"FORMULATION, DEVELOPMENT AND OPTIMIZATION OF ULTRA-FAST DISSOLVING TABLET"

A Thesis Submitted to

NIRMA UNIVERSITY

IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF

MASTER OF PHARMACY

IN

PHARMACEUTICAL TECHNOLOGY AND BIOPHARMACEUTICS

BY

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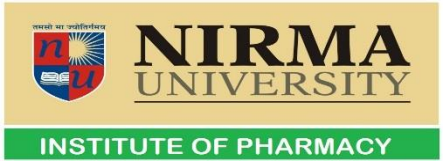

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MAY 2014

CERTIFICATE

This is to certify that the dissertation work entitled "Formulation development and optimization of ultra-fast dissolving tablets" submitted by Mr. Chintan Pansara with Regn. No. (12MPH101) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University and at Piramal Pharmaceutical Development Services Pvt. Ltd. under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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DECLARATION

I hereby declare that the dissertation entitled "Formulation, development and optimization of Ultra-fast dissolving tablet" is based on the original work carried out by me under the guidance of Dr. Vipan Dhall, Vice President and Site Head, Piramal Pharmaceutical Development Services and Dr. Jigar N. Shah, Assistant Professor, Department of Pharmaceutics, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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Education is a Shared commitment between dedicated teachers,
Motivated Students and
Enthusiastic Parents with great Confidence.

त्वमेव माता च पिता त्वमेव
त्वमेव बन्धुश्च सखा त्वमेव।
त्वमेव विद्या द्रविणं त्वमेव
त्वमेव सर्वं मम देव देव।

Dedicated to Beloved Pansara Family

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"Learn more & more about less & less until you know everything about nothing"

A single star cannot make the beautiful shiny sky at the night, same way a research work can never be an outcome of a single individual's talent or efforts. During my journey from objective to goal, I have experienced shower of blessings, guidance, and inspiration from my God, Family, Teachers, Friends and all my well-wishers. However, I take this opportunity to express my deep sense of gratitude to everyone.

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Success never comes alone but involves many partners. However much you succeed in your life, you should never forget that is the good wishes and the help of many around you who smoothened your path and helped you jump the toughest hurdles of life. Today, at the acme of life, I remember my good friends, ***Ronak, Hardik, Rajesh, Vishal, Neha, Tulsi,*** *for creating a pleasant and homely atmosphere during my stay at hostel. my parents, teachers, friends, relatives and well wishers without whom this dissertation would not have taken shape.*

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List of figures

Short	Abbreviation
IP	Indian Pharmacopoeia
BP	British Pharmacopoeia
USP	United States Pharmacopeia
USPNF	United States Pharmacopoeia National
UV	Ultra Violet
DT	Disintegration Time
CDR	Cumulative Drug Release
°C	Degree Centigrade
Conc.	Concentration
Abs	Absorbance
µg	Microgram
ml	Millilitre
mg	Milligram
W/W	Weight By Weight
W/V	Weight By Volume
kP	Kilo pond
API	Active Pharmaceutical Ingredient
RH	Relative Humidity
SD	Standard Deviation
OGD	Office of Generic Drug
FTIR	Fourier Transform Infra-Red

Formulation, development and optimisation of ultra-fast dissolving tablets

Compressed solids present one of the greatest challenges to formulation scientists, as they offer remarkable marketing opportunities to marketers. A solid oral dosage form is easy to ingest, is relatively more stable than other dosage forms (longer shelf life). There are opportunities to design delivery profiles to meet specific therapeutic requirements. As a result, almost two thirds of all dosage forms fall into this category. Immediate relief is required for those who suffer daily attacks, for them leukotriene antagonist or a mast cell stabilizer is recommended. PPDS_11YA, a BCS class I drug used as an Antiasthmatic agent, is highly recommended for treatment. Formulations are designed to achieve ultra-fast activated dissolution even under unfavourable physiological conditions so that fast and consistent absorption and efficacy are independent of gastrointestinal (GI) activity and pH. Tablets were prepared by direct compression method using pH Modulating agents (Sodium bicarbonate and citric acid), water uptaking agents (Lactose monohydrate, Avicel PH 112, Klucel EXF, starch 1500, Acdisol, polyplasdone XL 10, Primellose) and magnesium stearate as lubricant in different combinations and ratios using Cadmach compression machine. Formulation showed acceptable thickness, hardness, disintegration, friability and Invitro drug release profile. Blend has medium flow property but there were no issues of segregation, blend and content uniformity in the formulation. Target was to achieve the disintegration within 30 sec and % CDR in 3 minutes and 20 minutes should be more than 70% and 85% respectively. So to achieve the target product profile, 2^3 full factorial design was used to optimise the level of sodium bicarbonate, citric acid and polyplasdone XL 10 at low and high levels. Statistical analysis revealed that high level of all three ingredient is required to obtain the target product profile. Thus, use of DOE helps in accurate optimization of formulation with minimum efforts, time and energy. From above results, it can be concluded that the optimised formulation shows better results as compared to marketed formulation.

Chapter: 1

Aim Of Present Investigation

"The real act of discovering is not in finding in new lands, but in seeing with new eyes"

1. Aim of Present Investigation

Oral ingestion is the predominant and most preferable route for drug delivery mainly due to their convenience of administration, patient compliance and their suitability for delivery of drugs for systemic effects. Following oral administration, most drugs have to be absorbed into the blood to produce therapeutic action. However, certain drugs have a "region-specific absorption" or "absorption window". The region specific absorption may be due to various reasons, such as poor solubility at different pH values, poor stability in some GI regions, presence or absence of absorptive or efflux transporters, presystemic metabolism in the gut wall.

Improving the rate and extent of absorption of oral formulations of compounds has been the subject of substantial research. In general, once a solid swallow composition reaches the stomach, it undergoes disintegration and/or dissolution and passes into the small intestine where the active ingredient is absorbed across intestinal walls into the circulatory system via the portal vein and liver before reaching the site of action. For some drug, absorption is not rate limited, and in this case fast disintegration and fast dissolution of the active ingredient should promote fast absorption in vivo. Solid dosage forms for oral administration can be categorised into three major groups.

1. Those described as swallow formulations are intended to be swallowed whole.
2. Those described as orally disintegrating or orally dissolving or chewable, are intended to be dispersed or dissolved in the mouth before swallowing.
3. The third group is generally called dispersible or soluble formulations that are intended to be dissolved or dispersed in liquid before administration, such that the patient swallows the resultant solution or dispersion.

From the group of swallow formulations, some are designed for sustained or delayed release using coating or use of different polymers or other devices that control the release of the drug within the gastrointestinal tract. Other swallow formulations are designed for fast dissolution of the active ingredient, with the aim of achieving fast absorption and fast onset of action. This present invention relates to

formulations manufactured as solid dosage forms intended to be swallowed intact, which will achieve fast dissolution and fast absorption of the active ingredient.

The purpose of the present invention is to incorporate the advantages of improved absorption and reproducibility of dispersible and/or soluble formulations into swallow formulations that are more convenient, and remain the preferred dosage form for many patients, particularly for regular use.

- To develop and optimize the Fast dissolving swallow formulation compared to available marketed formulation.
- Application of experimental design, 2^3 full factorial design for formulation optimization.
- To optimize the level and composition of alkalizer and acidifier in the formulation to enhance the solubility of drug in gastric environment.
- To optimize the level of disintegrant in the formulation so as to achieve faster disintegration.
- Evaluation of experimental design batches.
- To compare dissolution profiles of optimized formulation with the market formulation in bio-relevant media.
- To perform stability study of optimised formulation at different condition of 25^0C/60% RH and 40^0C/75% RH.

Chapter: 2

"The more you Read, the more you Know.
The more you Learn, The Smarter you Grow."

2. Introduction (1, 2, 3)

Asthma is a chronic lung disease and is one of the most common chronic diseases among children. It causes airway inflammation. When this inflammation occurs, the lungs react and produce muscle tightening, mucous, and swelling in the breathing tubes of the lungs. People with asthma then start to wheeze, cough, feel chest tightness, and have a hard time breathing. During severe attack they may feel like they are suffocating.

A series of factors combines to produce increasing airway inflammation and airway hyper-responsiveness and, when these features reach a sufficient level, bronchoconstriction and asthma symptoms are triggered. Typically, the inhalation of an allergen in an asthmatic can result in an episode of asthma. Asthmatics have high levels of the antibody immunoglobulin E (IgE), which binds to receptors on inflammatory cells, most notably mast cells. The interaction of the inhaled allergen and IgE results in the activation of mast cells, releasing pre-formed mediators such as histamine, prostaglandins and leukotriene, which cause the smooth muscle of the airways to contract, thereby producing broncho constriction.

Asthma is a major public health problem in the United States. The disease affects approximately 20.3 million people, nearly 6.3 million of whom are under the age of 18 years. It accounts for an estimated 14.5 million lost workdays for adults and 14 million lost school days in children annually. The collective cost of the disease is estimated at $14.0 billion for the year 2002.

The concepts underlying asthma pathogenesis have evolved dramatically in the past 25 years and are still undergoing evaluation as various phenotypes of this disease are defined and greater insight links clinical features of asthma with genetic pattern. Central to the various phenotypic patterns of asthma is the presence of underlying airway inflammation, which is variable and has distinct but overlapping patterns that reflect different aspects of the disease, such as intermittent versus persistent or acute versus chronic manifestations. Acute symptoms of asthma usually arise from bronchospasm and require response to bronchodilator therapy. Acute and chronic inflammation can affect not only the airway calibre and

airflow but also underlying bronchial hyperesponsiveness, which enhances susceptibility to bronchospasm.

2.1 Respiratory System (4)

2.1.1 Anatomy and physiology of respiratory system

The respiratory system works with the circulatory system to deliver oxygen from the lungs to the cells and remove carbon dioxide, and return it to the lungs to be exhaled. The exchange of oxygen and carbon dioxide between the air, blood and body tissues is known as respiration. Healthy lungs take in about 1 pint of air about 12–15 times each minute. All of the blood in the body is passed through the lungs every minute. The respiratory tract is divided into two main parts: the upper respiratory tract, consisting of the nose, nasal cavity and the pharynx; and the lower respiratory tract consisting of the larynx, trachea, bronchi and the lung shown in figure 2.1.

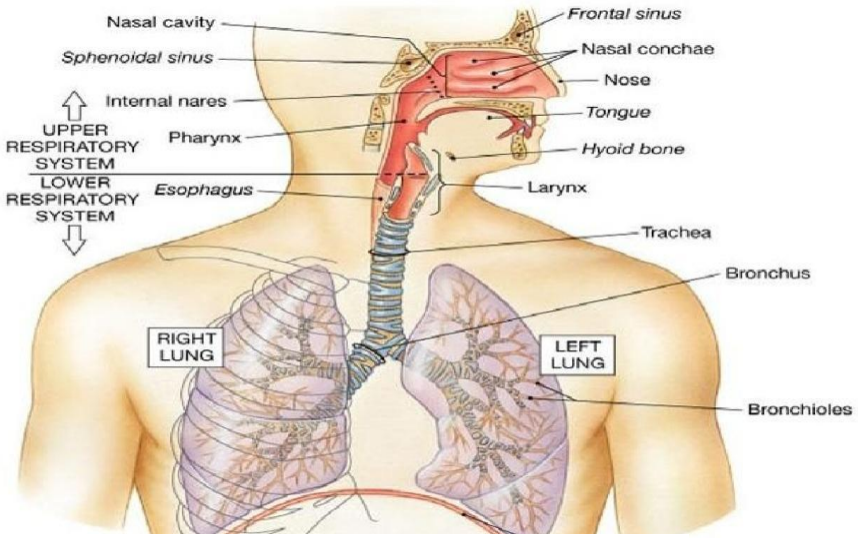

Figure 2.1 Diagram of Respiratory system

The trachea, which begins at the edge of the larynx, divides into two bronchi and continues into the lungs. The trachea allows air to pass from the larynx to the bronchi and then to the lungs. The bronchi divide into smaller bronchioles which branch in the lungs forming passage ways for air.

2.1.1.1 Anatomy of lung

The lungs are the primary organ of the respiratory system. Each lung is divided into lobes. The right lung, which has three lobes, is slightly larger than the left, which has two lobes. The lungs are housed in the chest cavity, or thoracic cavity, and covered by a protective membrane called the pleura. The diaphragm, the primary muscle involved in respiration, separates the lungs from the abdominal cavity. The main function of the human respiratory system is to transport oxygen from the atmosphere into the blood, and to expel carbon dioxide from the body. Healthy levels of oxygen are absolutely crucial for the human body, as oxygen gives our cells energy and helps them regenerate. Alveoli are mainly responsible for exchange of gas.

- **Alveoli**

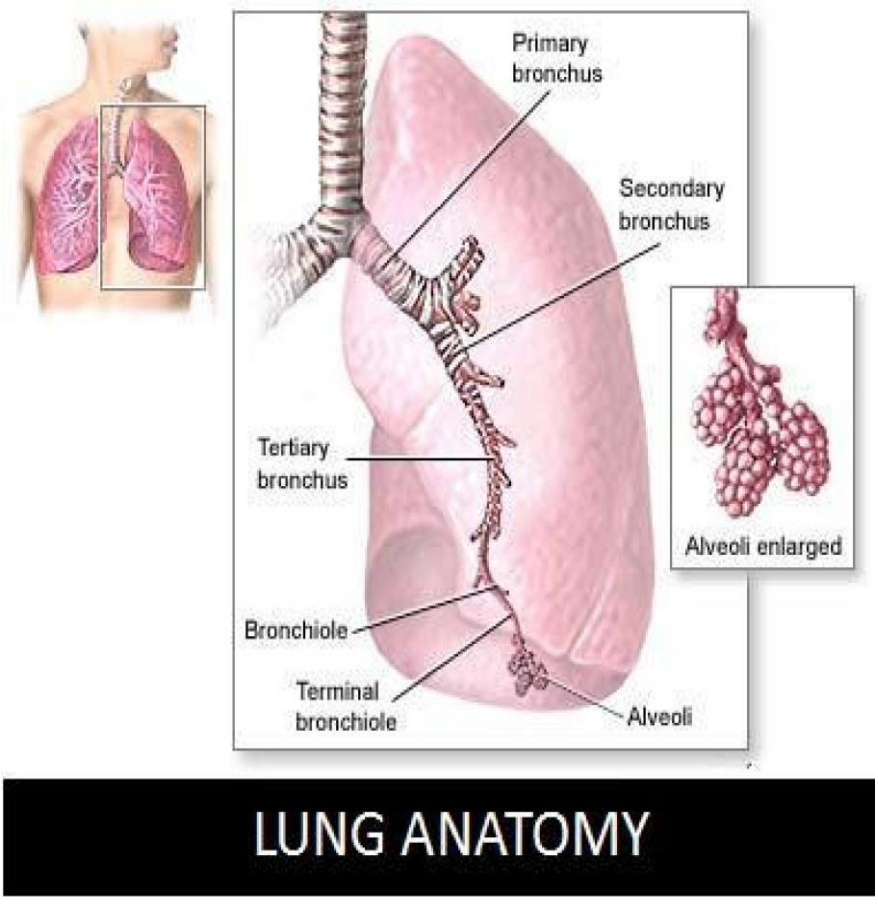

Figure 2.2 Anatomy of lung

The alveoli are the functional units of the lungs and they form the site of gaseous exchange. Each bronchiole ends in a group of tiny sac-like structures, each one called an alveolus. Each lung has about 300 million alveoli. Each alveolus is surrounded by a capillary blood vessel. Gases, e.g. oxygen and carbon dioxide, move across the alveolar membrane into the blood vessels and vice versa. A continuous exchange of gases takes place between the alveoli and the capillary blood vessels that surround them. The blood barrier between the alveolar space and the pulmonary capillaries is very thin to allow for rapid gas exchange. During inspiration, oxygen diffuses through the alveoli walls and the interstitial space, into the blood. Carbon dioxide diffuses in the opposite direction during exhalation is shown in diagram of alveoli figure 2.3.

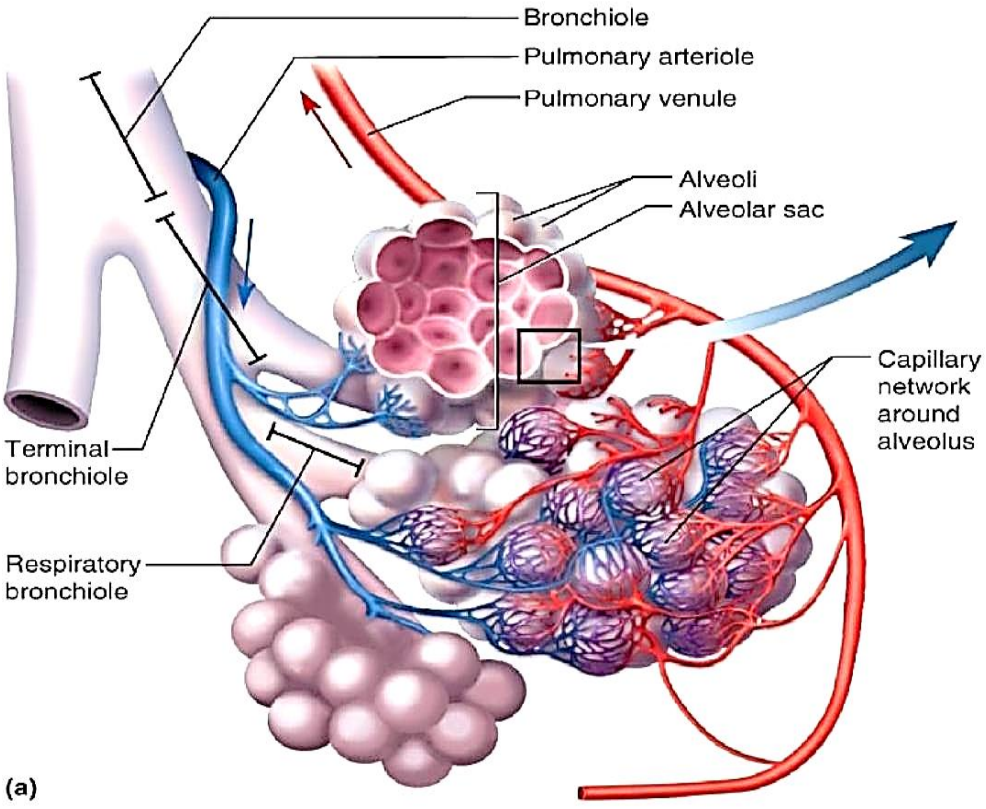

Figure 2.3 Diagram of alveoli

2.1.2 Breathing system of lung

To take a breath in, the external intercostal muscles contract, moving the ribcage up and out. The diaphragm moves down at the same time, creating negative pressure within the thorax. The lungs are held to the thoracic wall by the pleural membranes, and so expand outwards as well. This creates negative pressure within the lungs, and so air rushes in through the upper and lower airways. Expiration is mainly due to the natural elasticity of the lungs, which tend to collapse if they are not held against the thoracic wall. This is the mechanism behind lung collapse if there is air in the pleural space (pneumothorax).

We breathe 15-18 times a minute exchanging about 500 ml of air. Under these conditions, an average adult male can flush his lungs with about four litre of air at each breath. This is called the vital capacity. Even with maximum expiration, about 1200 ml of residual air remain. Composition of atmospheric air and expired air in a typical subject. Note that only the lungs take up a fraction of the oxygen inhaled.

Table 2.1 : Composition of Air

Component	Atmospheric air (%)	Expired Air (%)
N_2 (plus inert gases)	78.62	74.3
O_2	20.85	15.3
CO_2	0.03	3.6
H_2O	0.5	6.2
Total	100 %	100 %

The table shows what happens to the composition of air when it reaches the alveoli. Some of the oxygen dissolves in the film of moisture covering the epithelium of the alveoli. From here, it diffuses into the blood in a nearby capillary. It enters a red blood cell and combines with the haemoglobin therein. At the same time, some of the carbon dioxide in the blood diffuses out into the

alveoli and can be exhale out.

2.2 Lung Diseases

Different respiratory diseases affect different parts of the lungs and produce specific signs and symptoms. The most common lung diseases shown in figure 2.4.

2.2.1 Acute Bronchitis

Acute bronchitis is an inflammation of the bronchial tubes, the major airways into the lungs. This can be the outcome of variety of bacteria and viruses. However, the cough that comes with acute bronchitis may last for several weeks after the infection has gone. Acute bronchitis may develop on its own, or because of an upper respiratory infection, pertussis (whooping cough) or other infection. It shows sign and symptoms like wheezing, low fever, chest tightness or pain, shortness of breath. In treatments given humidifier or steam to ease breathing and aid loosen mucus, inhaled medicine to open airways and cough medicine.

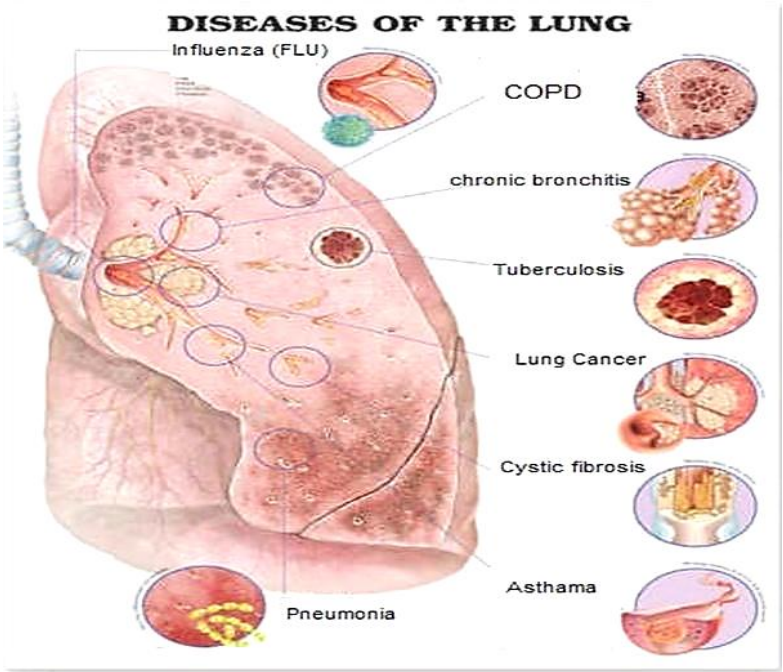

Figure 2.4: Diseases of the lung

2.2.2 Pneumonia

Pneumonia is an infection in one or both of your lungs. Many small germs, such as bacteria, viruses, and fungi, can cause pneumonia. Pneumonia affects your lungs in two ways. Lobar pneumonia affects a section (lobe) of a lung. Bronchial pneumonia (or bronchopneumonia) affects patches throughout both lungs. Sign and symptoms are cough, fever which may be mild or high, shaking chills, shortness of breath, headache, excessive sweating and clammy skin, loss of appetite, low energy, and fatigue. For treatments bronchodilators, steroids and anticholinergic are given.

2.2.3 Tuberculosis

Tuberculosis is an infectious disease that usually attacks the lungs, but can attack almost any part of the body. Tuberculosis is spread through the air. Multi-drug resistant tuberculosis (MDR-TB) is a very dangerous form of tuberculosis. Sign and symptoms like persistent cough, constant fatigue, weight loss, loss of appetite, fever. The most common preventive therapy is a daily dose of isoniazid for 6 to 9 months. The most common treatment for active TB is INH plus two to three other drugs including rifampicin, pyrazinamide and ethambutol.

2.2.4 Lung cancer

Lung cancer is a disease, which consists of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis; which is the invasion of adjacent tissue and infiltration beyond the lungs. The vast majority of primary lung cancers are carcinomas of the lung, derived from epithelial cells. The most common cause of lung cancer is long-term exposure to tobacco and smoke. The occurrence of lung cancer in non-smokers is often attributed to a combination of genetic factors, radon gas, asbestos annd air pollution. Sign and symptoms like chronic coughing or change in regular coughing pattern, wheezing, chest pain or pain in the abdomen, cachexia (weight loss), fatigue, loss of appetite. Surgery, chemotherapy, and radiotherapy are most common treatment for lung cancer.

2.2.5 Chronic Obstructive Pulmonary Disease (COPD) (5)

The global initiative on obstructive lung disease (GOLD) defines COPD as a disease state characterized by airflow limitation that is not fully reversible. The

airflow limitation is usually progressive and this limitation is associated with an abnormal inflammatory response of the lungs to noxious particles and gases.

This definition encompasses the idea that COPD is a chronic inflammatory disease, which is characterised by acceleration in the normal decline of lung function seen with age. Amongst other inflammatory mediators, the key inflammatory cells that play a pivotal role in COPD include neutrophils, macrophages, B-lymphocytes.

In developed countries, cigarette smoking is by far the commonest cause of COPD accounting for >95% of cases, but there are several other risk factors, including air pollution, poor diet and occupational exposure. Inflammatory mediators attract inflammatory cells such as neutrophils, which secrete proteases that contribute to alveolar destruction and mucus hyper-secretion. Furthermore, macrophages generate reactive oxygen species and nitric oxide, which together with peroxynitrate may contribute to steroid therapy resistance in COPD. (6)

2.2.6 Asthma

A series of factors combines to produce increase in airway inflammation and airway hyper-responsiveness, when these features reach a sufficient level, bronchoconstriction and asthma symptoms are triggered. Typically, the inhalation of an allergen in an asthmatic can result in an episode of asthma. Asthmatics have high levels of the antibody immunoglobulin E (IgE), which binds to receptors on inflammatory cells, most notably mast cells. The interaction of the inhaled allergen and IgE results in the activation of mast cells, releasing pre-formed mediators such as histamine, prostaglandins and leukotriene, which cause the smooth muscle of the airways to contract, thereby producing bronchoconstriction. (7)

The inflammatory response in asthma is highly complex involving inflammatory cells such as mast cells, eosinophil, B-lymphocytes and T- lymphocytes. These inflammatory mediators regulate the response of other mediators and have a number of effects resulting in contraction of airway smooth muscle, increase of vascular permeability and stimulation of airway mucus secretion. Hence, oedema, and cellular infiltration, thereby increasing smooth muscle mass and glands thicken the wall of the airway in asthma. With increasing severity of the disease, remodelling

of the airways leads to fibrosis, fixed narrowing of the airway and reduced response to therapy. (8)

2.2.6.1 Symptoms of Asthma

❖ **The clinical hallmarks of Asthma**

Coughing, Shortness of Breath, Chest tightness, wheezing, etc.

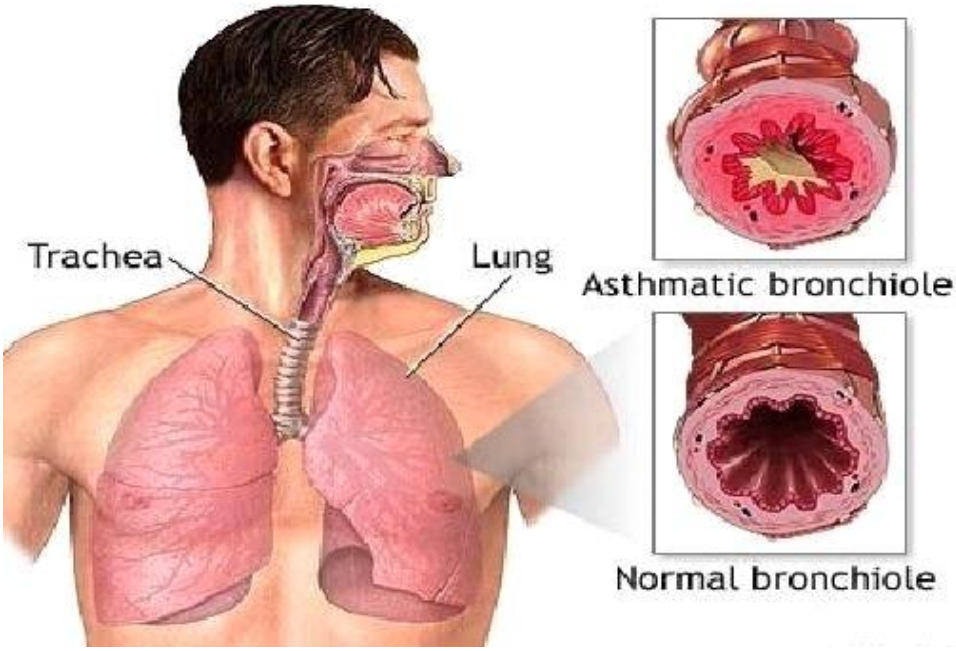

Figure 2.5: Comparison of Normal and Asthmatic airway

❖ **The Symptoms of Asthma**

Smooth muscle contraction, Vascular congestion Bronchial wall oedema Thick, tenacious secretion etc.

2.2.6.2 Causes of Asthma:

Allergens (IgE): pollens, mites, animal dander, cockroaches

Drugs: B-antagonist, sulphites, benzalkonium chloride

Respiratory Infection: respiratory syncytial virus (RSV), rhinovirus

Air pollution: fog, smoke, ozone, nitrogen dioxide, sulphur dioxide

Emotional: Stress, Laughter, anxiety

Exercise: dry, cold weather especially

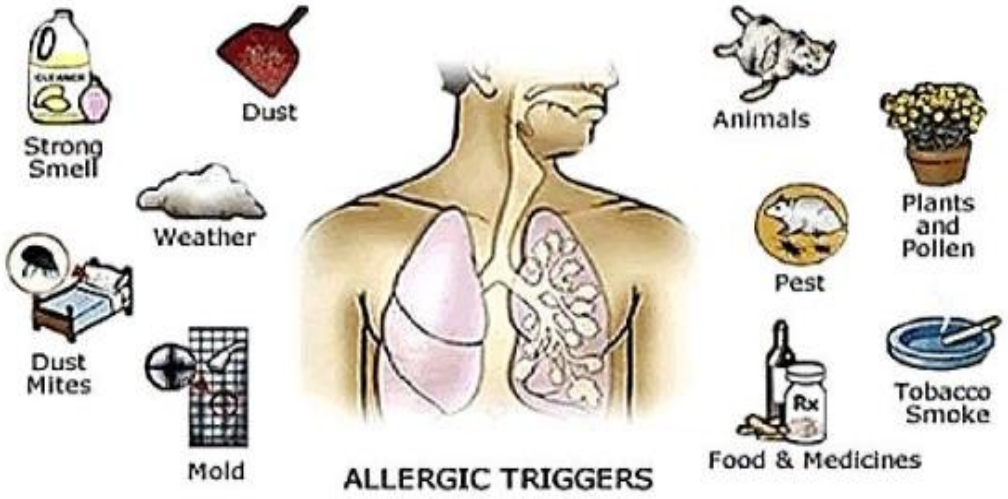

Figure 2.6 Causes of asthma

2.2.6.3 Pathophysiology of asthma (9)

A rational approach to the pharmacotherapy of asthma depends on an understanding of the pathogenesis of disease. In the classic immunologic model, asthma is a disease mediated by (IgE) antibodies bound to mast cells in the airway mucosa (Figure 2.7). On re-exposure to an antigen, antigen-antibody interaction on the surface of the mast cells triggers both the release of mediators stored in the cells' granules and the synthesis and release of other mediators. The agents responsible for the early reaction—immediate bronchoconstriction include histamine, tryptase and other neutral proteases, leukotriene C4 and D4 and prostaglandins. These agents diffuse throughout the airway wall and cause muscle contraction and vascular leakage. Other mediators are responsible for the more sustained bronchoconstriction, cellular infiltration of the airway mucosa, and mucus hyper secretion of the late asthmatic reaction that occurs 2–8 hours later. These mediators are cytokines characteristically produced by TH2 lymphocytes, especially interleukins 4, 5, 9, and 13, which attract and activate eosinophil and stimulate IgE production by B-lymphocytes. It is not clear whether lymphocytes or mast cells in the airway mucosa are the primary source of the cytokines and other mediators responsible for the late inflammatory response, but it is now thought that the benefits of corticosteroid therapy may result from their inhibition of cytokine production.

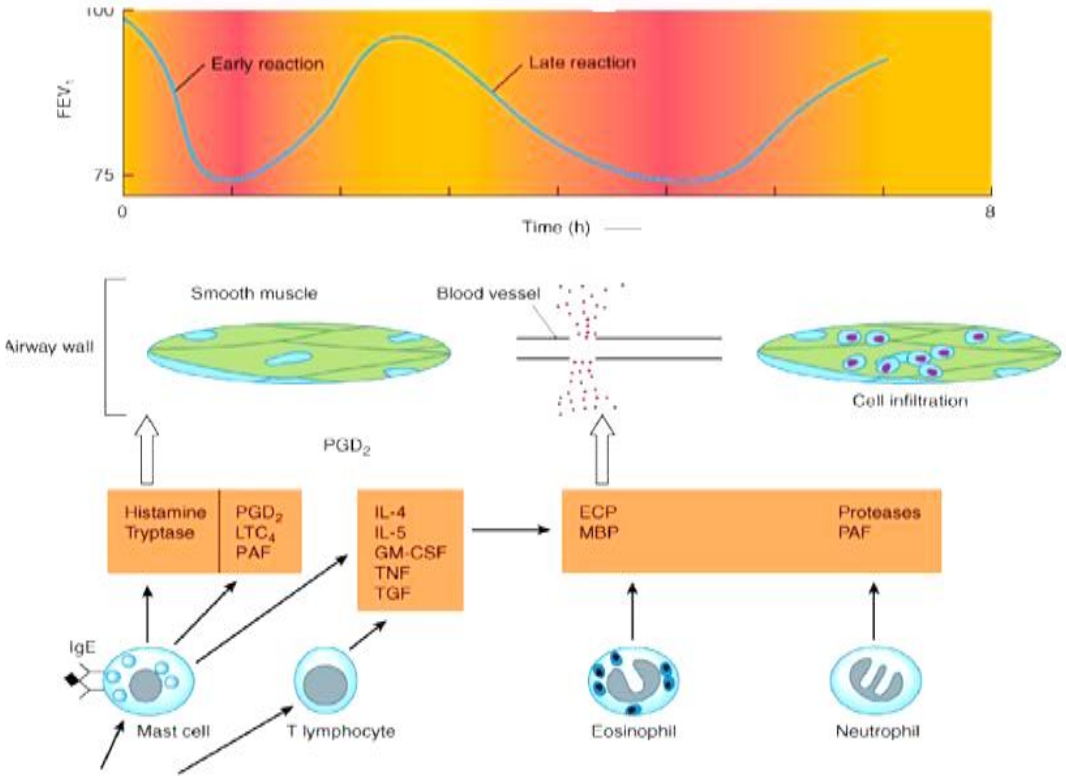

Figure 2.7 : Pathogenesis of Asthma

2.2.6.4 Management of asthma

Patient with asthma should understand the importance of reducing exposure to allergens, testing to assess the severity of symptoms, and the usage of medications. The treatment plan is scheduled and proper adjustments are to be incorporated to aid relieve in symptoms.

The most effective treatment for asthma is identifying triggers, such as cigarette smoke, pets, or aspirin, and eliminating exposure to them. If trigger avoidance is insufficient, medical treatment is recommended. Medical treatments used depend on the severity of illness and the frequency of symptoms. Specific medications for asthma is broadly classified into fast-acting and long-acting categories. Bronchodilators are recommended for short-term relief of symptoms. In those with occasional attacks, no other medication is needed. If mild persistent disease is present, (more than two attacks a week), low-dose inhaled glucocorticoids or alternatively, an oral leukotriene antagonist or a mast cell stabilizer is recommended. For those who suffer daily attacks, a higher dose of inhaled glucocorticoid is used. In a severe asthma exacerbation, oral glucocorticoids are incorporated to these treatments.

❖ **Lifestyle modification**

Avoidance of triggers is a key component of improving control and preventing attacks. The most common triggers include allergens, smoke (tobacco and other), air pollution, non-selective beta-blockers, and sulphite-containing foods. Cigarette smoking and second hand smoke (passive smoke) concerning people with asthma causes problems in effectiveness of management medications such as steroid/corticosteroid therapies.

2.2.6.5 Antiasthmatic drugs

Table 2.2 : Class of drugs used in Asthma

Sr.No	Type	Sub type	Example
1	Bronchodilators	B2 Sympathomimetic	Salbutamol
			Formoterol
		Methylxanthines	Theophylline
			Doxophyline
		Anticholinergic	Ipratropium Bromide
			Tiotropium Bromide
2	Leukotriene antagonist		Montelukast
			Zafirlukast
3	Corticosteroids	Systemic	Hydrocortisone
			Prednisolone
		Inhalation	Beclomethasone Dipropionate
			Budesonide
			Fluticasone Propionate
4	Mast cell stabiliser		Sodium Chromoglycate
5	Anti IgE antibody		Omalizumab

2.3 Introduction to Solid Oral Dosage Forms (10)

Compressed solids present one of the greatest challenges to formulation scientists, as they offer remarkable marketing opportunities to marketers. A solid oral dosage

form is easy to ingest, is relatively more stable than other dosage forms (longer shelf life), and with it, opportunities to design delivery profiles to meet specific therapeutic requirements are offered. As a result, almost two-thirds of all dosage forms fall into this category. The challenge in formulating these products includes finding an optimum medium of compromises that will ensure releases of an active drug at the most desired and consistent rate. The formulation components and process of manufacturing thus take pivotal importance.

The formulation of compressed solids involves a highly intricate series of events, from the characterization of the active pharmaceutical ingredient, to the choice of excipients, to the selection of processing, compression, and coating equipment and packaging systems appropriate for the specific drug and the dosage form.

Drugs are administered into the body via several routes. They may be taken by mouth (*Oral*); placed under the tongue (*Sublingual*); sprayed into the nose and absorbed through the nasal membranes (*Nasal*); breathed into the lungs, usually through the mouth (*Inhalation*); given by injection into a vein (*Intravenous*), into a muscle (*Intramuscular*), into the space around the spinal cord (*Intrathecal*), or beneath the skin (*Subcutaneous*); inserted in the rectum (*Rectal*) or vagina (*Vaginal*); installed in the eye (*Ocular*); applied to the skin (*Cutaneous*) for a local (*Topical*) or body wide (*Systemic*) effect; or delivered through the skin by a patch (*Transdermal*) for a systemic effect. Each route has specific purposes, advantages, and disadvantages.

Solid dosage forms are the least expensive, most popular and convenient methods for drug delivery. They are produced in a non-sterile environment and the technology is well known after more than 100 years of development. Most pharmaceuticals are produced in solid dosage forms.

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are classified according to the method of manufacture, as compressed tablets or molded tablets. The vast majority of all tablets manufactured are made by compression, and compressed tablets are the most widely used dosage form in the U.S. Compressed tablets are prepared by the application of high pressures, utilizing steel punches and dies, to powders or granulations. Tablets can be

produced in a wide variety of sizes, shapes, and surface markings, depending upon the design of the punches and dies. Capsule-shaped tablets are most commonly referred to as caplets.

Boluses are large tablets intended for veterinary use, usually for large animals. Molded tablets are prepared by forcing dampened powders under low pressure into die cavities. Solidification depends upon crystal bridges built up during the subsequent drying process and not upon the compaction force.

Tablet triturates are small, usually cylindrical, molded or compressed tablets. Tablet triturates were traditionally used as dispensing tablets in order to provide a convenient, measured quantity of a potent drug for compounding purposes. Such tablets are rarely used today.

Hypodermic tablets are molded tablets made from completely and readily water soluble ingredients and formerly were intended for use in making preparations for hypodermic injection. They are employed orally, or where rapid drug availability is required, such as in the case of nitroglycerin tablets, sublingually.

Buccal tablets are to be place in the buccal pouch, and sublingual tablets beneath the tongue, where the active ingredient is absorbed directly through the oral mucosa. Few drugs are readily absorbed in this way, but for those that are (such as nitroglycerin and certain steroid hormones) there are a number of advantages.

Soluble, effervescent tablets are prepared by compression and contain, in addition to active ingredients, mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water. They have to be dissolved or dispersed in water before administration. Effervescent tablets should be stored in tightly closed containers or moisture-proof packs and should be labelled, to indicate that they are not to be swallowed directly.

Chewable tablets are formulated and manufactured so that they may be chewed, producing a pleasant-tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste. These tablet formulations are used for children, especially in multivitamin formulations, and for the administration of antacids and selected antibiotics. Chewable tablets are prepared by compression,

usually utilizing mannitol, sorbitol, or sucrose as binders and fillers, and containing colours and flavors to enhance their appearance and taste.

Most compressed tablets consist of the active ingredient and a diluent (filler), binder, disintegrating agent, and lubricant. Approved FD&C and D&C dyes or lakes (dyes adsorbed onto insoluble aluminium hydroxide), flavors, and sweetening agents may also be present. Diluents are added where the quantity of active ingredient is small or difficult to compress. Common tablet fillers include lactose, starch, dibasic calcium phosphate, and microcrystalline cellulose. Chewable tablets often contain sucrose, mannitol, or sorbitol as fillers. Where the amount of active ingredient is small, the overall tableting properties are, in large measure, determined by the filler. Because of problems encountered with the bioavailability of hydrophobic drugs of low water solubility, water-soluble diluents are used as fillers for these tablets.

Binders give adhesiveness to the powder during the preliminary granulation and to the compressed tablet. They add to the cohesive strength already available in the diluent. While binders may be added dry, they are more effective when added out of solution. Common binders include acacia, gelatin, sucrose, povidone, methylcellulose, carboxymethylcellulose, and hydrolysed starch pastes. The most effective dry binder is microcrystalline cellulose, which is commonly used for this purpose in tablets prepared by direct compression.

A disintegrating agent serves to assist in the fragmentation of the tablet after administration. The most widely used tablet disintegrating agent is starch. Chemically modified starches and cellulose, alginic acid, microcrystalline cellulose, and cross-linked povidone, are also used for this purpose. Effervescent mixtures are used in soluble tablet systems as disintegrating agents. The concentration of the disintegrating agent, method of addition, and degree of compaction play roles in effectiveness.

Lubricants reduce friction during the compression and ejection cycles. In addition, they aid in preventing adherence of tablet material to the dies and punches. Metallic stearates, stearic acid, hydrogenated vegetable oils, and talc are used as lubricants. Because of the nature of this function, most lubricants are hydrophobic, and as such, tend to reduce the rates of tablet disintegration and dissolution. Consequently,

excessive concentrations of lubricant should be avoided. Polyethylene glycols and some lauryl sulphate salts have been used as soluble lubricants, but such agents generally do not possess optimal lubricating properties, and comparatively high concentrations are usually required.

Glidant are agents that improve powder fluidity, and they are commonly employed in direct compression where no granulation step is involved. The most effective glidant are the colloidal pyrogenic silica.

Colorants are often added to tablet formulations for aesthetic value or for product identification. Both D&C and FD&C dyes and lakes are used. Most dyes are photosensitive, and they fade when exposed to light. The U.S. FDA regulates the colorants employed in drugs.

2.3.1 Advantages of Tablet (11)

- It is easy to administer.
- It is a unit dosage form, and offer the greater capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Manufacturing cost is lowest of all oral dosage forms.
- It is the lightest and most compact of all oral dosage forms.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.

2.3.2 Disadvantages of Tablet

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate bioavailability.

- ❖ Bitter drugs, drugs with objectionable odour or drugs that are sensitive to oxygen or atmosphere moisture may require encapsulation or a special type of coating which may increase the stability of the finished tablets.
- ❖ Irritant effects on the GI mucosa by some solids (e.g., aspirin).
- ❖ Possibility of bioavailability problems resulting from slow disintegration and dissolution.

2.3.3 Methods of Manufacturing (12, 13, 14, 15, 16)

Typically, solid dosage forms administered orally are an intricate blend of excipients (diluents, binders, disintegrants, glidant, lubricants and flavours) and APIs. To manufacture acceptable pharmaceutical products, these materials must be mixed and/or granulated to ensure that the resultant agglomerates or blend of all ingredients possess the required flow and compressibility, and avoid de-mixing during post granulation processes.

Currently, the techniques in existence for the agglomeration and mixing of pharmaceutical powders involve either wet or dry methods. Although dry techniques lead to associated decreases in process time and the avoidance of wetting and drying processes, the inherent difficulties in compressing crystalline solids, the uneven and erratic flow properties of APIs, and the development costs associated with dry methods, culminates in wet granulation remaining the preferred and most widely accepted method for powder agglomeration.

2.3.3.1 Wet Granulation (17, 18, 19)

Most pharmaceutical tablets are processed by wet granulation, and yet it is the most complex means of tablet processing. The popularity of wet granulation is because it can be applied to all drugs, and for many formulators it is the method of choice for drugs with a high dose and a very low dose.

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying. Granulation can be define as a size enlargement process, which converts small particles into physically stronger & larger agglomerates.

❖ **Important steps involved in the wet granulation** (20)

- Dispensing, Sifting, Mixing of the drug(s) and excipients
- Preparation of binder solution
- Mixing of binder solution with powder mixture to form wet mass.
- Coarse screening of wet mass using a suitable sieve.
- Drying of wet granules.
- Screening of dry granules through a suitable sieve.
- Mixing of screened granules with disintegrants, glidant, lubricant or any other extra granular material.

Typically, a wet granulate formulation will contains one or more diluents for bulk or to aid processing, a binder to facilitate granule growth and to aid compaction into hard tablets, a disintegrant and a lubricant. Additionally wetting agents, stabilising agents and colourants are used as required.

❖ **Ideal characteristics of granules**

The ideal characteristics of granules include uniformity, good flow, and compactibility. These are usually accomplished through creation of increased density, spherical shape, narrow particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), and incorporation of binder, if necessary. The effectiveness of granulation depends on the following properties.

- Particle size of the API and excipients.
- Type of binder (strong or weak).
- Volume of binder (less or more).
- Concentration of binder
- Granulation time (less or more).
- Amount of shear applied to distribute drug, binder and moisture content.
- Drying rate (Hydrate formation and polymorphism)

❖ Advantages of Wet Granulation

- Wet granulation improves the flow property and compression characteristics.
- It reduces the dust hazards.

- Prevent segregation of powders mix.
- Make hydrophobic surface more hydrophilic.
- Better distribution of colour and soluble drugs if added in binder solution.

❖ Disadvantages of Wet Granulation

- Major disadvantage of wet granulation is its cost.
- It is expensive process because of labour, time, equipment, energy and floor space requirement.
- Loss of material during various stages of manufacturing.
- Stability may be the concerning issues for the moisture sensitive and thermolabile actives.
- Multiple processing steps add complexity and make validation and control difficult.
- An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

Table 2.3 : Commonly used excipients in wet granulation

Function	Excipients	Typical level (approximate)
Diluents	Microcrystalline cellulose	10 – 30%
	Lactose Monohydrate	Up to 90%
	Dibasic calcium phosphate	Up to 90%
	Mannitol	Up to 90%
Binder	Pregelatinised starch	2% - 5 %
	Povidone	1% - 3%
	Hydroxypropyl cellulose	1% - 3%
	Hypromellose	1% - 3%
Disintegrant	Pregelatinised starch	5% - 20%
	Sodium Starch glycolate	2% - 6%
	Croscarmellose sodium	2% - 6 %
	Crospovidone	2% - 6 %
Lubricant	Magnesium stearate	0.5% - 1%
	Sodium Stearyl fumarate	0.5% - 1%
	Talc/stearic acid	3% - 5% / 1% - 2%
Glidant	Colloidal silicon dioxide	0.1% - 0.3%

2.3.3.2 Direct Compression (DC) (21, 22, 23)

Direct compression is viewed as the technique of choice for the manufacture of tablets containing thermolabile and moisture-sensitive drugs, and although it affords many advantages, it is still not as popular as wet granulation. One mode of tablet manufacture is that of direct compression of the active ingredient with other appropriate excipients to form a tablet, normally for medium- to high-potency compounds where the drug content is less than 30% of the formulation.

Direct compression (DC) is by far the simplest means of production of a pharmaceutical tablet. It requires only that the active ingredient is properly blended with appropriate excipients before compression. Apart from simplicity of formulation and manufacture, the key advantages of direct compression include reduced capital, labour and energy costs for manufacture and the avoidance of water for granulation for water sensitive drug substances.

The most obvious factor in determining whether DC is applicable to a certain drug substance is dose. Three key factors for successful tableting are flow and compactibility of the compression mix, and drug content uniformity in the mix and the final tablets. All of these factors are likely to be affected by drug dose. Here, low dose is taken to mean 10 mg or below, medium dose is taken to mean 10 mg to 50 mg and high dose is taken to mean above 50 mg.

For low dose drugs, flow and compaction of the compression mix are largely conferred by the excipients and the primary concern is likely to be achievement of good content uniformity in the blend and in the tablets. For medium dose drugs flow of the compression mix may become a critical factor, and for high dose drugs the flow and compaction are highly dependent on the properties of the drug substance.

❖ Advantages of Direct Compression (24, 25)

- The advantages of direct compression are well known, the most important being fewer processing stages and the elimination of heat and moisture effects.
- Shorter processing time and lower energy consumption.
- Fewer stability issues for actives that are sensitive to heat or moisture.

- For certain compounds, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation.
- Fewer excipients may be needed in a direct compression formula.

❖ Disadvantages of Direct Compression (26)

- Issues with segregation – these can be reduced by matching the particle size and density of the active drug substance with excipients
- May not be applicable for materials possessing a low bulk density because after compression the tablets produced may be too thin.
- Not suited for poorly flowing drug compounds.
- Static charges may develop on the drug particles or excipients during mixing, which may lead to agglomeration of particles producing poor mixing.

Table 2.4 : Some factors determining the applicability of direct compression tableting

Description	Low dose	Medium Dose	High Dose
Drug Dose	< 10 mg	10 – 50 mg	> 50 mg
% of 250 mg tablet	< 4%	4 – 20 %	> 20 %
Content Uniformity	Primary concern	Not likely to prove a problem	Minimal concern
Flow	Largely taken care by excipients.	Milled drugs may interfere with flow.	Highly dependent on drug properties.
Compaction	Largely taken care by excipients.	Unlikely to be a major issue.	Highly dependent on drug properties.

Direct compression formulations can be developed with minimal numbers of excipients. Typically, the minimum excipients needed are a diluent (filler-binder), a disintegrant and a lubricant. Additional components may include a glidant, a surfactant, pigments and stabilising agents. Commonly used excipients in these categories are listed in the table below. Of course some excipients are described as multifunctional.

Table 2.5 : Commonly used excipients in Direct Compression Formulation (27)

Function	Common examples
Diluents	Lactose Monohydrate, Anhydrous lactose, Microcrystalline cellulose, Pregelatinised Starch, mannitol, dibasic calcium phosphate (anhydrous & dihydrate).
Superdisintegrant	Croscarmllose sodium, Sodium starch glycolate, crospovidone, Partly Pregelatinised starch, low substituted hydroxypropyl cellulose.
Lubricant	Magnesium stearate, Calcium stearate, Sodium Stearyl fumarate, stearic acid.
Glidant	Colloidal silicon dioxide, talc
Pigments	aluminium lakes, iron oxides
Stabilisers	Buffers such as sodium carbonate and citric acid. Antioxidants such as butylated hydroxyl anisole and butylated hydroxyl toluene.
Surfactant	Sodium lauryl sulphate, polysorbates.

2.4 Introduction to Technology (28, 29, 30, 31)

2.4.1 Technology Overview

Surge Dose® formulations are designed to achieve ultra-fast activated dissolution even under unfavourable physiological conditions so that fast and consistent absorption and efficacy are independent of gastrointestinal (GI) activity and pH. Surge Dose® maximizes the impact of pH dependent drug solubility to increase the rate of absorption, and is also effective for drugs where solubility is independent of pH. Although low relative humidity (RH) and unit packaging are required, Surge Dose® tablets use conventional excipients and manufacturing processes which should not present any major regulatory challenges.

❖ **Imaginot's Surge Dose® technology provides clinical benefits for drugs with:**

- A requirement for fast and reproducible onset of action when taken 'on demand' for acute episodic indications such as pain, migraine, allergy, nausea and erectile dysfunction.
- High passive absorption without significant intestinal metabolism or active efflux.
- Evidence of variable absorption associated with gastric emptying and/or *in vivo* dissolution when comparing absorption from solutions and solid dosage forms.
- A direct temporal relationship between plasma concentrations and PD effects with no significant lag time.

Surge Dose® formulations may also provide a clinical benefit for drugs taken on a regular basis, such as in the treatment of Parkinson's disease and other chronic indications, where GI conditions and resultant absorption can be highly variable. Surge Dose® tablets provide a more convenient alternative to solutions and liquid formulations which provide faster drug absorption compared with conventional solid dosage forms. Disadvantages of liquids and solutions include stability issues, the need for extensive flavouring for acceptable taste, preservation against microbial spoilage, reduced convenience for the patient unless doses are unit packed, the need for controlled storage and higher manufacturing and packaging costs. Surge Dose® tablets also offer benefits over newer heavily promoted second generation fast acting formulations such as liquid filled soft capsules, orally disintegrating tablets (ODTs) and absorption enhanced formulations. These do not always deliver the promised rapid onset of action required for drugs taken 'on demand'.

Surge Dose® tablets are designed to act more like a solution, causing the drug to rapidly dissolve in the co-administered water and stomach contents after oral administration regardless of gastric pH and motility. This means that dissolved drug rapidly reaches the small intestine and is available for absorption. Conventional formulations are associated with variable lag times resulting from *in vivo* capsule rupture, tablet disintegration, dispersion of capsule contents and drug dissolution which typically result in slower and more variable absorption.

This report highlights the improved *in vitro* dissolution that can be achieved with Surge Dose® montelukast sodium tablets compared with Singulair® tablets and considers published data on montelukast sodium to determine if faster *in vivo* dissolution is likely to lead to improved and more consistent absorption and therapeutic outcomes.

2.4.2 Clinical premise for Surge Dose (32, 33, 34)

2.4.2.1 Physiological variability affecting drug absorption

2.4.2.1.1 Gastrointestinal (GI) motility

The underlying MMC (migrating motor complex) influences gastric emptying, contributing to the inter- and intra-subject variability seen in oral PK studies with solid dosage forms and solutions. MMC effects are significant and can mask differences between formulations and other variables particularly in fasted PK studies.

In the fasted state, subjects will be cycling through the three MMC phases which together generally last from 80 to 150 min. Phase I lasts 20 – 90 min, a quiescent period with little gastric motility; Phase II lasts 10 – 135 min, with intermittent contractions increasing in strength; Phase III (known as the housekeeper wave) is the shortest, most active phase lasting 3 – 25 min, characterised by intense contractions emptying gastric contents into the small intestine.

Independent of these MMC phases, liquids empty relatively quickly and exponentially from the stomach with a half-life in the region of 20 min during Phase I, reduced to 12 and 5 min respectively in Phase II and Phase II.

When a drug is administered to a fasted subject, they may be in any phase of the MMC. Thus, for the same formulation, a subject in Phase I will absorb the drug slower than if they were in Phase II, with the fastest absorption occurring when the subject is in Phase III. This means that even a slow dissolving product can result in fast absorption occasions as well as slow absorption occasions according to the phase of the MMC. However, the frequency of fast absorption occasions will be less for a slow dissolving product than for a fast dissolving product.

Gastric emptying effects are responsible for the double or multiple absorption peaks often seen during the first two hours in individual subject PK profiles particularly where there is frequent plasma sampling. These are well documented for a variety of different drugs and differ from later peaks due to entero-hepatic recycling.

Multiple peaks are reported for the acidic NSAID diclofenac which has low solubility at under acidic gastric conditions but higher solubility under the alkaline pH of the small intestine.

In late Phase II or Phase III, fast absorption will occur as the gastric contents are rapidly emptied into the small intestine resulting in a short T. However, in Phase early Phase II, there or I will be slower absorption with a longer T max although there will be fast absorption of any dissolved drug that drains passively from the stomach. This is followed by later absorption phase when remaining gastric contents are emptied by Phase III MMC. Gastric contents include any dissolved drug retained in the mucosal folds of the stomach as well as any tablet fragments and undissolved drug particles. The amount of dissolved drug in the initial absorption phase and the relative sizes of any multiple peaks will depend on drug solubility and the dissolution characteristics of the dosage form.

In addition to the MMC, GI motility can be influenced by other factors, and where slowing occurs, this will have an impact on gastric emptying and subsequent drug absorption. Delayed absorption and reduced variability in fed studies result from interruption of the underlying MMC by food which triggers Phase I MMC. Certain pathological conditions will reduce GI activity such as diabetes mellitus and also migraine where drug efficacy can be delayed by gut stasis. Opiates generally reduce GI activity which will slow absorption and hence slow onset of action.

Surge Dose® formulations are designed to achieve ultra-fast activated dissolution of drug in co-administered liquid and stomach contents allowing the resultant solution to drain passively from the stomach independent of MMC activity.

2.4.2.1.2 GI pH (35, 36, 37)

Although gastric contents are acidic in the fasted healthy state, there is significant variability in inter- and intra-subject gastric pH. Gastric pH typically varies between

one and seven during the course of the day in the general population depending on age, presence of food, concomitant medication and pathophysiology:

- A significant proportion of the population has low gastric acidity such as those with achlorhydria where gastric pH does not drop below pH 4, and hypochlorhydria, which affects up to 50 % of the population increasing with age or pathology such as diabetes mellitus and autoimmune conditions.
- Patients taking drugs such as antacids and proton pump inhibitors will experience relatively high gastric pH most of the time.
- Food increases gastric pH and patients using 'on demand' medication will often be in the post-prandial or partial prandial state where gastric pH will be less acidic.

Many drugs exhibit pH dependent solubility and the proportion present as the more readily absorbed unionized species will depend on the pKa of the drug. Higher solubility favours faster dissolution. Acidic drugs with a low pKa are more soluble and will dissolve faster at high pH but the proportion of the readily absorbed unionized species is lower. Basic drugs with a high pKa are more soluble and dissolve faster in acidic conditions but the proportion of readily absorbed unionized species will be lower.

When formulating for fast absorption, both solubility and degree of ionization must be considered. However, for drugs with a high permeability coefficient, the effects of increased solubility more than compensate for the ionization effects.

Consequently, gastric pH significantly affects the rate of dissolution of an orally administered drug depending on its physicochemical properties. Increased drug solubility is associated with an increased dissolution rate in any co-administered water before it empties from the stomach. Conversely, reduced solubility slows the rate of dissolution, with less dissolved drug available for absorption when emptied into the small intestine.

Hence the importance of optimizing drug formulations to ensure adequate solubility and fast dissolution under a wide range of physiological conditions.

Surge Dose® formulations are designed to maximize solubility by controlling the pH in the microenvironment of the dissolving drug particles, ensuring fast dissolution into available liquids in the stomach independent of gastric pH.

2.4.3 Clinical rationale (38)

Drug absorption following oral administration is influenced by:

- The rate at which the drug dissolves from the dosage form into available fluids in the stomach including any co-administered liquid.
- The underlying GI motility or phase of the MMC which periodically empties the stomach contents into the small intestine, and
- The rate of passive emptying of liquids, including dissolved drug, from the stomach into the small intestine, which is independent of the MMC.

Dosage forms will not change physiological conditions but strategic formulation design can improve the probability of rapid absorption by modifying the pH of the dissolution reaction and creating a mechanism for activated dissolution *in vivo*. Surge Dose® tablets achieve ultra-fast activated dissolution under the wide range of conditions occurring in the general population. This is important for drugs taken 'on demand' for immediate effect where delayed absorption often results from prevailing physiological conditions.

Where speed and consistency of *in vivo* dissolution directly impact the clinical outcome, improvement in the *in vitro* dissolution profiles relative to currently marketed formulations can offer significantly improved patient outcomes and associated compliance. Dissolved drug will reach the small intestine quickly independent of gastric motility. The higher the drug concentration, the greater will be the driving force across the intestinal mucosa for rapid absorption and high C. Total dissolution of the drug from a solid dosage form into the co-administered liquid and gastric contents provides the maximum concentration to drive absorption and distribution to effect compartments by passive diffusion resulting in faster onset of action and improved efficacy.

Conversely, slow dissolution generally leads to slow absorption associated with lower and sometimes sub-therapeutic plasma concentrations. Where there is slow

drug dissolution, gastric emptying will be the major factor in transferring drug into the small intestine where dissolution and absorption occur. This means that early absorption can occur with slow dissolving formulations on some occasions if Phase III MMC occurs soon after ingestion. There may be some initial dissolution, which results in absorption from the resultant solution, but drug concentrations will be low and absorption slow as a result of the low driving force. Such variability is evident in many PK studies reporting individual subject data and may explain the lack of efficacy demonstrated by some patients.

Surge Dose formulations are designed to maximize the rate and extent of drug dissolution *in vivo* leading to improved clinical outcomes. The following Surge Dose cascade is summarized in Figure 2.8.

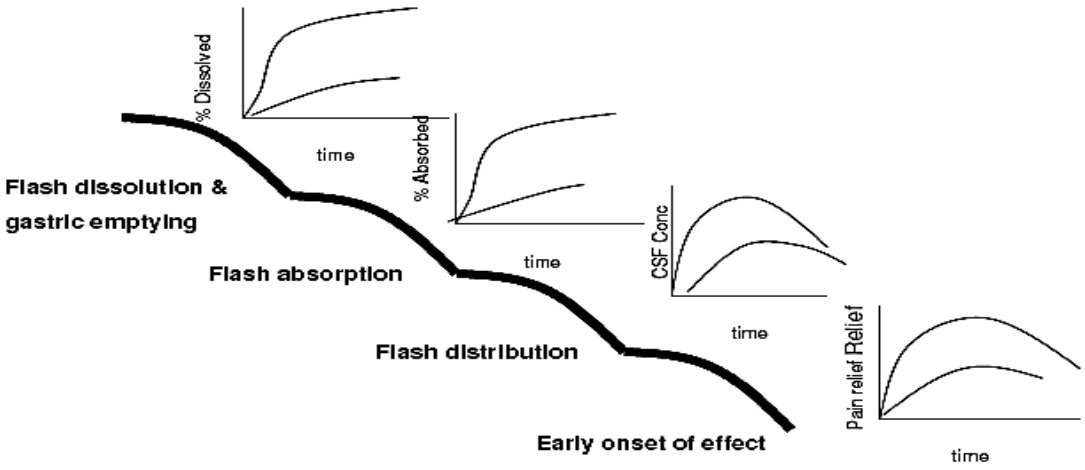

Figure 2.8 : Cascade of events in surge dose formulation

I. Drug undergoes ultra-fast activated dissolution in co-administered water and available gastric contents Dissolved drug empties rapidly and passively from the stomach in both fed and fasted states independent of the MMC, i.e. the drug empties as fast as if it had been taken as a solution.

II. The concentrated bolus of dissolved drug reaching the small intestine sets up a high concentration gradient providing high driving forces for rapid absorption.

III. Fast absorption quickly saturates any protein binding sites and saturable metabolic and transport processes achieving earlier therapeutic plasma concentrations with short Tmax, high Cmax and reduced intra- and inter-subject variability.

IV. High plasma concentrations drive rapid distribution to effect compartments resulting in rapid onset of action and rapid peak effect.

Imaginot has developed an ultra-fast activated dissolution drug delivery technology based on the use of pH modulating agents for swallow tablets. These are designed to achieve rapid pH-controlled in vitro dissolution under test conditions simulating the wide range of physiological conditions encountered in vivo among healthy fed and fasted individuals, as well as patients with impaired gastric function or on concurrent medication to reduce gastric acidity.

This technology was developed using paracetamol as a marker drug for gastric emptying and subsequently has been evaluated in vitro and in vivo with paracetamol and two NSAIDs (non-steroidal anti-inflammatory drugs), lornoxicam and diclofenac. Imaginot formulations demonstrated increased in vitro dissolution rates compared with conventional tablets and significantly faster absorption compared with leading commercial products claiming rapid dissolution and rapid action.

In the PK (pharmacokinetic) studies in fasted healthy subjects it was notable that all products showed some fast absorbing occasions and some slow absorbing occasions. However, faster absorbing occasions occurred with the Imaginot formulations even compared with a pre-dispersed diclofenac product. From a clinical perspective, the improved absorption profile of rapidly dissolving formulations will lead to earlier distribution, earlier onset of action, and more consistent achievement of therapeutic levels.

The in vitro dissolution methodologies developed by Imaginot demonstrated good IVIVC (in vitro in vivo correlation) in the paracetamol PK study in 25 healthy fasted subjects. Therefore, these methods are used to optimise tablet formulations for maximum dissolution rates that will be indicative of fast absorption in vivo. Some 20 drugs, including a combination product of paracetamol and tramadol, have now been assessed to determine the effect of Imaginot's formulation technology and methodology on dissolution rates. These drugs cover a wide range of therapeutic classes, and include acidic, basic, amphoteric and unionised molecules. This report summarises dissolution results for Imaginot formulations compared with the corresponding commercial tablets, including any with fast dissolution or fast

absorption claims. Drug concentrations were measured continuously in 900mL 0.0033 M HCl (hydrochloric acid) using USP dissolution apparatus II with paddles at 30 rpm and 37^0C with the percentage drug dissolved compared at 3 and 15 minutes. (39)

In all cases, drug dissolution rates can be increased using the Imaginot formulation approach, confirming its potential application as a platform technology with the levels and composition of the pH modulating agents and water uptake agents optimised for each drug. As demonstrated for the combination of paracetamol and tramadol, the levels of bicarbonate and acid need to be optimised, since the levels from the individual optimisations did not achieve the fastest dissolution when combined. However once the combination formulation was optimised, dissolution exceeded 90 % in 3 minutes for both actives, significantly faster than the commercial combination product.

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For acidic drugs where the solubility is low in acidic conditions, 400 - 600mg sodium bicarbonate per tablet will maximise in vitro dissolution which in some cases can be further increased by the addition of an organic acid. Typically, up to 90 % dissolution in 3 minutes was achieved, often reaching concentrations more than 100 times higher than those seen with conventional commercial products.

For basic drugs where the solubility is lower under alkaline conditions, lower levels of sodium bicarbonate per tablet were effective, with the addition of an organic acid often further increasing the dissolution rate. Typically, dissolution exceeded 80 – 90 % in 3 minutes, reaching concentrations 10 - 100 times higher than conventional commercial products. Compared with a fast absorbing commercial sumatriptan product, the Imaginot formulation showed comparable in vitro dissolution, both being faster than the conventional commercial tablet.

For unionised drugs where solubility is not pH dependent, maximum dissolution was usually achieved with a mixture of sodium bicarbonate and an organic acid. Optimised paracetamol tablet formulations containing sodium bicarbonate with fumaric acid exceeded 80 % dissolution after 3 minutes compared with those containing sodium bicarbonate alone that achieved around 70 % dissolution. These formulations demonstrated faster dissolution than those used in the paracetamol PK study which showed faster absorption in vivo than conventional tablets. It is therefore expected that the optimised paracetamol formulations reported here would result in faster absorption in vivo.

Based on these in vitro results, the IVIVC established for paracetamol, and in vivo PK data for paracetamol, lornoxicam and diclofenac, ultra-fast dissolving Imaginot formulations of other drugs are expected to show improved in vivo absorption providing their absorption is not limited by intestinal permeability. This is further supported by the correlation between the in vitro dissolution of the Imaginot sumatriptan formulation and an approved fast absorbing formulation of this drug. Hence, Imaginot's fast dissolving drug delivery technology is expected to provide faster absorption for a wide range of therapeutic agents which will be associated with faster onset of action.

2.5 Introduction to API (40, 41, 42, 43)

- **Name : PPDS_11YA**
- **Category:** Antiasthmatic (add-on therapy for mild to moderate asthma)

2.5.1 Physicochemical Properties:

- **BCS Class : Class I (High Solubility, High Permeability)**
- **Appearance:** A white to pale yellow hygroscopic and optically active powder.
- **Solubility:** Soluble in organic solvents such as ethanol, methanol, DMSO, Sparingly soluble in aqueous buffer. Insoluble in acetonitrile.
- **Melting Point:** 76-81^{0}C
- **Partition co-efficient:** LogP: 7.9
- **Dissociation constant:** pKa: 5.7

- **Storage:** Protected from light and moisture, at a temperature not exceeding 30°C.

2.5.2 Mechanism of Action:

The Leukotriene's (LTs) are lipoxygenase products formed from the metabolism of arachidonic acid (AA), an essential fatty acid found in the membrane of all cells. The LTs are synthesized by the action of key enzyme 5-lipoxygenase on AA in the presence of 5-lipoxygenase-activating protein (FLAP). The biosynthesis of the LTs proceeds as a result of the sequential catalytic actions on AA, forming leukotriene A4 (LTA4), leukotriene B4 (LTB4), leukotriene C4 (LTC4), leukotriene D4 (LTD4), and leukotriene E4 (LTE4). Because LTC4, LTD4 and LTE4 all contain the amino acid cysteine, they are collectively referred to as the cysteinyl leukotriene.

The non-cysteinyl LT, LTB4, binds to the B leukotriene (BLT) receptor, which is responsible for recruitment and activation of leukocytes, in particular neutrophils. Leukotriene B4 does not appear to exert biological effects associated with asthma and acts more as a chemotactic agent. On the other hand, the cysteinyl LTs, LTC4, LTD4 and LTE4, are potent recruiters for eosinophil in vivo and in vitro and have been correlated with the pathophysiology of asthma and allergic rhinitis.

In asthma, leukotriene-mediated effects include airway oedema, smooth muscle contraction and altered cellular activity associated with the inflammatory process, In allergic rhinitis, CysLTs are released from the nasal mucosa after allergic exposure during both early and late phase reactions and are associated with symptoms of allergic rhinitis.

The CysLTs exert their biologic actions by binding to two CysLT receptors, CysLT1 and CysLT2. However, most of the actions of the CysLTs relevant to asthma are mediated through CysLT1 receptor stimulation, which is stimulated mostly by LTC4 and LTD4. The CysLT1 receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophil and certain myeloid stem cells).

PPDS_11YA binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic or beta-adrenergic receptor) and inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.

2.5.3 Pharmacokinetic Parameters:

- **Oral Bioavailability:** 64%
- **Protein Binding:** 99%
- **Metabolism:** Extensively metabolised by CYP450-3A4 and 2C9. Plasma concentration of metabolites are undetectable at steady state.
- **Volume of distribution:** 8 – 11 litres/kg
- **Elimination half Life:** 2.7 to 5.5 hours.
- **Drug- Drug interaction:** Phenytoin, rifampicin, tolbutamide and carbamazepine, decrease the plasma concentration of API.
- **Adverse effect:** Headache, abdominal or stomach pain, cough, dental pain, dizziness, fever, heartburn, skin rash, stuffy nose, weakness or unusual tiredness.

Table 2.6 : List of Marketed Formulation

Route	Dosage Form	Strength
Oral	Film Coated tablets	10 mg
	Chewable Tablet	4 mg
		5 mg
	Oral Granules Sachets	4 mg

2.6 Introduction to Excipients (44)

The quality of medicines depends on not only the active principles and production processes, but also the performance of the excipients. The traditional concept of the excipient as any component other than the active substance has undergone a substantial evolution from an `inert' and cheap vehicle to an essential constituent of the formulation. The rapid evolution of scientific, regulatory and economic factors, the introduction of delivery systems and the advance in biopharmaceutics have led to a new interest in the role and functionality of the excipients.

More than one thousand raw materials are available from a multitude of sources and are used today in the pharmaceutical industry. Their chemical structures vary

from small molecules to complex natural or synthetic polymeric mixtures. Excipients are now chosen to perform a variety of functions to guarantee the stability and bioavailability of the drug substance from the drug product and its manufacturability on a production scale.

Beyond the dosage form necessities, excipients are required to perform important and specific technological functions, particularly in the case of solid dosage forms. As a consequence, their characterisation must go beyond the simple tests for identity, purity and strength as prescribed in general by the Pharmacopoeia monographs. With the exception of the Textbook of Pharmaceutical Excipients, not many reference sources describing the physical mechanical characteristics of the powders for a specific role are available. Full physical characterisation of solid materials is now made possible with the help of high resolution analytical techniques on the molecular, particulate and bulk levels.

This systematic approach is necessary to guarantee the behaviour of the excipient during the formulation and production phases. Three main approaches are followed by the industry: physical or minor chemical manipulation of materials already known, combination of two or more marketed excipients in order to reduce unwanted defects and, finally, preparation of new chemical entities with huge investments for the toxicity studies. Excipient harmonisation, standardised functionality tests, preformulation data bases and expert systems will contribute to change the conventional trial-and-error formulation approach into a far more scientific and technological development.

- **Characteristics of an ideal excipient**

- Pharmacologically and toxicologically inactive.
- Chemically and physically inert vs. the drug.
- Compatible with other formulation ingredients.
- Colourless and tasteless.
- High fluidity or flow ability.
- High compressibility.

- ❖ Available worldwide from many sources and inexpensive.
- ❖ Well characterised by suppliers.
- ❖ Easy to store.
- ❖ Lot-to-lot reproducible.
- ❖ Performance consistent with the specific dosage form.

2.6.1 pH Modulating agents

A "pH modulating agent" includes one or more than one pH modulating agents, which alter the pH of an aqueous solution. These may include acids, bases or a combination of one or more and/ or bases.

The carbonate may be any pharmaceutically acceptable carbonate or a mixture thereof. Reference to a "carbonate" includes a single agent or multiple (ie. two or more) agents. Preferred carbonates include but are not limited to sodium carbonate, sodium bicarbonate, calcium carbonate, magnesium carbonate, ammonium carbonate, ammonium bicarbonate, potassium bicarbonate, sodium glycine carbonate, disodium glycine carbonate, arginine carbonate, lysine carbonate and/or other pharmaceutically acceptable carbonates or homologs or functional equivalents thereof and combinations thereof.

Other pH modulating agents may be pharmaceutically acceptable acids or acidic salts including citric acid, tartaric acid, succinic acid, ascorbic acid, malic acid, fumaric acid, metatartaric acid, adipic acid, sodium acid citrate, potassium acid citrate, glycine citrate, potassium acid tartrate, sodium acid tartrate, aspartic acid, glutamic acid, glycine, leucine, tyrosine, tryptophan, glycine fumarate, glycine hydrochloride, monophosphate glycine and combinations thereof.

2.6.1.1 Sodium Bicarbonate

- **Non-proprietary Names:**

BP: Sodium Bicarbonate

JP: Sodium Bicarbonate

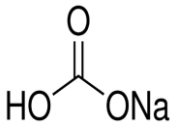
PhEur: Sodium Hydrogen Carbonate

USP: Sodium Bicarbonate

- **Synonyms:**

Baking soda; E500; Effer-Soda; monosodium carbonate; natrii hydrogeno carbonas; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

- **Chemical Name**: Carbonic acid monosodium salt
- **Empirical Formula:** $NaHCO_3$
- **Structural Formula**:



- **Molecular Weight:** 84.01
- **Description:**

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available.

- **Functional Category:**

Alkalizing agent,

Therapeutic agent.

- **Applications in Pharmaceutical Formulation or Technology**

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation. In effervescent tablets and granules, sodium bicarbonate is usually formulated with citric and/or tartaric acid; combinations of citric and tartaric acid are often preferred in formulations as citric acid alone produces a sticky mixture that is difficult to granulate, while if tartaric acid is used alone, granules lose firmness. When the tablets or granules come into contact with water, a chemical reaction occurs, carbon dioxide is evolved, and the product

disintegrates. Melt granulation in a fluidized bed dryer has been suggested as a one-step method for the manufacture of effervescent granules composed of anhydrous citric acid and sodium bicarbonate, for subsequent compression into tablets.

Tablets may also be prepared with sodium bicarbonate alone since the acid of gastric fluid is sufficient to cause effervescence and disintegration. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation.

The effects of tablet binders, such as polyethylene glycols, microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, and povidone, on the physical and mechanical properties of sodium bicarbonate tablets have also been investigated. Additionally, sodium bicarbonate is used in solutions as a buffering agent for erythromycin, lidocaine, local anesthetic solutions, and total parenteral nutrition (TPN) solutions. In some parenteral formulations, e.g. niacin, sodium bicarbonate is used to produce a sodium salt of the active ingredient that has enhanced solubility. Sodium bicarbonate has also been used as a freeze-drying stabilizer and in toothpastes.

Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raft systems and in floating, controlled release oral dosage forms for a range of drugs. Tablet formulations containing sodium bicarbonate have been shown to increase the absorption of paracetamol, and improve the stability of levothyroxine. Sodium bicarbonate has also been included in formulations of vaginal bio adhesive tablets and in carbon dioxide releasing suppositories.

Therapeutically, sodium bicarbonate may be used as an antacid, and as a source of the bicarbonate anion in the treatment of metabolic acidosis. Sodium bicarbonate may also be used as a component of oral rehydration salts and as a source of bicarbonate in dialysis fluids; it has also been suggested as a means of preventing radiocontrast-induced nephrotoxicity. Sodium bicarbonate is used in food products as an alkali or as a leavening agent, e.g. baking soda.

- **Incompatibilities:**

Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of

salicylates. In powder mixtures, atmospheric moisture or water of crystallization from another ingredient is sufficient for sodium bicarbonate to react with compounds such as boric acid or alum. In liquid mixtures containing bismuth sub nitrate, sodium bicarbonate reacts with the acid formed by hydrolysis of the bismuth salt. In solution, sodium bicarbonate has been reported to be incompatible with many drug substances such as ciprofloxacin, amiodarone, nicardipine, and levofloxacin.

- **Handling Precautions:**

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

- **Regulatory Status**:

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (injections; ophthalmic preparations; oral capsules, solutions, and tablets). Included in parenteral (intravenous infusions and injections) and nonparenteral medicines (chewing gums; ear drops; eye lotions; oral capsules, chewable tablets, effervescent powders, effervescent tablets, granules, soluble tablets, orodispersible tablets, and tablets; suppositories and suspensions) licensed in the UK.

2.6.1.2 Citric Acid

- **Non-proprietary Names**

BP: Citric Acid Monohydrate

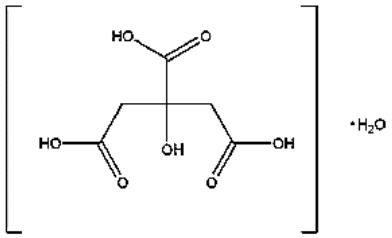
JP: Citric Acid Hydrate

PhEur: Citric Acid Monohydrate

USP: Citric Acid Monohydrate

- **Synonyms:** Acidum citricum monohydricum; E330; 2-hydroxypropane-1,2,3-tricarboxylic acid monohydrate.
- **Chemical Name**: 2-Hydroxy-1,2,3-propanetricarboxylic acid monohydrate.
- **Empirical Formula**: $C_6H_8O_7.H_2O$

- **Structural Formula**:



- **Molecular Weight:** 210.14

- **Description**:

Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odourless and has a strong acidic taste..

- **Functional Category**:

Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer; preservative.

- **Applications in Pharmaceutical Formulation or Technology:**

Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions.

It has also been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery. Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets. Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalation formulations.

In food products, citric acid is used as a flavor enhancer for its tart, acidic taste. Citric acid monohydrate is used as a sequestering agent and antioxidant synergist; see Table I. It is also a component of anticoagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal calculi.

- **Incompatibilities**:

Citric acid is incompatible with potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, and sulfides. Incompatibilities also include oxidizing agents, bases, reducing agents, and nitrates. It is potentially explosive in

combination with metal nitrates. On storage, sucrose may crystallize from syrups in the presence of citric acid.

- **Handling Precautions:**

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Direct contact with eyes can cause serious damage. Citric acid should be handled in a well-ventilated environment or a dust mask should be worn. It is combustible.

- **Regulatory Status:**

GRAS listed. The anhydrous form is accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations; IM, IV, and other injections; ophthalmic preparations; oral capsules, solutions, suspensions and tablets; topical and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in Japan and the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

2.6.2 Water Uptaking Agents

A "Water uptake agent" is any agent, which will facilitate the uptake of water by absorbing, dissolving in or wicking water, used alone or in combination. These may include wicking agents, disintegrants, binders, carriers and other hydrophilic excipients. Generally, but not exclusively, a "Water uptake agent" facilitates uptake of water into the swallow formulation.

Suitable Water uptake agents include cross-linked polyvinylpyrrolidone (crospovidone), Croscarmellose sodium, sodium starch glycolate, starch, starch derivatives, hydroxypropylcellulose, low substituted hydroxypropylcellulose, hydroxyl propyl methylcellulose, alginic acid, sodium alginate, calcium sulphate, calcium carboxy methyl cellulose, microcrystalline cellulose, powdered cellulose, colloidal silicon dioxide, docusate sodium, guar gum, magnesium aluminium silicate, methylcellulose, polacrilin potassium, silicified microcrystalline cellulose, magnesium oxide, tragacanth, mannitol, sorbitol, xylitol, sucrose, lactose, fructose, maltose, polyethylene glycol, amino acids, cyclodextrin, urea and/or polyvinylpyrrolidone (povidone, PVP).

The Water uptake agent may be present in an amount from 5% to 95% by weight of the swallow formulation and more preferably between 10% and 90% by weight of the swallow formulation.

2.6.2.1 Diluents

2.6.2.1.1 Lactose Monohydrate

- **Non-proprietary Names**:

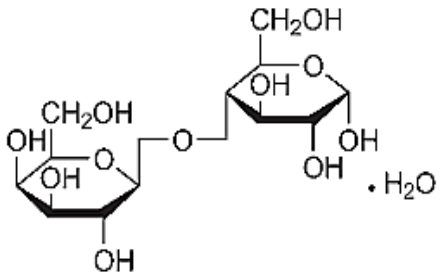
BP: Lactose

PhEur: Lactose Monohydrate

JP: Lactose Hydrate

USP-NF: Lactose Monohydrate

- **Synonyms**: CapsuLac; GranuLac; Lactochem; lactosum monohydricum; Monohydrate; Pharmatose; PrismaLac; SacheLac; SorboLac; SpheroLac; SuperTab 30GR; Tablettose.
- **Chemical Name:** O-β-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate.
- **Empirical Formula:** $C_{12}H_{22}O_{11}.H_2O$
- **Structural Formula:**



- **Molecular Weight**: 360.31
- **Description**

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. The stable crystalline forms of lactose are α-lactose monohydrate, β-lactose anhydrous, and stable α-lactose anhydrous. Lactose

occurs as white to off-white crystalline particles or powder. Lactose is odourless and slightly sweet tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

- **Functional Category**: Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

- **Applications in Pharmaceutical Formulation or Technology**:

Lactose is widely used as a filler and diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry powder inhalation; Inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used.

Usually, fine grades of lactose are used in the preparation of tablets by the wet granulation method or when milling during processing is carried out, since the fine size allows better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions. It may also be used in intravenous injections. Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions.

Direct-compression grades of lactose monohydrate are available as granulated/agglomerated a-lactose monohydrate, containing small amounts of anhydrous lactose. Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation. Other directly compressible lactoses are spray-dried lactose and anhydrous lactose; see Lactose, Spray-Dried and Lactose, Anhydrous.

- **Incompatibilities**:

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. The Maillard interaction has also been shown to occur between lactose and secondary amine. However, the reaction sequence stops with the formation of the imine, and no yellow-brown coloration develops. Lactose is also incompatible with amino acids, amphetamines, and lisinopril.

- **Handling Precautions**:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive generation of dust, or inhalation of dust, should be avoided.

- **Regulatory Status**:

GRAS listed. Included in the FDA Inactive Ingredients Database (IM, IV, and SC: powder for injections; oral: capsules and tablets; inhalation preparations; vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

2.6.2.1.2 Microcrystalline cellulose

- **Non-proprietary Name**:

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

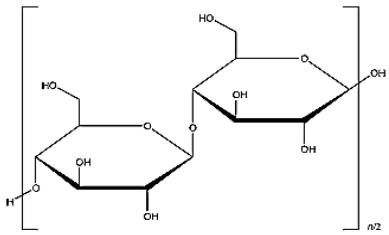
USP-NF: Microcrystalline Cellulose

- **Synonyms**: Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.
- **Chemical Name**: Cellulose
- **Empirical Formula**: $(C_6H_{10}O_5)_n$ where n= 220

- **Description**:

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

- **Molecular Weight**: 36,000
- **Functional Category**: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.
- **Structural Formula**:



- **Applications in Pharmaceutical Formulation or Technology**:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

- **Incompatibilities**:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

- **Handling Precaution**:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the workplace exposure limits for cellulose have been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m^3.

- **Regulatory Status**:

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Nonmedicinal Ingredients.

2.6.2.2 Super disintegrant

2.6.2.2.1 Croscarmellose Sodium

- **Non-proprietary Name**:

BP: Croscarmellose Sodium

JP: Croscarmellose Sodium

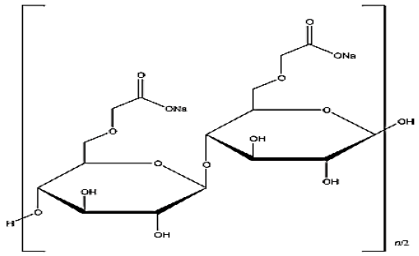
PhEur: Croscarmellose Sodium

USP-NF: Croscarmellose Sodium

- **Synonyms**:

Ac-Di-Sol; carmellosum natricum conexum; cross-linked carboxy methyl cellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

- **Chemical Name**: Cellulose, carboxy methyl ether, sodium salt, cross-linked
- **Empirical Formula**: The USP 32 describes carboxy methyl cellulose sodium as the sodium salt of a poly carboxy methyl ether of cellulose.
- **Structural Formula**:



- **Description**: Croscarmellose sodium occurs as an odourless, white or grayish white powder.

- **Functional Category**: Tablet and capsule disintegrant.

- **Applications in Pharmaceutical Formulation or Technology**:

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

- **Incompatibilities**:

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminium, mercury, and zinc.

- **Handling Precaution**:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Croscarmellose sodium may be irritant to the eyes; eye protection is recommended.

- **Regulatory Status**:

Included in the FDA Inactive Ingredients Database (oral capsules, granules, sublingual tablets, and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

2.6.2.2.2 Crospovidone

- **Non-proprietary Name**:

BP: Crospovidone

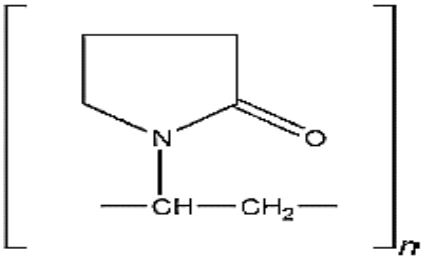
PhEur: Crospovidone

USP-NF: Crospovidone

- **Synonyms**:

Crospovidonum; Crospopharm; cross linked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinyl poly pyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

- **Chemical Name**: 1-Ethenyl-2-pyrrolidinone homopolymer
- **Empirical Formula**: $(C_6H_9NO)_n$
- **Structural Formula**:



- **Molecular Weight**: > 10,00,000
- **Description**: Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.
- **Functional Category**: Tablet Disintegrant
- **Applications in Pharmaceutical Formulation or Technology**:

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

- **Incompatibilities**:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some material.

- **Handling Precaution**:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

- **Regulatory Status**:

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IM injections, oral capsules and tablets; topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

2.6.2.3 Binder

2.6.2.3.1 Starch

- **Non-proprietary Name**:

BP: Maize starch, Potato starch, Rice Starch, Tapioca Starch, Wheat Starch,

JP: Corn Starch, Potato Starch, Rice Starch, Wheat Starch,

PhEur: Maize Starch, Pea Starch, Potato Starch, Rice Starch, Wheat Starch

USP-NF: Corn Starch, Potato Starch, Tapioca Starch, Wheat Starch

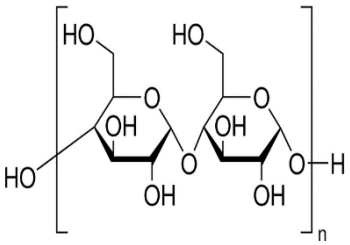
- **Synonyms**:

Amido; amidon; amilo; amylum; C*PharmGel; Eurylon; fecule; Hylon; maydis amylum; Melojel; Meritena; oryzae amylum; Pearl; Perfectamyl; pisi amylum; Pure-Dent; Purity 21; Purity 826; solani amylum; tritici amylum; Uni-Pure.

- **Chemical Name**: Starch

- **Empirical Formula**: $(C_6H_{10}O_5)_n$ Where n = 300 – 1000.

- **Structural Formula**:



- **Molecular Weight**: Range between 50 and 500 million Da.

- **Description**:

Starch occurs as an odourless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

- **Functional Category**:

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder; thickening agent.

- **Applications in Pharmaceutical Formulation or Technology**:

Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix, and to improve powder flow, especially when using dried starches. Starch quantities of 3–10% w/w can act as an anti-adherent and lubricant in tableting and capsule filling.

In tablet formulations, freshly prepared starch paste is used at a concentration of 3 to 20% w/w (usually 5–10%, depending on the starch type) as a binder for wet granulation. The required binder ratio should be determined by optimization studies, using parameters such as tablet friability and hardness, disintegration time, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25% w/w; a typical concentration is 15%. When using starch, a prior granulation

step is required in most cases to avoid problems with insufficient flow and segregation. A starch–lactose compound has been introduced enabling the use of granular starch in direct compression, improving the tableting process and the disintegration time of the tablets. However, starch that is not Pregelatinised does not compress well and tends to increase tablet friability and capping if used in high concentrations. Balancing the elastic properties of starch with adapted excipients has been shown to improve the compaction properties in tableting.

Starch, particularly the fine powders of rice and wheat starch, is also used in topical preparations for its absorbency of liquids. Starch paste is used in ointment formulations, usually in the presence of higher ratios of glycerine. Starch has been investigated as an excipient in novel drug delivery systems for nasal, and other site-specific delivery systems. The retrogradation of starch can be used to modify the surface properties of drug particles. Starches are useful carriers for amorphous drug preparations, such as pellets with immediate or delayed drug release obtained, for example, by melt extrusion, and they can improve the bioavailability of poorly soluble drugs.

Starch, particularly rice starch, has also been used in the treatment of children's diarrheal diseases. Specific starch varieties with a high amylose content (resistant starches) are used as insoluble fibre in clinical nutrition, and also for colon-targeting applications. Due to their very high gelatinization temperature, these starches are used in extrusion/spheronization processes. Starches with a high amylopectin content (waxy starches) are used as the starting material for the synthesis of hydroxyethyl starch, a plasma volume expander.

Native starches conforming to Pharmacopoeial specifications are used as the raw materials for the production of starch-based excipients and active pharmaceutical ingredients, frequently covered with their own Pharmacopoeial monographs.

- **Incompatibilities**:

Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.

- **Handling Precaution**:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosion. The minimal explosive concentration of corn starch is 30–60 g/m^3 air. In the UK, the long-term (8-hour TWA) workplace exposure limits for starch are 10 mg/m^3 for respirable dust. for total inhalable dust and 4 mg/m^3.

- **Regulatory Status**:

GRAS listed. Included in the FDA Inactive Ingredients Database (buccal tablets, oral capsules, powders, suspensions and tablets; topical preparations; and vaginal tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

2.6.2.3.2 Hydroxypropyl Cellulose

- **Non-proprietary Name**:

BP: Hydroxypropylcellulose

JP: Hydroxypropylcellulose

PhEur: Hydroxypropylcellulose

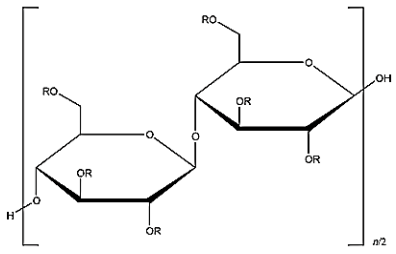
USP-NF: Hydroxypropyl Cellulose

- **Synonyms**:

Cellulose, hydroxypropyl ether; E463; hydroxypropylcellulosum; hyprolose; Klucel; Nisso HPC; oxypropylated cellulose.

- **Chemical Name**: Cellulose, 2-hydroxypropyl ether

- **Structural Formula**:



- **Molecular Weight**: 50,000 to 12,50,000

- **Description**:

Hydroxypropyl cellulose is a white to slightly yellow-colored, odourless and tasteless powder.

- **Functional Category**:

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

- **Applications in Pharmaceutical Formulation or Technology**:

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations. In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film coating, and extended-release-matrix former. Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct compression tableting processes.

Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release. The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Blends of hydroxypropyl cellulose and other cellulosic polymers have been used to improve wet granulation characteristics and tableting characteristics, as well as to achieve better control and manipulation of the rate of drug release. As an alternative technology to wet granulation, dry granulation and direct compression of hydroxypropyl cellulose formulations have been reported to exhibit acceptable tableting and flow characteristics for application in extended-release matrix tablets. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose together with an amount of methyl cellulose or ethanolic solutions have been used. Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. Environmental concerns have limited the use of ethanol in film coating solutions. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations. Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

- **Incompatibilities**:

Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions.

The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration. Hydroxypropyl cellulose may not tolerate high concentrations of other dissolved materials. The balance of the hydrophilic–lipophilic properties of the polymer, which are required for dual solubility, reduces its ability to hydrate with water and it therefore tends to be salted out in the presence of high concentrations of other dissolved materials. The precipitation temperature of hydroxypropyl cellulose is lower in the presence of relatively high concentrations of other dissolved materials that compete for the water in the system.

- **Handling Precaution**:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl cellulose dust may be irritant to the eyes; eye protection is recommended. Excessive dust generation should be avoided to minimize the risk of explosions.

- **Regulatory Status**:

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral capsules and tablets; topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

2.6.2.4 Lubricant

2.6.2.4.1 Magnesium Stearate

- **Non-proprietary Name**:

BP: Magnesium Stearate

JP: Magnesium Stearate

PhEur: Magnesium Stearate

USP-NF: Magnesium Stearate

- **Synonyms**:

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

- **Chemical Name**: Octadecanoic acid magnesium salt
- **Empirical Formula**: $C_{36}H_{70}MgO_4$
- **Molecular Weight**: 591.24
- **Description**:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

- **Functional Category**: Tablet and Capsule Lubricant
- **Applications in Pharmaceutical Formulation or Technology**:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

- **Incompatibilities**:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

- **Handling Precaution**:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended. In the USA, the OSHA limit is 10 mg/m^3.

- **Regulatory Status**:

GRAS listed. Accepted as a food additive in the USA and UK. Included in the FDA Inactive Ingredients Database (oral capsules, powders, and tablets; buccal and vaginal tablets; topical preparations; intravitreal implants and injections). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients. Listed on the US TSCA inventory.

Chapter: 3

Review Of Literature

"That is good to study, which is opened with expectation & close with delight"

3. Literature Review (45, 46, 47, 48, 49)

3.1 Literature Review for Technology

3.1.1 Patents search

- **Roberts et al.**: Patent no. US 2005/0276847 A1, publication Date: Dec. 15, 2005. The present invention relates generally to formulations comprising paracetamol. More particularly, the present invention provides a swallow formulation comprising paracetamol which facilitates the rapid delivery of paracetamol into the circulatory system following oral administration. The present invention further relates to methods for inducing efficient pain relief including an analgesic effect by the administration of the paracetamol formulation.

- **Roberts et al.**: Patent no. US 2013/0065885 A1, publication Date: MAR. 14, 2013. The present 1nvent10n relates generally to therapeutic formulations. More particularly, this present invention provides an oral delivery system for a therapeutic compound that is a base, a salt of a base or an amphoteric compound or a salt of a amphoteric compound with pharmacological, physiological or biochemical activity or a proactive form thereof. The present invention even more particularly provides a swallow formulation comprising a therapeutic compound that is a base, a salt of a base, an amphoteric compound or a salt of an amphoteric compound which facilitates the rapid delivery of the therapeutic compound to the circulatory system.

- **Roberts et al.**: Patent no. US 2009/0311327 A1, publication Date: DEC. 17, 2009. The present, invention provides an oral delivery system for a therapeutic compound that is an acid, a salt of an acid or an unionized compound or a proactive form thereof with pharmacological, physiological or biochemical activity. The present invention particularly provides a swallow formulation comprising a therapeutic compound that is an acid, a salt of an acid or an unionized compound or a proactive form thereof which facilitates the rapid delivery of the therapeutic compound to the circulatory system.

3.2 Literature for excipients

- **Na Zhao et al:** (50)

Compared the disintegration efficiency, and developed a discriminating test model for the three classes of super disintegrants represented by Acdisol, Primojel, and Polyplasdone XL10. Using a digital video camera to examine the disintegration process of tablets containing the same wt/wt percentage concentration of the disintegrants, Acdisol was found to disintegrate tablets rapidly into apparently primary particles; Primojel also apparently disintegrated tablets into primary particles but more slowly; Polyplasdone XL10 disintegrated tablets rapidly but into larger masses of aggregated particles. The differences in the size distribution generated in the disintegrated tablets likely contribute to the drug dissolution rate differences found for aspirin tablets with similar disintegration rates. The aspirin tablet matrix is proposed as a model formulation for disintegrant efficiency comparison and performance consistency testing for quality control purposes.

- **Kulkarni et al,:** (51)

Formulated and evaluated the fast dissolving tablet of Rofecoxib using wet granulation process. The preparation of fast dissolving tablet using various super disintegrant L-HPC, SSG, croscarmellose sodium, crospovidone. Various evaluation parameters such as hardness, thickness, disintegration time and Invitro dissolution study was carried out. Effect of different disintegrant on the tablet formulation was studied.

- **Ito et al:** (52)

Developed rapidly disintegrating tablet using agar powder and treated agar powder. When compression force was changed from 0.4 to 2 ton/cm^2, the disintegration time increased from 60 seconds to 160 seconds, and hardness of the tablet increased significantly from 3 to 13 N. Finally, the conclusion was drawn that as the compression force was increased there was significant increase in the disintegration time and hardness of the tablets.

- **Swamy et al:** (53)

Designed orodispersible tablet of pheneramine maleate to enhance patient compliance using effervescent technique. In this method, mixture of sodium bicarbonate and tartaric acid each 12 % were used along with the Superdisintegrant i.e. sodium starch glycolate, croscarmellose sodium and crospovidone. The prepared tablets were evaluated for hardness, friability, content uniformity, in vitro dispersion time. Based on in vitro dispersion time three formulation were tested for Invitro drug release pattern in phosphate buffer pH 6.8. stability study at 40^0C/75% RH for 3 month was carried out. Results shows that batch containing 4 % w/w crospovidone with mixture of sodium bicarbonate and citric acid at 12 % shows good in vitro drug release profile.

- **Sameer et al:** (54)

Studies were carried out to check the effect of calcium silicate (disintegration promoting agent) and various lubricants on an optimised cyclodextrin based fast dissolving tablet formulation. Effect of moisture treatment was also studied at 75, 85 and 95 % relative humidity. A two factor three level (3^2) full factorial design was used to optimise the level of calcium silicate and lubricant. Magnesium stearate , being commonly used lubricant was used in optimisation study. Desiccator with saturated salt solution was used to analyse the effect of moisture treatment. Results of multiple regression analysis revealed that the concentration of calcium silicate has no significant effect. However, concentration of lubricant has significant effect on the disintegration and Invitro drug release profile.

- **Gohel et al:** (55)

Developed and evaluated the mouth dissolving tablet if nimesulide using vacuum drying technique. The preliminary trial were conducted using 2% super disintegrant (croscarmellose sodium, Sodium starch glycolate and crospovidone) intragranularly and 2% extra granularly. Camphor was used as a sublimating agent. Tablets were prepared by wet granulation technique. Camphor was sublimed from dry granules by exposure to vacuum. The porous granules were compressed into tablets and evaluated. A 3^2 full factorial design was employed to study the joint effect of amount of disintegrant and camphor. The results of multiple regression analysis revealed that

for obtaining rapid disintegrating dosage form, tablet should be prepared using optimum concentration of camphor and super disintegrant.

3.3 Literature Review for pH modulating agent

- **Sherif I. et al** (56)

Micro environmental pH has a significant impact on stability of compounds which demonstrate pH dependent stability in solution. Degradation kinetics of such compounds, and in some cases degradation profile as well, are dependent on the micro environmental pH of the solid. Modulation of the micro environmental pH through the use of pH modifiers can hence prove to be a very effective tool in maximizing solid dosage form stability. Micro environmental pH modulation was also shown to control the dissolution profile of both immediate and controlled release dosage forms of compounds with pH dependent solubility. The pH modifiers have been used in conjunction with high energy or salt forms in immediate release formulations to minimize the precipitation of the less soluble free form during initial dissolution.

- **Pallavi Bassi:** (57)

For overcoming pH-dependent behaviour of drugs, pH-modifying excipients (which alter the microenvironment pH inside the formulation) are most commonly used. A combination of enteric and sustained release polymers can be used for weakly basic drugs. Other strategies include conversion of crystalline drug to amorphous form, enhancement of partitioning of unionized fraction of drug from the formulation, and using a combination of pH modifier and enteric polymer, micellar solubilisation and inclusion complexation.

- **Kilian Kelly et al.:** (58)

Investigated the hypothesis that faster drug absorption from a new paracetamol formulation containing sodium bicarbonate compared to that from a conventional formulation results from a combination of enhanced gastric emptying and disintegration/dissolution.

3.4 Literature Review on In vitro dissolution study

- **Arthur Okumu et al.:** (59)

Developed a dissolution test method that can be used to predict the oral absorption of montelukast sodium, and to establish an in vitro/in vivo correlation (IVIVC) using computer simulations. Drug solubility was measured in different media. The dissolution behaviour of montelukast sodium 10 mg film coated tablets was studied using the flow-through cell dissolution method following a dynamic pH change protocol, as well as in the USP Apparatus II, buffers was used as the dissolution media, as well as the USP simulated intestinal fluid (SIF) pH 6.8 and blank FaSSIF pH 6.5 were used under a constant pH condition, while the pH range used in the flow through cells was pH 2.0 to 7.5. The in vitro data were used as input functions into GastroPlus™ to simulate the in vivo profiles of the drug. The solubility of montelukast sodium was low at low pH, but increased as the pH was increased. There was no significant difference in solubility in the pH range of 5.0 to 7.5 in blank buffers, but the drug solubility was higher in biorelevant media compared with the corresponding blank buffers at the same pH. Using the flow through cells, the dissolution rate was fast in simulated gastric fluid containing 0.1% SLS. The dissolution rate slowed down when the medium was changed to FaSSIF pH 6.5 and increased when the medium was changed to FaSSIF medium at pH 7.5. In the USP Apparatus 2, better dissolution was observed in FaSSIF compared with the USP buffers and blank FaSSIF with similar pH values. Dissolution was incomplete with less than 10% of the drug dissolved in the USP-SIF, and was practically non existent in blank FaSSIF pH 6.5. The in vitro results of the dynamic dissolution test were able to predict the clinical data from a bioavailability study best.

- **E. Galia et al.:** (60)

Dissolution behaviour of two class I drugs, i.e., acetaminophen and metoprolol, and of three class II drugs, i.e. danazol, mefenamic acid and ketoconazole, was studied with USP Apparatus 2 in water, SGF, milk, Simulated Intestinal Fluid without pancreatine (SIF) and in two media simulating the small intestinal contents in the fed (FeSSIF) and fasted (FaSSIF) states, respectively.

- **Sunil S. et al** (61)

Oral bioavailability of a drug is determined by a number of properties, including drug dissolution rate, solubility, intestinal permeability and pre-systemic metabolism. Frequently, the rate limiting step in drug absorption from the gastrointestinal tract is drug release and drug dissolution from the dosage form. Therapeutic agents with aqueous solubility less than 100 mg/ml often present dissolution limitations to absorption. Physicochemical, formulation-related and physiological factors can all influence drug dissolution. The important physicochemical properties of a drug and physiological conditions in the gastrointestinal tract that play an important part in drug dissolution and absorption processes and, consequently, the bioavailability of a drug.

Chapter: 4

Experimental Work

"Art & Science have their meeting point in methods"

4. Experimental Work

4.1 Apparatus and Instrumentation

Table 4.1: List of Equipments

Equipment	Company Name
Electronic Weighing Balance	Mettler Toledo, Mumbai, India
Moisture analyzer	Mettler Toledo HG63 Halogen, Mumbai, India
Sieve Shaker	Retsch GmbH, Germany
Roche Friabilator	Labindia FT020,Thane, India
Tap density tester	Labindia TD1025, Thane, India
USP dissolution apparatus	Labindia, Thane, India
Tablet Compression machine	Korsch, Silverwater, Australia.
UV Spectrophotometer	Shimadzu 1800, Shanghai, China.
Ultrasonicator bath	EIE Instruments Pvt ltd (India)
Disintegration apparatus USP	Labindia DT1000, Thane, India
Hardness Tester	Dr. Schleuniger Pharmatron 8M, Switzerland
Turbula Blender	WAB (Willy A.Bachofen AG Maschinenfabrik), Mahopac, New York.
16 station punching machine	Cadmach CMD4 (D tooling), Ahmedabad, India
Segregation tester	Jenike & Johanson INC, USA
Ring Shear Tester	Dr. Dietmar Schulze Wolfenbuttel, Germany
Flowdex	Retsch GmbH, Germany
Quadro Co-mill	Quadro Engineering, Waterloo, Canada

4.2 Materials and Reagents

Table 4.2 List of Materials and Reagents

Material Used	Category	Name of Supplier
PPDS_11YA	Drug	Piramal pharmaceutical Development Services
Sodium Bicarbonate	pH modulating agents	Canton Laboratories Pvt. Ltd. Vadodara.
Citric Acid		
Lactose Monohydrate	Diluents	DFE Pharma, DMV Fonterra Excipients GmbH & Co. Germany.
Avicel PH 112		FMC Biopolymer, Wallingstown, Ireland.
Starch 1500	Binder	Colorcon, Indianapolis, USA
Klucel EXF		ASHLAND, DKSH India Pvt. Ltd. Bhiwandi.
Acdisol	Disintegrant	FMC Biopolymer, Philadelphia, USA
Primellose		DFE Pharma, DMV Fonterra Excipients B.V. Netherland.
Polyplasdone XL 10		ISP (Singapore) Pte Ltd
Magnesium Stearate	Lubricant	Peter Grevans, Plus Pharma Inc.

4.3 Methodology

4.3.1 Preformulation Studies

4.3.1.1 Physicochemical properties

Table 4.3: Physicochemical properties of PPDS_11YA

Parameter	Results
Bulk Density	0.59 gm./ml
Tapped Density	0.73 gm./ml
Carr's Index	19%
Hausner's Ratio	1.22
Angle of Repose	36^0

4.3.2 Melting point Determination

Melting points of API was determined using melting point apparatus. The melting point of the pure drug was taken by open capillary method.

Table 4.4: Melting point of PPDS_11YA

Reported Melting Point (^{0}C)	Observed Melting point (^{0}C)
76 – 81	75 - 77

Conclusion: The melting point determined is within the range of standard value, hence, it is concluded that the drug sample having intimate physical property as standard drug according to USP.

4.3.3 Solubility Study (62)

API is reported to have two pKas (pka1=2.7 and pKa2=5.8), thus causing the drug to have amphiphilic behavior. The value of pKa2 is within the biological pH range in the small intestine, therefore it is expected that its dissolution behavior in vivo vary as the drug moves down the GI-tract, with faster dissolution taking place further down in the gut where the pH is higher. Keeping this point in view the pH solubility was performed in following media (Purified water, 0.1N HCl, pH 4.5 Acetate Buffer, pH 6.8 Phosphate Buffer).

4.3.3.1 Experimental Protocol:

Approximate 10 mg of API (PPDS_11YA) was taken into 50 mL volumetric flask. To that, 25 mL of each diluent/media as stated above was added. All samples were shaken constantly on a rotary shaker at 200 RPM for 2 hours. After 2 hours, samples were taken out and filtered through 0.45µ nylon syringe filter. Last 5mL aliquot of filtrate were collected for each samples. Then each sample was analysed by using proper assay technique.

Table 4.5: pH Solubility profile in different media

Name of medium	Initial pH of medium	Final pH of medium after addition of 10 mg API	ΔpH	Mean Solubility (mg/ml)
Purified water	5.386	9.014	3.628	0.3543
0.1N HCl	1.187	1.387	0.2	0.0004
pH 4.5 Acetate Buffer	4.513	4.299	- 0.214	0.0014
pH 6.8 Phosphate Buffer	6.806	6.839	6.033	0.0006

❖ **Observation**:

From above study, this can be inferred that API is highly soluble in water as compared to other medium. Similarly, pH solubility study for verification of pH with and without addition of API was performed and the results obtained are as given below in the table.

Table 4.6 : Verification of pH with and without addition of API

Sample Detail	Observed pH
25mL of Water - As such medium	5.386
25mL of Water + 10mg of API	9.014
900mL of Water+ 5mg of API	5.955
25mL of Water + 0.5 % SLS	5.282
25mL of Water + 0.5 % SLS+ 10mg of API	7.719
900mL of Water + 0.5 % SLS+ 5mg of API	5.968

❖ **Result**:

Above results confirms that API on dissolving increases the pH of the medium, which in turns enhances the solubility of the API.

4.3.4 Identification of Drug

4.3.4.1 Determination by FTIR study

IR spectra of drug in KBR pellets at moderate scanning speed between 4000-400 cm^{-1} was carried out using FTIR (Jasco FTIR 6100 TYPE A, Japan).

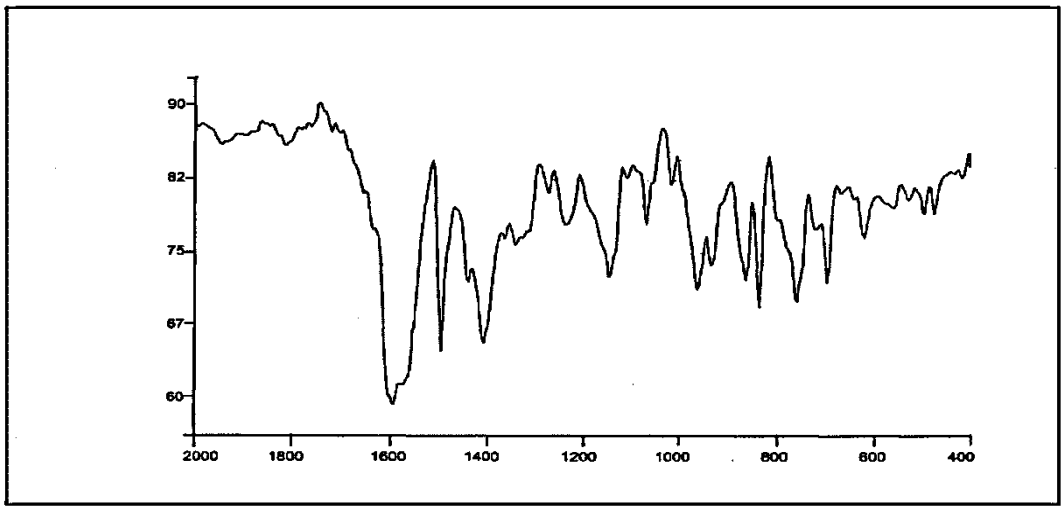


Figure 4.1: Reported FTIR Spectra of PPDS_11YA (I.P 2014)

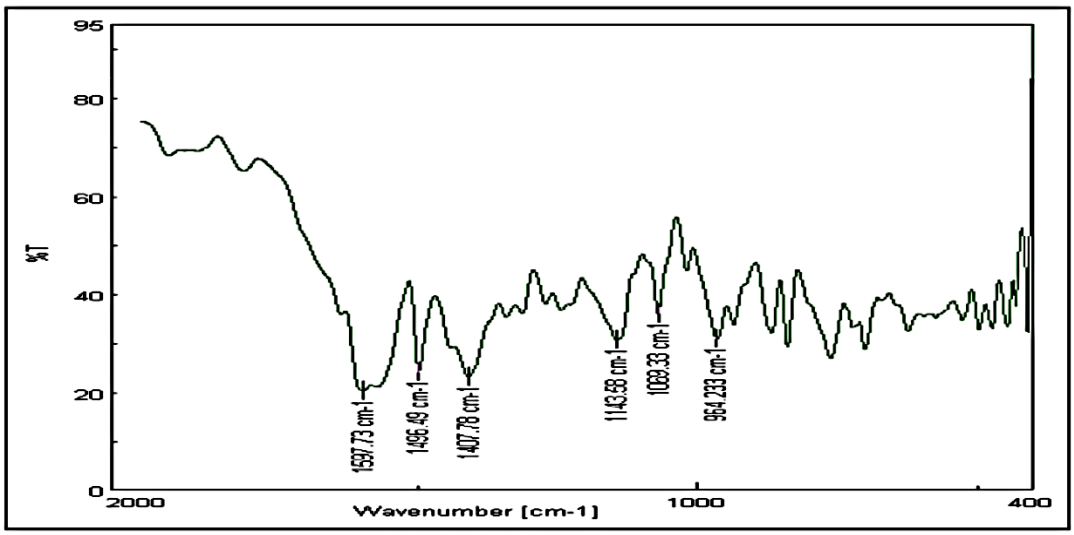


Figure 4.2: Recorded FTIR Spectra of PPDS_11YA

❖ **Discussion:**

The sample spectrum of PPDS_11YA was compared with standard one and both spectra were found similar in peak values representing wave numbers. Thus, it can be concluded that procured drug sample was a pure.

4.3.4.2 Determination by UV Spectroscopy study

10µg/mL solutions was prepared separately in methanol and scanned in UV Visible Spectrophotometer in range of 200-400 nm to determine the absorption maxima of PPDS_11YA. (UV 1800, Schimadzu)

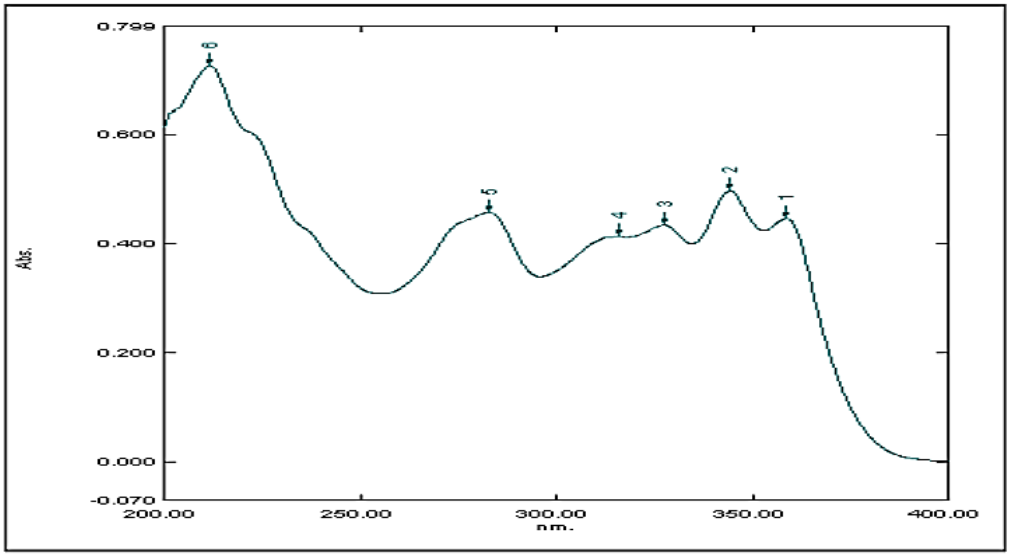


Figure 4.3: UV Spectra of PPDS_11YA in Methanol

Reported Peaks (nm)	Observed Peaks (nm)
359	359.8
345	344.2
328	327.2
284	282.8

Figure 4.4: List of Reported and Observed peak in UV Spectra

❖ **Result**:

The UV spectra of drug shows λmax at 359.8 nm, which remains constant after dilution and is nearly similar to the reported standard value 359 nm. This also indicates identity and purity of the drug sample.

4.3.5 Preparation of Calibration Curve in different solvents

4.3.5.1 Preparation of Regents and Solutions

❖ **Preparation of 0.5% SLS in Water Solution (Office of Generis Drugs media)**

Weigh accurately 5 gram of SLS and dissolve it in 1000 ml water to produce 0.5% SLS in water media.

❖ **Preparation of 0.015 M HCl**

Accurately measure 12.75 ml of concentrated hydrochloric acid and transferred it to 10 litres to produce 0.015M Hydrochloride acid.

❖ **Preparation of 0.0033 M HCl**

Accurately measure 2200 ml of 0.015 M hydrochloric acid and transferred it to 10 litres to produce 0.0033 M Hydrochloride acid.

4.3.5.2 Preparation of Standard Stock Solution of Drug (100 µg/mL)

Accurately weighed quantity of API (25 mg) was transferred to 25 ml amber colored volumetric flasks and dissolved in methanol. The solution was sonicated for 5 minutes. The flasks was shaken and volume was made up to the mark with methanol to give solution containing 1000 µg/ml. Aliquot of 2.5 ml was pipetted out from stock solution (1000 µg/mL) and transferred to 25 mL amber colored volumetric

flask. The volume was made with methanol to obtain final concentration of 100 µg/ml.

4.3.5.3 Preparation of standard curve in methanol

From the stock solution pipette out 0.5, 1, 1.5, 2, 2.5, 3, 3.5 ml of samples and transfer it to 10 ml volumetric flask and make up the volume up to the mark with methanol to obtain concentration of 5 - 35µg/ml respectively. The wavelength maxima of drug in methanol was found to be 359 nm. Absorbance of each solution was measured at 359 nm. All dilutions were made in triplicates.

Figure 4.5: Standard Curve of PPDS_11YA in methanol

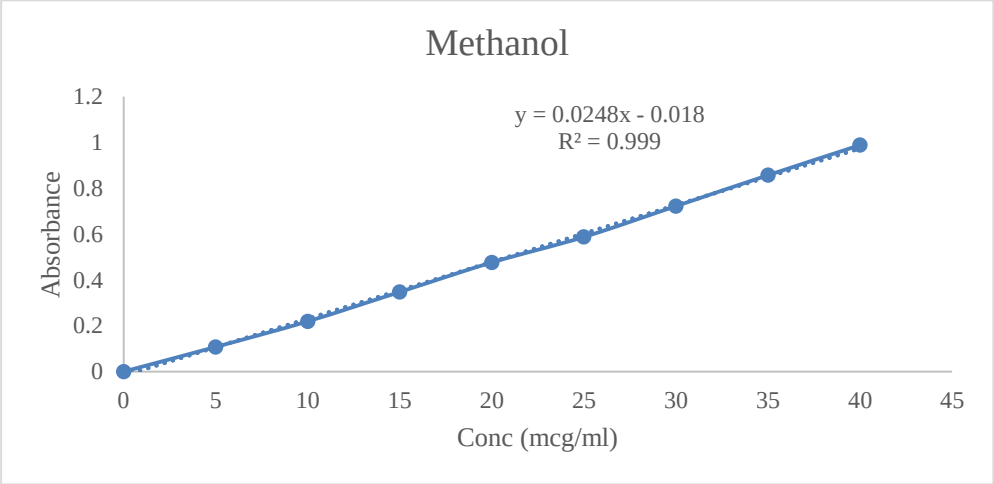


Table 4.7: Standard Curve of PPDS_11YA in methanol

Conc. (µg/ml)	Absorbance			
	I	II	III	Average
0	0	0	0	0
5	0.1076	0.1077	0.1077	0.1077
10	0.2191	0.2193	0.2192	0.2192
15	0.3478	0.3475	0.3475	0.3476
20	0.4765	0.4763	0.4764	0.4764
25	0.5876	0.5875	0.5873	0.5875
30	0.7220	0.7221	0.7219	0.7220
35	0.8569	0.8571	0.8570	0.8571
40	0.9883	0.9882	0.9883	0.9883

Table 4.8: Regression Analysis for Standard Curve of PPDS_11YA in Methanol

Regression parameter	Value
Correlation coefficient	0.999
Slope	0.0248
Intercept	-0.018

4.3.5.4 Preparation of standard curve in OGD Media (0.5% SLS in water)

From the stock solution pipette out 0.5, 1, 1.5, 2, 2.5, 3, 3.5 ml of samples and transfer it to 10 ml volumetric flask and make up the volume up to the mark with 0.5% SLS in water to obtain concentration of 5 - 35µg/ml respectively. The wavelength maxima of drug in 0.5% SLS in water was found to be 366 nm. Absorbance of each solution was measured at 366 nm. All dilutions were made in triplicates.

Figure 4.6: Standard Curve of PPDS_11YA in 0.5% SLS in water

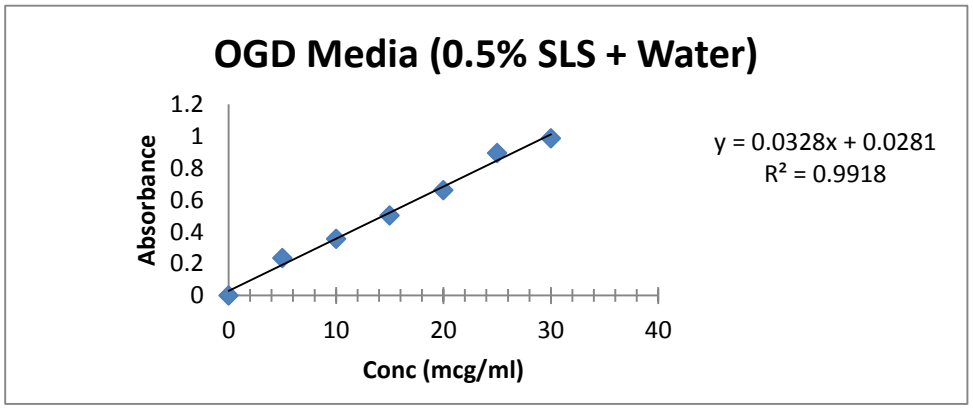


Table 4.9: Standard Curve of PPDS_11YA in 0.5% SLS in water

Conc. (µg/ml)	Absorbance			
	I	II	III	Average
0	0	0	0	0
5	0.2356	0.2342	0.2349	0.2349
10	0.3545	0.3556	0.3589	0.3563
15	0.5111	0.5001	0.5011	0.5041
20	0.6589	0.6595	0.6651	0.6612
25	0.8958	0.8961	0.8953	0.8957
30	0.9889	0.9886	0.9879	0.9885

Table 4.10: Regression Analysis for Standard Curve of PPDS_11YA in 0.5% SLS in water

Regression parameter	Value
Correlation coefficient	0.9918
Slope	0.0328
Intercept	0.0281

4.3.5.5 Preparation of standard curve in 0.015 M Hydrochloric acid

From the stock solution pipette out 0.5, 1, 1.5, 2, 2.5, 3, 3.5 ml of samples and transfer it to 10 ml volumetric flask and make up the volume up to the mark with 0.015 M HCl to obtain concentration of 5 - 35µg/ml respectively. The wavelength maxima of drug in 0.015 M HCl was found to be 366 nm. Absorbance of each solution was measured at 366 nm. All dilutions were made in triplicates.

Figure 4.7: Standard Curve of PPDS_11YA in 0.015 M HCl

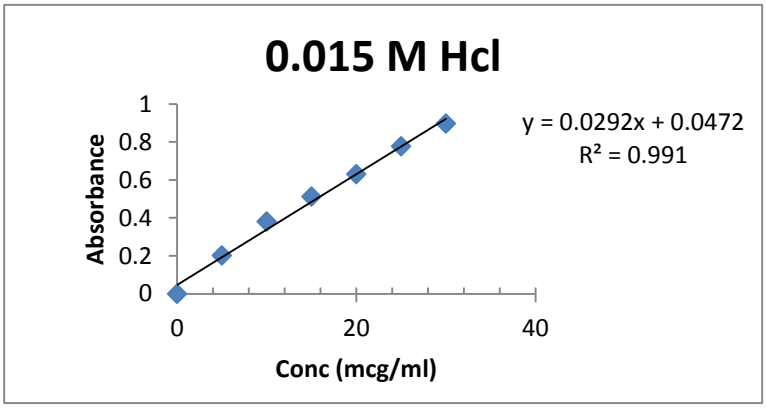


Table 4.11: Standard Curve of PPDS_11YA in 0.015 M HCl

Conc. (µg/ml)	Absorbance			
	I	II	III	Average
0	0	0	0	0
5	0.1990	0.2051	0.2009	0.2017
10	0.3806	0.3794	0.3812	0.3804
15	0.5124	0.5118	0.5099	0.5114
20	0.6287	0.6299	0.6307	0.6298
25	0.7728	0.7759	0.7801	0.7763
30	0.8968	0.8953	0.8962	0.8961

Table 4.12: Regression Analysis for Standard Curve of PPDS_11YA in 0.015 M HCl

Regression parameter	Value
Correlation coefficient	0.991
Slope	0.0292
Intercept	0.0472

4.3.5.6 Preparation of standard curve in 0.0033 M Hydrochloric acid

From the stock solution pipette out 0.5, 1, 1.5, 2, 2.5, 3, 3.5 ml of samples and transfer it to 10 ml volumetric flask and make up the volume up to the mark with 0.0033 M HCl to obtain concentration of 5 - 35µg/ml respectively. The wavelength maxima of drug in 0.0033 M HCl was found to be 366 nm. Absorbance of each solution was measured at 366 nm. All dilutions were made in triplicates.

Figure 4.8: Standard Curve of PPDS_11YA in 0.0033 M HCl

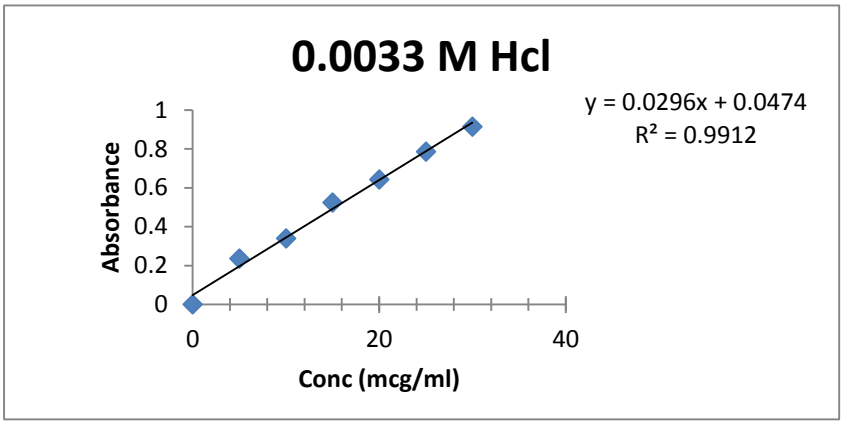


Table 4.13: Standard Curve of PPDS_11YA in 0.0033 M HCl

Conc. (µg/ml)	Absorbance			
	I	II	III	Average
0	0	0	0	0
5	0.2345	0.2351	0.2387	0.2361
10	0.3391	0.3389	0.3374	0.3385
15	0.5230	0.5228	0.5235	0.5231
20	0.6411	0.6399	0.6459	0.6423
25	0.7851	0.7865	0.7850	0.7855
30	0.9134	0.9148	0.9121	0.9134

Table 4.14: Regression Analysis for Standard Curve of PPDS_11YA in 0.0033 M HCl

Regression parameter	Value
Correlation coefficient	0.9912
Slope	0.0296
Intercept	0.0474

4.3.6 Excipient Compatibility Study

Excipient compatibility study is an essential part of preformulation studies in which active ingredient was mixed with several inactive ingredients by physical admixture in different ratios. 4 week studies are carried out in various conditions as mentioned below.

- 25^0C/60 % RH: Accelerated conditions of heat.
- 40^0C/75 % RH: Accelerated conditions of heat and humidity.

Table 4.15: Drug Excipient Compatibility plan

Ingredients	Ratio	Initial Observation
API	1	White to off white powder
API + Sodium bicarbonate	1:5	White Fine powder
API + Citric acid	1:3	White Fine powder
API + Lactose Monohydrate	1:3	White Fine powder
API + Avicel PH 112	1:3	White to off white powder
API + Acdisol	1:2	White Fine powder
API + Primellose	1:2	White to off white powder
API + Polyplasdone XL-10	1:2	White Fine powder
API + Starch 1500	1:2	White Fine powder
API + Klucel EXF	1:2	White Fine powder
API + Magnesium Stearate	1:1	White fine powder

Observation: Initially the observation are made as given in table 4.16. Finally, after 4 weeks the sample are visually examined and it was found that there was no significant changes in the appearance of different conditions vials.

Table 4.16: Description of Drug Excipient Compatibility study

Ingredients	Observations		
	Initial	25^0C/60 % RH	40^0C/75 % RH
API	White to off white powder	No Change	No Change
API + Sodium bicarbonate	White Fine powder	No Change	No Change
API + Citric acid	White Fine powder	No Change	No Change
API + Lactose Monohydrate	White Fine powder	No Change	No Change
API + Avicel PH 112	White to off white powder	No Change	No Change
API + Acdisol	White Fine powder	No Change	No Change
API + Primellose	White to off white powder	No Change	No Change
API + Polyplasdone XL-10	White Fine powder	No Change	No Change
API + Starch 1500	White Fine powder	No Change	No Change
API + Klucel EXF	White Fine powder	No Change	No Change
API + Magnesium Stearate	White fine powder	No Change	No Change

Observation: Since visual inspection shows that there was no significant change in the appearance. Therefore, percentage drug content was estimated using proper assay procedure so as to confirm that there was no any issues of incompatibility.

Table 4.17 : Results of Drug Excipient Compatibility study

Ingredients	% Drug Content		
	Initial	25^0C/60 % RH	40^0C/75 % RH
API	99.96	99.78	98.86
API + Sodium bicarbonate	99.21	98.99	98.36
API + Citric acid	98.79	98.60	98.18
API + Lactose Monohydrate	99.17	98.85	98.35
API + Avicel PH 112	99.38	99.18	98.76
API + Acdisol	99.29	98.89	98.39
API + Primellose	98.89	98.86	98.68
API + Polyplasdone XL-10	99.36	99.01	98.72
API + Starch 1500	99.87	99.37	99.03
API + Klucel EXF	99.47	99.25	98.99
API + Magnesium Stearate	99.65	99.13	99.01

Conclusion:

- From Above observations and results this can be confirmed that there is no incompatibility observed between API and the other inactive ingredients.
- It was observed that there was decrease in the % assay of pure API from initial stage but, it is with in the assay range as per USP (98% - 102%).

4.3.7 Manufacturing Procedure

Direct compression is viewed as the technique of choice for the manufacture of tablets containing thermolabile and moisture-sensitive drugs, and although it affords many advantages.

Direct Compression techniques involves following steps:

4.3.7.1 Dispensing

Accurately weigh the required amount of API and other inactive ingredients individually as per the formula required for the batch.

4.3.7.2 Sifting and mixing

1. After weighing the accurate amount of excipient, pass individually through 40 # sieve.
2. Shift API with Polyplasdone XL 10 through ASTM 40 # sieve & Mix well.
3. Shift Klucel EXF with step 2 through ASTM 40 # sieve & mix well.
4. Shift Avicel PH 112 with step 3 through ASTM 40 # sieve & mix well.
5. Shift Sodium Bicarbonate with step 4 through ASTM 40 # sieve & mix well.
6. Shift Citric Acid with step 5 through ASTM 40 # sieve & mix well.
7. All mixing procedures were carried out in Turbula blender for 3 minutes at 30 RPM.

4.3.7.3 Comilling

After mixing of all ingredients, pass it through Quadro Comill using ASTM 1143 # with Radial Impeller at 1000 RPM.

4.3.7.4 Blending

After Comilling, blending was done in Turbula blender for 10 minutes at 30 RPM.

4.3.7.5 Lubrication

Accurately weighed amount of Magnesium stearate is pass through 60 # mesh Sieve.

Lubrication of blend was done using Turbula blender for 3 minutes at 30 RPM.

4.3.7.6 Compression

Compression of tablet was carried out using 16 station Cadmach CD4 rotary tablet compression machine using different punches.

4.3.8 Evaluation parameters of Blend

4.3.8.1 Moisture Content (% Loss on drying):

Weigh accurately 1.5 gm of powder sample & place it in the moisture analyzer disk. Keep the temperature at 105°C for 5 mins. % Loss on drying observed should be less than 5.

4.3.8.2 Bulk Density (D_b):

The bulk density of a powder may be described as the density of the powder 'as poured' into a measuring vessel. Bulk density was measured using Scott Volumeter Bulk Density Tester. Powder was poured from top of the instrument having 18# screen and it flows through 4 glass baffles and gets accumulated in the receiving cup of 25 ml. Weight of the powder was noted and bulk density was calculated. It is the ratio of total mass of powder to the bulk volume of powder. It is expressed in gm/ml and is given by

$$D_b = M/V_b$$

Where, M is the mass of powder, V_b is the Bulk volume of the powder.

4.3.8.3 Tapped Density (D_t):

Tapped density was measured into a 100 ml graduated measuring cylinder in Tap density tester. The tapped volume was noted after 250 taps followed by 500 taps if difference in volume is less than 2%. If difference is more than 2% then granules was subjected for 1250 taps to bring the difference in volume less than 2%.

$$D_t = M/V_t$$

Where, M is the mass of powder, V_t is the tapped volume of the powder.

4.3.8.4 Carr's index (CI) & Hausners Ration (HR):

Carr's index and Hausners ratio were determined using following formula.

$$\text{Carr's Index} = D_t - D_b/D_t$$

$$\text{Hausners ratio} = D_t/D_b$$

Where, D_t is the tapped density of the powder,

D_b is the Bulk Density.

Table 4.18: Scale of flow ability

Flow Character	Carr's Index	Hausners Ratio	Angle of Repose (^{0})
Excellent	≤ 10	1.00 - 1.11	25 – 30
Good	11 to 15	1.12 – 1.18	31 – 35
Fair (aid not needed)	16-20	1.19 – 1.25	36 – 40
Passable (may hang up)	21-25	1.26 – 1.34	41 – 45
Poor (Must agitate OR vibrate)	26-31	1.35 – 1.45	46 – 55
Very Poor	32-37	1.46 – 1.59	56 – 65
Very very poor	> 38	> 1.60	> 66

4.3.8.5 Angle of Repose:

The frictional forces in a loose powder can be measured by the angle of repose, θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. The powder mixture was allowed to flow through the funnel positioned at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

$$\theta = \tan^{-1} h/r$$

Where, θ is the angle of repose, h is the height in cm, r is the radius.

4.3.8.6 Flow function Coefficient: ([63])

Ring Shear Tester (Model: RST-XS) is an easy to operate tester for the precise determination of flow properties of fine-grained powders and bulk solids. The powder sample is contained in an annular shear cell (Figure 4.10) A vertical load F_N is applied through a thin loading rod on the annular lid. To shear the sample, the shear cell rotates relative to the lid (direction ω) and the torque necessary for shearing was determined from forces F_1 and F_2 acting in a tie rod and a push rod.

Computer controlled well-defined procedure is followed and the flow properties were measured accurately.

Figure 4.9: Shear cell of Ring Shear Tester

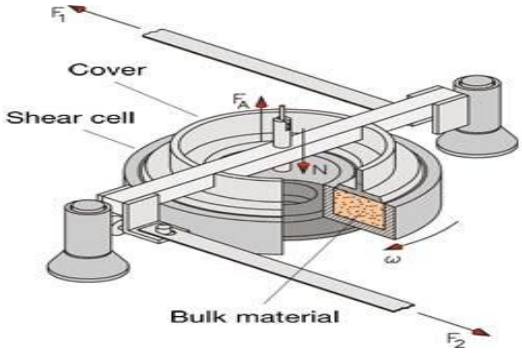


Figure 4.10: Instrumentation of Ring Shear Tester

Table 4.19 : Measurement of Flow ability using Ring Shear tester

Flow Function Coefficient (FFC value)	Powder property
Less than 1	Not Flowing
1 – 2	Very Cohesive
2 – 4	Cohesive
4 – 10	Easy Flowing
More than 10	Free flowing

4.3.8.7 Flowdex: ([64])

It is composed of a cylinder with the interchangeable discs with holes of various diameters at the bottom. The determination of fluidity is based on the capacity of the powder to fall freely by a hole in the disc. The hole is carefully charged by which a powder fall freely. If the hole is small, greater its flow. 60 grams are carefully charged in

the cylindrical container. Tap the funnel slightly so that the powder is passing without compacting itself. After loading, wait approximately 30 seconds; release the lever and observe if the powder runs. Start with a disc of 16 mm for unknown powders. If the test is positive, repeat the process with smaller discs until the test is negative. If the powder does not run, repeat the test with discs with larger holes until the test is positive. Flow ability can be measured from table 4.20 and 4.21.

Figure 4.11: Instrumentation of Flowdex

Table 4.20: Scale of flow ability by Flowdex Value

Flowdex	Flow ability
200 and above	Excellent
100 – 199	Good
50 – 99	Medium
Below 50	Poor

Table 4.21: Flow Property and its corresponding Disc number in Flowdex

Flowdex	
Disc # (mm)	Flowdex (1000/Disc #)
4	250
5	200
6	167
7	143
8	125
9	111
10	100
12	80
14	71
16	63
18	56
20	50
22	45
24	42
26	38
28	36
30	33
32	31
34	29

4.3.8.8 Blend Uniformity:

Diluent: Methanol

1. **Blank Preparation:** Use diluent as blank.

Precautions: Immediately after preparation store sample solution at 7°C to 15°C condition protected from light. While preparing standard and sample solution avoid light. Use sodium vapour lamp.

Notes: The standard and sample solutions is stable in solution form up to 48 hours at room temperature when protected from light and stored in amber colored flask.

2. **Standard preparations:**
   - **Stock standard:** Accurately weigh and transfer about 52 mg of PPDS_11YA working standard/reference standard in to a 100 mL amber color volumetric flask. Add about 50 mL of diluent and sonicate to dissolve (Don't allow temperature to rise). Dilute to volume and mix well.

- **Working standard for content uniformity:** Dilute 10mL of stock standard solution to 100mL amber color volumetric flask. Dilute to volume with diluent and mix well.

3. **Sample Preparation:**
   - **Stock sample preparation:** Transfer 10 tablets to 100 mL amber color volumetric flask, add 50 mL of diluent allow to disperse (sonicate if required) and further sonicate for 20 minutes with occasional shaking. Visually observe the disintegration, tablet should disintegrate completely. Do not allow the temperature to rise while sonication. Dilute to volume with diluent and mix.
   - **Working sample preparation for blend uniformity:** Centrifuge 20 ml of stock sample at 3000 RPM for 2 min. pipette 10.0 mL of supernatant stock sample preparation in to 100 ml amber color volumetric flask, dilute to volume with diluent and mix well. Filter the sample through 0.22 µm nylon filter discarding the first 3 ml of filtrate before collecting the sample in vial. Immediately keep the sample solution in cool (from 7°C to 15°C) condition protected from light.

Blend uniformity sample preparation: Accurately weigh 10 mg equivalent blend, transfer 100 mL amber color volumetric flask, add 50 mL of diluent and sonicate for 10 minutes with occasional shaking. Do not allow the temperature to rise while sonication. Dilute to volume with diluent and mix. Further, dilution are done if the absorbance values are greater.

Procedure: Auto zero is done using methanol as a blank in both the cuvettes. Separately keep diluent as blank in one cuvette, and the other cuvette with the standard solution. Similarly, measure the absorbance of all the test solution at 359 nm using a double beam UV visible spectrophotometer and relative standard deviation was also calculated.

4.3.9 Evaluation parameters of tablets

4.3.9.1 Weight variation:

Randomly select twenty tablets from the lot and weigh individually to check for weight variation. Limits as per IP for weight variation are given in table

Average weight of tablet(mg)	Maximum % difference allowed
130 or less	10
130 to 324	7.5
More than 324	5.0

Table 4.22: Acceptance limit for Weight Variation as per IP

4.3.9.2 Thickness:

Thickness of the the tablet was measured using digital Vernier calliper.

4.3.9.3 Hardness:

Hardness of six individual tablet was measured using hardness tester (Model: Dr. Schleuniger Pharmatron 8 M hardness tester).

4.3.9.4 Disintegration time:

The *In vitro* disintegration time was determined using Labindia DT1000 disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

4.3.9.5 Friability:

For tablets weighing up to 650 mg each, take a sample consisting of the minimum number of tablets that makes a total mass of more than 6.5 g. For tablets weighing more than 650 mg each, take a sample of ten tablets. Dust should be carefully removed from the tablets prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before. If no tablets are cracked, split or broken, accurately weigh the tablets, and determine the friability (mass per cent of the lost mass with respect to the initial mass).

$$\% \, Friability = \frac{Initial\ weight - Final\ weight}{Initial\ Weight} \text{ X } 100$$

4.3.9.6 In vitro Dissolution study:

In vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) at 30 rpm. Different medias were used to study the dissolution profile in different media.

Parameter	Observation
Media used	0.015 M HCl
	0.0033 M HCl
	OGD media (0.5% SLS in water)
Amount of media in vessel	900 ml
Dissolution Apparatus	USP type II (Paddle apparatus)
Sampling Time point (Min)	1,2,3,4,5,10,15,20,
Vessel Temperature (^{0}C)	37±0.5 ^{0}C
Paddle Speed	30 rpm
Recovery	150 rpm for 10 min

Figure 4.12: Dissolution Consideration

4.3.9.6.1 Different media used for Dissolution study: ([65])

1. **OGD media (0.5%SLS in water):**

This dissolution media was prescribed US FDA.

❖ **Preparation of 0.5% SLS in Water Solution (OGD media)**

Weigh accurately 50 gram of SLS and dissolve it in 10 litres of water to produce 0.5% SLS in water media.

2. **0.015 M HCl**

0.015 M HCl simulates in vivo conditions based on an estimate of approximately 30 ml residual gastric acid in a fasted subject, diluted with 170 mL water co-administered with the formulation.

When 200 mL dissolution medium is used, the pH may be changed by the pH modulating agents in the formulations that is important where drug solubility is pH

dependent. However, when testing was conducted in 900 mL dissolution medium, there is excess acid preventing any significant pH change.

0.0033 M HCl achieves a pH change in 900mL of medium, which contains the same absolute amount of acid as 200mL 0.015 M HCl. This concentration mimics low gastric acid conditions such as in fed patients or those with low gastric acid secretion.

❖ **Preparation of 0.015 M HCl**

Accurately measure 12.75 ml of concentrated hydrochloric acid and transferred it to 10 litres to produce 0.015M Hydrochloride acid.

3. 0.0033 M HCl

In vitro dissolution testing was conducted in a dissolution medium containing 900 ml of 0.0033 M hydrochloric acid at 37°C. Which is effective in discriminating between fast dissolving formulations. 900 mL of this medium contains the absolute amount of acid estimated to be present in the gastric contents in vivo, namely 3 millimoles, and its pH will change when high levels of sodium bicarbonate used in some formulations are added.

❖ **Preparation of 0.0033 M HCl**

Accurately measure 2200 ml of 0.015 M hydrochloric acid and transferred it to 10 litres to produce 0.0033 M Hydrochloride acid.

Procedure:

Different dissolution medium which are maintained at 37±0.5ºC. Aliquot from dissolution medium (5ml) was withdrawn at specific time intervals and was filtered. The same volume of dissolution medium was replaced to maintain sink condition. The absorbance of these aliquots was measured at specific wavelengths using UV-Visible spectrophotometer (Shimadzu 1800). Cumulative percentage release of drug was calculated using an equation obtained from respective standard curve in different media.

4.3.9.7 Content Uniformity:

Diluent: Methanol

1. **Blank Preparation:** Use diluent as blank.

Precautions: Immediately after preparation store sample solution at 7°C to 15°C condition protected from light. While preparing standard and sample solution avoid light. Use sodium vapour lamp.

Notes: The standard and sample solutions is stable in solution form up to 48 hours at room temperature when protected from light and stored in amber colored flask.

2. **Standard preparations:**

- **Stock standard:**

Accurately weigh and transfer about 52 mg of PPDS_11YA working standard/reference standard in to a 100 mL amber color volumetric flask. Add about 50 mL of diluent and sonicate to dissolve (Don't allow temperature to rise). Dilute to volume and mix well.

- **Working standard for content uniformity:** Dilute 10mL of stock standard solution to 100mL amber color volumetric flask. Dilute to volume with diluent and mix well.

3. **Sample Preparation:**

- **Stock sample preparation:**

Transfer 10 tablets to 100 mL amber color volumetric flask, add 50 mL of diluent allow to disperse (sonicate if required) and further sonicate for 20 minutes with occasional shaking. Visually observe the disintegration, tablet should disintegrate completely. Do not allow the temperature to rise while sonication. Dilute to volume with diluent and mix.

- **Working sample preparation for blend uniformity:**

Centrifuge 20 ml of stock sample at 3000 RPM for 2 min. pipette 10.0 mL of supernatant stock sample preparation in to 100 ml amber color volumetric flask, dilute to volume with diluent and mix well. Filter the sample through 0.22 µm nylon filter discarding the first 3 ml of filtrate before collecting the sample in vial.

Immediately keep the sample solution in cool (from 7°C to 15°C) condition protected from light.

- **Content uniformity sample preparation:**

Randomly select and weigh 10 tablets, transfer each tablet in to ten separate 100 mL amber color volumetric flask, add 50 mL of diluent and sonicate for 10 minutes with occasional shaking. Visually observe the disintegration, tablet should disintegrate completely. Do not allow the temperature to rise while sonication. Dilute to volume with diluent and mix

Procedure: Auto zero is done using methanol as a blank in both the cuvettes. Separately keep diluent as blank in one cuvette, and the other cuvette with the standard solution. Similarly, measure the absorbance of all the test solution at 359 nm using a double beam UV visible spectrophotometer and calculate acceptance value.

$$\text{Acceptance Value} = |M - X| + ks$$

if n = 10 then k = 2.4, if n = 30 then k = 2.0

M (case 1) when T ≤ 101.5

Conditions	Value	
If 98.5% ≤ X ≤ 101.5	M = X	AV = ks
If X < 98.5%	M = 98.5%	AV = 98.5 – X + ks
If X > 101.5%	M = 101.5%	AV = X – 101.5 + ks

M (case 2) T > 101.5

Conditions	Value	
If 98.5% ≤ X ≤ T%	M = X	AV = ks
If X < 98.5%	M = 98.5%	AV = 98.5 – X + ks
If X > T%	M = T%	AV = X – T + ks

4.3.10 Innovator Characterisation

Table 4.23: Details of Innovator product

Sr.No.	Attributes	Description
1	Dosage Form	Tablet
2	RLD	10 mg
3	Batch No.	J301815
4	Manufacturing Date	08/2013
5	Expiry Date	01/2015
6	Manufactured by	Lupin Ltd, SIDCO kartholi, Bari Brahamana, Jammu, 181133, J&K.
7	Description	Circular shaped, Standard Concave punch, Beige colour, Film coated tablet.
8	Inactive ingredients	Red oxide of iron, yellow oxide of iron, Titanium dioxide IP
9	Pack description	Blister pack (10's count Blister)
10	Storage Condition	At temperature NMT 30^0C & protect from light

Table 4.24: Evaluation Parameter of Innovator Product

Sr.No.	Thickness (mm)	Hardness (kP)	Disintegration Time (seconds)	Diameter (mm)
1	3.66	9.8	108	8.15
2	3.65	8.2	136	8.13
3	3.66	10.0	141	8.18
4	3.65	10.7	153	8.15
5	3.66	9.6	164	8.16
6	3.69	9.8	178	8.19
Average	3.66	9.68	147	8.16

Table 4.25 Weight Variation of Innovator product

Weight of Individual Unit (mg)				
186.2	186.6	189.2	187.4	187.6
186.0	190.4	186.6	186.2	183.6
187.4	190.8	187.9	185.3	180.8
185.2	188.5	185.4	187.7	183.3
Average weight = 186.31 mg				
Standard Deviation = 2.59				

4.3.10.1 Invitro Dissolution study of Innovator:

- **Results:**

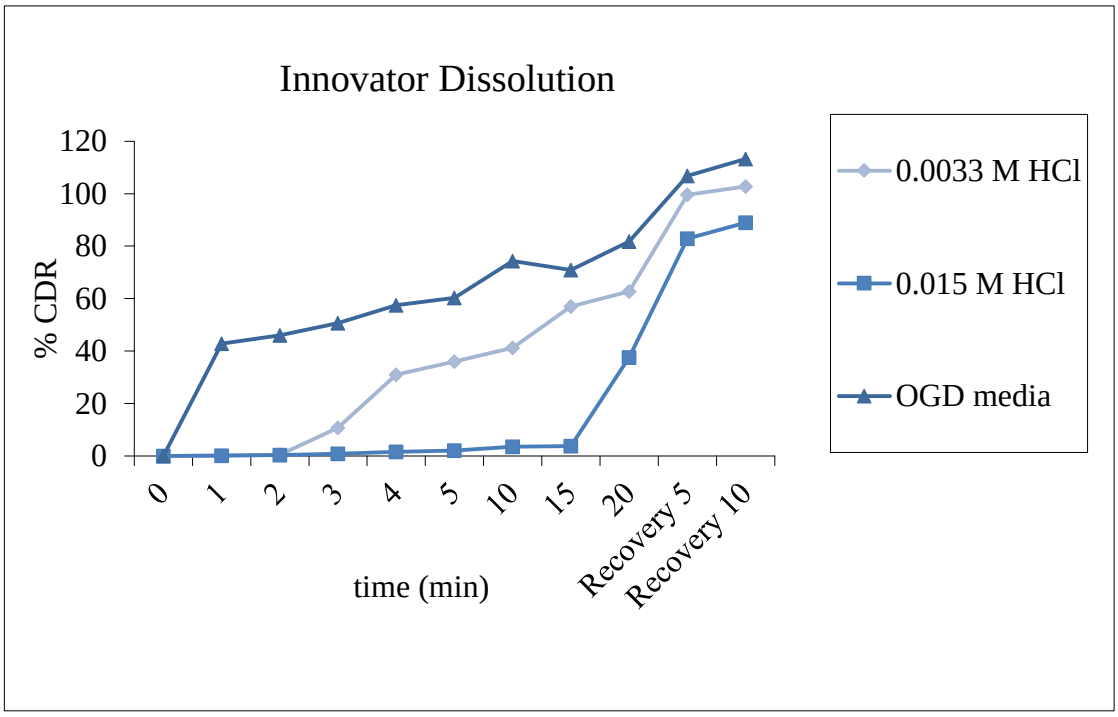


Figure 4.13: Drug Release profile of Innovator Product

- **Discussion:**

The in-vitro dissolution study of the innovator product in different media indicated that drug was released in 0.015 M HCl was not promising as compared to that of the drug release observed in OGD media (0.5% SLS in water).

In-vitro dissolution of innovator product in OGD media indicates that rapid release of drug in short period of time is required for the fast onset of action.

In-vitro dissolution of innovator product in 0.0033 M HCl indicates that drug release rate was slower as compared to the release rate observed in OGD media. Hence, OGD media is the preferred media to study the in vitro drug release profile.

4.3.11 Preliminary trials

4.3.11.1 Formulation Consideration

- Assess the effect of different levels of sodium bicarbonate on drug dissolution and select the level that provides maximum dissolution.
- Assess the impact of different levels of citric acid on the dissolution rate using the selected level of sodium bicarbonate.
- Optimize levels and type of Disintegrant in the formulation to obtain the desired disintegration time.

➢ **Back up Strategy**

- Assess the impact of wet granulation to provide a robust and easy to manufacture tablet whilst maintaining disintegration and dissolution performance.
- Optimize the granule size for flow properties and dissolution characteristics.

4.3.11.2 Target Product Profile

- ➢ Disintegration time should be with in 30 to 40 seconds.
- ➢ % Cumulative drug release in 3 minutes should be more than 70 %.
- ➢ % Cumulative drug release in 20 minutes should be more than 85 %.
- ➢ RSD for Blend uniformity should be less than 5.
- ➢ Acceptance Value for Content uniformity Study should be less than 15.
- ➢ % Assay should be within limits (98-102%)
- ➢ FFC (ring shear tester) - greater than 8.
- ➢ Flowdex -10 or less than 10.

4.3.11.3 To study the Effect of different punches

4.3.11.3.1 Batch no.: 11YA(201)003

Table 4.26: Formulation Composition of Batch 11YA(201)003

Ingredients	(mg/tablet)	% of excipients	Qty for 500 tablets in gm.	Qty for 250 tablet in gm.
API	10.4	1.02	5.20	2.6
Sodium Bicarbonate	600	59.06	300.00	150
Citric Acid Anhydrous	76	7.48	38.00	19
MCC (Avicel PH112)	126.4	12.44	63.20	31.6
Starch 1500	81	7.97	40.50	20.25
Lactose Monohydrate	61.24	6.03	30.62	15.31
Acdisol	50.8	5.00	25.40	12.70
Magnesium Stearate	10.16	1.00	5.08	2.54
Total	**1016**	**100.00**	**508.00**	**254**

- **Observation:**

Accurate dispensing of material was done, sifting through 40# mesh sieve, Blending in Turbula blender at 30 rpm for 10 Min, and Lubrication in Turbula blender at 30 rpm for 3 Min, and finally, Compression of tablet was done using Cadmach compression machine using 2 sets of 20.5 X 9.5 mm punches, capsule shaped, plain surface, D- tolling.

- **Results:**

Table 4.27: Evaluation parameter of 11YA(201)003 blend

Evaluation parameter	Observed Value
Bulk Density (gm/ml)	0.7895
Tapped Density (gm/ml)	1.0715
Carr's index (%)	26.3158
Hausners ratio	1.0357
Loss on drying (%)	1.08

Table 4.28: Evaluation parameters of 11YA(201)003 tablets

Parameter	Punch Dimensions		
	20.5 X 9.5 mm	**18 X 8 mm**	**17 X 7.5 mm**
Thickness (mm)	4.16±0.04	5.74±0.10	5.67±0.09
Hardness (kP)	9.03±0.77	9.38±0.48	9.45±1.01
DT (min:sec)	50 Seconds to 1 Min 25 Seconds	1 Min 40 Seconds to 1 min 52 seconds	1 min 54 seconds to 2 min 14 seconds
Average Weight (mg)	1056.37±5.76	1023.93±5.64	996.79±2.98

- **Discussion:**

- Thickness of the tablet was too small as compared to punch dimension; hence, further compression was carried out with smaller dimension punches (B - Tooling. 18 X 8 mm & 17 X 7.5 mm).
- Average weight and disintegration time of tablet was on higher side as compared to target value but, average weight of the tablet was within the range of ± 5%.
- Capping Defect was observed while compressing tablets using 17 X 7.5 mm Punch. Hence, Binder concentration is to be increased & Lactose monohydrate was finer grade therefore it is to be replaced with Avicel PH 112.

4.3.11.4 Effect of different diluent and binder

Here, in this trial Lactose monohydrate was replaced with Avicel PH 112 and Starch 1500 was replaced with hydroxy propyl cellulose (Klucel EXF).

4.3.11.4.1 Batch no.: 11YA(201)008

- **Formula:**

Table 4.29: Formulation Composition of Batch 11YA(201)008

Ingredients	(mg/tablet)	% of excipients	Qty for 250 tablet in gm.
API	10.4	1.02	2.6
Sodium Bicarbonate	600	59.06	150
Citric Acid Anhydrous	76	7.48	19
MCC (Avicel PH112)	187.64	18.47	46.91
Klucel EXF	81	7.97	20.25
Acdisol	50.8	5.00	12.70
Magnesium Stearate	10.16	1.00	2.54
Total	**1016**	**100.00**	**254**

- **Observation:**

Accurate dispensing of material was done, sifting through 40# mesh sieve, Blending in Turbula blender at 30 rpm for 10 Min, and Lubrication in Turbula blender at 30 rpm for 3 Min, and finally, Compression of tablet was done using Cadmach compression machine using single set of 18 X 8 mm and 17 X 7.5 mm punches, capsule shaped, plain surface, B - tolling.

- **Results:**

Table 4.30: Evaluation parameter of 11YA(201)008 blend

Evaluation parameter	Observed Value
Bulk Density (gm/ml)	0.7697
Tapped Density (gm/ml)	1.0351
Carr's index (%)	25.641
Hausners ratio	1.3448
Loss on drying (%)	1.06

Table 4.31: Evaluation parameters of 11YA(201)008 tablets

Parameter	Punch Dimensions	
	18 X 8 mm	**17 X 7.5 mm**
Thickness (mm)	5.32±0.04	6.14±0.35
Hardness (kP)	4.33±0.54	3.38±0.31
DT (min:sec)	1 min 30 Seconds to 1 min 55 seconds	1 min 15 seconds to 1 min 30 seconds.
Average Weight (mg)	1015.35±1.52	1009.12±1.81

- **Discussion:**

- Thickness of the tablet was in acceptable range ± 5 % as per the limits of IP 2010.
- Hardness of tablet was less in both the punches, and Disintegration time was on higher side. To obtain the desired disintegration time, another trial is to taken by 5% granulation of sodium bicarbonate & Klucel EXF with water so as to check whether it affect disintegration time significantly or not.

4.3.11.4.2 Batch no.: 11YA(201)011

- Target was to achieve the Disintegration time around 30 seconds.
- But, from earlier batches this was not achieved, so as to achieve the target disintegration time, granulation (5% water) of Sodium bicarbonate and Klucel EXF was carried out in Rapid Mixture Granulator.
- Further, Drying of granules was done in Fluidised Bed Dryer at 35 ^{0}C at optimum fluidisation airflow rate.
- Granules obtained after drying were passed through 20# sieve. And the granules were used in the formulation as per the formula given table no 4.31.

- **Formula:**

Table 4.32: Formulation Composition of Batch 11YA(201)011

Ingredients	(mg/tablet)	% of excipients	Qty for 50 tablet in gm.
API	10.4	1.02	0.52
Sodium Bicarbonate + Klucel EXF Granules	681	67.03	34.05
Citric Acid Anhydrous	76	7.48	3.80
MCC (Avicel PH112)	187.64	18.47	9.38
Acdisol	50.8	5.00	2.54
Magnesium Stearate	10.16	1.00	0.51
Total	**1016**	**100.00**	**50.80**

- **Observation:**

- Accurate dispensing of material was done, sifting through 40# mesh sieve, Blending in Turbula blender at 30 rpm for 10 Min, and Lubrication in Turbula blender at 30 rpm for 3 Min, and finally, Compression of tablet was done using Cadmach compression machine using single set of 17 X 7.5 mm punches, capsule shaped, plain surface, B - tolling.

- **Results:**

Table 4.33: Evaluation parameter of 11YA(201)011 blend

Evaluation parameter	Observed Value
Bulk Density (gm/ml)	0.7575
Tapped Density (gm/ml)	0.9259
Carr's index (%)	18.1818
Hausners ratio	1.2222
Loss on drying (%)	1.89

Table 4.34: Evaluation parameters of 11YA(201)011 tablets

Parameter	17 X 7.5 mm
Thickness (mm)	6.22±0.20
Hardness (kP)	20.32±1.91
DT (min:sec)	1 min 5 seconds to 1 min 25 seconds.
Average Weight (mg)	1033.51±1.61

- **Discussion:**
- There was significant effect of granulation on hardness & Disintegration time as the hardness of the tablet was on higher side therefore, disintegration time of the tablet was prolonged.
- This can be inferred from the trial that to achieve the target disintegration time hardness of the tablet is to be decreased slightly.
- Moreover, above results justifies that granular grade of sodium bicarbonate will be required for optimisation of disintegration time.

4.3.11.5 Effect of different disintegrant on DT

- Target was to achieve the Disintegration time around 30 seconds.
- But, from earlier batches this was not achieved, so as to achieve the target disintegration time, granular grade of sodium bicarbonate was used.
- Different types of disintegrants were tried so as to optimise the disintegration time.

Table 4.35: Formulation Composition of Batch 11YA(201)013 & 11YA (201)016

Ingredients	(mg/tablet)	% of excipients	11YA(201)013	11YA(201)016
			Qty for 250 tablet in gm.	Qty for 250 tablet in gm.
API	10.4	1.02	2.6	2.6
Sodium Bicarbonate	600	59.06	150	150
Citric Acid Anhydrous	76	7.48	19	19
MCC (Avicel PH112)	187.64	18.47	46.91	46.91
Klucel EXF	81	7.97	20.25	20.25
Polyplasdone XL-10	50.8	5.00	12.70	0
Primellose	50.8	5.00	0	12.70
Magnesium Stearate	10.16	1.00	2.54	2.54
Total	**1016**	**100.00**	**254**	**254**

- **Observation:**
  - Accurate dispensing of material was done, sifting through 40# mesh sieve, Blending in Turbula blender at 30 rpm for 10 Min, and Lubrication in Turbula blender at 30 rpm for 3 Min, and finally, Compression of tablet was done using Cadmach compression machine using single set of 17 X 7.5 mm punches, capsule shaped, plain surface, B - tolling.

- **Results:**

Table 4.36: Evaluation parameter of 11YA(201)013 & 11YA(201)016 blend

Evaluation parameter	Observed Value	
	11YA(201)013	11YA(201)016
Bulk Density (gm/ml)	0.6756	0.6849
Tapped Density (gm/ml)	0.9091	0.9091
Carr's index (%)	25.6756	24.6575
Hausners ratio	1.3454	1.3272
Loss on drying (%)	1.56	1.49

Table 4.37: Evaluation parameter of 11YA(201)013 & 11YA(201)016 blend

Parameter	17 X 7.5 mm	
	11YA(201)013	11YA(201)016
Thickness (mm)	6.39±0.03	6.37±0.03
Hardness (kP)	16.5±0.21	17.53±0.49
DT (min:sec)	50 seconds to 1 min 10 seconds.	1 min 5 seconds to 1 min 16 seconds.
Average Weight (mg)	1012.05±8.36	1009.80±8.98

- **Discussion:**
  - Minimum disintegration time was observed for polyplasdone XL 10 as compared to other disintegrants. Moreover, effect of different disintegrant on dissolution profile need to be studied.

4.3.11.6 Effect of different disintegrant on dissolution profile in different media

- Since, minimum disintegration time was observed with polyplasdone XL 10. So, further the effect of disintegrant on dissolution profile in different media is to be checked.

Table 4.38: Formulation Composition of Batch 11YA(201)019, 11YA (201)023,& 11YA(201)026

Ingredients	(mg/tablet)	% of excipients	11YA(201)019	11YA(201)023	11YA(201)026
			Qty for 250 tablet in gm.	Qty for 250 tablet in gm.	Qty for 250 tablet in gm.
API	10.4	1.02	2.6	2.6	2.6
Sodium Bicarbonate	600	59.06	150	150	150
Citric Acid Anhydrous	76	7.48	19	19	19
MCC (Avicel PH112)	187.64	18.47	46.91	46.91	46.91
Klucel EXF	81	7.97	20.25	20.25	20.25
Acdisol	50.8	5.00	12.70		
Primellose	50.8	5.00	0	12.70	0
Polyplasdone XL-10	50.8	5.00	0	0	12.70
Magnesium Stearate	10.16	1.00	2.54	2.54	2.54
Total	**1016**	**100.00**	**254**	**254**	**254**

- **Observation:**

Accurate dispensing of material was done separately for all three batches, sifting through 40# mesh sieve, Blending in Turbula blender at 30 rpm for 10 Min, and Lubrication in Turbula blender at 30 rpm for 3 Min, and finally, Compression of tablet was done using Cadmach compression machine using single set of 17 X 7.5 mm punches, capsule shaped, plain surface, B - tolling.

- **Results:**

Table 4.39: Evaluation parameter of 11YA(201)019, 11YA(201)023 11YA(201)026 blend

Evaluation parameter	Observed Value		
	11YA(201)019	11YA(201)023	11YA(201)026
Bulk Density (gm/ml)	0.7058	0.7149	0.7045
Tapped Density (gm/ml)	0.9280	0.9267	0.9223
Carr's index (%)	23.9436	22.8571	23.6111
Hausners ratio	1.3148	1.2963	1.3691
Loss on drying (%)	1.74	1.54	1.80

Table 4.40: Evaluation parameter of 11YA(201)019, 11YA(201)023 & 11YA(201)026 blend

Parameter	17 X 7.5 mm		
	11YA(201)019	11YA(201)023	11YA(201)026
Thickness (mm)	6.63± 0.02	6.69±0.02	6.82±0.07
Hardness (kP)	15.75±1.76	17.71±1.89	18.33±1.91
DT (min:sec)	1 min 7 seconds to 1 min 28 seconds.	1 min 5 seconds to 1 min 35 seconds.	30 seconds to 50 seconds.
Average Weight (mg)	1027.08±15.35	1043.11±18.9	1009.80±8.98

- **Discussion:**
  - Observed Disintegration time was minimum for polyplasdone XL 10 as compared to other disintegrants, so further optimisation should be carried out for the polyplasdone XL 10.
- **Invitro dissolution study:**
  - In vitro dissolution study was performed by using USP Type II (Paddle apparatus) at 30 rpm. Different media were used to study the dissolution profile.

Table 4.41: Dissolution Observation

Parameter	Observation
Media used	0.015 M HCl
	0.0033 M HCl
	OGD media (0.5% SLS in water)
Amount of media in vessel	900 ml
Dissolution Apparatus	USP type II (Paddle apparatus)
Sampling Time point (Min)	1,2,3,4,5,10,15,20,
Vessel Temperature (^{0}C)	37±0.5 ^{0}C
Paddle Speed	30 rpm
Recovery	150 rpm for 10 min

➢ **Results:**

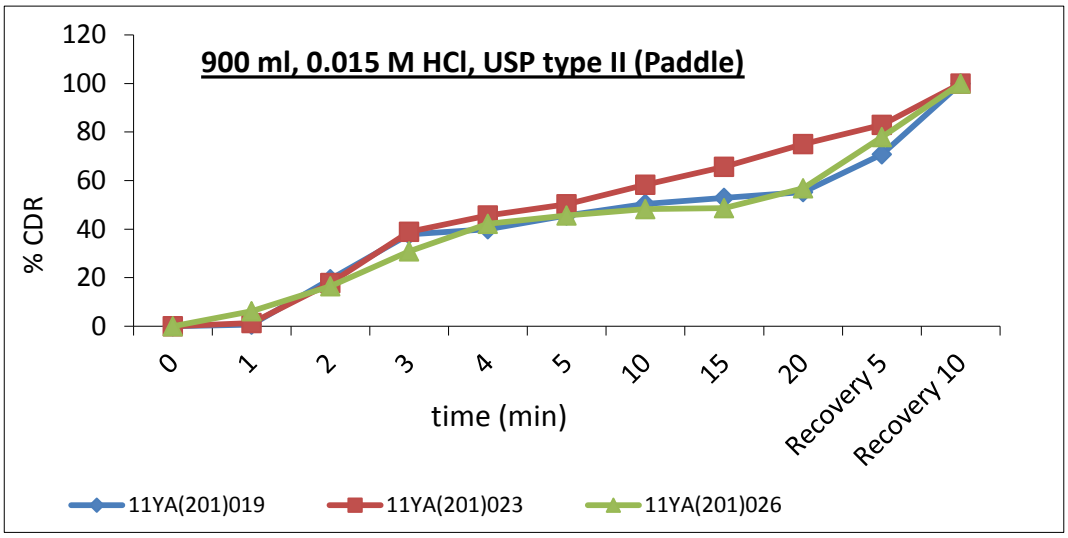


Figure 4.14: Invitro drug release profile of all three batches in 0.015 M HCl

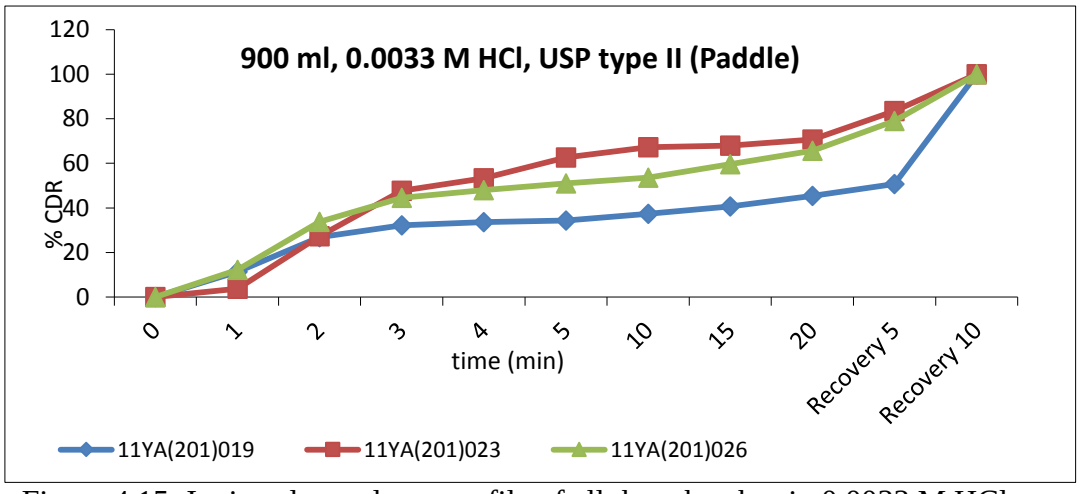


Figure 4.15: Invitro drug release profile of all three batches in 0.0033 M HCl

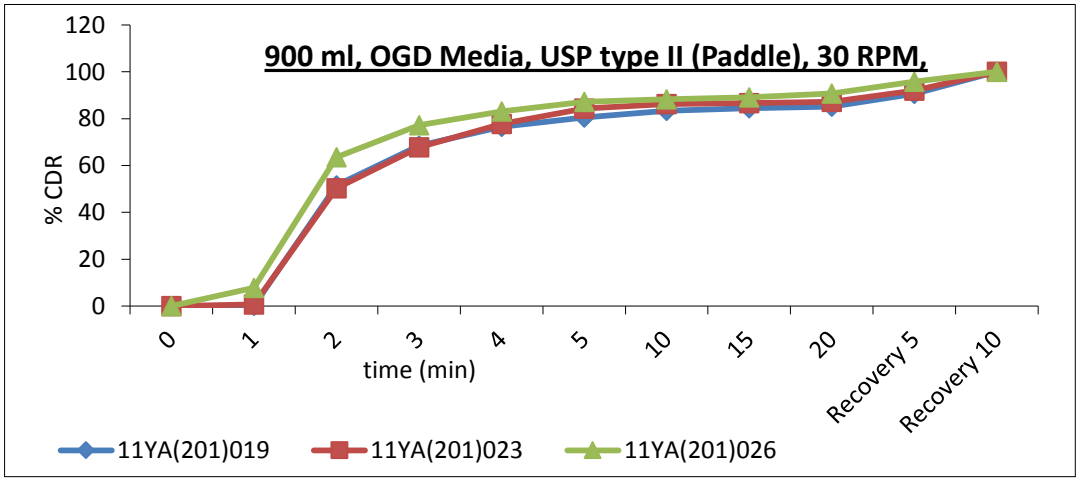


Figure 4.16: Invitro drug release profile of all three batches in OGD media

➢ **Discussion:**

- **0.015 M HCl**

The amount of drug release at the end of 3 minutes for batches 019, 023 and 026 was found to be 33.08, 38.23, and 37.42 % respectively. Similarly, % CDR at he end of 20 minutes was found to be 49.16, 70.45 and 59.66 % respectively. Since, the target dissolution profile was to achieve % CDR in 3 minutes should be more than 70 % and % CDR in 20 minutes should be more than 85 %.

- **0.0033M HCl**

The amount of drug release at the end of 3 minutes for batches 019, 023 and 026 was found to be 16.41, 45.07 and 41.37 % respectively. Similarly, % CDR at the end of 20 minutes was found to be 24.48, 68.79 and 61.72 % respectively.

- **OGD media (0.5% SLS in water)**

The amount of drug release at the end of 3 minutes for batches 019, 023 and 026 was found to be 70.92, 84.18 and 86.82 % respectively. Similarly, % CDR at the end of 20 minutes was found to be 81.76, 84.30 and 91.20 % respectively.

Since, the target dissolution profile was to achieve % CDR in 3 minutes should be more than 70 % and % CDR in 20 minutes should be more than 85 %. This type of release profile was not observed in 0.015 M HCl, 0.0033M HCl media. Only OGD media show the desired percentage release at both the time point i.e. 3 minutes and 20 minutes so, further Invitro dissolution studies should be carried out in the OGD media.

Therefore, from preliminary trials data this can be concluded that levels of sodium bicarbonate, citric acid and polyplasdone XL 10 need to be optimized so as to achieve the target product profile of disintegration and dissolution of the tablet formulation.

4.3.12 Formulation Optimisation

Formulation optimisation was carried out using experimental design with the help of Design Expert software. It is the methodology of how to conduct and plan experiments in order to extract the maximum amount of information in the fewest number of runs.

The traditional experiments require greater efforts and time, especially where complex formulations are to be developed. A very efficient way to enhance the value of research and to minimize the process development time is through use of experimental design. Factorial designs are used in experiments when the effects of different factors or conditions, on experiment results are to be elucidated. Factors may be qualitative or quantitative. The levels of an each factor are the value or designation assigned to combination of all levels of all factor.

4.3.12.1 Types of Experimental Design

Choice of experiments depends on level of knowledge before experiments, resource available and objectives of the experiments. Different types of experimental design are listed below according to their application in formulation development.

- Discovering important process factors
  - Placket-Burman
  - Fractional Factorial
- Estimating the effect and interaction of several factors
  - Full Fractional
  - Fractional Factorial
  - Tiguchi
- For optimization
  - Central composite
  - Simplex lattice
  - D-optimal

4.3.12.2 2^3 Full Factorial Design

The two level design is written as a 2^3 factorial design. It means that 3 factors are consider, each at 2 levels which are usually referred to as low and high levels. These levels are numerically expressed as -1 and +1. It is a simplest two level design.

All responses were fitted to a linear equation model and the adequacy of this model was verified by ANOVA, lack of fit, and multiple correlation coefficient R^2 tests. The linear interactive model is represented as follows

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3$$

Where Y is dependent variable, X_1, X_2 and X_3 are the coded levels of factors, b_1, b_2, b_3 are estimated coefficient of X_1, X_2, X_3 respectively.

Table 4.42: Design matrix for 2^3 Full factorial design

Trial	Amount of Sodium Bicarbonate (SB)	Amount of Citric Acid (CA)	% of polyplasdone XL 10
1	-1	-1	-1
2	1	-1	-1
3	-1	1	-1
4	1	1	-1
5	-1	-1	1
6	1	-1	1
7	-1	1	1
8	1	1	1
Centre point 1	0	0	0
Centre point 2	0	0	0

Table 4.43: list of Factors and levels

Factor	Low level (-1)	High level (+1)
X_1 = Amount of Sodium bicarbonate (mg)	200	600
X_2 = Amount of citric acid (mg)	25	75
X_3 = % of Polyplasdone XL 10 (%)	2	5

Table 4.44: Amount of material as per the design matrix

Trial	Amount of (SB) in mg	Amount of (CA) in mg	% of polyplasdone XL 10
1	200	25	2
2	600	25	2
3	200	75	2
4	600	75	2
5	200	25	5
6	600	25	5
7	200	75	5
8	600	75	5
Centre point 1	400	50	3.5
Centre point 2	400	50	3.5

Table 4.45: Formula for DOE trials

Ingredients	Batch Size: 200 tablets (gm.)									
	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	Trial 9	Trial 10
API	2.08	2.08	2.08	2.08	2.08	2.08	2.08	2.08	2.08	2.08
Sodium Bicarbonate	40	120	40	120	40	120	40	120	80	80
Citric Acid Anhydrous	5	5	15	15	5	5	15	15	10	10
MCC (Avicel PH112)	135.8	55.8	125.8	45.8	129.7	49.7	119.7	39.7	87.74	87.74
HPC (Klucel EXF)	16.26	16.26	16.26	16.26	16.26	16.26	16.26	16.26	16.26	16.26
Polyplasdone XL 10	4.06	4.06	4.06	4.06	10.16	10.16	10.16	10.16	7.12	7.12
Magnesium Stearate	2.032	2.032	2.032	2.032	2.032	2.032	2.032	2.032	2.032	2.032
Total (gm.)	203.2	203.2	203.2	203.2	203.2	203.2	203.2	203.2	203.2	203.2

4.3.12.3 Evaluation parameters of blend

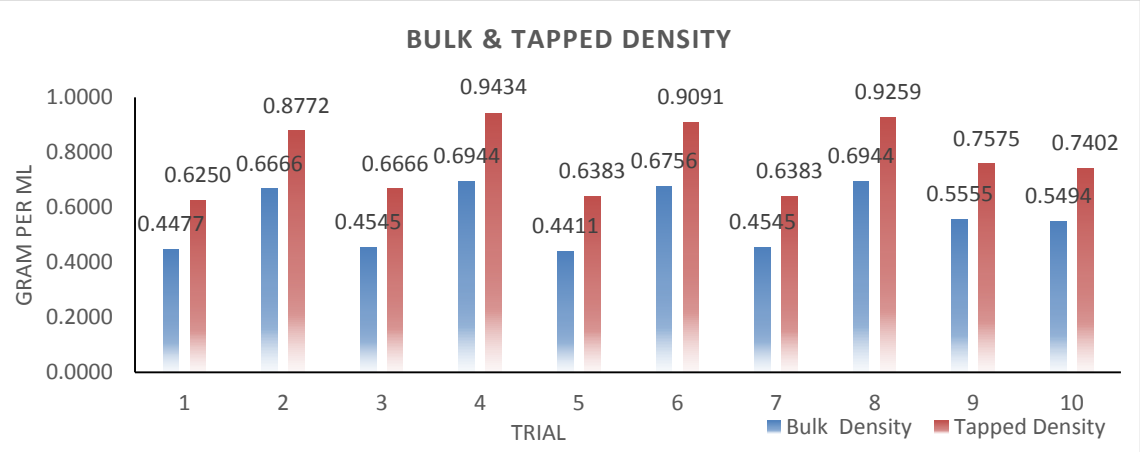


Figure 4.17: Bulk and tapped density

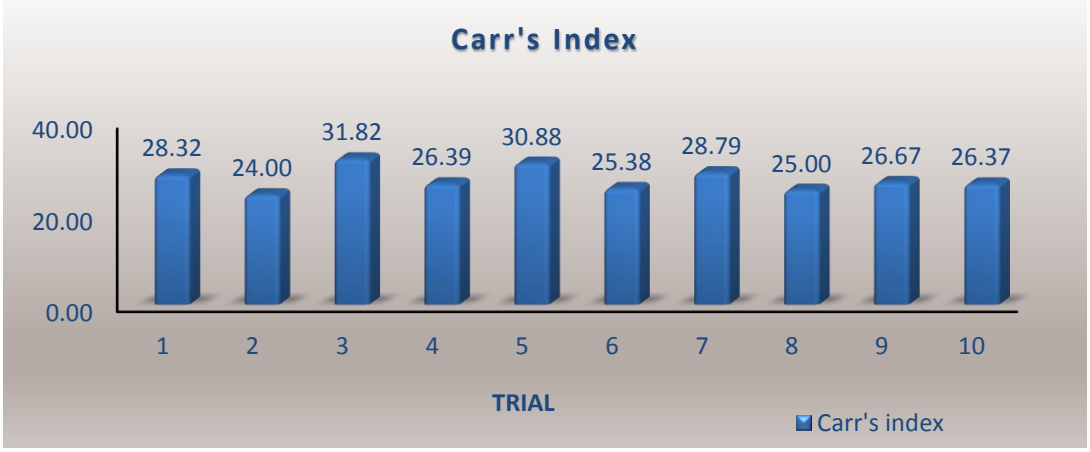


Figure 4.18 Carr's index

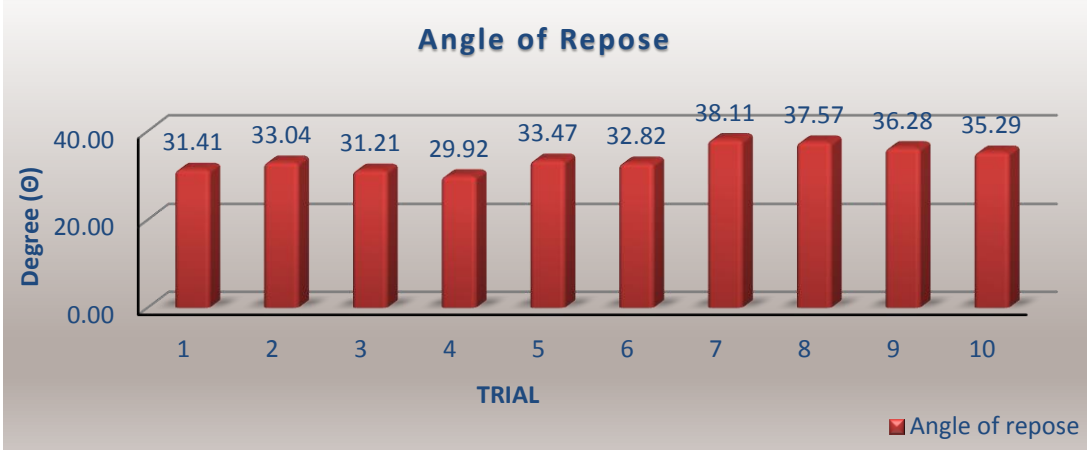


Figure 4.19 Angle of Repose

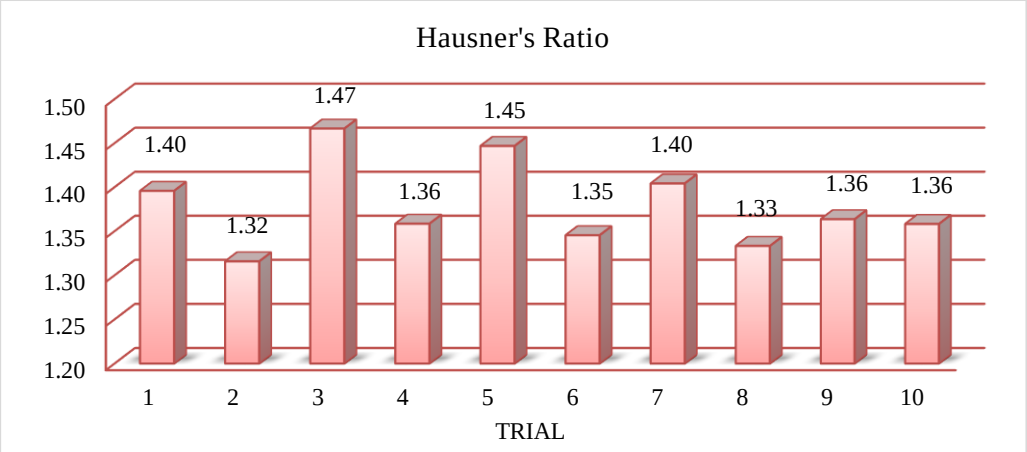


Figure 4.20: Hausners Ratio

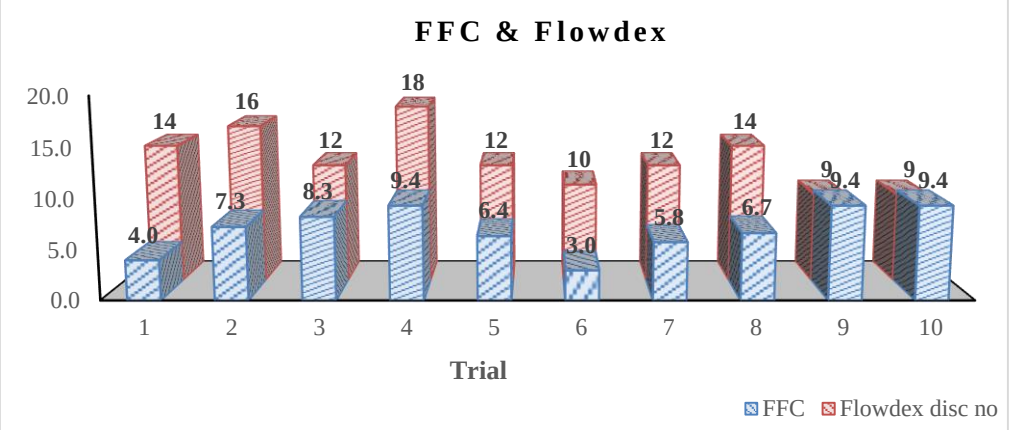


Figure 4.21 Flow Function Coefficient and Flowdex value

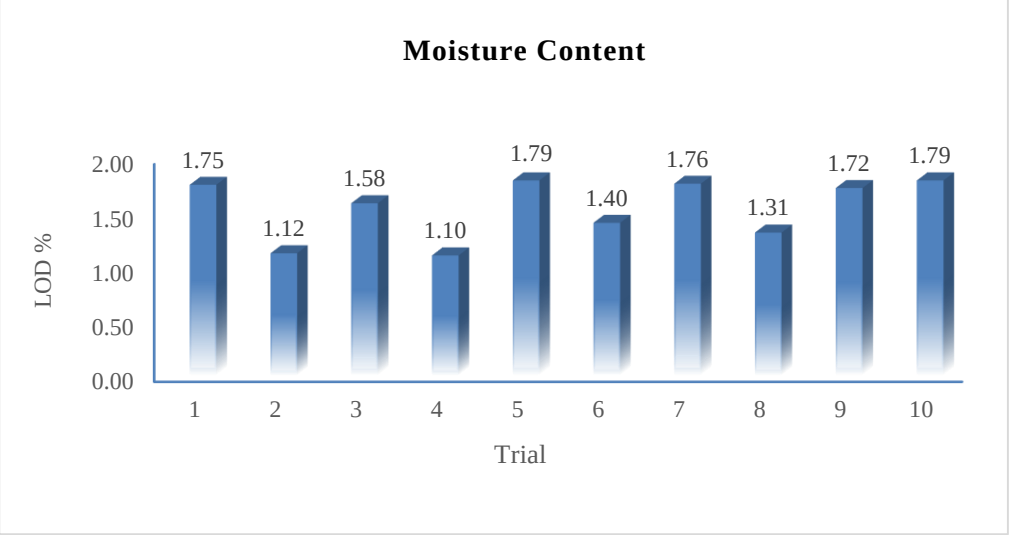


Figure 4.22: Moisture content

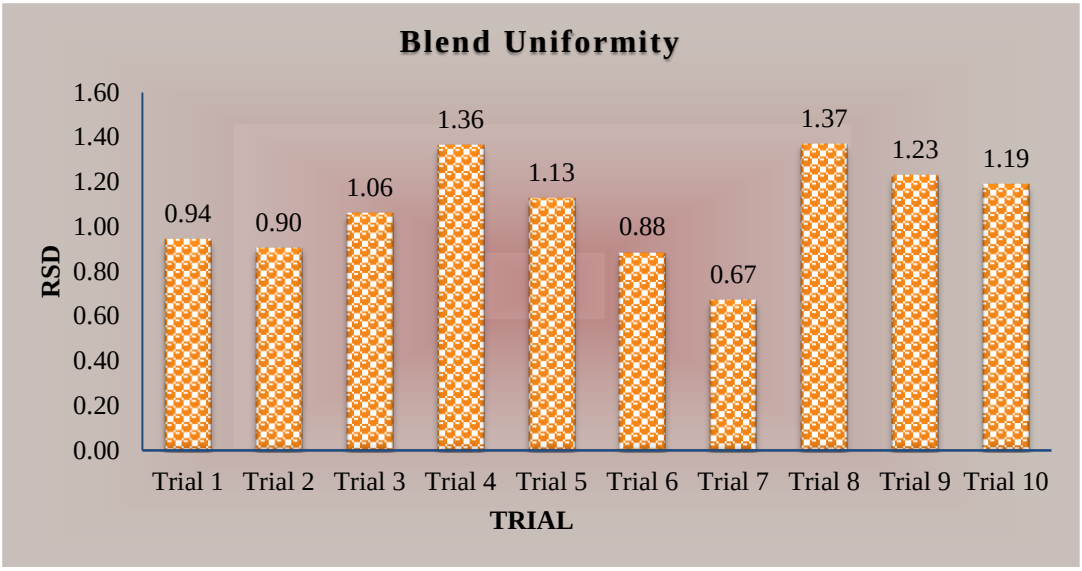


Figure 4.23: Blend Uniformity

❖ **Discussion:**

Characterisation of blend revealed that the bulk density of the all trial was good so as to obtain good compressibility during compression cycle.

Flow characteristics of blend was evaluated using angle of repose, flow function coefficient, and Flowdex, which shows that the blend has medium to good flow. This signifies that there will be no issues in the flow from hopper.

Moisture content in the blend was evaluated by measurement of loss on drying and it was found that it was less than 2 % in all the trial batches.

Blend uniformity is the major issue in case of direct compression method, so as to avoid blend uniformity issues Comilling was used and the random samples were collected from different location of blender were evaluated, it was found that there were no issues of the blend uniformity. This shows that API was evenly distributed in the whole blend.

4.3.12.4 Evaluation parameters of tablets:

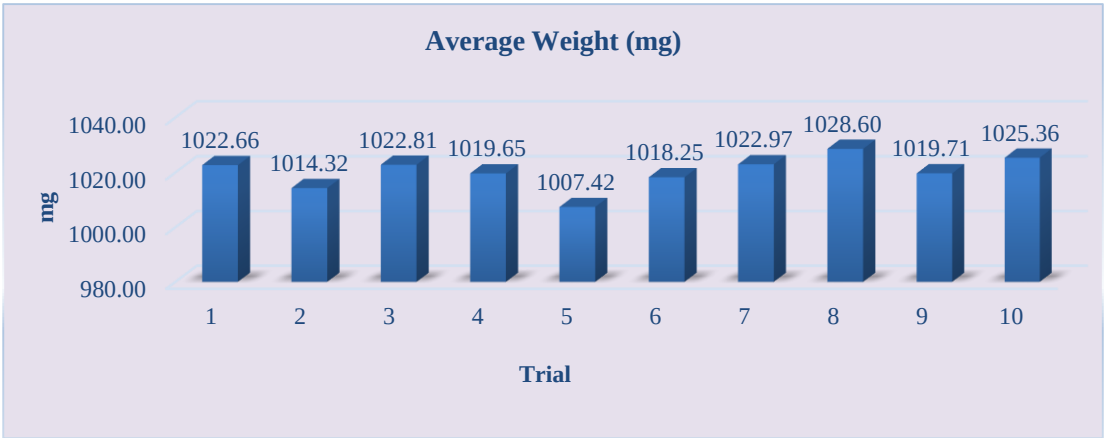


Figure 4.24: Weight variation

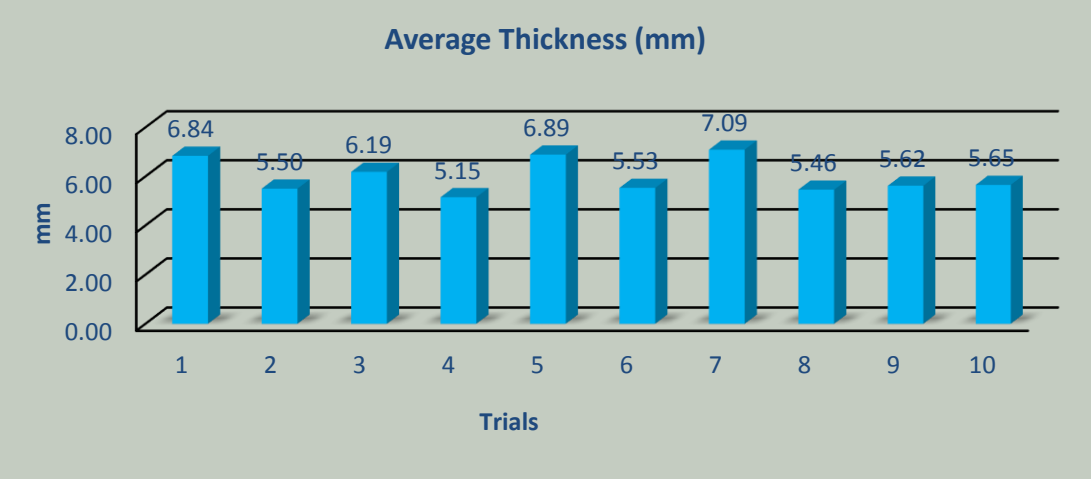


Figure 4.25: Average thickness

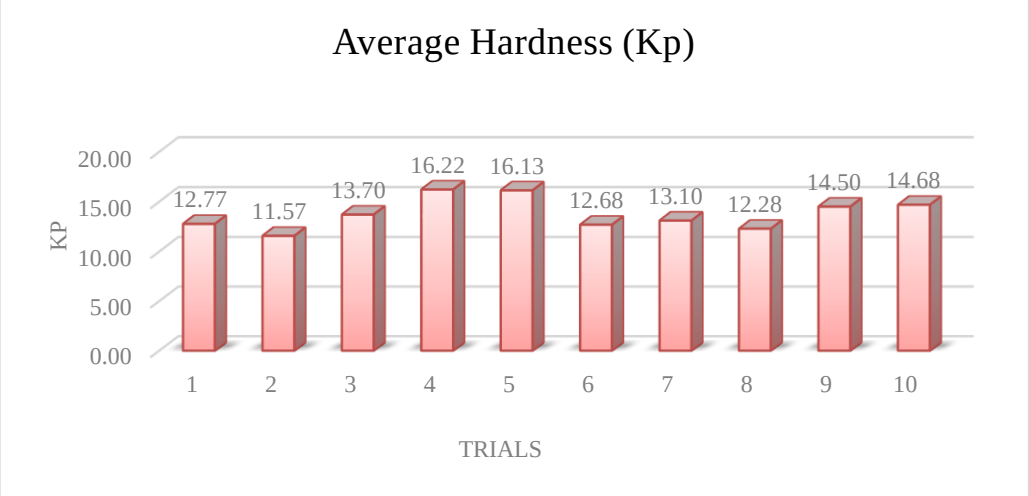


Figure 4.26: Hardness

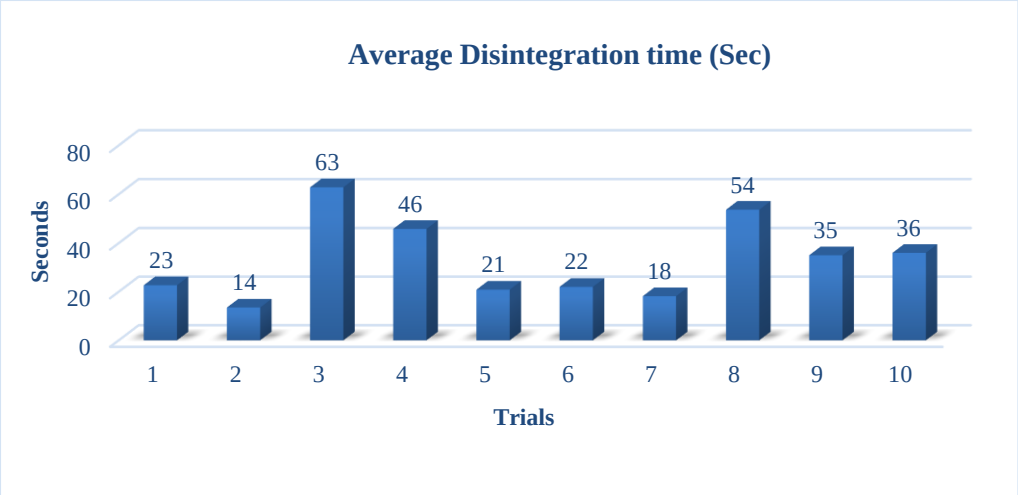


Figure 4.27: Disintegration time

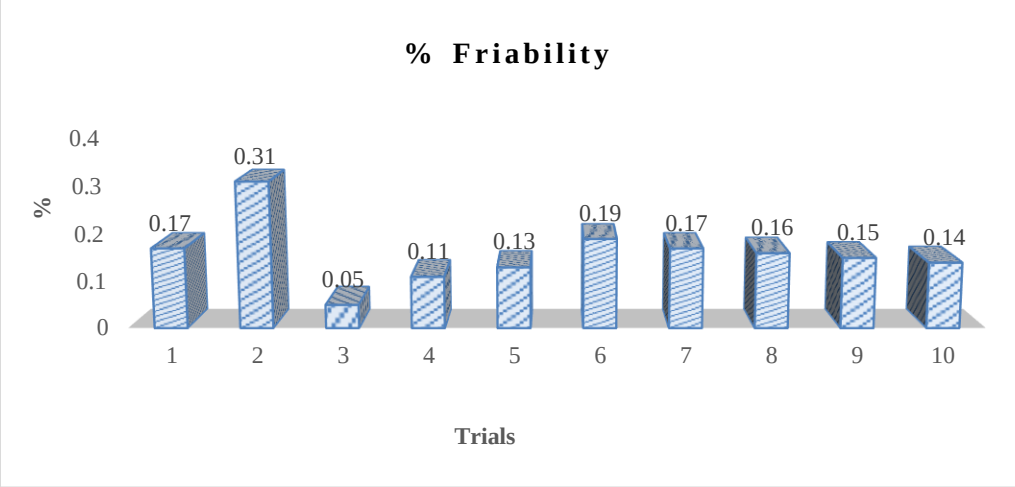


Figure 4.28: Friability

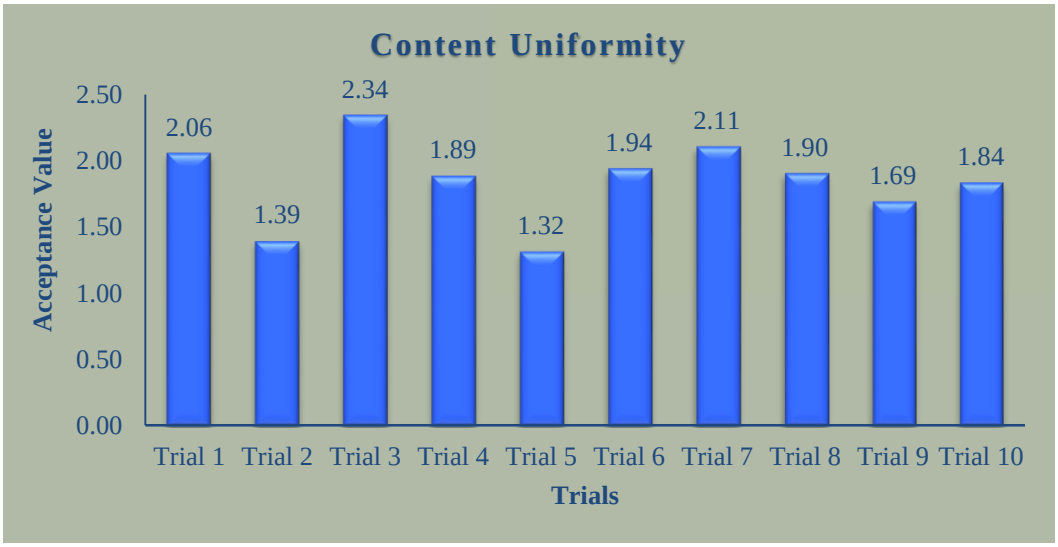
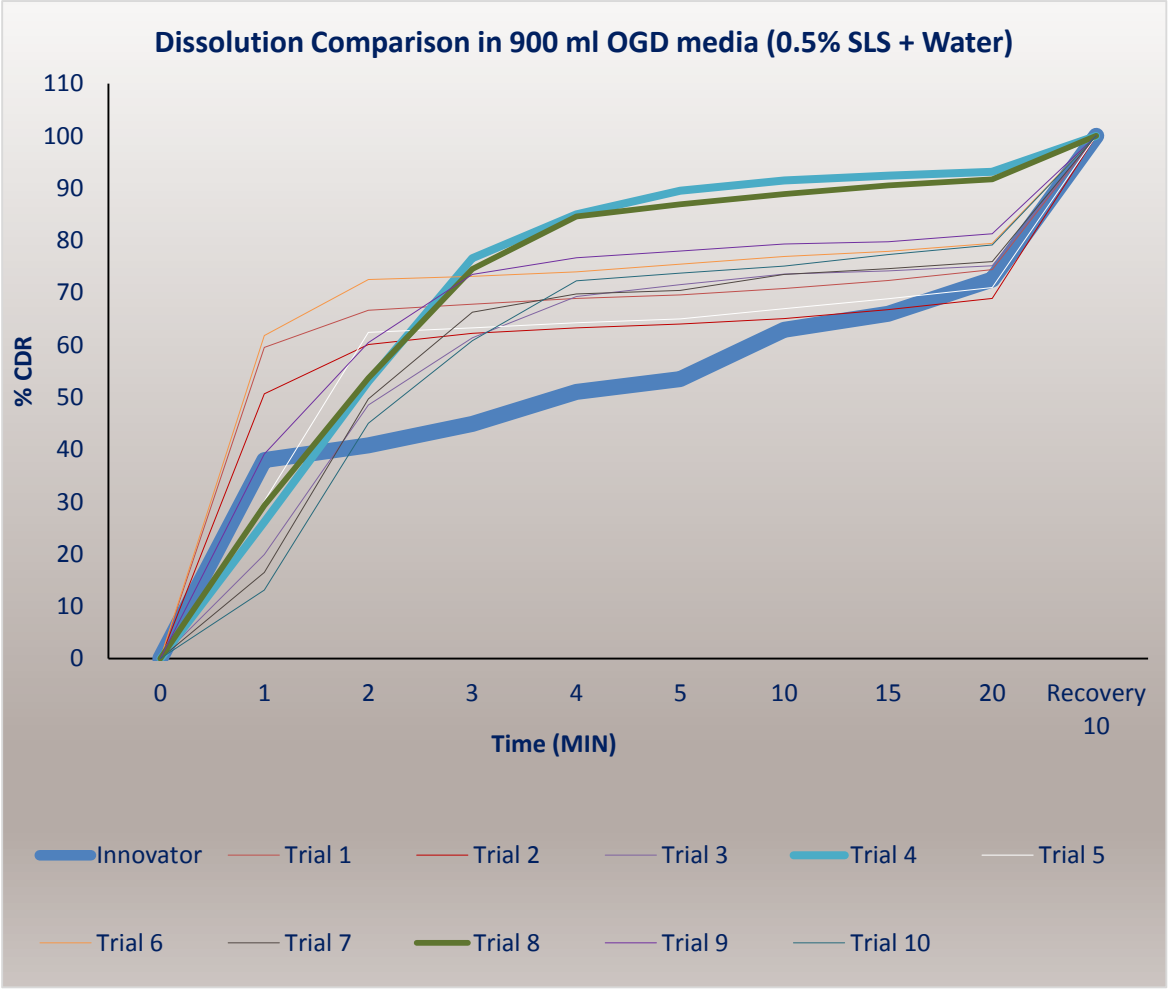


Figure 4.29: Content Uniformity

Figure 4.30: Invitro drug release profile of all batch compared with innovator product



❖ **Discussion:**

In process quality control testing of the compressed tablet was performed for weight variation, thickness, and hardness. It was found that there was no fluctuation in the result observed in case of all evaluation parameter.

According to IP 2010, weight variation of tablet was with in the range of ± 5%. Thickness of the tablet was good as compared to the punch dimensions. Hardness of the tablet was targeted between 10 – 20 kP, and it was observed that the hardness of all trials was in this range.

Disintegration time for trial 3, 4 and 8 was slightly prolonged to 63, 46, and 54 seconds which was on higher side from the targeted disintegration time of 30 seconds.

Friability testing of all trial was performed and it was observed that trial 2 shows maximum friability of 0.31% which is acceptable.

Content uniformity study of tablet was performed using suitable method and finally acceptance value was calculated as per USP. According to USP, if the acceptance value of tablet is less than 15 then the tablet pass the content uniformity test. Here from th e result it can be concluded that there were no issues of content uniformity in any of the trials.

Invitro dissolution study was carried out in the OGD media and % CDR is calculated. Targeted % CDR in 3 minute and 20 minute was to achieve more than 70% and 85% respectively. Trial 4, 6, 8 and 9 shows % CDR of 76.59, 73.12, 74.54 and 73.53% in 3 minutes respectively. But, in 20 minutes % CDR for trial 4 and 8 was found to be 93.14 and 91.72% respectively. Hence this can be confirmed that only trial 4 and 8 shows % CDR as per our target product profile.

Table 4.46: List of independent factors and Response

Independent Factors	Response
A = Amount of Sodium bicarbonate (SB) in mg	Y_1 = Disintegration Time (seconds)
B = Amount of Citric acid (CA) in mg	Y_2 = % CDR in 3 minutes
C = % of polyplasdone XL 10	Y_3 = % CDR in 20 minutes

4.3.12.5 Response

- **Response : Y_1 = Disintegration time**

Figure 4.31: Contour plot & 3-D Surface plot of disintegration time at Low level of Polyplasdone XL 10

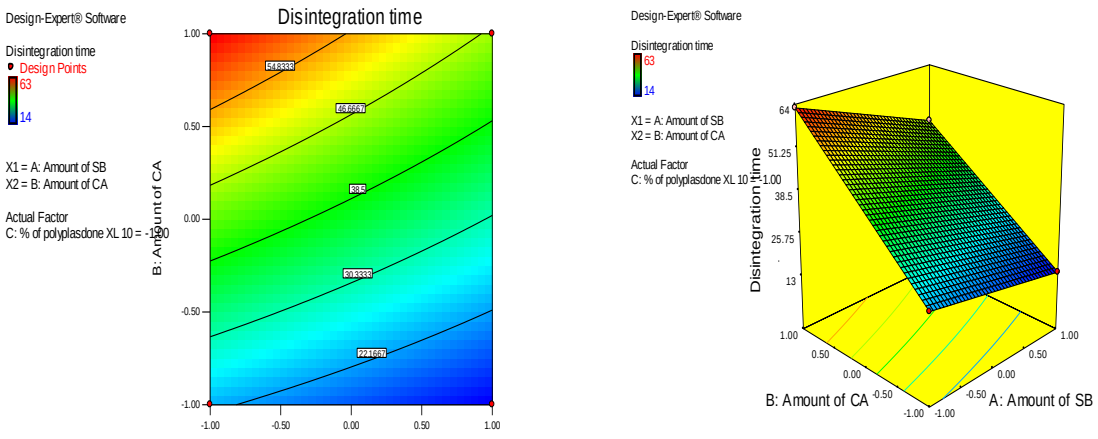


Figure 4.32: Contour plot & 3-D Surface plot of disintegration time at medium level of Polyplasdone XL 10

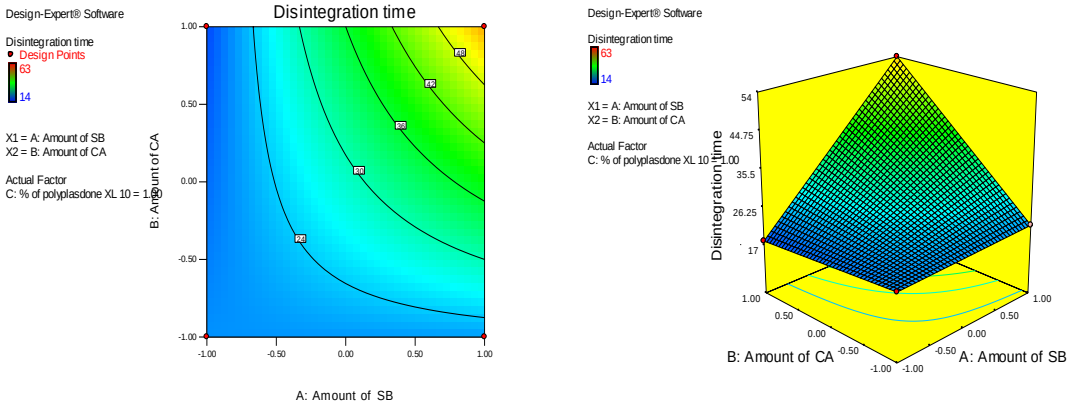
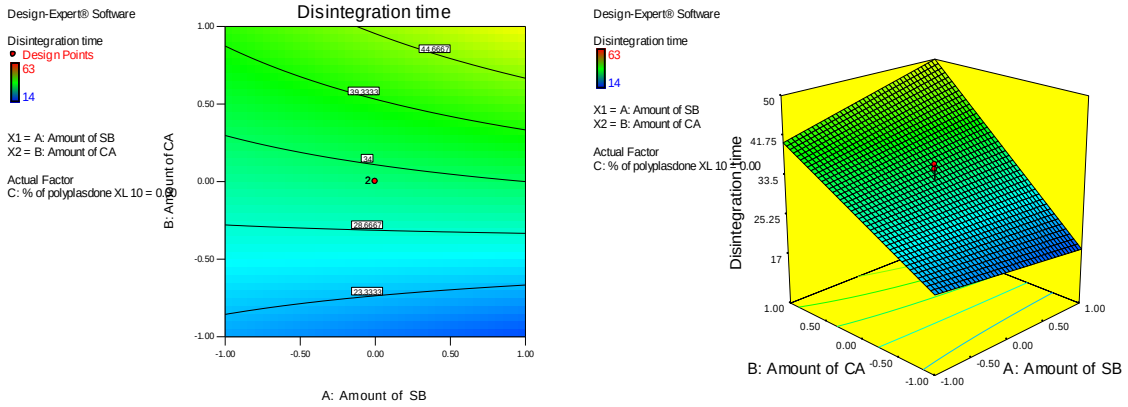


Figure 4.33: Contour plot & 3-D Surface plot of disintegration time at high level of Polyplasdone XL 10



❖ Statistical analysis:

Table 4.47: Statistical analysis of Disintegration time

Parameter	P Value	Coefficient
A = Amount of SB (mg)	0.1145	+1.38
B = Amount of CA (mg)	0.0126	+12.63
C = % of Polyplasdone XL 10	0.0410	-3.88
AB	0.0471	+3.37
AC	0.0202	+7.88
BC	0.0296	-5.38
ABC	0.0296	+5.37

Final equation in terms of coded values

DT = +32.63 +1.38A +12.63B –3.88C + 3.37AB +7.88AC -5.38BC +5.37ABC

❖ **Discussion:**

From statistical analysis it was concluded that at low level of polyplasdone XL 10 the disintegration time was prolonged even at high concentration of sodium bicarbonate and citric acid. As the amount of polyplasdone XL 10 was increased there was significant decrease in disintegration time and the amount of sodium bicarbonate and citric acid required was also less. Finally, when the concentration of polyplasdone XL 10 was maximum then disintegration time was minimum even at the minimum level of sodium bicarbonate and citric acid. Hence, this can be concluded that 5% polyplasdone XL 10 is required so as to obtain the desired disintegration time.

❖ **Response: Y_2 = % CDR in 3 minutes**

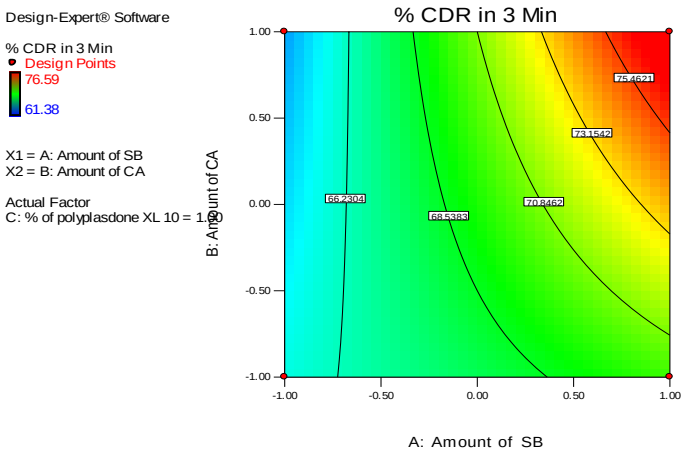


Figure 4.34: Contour plot of % CDR in 3 min at high level of Polyplasdone XL 10

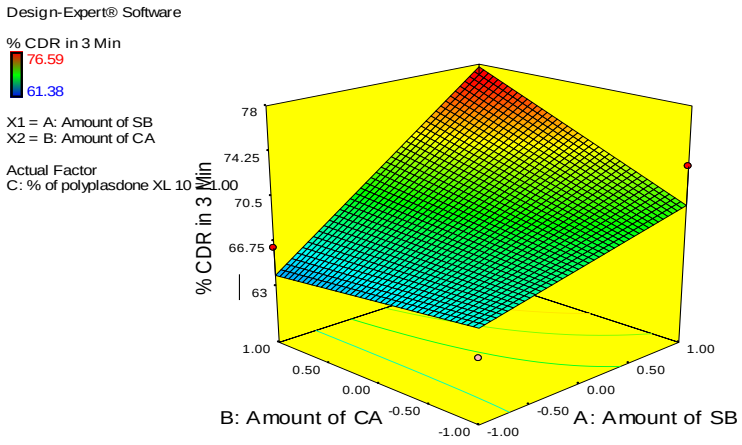


Figure 4.35: 3-D plot of % CDR in 3 min at high level of Polyplasdone XL 10

❖ **Statistical analysis:**

Table 4.48: Statistical analysis of % CDR in 3 min

Parameter	p Value	Coefficient
A = Amount of SB (mg)	0.1420	+3.47
B = Amount of CA (mg)	0.4440	+1.54
C = % of Polyplasdone XL 10	0.5584	+1.15
AB	0.2636	+2.4
AC	0.5887	+1.06

Final equation in terms of coded values

% CDR in 3 Min = +68.13 +3.47A +1.54B +1.15C + 2.4AB +1.06AC

❖ **Discussion:**

From statistical analysis this can be inferred that at high concentration of polyplasdone XL 10, sodium bicarbonate and citric acid are required to achieve the target disintegration time along with the percentage cumulative drug release as per the target profile.

Here also level of polyplasdone XL 10 plays an important role in dissolution in 3 min. at low levels of polyplasdone XL 10 the target release profile was not achieved in 3 min.

❖ **Response: Y_3 = % CDR in 20 minutes**

Figure 4.36: Contour plot of % CDR in 20 min at high level of Polyplasdone XL 10

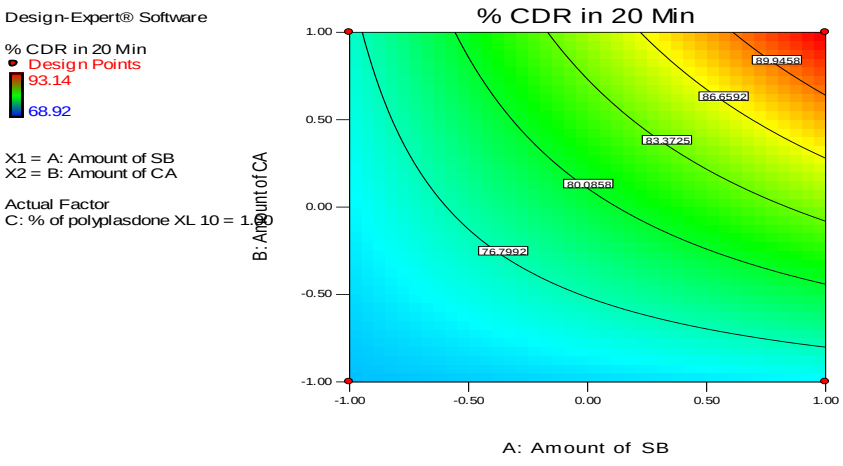
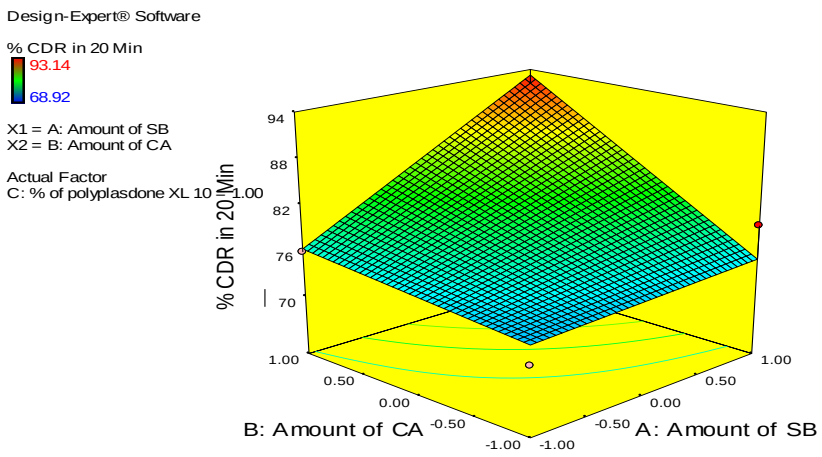


Figure 4.37: 3-D plot of % CDR in 20 min at high level of Polyplasdone XL 10



❖ **Statistical analysis:**

Table 4.49 : Statistical analysis of % CDR in 20 min

Parameter	p Value	Coefficient
A = Amount of SB (mg)	0.0286	+4.59
B = Amount of CA (mg)	0.0184	+5.27
C = % of Polyplasdone XL 10	0.5895	+0.80
AB	0.0482	+3.85

Final equation in terms of coded values

% CDR in 20 Min = +78.72 +4.59A +5.27B +0.80C + 3.85AB

❖ **Discussion:**

Sodium bicarbonate and citric acid does not affect significantly at any of the low, medium and high levels of polyplasdone XL 10. But, maximum amount of sodium bicarbonate and citric acid are required so as to achieve the target drug release profile.

From above all trials it was concluded that high level of polyplasdone XL 10 is must in order to achieve the target product profile. This was only achieved in case of trial 8, which contains high level of all three ingredients. So from DOE trials it was concluded that trial 8 meets the criteria of target product profile, hence it is considered to be the final optimised batch.

Figure 4.38: Desirability plot

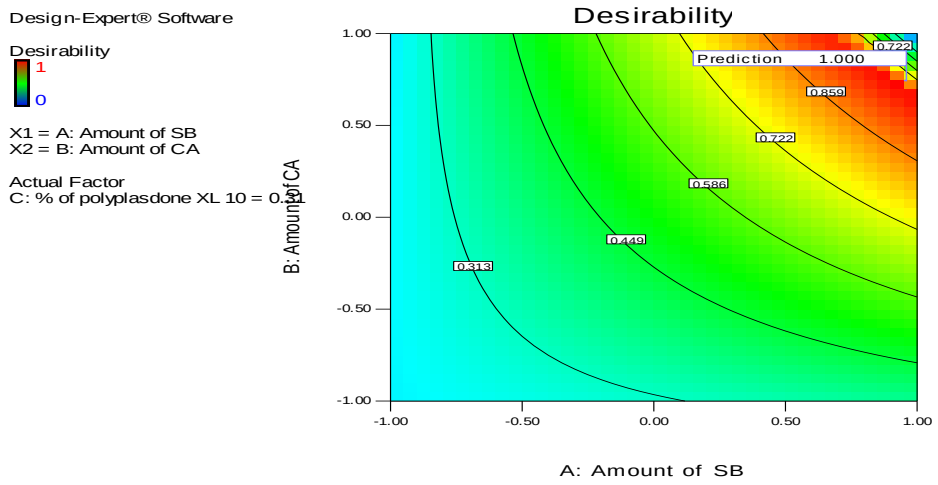


Figure 4.39: Overlay plot

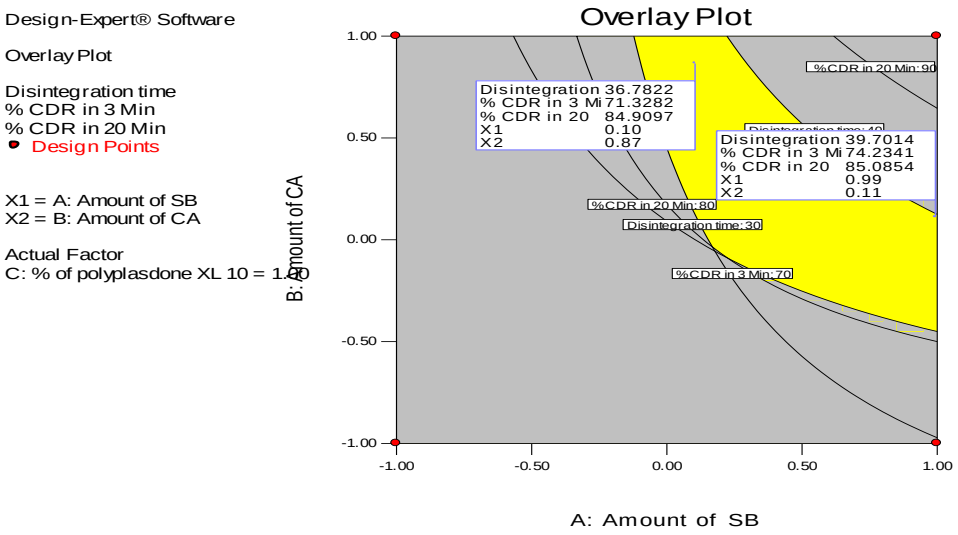


Table 4.50 : Level of ingredients in Checkpoint batch

Ingredient	CP 1	CP 2
Polyplasdone XL 10	5 %	5%
Sodium bicarbonate	0.10	0.99
Citric acid	0.87	0.11

Table 4.51: Composition of Checkpoint batch 1

Ingredients	(mg/tablet)	% of excipients	Qty for 250 tablet in gm.
API	10.4	1.02	2.6
Sodium Bicarbonate	420	41.34	105
Citric Acid Anhydrous	71.8	7.07	17.95
MCC (Avicel PH112)	371.84	36.60	92.96
Klucel EXF	81	7.97	20.25
Polyplasdone XL-10	50.8	5.00	12.70
Magnesium Stearate	10.16	1.00	2.54
Total	**1016**	**100.00**	**254**

Figure 4.40: Composition of Checkpoint batch 2

Ingredients	(mg/tablet)	% of excipients	Qty for 250 tablet in gm.
API	10.4	1.02	2.6
Sodium Bicarbonate	598	58.86	149.5
Citric Acid Anhydrous	52.9	5.21	13.225
MCC (Avicel PH112)	21.74	20.94	53.185
Klucel EXF	81	7.97	20.25
Polyplasdone XL-10	50.8	5.00	12.70
Magnesium Stearate	10.16	1.00	2.54
Total	**1016**	**100.00**	**254**

- **Observation:**

Accurate dispensing of material was done separately for all two batches, sifting through 40# mesh sieve, Blending in Turbula blender at 30 rpm for 10 Min, and Lubrication in Turbula blender at 30 rpm for 3 Min, and finally, Compression of tablet was done using Cadmach compression machine using two sets of 19 X 9.5 mm punches, capsule shaped, plain surface, B - tolling.

Table 4.52: Comparison of Evaluation parameter of checkpoint batch and optimised batch

Parameter	Optimised batch	Checkpoint 1	Checkpoint 2
Bulk Density (gm/ml)	0.6944	0.6956	0.6949
Tapped Density (gm/ml)	0.9254	0.9091	0.8991
Carr's index (%)	25.0000	25.6756	24.6575
Hausners ratio	1.33	1.3454	1.3272
Angle of Repose (^{0})	37.57	37.29	35.81
FFC value	6.7	7.0	7.3
Flowdex	14	14	12
Loss on drying (%)	1.31	1.56	1.49
Blend Uniformity (RSD)	1.37	1.35	1.40
Average Weight (mg)	1028.60±8.83	1012.05±8.36	1009.80±8.98
Thickness (mm)	5.46±0.03	6.39±0.03	6.37±0.03
Hardness (kP)	12.28±0.45	16.5±0.21	17.53±0.49
DT (min:sec)	54 seconds	38 seconds	42 seconds
Friability (%)	0.16%	0.13%	0.19%
Content Uniformity (AV)	1.90	2.1	2.5
% CDR in 3 min	74.54%	73.12%	74.91%
% CDR in 20 min	91.72%	85.89%	85.14%

❖ **ANOVA analysis:**

Table 4.53: ANOVA analysis of optimised Batch and checkpoint batch 1

Parameter	Optimised Batch	Checkpoint 1	P value	Summary
Bulk Density (gm/ml)	0.6944	0.6956	P > 0.05	Non-Significant
Tapped Density (gm/ml)	0.9254	0.9091	P > 0.05	Non-Significant
Carr's index (%)	25.0000	25.6756	P > 0.05	Non-Significant
Hausners ratio	1.33	1.3454	P > 0.05	Non-Significant
Angle of Repose (^{0})	37.57	37.29	P > 0.05	Non-Significant
FFC value	6.7	7.0	P > 0.05	Non-Significant
Flowdex	14	14	P > 0.05	Non-Significant
Loss on drying (%)	1.31	1.56	P > 0.05	Non-Significant
Blend Uniformity (RSD)	1.37	1.35	P > 0.05	Non-Significant
Average Weight (mg)	1028.60±8.83	1012.05±8.36	P > 0.05	Non-Significant
Thickness (mm)	5.46±0.03	6.39±0.03	P > 0.05	Non-Significant
Hardness (kP)	12.28±0.45	16.5±0.21	P > 0.05	Non-Significant
DT (min:sec)	54 seconds	38 seconds	P > 0.05	Non-Significant
Friability (%)	0.16%	0.13%	P > 0.05	Non-Significant
Content Uniformity (AV)	1.90	2.1	P > 0.05	Non-Significant
% CDR in 3 min	74.54%	73.12%	P > 0.05	Non-Significant
% CDR in 20 min	91.72%	85.89%	P > 0.05	Non-Significant

Table 4.54 : ANOVA analysis of optimised Batch and checkpoint batch 2

Parameter	Optimised Batch	Checkpoint 2	P value	Summary
Bulk Density (gm/ml)	0.6944	0.6949	P > 0.05	Non-Significant
Tapped Density (gm/ml)	0.9254	0.8991	P > 0.05	Non-Significant
Carr's index (%)	25.0000	24.6575	P > 0.05	Non-Significant
Hausners ratio	1.33	1.3272	P > 0.05	Non-Significant
Angle of Repose (^{0})	37.57	35.81	P > 0.05	Non-Significant
FFC value	6.7	7.3	P > 0.05	Non-Significant
Flowdex	14	12	P > 0.05	Non-Significant
Loss on drying (%)	1.31	1.49	P > 0.05	Non-Significant
Blend Uniformity (RSD)	1.37	1.40	P > 0.05	Non-Significant
Average Weight (mg)	1028.60±8.83	1009.80±8.98	P > 0.05	Non-Significant
Thickness (mm)	5.46±0.03	6.37±0.03	P > 0.05	Non-Significant
Hardness (kP)	12.28±0.45	17.53±0.49	P > 0.05	Non-Significant
DT (min:sec)	54 seconds	42 seconds	P > 0.05	Non-Significant
Friability (%)	0.16%	0.19%	P > 0.05	Non-Significant
Content Uniformity (AV)	1.90	2.5	P > 0.05	Non-Significant
% CDR in 3 min	74.54%	74.91%	P > 0.05	Non-Significant
% CDR in 20 min	91.72%	85.14%	P > 0.05	Non-Significant

Table 4.55: ANOVA analysis of checkpoint batch 1 and checkpoint batch 2

Parameter	Optimised Batch	Checkpoint 2	P value	Summary
Bulk Density (gm/ml)	0.6944	0.6949	P > 0.05	Non-Significant
Tapped Density (gm/ml)	0.9254	0.8991	P > 0.05	Non-Significant
Carr's index (%)	25.0000	24.6575	P > 0.05	Non-Significant
Hausners ratio	1.33	1.3272	P > 0.05	Non-Significant
Angle of Repose (^{0})	37.57	35.81	P > 0.05	Non-Significant
FFC value	6.7	7.3	P > 0.05	Non-Significant
Flowdex	14	12	P > 0.05	Non-Significant
Loss on drying (%)	1.31	1.49	P > 0.05	Non-Significant
Blend Uniformity (RSD)	1.37	1.40	P > 0.05	Non-Significant
Average Weight (mg)	1028.60±8.83	1009.80±8.98	P > 0.05	Non-Significant
Thickness (mm)	5.46±0.03	6.37±0.03	P > 0.05	Non-Significant
Hardness (kP)	12.28±0.45	17.53±0.49	P > 0.05	Non-Significant
DT (min:sec)	54 seconds	42 seconds	P > 0.05	Non-Significant
Friability (%)	0.16%	0.19%	P > 0.05	Non-Significant
Content Uniformity (AV)	1.90	2.5	P > 0.05	Non-Significant
% CDR in 3 min	74.54%	74.91%	P > 0.05	Non-Significant
% CDR in 20 min	91.72%	85.14%	P > 0.05	Non-Significant

❖ **Discussion:**

From ANOVA analysis of optimised batch, Checkpoint batch 1 and checkpoint batch 2, it was inferred that there was no significant difference between checkpoint batches and the optimised batch.

4.3.13 STUDIES OF DRUG RELEASE KINETICS

Release of the drug from the insoluble matrix is extremely highlighted in the literature. To obtain the dissolution rate constants of the drug from matrices, various models are reported. They are tried to fit the optimized batch to determine the mechanism of drug release.

❖ **Zero order model:**

In many of the modified release dosage forms, particularly controlled or sustained release dosage forms, drug release follows zero order kinetics.

$$M=K*t$$

Where K is zero order rate constant, M is % drug unreleased (or released) and t is time. The plot of % drug unreleased (or released) vs. time is linear.

❖ **First order model:**

Most conventional dosage forms exhibits this dissolution mechanism. Some modified release preparations, particularly prolong release formulations, adhere to this type of dissolution pattern.

$$M= e^{a} * e^{-bt}$$

Where, a is intercept and b is slop.

It assumes that the drug molecules diffuse out through a gel like layer formed around the drug during the dissolution process. A plot of log % drug release vs. time is linear.

❖ **Higuchi model:**

A large number of modified released forms contain some sort of matrix system. In such instances, the drug dissolves from the matrix. The dissolution pattern of the

drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies.

M= (100-Q)*sqrt of time

Where, q is the Higuchi constant (% per square root of time)

In Higuchi model, a plot of % drug unreleased (or released) vs. sqrt of time is linear.

❖ **Korsmeyer-Peppas model:**

$$Mt/M = k*t^n$$

Where, Mt/M is the fraction of drug released at time't'. n is diffusion exponential;

If n>1, the release is of zero order

If n=0.5, release best explained by Fickian diffusion,

0.5<n<1, releas is through anamolous diffusion

A plot of log fraction of drug release vs. log t is linear.

❖ **Hixon-crowell model:**

Some dosage forms contain many particles of the same size and shape or their agglomerates that dissolve evenly. In such instances the cube root law can express the dissolution process.

$$M= (100^{1/3}-(k*t))^3$$

Where, k is Hixon-crowell constant (mass/time) $^{1/3}$

In this model, the % drug unreleased vs. cube root of time is linear.

❖ **Weibull distribution model:**

When applied to the dissolution data, the Weibull equation express the accumulated fraction of material in solution at time by:

$$M=1-exp\ (-(t=ti)^{b/a})$$

Where, a = scale parameter which defines the time scale of the process. It is location parameter which represents the lag period before the actual onset of dissolution process (in most cases, ti=0) and b is the shape parameter.Plot of log time vs. In (I-m) is linear.

❖ **Results**:

Model	R Square	SSR	Fischer Ratio
Zero Order	0.9734	198.05	24.55
First Order	0.9589	12811.30	1601.41
Higuchi	0.9841	450.14	56.27
Korsmeyer – Peppas	0.9881	32599.05	4657.01
Weibull model	0.9705	14674.59	2096.37
Hixson - Crowell	0.9389	12840.00	1834.29

❖ **Discussion**:

From Above results of drug release kinetics, it was observed that R square value in Higuchi model and Korsmeyer –Peppas was higher. But, SSR and F value in Higuchi Model was less. So, it was concluded that Higuchi Model was best fitted to the optimised batch.

4.3.14 Stability Study

4.3.14.1 Product Details and Label claim**:**

Each tablet contains 10 mg of PPDS_11YA.

4.3.14.2 Packaging:

Close condition: Each HDPE bottle contains 50 Tablets.

4.3.14.3 Sampling plan:

Table 4.56: Sampling plan

Time point	Storage Temperatures	
	25°C/ 60%RH	40°C/ 75%RH
Initial	ab	ab
2 weeks	a	a
4 Weeks	a	a
Total No of Bottles	3	3

ab: Initial sample for testing a: Time point for testing

4.3.14.4 Product Specifications:

Table 4.57 Product Specifications

Sr. No	Test	Specification
1	Appearance	To be observed
2	Disintegration Time (sec)	To be observed
3	In vitro Dissolution (%CDR in 3 min)	To be observed
4	In vitro Dissolution (%CDR in 20 min)	To be observed

4.3.14.5 Result:

Table 4.58: Results of Stability study of optimised batch

Time point	**Test**	**Storage Temperatures**	
		25°C/ 60%RH	**40°C/ 75%RH**
Initial	Appearance	White colour	White colour
	Disintegration Time (Sec)	54	54
	In vitro Dissolution (%CDR in 3 min)	74.54	74.54
	In vitro Dissolution (%CDR in 20 min)	91.72	91.72
2 weeks	Appearance	White colour	White colour
	Disintegration Time (Sec)	60	63
	In vitro Dissolution (%CDR in 3 min)	73.51	72.76
	In vitro Dissolution (%CDR in 20 min)	89.59	87.63
4 weeks	Appearance	White colour	White colour
	Disintegration Time (Sec)	63	72
	In vitro Dissolution (%CDR in 3 min)	70.58	71.34
	In vitro Dissolution (%CDR in 20 min)	88.65	86.25

Table 4.59: Results of Stability study of Checkpoint batch 1

Time point	Test	Storage Temperatures	
		25°C/ 60%RH	40°C/ 75%RH
Initial	Appearance	White colour	White colour
	Disintegration Time (Sec)	38	38
	In vitro Dissolution (%CDR in 3 min)	73.12	73.12
	In vitro Dissolution (%CDR in 20 min)	85.89	85.89
2 weeks	Appearance	White colour	White colour
	Disintegration Time (Sec)	40	43
	In vitro Dissolution (%CDR in 3 min)	72.54	70.29
	In vitro Dissolution (%CDR in 20 min)	84.53	83.71
4 weeks	Appearance	White colour	White colour
	Disintegration Time (Sec)	48	52
	In vitro Dissolution (%CDR in 3 min)	69.79	71.34
	In vitro Dissolution (%CDR in 20 min)	81.26	80.79

Table 4.60: Results of Stability study of Checkpoint batch 2

Time point	Test	Storage Temperatures	
		25°C/ 60%RH	40°C/ 75%RH
Initial	Appearance	White colour	White colour
	Disintegration Time (Sec)	42	42
	In vitro Dissolution (%CDR in 3 min)	74.91	74.91
	In vitro Dissolution (%CDR in 20 min)	85.14	85.14
2 weeks	Appearance	White colour	White colour
	Disintegration Time (Sec)	45	46
	In vitro Dissolution (%CDR in 3 min)	73.51	72.12
	In vitro Dissolution (%CDR in 20 min)	84.89	83.01
4 weeks	Appearance	White colour	White colour
	Disintegration Time (Sec)	55	58
	In vitro Dissolution (%CDR in 3 min)	70.21	69.18
	In vitro Dissolution (%CDR in 20 min)	82.34	81.65

- **Discussion:** After the four weeks of Stability Study, it was found that there was increase in the disintegration time and decrease in % CDR as compared to initial testing. But, it was with in the limit of 98% - 102% at the end of dissolution.

Chapter: 5

Summary

96% of the time you can predict the outcome of a conversation based on the first three minutes of the discussion

5. Summary

Solid oral dosage forms are the least expensive, most popular and convenient methods for drug delivery. They are produced in a non-sterile environment and the technology is well known after more than 100 years of development. Oral route is most acceptable drug delivery route due to its better therapeutic efficacy and high patient compliance. Therefore, most of the advances are done in developing new dosage form for the oral route.

PPDS_11YA is a BCS class 1 drug used as an Antiasthmatic agent. Leukotriene antagonist and mast cell stabilisers are recommended for those who suffer daily attack of asthma. Therefore, immediate release dosage form is required for treatment of this condition.

The objective of this research was to develop ultra-fast dissolving tablets for immediate release of the drug from the dosage form to obtain early onset of action.

In the present study, ultra-fast dissolving drug delivery systems of PPDS_11YA were successfully developed in the form of tablet, which offers fast disintegration and dissolution characteristics.

Preformulation studies such as melting point determination, solubility study in different media and FT-IR study was conducted to verify the purity of the API. Furthermore, drug and excipients compatibility study was conducted so as to check regarding any incompatibility of API with other inactive ingredients. Results showed that there were no drug excipients interaction. Finally, the percentage drug content in each vial was estimated by proper assay procedure and it was with in the acceptable range as per USP.

In preliminary trials tablets were manufactured using pH modulating agents (Sodium bicarbonate and citric acid), water uptaking agents (Lactose monohydrate, Avicel PH 112, Klucel EXF, starch 1500, Acdisol, polyplasdone XL 10, Primellose) and magnesium stearate as lubricant in different combinations and ratios using Cadmach compression machine. From preliminary trials it was found that level of pH modulating agents and disintegrant needs to be optimised in the formulation so as to achieve the target product profile of disintegration and dissolution.

Optimisation of polyplasdone XL 10, sodium bicarbonate and citric acid was done using 2^3 full factorial design. Pre compression parameters of blend such as bulk density, tapped density, carr's index, Hausners ratio, angle of repose, flow function coefficient, Flowdex, moisture content and blend uniformity were evaluated. Finally, All design batches were manufactured using Cadmach compression machine and tablets were evaluated for following parameters such as weight variation, thickness, hardness, disintegration time, friability, content uniformity and In vitro drug release profile in different bio-relevant media.

Invitro dissolution profile was compared with the marketed formulation and it was found that the ultra-fast dissolving tablet shows promising results as compared to the marketed product.

Stability study was performed for optimised batch at 25^0C/60% RH and 40^0C/75% RH for one month. During the period of stability study, the samples were examined at the end of 2^{nd} week and 4^{th} week. General appearance, disintegration time and Invitro drug release profile were examined. It was found that after 2^{nd} week there was no significant changes in the formulation. However, at the end of 4^{th} week, it was seen that % CDR in 3 minutes was decreased as compared to the initial release profile.

Chapter: 6

References

"Google can bring you back million answers,
A book can bring you back to the right one"

7. References

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