by speakers [Nahj-al-Balagha].

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Dedicated to my deceased mother and loving father and brother.

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Abstract

The purpose of this study was to prepare aqueous coated tablets of famoscot, having famotidine as active ingredient of tablet. In commercial manufacturing of famotidine tablets organic solvents had been used, which were hazardous not only for people working in industries but also for environment, residual solvents in drug were also harmful to patients. In this research work, in order to overcome this drawback organic solvents were replaced with water. For this purpose core of tablets having famotidine were prepared by direct compression method, evaluation tests were performed. This core was coated by varying amount of different polymers i.e. HPMC, PVA and PVP. It was observed that best coating was done using a blend of HPMC and PVA. The coated tablets were evaluated for hardness, weight variation, friability, in vitro dissolution and uniformity of content, obtained results showed that all parameters were within USP limits. FTIR was also done to check drug and polymer interaction, UV-Visible spectroscopy was used for dissolution studies. The formulation prepared by using blend of HPMC and PVA had no visual defects. IR studies of PVA and HPMC showed that no interaction had been observed between polymer and famotidine. Its disintegration time was also 1 minute, assay and dissolution time was 98%. Further, selected formulation was also subjected to accelerated stability studies and tablet remained stable for 6 months.All the obtained results of aqueous coated famotidine tablets fulfilled the criterion of the USP, by the replacement of organic solvents with water they will be expected to have no side effects caused by organic solvents and can be used commercially.

CHAPTER 1

Introduction

1.1 Solvents

For hundreds of years solvents and dissolution are integral to all industries. In 1400s chemists focused on dissolution process and solvents. Today, all the processing and manufacturing industries- paper and pulp, automotive, mining, chemical, food, uses organic solvents in various processes. To meet this increasing demand 15 billion kg organic solvents are being produced. These halogenated solvents are used widely in pharmaceutical industries for processing [1].

Advancement in science finds cure for every disease. Tablets, capsules, ampoules, ointments, injections are being prepared to cure all types of diseases. On one side these drugs are good for health, cure our diseases but on other side these drugs are also harming our health as well as environment. In preparation of drugs organic solvents are used, these solvents are very hazardous, some are even carcinogenic [2].

These solvents are hazardous not only for the people working in industries but also for those who are using the products which have residues of organic solvents. Chlorinated solvents are cancer causing, besides health, organic solvents can affect the environment badly. If environment is not clean then automatically human health is affected, these solvents disturbs whole ecosystem. Hexane is widely used in various industries. The Environmental Protection Agency of U.S. called hexane hazardous air pollutant. Since 1960s, different events raised the International concerns about toxins released in environment but no alternative was suggested [3].

Environmental advantages alone will not help to eliminate use of organic solvents, but the advantages related to cost and health must be considered. Using solvent alternatives is not an easy task because solubility issues, cost and future environmental demands must be considered. Now world is moving towards Green Chemistry, in which those solvents are used which neither can affect health nor environment [4].

Water is most suitable and easily available solvent, it is cost effective as well as environment friendly. Besides water ionic liquids and super critical fluids can also be used as alternatives of organic solvents.

In pharmaceutical industries these solvents are widely used for preparation of core as well as for coating. But these solvents are dangerous for patients as well as for people working in industry [5].

Solvents can be used at different steps e.g. for active or excipients synthesis, for formulation of drug, but mostly organic solvents are used in coating of tablet [6]. Although most of the solvent is evaporated but organic solvents cannot be completely removed from the drug due to some chemical and physical barriers. The solvent left inside the drug is known as residual solvents (RS), it can also be called as organic volatile impurities (OVI) [7]. Besides this drug can be contaminated by these solvents from warehouse storage, packaging and from transportation and shipping [8].

1.2 Effects of Organic Solvents

General hazards caused by exposure of organic solvents include toxicity to reproductive organs, CNS, kidney and liver function, cancer, respiratory problems and dermatitis. Chloroform and diethyl ether causes cancer and neurotoxicity. Methanol is very dangerous, it can cause death or permanent blindness. Ethanol is a psychoative drug, if it is used with other solvents it can cause vomiting. Some solvents like benzene and chloroform are carcinogenic. Long term exposure of organic solvents can cause neuropsychiatric effects [9].

One of the other pathway which can cause health effects is the leakage of solvents that reach underlying soil. By the spill of these solvents, aquifers are affected. Besides this, when these solvents are evaporated they can pollute the environment, so their use should be reduced or eliminated in pharmaceutical industries [10].

People working in pharmaceutical industries are exposed to organic solvents for long term it has adverse effects on body. Their exposure can cause leukaemia, chlorinated hydrocarbons exposure causes renal cancer and neurotoxicity [11]. Studies revealed that high level, long term exposure can cause memory impairment, neurological deficits, personality change syndrome or solvent neurotoxicity. This can also be termed as “Danish painter’s syndrome”[12].

Recent studies revealed that highly exposure of solvents effects cognitive functions. Cognitive functions affected by exposure of solvents are verbal memory, attention and visuospatial skills. These effects are mostly observed in people who were exposed to solvents for 10 years. Mechanism by which solvent affects nervous system is not known yet. Some evidence has been

found that enzyme activity that help in metabolism of foreign chemicals may cause solvent neurotoxicity[13].

1.3 Commonly Used Organic Solvents in Pharmaceuticals

In pharmaceutical industry organic solvents are commonly used, these solvents are used for preparation of coating solution for tablets. Commonly used solvents are methylene chloride and isopropyl alcohol. Organic solvents are used because they are volatile and can easily be removed from drug. But they are very toxic. Their vapors in the environment, act as environmental hazard. Besides this, minute quantity of solvents left behind in the drug is also a health hazard [14].

1.3.1 Methylene Chloride

Dichloromethane commonly known as methylene chloride, is an organic liquid and is used in different industries as solvent, it is selected because it can easily dissolve organic compounds. In pharmaceuticals, most of the excipients and active ingredients of drug is organic in nature, so this solvent is preferred, but it has lot of health hazards. Commonly observed toxicity is hepatic toxicity which is caused by inhalation of methylene chloride [15].

As it is volatile liquid so it can easily be inhaled. Its exposure cause impairment of CNS and interference to oxygen delivery. If 300 ppm concentration of methylene chloride is inhaled for short period of time, it can cause impairment of vision. If greater amount 800 ppm is inhaled, it can cause impairment of hand movements [16]. Prolonged exposures can cause dizziness, nausea, headaches, numbness in toes and fingers, tingling in legs and arms. In most of cases, these effects are short termed. Its 200-300 ppm concentration can be detected but odor threshold varies from person to person.

If women were exposed to methylene chloride on daily basis, it leads to reduce fertility rate. The route of organic solvents to enter in the body is mainly via vapor absorption or by inhalation. These vapors of organic solvents are absorbed through skin and their metabolites are distributed to blood tissues by the bloodstream, and have chronic effects on body. Exposure of organic solvents have adverse effect on fecundability. If pregnant women were exposed to organic solvents it leads to abortion, so exposure of organic solvents leads to infertility [17].

Methylene chloride is metabolized to CO, so it leads to carbon monoxide poisoning in body. It can be carcinogenic. It is linked to liver, lungs and pancreas cancer. However its carcinogenic effects are under studied. If heart patients are exposed to methylene chloride, it causes heart attacks or abnormal heart rhythms. People having skin, liver and nervous problems, severely affected by exposure to methylene chloride [15].

1.3.2 Isopropyl alcohol

Isopropyl alcohol (IPA) is also called as rubbing alcohol. It is used in various industries as hand sanitizers or for cleaning purposes. It is 70% pure alcohol and remaining part is additives. It can dissolve organic compounds, so it is widely used in pharmaceutical industries as solvent [18].

IPA ingestion causes intoxication and it affects that part of CNS which controls involuntary actions such as, breathing rate, heart rate and it slows down these functions. It can also cause cardiac arrest or hypothermia, thinning of blood causes blood sugar level to fall, it results in seizures [19].

Working with IPA can cause headaches. In pharmaceutical industries it is used as solvent. When it evaporates during drying process, it vapors are inhaled by workers. Inhaling large quantity of IPA causes vomiting, throat irritations and difficulty in breathing [20].

IPA is also absorbed by skin, small amount of IPA is not dangerous but prolong exposure causes drying, rashes and itching to skin.

1.3.3 Acetonitrile

Acetonitrile is also a harmful organic solvent, it can prompt death. It enters in human body by inhalation or vapors enters through eyes and skin and it leads to cytotoxic anoxia. Effects of acetonitrile depends on time, intensity and recurrence of exposure.

It leads to redness in eyes and skin, stomach disorders, breathing problems. Long term exposure can affect lungs, liver, kidney and sensory system. Its cancerous affects are very low. Acetonitrile once entered in body is readily consumed by gastrointestinal tract and lungs and then distributed to all the body. So, it should be readily expelled from body. Most ideal thing is to maintain a distance from it or its alternatives should be used [21].

1.3.4 Toluene

CNS is primarily affected by toluene toxicity in both animals and humans. Long term exposure of toluene leads to narcosis along with CNS disorders showing symptoms of nausea, headache and drowsiness. If concentration of toluene is high then it can cause cardiac arrhythmia. It can also cause CNS depression, which includes symptoms of ataxia, hemorrhage, cerebral atrophy, tremors, and impaired speech. Further studies revealed that prolonged exposure can cause irritation of eyes, headache, sore throat and insomnia [22].

Exposure of toluene to pregnant women can cause renal acidosis, musculoskeletal and disabilities in the children. It can also leads to spontaneous abortions. These cases were mostly observed in women, who were occupationally exposed to toluene [23].

1.3.5 Xylene

Xylene is a aromatic hydrocarbon but highly toxic, it is widely used as solvent in pharmaceutical industries. Its threshold limit is 100 ppm. Xylene vapors are absorbed through skin. Its vapors can be inhaled through lungs. 95% of xylene absorbed by skin is converted to methyl hippuric acid and remaining is excreted through urine. Higher concentration of xylene leads to neuro-physiological and neuropsychological dysfunction. Prolonged exposure can cause anemia, thrombocytopenia, cyanosis, chest pain and electrocardiogram (ECG) abnormalities. Xylene can also affect liver enzymes and size and visual abstraction. It also increases serum bile acids which damages liver [24].

Table 1: Concentration Limit of Solvents

Solvent	PDE (mg/day)	Concentration (ppm)
Cyclohexane	38.8	3880
Acetonitrile	4.1	410
Hexane	2.9	290
Chlorobenzene	3.6	360
Pyridine	2.0	200
Chloroform	0.6	60
Ethylene glycol	6.2	620
1,2 Dicholoroethene	18.7	1870
2-Ethoxyethanol	1.6	160
Dichloromethane	0.6	60
1,4-Dioxane	3.8	380
N,N-Dimethylformamide	8.8	880
N,N-Dimethylacetamide	10.9	1090
Methanol	20.0	2000
Xylene	21.7	2170
Nitromethane	0.5	50
Formamide	2.2	220
Sulfolane	1.6	160

These are some concentration limits of solvents, within these limits use of solvents is allowed. Beyond these limits solvents have hazardous effects on human as well as on environment [1].

1.4 Reasons to Control Organic Solvents

Main reason to control residual solvent is toxicity. Even if residual solvent levels are within limits, it leads to phase transformations so affecting stability of active ingredient in the drug, also affecting the quality of dosage [25]. Some of the reports of residual solvent effects are studied in literature e.g. methylene chloride effect on ampicillin trihydrate crystallinity. Residual ethanol leads to

transformation of phase of orthorhombic paracetamol. Other reasons for removal of organic solvents is taste or the odor they cause.

Other reasons to control organic solvents are described below:

1.4.1 Environmental Contamination

Organic solvents are not only a health hazard but they are also affecting environment severely. Almost 5000 sites have subsurface contamination of solvent. If they reach aquifers they are risk for aquatic life [26]. Mostly industries waste their solvents in oceans and sea, so these solvents contaminate water and also destroy marine life. Fishes and other animals which are a source of food for humans are also died because of these solvents.

When organic solvents are heated, their vapors contaminate the air, which when inhaled by living organisms, can cause health hazards [27].

1.4.2 Economic Loss

Besides a hazard for health and environment, organic solvents are also an economic burden. Price of these solvents is very high. So industries import them at high rates and use them for preparation of medicines, as a result cost of medicines also increase. So it will become an economic burden on society [28].

Solvents used for drug preparation are isopropyl alcohol, ethanol, acetonitrile etc. these solvents are costly and mostly solvents are imported from other countries so custom tax is also included in it, so it is need of hour to replace these solvents.

In this study these solvents are replaced by water. Comparative study is done, in one formulation organic solvents are used and cost is calculated and in other water is used and cost is calculated.

1.5 Steps Involved in Tablet Preparation

In preparation of tablets two major steps are involved:

i. Formation of core
ii. Coating of tablet

1.5.1 Formation of core

In core formation, following three methods are generally used:

i. Wet Granulation

Widely used method of agglomeration in pharmaceutical industries is wet granulation. In this method, granulating liquid is blended with wet mass of powder blend which leads to wet sizing and drying. Some of the steps involved in wet granulation are:

First of all excipients and drugs are mixed, then binder solution is prepared. Wet mass can be formed by mixing binder solution with powder mixture. As a result moist granules are formed. These granules are dried then mixed with lubricant, glidant and disintegrant.

This method has several advantages i.e. it increases sphericity and particle sizes, also improves powder flow, it allows mechanical handling of powder, without any loss, helps in making hydrophobic surfaces hydrophilic, improves and increase powder uniformity and also reduces air entrapment in powder [29].

ii. Dry Granulation

In this method no solvent or heat is used and powder mixture is compressed directly. It is not a desirable method. Basic processes in dry granulation is to compress and then mill the powder to form granules. For dry granulation two methods are used. Commonly used method is slugging, in which powder is recompressed and slug or tablet are milled, as a result granules are obtained [30].

iii. Direct Compression

In this method active powder mixture and excipients are compressed directly, as a result tablets are formed. In direct compression no pre-treatment for powder by dry and wet granulation is required. This method has a lot of advantages: it saves handling cost, energy, material and equipment. It has some disadvantages as well i.e. it leads to dust generation, drug uniformity problem and segregation issues. In this study direct compression method is used [31].

1.5.2 Tablet Coatings

Tablet coating is a popular pharmaceutical process. Over past few years this technology has been evolved from sugar coating, leads to film coating [32]. It is a process in which coating material is

applied in form of layers on the core of tablet which contains active pharmaceutical ingredient, to confer benefits over the uncoated tablets. Mostly a sugar or polymeric coat is applied on the tablet[5]. During the last few years, almost half of tablets were coated by functional coatings. Reason of functional coatings is to change dissolution profile or to mask the taste. Dissolution rate is controlled by using a polymer which makes tablet resistant to gastric juice. While the non-functional coatings are mostly used to enhance its appearance or to make it appealing and to improve its handling [33].

Coating of tablets is done to mask the taste, improve appearance, prolong shelf life, increase stability, increase mechanical integrity and also control the release of drug. Furthermore, coatings protect the drug from gastric acidity and from external environment (light, moisture, air).

1.6 Basic Requirements for Coating

For the coating of tablets, there are some basic requirements such as, agitation and mixing of tablet bed, atomization of spray liquid, sufficient heat required for evaporation of solvent. This is important for aqueous coating of tablets because removal of water needs greater heat. Besides this, a good exhaust is also required to remove solvent and dust [34].

1.7 Steps in Tablet Coating

Coating process is a batch driven method. It consists of following steps.

a. Identification of batch.
b. Dispensing or loading of material.
c. Spraying.
d. Drying.
e. Cooling.
f. Unloading.

1.8 Types of Tablet Coating

Coating of tablets has been classified into different types. Some of the types of coatings are following:

1.8.1 Sugar Coating

In this coating a sugar layer is coated on compressed tablets. This coating is soluble in water and it dissolves quickly after swallowing. The advantages of sugar coating is that it enhances the appearance, protect drug the from external environment and also makes tablet sweet. But this coating also has so many disadvantages, it is time consuming and it increases size of tablet, along its weight and shipping cost also increases. Operations involved in sugar coating are, sealing, smoothing, subcoating, coloring and polishing [35].

1.8.2 Enteric Coating

One of the other type of coating is enteric coating. This type of coating is applied on core to delay the release of the drug and is pH-dependent coating. Enteric coating is done to target release of drug in lower intestine. For enteric coatings weakly acidic polymers are being used, these polymers are unionized and insoluble in the acidic environment of stomach. That's why core of tablet is coated with thick layer of polymer so that active ingredient of tablet would not be released in stomach. But under high pH, in intestine, polymers are ionized and deprotonated so active ingredient is released [36].

1.8.3 Film Coating

Sugar coatings has been replaced by film coatings because of its advantages which includes decrease in volume and weight of coating, modify the release of drug, less time is consumed in preparation and it also keeps tablet intact during storage. In film coating uniform and thin film is deposited on substrate surface. These film coatings involve blends of polymer, opacifiers, plasticizer, antitacking agents and solvents. Film coatings have lot of advantages it provides pleasant appearance and also act as a protective barrier [37].

In this study our focus is on film coating of tablets.

1.9 Materials for Film Coating

Materials required for film coatings are plasticizers, colorants, solvent, opaquants, but the essence of film coating solution is polymers. Polymers form actual film around the core of tablet. The

polymers used in immediate release tablet coatings are acrylic polymers, polyvinyl derivatives, cellulose ethers and natural gums. In this study hydrophilic polymers are used [38].

1.9.1 Film Formers

Film coating materials should be stable against light, moisture, heat, air and substrate, soluble in the aqueous solvent, produce elegant product in appearance, compatible with additives and other coating materials, no inheret taste, color or odor, non-toxic, cheap, resistant against cracking, compatible to printing and it also should not give filling or bridging to tablets [39].

i. Hydroxypropyl Methyl Cellulose(HPMC)

HPMC is a hydrophilic polymer due its global availability, regulatory acceptance, desired release profile and cost. HPMC is used as film forming agent in aqueous or organic coating of tablets. Its nature is inert and it does not react with ionic organics or metals. So, it does not cause any interaction with other excipients. It is non-irritating and non-toxic in nature,it has good viscosity and is stable under alkaline and acidic conditions. HMPC does not produce any heat, as it is metabolized in body, with increasing temperature its viscosity is reduced. Its aqueous solutions are enzyme resistant and stable for long term. It is also incompatible with oxidizing agents [40]. HPMC is mostly used in oral pharmaceutical formulations because it can control release of drug. Besides this, it is used in food products and cosmetic industries. HPMC having low viscosity grade are used as disintegrant and binder but higher grades are only used as binder. It is mainly used as film coating material, which change weight, hardness, friability, hygroscopicity and disintegration of tablets. In aqueous coating of tablets lower viscosity grades of HPMC are used because drug release slows down with higher viscosity. Structure of HPMC is shown in figure 1. For treatment of vaginal and oral mucosal diseases HPMC can be used. Gelatin is widely used for capsule wall formation, but it has problems i.e less dissolution, oxygen sensitive and early disintegration, so HPMC is used as its substitute. Hence HPMC is best known polymer for pharmaceutical industries, because of its properties and cost effectiveness [41].

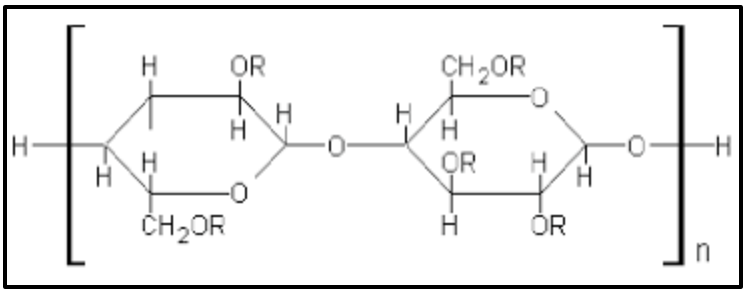

Figure 1: Structure of HPMC

ii. Polyvinyl Alcohol (PVA)

Polyvinyl alcohol is synthesized by polymerization reaction of vinyl acetate. As a result of this reaction polyvinyl acetate is formed, it is then hydrolyzed and converted into PVA. Acetate groups and hydrolysis affect solubility and crystallizability of PVA, the structure of PVA is shown in figure 2.

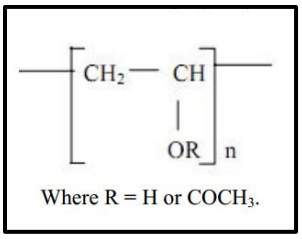

Figure 2: Structure of PVA

PVA is soluble in hydrophilic solvents and in highly polar solvents, such as Ethylene Glycol, water, Dimethyl Sulfoxide [42] . Water is most favorable solvent for PVA, It's solubility in water depends on hydrolysis, solution temperature and degree of polymerization. These factors affects character and degree of hydrogen bonding, and hence PVA solubility in water. The viscosity, surface tension, solubility of PVA depends upon % hydrolysis, molecular weight and temperature of material. PVA is used for various pharmaceutical applications such as, topical and ophthalmic formulations. It is used as solvent in coating of tablets [43].

iii. Polyvinyl Pyrrolidone

Polyvinyl Pyrrolidone is a hydrophilic polymer. It is synthesized by vinyl Pyrrolidone polymerization in water. Its structure is shown in figure 3.

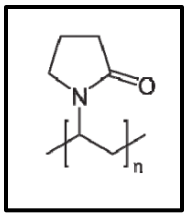

Figure 3: Structure of PVP

Different grades of PVP is available on the basis of molecular weights. In tablet formulations it is used as binder, its other uses are shown in table 2. But as it is hydrophilic in nature so it can be used as film forming agent in aqueous coating of tablets. PVP has low friability, good flowabilty and higher binding. In addition to this, PVP also enhances active ingredient dissolution and can also be used to increase the bioavailability of the drug. It increases bioavailability by forming water-soluble complexes with active ingredient of tablet, it also provides stability to the tablets [44].

Table 2. Uses of PVP

Function	Pharmaceutical form
Binder	Capsules, tablets
Improved bioavailability tablets	Suppositories, pellets
Film forming agents	Tablets
Solubilizing agents	Parenteral, oral
Adhesive	Adhesive gels
Stabiliser	Suspensions
Toxicity reducer	Oral preparations

1.9.2 Plasticizers

Plasticizers are mainly used to get desired effect in the tablet. Concentration of plasticizer in the tablet depends on the polymer being used. According to USP pharmacopeia plasticizers are added 1-50% by weight of polymer. Glycerin, PEG, Tetraethyl citrate, Dibutyl sebacate are commonly used as plasticizers. Plasticizer choice depends on coating type and film former used for coating [45]. For aqueous film coatings mostly PEG and PG are used, for organic-solvent coatings castor

oil, glycerin are used. Film former and plasticizer should be soluble with each other. Plasticizer should also be miscible in the solvent, used for dissolving plasticizer and film former. Primarily plasticizers alters permeability for drug, reduces polymeric film brittleness and in formation of aqueous polymer dispersion, it helps in film formation[45] .

i. Polyethylene Glycol (PEG)

PEG is one of famous polymers used as plasticizer, because of its high hydration capacity, amphiphilicity, biocompatibility and structure flexibility,[46] PEG is available in different grades, PEG 100 - 700 are liquids, while 1000 to 2000 are soft solids in nature. PEG is highly polar so it is soluble in water. It is important for permeation and solubilization [38].

1.9.3 Colorants

Colorants are added in coating of tablets in suspension form or in solution form. Mostly powdered colorants are used, because they are properly distributed. Commonly used colorants are certified D & C or FD & C. these all are synthetic lakes and dyes. In film coating mostly lakes are used as they have effective results. Color concentration depends on type of dye, color shade and opaquant concentration. If dark shade is required, then concentration should be more than 2.0% and for light shades it should be less than 0.01%. Natural colorings such as carotenoids and inorganic materials e.g. iron oxide, can be used in preparation of coating solution[47] .

1.9.4 Opaquant

Opaquants are inorganic powders. They are mostly used to increase film coverage and provide pastel colors, they mostly provide mask colors or white coat to core of the tablet. Colorants are mostly expensive but opaquants are cheap [48]. When opaquants are applied, colorants amount will be reduced. Widely used opaquants are talc, titanium dioxide, hydroxides and carbonates.

1.9.5 Solvents

In film coating process solvents play an important role. Solvents are used to disperse and dissolve polymers and other excipients and apply them to core of tablet.

Solvent used in pharmaceutics should be cheap, non-toxic, soluble in polymer and other additives, tasteless, colorless, odorless, should not be viscous, dry rapidly, non-inflammable and it should not be hazardous for environment [49].

Mostly organic solvents are used in pharmaceutical industries, because they have rapid drying rate. But these solvents are hazardous not only for patients but also for workers. These solvents can also pollute environment. So nowadays water is used as solvent because it has no economic and environmental considerations [50].

1.10 Process of Film Coating

Film coating is a process in which polymeric thin film surrounds the tablet core. For this purpose conventional pan can be used but now more advanced equipment are used. In this process polymer is solubilized in the solvent. Besides polymer, other additives are also added, like pigments and plasticizers. The solution prepared is sprayed on the tablet core. Solvent can be removed by drying.

For the preparation of film coated tablets, spray process is employed. Accela cota is a cylindrical drum used for this process, it is shown in figure 4. It provides high drying air capacity. Fluidized bed reactor can also be used for coating process. In this reactor tablets move in air stream, which pass through cylindrical column bottom. But the problem is that, fluidized bed coating required hard tablets [51].

Modern pan coaters can have batch size from 500g-2000kg. Fluidized coaters can process continuous coating. But we will use pan coaters. Although this process is being used for decades but still it is difficult to understand that how operating parameters affect tablets and problems like blistering, blooming, peeling, twinning, chipping, cratering, pitting, blushing are being arised [33].

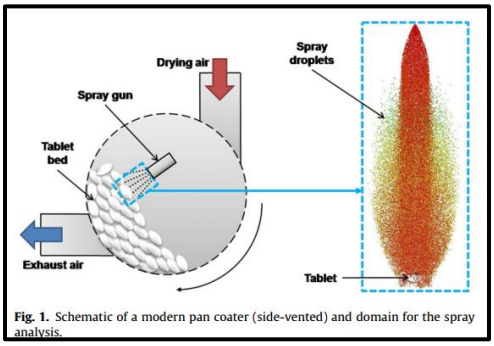

Figure 4: Pan Coater for spray coating

1.10.1 Equipment Used in Coating

a. Coating pans
b. Spray guns

c. Mixers and blenders
d. Solution tanks
e. Polishing pan
f. Steam jackets
g. Mills
h. Homogenizers
i. Peristaltic pump

1) Coating Pan

Function of coating pan is to form a film around the core of tablet. It is a basic requirement in pharmaceutical industries. Different type of coating techniques can be applied using coating pans. In coating pan tablets are continuously fed at controlled rate. Tablets are heated in pan by process air, then coating solution is applied on the core with the help of spray gun. Tablets are moved in the pan so solution is applied homogeneously and required weight is gained by tablet. Coating pan is shown in figure 5 [52].

Features of coating pan: following are some salient features of coating pan.

- Coating pans are flameproof.
- Temperature of pan can be controlled by temperature controller.
- Pans can be easily installed on the floor.
- Hot air blower is used to heat the pan.
- Coating pan has mounting facility so it be easily changed.

2) **Spray Gun**

Function of spray gun is to produce fine mist of the coating solution. This solution dries when it has contact with tablet. This liquid spray is dried when applied on the tablet with help of heated air of inlet fan. In coating process drum pressure is maintained negative to pressure of room. Flow of air is also regulated for volume and temperature, so that it provides controlled extraction and drying rate [53].

Figure 5: Coating Pan

1.11 Aqueous Film Coating

In this study film coating is done in aqueous medium, water is used as a solvent. This method has replaced solvent-based coatings for environmental, safety and economic reasons. Different factors affect aqueous film coatings such as process conditions, coating solution, coating equipment and composition of core. All these factors finally affect quality of product. High quality coating should be uniform, smooth and provides chemical stability to the drug [54]. For employing aqueous film coating famoscot 40 mg drug has been selected, active ingredient of this drug is famotidine.

1.11.1 Famotidine

Famotidine is the active ingredient of tablet Famoscot. It is H_2 receptor antagonist, used for gastroesophageal reflux diseases[55] . Famotidine actions same like cimetidine and ranitidine but it is 20 and 7.5 times more potent than cimetidine and ranitidine, respectively, in inhibiting the secretion of gastric acid and it has no side effect besides this, famotidine also have no antiandrogenic effect, which are the cause of gynecomastia and sexual dysfunction [56].

Famotidine structure is related to ranitidine and cimetidine, only difference is that famotidine has thiazole nucleus while ranitidine has furan and cimetidine has imidazole nucleus. Structure of famotidine is given in figure 6.

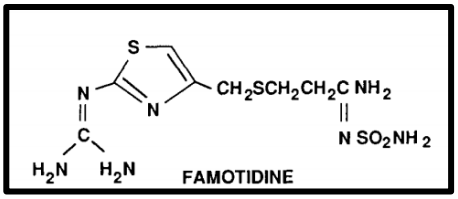

Figure 6: Structure of Famotidine

1.12 Parameters Influencing Tablet Coating

Coating of tablet is a very complex process. It is affected by many variables. Some variable can be controlled. Some of parameters can be evaluated and checked.

i. Tablet Quality

A good quality tablet must have proper hardness, surface, porosity and moisture content.

ii. Waiting Period

Immediately after compression tablets cannot be coated, it is because tablets are warm and have high energy. Hardness of tablets also change from 24-48 hours. So tablets should be coated after one or two days. These uncoated tablets can be tested for assay and all other specifications by quality control. After all the confirmation tests, tablets are ready for coating [57].

iii. Temperature

Like other problems in tablet coating, temperature control is also a problem. Optimum temperature is also necessary for proper coating of tablet. Temperature of tablet's surface can be checked by using infrared thermometer. Temperature can be controlled accordingly using hot air blower.

iv. Preparation of Coating Solution

Coating solution should be prepared according to BP and USP. Mixer speed, temperature of solution and time of storage should be observed [58].

v. Batch Size

Batch size variation changes the conditions for coating e.g. spray rate, pan speed, temperature and gun geometry. Variation in batch size leads to quality issues. If batch size is greater than pan speed should be increased, and if number of tablets is reduced then pan speed should also be reduced.

vi. Spray Gun Geometry

Geometry of spray gun means distance from gun to end of pan, gun-to-gun alignment and gun-to-tablet alignment. It should also be noted that spray pattern of gun should be same. Connection and tubing should not interfere with alignment.

vii. Gun Nozzle

Nozzle of spray gun should be free of product and clean.

viii. Spray Gun Calibration

Spray guns should be calibrated time to time. In calibration filter of gun, condition of needle and nozzle alignment is checked [53].

1.12 Defects in Tablet Coating

During coating of tablets a number of defects have been observed. Following are some common defects and their remedies.

i. Picking and Sticking

This type of defect is observed when little bit of coating is removed from core of tablet, this is caused by film tackiness and over wetting. Due to it tablets either stick together or with the drying pan. When tablet is dried its piece sometimes remain adhere to pan or to tablet. As a result, small surface of the tablet core is exposed and it gives picked appearance. It is due to under-drying, over-wetting or by poor quality of tablets [59].

Remedy: This defect can be reduced by increase in drying rate, slow rate of application of liquid. But tackiness is due to poor tablet formulation.

ii. Twinning

Twinning is term used for two tablets that stick together. This problem is mainly observed with capsule shaped tablets.

Remedy: this problem can be reduced by changing the speed of pan and spray rate. Spray rate should be reduced and pan speed should be increased. Changing tablet shape also reduce this

problem. Sometimes radius of pan is slightly changed. It is a very slight change but it prevents the problem of twinning [60].

iii. Color Variation

Variation in color of tablets is observed when there is problem in processing conditions. Insufficient coating, improper mixing or uneven spray pattern result in color variation. Plasticizers, dyes and other additives gives the coating spotted or mottled appearance.

Remedy: this problem can be reduced by using lake dyes. By using different formulations with different additives and plasticizers color variation can be easily reduced.

iv. Orange Peel

Orange peel is the defect which is referred to that coating whose surface resembles to the surface of orange. It is caused due to insufficient spreading of coating solution before drying. It causes a bumpy appearance. It is due to high pressure of atomization and higher spray rate. It indicates that solution viscosity is very high and spreading of solution is impeded by rapid rate of drying.

Remedy: This problem is solved by lowering the viscosity of solution by adding more solvent. When viscosity is lowered solution spreading becomes more uniform [61].

v. Mottled Color

This defect is observed when tablets are cold, drying rate is not according to specification, coating solution is not prepared properly and spray rate varies from the spray rate of target.

Remedy: It is reduced by heating tablets before coating and by uniform spray rate.

vi. Lamination and Capping

Capping is complete or partial separation of bottom and top crowns from main body of tablet. It is observed when tablets separates in the laminar way. Friability test can detect this problem. Its main cause is improper compression of tablet but it is exposed when tablet is coated [62].

Remedy: It can be prevented by careful pre-heating. Over-drying makes the tablets brittle and capping is produced.

vii. Roughness

Rough surface of tablet is observed when coating is done by spray. Solution droplets sometimes dry before reaching tablet core, results in deposits on tablet surface instead of fine and uniform coating. This defect is also observed when polymer or pigment concentration is increased in coating solution.

Remedy: Roughness of tablets is reduced by placing nozzle close to bed of tablet and reducing atomization degree.

viii. Pitting

It is a defect in which pits appear on the surface of tablet but tablet coating is not disrupted. Rowe firstly reported this defect. According to him, this defect arises when stearic acid is used as a lubricant. He reasoned that dissolution of stearic acid in organic solvent causes pits. Recently, it was this defect also arises when aqueous solvents were used. So reason of pitting is process conditions.

Remedy: Pitting can be eliminated by changing process conditions. Its remedy is that temperature of core should not exceed the melting point of additives used in tablet [63].

1.14 Problem Statement

In pharmaceutical industries organic solvents are widely used in various steps of drug preparation. Trace amount of these solvents when left behind in drug, can be hazardous for health. Chlorinated solvents even can cause cancer. Also during manufacturing of tablets workers are exposed to organic solvents on daily basis, and this is injurious for their health. Besides this, these solvents can contaminate environment which in turns affect human health. If these organic solvents can be replaced with water their hazardous affects can be minimized, as water is a safe solvent. It is environment friendly as well as cheap and easily accessible. In this study we aimed to replace organic solvents in the preparation of tablets with water.

1.15 Objectives of Study

Present study is based on following objectives:

- To prepare core of drug famoscot 40 mg having famotidine as active of drug and to replace organic solvent commercially used in tablet coating with water.
- To check drug interaction with different hydrophilic polymers.
- To prepare aqueous coating solution by varying polymers and concentration of polymers.
- To coat the prepared core of tablet with different prepared coating solutions.
- To evaluate the quality of prepared tablets by weight variation, friability, hardness, disintegration and dissolution tests.
- To check cost effectiveness of aqueous coated tablet in comparison to tablet coated with organic solvent.

Chapter 2

EXPERIMENTAL

2.1 Materials

Active ingredient famotidine was obtained from Scotmann Pharmaceuticals I-9 Islamabad. Excipients used for preparation of core were avicel (fmc international), starch (Rafhan maize Faislabad), primojel, magnesium stearate, polyvinyl pyrrolidone (Anhui sunhere pharmaceutical excipients Co.,Ltd) aerosol (Henan xanyu chemical co.ltd, China), talcum(Guangxi longguang talc development Co.Ltd), green and brown color. For coating of tablet hydroxy propyl methyl cellulose (pharmacoat), polyvinyl alcohol (Applichem GmbH Germany), talcum, titanium (Cristal Inorganic Chemical Switerzland Ltd), triacetin (China), PEG 400 (Sabik Saudi Arabia), PEG 6000 (Bass Germany) were used. All these chemicals were of analytical and pharmaceutical grade and obtained from Scotmann Pharmaceuticals. RO water was used as a solvent.

2.2 Preparation of Core

First of all core of drug famotidine was prepared, this is the active ingredient of drug. For the preparation of core direct compression method was used.

Firstly all the ingredients were dispensed and transferred to manufacturing area. 40 mg of Famotidine with 80 mg of avicel were passed through mesh # 16 and transferred to mixer. Then 40 mg avicel, 0.5 mg Mg stearate, 20 mg starch and 6 mg talcum were sieved through mesh # 16 and transferred to mixer. 3 mg primojel, 1.5 mg aerosil with 0.02 mg brown color Euro Lake and 0.02 mg green pealake were mixed and sieved through mesh # 80, then it was also transferred to mixer. All the ingredients were mixed for 45 minutes in mixer, and pre-compression tests of powder were performed. Mixer is shown in figure 7. All ingredients and their quantities are mentioned in table 3. The batch was sampled for QC analysis. After the approval from QC the batch was transferred to compression area.

Table 3: Preparation of Core

Chemicals	Q.ty/ Tab (mg)
Famotidine	40 + 5%
Avicel	120
Starch	20
Aerosil	1.5
Primojel	3.00
Magnesium stearate	0.5
Talcum	6.00
Green Lake Colour	0.02
Brown Colour	0.02

Figure 7: Mixer

2.3 Pre-Compression Evaluation of Tablets

Before compression of tablets different parameters were checked, to estimate flow of powder.

2.3.1 Angle of Repose

To check drug flow, its angle of repose is measured. Flow of active ingredient of drug was calculated by measuring angle of repose (θ).

$$\text{Tan } \theta = h/r$$

Where, h = height of pile, r = radius of pile, θ = angle of repose.

2.3.2 Tapped Density

Tapped density of active ingredient is found by taking 10 mL powder in measuring cylinder. Cylinder was tapped and density was again noted [64]. Tapped density was calculated by following formula:

$$Tapped\ density = \frac{mass}{volume}$$

2.3.3 Bulk Density

Bulk density or granules and pure ingredient in drug, can be determined by following formula:

$$Bulk\ density = \frac{mass}{volume}$$

2.3.4 Hausner's Ratio

Hausner's ratio of granules and pure drug can also be determined by following formula:

$$Hausner's\ ratio = \frac{tapped\ density}{bulk\ density}$$

2.3.5 Carr's Index

Compressibility ratio or Carr's ratio of granules and pure drug can be determined by using following equation:

$$Percentage\ compressibility = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} X\ 100$$

The ranges of all above parameters are given in table 4. These ranges correspond to values of all parameters and their flow property [65].

Table 4: Flow Property and Corresponding Parameters

Flow property	Angle of Repose[°]	Hausner's Ratio	Carr's Index [%]
Excellent	25-30	1-1.11	<10
Good	31-35	1.12-1.18	11-15
Fair	36-40	1.19-1.25	16-20
Passable	41-45	1.26-1.34	21-25
Poor	46-55	1.35-1.45	26-31
Very poor	56-65	1.46-1.59	32-37
Very poor	>66	>1.60	>38

2.3.6 Assay

Before compression of powder, uniformity of drug content was checked according to USP method. For this purpose first of all 0.1 N HCl was prepared. Then active ingredient of drug was taken as standard. In this study active was Famotidine. In 50 mg of famotidine 30 mL 0.1 N HCl was added. Solution was sonicated and then volume was make up to 50 mL. It was the stock solution. Then 0.02 N dilution was prepared from this stock solution.

Powder before compression was taken and its stock solution was prepared. Weight of sample was taken according to following formula:

$$Weight\ of\ Sample = \frac{weight\ of\ tablet}{claimed\ concentration}\ x\ equivalent\ weight$$

261 g of sample was taken in 50mL flask, 20mL HCl was added. Solution was sonicated and then volume was make up using HCl. It was stock solution of sample. From this stock solution 0.02N dilution was prepared.

Absorbance of dilutions prepared from standard was measured using U.V Spectrophotometer. Similarly, absorbance of sample was also observed. Maximum absorbance was 265mm. Assay was calculated according to formula. If results were within limit of United State Pharmacopoeia then sample was passed [66].

$$Assay = \frac{(Absorbance\ of\ sample)}{(Absorbance\ of\ standard)} x\ 100$$

Limit: ±90-110%

2.4 Compression

For compression of powder single punch compression machine DP-50 was used, shown in figure 8. In this process the respective dies and punches were placed. Machine was adjusted according to approved compressed weight and other parameters. Then compression was started and weight of tablet was maintained. When core of tablets were prepared, it was transferred to coating area.

Figure 8: Compression Machine

2.5 Post-Compression Evaluation of Tablets

2.5.1 General Appearance

The general appearance of tablet includes tablet's shape, size, color, surface texture, absence or presence of odor. Its elegance and visual identification is necessary for consumer's acceptance and to enhance its market value.

2.5.2 Weight Variation

In this evaluation method weight of different tablets has been calculated as per method of Pharmacopoeia. According to this method randomly 20 tablets were selected and weighed together and then individually on electronic balance, average weight of tablet was calculated. Determine minimum and maximum acceptable weight range for every sample was determined, by applying below mentioned deviation limits to the average weight W_{av}. Deviation limits from average weight are described in table 5[54].

Table 5: USP limits of Deviation from Average Weight

Average Weight of Sample Tablet	Deviation
80 mg or less	7.5%
More than 80 mg, less than 250 mg	5%
250 mg or more	3%

For the finished product, British Pharmacopoeia limits for uniformity of weight are following:

Table 6: British Pharmacopoeia Limits of Deviation from Average Weight

Average Weight of Sample Tablet	Deviation
80 mg or less	10%
More than 80 mg, less than 250 mg	7.5%
250 mg or more	5%

2.5.3 Tablet Thickness

Thickness of tablet is an important characteristic for appearance. To evaluate the thickness ten tablets were taken and thickness of each tablet was recorded using Hardness Tester.

2.5.4 Hardness Test

Tablet crushing strength was tested by Pfizer Hardness Tester (Pharma Test D-63512), shown in figure 9. In this tester a tablet is placed between anvils, the point at which tablet break, was recorded. Hardness of tablets effects its disintegration time. To calculate hardness five tablets from each batch were taken and hardness were measured. After it the average tablet hardness was calculated [67].

Figure 9: Pfizer Hardness Tester

2.5.5 Uniformity of Drug Content

For determination uniformity of drug content, UV spectrophotometer was used. Absorbance was measured in nm, according to USP. In this method drug content is determined by randomly selecting 10 tablets. These tablets were dissolved in solvent and absorbance was measured.

2.5.5.1 Assay

Compressed tablets were taken and uniformity of the drug content was checked. In each of the tablet drug content should be same. USP method was used to check it, for this purpose first of all 0.1N HCl was prepared. Then active ingredient of drug was taken as standard, in this study active was Famotidine. In 50 mg of famotidine 30mL 0.1N HCl was added then solution was sonicated and then volume was make up to 50mL. It was the stock solution, from this stock solution 0.2N dilution was prepared. These were stock solution and dilutions of standard.

Sample was taken and its stock solution was prepared. Weight of sample was taken according to following formula:

$$Weight\ of\ Sample = \frac{weight\ of\ tablet}{claimed\ concentration}\ x\ equivalent\ weight$$

Then 261g of sample was taken in 50mL flask, 20mL HCl was added. Solution was sonicated and volume was make up using HCl. It was stock solution of sample. From this stock solution 0.02N dilution was prepared.

Absorbance of dilutions prepared from standard taken using U.V Spectrophotometer. Similarly, absorbance of sample was also observed, maximum absorbance was 265mm. Assay was calculated according to formula. If results were within limit of USP then sample was passed [68].

$$Assay = \frac{Absorbance\ of\ sample}{Absorbance\ of\ standard}\ x\ 100$$

Limit: ±90-110%

2.5.6 Friability:

Strength of tablet was tested by Roche Friabilator Tester (Pharmalab CS-2A), shown in figure 10. For the friability test 10 tablets were taken from each batch. These tablets were weighed, then subjected to friabilator for 100 revolutions in 4 min. After it again tablets were reweighed and variation in weighed were calculated.

$$W = W_1 - W_2$$

$$Friability = W/ W_1 * 100$$

A minimum weight loss of not more than 1% of the weight of tablet being tested is considered acceptable for most of the products.

Figure 10: Roche Friabilator

2.5.7 Disintegration Time

Disintegration time is the time in which a tablet disintegrates. It was determined by using basket apparatus, Disintegration Tester (Pharma Lab BJ-2), shown in figure 11. USP limits for disintegration time of uncoated and film coated tablets are given in table 7. In this method 6 tablets were placed inside the basket, temperature was set according to body temperature i.e. 37°C. As

tablet was uncoated so time limit was set 15 minutes and then the time in which tablet disintegrates was noted [69].

Table 7: USP Limits for Disintegration Time

Tablets	Disintegration Time
Uncoated tablets	15 min
Film coated	30 min
Capsules	30 min

Figure 11: Disintegration Tester

2.6 Drug and Polymer Compatibility Studies

After preparation of core, film coating should be applied on it. This film coating not only protect tablet but also control its release pattern. So the coating materials should be compatible with each other and does not interact with drug. If there is interaction between coating materials and active ingredient of drug then it leads to failure of drug. In this coating water is being used as a solvent, polymers are film forming agents. So polymers should be soluble in water and does not interact with active ingredient of tablet. For compatibility studies of drug and polymer FTIR spectroscopy is done [70].

2.6.1 FTIR Spectroscopy

The interaction of drug polymer was studied by: Fourier transform infra-red spectroscopy

In this studies, FTIR is done to check the interaction of drug with other excipients. If there is no peak showing interaction of drug and polymer then that polymer can be used. FTIR studies are done to check compatibility of polymer and active ingredient of drug. Entrapment of active ingredient of drug and polymer should only be physical and does not involve any chemical interaction. To confirm this samples of drug and polymers are prepared in 1:1. Absorption spectra of pure drug, polymers and their 1:1 mixtures were recorded. By these spectra interaction of drug with excipients can be detected [71].

2.7 Coating Formulations of Famotidine

Different coating formulations have been prepared by varying polymers as well as by changing amount of polymer and plasticizer.

2.7.1 Formulation 1

Trial size: 1000 tablets

Preparation of solution

All the material were dispensed. pharmacoat was soaked 3-4 hours before coating. PEG 6000 was melted on water bath at 100°C. Given quantity of talcum, color and titanium were mixed to prepare solution A. RO water was added in solution A. Melted PEG 6000, PEG 400 and triacetin were mixed to prepare solution B. Solution B was passed through milling machine 4-5 times. HPMC was added in solution B. Solution A and B was mixed slowly with continuous stirring. This solution was coated on tablets.

Table 8: Coating Formulation 1

Sr No:	Name of Ingredients	Qty/Tab Mg	Qty/Trial gm
1.	Pharmacoat (HPC)	8.00	8.00
2.	Talcum	3.00	3.00
3.	Titanium Dioxide	1.00	1.00
4.	Triacetin	0.50	0.50
5.	PEG 400	2.00	2.00
6.	PEG 6000	1.50	1.50
7.	Green Pea Lake Color	0.03	0.03
8.	RO Water	Q.s	Q.s

2.7.2 Formulation 2

Trial size: 1000 Tablets

Preparation of solution

This formulation was prepared by using same method as for **formulation 1**. In this formulation amount of PEG 400 and PEG 6000 was varied.

Table 9: Coating Formulation 2

Sr No:	Name of Ingredients	Qty/Tab mg	Qty/ Trial gm
1.	Pharmacoat (HPC)	8.00	8.00
2.	Talcum	3.00	3.00
3.	Titanium Dioxide	1.00	1.50
4.	Triacetin	0.50	0.50
5.	PEG 400	3.00	3.00
6.	PEG 6000	2.50	2.50
7.	Pink Lake Color	0.03	0.03
8.	RO Water	Q.s	Q.s

2.7.3 Formulation 3

Preparation of solution

In this formulation quantity of pharmacoat was increased. For preparation of solution, same method was followed as for **formulation 1**. But in this formulation sodium metabisulphite was added and quantity of PEG 400 and PEG 6000 was varied.

Table 10: Coating Formulation 3

Sr No:	Name of Ingredients	Qty/Tab mg	Qty/ Trial gm
1.	Pharmacoat (HPC)	10.00	10.00
2.	Talcum	3.00	3.00
3.	Titanium Dioxide	1.00	1.00
4.	Triacetin	0.50	0.50
5.	PEG 400	3.00	3.00
6.	PEG 6000	1.00	1.00
7.	Sodium Metabisulphite	0.10	0.10
8.	Green Pea Lake Color	0.04	0.04
9.	RO Water	Q.s	Q.s

2.7.4 Formulation 4

Solution Preparation:

Solution was prepared by same method as used for above formulations, only one plasticizer was removed.

Table 11: Coating Formulation 4

Sr No:	Name of Ingredients	QtyTab mg	Qty/ Trial gm
1.	Pharmacoat (HPC)	10.00	10.00
2.	Talcum	3.00	3.00
3.	Titanium Dioxide	1.00	1.00
4.	Triacetin	0.50	0.50
5.	PEG 6000	2.00	2.00
6.	Sodium Metabisulphite	0.10	0.10
7.	Green Pea Lake Color	0.04	0.04
8.	RO Water	Q.s	Q.s

2.7.5 Formulation 5

Solution preparation

In formulation 5 amount of plasticizers was increased, method of solution preparation was same as mentioned above.

Table 12: Coating Formulation 5

Sr No:	Name of Ingredients	Qty/Tab mg	Qty/ Trial gm
1.	Pharmacoat (HPC)	10.00	10.00
2.	Talcum	3.00	3.00
3.	Titanium Dioxide	1.00	1.00
4.	Triacetin	2.50	2.50
5.	PEG 400	6.00	6.00
6.	PEG 6000	1.00	1.00
7.	Sodium Metabisulphite	0.10	0.10
8.	Green Pea Lake Color	0.04	0.04
9.	RO Water	Q.s	Q.s

2.7.6 Formulation 6

Trial size: 1000 Tablets

Solution preparation

In this formulation polymer was replaced. Instead of hydroxy propyl methyl cellulose, polyvinyl alcohol was used. Solution was prepared by same method as used for preparation of **formulation 1.**

Table 13: Coating Formulation 6

Sr No:	Name of Ingredients	Qty/Tab mg	Qty/ Trial gm
1.	PVA	17.5	17.5
2.	Talcum	12.50	12.50
3.	Titanium dioxide	14.50	14.50
4.	PEG 6000	4.50	4.50
5.	Green Pea lake color	0.05	0.05
6.	RO Water	Q.s	Q.s

2.7.7 Formulation 7

Solution Preparation

In this formulation instead of PVA, PVP was used, amount of plasticizer was also varied.

Method of preparation was same.

Table 14: Coating Formulation 7

Sr No:	Name of Ingredients	Qty/Tab mg	Qty/ Trial gm
1.	PVP K30	6.00	6.00
2.	Talcum	3.00	3.00
3.	Titanium Dioxide	1.00	1.00
4.	Triacetin	2.50	2.50
5.	PEG 400	6.00	6.00
6.	PEG 6000	1.00	2.00
7.	Sodium Metabisulphite	0.10	0.10
8.	Green Pea Lake Color	0.04	0.04
9.	RO Water	Q.s	Q.s

2.7.8 Formulation 8

Solution preparation

In this formulation blend of polymers were used. PVA and HPMC were used as polymer. First of all the material was dispensed. Pharmacoat was soaked in RO water 3-4 hours before coating. Desired concentration of PVA and water were mixed in an air tight container and heat it in water bath till 80°C for 30 min till a clear homogeneous solution (A) is attained. Humidity and temperature of area was checked. Titanium dioxide, color, talcum and PEG 400 were added in a beaker and mixed them. RO water was added to prepare solution B. Solution B through milling machine 4-6 times. After milling solution A was added slowly to solution B with continuous stirring. Final solution was stirred for 20 minutes and passed through mesh # 100. This solution was coated on tablets.

Table 15: Coating Formulation 8

Sr No:	Name of Ingredients	Qty/ Tab mg	Qty/ Trial gm
1.	Pharmacoat	30.00	30.00
2.	Polyvinyl Alcohol	10.00	10.00
3.	Titanium Dioxide	3.00	3.00
4.	Talcum	20.00	20.00
5.	PEG 6000	4.00	4.00
6.	Eryhtrosine Red Color	3.00	3.00
7.	RO Water	Q.s	Q.s

2.8 Coating Methodology

For coating of tablets, all the tablets were de-dusted using de-dusting machine. Then the coating pan was loaded with compressed tablets. Coating was started according to following specifications:-

- Pan speed 12-16 rpm
- Spray gun distance 6-10 inches
- Atomization air 2-10 bar
- Air pressure for solution 0-02 bar
- Air pressure for spray 2-06 bar

During the coating process, hot air blower was used (temperature 60-70°C) to dry the tablets. The temperature of internal bed coating pan was 35-40°C. Coating material was applied to compressed tablets and the weight of 10 compressed tablets should be increased from 1.5- 5% from its compression weight. Pan coater was used in this coating, solution was applied by using spray gun. It is shown in figure 12. After the completion of coating, the batch was sampled for Q.C analysis [72].

Figure 12: Pan Coater and Spray Gun

2.9 Sorting of Tablets

For sorting of tablets the cleanliness of sorting area was checked. Besides humidity and temperature were also checked. The tablets were weighed before sorting, so loss can be calculated. Damaged, defected or uncoated tablets were removed. After this tablets were weighed again. The % loss of tablets was calculated. Then tablets were transferred for blistering.

2.10 Evaluation of Tablets after Coating

After coating, tablets were evaluated by dissolution and stability tests.

2.10.1 In-vitro Dissolution Test

Drug release profile can be studied in-vitro, by using dissolution apparatus. The USP type I (Basket type) method was selected to check dissolution of famotidine. Dissolution of film coated tablet was done according to USP method. Samples were filtered and then analyzed by UV-Visible spectrophotometer and HPLC (Shimadzu., Japan).

Medium: 0.1M phosphate buffer, 900mL

Apparatus: Basket type apparatus, 50rpm

Time: 30 min

Standard solution: USP Famotidine in medium in a concentration same as in sample solution.

Sample solution: Pass small portion of sample under study through filter paper.

Analytical wavelength: 265nm

Limit: Not less than 80%

Methodology:

0.1M phosphate buffer was prepared. For dissolution basket apparatus was used, it is shown in figure 13. In basket apparatus 6 dissolution bowls were used. 900 mL of buffer was added in each bowl, set the conditions and temperature was maintained up to 37°C. When temperature is reached add one tablet in each basket and set time for 30 minutes.

Now standard stock solution was prepared. Then its dilutions were being prepared. After 30 minutes take 6 beakers and add 5mL of solution from each dissolution bowl. Now make up volume of each beaker up to 10 mL by adding buffer. Prepare a blank and then take the absorption of blank as well as sample solution [73] .

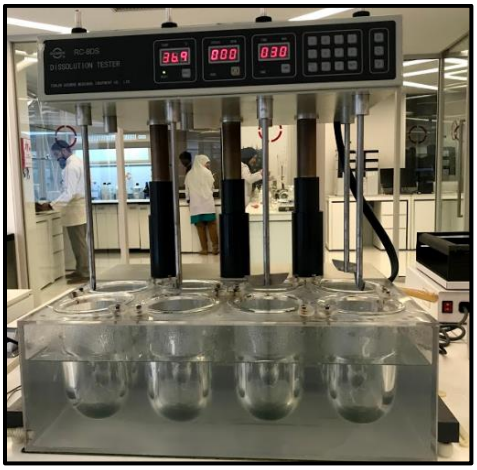

Figure 13: Basket Dissolution Apparatus

2.10.2 Uniformity of Drug Content

After coating of tablets uniformity of drug content was checked according to USP method. For this, first of all 0.1N HCl was prepared. Then active ingredient of drug was taken as standard. In this study active was Famotidine. In 50 mg of famotidine 30 mL 0.1N HCl was added. Solution was sonicated and then volume was make up to 50 mL. It was the stock solution. Then 0.02 N

dilution was prepared from this stock solution. This was stock solution and dilutions of standard. Coated tablets were taken and its stock solution was prepared. Weight of sample was taken according to following formula:

$$Weight\ of\ Sample = \frac{weight\ of\ tablet}{claimed\ concentration}\ x\ equivalent\ weight$$

Then 261g of sample was taken in 50 mL flask, 20 mL HCl was added. Solution was sonicated and volume was make up using HCl. It was stock solution of sample. From this stock solution 0.02N dilution was prepared.

Absorbance of prepared dilutions from standard, was taken using U.V Spectrophotometer. Similarly, absorbance of sample was also observed. Maximum absorbance was 265 nm. Assay was calculated according to formula. If results were within limit of USP then sample was passed [74].

$$Assay = \frac{Absorbance\ of\ sample}{Absorbance\ of\ standard}\ x\ 100$$

Limit: ± 90-110%

2.10.3 Disintegration Time

Disintegration time is the time in which a tablet disintegrates. It was determined by using basket apparatus, Disintegration Tester (Pharma Lab BJ-2). In this method 6 film coated tablets were placed inside the basket. Temperature was set according to body temperature i.e 37°C. As tablet was coated so time limit was set 30 minutes and then the time in which tablet disintegrates was noted. If tablet disintegrates within limit then coating of tablet will be successful.

2.10.4 Weight Variation

In this evaluation method weight of different tablets has been calculated as per method of Pharmacopoeia. According to this method, after coating, randomly 20 tablets were taken and weighed together and individually on electronic balance, then average weight was calculated. According to surface area to size ratio 5% weight should be increased after coating of tablet. Determine minimum and maximum acceptable weight range was determined, by applying deviation limits to the average weight W_{av}[75].

2.10.5 Stability Studies

After coating, the tablets which have passed all the evaluation tests were kept in a stability chamber under controlled temperature and moisture. Humidity of chamber was maintained. Samples were withdrawn after interval of days and various parameters were evaluated such as drug release, physical appearance and drug content. All these studies were performed thrice.

Two types of stability studies can be done.

2 Accelerated Stability

3 Long Term Stability

In accelerated stability studies samples were placed in chamber, temperature is maintained 40±2°C. This sample was tested after 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, 5^{th} and 6^{th} months. After each month sample appearance, disintegration time, assay and dissolution studies were performed. Results should be within range of pharmacopeia, limit is 75±5% [76].

In long term stability studies samples were placed in long term stability chamber, temperature is maintained 30±2°C. This sample was tested after 3^{rd}, 6^{th}, 9^{th}, 12^{th}, 18^{th} and 24^{th} month. After each month sample appearance, disintegration time, assay and dissolution studies were performed. Results should be within range of pharmacopeia, limit is 65±5% [77].

In both types of stability studies the parameters that are checked include:

- General appearance
- Disintegration time
- In-vitro dissolution

2.11 Blistering and Packing

Before start of packing and blistering sanitation and cleaning of blister machine was checked. Temperature and humidity of area were also checked, then all the tablets were blistered by blistering machine shown in figure 14. After blistering, tablets were kept under specified conditions for stability studies.

Figure 14: Blistering Machine

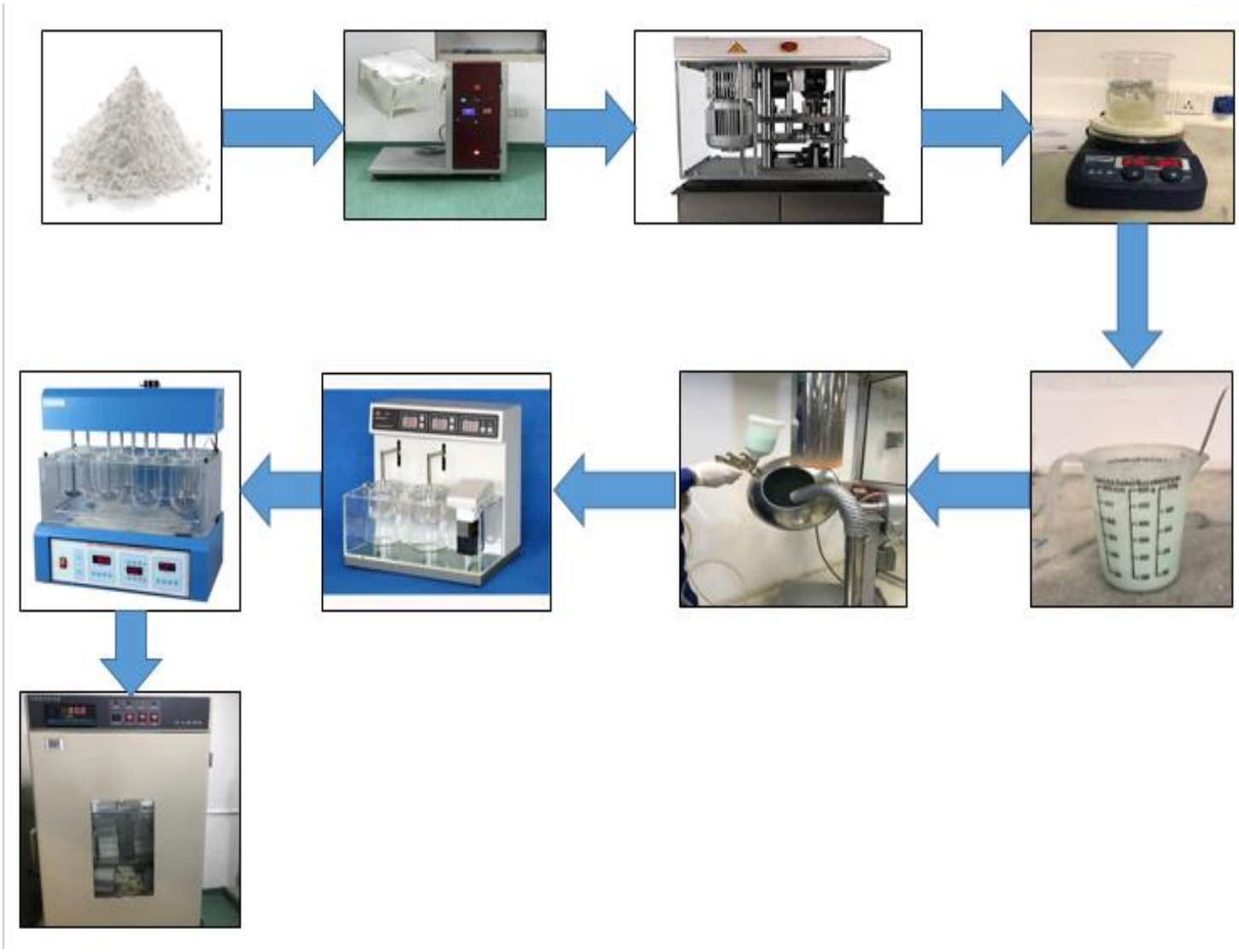

Figure 15: Schematic Representation of Tablet Manufacturing and Coating

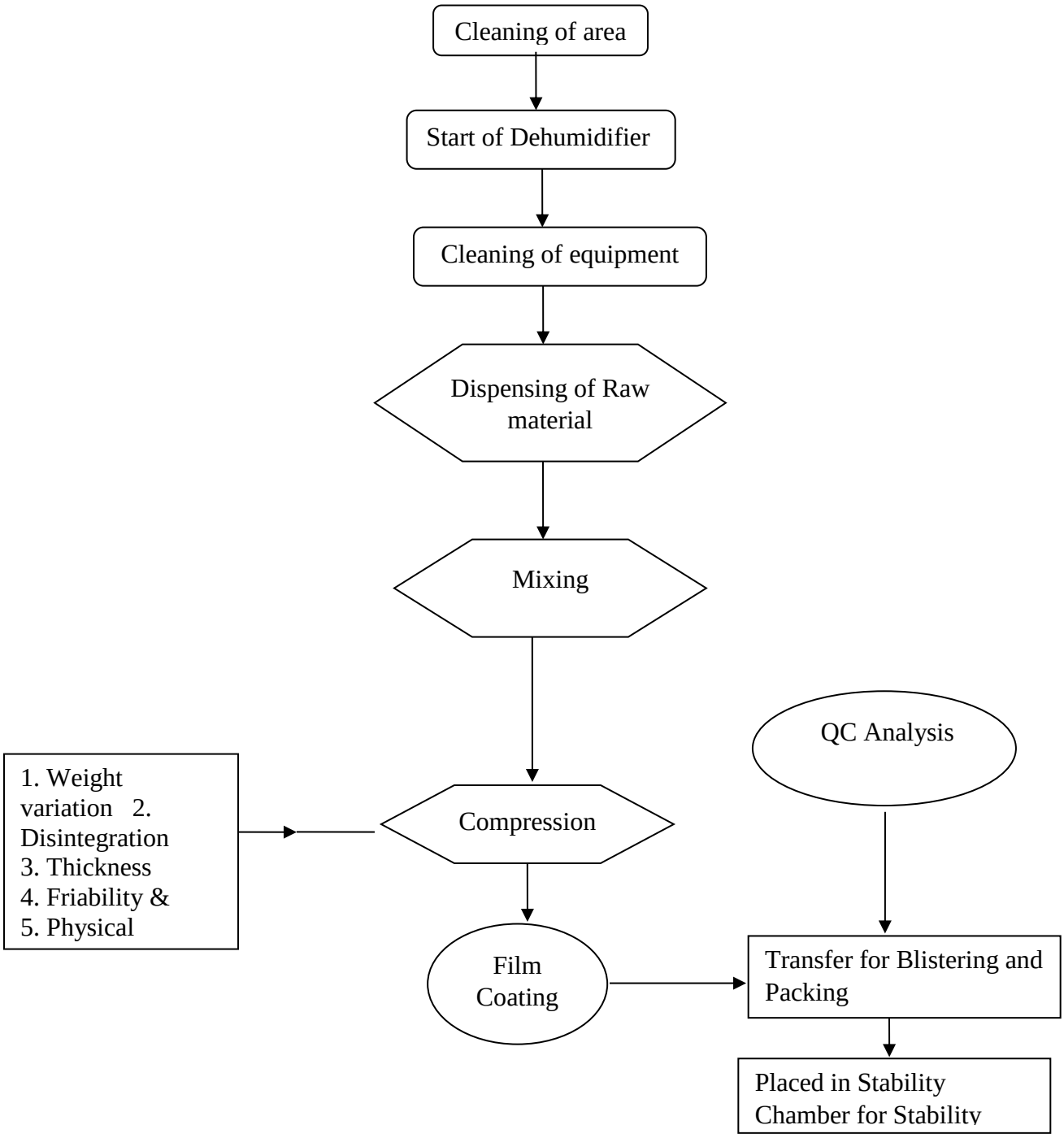

Figure 16: Schematic Representation of Tablet Manufacturing and Coating

CHAPTER NO 3

RESULTS AND DISCUSSION

3.1 Preparation of Core

In core preparation first of all active ingredient of drug i.e Famotidine and all other excipients were dispensed, passed through sieves so that their particle size becomes equal and then mixed. After mixing this powder is evaluated by some tests, to check flow property of the powder.

3.2 Pre-Compression Evaluation Tests

Table 16: Pre-Compression Parameters

Formulation	Angle of Repose	Tapped Density (g/mL)	Bulk Density (g/mL)	Hausner's Ratio	Carr's Index [%]	Compressibility Index
F1	32°	0.55	0.5	1.11	9.09	10

Angle of repose illustrates the interparticle force present between particles of powder. Tapped and bulk density depends on spatial arrangement and density of particles of powder. If spatial arrangement is proper and density is within limits then flow of powder will be good. Compressibility index basically measure powder's propensity to consolidate and hausner's ratio is the measure of ability of powder to settle down. All above parameters tells about the flow of powder because flow of powder effects during compression of tablets.

The results of pre-compression evaluation parameters such as angle of repose, hausner's ratio, tapped density, bulk density, carr's index and compressibility index were reported in table 16. These results showed that all parameters fall in excellent range according to USP. So flow property of powder used for core preparation was excellent [78].

3.3 Compression of Core

After checking flow of powder, it was compressed to form core. During compression hardness of core was taken under consideration. Hardness should be medium because hardness affect tablet disintegration time, if hardness was increased then disintegration time would also increase. Besides this weight of core should also be checked during compression, all tablets formed had weight within limits. When powder was compressed and core was formed, some post compression evaluation tests were performed.

3.4 Post-Compression Evaluation Tests

For evaluation of core, following evaluation tests are performed.

1) General Appearance

First of all appearance of core was observed. The surface texture of core was smooth. There was no pitting. Tablet was round in shape.

2) Weight Variation

As per method reported in Pharmacopoeia randomly 20 tablets were selected and their weight was checked on weighing balance. The weight of 20 tablets were given in table 17, average weight was calculated and it was within limits. According to Pharmacopoeia 7.5% deviation is acceptable in tablets below 80 mg. So tablet under study was 40 mg and 3% deviation was observed which was within limits [78].

Table 17: Weight of 20 Tablets (g)

0.198	0.198	0.200	0.199	0.199
0.200	0.198	0.199	0.199	0.197
0.196	0.198	0.198	0.198	0.198
0.200	0.197	0.200	0.198	0.199

Weight of 20 tablets = 3.969 g

Average weight of tablet = 198.45 mg

Q.C. Limit = 1.95 – 2.00g/ 10 tablets

Deviation Limit = ± 3 %

The results of weight variation were within limits, each tablet had weight 198.45 mg ±3 % deviation was allowed. If deviation exceeds than ±3 % then that batch would be rejected because weight affects tablet thickness and hardness.

3) Tablet Thickness

According to method reported in Pharmacopoeia, 6 tablets were taken and their thickness and diameter were found by Vernier caliper. Thickness and diameter of 6 tablets were given in table 18. Average thickness and diameter were calculated and it was well within range.

Table 18: Tablet Thickness and Diameter

Thickness (mm)	Diameter (mm)	Hardness (Kp)
3.93	8.04	5.6
3.92	8.05	4.8
3.93	8.04	5.7
3.97	8.03	5.3
3.91	8.04	6.1
3.94	8.04	5.1

Thickness of 6 tablets = 23.6 mm

Average thickness of tablets =3.93 mm

Diameter of 6 tablets = 48.24 mm

Average diameter of tablets= 8.04 mm

Thickness and diameter of each tablet was 3.93 mm and 8.04 mm respectively. These values were within limits, this showed that all tablets had same thickness and diameter, if these parameters of

each tablet varies then hardness and disintegration time would be affected. So, all tablets should had same thickness and diameter.

4) Hardness Test

Hardness of tablets affect its disintegration time. If hardness increases then tablet takes longer time to disintegrate. 6 tablets were taken and their hardness was find one by one, as reported in table 9. Then average hardness was calculated, it was 5.4 Kp and was within limits.

Hardness of 6 tablets = 32.6 Kp

Average hardness = 5.4 Kp

These results illustrates that average hardness of this batch was 5.4 Kp, it was within limits. Hardness was affected by weight of tablet if each tablet had different weight then their hardness would also be different and then disintegration time would increase. So it hardness should be within limits.

5) Friability Test

This test is done to check strength of tablets. Randomly 10 tablets were selected from batch, weighed as reported in table 19, their weight was 1.986 g. Then subjected to friabilator for 100 revolutions in 4 minutes, after this tablets were reweighed. Again weight was 1.986 g, so friability was 0%, which shows tablets have good strength [79].

Table 19: Friability of Tablets

No of units checked	Weight before checking (g)	Weight after checking (g)	Results (%)	Limit (%)
10	1.986	1.986	0	NMT 1

W = weight before checking (W_1) - weight after checking (W_2)

W= 1.986 - 1.986

W = 0

Friability = W/W_1* 100

Friability = 0/1.986 * 100

Friability= 0 %

0 % friability indicated that tablets had very good tensile strength, it showed that there would be no loss in weight of tablets during shipping and exporting.

6) Disintegration Time

In this test, time in which a tablet disintegrates was calculated. 6 tablets were taken in basket apparatus, medium used was water and temperature was set according to body temperature. After setting all parameters apparatus was turned on and time in which tablet disintegrates, was noted. These 6 tablets were disintegrated within 1 minute. Limit for uncoated tablets is 30 minutes but these tablets disintegrates in 1 minute so results were within limits of Pharmacopoeia.

No of tablets checked = 6

Medium used = water

Temperature = 37°C

Observed Disintegration Time = 1 min

Limit = NMT 30 mins

The limit for disintegration time was 30 minutes but tablet was disintegrated in 1 minute. So results were excellent and it showed that when a patient take tablet, it would disintegrate instantly.

7) Uniformity of Drug Content

This test was done to check that active ingredient of drug was uniformly distributed throughout the core. For this purpose dilutions of sample and standard were prepared and their absorbance was measured using UV spectrophotometer, given in table 20. UV Spectrum is shown in figure 17.

Table 20: Absorbance of Sample and Standard

No	Wavelength	Absorbance
Std.	**265.5**	**0.618**
1	409.0	0.006
2	400.0	0.011
3	393.0	0.012
4	387.0	0.012
5	**265.5**	**0.631**
6	204.5	1.268

After measuring absorbance %age of drug content was calculated by the formula.

$$Assay = \frac{Absorbance\ of\ sample}{Absorbance\ of\ standard} x\ 100$$

$$Assay = \frac{0.631}{0.618} x\ 100$$

$$Assay = \ 102.1\%$$

According to USP limit for assay ±90-110%. So results were in desired limits. These results indicated that active ingredient of drug was uniformly distributed in each tablet. So this test was passed and core can be used for coating.

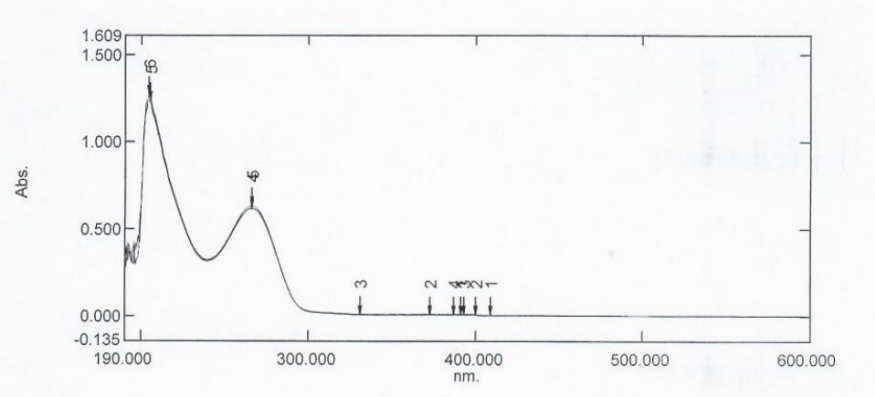

Figure 17: UV Spectrum of Uniformity of Drug Content of Core

3.5 Drug and Polymer Compatibility Study

3.5.1 FTIR Spectroscopic Study of Famotidine

Famotidine is the active ingredient of drug, FTIR spectrum of famotidine shows strong bond at 1534 which indicated presence of imine group, stretching vibration at 1286 indicated presence of sulfonyl group, 3486 band indicates presence of NH stretching vibration and bending vibrations at 981, 850 and 773 cm^{-1} indicated presence of amine group. These were the characteristic IR bands of famotidine. All other peaks were shown in table 21 and FTIR spectrum is shown in figure 18 [80].

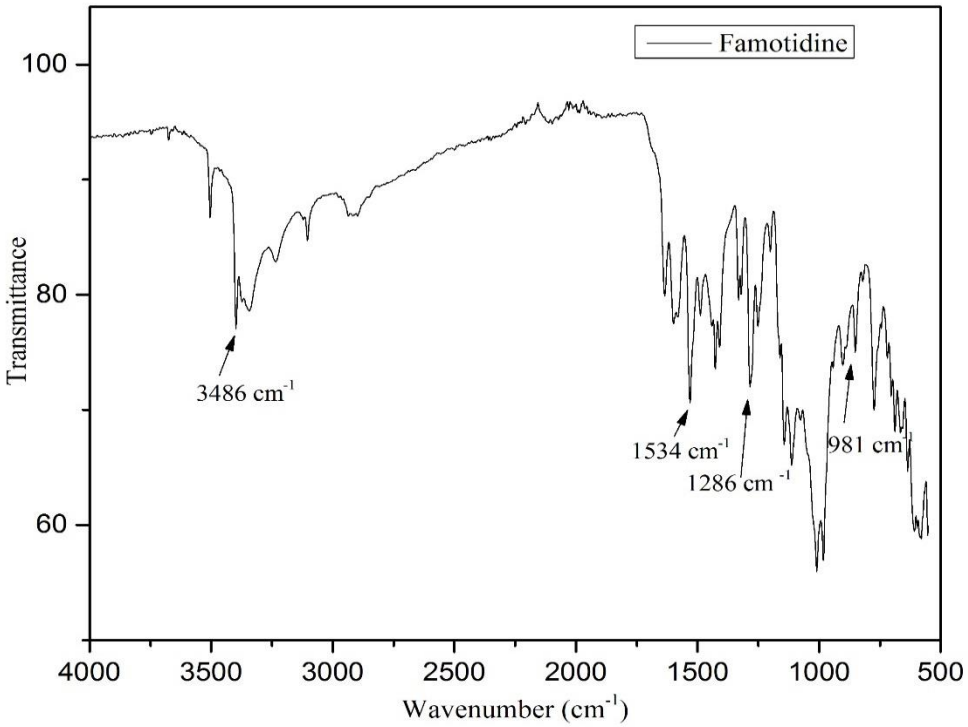

Figure 18: FTIR Spectrum of Pure Drug (Famotidine)

Table 21: FTIR Data of Famotidine

IR Value	Functional Groups
3486 cm^{-1}	NH Stretch
2792 cm^{-1}	CH Stretch
1633cm^{-1}	C=C Stretch
1534 cm^{-1}	C=N Stretch
1286 cm^{-1}	S=O Stretch
1276 cm^{-1}	CH Bend
1143 cm^{-1}	C=S Stretch
981 cm^{-1}	NH Bend
688 cm^{-1}	CH Bend

3.5.2 Drug Excipients Compatibility Test

Drug excipients compatibility test was performed by comparing FTIR spectra of pure drug, with drug: HPMC, drug: PVA, drug: PVP in figure 18-21, no changes were observed in the functional groups of famotidine which indicated that there was no chemical interaction between famotidine and polymers, they were held together physically.

3.5.2.1 FTIR Spectroscopic Study of Drug: HPMC

HPMC is a polymer used for coating active ingredient of drug. In FTIR study of HPMC strong IR bonds observed at 3446 cm^{-1} due to O-H stretching vibrations, bands at 1373.32, 1190.08 cm^{-1} were due C-O stretching vibrations. O-H bending vibration had also been observed at 945 cm^{-1}. These functional groups confirmed presence of HPMC. Some other functional groups present in HPMC are tabulated in table 22. FTIR spectrum of HPMC and HPMC + Famotidine and Famotidine were shown in figure 19 [81].

Table 22: FTIR Data of HPMC

IR Value	Functional Groups
3446 cm^{-1}	OH Stretch
2897 cm^{-1}	CH_2 Stretch
1631 cm^{-1}	C=C Stretch
1454 cm^{-1}	C-C Stretch
1190 cm^{-1}	C-O Stretch
945 cm^{-1}	OH Bending

Interaction of drug and HPMC was studied by taking 1:1 quantity of drug and polymer. FTIR spectrum confirmed that drug and polymer did not show any chemical interaction. So this polymer can be used for coating of drug.

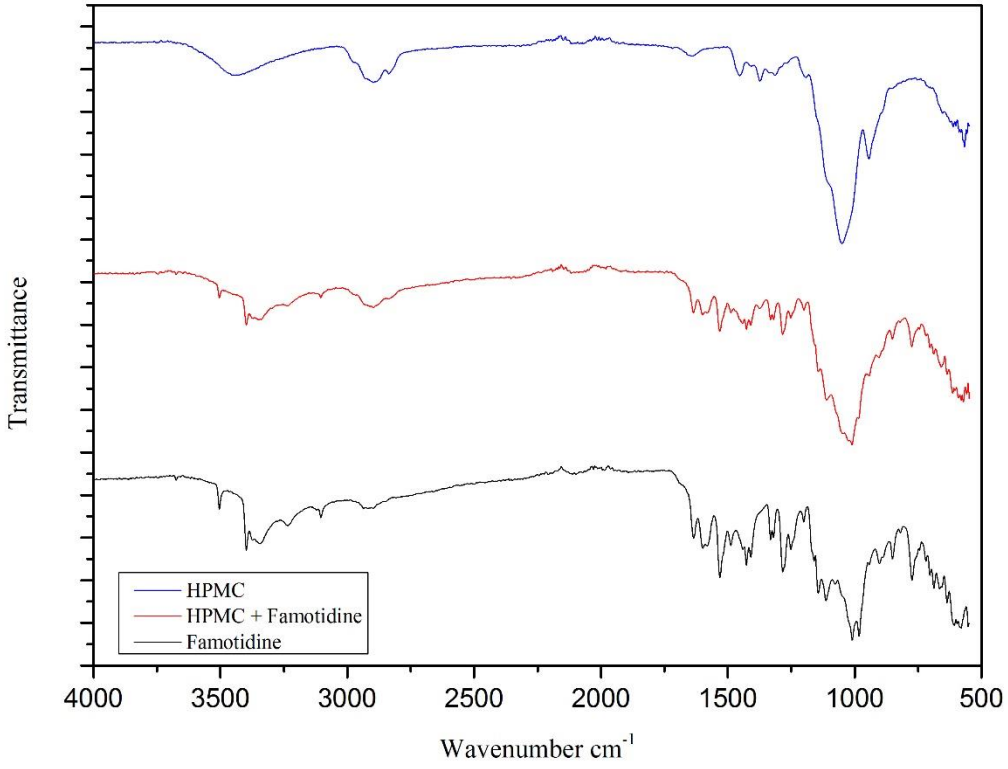

Figure 19: FTIR Spectrum of HPMC, HPMC + Famotidine and Famotidine

3.5.2.2 FTIR Spectroscopic Study of PVP, Drug: PVP

PVP is also a hydrophilic polymer used for coating active ingredient of drug. In FTIR study of PVP strong bonds observed at 3446 cm^{-1} due to O-H stretching vibrations, bands at 1373, 1190 cm^{-1} were due C-O stretching vibrations. O-H bending vibration had also been observed at 945 cm^{-1}. These functional groups confirmed presence of PVP. Some other functional groups present in PVP were described in table 23[82].

Table 23: FTIR Data of PVP

IR Value	Functional Groups
2949 cm^{-1}	CH_2 Stretch
1651 cm^{-1}	C=C Stretch
1460 cm^{-1}	NH Bend
1373 cm^{-1}	CH_2, Stretch
1269 cm^{-1}	C-H Stretch
1001 cm^{-1}	C-N Stretch

Interaction of drug and PVP was studied by taking 1:1 quantity of drug and polymer. FTIR spectrum confirmed that drug and polymer did not show any chemical interaction. So this polymer can be used for coating of drug. FTIR spectrum of PVP, PVP + Famotidine and pure Famotidine were shown in fig 20.

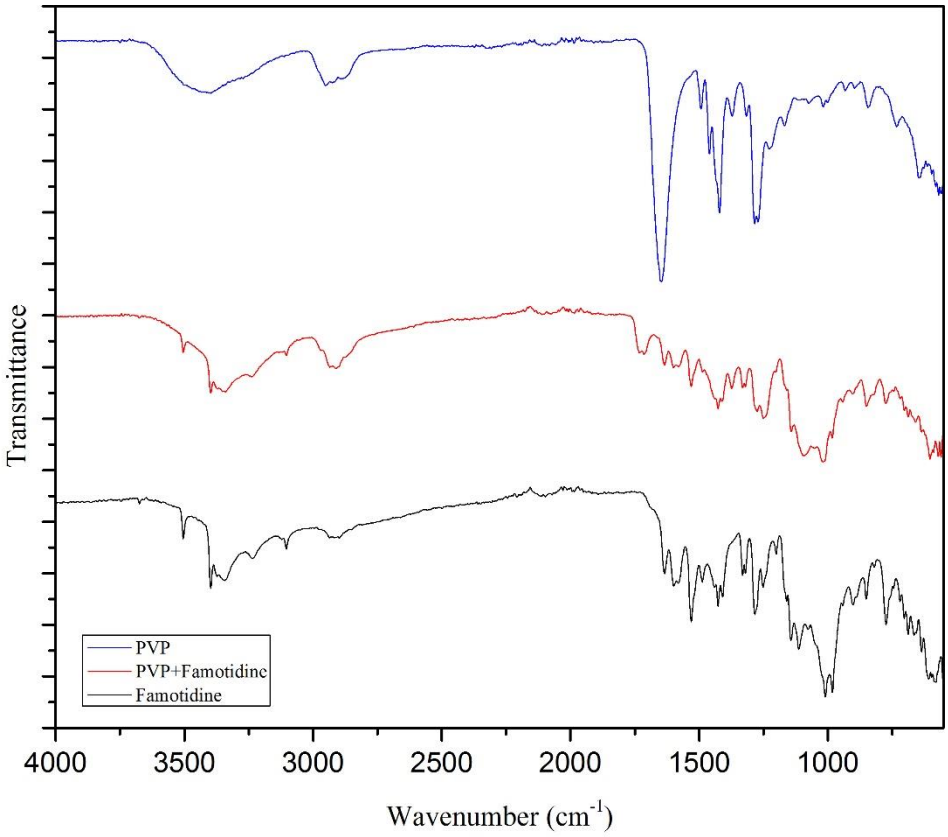

Figure 20: FTIR Spectrum of PVP, PVP+ Famotidine and Famotidine

3.5.2.3 FTIR Spectroscopic Study of Drug: PVA

PVA is also a hydrophilic polymer used for coating active ingredient of drug, interaction of drug and PVA was studied by taking 1:1 quantity of drug and polymer. FTIR spectrum confirmed that drug and polymer did not show any chemical interaction, so this polymer can be used for coating of drug. FTIR spectrum of PVA, PVA+ Famotidine and Famotidine were shown in figure 21 [83].

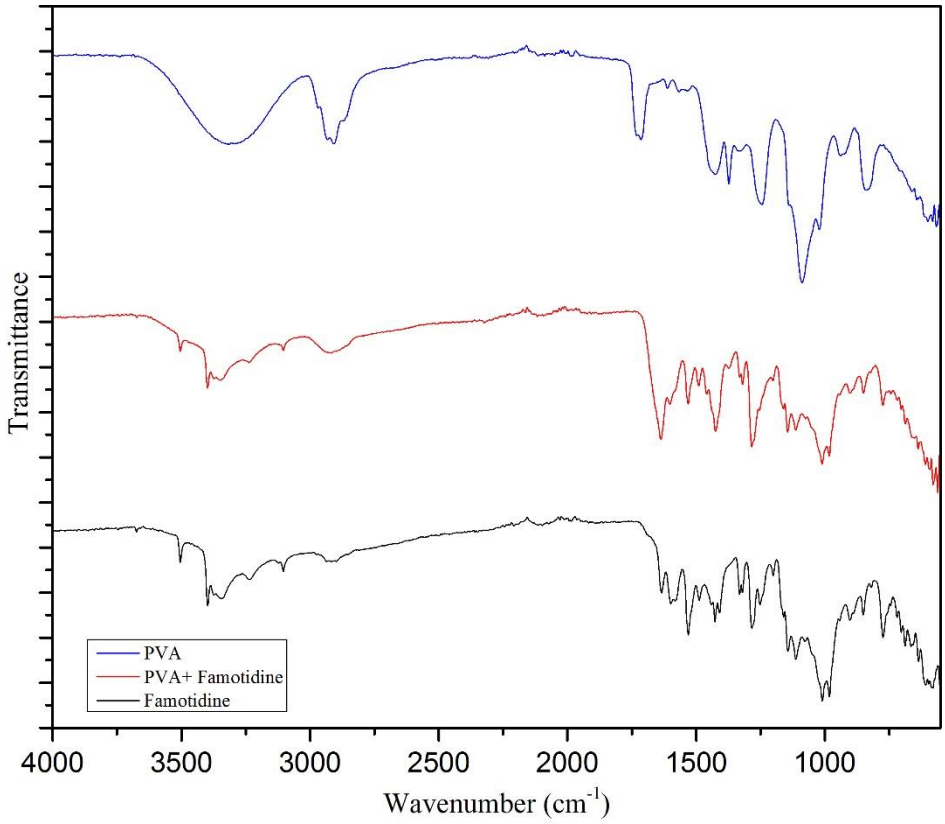

Figure 21: FTIR Spectrum of PVA, PVA + Famotidine and Famotidine

3.6 Coating Formulations

After selecting the hydrophilic polymers, different coating formulations were being prepared by varying polymer as well as by changing the concentration of these polymer and plasticizers.

In 1st formulation hydroxy propyl methyl cellulose(HPMC) was used as polymer and PEG 400 and 6000 were used as a plasticizer did not gives smooth texture, visual appearance of tablet was not appealing so this formulation was rejected. Then amount of polymer and plasticizer were increased this still did not work.

In other formulation polyvinyl alcohol (PVA) was used as polymer, as it is also a hydrophilic polymer but this coating solution was not uniformly sprayed, so this resulted to problem of pitting. This formulation was again rejected.

Then polyvinyl pyrrolidone (PVP) was used as polymer and coating solution was prepared. This solution was coated but as a result of coating tablets start sticking together and to coating pan as well. This polymer also increases disintegration time of tablet, so it was rejected.

Final successful formulation was prepared by using blend of HPMC and PVA, in this coating plasticizer was also used and amount of colorant was increased. As a result desired results were obtained and this coating had no drawback. It gives smooth texture, appearance was elegant, besides this all parameters were within limits. So these two polymers were used for further aqueous coating of tablets.

3.7 Evaluation Tests after Coating of Tablets

After coating the core of tablet with coating solution. Evaluation of this tablet coating was done by checking following parameters.

i. General Appearance

General appearance is the first and most important parameter to evaluate coating of tablet. After every coating first of all appearance was checked. If general appearance is not elegant, texture is not smooth and tablet does not have shinning look then it is rejected.

In this study tablets which were coated using PVA and HPMC as polymer were accepted because that tablets had smooth texture, shinning look and had elegance.

ii. Weight Variation

After coating core of tablet, some evaluation tests were performed. One of it was weight variation, on the core of tablet 5% coating was done. The weight of core was 198.5 mg so after coating weight should be upto 0.203g. If weight of tablets were out of limits then it affects tablet quality, because increase in weight leads to increase in dissolution and disintegration time of tablet. So weight should be within limits.

For this evaluation test randomly 20 tablets were selected, their weight was measured on weighing balance and average weight was calculated, weight of 20 tablets were given in table 24. Average weight was 0.200 g, it was within pharmacopoeia limits [54].

Table 24: Weight of 20 Tablets (g)

0.201	0.199	0.200	0.201	0.203
0.200	0.200	0.199	0.200	0.202
0.202	0.203	0.201	0.202	0.202
0.200	0.202	0.200	0.200	0.200

Weight of 20 tablets = 4.017g

Average weight of tablet = 0.200g

Q.C. Limit = 1.95 – 2.00g/ 10 tablets

Deviation Limit = ± 5 %

These results indicated that after coating tablet weight of each tablet was increased but it was within limits.

iii. Disintegration Time

Disintegration time is an important parameter. It is the time in which a tablet disintegrates within the body. For this evaluation parameter 6 coated tablets were selected randomly and placed in the basket of disintegration apparatus. Medium used was water. Limit of pharmacopoeia was 30 minutes but tablet disintegrated within 1 minute.

No of tablets checked = 6

Medium used = water

Temperature = 37°C

Observed Disintegration Time = 1 min

Limit = NMT 30 mins

These results indicated that disintegration time was not affected by coating, even after coating of tablet it disintegrated within 1 minute. As tablet was immediate release so results also confirmed and it had instant affect.

iv. Uniformity of Drug Content

This test was done to check that active ingredient of drug was uniformly distributed throughout the tablet. For this purpose dilutions of sample and standard were prepared and their absorbance was measured using UV spectrophotometer, given in table 25, UV spectrum is shown in figure 24.

Table 25: Absorbance of Sample and Standard

No	Wavelength	Absorbance
Std.	**265.5**	**0.608**
1	372.5	0.001
2	345.0	0.001
3	**265.5**	**0.616**
4	203.0	1.349

After measuring absorbance %age of drug content was calculated by the formula.

$$Assay = \frac{Absorbance\ of\ sample}{Absorbance\ of\ standard} x\ 100$$

$$Assay = \frac{0.608}{0.616} x\ 100$$

$$Assay = \ 98.7\%$$

According to USP limit for assay ±90-110%. So results were in desired limits. These results indicate that active ingredient of drug was uniformly distributed in each tablet. So this test was passed and tablet can be used for further tests.

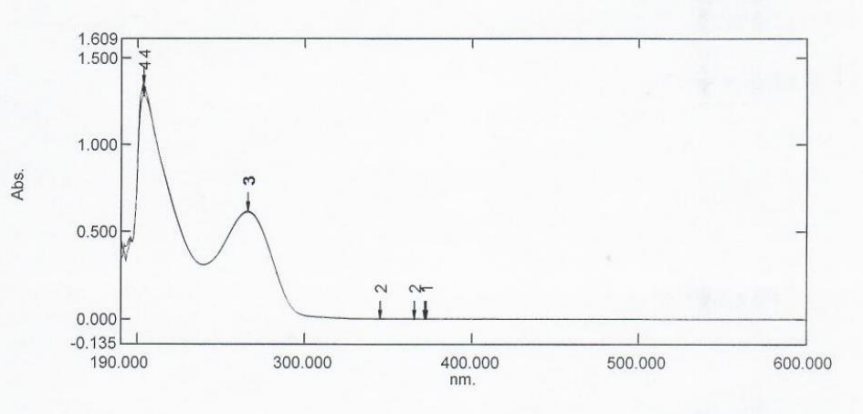

Figure 22: UV Spectrum of Uniformity of Drug Content of Finish

v. Dissolution Time

In vitro dissolution studies of coated tablets were performed according to USP method. 6 tablets were selected randomly and placed in dissolution medium, phosphate buffer, after 30 minutes sample was taken and absorption was calculated using UV Spectrophotometer. First of all standard was prepared using Famotidine, which is active ingredient of drug and its absorbance was observed, λ_{max} for famotidine was 265 nm. Then absorbance of 6 samples were observed. The absorbance of 6 samples and a standard were shown in table 26. U.V spectrum of in vitro dissolution shown in figure 25.

After taking absorbance %age dissolution was calculated using following formula:

$$\%age\ Dissolution = \frac{Absorbance\ of\ Sample}{Absorbance\ of\ Standard} x\ 100$$

If results are within limit i.e not less than 80% then coating formulation is successful. The results of our formulation were 98%, which shows that formulation is successful [67].

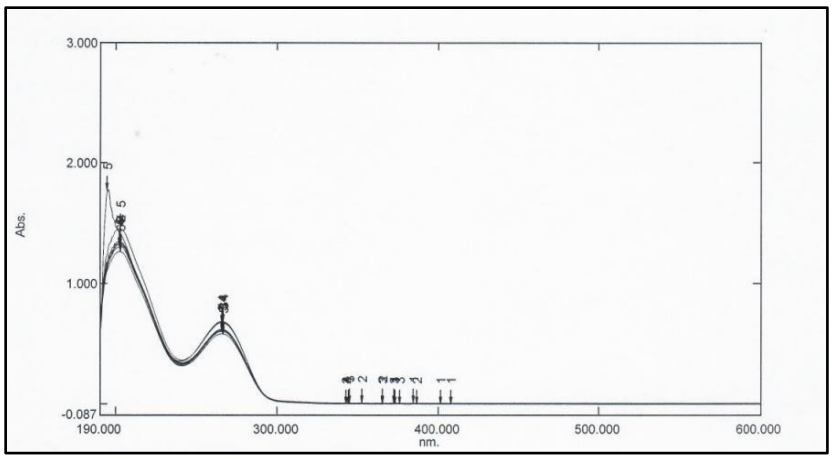

Figure 23: U.V Spectrum of In-Vitro Dissolution

Table 26: Absorbance of Standard and Sample

Sample	Wavelength(nm)	Absorption
Standard	402.0	0.000
	266.0	0.678
	195.0	1.747
Sample 1	366.5	0.005
	266.0	0.650
	202.0	1.425
Sample 2	373.0	0.005
	266.0	0.673
	202.0	1.471
Sample 3	365.5	0.006
	265.5	0.703
	202.0	1.510
Sample 4	373.0	0.005
	266.0	0.604
	201.5	1.455
Sample 5	384.5	0.008
	373.0	0.009
	266.0	0.651
	202.0	1.425
Sample 6	366.0	0.006
	266.0	0.683
	203.0	1.485

This table shows absorbance of standard and sample. The absorbance around 265 nm was selected and %age dissolution of each tablet was calculated, then average was calculated. The results were 98%, this showed that formulation was successful.

Table 27: Dissolution Results

	Std.	1	2	3	4	5	6
Absorbance	0.678	0.650	0.673	0.703	0.640	0.651	0.683
%age Dissolved		95.8	99.2	103.6	94.3	96.0	100.7
Average	98.2 %						

3.8 Stability Studies

All results of coated tablets were within limits then stability studies were performed. In this studies accelerated stability studies were done, in which samples were placed in accelerated chamber, temperature was maintained 40 ± 2°C. This sample was tested after 1st, 2nd, 3rd, 4th, 5th and 6th months. After each month sample appearance, disintegration time, assay and dissolution studies were performed. Results should be within range of pharmacopeia, limit is 75±5% [68].

i. General Appearance

First parameter was, to check appearance of tablet. After every month, tablets were taken out from stability chamber and their appearance was checked. It was observed that within 6 months there was no defect in appearance. Tablets remained same as they were placed in the stability chamber. Their texture and shinning appearance was not changed with the time.

ii. Disintegration Time

In stability studies disintegration time was also checked after every month. It was observed that disintegration time of tablets remained same i.e. 1 minute.

iii. Dissolution Time

In stability studies dissolution time of drug was studied for 6 months. In this study after every month sample of 6 tablets were taken out and in vitro dissolution was performed according to same parameters as described above. Results of all tablets were within limits so drug was passed.

Dissolution Test after 1st Month

After placing tablets in stability chamber for 1 month, sample of 6 tablets were taken and in vitro dissolution test was performed. U.V spectrum of in vitro dissolution was shown in figure 26.

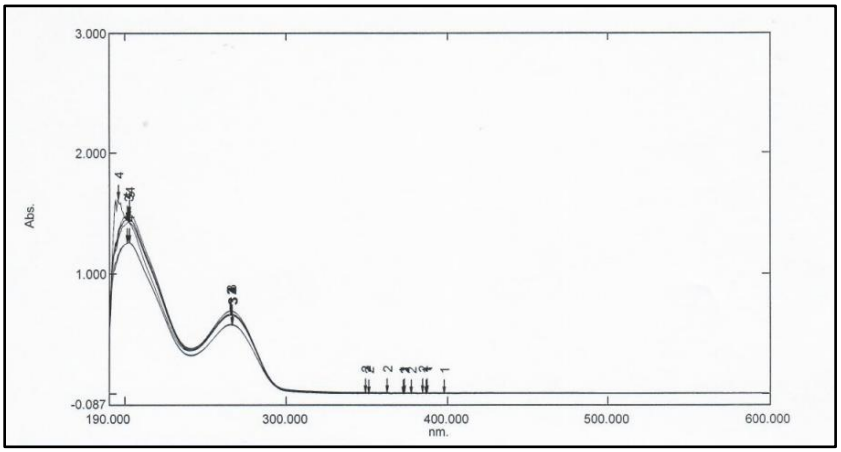

Figure 24: U.V spectrum of In-Vitro Dissolution after 1st Month

Absorbance of 6 tablets were observed using UV spectrometer, their values were shown in tablet 28. From this table absorbance at 265nm of each tablet was noted and dissolution results were calculated. These results shows 96% dissolution which was within limits of USP. Dissolution results shown in table 28 [85].

Table 28: Absorbance of Standard and Sample

Sample	Wavelength	Absorption
Standard	372.5	0.002
	351.0	0.000
	266.0	0.687
	195.5	1.626
Sample 1	373.0	0.005
	349.0	0.006
	266.0	0.661
	201.5	1.455
Sample 2	387.0	0.001
	266.0	0.650
	202.0	1.430
	202.5	1.461
Sample 3	387.0	0.003
	377.5	0.003
	266.0	0.684
	202.5	1.500
Sample 4	373.0	0.005
	349.0	0.006
	266.0	0.661
	201.5	1.455
Sample 5	398.0	0.003
	385.0	0.004
	266.0	0.663
	202.5	1.461
Sample 6	387.0	0.001
	266.0	0.650
	202.0	1.430

Table 29: 1st Month Stability Results

	Std.	1	2	3	4	5	6
Absorbance	0.687	0.6611	0.650	0.684	0.661	0.663	0.650
%age Dissolved		96.2	94.6	99.5	96.2	96.5	94.6
Average					**96.25 %**		

Dissolution Test after 2nd Month

After placing tablets in stability chamber for 2 month, sample of 6 tablets were selected and in vitro dissolution test was performed. U.V spectrum of in vitro dissolution was shown in figure 27.

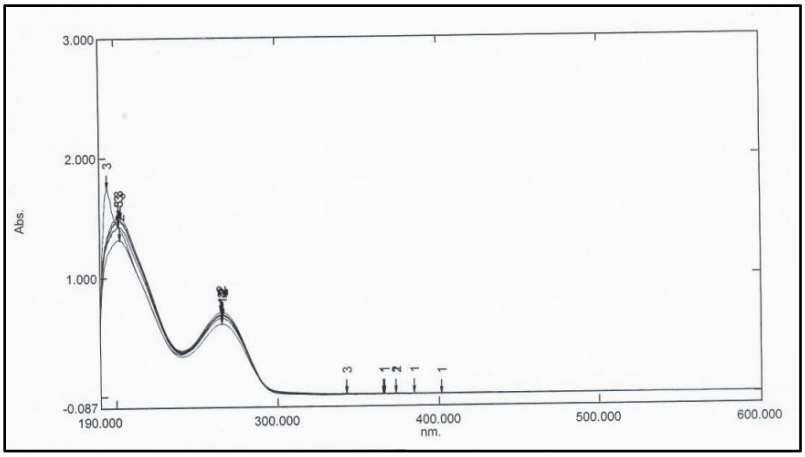

Figure 25: U.V Spectrum of In-Vitro Dissolution after 2nd Month

Absorbance of 6 tablets were observed using UV spectrometer, their values were shown in table 30. From this table absorbance at 265nm of each tablet was noted and dissolution results were calculated. These results shows 98 % dissolution which is within limits of USP. Dissolution results shown in table 31.

Table 30: Absorbance of Standard and Sample after 2nd Month

Sample	Wavelength	Absorption
Standard	402.0	0.000
	266.0	0.678
	195.0	1.747
Sample 1	366.5	0.005
	266.0	0.650
	202.0	1.425
Sample 2	373.0	0.005
	266.5	0.673
	202.0	1.471
Sample 3	365.5	0.006
	265.5	0.703
	202.0	1.510
Sample 4	384.0	0.005
	266.0	0.604
	202.0	1.313
Sample 5	373.0	0.009
	266.0	0.651
	202.5	1.425
Sample 6	366.0	0.006
	266.0	0.683
	203.5	1.485

Table 31: 2st Month Stability Results

	Std.	1	2	3	4	5	6
Absorbance	0.678	0.650	0.673	0.703	0.640	0.651	0.683
%age Dissolved		95.8	99.2	103.6	94.3	96.0	100.7
Average				98.2 %			

Dissolution after 3rd Month

After placing tablets in stability chamber, after 3 months sample of 6 tablets were withdrawn and in vitro dissolution test was performed. U.V spectrum of in vitro dissolution was shown in figure 28.

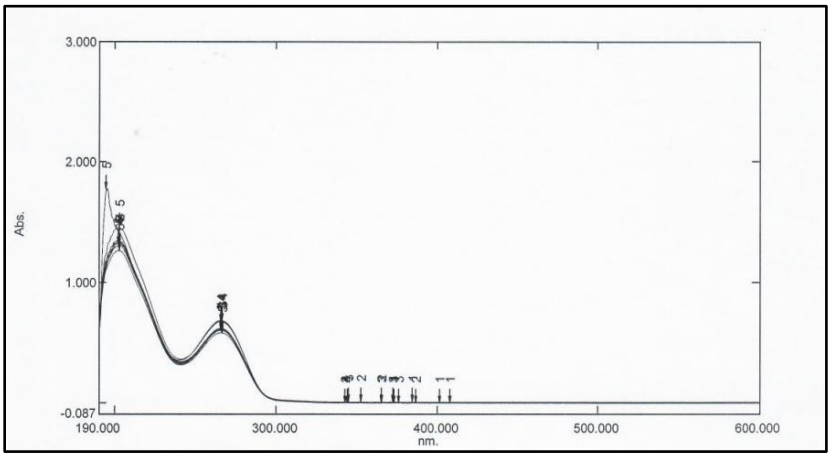

Figure 26: U.V Spectrum of In-Vitro Dissolution after 3rd Month

Absorbance of 6 tablets were observed using UV spectrometer, their values are shown in table 32. From this table absorbance at 265 nm of each tablet was noted and dissolution results were calculated. These results shows 90 % dissolution which is within limits of USP. Dissolution results shown in table 33.

Table 32: Absorbance of Sample and Standard

Sample	Wavelength	Absorption
Standard	372.5	0.002
	351.0	0.000
	266.0	**0.682**
	195.5	1.626
Sample 1	373.0	0.005
	349.0	0.006
	266.0	**0.615**
	201.5	1.455
Sample 2	387.0	0.001
	266.0	**0.599**
	202.0	1.430
	202.5	1.461
Sample 3	387.0	0.003
	377.5	0.003
	266.0	**0.603**
	202.5	1.500
Sample 4	373.0	0.005
	349.0	0.006
	266.0	**0.615**
	201.5	1.455
Sample 5	398.0	0.003
	385.0	0.004
	266.0	**0.671**
	202.5	1.461
Sample 6	387.0	0.001
	266.0	**0.613**
	202.0	1.430

Table 33: 3rd Month Stability Results

	Std.	1	2	3	4	5	6
Absorbance	0.682	0.615	0.599	0.603	0.615	0.671	0.613
%age Dissolved		90.1	87.8	88.4	90.1	98.3	89.8
Average					**90.8 %**		

Dissolution Test after 4th Month

Tablets were placed in stability chamber for 4 months then sample of 6 tablets were taken randomly and in vitro dissolution test was performed. U.V spectrum of in vitro dissolution is shown in figure 29.

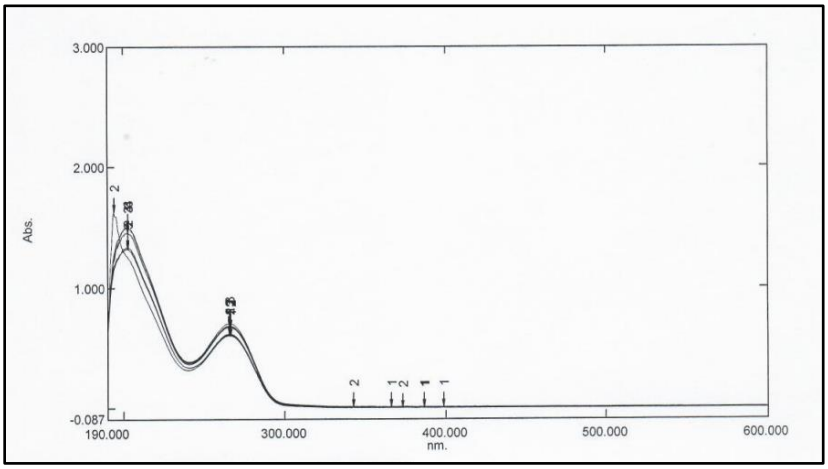

Figure 27: U.V Spectrum of In-Vitro Dissolution after 4th Month

Using UV spectrometer absorbance of 6 tablets were checked, their values were shown in tablet 34. From this table absorbance at 265nm of each tablet was noted and dissolution results were calculated. These results shows 96 % dissolution which is within limits of USP. Dissolution results shown in table 35.

Table 34: Absorbance of Standard and Sample

Sample	Wavelength	Absorption
Standard	372.5	0.002
	351.0	0.000
	266.0	**0.671**
	195.5	1.626
Sample 1	373.0	0.005
	349.0	0.006
	266.0	**0.613**
	201.5	1.455
Sample 2	387.0	0.001
	266.5	**0.599**
	202.0	1.430
	202.5	1.461
Sample 3	387.0	0.003
	377.5	0.003
	266.0	**0.606**
	202.5	1.500
Sample 4	373.0	0.005
	349.0	0.006
	266.0	**0.700**
	201.5	1.455
Sample 5	398.0	0.003
	385.0	0.004
	266.5	**0.669**
	202.5	1.461
Sample 6	387.0	0.001
	266.0	**0.680**
	202.0	1.430

Table 35: 4th Month Stability Results

	Std.	1	2	3	4	5	6
Absorbance	0.671	0.613	0.599	0.606	0.700	0.669	0.680
%age Dissolved		91.36	90.27	90.31	104.32	99.70	101.34
Average				**96.0 %**			

Dissolution Test after 5th month

Tablets were placed in stability chamber for 5 months then sample of 6 tablets were taken randomly and in vitro dissolution test was performed. U.V spectrum of in vitro dissolution is shown in figure 30 [86] .

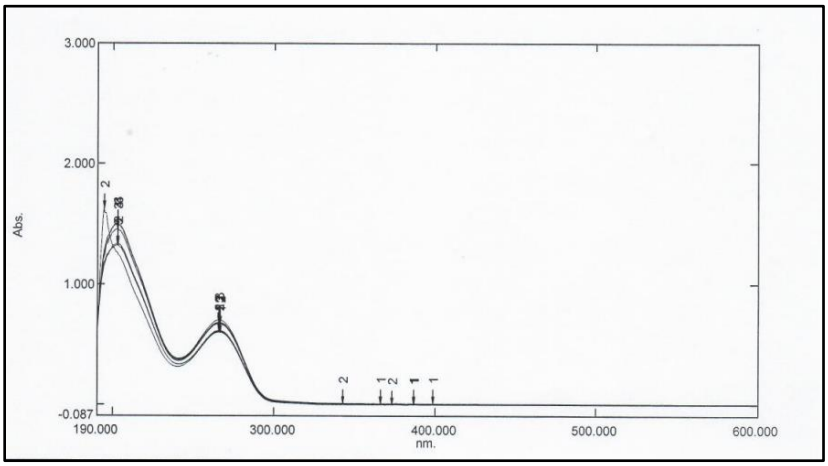

Figure 28: U.V Spectrum of In-Vitro Dissolution after 5th Month

Using UV spectrometer absorbance of 6 tablets were checked, their values were shown in tablet 36. From this table absorbance at 265nm of each tablet was noted and dissolution results were calculated. These results shows 96.0 % dissolution which is within limits of USP. Dissolution results shown in table 37.

Table 36: Absorbance of Standard and Sample

Sample	Wavelength	Absorption
Standard	372.5	0.002
	266.0	**0.687**
	195.5	1.626
Sample 1	373.0	0.005
	266.0	**0.661**
	201.5	1.455
Sample 2	387.0	0.001
	266.0	**0.650**
	202.5	1.461
Sample 3	387.0	0.003
	266.0	**0.684**
	202.5	1.500
Sample 4	373.0	0.005
	266.0	**0.661**
	201.5	1.455
Sample 5	398.0	0.003
	266.0	**0.663**
	202.5	1.461
Sample 6	387.0	0.001
	266.0	**0.650**
	202.0	1.430

Table 37: 5th Month Stability Results

	Std.	1	2	3	4	5	6
Absorbance	0.671	0.613	0.600	0.606	0.700	0.669	0.680
%age Dissolved		91.36	90.27	90.31	104.32	99.70	101.34
Average					**96.0 %**		

Dissolution after 6th Month

Tablets were placed in stability chamber for 6 months then sample of 6 tablets were taken randomly and in vitro dissolution test was performed. U.V spectrum of in vitro dissolution was shown in figure 31.

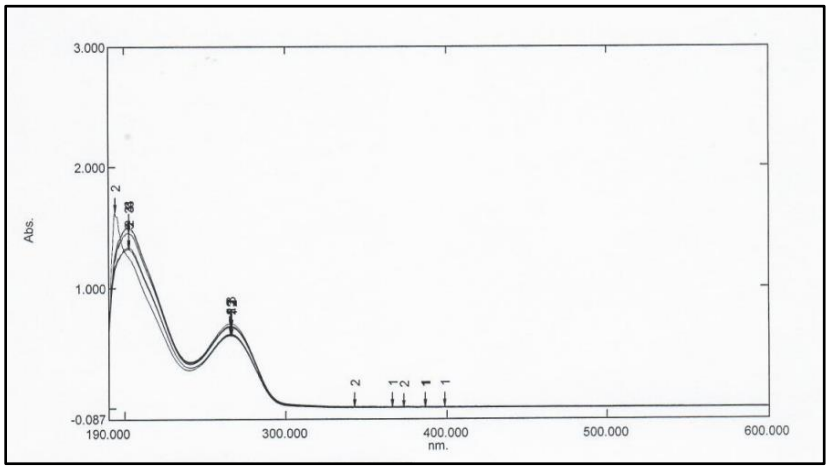

Figure 29: U.V Spectrum of In-Vitro Dissolution after 6th Month

Using UV spectrometer absorbance of 6 tablets were checked, their values were shown in table 38. From this table absorbance at 265nm of each tablet was noted and dissolution results were calculated. These results showed 93.6 % dissolution which is within limits of USP. Dissolution results shown in table 39 [87].

93.6% dissolution results showed that tablet ingested would dissolve 93 % inside body. It is in-vitro in-vivo correlation.

Table 38: Absorbance of Standard and Sample

Sample	Wavelength	Absorption
Standard	387.0	0.010
	266.0	**0.671**
	202.5	1.458
Sample 1	373.0	0.005
	266.0	**0.613**
	203.0	1.337
Sample 2	360.5	0.010
	266.5	**0.599**
	194.0	1.636
Sample 3	399.0	0.005
	266.0	**0.606**
	203.0	1.322
Sample 4	343.0	0.006
	266.0	**0.700**
	203.0	1.503
Sample 5	387.0	0.007
	266.5	**0.669**
	202.5	1.456
Sample 6	387.0	0.007
	266.0	**0.680**
	202.5	1.501

Table 39: 6th Month Stability Results

	Std.	1	2	3	4	5	6
Absorbance	0.694	0.637	0.640	0.648	0.656	0.662	0.656
%age Dissolved		91.79	92.22	93.37	94.52	95.39	94.52
Average					**93.6 %**		

thThese all are results of accelerated stability studies, which shows that all parameters are within limits. So, it can be declared that there is no physical or chemical change observed in drug and drug can be used for commercial purposes.

CONCLUSION

In this research work preparation of core and coating of tablet famoscot 40 mg having famotidine as active ingredient was studied. Core of drug was prepared by direct compression method. By pre compression test flow property of drug was checked and it showed that drug had excellent flow. Hydrophilic polymers were selected and FTIR analysis was done to confirm that there was no interaction between active ingredient of drug and polymers. Drug was coated with different polymers i.e. HPMC, PVA and PVP. In this coating organic solvent was replaced with water, coating having blend of HPMC and PVA showed best results. Obtained results of all parameters: general appearance, weight variation, hardness test, disintegration time, dissolution time and uniformity of drug content, were within USP limits. Dissolution and content uniformity test performed by UV-Visible spectroscopy showed that results were 98%. Stability studies of HPMC and PVA coated tablets were also done, which confirmed tablets were stable for 6 months and can be used for commercial purposes. As organic solvents are very hazardous they can cause infertility, headache, CNS and kidney disorders, residual solvents in drug would lead to cancer. So, use of organic solvents in pharmaceuticals are very harmful not only for people working in industry but also for patients. In this research organic solvents were completely removed so it not only saved environment but also helped to reduce economic burden. 44 % cost was saved by using water as solvent, by reducing cost drug availability of drug become easier. This was overall cost saved on single batch, when amount of batch was increased more amount could be saved. The drug prepared by aqueous coating fulfilled all the parameters like the drug prepared by organic coating but it is environment friendly and cost effective.

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