FORMULATION AND EVALUATION OF OMEPRAZOLE AND DOMPERIDONE BILAYER TABLETS

A Dissertation submitted to
THE TAMILNADU Dr. M.G.R.MEDICAL UNIVERSITY,
CHENNAI.

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

BY

REG .NO: 26091387

Under the guidance of

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Principal, Prof. & HOD of Pharmaceutics

OCTOBER - 2011

THE ERODE COLLEGE OF PHARMACY AND RESEARCH INSTITUTE

ERODE- 638112,

TAMIL NADU.

Dedicated to

My

Family,

&

Friends

Certificates

The Erode College Of Pharmacy And Research Institute

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CERTIFICATE

This is to certify that the investigation in this thesis entitled **"FORMULATION AND EVALUATION OF OMEPRAZOLE AND DOMPERIDONE BILAYER TABLETS"** submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** for the partial fulfillment of the award of Degree of **MASTER OF PHARMACY** in **PHARMACEUTICS,** was carried out by **Regd. No. 26091387** in the Department of Pharmaceutics, **The Erode College of Pharmacy and Research Institute, Erode 638112,** under my guidance and supervision.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of this or any other university.

Place: Erode **Dr.V.Ganesan, M.Pharm., Ph.D.,**

Date:

ENDORSEMENT BY THE PRINCIPAL

This is to certify that the work embodied in this thesis entitled, **"FORMULATION AND EVALUATION OF OMEPRAZOLE AND DOMPERIDONE BILAYER TABLETS"** submitted to **The TamilNadu Dr. M.G.R. Medical University, Chennai**, for the partial fulfillment of the award of Degree of **MASTER OF PHARMACY in PHARMACEUTICS**, was carried out by **Regd.No.26091387** under the guidance of **Dr.V.Ganesan, M.Pharm., Ph.D.,** The Erode College of Pharmacy and Research Institute, Erode.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of this or any other university.

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DECLARATION

The research work embodied in this dissertation work entitled **"FORMULATION AND EVALUATION OF OMEPRAZOLE AND DOMPERIDONE BILAYER TABLETS"** was carried out by me in the Department of Pharmaceutics, The Erode College of Pharmacy, Erode, under the direct supervision of **Dr.V.Ganesan, M.Pharm., Ph.D., Principal, Prof., and Head, Dept. of Pharmacetuics** , The Erode College of Pharmacy and Research Institute, Erode – 638 112.

This dissertation submitted to **The Tamil Nadu Dr. M.G.R Medical University**, **Chennai,** as a partial fulfillment for the award of **Degree of Master of Pharmacy** in Pharmaceutics during the academic year 2010 – 2011.

The work is original and has not been submitted in part or full for the award of any other Degree or Diploma of this or any other University.

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Acknowledgement

I take this as an opportunity to express my sincere appreciation and thanks to my guide ***Dr. V.Ganesan., M.Pharm., Ph.D., Principal, Prof. and Head, Department of Pharmaceutics, The Erode college of Pharmacy and Research Institute, Erode*** *for his esteemed guidance all through the course of this work and I am extremely thankful to him for the encouragement and kind advice throughout the progress of work.*

I express my heartly and humble thanks to ***Dr.G.Mallikarjun Rao****, Deputy General Manager and* ***Mr G.Ramana Reddy*** *F R&D Head, of Combat Drugs Ltd. Hyd, for making all facilities available their timely help, encouragement, boosting my confidences in the progress of my industrial training in carrying out my dissertation work.*

I owe a debt of gratitute to ***Prof. S.P. Senthil. M.Pharm., (Ph.D.,),*** *Department of Pharmaceutics, The Erode college of Pharmacy and Research Institute, Erode for spending his valuable time on several occasions to impart me the gains of his knowledge.*

We also thankful to our Department staff ***Mrs.S.Allimalarkodi, M.Pharm., Mrs. T.Sudhamani, M.Pharm., and Mr.T.Ethiraj,M.Pharm.****, for providing the facilities in department and their timely help and constant encouragement throughout duration of my course.*

I express my gratitude to ***Dr V.S. Saravanan****., Vice Principal and Head of Department of Pharmaceutical Analysis,,****Mr.T.M.Kulanthaivel****, Deaprtment of Pharmaceutical Analysis for helping me in guiding through out the research work.*

I wish to thanks to ***Dr.Shivakumar,*** *Professor, Head of Department of Pharmacy Practise The Erode College of Pharmacy and Research Institute, Erode for his suggestions and support during my dissertation work.*

I am also thankful to ***Mr. A.Natarajan****, Secretary and Correspondents, The Erode college of Pharmacy and Research Institute, Erode for my achievement in this college.*

I am greatly indebted to ***All Department Faculties*** *of The Erode College of Pharmacy and Research Institute, Erode, for their scholarly guidance, precious advice, direct supervision and constant encouragement for carrying out this work successfully.*

I would like to express our heartfelt thanks to my classmates ***Appalraju, Ayyappa, Ismail Khan, Noveen kumar, Phaniradha Krishna, Ramkumar, ,*** *for their constant inspiration, kind co-operation and timely help throughout my post graduation..*

A simple word like thanks would be insufficient to express my gratitude to my friends ***T.G.P.Chandra Sekhar, G.V.Ramana Reddy, P.Sudhakar Reddy and P.Sharath*** *for their valuable help during the research.*

I wish to thank to ***Librarian, Lab Assistants, All Office Staff and Non Teaching Staff*** *for providing timely assistance through out the course.*

The completion of this dissertation is not fulfillment of my dreams but also the dreams of my ***Parents*** *and my* ***Brother*** *who have taken lots of pain for me in completion of higher studies.*

Finally I thank one and all, who helped me directly or indirectly for the successful completion of dissertation

Date:

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LIST OF ABBREVIATIONS

IP	:	Indian Pharmacopoeia
BP	:	British Pharmacopoeia
USP	:	United State Pharmacopoeia
NF	:	National Formulary
Ph. Eur	:	European Pharmacopoeia
DR	:	Delayed Release
SR	:	Sustained Release
GERD	:	Gastroesophageal reflux disease
FTIR	:	Fourier Transform Infra Red
UV	:	Ultraviolet
HPLC	:	High Performance Liquid Chromatography
nm	:	Nanometre
RH	:	Relative Humidity
NMT	:	Not more than
NLT	:	Not less than
KP	:	Kilo Pascal's
N	:	Newton's
Gm	:	Gram
hrs	:	Hours
Log	:	Logarithm
R^2	:	Regression coefficient
min	:	Minutes
mg	:	Milligram
mL	:	Millilitre
mm	:	Millimeter
rpm	:	Revolutions per minute

S.D	:	Standard deviation
%	:	Percentage
^{o}C	:	Degree Celsius
µL	:	Micro litre
µg	:	Microgram
µm	:	Micrometer
mpas	:	Milli pascals
BD	:	Bulk Density
TD	:	Tapped Density
CAS	:	Chemical abstract science
FDA	:	Food and drug administration
ICH	:	International Conference on Harmonization
Avg	:	Average
K_a	:	Absorption rate constant
HPMC	:	Hydroxy Propyl Methyl Cellulose
HPMC P	:	Hydroxy Propyl Methyl Cellulose Pthalate
PVP	:	Poly vinyl pyrrolidone
Mg Oxide	:	Magnesium Oxide
Mg stearate	:	Magnesium stearate
IPA	:	Isopropyl Alcohol
PEG	:	Polyethylene Glycol
HDPE	:	High Density poly Ethylene
BAP	:	Binding Agent preparation Vessel
API	:	Active Pharmaceutical Ingredient
RMG	:	Rapid Mixer Granulator
FBD	:	Fluid bed dryer
LOD	:	Loss on Drying

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Chapter 1

INTRODUCTION

1. INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in the body in order to promptly achieve and thereby maintain the desired drug concentration. The drug delivery system should deliver the drug at a rate dictated by the needs of the body over a period of treatment[1].

The best new therapeutic entity in the world is of little value without an appropriate delivery system. Tablet delivery system can range from simple immediate release formulations to complex extended or modified release dosage forms. The most important role of drug delivery system is to get the drug delivered to the site of action in sufficient amount & at the appropriate rate. However it should meet other important criteria such as physical & chemical stability, ability to be mass-produced in a manner that assures content uniformity.

Solid dosage forms are widely prevalent due to their age-old application. Especially, oral solid formulations hold a high potential as they serve to be most convenient for the administration of drugs. More than 50% of drug delivery systems available in the market are oral drug delivery systems. They offer convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost. Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules.

1.1 MULTILAYERED TABLETS[8]:

When two or more active pharmaceutical ingredients are needed to be administered simultaneously and they are incompatible, the best option for the formulation pharmacist would be to formulate multilayered tablet. It consists of several different granulations that are compressed to form a single tablet composed of two or more layers and usually each layer is of different colour to produce a distinctive looking tablet. Each layer is fed from separate feed frame with individual weight control. Dust extraction is essential during compression to avoidcontamination. Therefore, each layer undergoes light compression as each component is laid down. This avoids granules intermixing if the machine vibrates.

1.2 BILAYER TABLETS[9]:

Bilayer tablet is a unit compressed tablet dosage form intended for oral administration. It comprises of two layers in which one layer is formulated as a conventional or immediate release part and another layer as modified release part or both of the former or later of the same or different drugs.Bilayer tablets enjoys the benefit of combining two drug with modified release pattern and scores over other formulations in terms of ease of manufacture, scale- up feasibility that caters the demands of industries. Unlike conventional formulations, there is a lack of saw tooth kinetics ensuring effective therapy with better plasma drug level.[2,3.]

1.2.1 RATIONALE OF THE FORMULATION[9]:

The basic rational is to alter the pharmacokinetics and pharmacodynamic of the pharmacologically active moieties by using innovative drug delivery system or by modifying the molecular structure or by physiological parameters inherent in the selected route of administration.

- Where the two different drugs of same pharmacological category or dissimilar category are found to be incompatible.[4,5,6,7.]
- Where there is a therapeutic intention to formulate one layer as a immediate release layer and the other one as modified layer[3,4].
- Where we need the follow up therapy of one drug being released followed by the other drug in an sequential manner[4].

Based on the therapeutic intention to tackle the complicated disorder with multiple symptoms or monotherapy or adjuvant therapy , many layers are formulated belonging to similar pharmacological category of drug or dissimilar pharmacological category of drugs with altered biopharmaceutical parameters ranging from both the layers.

Advantages of bilayer tablet[2,3]:

1. Incompatible substances can be separated by formulating them in separate layers as two layered tablets.
2. Bilayer tablets require fewer materials when compared to the compression coated tablets.
3. The weight of each layer can be accurately controlled in contrast to putting one drug of a combination product in sugar coating.
4. Bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles.
5. Different release profiles of the drugs can be achieved by combining layers of drugs with various release patterns or by combining slow release with immediate release layers.
6. The pharmacokinetic advantage relies on the fact that the drug release from the fast releasing granules leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining granules.
7. Bilayer tablets help in reducing the fluctuations that arise in the plasma concentrations of the drugs.
8. These bilayer tablets improve patient compliance by reducing the frequency of dosing.
9. Bilayer tablets help in maintaining the chemical and physical integrity of the drugs in the layers.

Disadvantages of bilayer tablets[2,3]:

1. Bilayer tablets are mechanically complicated to design or manufacture.
2. It is harder to predict their long term mechanical properties due to poor mechanical and compression characteristics of the constituent materials in the adjacent layers
3. There is a possibility of elastic mismatch of the layers.
4. Insufficient hardness.
5. Inaccurate individual mass control.
6. Reduced yield and tendency to delaminate at the interface between the adjacent layers.

1.3 COMPONENTS OF BILAYER FORMULATIONS[10]:

Bilayer tablets innovates the drug delivery systems by admixing two or more drugs in a separate layers and providing as a single unit dosage form. It comprises of the following layers.[8]

- Modified release layer
- Immediate release layer.

1.3.1 Modified release:

***1. Extended – release dosage form*:**

A dosage form, which allows at least a two-fold reduction in dosage frequency as compared to that drug presented as an immediate release (Conventional) dosage form. Examples of extended release dosage forms include controlled release and sustained release drug products

***2. Delayed release dosage form*:**

A dosage form that releases a discrete portion or portions of drug at times or at time other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

***3. Targeted release dosage form*:**

A dosage forms that release drug at or near the intended physiologic site of action. Targeted release dosage forms may have either immediate or extended release characteristics.

1.3.2 Immediate Release:

Immediate release dosage forms allows drug to dissolve without intention to delay or prolong the dissolution or say drug absorption which in turn is the consequence of the altered pharmacokinetic parameters of the drug. Drug release instantaneously from the fast release granules leads to sudden increase in blood concentration. [15,16.]

1.4 Sustained Release Drug Delivery System:

Controlled release pharmaceutical dosage forms have received much attention lately. Such controlled release tablets are highly desirable for providing a constant level of pharmaceutical agent to a patient. Attempts at controlled release tablets have been made in the past, with mixed success [11]

Rationale:

The basic rationale of a controlled drug delivery system is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using the smallest quantity of drug, administered by most suitable route[12]

Advantages of sustained release systems[13]:

1. **Sustained blood levels:** The size and frequency of dosing is determined by the pharmacodynamic and pharmacokinetic properties of the drug. The slower the rate of absorption, the less the blood concentrations fluctuate within a dosing interval. This enables higher doses to be given less frequently. For drugs with relatively short half-lives, the use of extended release products may maintain therapeutic concentrations over prolonged periods.
2. **Attenuation of adverse effects:** With conventional dosage forms, high peak blood concentrations may be reached soon after administration with possible adverse effects related to transiently high concentration. The use of extended release formulations avoids the high initial blood concentrations which cause the sudden reduction in the blood pressure.
3. **Improved patient compliance:** Drugs with short biological half lives need to be given at frequent intervals to maintain blood concentrations within the therapeutic range. The frequency of dosing and patient compliance is inversely related. Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local and systemic effects.
4. Increased safety margin of high potency drugs due to better control of plasma levels.
5. Maximum utilization of drug enabling reduction in total amount of dose administered.
6. Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personal time to dispense, administer and monitor the patient.
7. Opportunities for product differentiation, product life-cycle management, market expansion and patent expansion.

Disadvantages of sustained release forms [11,13, 14]:

1. The necessity to ensure that drug leakage, and other factors which would cause inadequate control and possibly lead to dangerous situations, do not occur.
2. Administration of sustained release medication does not permit the prompt termination of the therapy.
3. The necessity to ensure the adequate safety of the devices with respect to device components and their degradation products together with the biocompatibilities of the actual devices.
4. Sufficiently large dose to accommodate the longer dosing interval.
5. These dosage forms being bulkier than the immediate release analogs, larger proportion of release controlling excipients need to be incorporated.
6. Possibility of dose dumping due to food, physiological factors or formulation variables and thus increased risk of toxicity.

1.4.1 Suitable candidates for sustained release formulations[13,17]:

The extent of fluctuation in drug concentration at steady state is determined by the relative magnitude of the elimination half life and dosing interval. If a drug is given at an interval equal to the elimination half life, there is a two-fold difference between the maximum and minimum concentrations at steady state.

1. Drugs with short half lives and with a clear relationship between concentration and response.
2. Higher doses at less frequent intervals will result in higher peak concentrations with the possibility of toxicity.
3. They should possess narrow safety margin.
4. Chemically incompatible drugs.
5. Chemically different drugs with same therapeutic activity.

1.4.2 Types of oral extended release systems[19,20]:

A survey of commercial Extended release oral solid products indicates that most systems fall into one of three broad categories: matrix, reservoir (or membrane controlled), and osmotic systems.

Matrix systems:

The matrix system has been most widely utilized to provide extended delivery of drug substances because of its effectiveness and the capability of accommodating both low- and high-loading of drugs with a wide range of physical and chemical properties.

In a matrix system, the drug substance is homogeneously mixed into the rate-controlling material(s) and other inactive ingredients as a crystalline, amorphous or, in rare cases, molecular dispersion. Drug release occurs either by drug diffusion and /or erosion of the matrix system.

Based on the characteristics of the rate-controlling material, the matrix system can be divided into

(a) Hydrophilic matrix systems

(b) Hydrophobic matrix systems

1.4.3 Mechanism of drug release from matrices[18]:

After oral administration and exposure to the aqueous medium,

Hydration of the polymer on the surface of the tablet

↓

Formation of a gel layer around the tablet

↓

Attainment of dilution point by the outermost gelled layer

↓

Loss of structural integrity, disetanglement of the polymer and erosion

↓

As solubility of the drug reduces, erosion mechanism becomes more prominent.

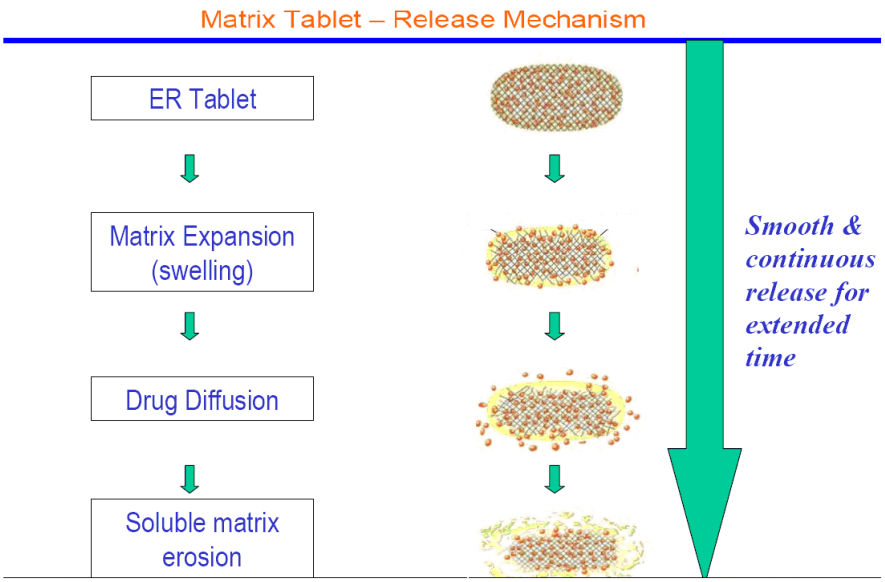


Fig No.1 Drug release mechanism from a matrix tablet.

1.5 Multi-Particulate Systems[21,25]:

Multi-particulate systems often employ pH-sensitive, enteric, or sustained release coatings upon aggregate or non-pareil granules of the API. These granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The API may also be blended or granulated with polymers before coating to provide an additional level of control; these systems may also appear as a blend of coated-beads with differing release rates for extended release or pulsitile release formulations. Regardless of the manner of manufacture, coated bead systems are extremely complex to produce, requiring large numbers of excipients, use of solvents and multiple manufacturing steps.

1.5.1 Tabletting Of Multiparticulate Systems[22,23,25]:

With regards to the final dosage form, multiparticulates can be filled into hard gelatine capsules or be compressed into tablets of which former is commen. Though multiparticulates can be filled into hard gelatine capsules, tablet formulation is preferred one because of various advantages associated with it. However, compression of coated multiparticulates is a challenging task necessitating the optimisation of various formulations and process variables.

Advantages[24,25]:

1. Multipartculate units well distribute along the GIT that could improve the bioavailability,which potentially could result in a reduction in local drug concentration, risk of toxicity, and side effects.
2. Inter and intra-idividual variations in bioavailability caused by, for example food effects, are reduced.
3. Premature drug release from enteric-coated dosage forms in the stomach, potentially resulting in degradation of drug or irritation of gastric mucosa, can be reduced with coated multiparticulate units because of more rapid transit time when compared to enteric coated tablets.
4. Administration of incompatible drugs in a single dosage unit by separating them in different multiparticulates and combination of multiparticulates with different release rates to obtain the desired overall release rates.
5. Tablets fron multiparticulate units are prepared at low cost when compared to multiparticulae units filled into capsules because of the higher production rates of tablets.
6. Reduced risk of tampering and lower tandency of adhesion of dosage form to esophagus during swallowing.

Disadvantages[21,22]:

The main disadvantage is the the compaction of pellets into tablets is a complex technology involving various manufacturing steps.

1.5.2 Types[26]:

Two categories of MUPS are possible, considering that the multiparticulate units to be compressed are modified release or have a specific dissolution profile –

1. Multiparticulate units comprising of polymer coating.
2. Multiparticulate units comprising of polymer matrix.

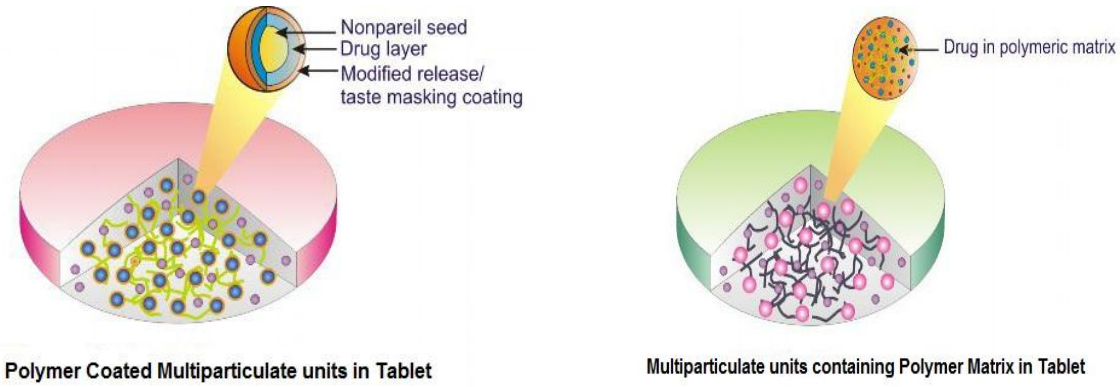


Fig No.2 Types of Multiparticulate unit systems.

1.5.3 Challenges in the Compression of Multiparticulate units into Tablet[21,25]:

Compression of multiparticulates into tablets is a challenging task as the polymer coatig may not withstand the compression force and the drug release may vary due to the unpredictable concentration of the deposited polymer left after compaction process and altered surface area during *in-vivo* dissolution. The optimisation of various process variables like compression force required, velocity of the punches, hardness, thickness and porosity of the tablets to be maintained is required.

Factors to be Considered[25,26] :

Formulation Variables

***Multiple unti core*:**

- Type – matrix or reservoir
- Composition – hard brittle e.g. sucrose or plastic, e.g. MCC
- Size
- Shape
- Porosity
- Elasticity – is directly related to pellet composition

***Membrane coating*:**

- Type of polymer – cellulosic or acrylic, etc.
- Coating thickness
- Type and amount of placticizer
- Presence of pigments
- Additional outer coat on polymer surface – plastic layer or powder layer

***Cushioning excipients*:**

- Nature – deformable (plastic) or fracturable (brittle)
- Size – powder or pellets
- Amount – ideally 50 to 75%

***Process variables*:**

- Compression force
- Compression speed

***Equipment variables*:**

- Design of tabletting machine, powder feeding mechanism, etc.

1.6 Challenges in formulation of bilayer tablets[27,28]:

One of the major challenges is lack of sufficient bonding and adhesion at the Interface between the adjacent compacted layers which is often the result of an interfacial crack driven by residual stresses in the tablet propagating a finite distance within the tablet and leads to delamination (layer-separation) which may not always be apparent immediately after compaction (e.g., during storage, packaging, shipping). In addition, if the compacted layers are too soft or too hard, they will not bond securely with each other which can lead to compromised mechanical integrity.

Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se (inefficient or uncontrolled process) and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

1.6.1 Limitations:

Limitations in single sided press[29]:

- Various types of bi-layer presses have been designed over the years. The simplest design is a single-sided press with both chambers of the double feeder separated from each other. The limitations of such single-sided press are:
- No weight monitoring/control of the individual layers
- No distinct visual separation between the two layers
- Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.
- To eliminate these limitations, a double sided tablet press is preferred over a single sided press.

Limitations of "compression force" - controlled tablet presses:

- Separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression of the bi-layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet.

1.6.2 Recommended ways to overcome the limitation[27,29]:

- Displacement-monitoring/control system for bi-layer compression
- Tablet weight control using 'displacement' is based on the measurement of thickness
- Variations under constant force and is measured at pre-compression. This measurement is possible when using the so-called 'pneumatic compensator'.
- The displacement-tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system's sensitivity does not depend on the operating point on the graph (i.e. it does not depend on the tablet weight) but depends on the applied pre compression force.

1.7 DISESE PROFILE

Gastroesophageal reflux disease (GERD):

Gastroesophageal reflux disease (GERD) is a condition in which the stomach contents (food or liquid) leak backwards from the stomach into the esophagus (the tube from the mouth to the stomach). This action can irritate the esophagus, causing heartburn and other symptoms.

1.7.1 Symptoms[30,31]:

- Feeling that food may be left trapped behind the breastbone.
- Heartburn or a burning pain in the chest (under the breastbone).
- Increased by bending, stooping, lying down, or eating.
- More likely or worse at night.
- Relieved by antacids.
- Nausea after eating.

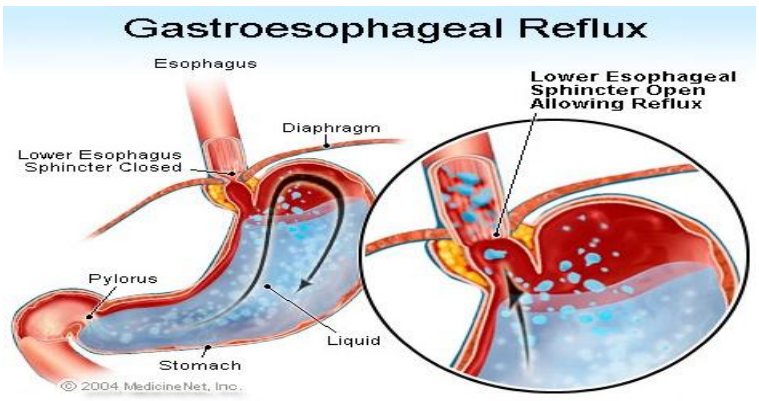


Fig No.3 Reflux of stomach contents into Esophagus during GERD

Causes Of GERD[31,32]:

The cause of GERD is complex. The factors that contribute to GERD are the lower esophageal sphincter, hiatal hernias, esophageal contractions, and emptying of the stomach.

1.7.2 Treatment[30,31]:

One of the simplest treatments for GERD is referred to as life-style changes, a combination of several changes in habit, particularly related to eating.

GERD Diet:

Certain foods are known to reduce the pressure in the lower esophageal sphincter and thereby promote reflux. These foods should be avoided and include chocolate, peppermint, alcohol, and caffeinated drinks.

Antacids:

Antacids neutralize the acid in the stomach so that there is no acid to reflux. Antacids may be Aluminum, Magnesium, or Calcium based.

Histamine antagonists:

The first medication developed for more effective and convenient treatment of acid-related diseases, including GERD, was a histamine antagonist, specifically Cimetidine. Four different H2 antagonists are available by prescription, including Cimetidine , Ranitidine , Nizatidine , and Famotidine.

Proton pump inhibitors:

The second type of drug developed specifically for acid-related diseases, such as GERD, was a proton pump inhibitor (PPI), specifically, Omeprazole. Five different PPIs are approved for the treatment of GERD, including Omeprazole ,Lansoprazole , Rabeprazole , Pantoprazole , and Esomeprazole .

Pro-motility drugs:

Pro-motility drugs work by stimulating the muscles of the gastrointestinal tract, including the esophagus, stomach, small intestine, and/or colon. One pro-motility drug, Metoclopramide is approved for GERD.

Foam barriers:

Foam barriers are tablets that are composed of an antacid and a foaming agent. There is only one foam barrier, which is a combination of Aluminum hydroxide gel, Magnesium trisilicate, and Alginate.

Surgery:

Sometimes drugs described above are not effective in treating the symptoms and complications of GERD. For example, despite adequate suppression of acid and relief from heartburn, regurgitation, with its potential for complications in the lungs, may still occur. In such situations, surgery can effectively stop reflux.

Chapter 2

LITERATURE REVIEW

2. LITERATURE REVIEW

Murat Tu rkoglu *et al.,* (**2004**) studied fluidized-bed manufactured enteric-coated Omeprazole pellets were compressed into tablets. The stability of the pellets and those of compressed tablets were evaluated for remaining Omeprazole and for degradation products under an accelerated stability protocol. It was found that enteric-coated Omeprazole pellets could be compressed into quickly disintegrating tablets using microcrystalline cellulose granules as the pressure absorbing matrix. Microcrystalline cellulose matrix showed a strong plastic deformation and all the pellets inside the tablet maintained their integrity with no significant change in their surface properties.

Baykara *et al.,* (2005) developed Acetaminophen granules by coating with a special test and odour masking Acrylate polymer, EudragitE30D with FBP. Then by direct compression method, tablet of these granules were prepared and consolidation and compressibility properties as well as in-vitro release studied were investigated.

Roland Bodmeier *et al.,* (**1994**) discusses the important formulation and process parameters necessary to obtain pellet-containing tablets, which, ideally, have the same properties, in particular drug release properties, as the individual coated pellets. Various formulation and process parameters have to be optimized in order to obtain tableted reservoir-type pellets having the same properties, and, in particular, release properties as the original, uncompacted pellets.

Horst Zerbe *et al.,* (**2007**) presented invention related to a multilayer pharmaceutical oral dosage form having delayed and immediate release properties and method of making the same. The delayed dosage formulation subsequentially behaves as an enterically dosage form but without formulation and application of enteric coating. The delayed release form is charecterised by a mixture of one or more active ingredients and one or more excepients selected from the group of solid aliphatic alcohols, mixture of esters of saturated fatty acids,neutal or synthetic waxes, hydrogenated vegetable oils,gums,and mixtures thereof.

Wu *et al.,* (**2008**) studied the compaction behaviour of bilayer tablet by using two pharmaceutical excipient, Microcrystalline Cellulose and Lactose is investigated. The effect of composition and compaction pressure on the compaction behaviour of bi layer tablet are explored. In this study it was also observed that using the same compaction process, the relative density of the tablets were generally different when different composition were used, especially when maximum compression pressure is relatively low. In this study they found that, for bi layer tablet with different composition delamination or horizontal branches of cracks that may lead to delamination occurs when the tablet is compressed with high maximum compression force

Viena Dias *et al.,* (**2007**) investigate drug release from compressed multiple-unit pellet systems, coated with an aqueous ethylcellulose dispersion (Surelease® E-7-19040). In order to protect the integrity of coated pellets, excipients with protective (cushioning) properties are incorporated into tablet formulations. Inclusion of 60-70% cushioning granules into the MUPS resulted in hard tablets with low friability and consistent drug release profiles.

Podeczeck *et al.,* (**2008**) studied the tensile strength of bi layer tablet using material dicalsium phosphate, microcrystalline cellulose, and Pregelatinised starch and compared to from tablets in the form of beam containing of two layers of equal thickness. It is found that microcrystalline cellulose as fracture propagated across the boundary between the layer.

Dashevsky *et al.,* (**2005**) worked on the compression of pellets coated with various aqueous polymer dispersions pellets coated with a new aqueous polyvinyl acetate dispersion, kollicoat sr 30 d, could be compressed into tablets without rupture of the coating providing unchanged release profiles. In contrast, the compression of pellets coated with the ethyl cellulose dispersion, aqua coated 30, resulted in rupture of the coating and an increase in drug release.

Guo *et al*., (**2002**) investigate the phenomena related to the compression behaviour and enteric film coating properties of pharmaceutical cellulose esters. The particle deformation in the tablet compression and drug diffusion of film-coated pellets were studied. Cellulose esters without any co-diluent (MCC) are not able to produce satisfactory direct compressed tablets either because of capping or poor flowability during mechanical compression.

Dannielle Combessis *et al*., (**2005**) patented an invention related to a multiparticulate tablet with improved gastro-protection comprising at least a pharmaceutical active substance in the form of enteric coated particles, and a mixture of tableting excepients. Accordimg to one embodiment of the invention, the active substance is Omeprazole or Esomeprazole. According to another embodiment in the tablet is a disintegrating tablet, which disintegrate in the mouth with or without chewing.

Remon *et al*., (**2002**) developed film-coated Diltiazem pellets to evaluate them as cushioning agents during tabletting in order to protect the film coat from damage. The cushioning properties of a-lactose monohydrate granules, microcrystalline cellulose pellets and wax/ starch beads were evaluated by comparing the dissolution profile of the coated pellets before and after compression. This study demonstrates that adding deformable wax pellets minimizes the damage to film-coated pellets during compression.

Patel Mehul *et al*., (**2005**) done a review article which explains why the development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc. Using a modified tablet press may therefore not be your best approach in producing a quality bi-layer tablet under GMP-conditions. Especially when high production output is required.

Goran Alderborn *et al*., (**2003**) investigate the influence of the size and the porosity of excipient microcrystalline cellulose (MCC) particles on the densification and the deformation during compaction and the consequent effect on the drug release from

reservoir pellets. Drug pellets consisting of salicylic acid and microcrystalline cellulose were prepared by extrusion spheronisation and spray-coated with ethyl cellulose (ethanol solution). The reservoir pellets were shown to undergo extensive deformation and densification during compaction, resulting in a preserved or even prolonged drug release time.

Peter C Schmidt *et al.,* (**1996**) developed enteric coated sucrose pellets containing a layer of bisacodyl beneath the coating were compressed into a tablet on an instrumented single punch machine using four different filler binders for direct compression. Different copolymers based on polymethacrylates were applied as coatings. Results indicate that the most important parameters are the coating agents itself and amount of coating applied to the pellets. High coating weights and coatings with better elatic properties lead to formulations, which liberate less bisacodyl after compression.

Jean-Paul Remon *et al.,* (2010) developed Omeprazole pellets containing mucoadh-esive tablets were developed by direct compression method. Three mucoadhesive polymers namely HPMC K4,Na CMC, Carbopol-934P and Ethyl cellulose were used for preparation of tablet. It concluded that, Carbopol-934P containing mucoadhesive tablets of Omeprazole pellets can be used for local action inthe ulcer disease.

Go ran Alderborn *et al.,* (**1999**) investigated the effect of incorporating a soft material (polyethylene glycol; PEG) into pellets of microcrystalline cellulose (MCC) on the compression behaviour and compact ability of the pellets. Low and high porosity MCC pellets were formed. The lowest total tablet porosity was seen with tablets made from pellets containing PEG. The inter granular porosity and the permeability of these tablets were similar to those of tablets made of the high porosity MCC pellets.

Sunil Jaiswal *et al.,* (**2010**) provides an update on this research area and discusses the phenomena and mechanisms involved during compaction of multiparticulate system and material and/or process-related parameters influencing tabletting of multiparticulates to produce multiple-unit pellet system (MUPS) or pellet-containing

tablets, which are expected to disintegrate rapidly into individual pellets and provide drug release profile similar to that obtained from uncoated pellets.

Sumnu *et al.,* (**1999**) studied about various coating solutions prepared in different concentrations and applied to previously subcoated omeprazole tablets to examine whether this coating prevented Omeprazole from degrading in acidic media. For formulation consideration, the most promising results were obtained from HPMCP4 and CAP4 (4% enteric coating with hydroxypropylmethyl cellulose phthalate solution and cellulose acetate phthalate solution, respectively).

De-Ying *et al.,* (**2009**) developed a drug-layered or drug-containing core pellets coated with salt (sodium chloride and disodium hydrogen phosphate), hydroxypropyl methyl cellulose (HPMC), and enteric film-coating layer, respectively. The multi-layer coated pellets were stable in gastric pH conditions and upper gastrointestinal (GI) tract in rats. Salt layer improved the drug stability, and its coating levels had little influence on the dissolution profiles of Omeprazole. The drug-layered pellets with multilayer film coatings not only provided delayed and rapid release of Omeprazole, but also could provide a good stable property for Omeprazole.

Chuanbin Wu *et al.,* (**2010**) developed a concept of admixing coated pellets with excipients to obtain a segregation-free combination of pellet-containing granules and cushioning granules during mixing and compression. Compared with the tablets directly compressed from coated pellets, the tablets prepared by pellet-containing granules showed improved uniformity in both weight and drug content. The granulation and compression processes did not significantly influence the drug-release behavior of coated pellets, and the enteric dissolution was retained.

Bhupendra Prajapati *et al.,* (2010) has prepared fast dissolving tablets of Domperidone by wet granulation. In the present research study, Sodium Starch Glycolate, was taken as super disintegrant and starch paste as a binder for the study. Here the Domperidone (anti-emetic) is taken as the model drug for the study and wet granulation as a method for preparation of the Fast Dissolving Tablet.

Horn *et al.*, (2005) has prepared a Review article on similarities and differences among delayed-release proton-pump inhibitor formulations. Similarities and differences between the various formulations of delayed release proton-pump inhibitors. Delayed-release Omeprazole and delayed-release Lansoprazole have been suspended in sodium bicarbonate for tube administration.

Prajapati *et al.*, (2009) worked on the matrix tablets of Domperidone were developed to prolongation of the gastric residence time of the drug and there by increase the drug bioavailability. The tablets were prepared by using different polymers by wet granulation technique.

Sanchez Rojas *et al*., (2007) done on review for estimation of Omeprazole in formulations and biological fluids by a variety of methods such as spectrophotometry, high-performance liquid chromatography with ultraviolet detection and liquid chromatography coupled with tandem mass spectrometry. The overview includes the most relevant analytical methodologies used in its determination since the origin still today.

Gerald Proehl *et al*., (**2005**) developed pharmaceutical formulations containing a proton pump inhibitor, one or more buffering agents, and a prokinetic agent. Methods are described for treating gastric order disorders, using pharmaceutical compositions comprising a proton pump inhibitor, one or more buffering agents, and a prokinetic agent.

Rajasekhar *et al*., (**2009)** simple and sensitive spectrophotometric method has been developed for the estimation of Domperidone in bulk and pharmaceutical formulations. The estimation of Domperidone was carried out on a UV/VIS spectrophotometer (Analytical technologies) using 1 cm quartz cell.. This method is extended to pharmaceutical additive and diluents. The results have been validated statistically and recovery studies confirmed the accuracy of proposed method.

Bhavesh Patel *et al*., (**2007**) developed a rapid, simple, and sensitive HPLC and a densitometric HPTLC method for the determination of Omeprazole and Domperidone

in capsule formulations were developed and validated. For HPLC, the separation of components was achieved on a Phenomenex Rp-C18 column. Isocratic elution with a mobile phase consisting of 0.01 M pH 6.5, ammonium acetate buffer: methanol: acetonitrile (40:30:30 v/v, pH 7.44+0.02), at a flow rate 1.0 mL/min was employed. The proposed method is applicable for routine determination of omeprazole and domperidone in pharmaceutical formulations.

Lakshmi Sivasubramanian *et al.,* (**2007**) presented a work which describes a simple redverse phase HPLC method for the determination of Omeprazole and Domperidone tablet formulations. The determination was carried out on a Hypersil, ODS, C-18 column using a mobile phase of methanol: 0.1 M ammonium acetate (pH 4.9) (60:40). The eluent was monitored at 280 nm. The method was reproducible, with good resolution between Omeprazole and Domperidone.

Jean-Paul Remon *et al.,* (**2004**) investigate the influence of formulation and compression parameters on the properties of tablets, containing enteric-coated pellets, and on the integrity of the enteric polymer of the individual pellets after compression. Tablets consisted of enteric-coated pellets (containing 2.5% (w/w) piroxicam in combination with microcrystalline cellulose and sodiumcarboxymethylcellulose (using Avicel® PH 101 and Avicel® CL 611 in a ratio of 1–3)), cushioning waxy pellets From the D-optimality experimental design it was concluded that the ratio of coated pellets to cushioning pellets (CoP/CuP) affected all tablet properties evaluated.

Chapter 3

AIM AND OBJECTIVE

3. AIM AND OBJECTIVE

3.1 Aim:

The main aim of the present work is to develop and evaluate bilaye tablet containing compressed Multiparticulate delayed release **Omeprazole** layer and **Domperidone** Sustained release layer.

Objectives:

- The main objective of the present work is to develop poly therapy for the treatment of **Gastroesophageal reflux disease** (GERD) by using Omeprazole and Domperidone.
- To achieve FDC in simplest manner of Drug Delivery System.
- To prepare Bilayer tablets by using compressible enteric coated granules of Omeprazole and sustained release granules of Domperidone.
- To evaluate the resistance to rupture of different enteric coating polymers to compression force.
- To maintain the drug concentration in blood for a longer time.
- To study the stability of dosage form and compare with the standard specifications.

Chapter 4

PLAN OF WORK

4. PLAN OF WORK

1. To carry out brief literature review
2. Procurement of API and Excipients
3. Preformulation Studies
4. Drug excipients compatibility studies
    - Physical characterisation
    - IR Studies
5. Analytical method development for the drug
6. Formulation of blend for tablet
7. Precompression evaluation
    - Angle of repose
    - Bulk Density
    - Tapped Density
    - Hausner Ratio
    - Compressibility Index
8. Formulation of bilayer Tablets
9. Evaluation of Formulated Tablets
    - Weight Variation
    - Thickness
    - Hardness
    - Friability
    - *In- vitro* Dissolution studies

10. Elucidation of release kinetics
11. Elucidation of transport mechanism
12. Similarity and dissimilarity factor assessment
13. Comparison with innovator brands
14. Stability Studies.

Chapter 5

DRUG PROFILE

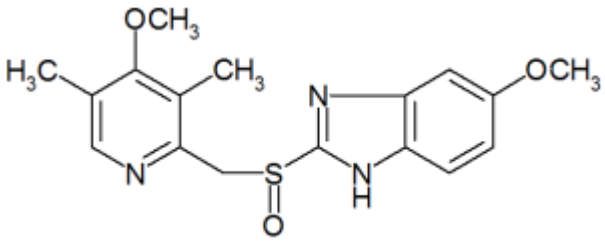
5. DRUG PROFILE

OMEPRAZOLE

Generic name : Omeprazole

Class : Proton Pump Inhibitor

Structure :



Chemical Name : 5-methoxy-2-[[(4-methoxy 3,5 dimethylpyridin2yl)methyl] Sulfinyl]-1H-benzimidazole

Molecular formula : $C_{17}H_{19}N_3O_3S$

Molecular weight : 345.4g /mol

Description : Omeprazole is a white to off-white crystalline powder

Solubility : Freely soluble in ethanol and methanol, slightly soluble in acetone and isopropanol and very slightly soluble in water

Standards : Omeprazole contains not less than 99.0 per cent and not more than 101.0 per cent of Omeprazole.

Heavy metals : Not more than 20ppm

Sulphated Ash : Not more than 0.2 %,

Loss on drying : Not more than 0.2%

Pharmacological profile[34]:

Omeprazole, a gastric acid pump inhibitor. the drug has greater antisecretory activity than histamine H2-receptor antagonists. in the maintenance therapy of duodenal ulcer,gastric ulcer and reflux esophagitis. Omeprazole binds to hepatic cytochrome P450 and inhibits oxidative metabolism of some drugs, the most important being phenytoin.

Mechanism of action[34]:

Omeprazole , the substituted benzimidazoles, suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of

the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, Omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

Pharmacokinetics[43]:

1**. Absorption**:

Omeprazole is rapidly absorbed from the gut. Peak serum levels occur within 0.5 to 3.5 hours and onset of action occurs within 1 hour. Bioavailability is 35-76%. The half-life of Omeprazole is short, 0.5-1 hour.

2**. Distribution**:

Omeprazole is distributed widely, but primarily in gastric parietal cells. In humans, approximately 95% is bound to albumin and alpha1-acid glycoprotein. The apparent volume of distribution of Omeprazole is about 0.3 to 0.4 L/kg.

3**. Metabolism**:

Omeprazole is completely metabolized by the cytochrome P450 system, mainly in the liver. Identified metabolites are the sulfone, the sulfide and hydroxy-Omeprazole, which exert no significant effect on the acid secretion.

4. Elimination:

About 80% of an orally given dose is excreted as metabolites in the urine and the remainder is found in the feces, primarily originating from bile secretion.

ADME of Omeprazole:

Table No.1 ADME of Omeprazole:

Oral absorption	32.5%
Pre systemic metabolism	20%
Volume of distribution	0.3 - 0.4 L/kg
Plasma protein binding	95%
Tmax	0.5 to 3.5 hrs
Pka	4 , 8.8

Drug interactions[44]:

- As Omeprazole can inhibit the cytochrome P-450 enzyme system, Omeprazole may decrease the hepatic clearance of diazepam, phenytoin or warfarin, thereby enhancing their effects and causing potential toxicity.
- Because Omeprazole can increase gastric pH, drugs that require low gastric pH for optimal absorption (e.g., ketoconazole, ampicillin esters or iron salts) may have their absorption reduced.
- PPIs are metabolized to varying degrees by the hepatic cytochrome P-450 enzymatic system and may alter drug metabolism by induction or inhibition of the cytochrome P enzymes. This is an important consideration in patients taking medications with a narrow therapeutic window, such as diazepam (Valium), phenytoin (Dilantin), and warfarin (Coumadin).

Adverse Reactions[43,44]:

- The most common adverse effects are headache, diarrhea, abdominal pain, and nausea.
- The severe or irreversible adverse effects of Omeprazole, which give rise to further complications include Epidermal necrolysis, Renal failure, Interstitial nephritis, Fulminant hepatic failure.

Therapeutic use[43]

- Treatment of gastric ulcer (GU), erosive esophagitis (EE), gastroesophageal reflux disease (GERD) with or without esophageal lesion.
- Maintenance therapy of EE.
- Eradication of Helicobacter pylori in triple therapy with clarithromycin and amoxicillin or in double therapy with clarithromycin only.

Overdosage/Toxicology[44]:

Symptoms of overdose include confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. Treatment for an overdose of Omeprazole will likely involve supportive care.

Dosage and Administration:

- PPIs are inactivated by exposure to gastric juice and are delivered in delayed-release forms. Omeprazole is supplied in doses of 10, 20, and 33 mg.It should be taken 30 minutes before meals.
- The usual oral adult dosage of Omeprazole seems to be 20mg once daily before breakfast for 2 to 4 weeks for DU,GERD and 4 to 8 weeks for GU,EE.
- In patients with Zollinger-Ellison syndrome it is 60mg.

Special Precautions:

Omeprazole is contraindicated in patients hypersensitive to it. Increased embryo-lethality has been noted in lab animals at very high dosages.

Stability:

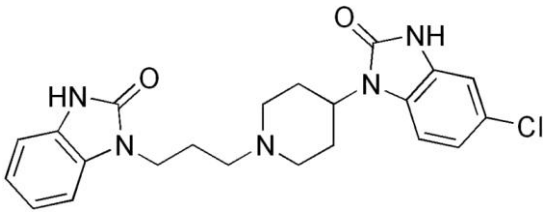
Stored below 33°C, should be kept away from moisture and light.

DOMPERIDONE

Generic name : Domperidone

Class : Dopamine-2 receptor antagonist

Structure :



Chemical Name : 5-chloro-1-[1-[[3-(2-oxo-1,3-dihydrobenzoimidazol-1-yl)propyl]-4-piperidyl]-1,3-dihydrobenzimidazol-2-one.

Molecular formula : $C_{22}H_{24}ClN_5O_2$

Molecular weight : 425.911g/mol

Description : A white or almost white powder.

Solubility : Soluble in dimethyl formamide, slightly soluble in methanol, practically insoluble in water

Standards : Domperidone contains not less than 99.0 per cent and not More than 101.0% of Domperidone

Heavy metals : Not more than 20ppm

Sulphated Ash : Not more than 0.1 %,

Loss on drying : Not more than 0.5%

Pharmacological profile[33]:

Domperidone is a dopamine-2 receptor antagonist. It acts as an antiemetic and a prokinetic agent, Domperidone elevates serum prolactin concentrations.

Mechanism of action[33]:

The gastroprokinetic properties of Domperidone are related to its peripheral dopamine receptor-blocking properties. Domperidone increases esophageal peristalsis and facilitates gastric emptying by augmenting gastric peristalsis and by improving antroduodenal coordination. The anti-emetic properties of dopamine are related to its dopamine (D2) receptor-blocking activity both at the chemoreceptor trigger zone in the area postrema and at the gastric level.

Pharmacokinetics[35,36]:

1. Absorption:

Domperidone is absorbed orally with time of peak serum concentration 30 minutes, but bioavailability is only ~ 15% due to first pass metabolism. The plasma half life is $t_{1/2}$ is 7 hours.

2. Distribution:

Domperidone is 91-93% bound to plasma protein. Volume of distribution is 5.71 L/Kg which indicates an extensive distribution of drug in the body.

3. Metabolism:

Domperidone is extensively metabolized in liver the major pathway of metabolism is N- dealkylation and hydroxylation catalyzed by cytochrome P 450. Metabolites are inactive.

4. Elimination:

The metabolites of Domperidone are excreted in urine and feces.

ADME of Domperidone:

Table No.2 ADME of Domperidone

Oral absorption	93%
Pre systemic metabolism	83-87%
Volume of distribution	5.71 L/kg
Plasma protein binding	91-93%
Tmax	30 min
Cmax	18.8 ng/ml
Pka	7.9

Drug interactions[37,38]:

- Concomitant administration of anti-cholinergic drugs may inhibit the anti-dyspeptic effects of Domperidone.
- Anti-muscarinic agents and opioid analgesics may antagonise the effect of Domperidone.
- Domperidone suppresses the peripheral effects (digestive disorders, nausea and vomiting) of dopaminergic agonists.
- As Domperidone interferes with serum prolactin levels, it may interfere with other hypoprolactinaemic agents.
- Antacids and anti-secretory agents lower the oral bioavailability of Domperidone. They should be taken after meals and not before meals, i.e. they should not be taken simultaneously with Domperidone.

Adverse Reaction[37,38,39]**:**

- Central nervous system: Headache/migraine (1%); does not cross blood-brain barrier; fewer CNS effects compared to metaclopramide.
- Gastrointestinal: Abdominal cramps, constipation, diarrhea, dizziness, dysuria, edema, extrapyramidal symptoms (EPS) rarely, galactorrhea, gynecomastia, heartburn, hot flashes, increased prolactin, insomnia, irritability, nervousness, thirst, lethargy, leg cramps, mastalgia, menstrual irregularities, nausea, palpitation, pruritus, rash, regurgitation, stomatitis, urinary frequency, urticaria, weakness.

Therapeutic uses:

- Domperidone is a first choice antiemetic in most countries.
- Domperidone has also been found effective in the treatment of gastroparesis, a stomach motility condition, and for paediatric gastroesophageal reflux (infant vomiting).
- For management of dyspepsia,heartburn and epigastric pain.

Overdosage/Toxicology:

Symptoms of overdose include CNS effects (drowsiness, disorientation, and extrapyramidal reactions) and cardiovascular effects (arrhythmias and hypotension). Treatment is supportive.

Dosage And Administration[35,36]:

- Upper Gastrointestinal Motility Disorders: The usual dosage in adults is 10 mg orally 3 to 4 times a day, 15 to 30 minutes before meals and at bedtime if required.
- Antiparkinsonian Agents: The usual dosage in adults is 20 mg orally 3 to 4 times a day.

Special Precautions:

Since Domperidone is highly metabolized in the liver, should be used with caution in patients with hepatic impairment (and in the elderly).

Stability:

Store at room temperature of 15°C to 30°C (59°F to 86°F); protect from light and moisture.

Chapter 6

EXCEPIENT PROFILE

6. EXCIPIENT PROFILE

6.1 HYPROMELLOSE[42]

Non-proprietary Names

BP **:** Hypromellose

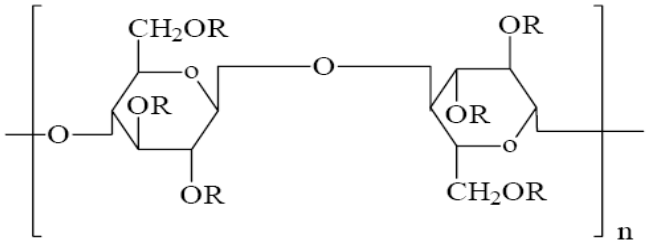
JP **:** Hypromellose

PhEur **:** Hypromellose

Synonyms :

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.

Structure:



Chemical Name and CAS Registry Number :

Cellulose hydroxypropyl methyl ether [9004-65-3].

Functional Category

Bioadhesive material, coating agent, controlled release agent, dispersing agent, dissolution enhancer, emulsifying agent, emulsion stabilizer, extended release agent, film forming agent, foaming agent, granulation aid, modified release agent, mucoadhesive agent, release modifying agent, solubilising agent, stabilizing agent, suspending agent, sustained release agent, tablet binder, thickening agent, viscosity increasing agent.

Description:

Hypromellose is an odourless and tasteless, white or creamy white fibrous granular powder.

Viscosity:

Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Wolff Cellulosics) and Metolose (Shin-Etsu Chemical Co.Ltd.) are given in the following table

Table No.3 Different viscosity grades of Hypromellose

Methocel and Metolose products	Nominal viscosity (mPa s)
Methocel K3 Premium LV	3
Methocel K100 Premium LVEP	100
Methocel K4M Premium	4000
Methocel K100M Premium	100000
Methocel E3 Premium LV	3
Methocel E5 Premium LV	5

Applications in Pharmaceutical formulation or technology;

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations.

Uses of Hypromellose:

Table No.4 Uses of Hypromellose

Dosage form	Use
Oral products	Tablet binder, in film coating and as a matrix for extended release tablets
Liquid oral dosage forms	Suspending or thickening agent
Topical formulations	Thickening agent
Ear drops and Tear fluids	Thickening agent

6.2 LACTOSE MONOHYDRATE[42]

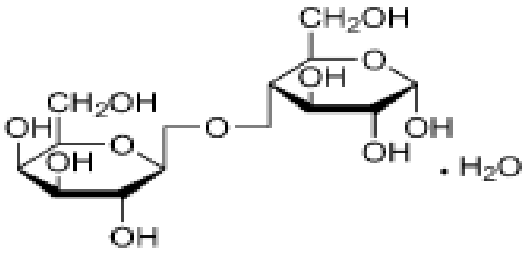
Nonproprietary Names:

BP **:** Lactose mono hydrate

USP **:** Lactose monohydrate

Synonyms : Pharmactose , Lactochem crystal

Structure :



α-Lactose monohydrate

Chemical Name : O-β-d-Galactopyranosyl-(1→4)-α-d-glucopyranose monohydrate

Empirical Formula : $C_{12}H_{22}O_{11}.H_2O$

Molecular weight : 360.31

Description:

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

Functional categories:

Binding agent, diluent for dry-powder inhalers, tablet binder, tablet and capsule diluent

Solubility:

Insoluble chloroform, ethanol, ether and soluble in water.

Loss on drying : ≤ 0.5%

Applications in Pharmaceutical Formulation or Technology:

1. Lactose is widely used as a filler or diluent in tablets and capsules.

2. Lactose is also used as a diluent in dry-powder inhalation.

3. 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

6.3 MANNITOL[42]

Nonproprietary Names:

BP : Mannitol.

JP : D-Mannitol.

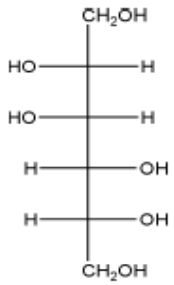
PhEur : Mannitolum.

USP : Mannitol.

Synonyms:

Cordycepic acid; C PharmMannidex; E421; manna sugar; D-mannite; mannite; Mannogem; Pearlitol.

Structure:



Chemical name and CAS registry number: D-Mannitol [69-65-8].

Molecular weight: 182.17

Description:

Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules.

Solubility:

Alkalis	**:**	Soluble
Ethanol (95%)	**:**	1 in 83

Functional Category:

Diluent; diluent for lyphilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.

Applications:

Used as a diluent (10–90% w/w) in tablet formulations, Mannitol may be used in direct-compression tablet applications. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.

6.4 MICROCRYSTALLINE CELLULOSE[42]

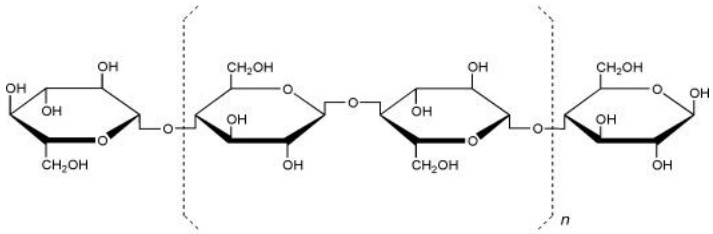
Non-proprietary Names:

BP **:** Microcrystalline cellulose

USPNF **:** Microcrystalline cellulose

Synonyms : Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose.

Structure:



Chemical Name and CAS Registry number: Cellulose [9004-34-6]

Empirical Formula: $(C_6H_{10}O_5)$ *n* where $n \approx 220$.

Functional Category: Adsorbent; suspending agent; tablet and capsule diluent

Description:

MCC is purified, partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles.

Solubility:

Slightly soluble in 5%w/v sodium hydroxide solution. Practically insoluble in water, dilute acids and most organic solvents.

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. It also has some lubricant and disintegrant properties.

Incompatibilities: MCC is incompatible with strong oxidizing agents

6.5 POVIDONE[42]

Non-proprietary Names

BP : Povidone

JP : Povidone

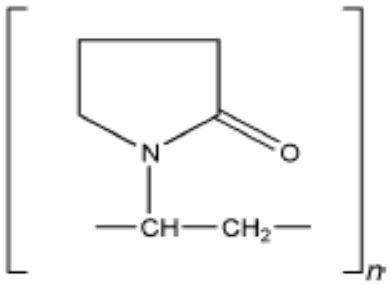
PhEur : Povidone

USP : Povidone

Synonyms:

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1- vinyl-2-pyrrolidinone polymer.

Structure:



Chemical Name and CAS Registry Number:

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Functional Category:

Disintegrant; dissolution enhancer; suspending agent; tablet binder

Description:

Povidone occurs as a fine, white to creamy-white colored, odourless or almost odourless, hygroscopic powder.

Viscosity:

Table No.5 Different viscosity grades of Povidone

Grade	**Dynamic viscosity(mPas)**
K-11/14	1.3-2.3
K-16/18	1.5-3.5
K-24/27	3.5-5.5
K-28/32	5.5-8.5

Applications in Pharmaceutical formulation or Technology:

Table No. 6 Uses of Povidone

Use	**Concentration**
Carrier for drugs	10-25
Dispersing agent	5
Suspending agent	5
Tablet binder, diluents or coating agent	0.5

6.6 HYPERMELLOSE PHTHALATE[42]

Nonproprietary Names:

BP : Hypromellose phthalate

JP : Hydroxypropylmethylcellulose phthalate

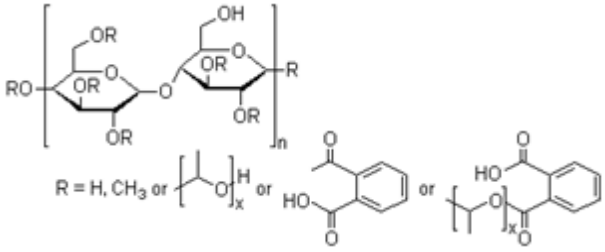
PhEur : Hypromellosi phthalas

USPNF : Hypromellose phthalate

Synonyms:

Cellulose phthalate hydroxypropyl methyl ether; HPMCP; hydroxypropyl methylcellulose benzene-1,2-dicarboxylate; 2-hydroxypropyl methylcellulose phthalate;methylhydroxypropylcellulose phthalate.

Structure:



Chemical Name and CAS Registry Number:

Cellulose, hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether [9050-31-1]

Functional Category: Coating agent.

Description:

Hypromellose phthalate occurs as white to slightly off-white, free-flowing flakes or as a granular powder. It is odorless or with a slightly acidic odor and has a barely detectable taste.

Solubility:

Readily soluble in a mixture of acetone and methyl or ethyl alcohol (1 : 1), in a mixture of methyl alcohol and dichloromethane (1 : 1), and in aqueous alkali. Practically insoluble in water and dehydrated alcohol and very slightly soluble in acetone.

Melting point: 150°C. Glass transition temperature is 137°C for HP-50 and 133°C for HP-55.

Moisture content: Hypromellose phthalate is hygroscopic; it takes up 2–5% of moisture at ambient temperature and humidity conditions

Applications:

Hypromellose phthalate is widely used in oral pharmaceutical formulations as an enteric coating material for tablets or granules

Hypromellose phthalate can be applied to tablet surfaces using a dispersion of the micronized hypromellose phthalate powder in an aqueous dispersion of a suitable plasticizer such as triacetin, triethyl citrate, or diethyl tartrate along with a wetting agent.

Hypromellose phthalate may be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug-release properties; the release rate is pH-dependent.

6.7 EUDRAGIT NE 30 D[40]

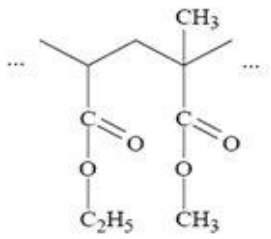
Nonproprietary Names:

Ph.Eur : Polyacrylate Dispersion 30 Per Cent

USP/NF : Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion - NF

JPE **:** Ethyl Acrylate Methyl Methacrylate Copolymer Dispersion

Structure:



CAS number : 9010 – 88 – 2

Chemical/IUPAC name: Poly(ethyl acrylate-co-methyl methacrylate) 2:1

INCI name: Acrylates Copolymer.

Molecular weight information: approx. 750,000 g/mol

Minimum Film Forming Temperature (MFT): ~5°C

Glastransition Temperature (Tg): -8°C

Product Form: Aqueous Dispersion 30%

Targeted Drug Release Area: Time controlled release, pH independent

Physical properties:

It is a milky-white liquid of low viscosity with a faint characteristic odour.

Dissolution:

Insoluble

Low permeability

pH independent swelling

Characteristics:

No plasticizer required

Highly flexible

Suitable for matrix structure

Applications:

1. pH-dependent drug release
2. EUDRAGIT® is employed as a coating material, usually for the coating of pellets or particles that are filled into capsules or compressed into tablets.

These pellets or particles act as diffusion cells in the digestive tract and release a constant drug quantity per unit of time (multi-unit dosage forms).

6.8 KOLLICOAT MAE 30DP[41]

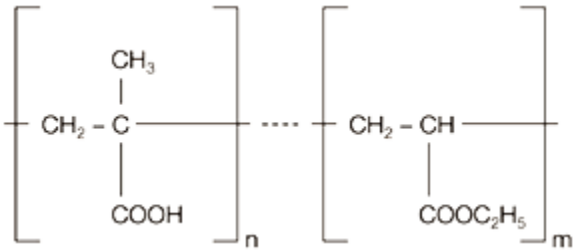
Nonproprietary Names:

Ph.Eur :Methacrylic acid-ethyl acrylate co-polymer(1:1),30% dispersion

USP-NF :Methacrylic acid co-polymer dispersion

JPE :Methacrylic acid co-polymer LD

Structure:



The chemical structure of both Kollicoat MAE grades consists of a methacrylic acid-ethyl acrylate co-polymer, the two monomers being bound in the molar ratio of 1:1.This is an anionic co-polymer that can be neutralized by bases such as sodium hydroxide

Description:

Kollicoat MAE 30DP is a low-viscosity, milk-like white dispersion with a solid content of 30%, it has typically slight inherent odour.

Viscosity : 15mPa's

Solid contents :28.5-31.5%

Solubility:

Kollicoat MAE 30DP is excellently miscible with water in any ratio without losing its milky white appearance. Even in a slightly alkaline aqueous medium it forms a clear solution. When the organic solution is being initially added, a precipitate is formed; this is redissolved on adding further solvent.

Applications:

Kollicoat MAE grades are used in enteric coating of tablets,granules and crystals

6.9 POLYETHYLENE GLYCOL[42]

Nonproprietary Names:

BP : Macrogols

JP : Macrogol

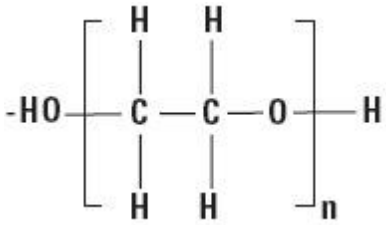
PhEur : Macrogola

USPNF : Polyethylene glycol

Synonyms:

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; PluriolE; polyoxyethylene glycol.

Structure:



Chemical Name and CAS Registry Number:

a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

Empirical Formula and Molecular Weight:

HOCH2(CH2OCH2)mCH2OH where m represents the average number of oxyethylene groups

Functional Category:

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Description:

Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures. Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste.

Solubility:

All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels.

Applications:

1. Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol
2. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers. The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films.
3. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed intotablets.

6.10 COLLOIDAL SILICON DIOXIDE[42]

Nonproprietary Names:

BP : Colloidal anhydrous silica.

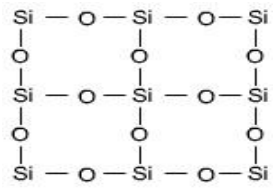
PhEur : Silica colloidalis anhydrica.

USPNF : Colloidal silicon dioxide.

Synonyms:

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed; Wacker HDK.

Structure:



Chemical name and CAS registry number: Silica [7631-86-9].

Molecular weight: 60.08

Description:

It is a light, loose, bluish-whitecolored, odorless, tasteless, nongritty amorphous powder.

Solubility:

Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide.

Functional Category:

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Applications:

Widely used in pharmaceuticals, cosmetics, and food products; used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension.

6.11 MAGNESIUM STEARATE[42]

Nonproprietary Names:

BP : Magnesium stearate.

JP : Magnesium stearate.

PhEur : Magnesii stearas.

USPNF : Magnesium stearate.

Synonyms:

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical name and CAS registry number:

Octadecanoic acid magnesium salt [557-04-0].

Molecular weight: 591.34.

Description:

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

Solubility:

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Functional Category: Tablet and capsule lubricant.

Applications:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet.

6.14 TALC[42]

Nonproprietary Names:

BP : Purified talc

JP : Talc

PhEur : Talcum

USP : Talc

Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical name and CAS registry number: Talc [14807-96-6].

Description:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Moisture content:

Talc absorbs insignificant amounts of water at 25ºC and relative humidities up to about 90%.

Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Functional Category:

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications:

1. Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, it is widely used as a dissolution retardant in the development of controlled-release products.
2. Talc is also used as a lubricant in tablet formulations in a novel powder coating for extended-release pellets, and as an adsorbant.

Chapter 7

MATERIALS & METHODS

7. MATERIALS AND METHODS

7.1 Materials used:

Table No.7 Materials used in formulation of Omeprazole and Domperidone bilayer tablets

S. No	Name of the material	Name of the supplier	Use
1.	Omeprazole	Scott Pharma Ltd.	API
2.	Domperidone	Scott Pharma Ltd.	API
3.	HPMCK4M	Dow Chemicals	Polymer
4.	HPMCK15M	Dow Chemicals.	Polymer
5.	Lactose	Sd fine Chem.Ltd	Diluent
6	Mannitol	Sd fine Chem.Ltd	Diluent
7	Avicel PH102	FMC Biochemicals	Disintegrant
8	Avicel PH200	FMC Biochemicals	Diluent
9	Povidone	Rankem	Binder
10	Na_2CO_3	Drugs India Pvt Ltd	Stabilizer
11	HPMC P	Qualigens fine chemicals	Enteric Coating
12	Eutragit NE30D	Qualigens fine chemicals	Enteric Coating
13	KollicoatMAE 30DP	Qualigens fine chemicals	Enteric Coating
14	PEG	Qualigens fine chemicals	Plastisizer
15	IPA	Rankem	Solvent
16	Aerosil	DMV Fonterra	Absorbent
17	Magnesiumstearate	DMV Fonterra	Lubricant
18	Talc	DMV Fonterra	Glident
19	Iron Oxide	Roha Dyechem pvt.ltd.	Colouring agent

7.2 LIST OF INSTRUMENTS

Table No.8 Instruments employed in the formulation of bilayer tablet

S.No	Name of the Equipment	Manufacturing Company
1.	Weighing balance	Electro lab.
2.	Sifter	Neo machine.
3.	Rapid mixing granulator	Prism Pharma.
4.	Fluid Bed Dryer	Pam Glatt.
5.	Octagonal Blender	Prism Pharma.
6.	Tapped density Apparatus	Electro lab.
7.	Double Sided Rotary tablet Press 27 station	Cadmach. India.
8.	Friabilator	Electrolab.
9	Hardness Tester	Pharma Test
10.	U.V Spectro Photometer	Elic.
11	HPLC	Shimadzu-Corporation, Japan
12.	Automatic tablet dissolution apparatus USP Type II	Electro Lab.
13.	pH Meter	Eutech
14.	Bath ultra sonicator	PCI, Mumbai.
15.	Digital vernier caliperse	Absolute Digimate, industrial stores.
16.	GPCG	Gansons
17.	Stability Chamber	Prism Pharma.

7.3 PRE-FORMULATION STUDIES[45]

Prior to the development of the dosage from, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information dictates many of the subsequent events and approaches in formulation development. This first learning phase is known as Pre-formulation.

Pre formulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of a new drug substance, in order to develop stable, safe and effective dosage forms. Ideally, the Pre formulation phase begins early in the discovery process such that appropriate physical, chemical data is available to aid in the selection of new chemical entities that enter the development process. During this evaluation possible interaction with various inert ingredients intended for use in final dosage form are also considered.

Pre-formulation commences when a newly synthesized drug shows sufficient pharmacological promise. These studies should focus on those physico-chemical properties of the compound that could affect the development of an efficacious dosage form. These studies provide a thorough understanding of the properties and ultimately provide a rational for the formulation design or support the need for molecular modification.

7.3.1 Organoleptic Properties:[11]

a) Colour:

A small quantity of powders were taken in butter paper and observed in well-illuminated place.

b) Taste and odour:

Very less quantity of powders is tasted and perceived to observe the odor as well.

Solubility:

The approximate solubility of substances are indicated by the descriptive terms. Solvents such as Methanol, alcohol and water and isopropyl alcohol are used for the solubility studies.[14]

Table No.9 Official solubility Grades

Descriptive Term	**Parts of Solvent Required for 1 part of Solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble or Insoluble	Greater than or equal to 10,000

7.3.2 Drug excipient compatibility studies[46]:

Drug Excipients compatibility studies are carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and rubber stopper was placed on the vial and sealed properly. Studies were carried out in glass vials at Accelerated conditions, 40º C ± 2° C / 75% RH ± 5 % RH for a storage period of 4 weeks. After storage, the sample was compared with control at 2-8° C and observed physically for liquefaction, caking and discoloration.

7.3.3 IR Studies[47]:

The IR studies for drug excipient compatibility are mainly meant to confirm the integration of the drugs active moiety when combined with the excipients. The samples are previously grounded and mixed thoroughly with Potassium bromide and compressed through the hydraulic press to form pellets. The spectral smoothening and the baseline corrections procedures are done prior to sampling and the sample being scanned at $400cm^{-1}$ to $4000cm^{-1}$ ambient temperature.

7.3.4 Particle size distribution:

The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieves were stacked one above the other so that

sieves with larger pore size (less sieve number) occupy top position followed by sieves of decreasing pore size (larger sieve number) towards the bottom.

Procedure:

A series of sieves are stacked one over the other arranged in ascending order of increasing mesh number from the top. The stated quantity of powder is placed over the top and are tapped mechanically for 15 to 20 minutes. The powder retained over every mesh and pan is weighed and from this the average mean diameter of the particles in µm is found by using the following formula,

Average mean diameter= Σnd/Σx

Where n= weight of the powder retained in grams

d= arithmetic mean size openings in µm

x= percentage weight of the powder retained.

The same procedure is repeated for all the powders.

7.4 Analytical method development for Omeprazole and Domperidone:

Determination of absorption maxima:

A spectrum of the working standards is obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λ_{max} is found out and all further investigations are being carried out at that same wavelength.

Preparation of Phosphate Buffer pH 6.8:

Placed 11.45 gms of potassium dihydrogen phosphate and 28.80 gms of disodium hydrogen phosphate and made up to 1000 ml with distilled water.

Preparation of standard graph in pH 6.8 Phosphate buffer:

Accurately weighed 20 mg of Omeprazole and Domperidone each and is dissolved in 100ml of 6.8 pH phosphate buffer. This is regarded as the primary stock solution. From this primary stock solution, 1ml, 2ml, 3ml, 4ml, 5ml and 6ml is pipetted out and made up to 100ml with pH 6.8 phosphate buffer, to produce 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml and 12µg/ml respectively. The absorbance was measured at 295 nm by using a UV-Vis spectrophotometer.

Characterization of Tablets:

7.5. Pre compression properties:

7.5.1 Angle of Repose[49,50,51]:

The angle of repose is the maximum angle that the plane of powder makes with the horizontal surface on rotation. Angle of repose is helpful in assessment of flow properties of particles which could be further related to packing densities and mechanical arrangements of particles.

The angle of repose of granules was determined by the fixed funnel and free standing cone method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation:

$$\tan \theta = h/r$$

Where, h = height of the powder

r = radius of the powder heap

θ = is the angle of repose.

Angles of Repose:

Table No.10 Relationship between Angle of repose and Flow property

S.No	Angle of Repose (degrees)	Flow Property
1	25–30	Excellent
2	31–35	Good
3	36–40	Fair—aid not needed
4	41–45	Passable—may hang up
5	46–55	Poor—must agitate, vibrate
6	56–65	Very poor
7	>66	Very, very poor

7.5.2 Determination of Bulk Density and Tapped Density:

Bulk density of a compound varies substantially with the method of crystallisation, milling or formulation. It is of great importance when one considers the size of a high – dose capsule product or the homogeneity of a low dose formulation in which there are large differences in drug and excipient densities. In addition to bulk density, it is frequently desirable to know the true density of a powder for computation of void volume or porosity of packed powder beds.

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulae.

$$\textbf{Bulk density} = W/V_0$$

$$\textbf{Tapped density} = W/V_f$$

Where,

W = Weight of the powder

V_0 = Initial volume

V_f = final volume

7.5.3 Carr's Compressibility Index[49]:

An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below:

$$\textbf{Carr's Compressibility Index (\%)} = [(TD-BD) \times 100] / TD$$

Where,

TD = Tapped density

BD = bulk density

Table.No.11 Relationship between Carr's index and Flow property

S.No	Compressibility Index (%)	Flow Character
1.	10	Excellent
2.	11–15	Good
3.	16–20	Fair
4.	21–25	Passable
5.	26–31	Poor
6.	32–37	Very poor
7.	>38	Very, very poor

7.5.4 Hausner's Ratio

Hausner's Ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density. It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Hausner's Ratio = Tapped density/Bulk Density

Table No.12 Limits of Hausner's ratio values as per USP

S.No	Hausner Ratio	Flow Character
1	1.00–1.11	Excellent
2	1.12–1.18	Good
3	1.19–1.25	Fair
4	1.26–1.34	Passable
5	1.35–1.45	Poor
6	1.46–1.59	Very poor
7	>1.60	Very, very poor

7.5.5 Loss on Drying (LOD):

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified conditions. The test is carried out on a well-mixed sample of the substance. If the substance is in the form of large crystals, reduce the size by rapid crushing to a powder.

Procedure:

Loss on drying is performed using the IR moisture analyzer. 1gm of granules was taken and placed in an IR moisture analyzer containing the plate at the centre, spread the granules on to the plate uniformly, and adjust temperature of the analyzer at 105^{o}C. Switch on the analyzer and wait until the alert sound comes from the analyzer, readings was noted down from the digital display.

7.6 THE COMPOSITION OF BILAYER TABLETS PREPARED USING OMEPRAZOLE AND DOMPERIDONE:

Table No.13 Formulation Code of Omeprazole Layer

S.No	Name of the Ingredient	F1	F2	F3	F4	F5	F6
Dry Mixing							
1	Omeprazole	20	20	20	20	20	20
2	Mannitol	38	38	38	38	38	38
3	Na_2CO_3	27	27	27	27	27	27
4	Avicel PH102	16	16	16	16	16	16
5	Aerosil	0.6	0.6	0.6	0.6	0.6	0.6
Granulation							
6	Povidone	7	7	7	7	7	7
7	IPA	q.s	q.s	q.s	q.s	q.s	q.s
Sub coating							
8	HPMC	2.4	2.4	2.4	2.4	2.4	2.4
9	IPA	q.s	q.s	q.s	q.s	q.s	q.s
Enteric Coating							
10	HPMC P	12	16	_	_	_	_
11	Kollicoat MAE30DP	_	_	12	16	_	_
12	Eutragit NE30D	_	_	_	_	12	16
13	PEG	4	4	4	4	4	4
14	Talc	0.6	0.6	0.6	0.6	0.6	0.6
15	Water	q.s	q.s	q.s	q.s	q.s	q.s
Tabletting Excepients And Lubrication							
16	Avicel PH200	68	64	68	64	68	64
17	Iron Oxide Red	0.4	0.4	0.4	0.4	0.4	0.4
18	Magnesiumstearate	2	2	2	2	2	2
19	Talc	2	2	2	2	2	2
	Total Weight	200	200	200	200	200	200

Table No.14 Formulation Code of Domperidone Layer

S.No	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
1	Domperidone	**20**	**20**	**20**	**20**	**20**	**20**	**20**
2	HPMCK4M	32	48	_	_	24	16	32
3	HPMCK15M	_	_	32	48	8	32	16
4	Lactose	72.5	56.5	72.5	56.5	72.5	56.5	56.5
5	Microcrystalline cellulose	32	32	32	32	32	32	32
6	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0
8	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total Weight	160.0	160.0	160.0	160.0	160.0	160.0	160.0

PREPARATION OF OMEPRAZOLE ENTERIC COATED GRANULES:

- **Sifting of the granulation Material:**
  - The Excipients were sifted by using mechanical sifter by using #40 screens.
  - API should be sifted separately.
- **Binder preparation:**
  - Povidone is dissolved in sufficient quantity of Iso Propyl Alcohol to get a clear solution.
- **Mixing & granulation(RMG):**
  - The excipients Mannitol and Avicel PH102 were loaded into RMG and Mixed for two minutes.
  - After dry mixing add Omeprazole (API) in to the RMG. Then mix for 15 minutes.
  - Aerosil was added to the dry mixed blend to absorb the moisture in the drug.
  - Then gently add binding agent in to the RMG and mix them thoroughly. By using impellor and chopper blades.
  - After granulation the material is transfer from RMG to the FBD for proper drying.

- **Drying(FBD):**
  - The wet mass is dried by using Fluid Bed Dryer.
- **Sifting & milling:**
  - The lumps which are formed in the process is separated by sifting.
  - The lumps were milled by using multi mill to reduce the size.
- **Coating solution preparation:**
  - Talc and plastisizer are homogenized in water using homogenizer for 10 min(excepient suspension)
  - Pour the excepient suspension slowly into the Enteric coating dispersion while stirring with conventional stirrer.(Spray suspension)
  - Pass the spray suspension through a 0.5mm sieve.
- **Enteric coating of Omeprazole Granules:**
  - The enteric coating of granules was done by using Fluidized Bed Processer (FBP).
  - Before starting the coating process in FBP the spray gun pattern was adjusted in order to get uniform coating.
  - The base plate and mesh was stetted as per the size of the granules. i.e. A plate and 100 # mesh.
  - After proper arrangement the equipment was given for pre warming in order to reach the bed temperature 28-30°C.
  - After attaining the bed temperature the granules were loaded into FBP.
  - Then the subcoating solution was sprayed with the help of peristaltic pump through the spray gun and dried.
  - After subcoating the enteric coating solution was sprayed with the help of peristaltic pump through the spray gun.
  - The coating process was continued until the coating solution gets finished.
  - Finally 10- 15 minutes drying has to be given for the coated granules.
  - The granules were collected from the FBP and weighed to check the process efficiency.
  - The main process parameters for the granules are as follows.

Table No.15 Parameters of GPCG

S.No	In process Parameters of Coating	
1.	Inlet temperature	40-45º C.
2.	Outlet temperature	28-30º C.
3.	Pump speed	1-4 rpm.
4.	Bed temperature	28-32º C.
5.	Atomization Pressure	0.3-0.7 bar

- **Pre lubrication of the granules:**
  - The enteric coated granules were loaded in to the octagonal blender.
  - Then add previously weighed Avicel PH200 and mixed for 15 min.
- **Lubrication:**
  - Pre-lubricated granules are lubricated with Magnesium stearate for 2 minutes

PREPARATION OF DOMPERIDONE GRANULES:

- **Sifting of the granulation Material:**
  - Domperidone, HPMCK4, HPMCK15, Avicel PH102 and Lactose talc Magnesium Stearate were sifted by using mechanical sifter by using #40 screens.
- **Dry Mixing:**
  - The excipients Lactose and Avicel PH102 and Polymer were loaded into RMG and Mixed for two minutes.
  - After dry mixing add Domperidone (API) in to the RMG. Then mix for 15 minutes.
- **Granulation:**
  - Granulation is done by adding sufficient quantity of the water to the dry mixed blend continuously until the granules are formed.
  - After granulation the material is transfer from RMG to the FBD for proper drying.
- **Drying the granules by using :**
  - The wet mass is dried by using Fluid Bed Dryer.
- **Sifting & milling:**
  - The lumps which are formed in the process are separated by sifting.
  - The lumps were milled by using multi mill to reduce the size.

- **Lubrication of the granules:**

- The granules were loaded in to the octagonal blender.
- Then add previously weighed lubricating material Magnesium state and talc.
- Then blend the material for 5 minutes.

COMPRESSION OF BILAYER TABLETS:

The blends of the two layers obtained are subjected to compression using CADMACH double sided compression machine.

Compression involves two steps

- Compression of the Domperidone layer with the desired parameters.
- The Domperidone layer compression is followed by the compression of the Omeprazole layer.

Table No.16 Punches Specification

S.No	Punch Parameters	
1.	Punch dimension	10.00 mm.
2.	Punch shape	Circular, Flat punches.
3.	Upper punch	Plain.
4.	Lower punch	Plain.

The following pre formulation studies were performed for the Omeprazole and Domperidone bi layer tablet formulations.

EVALUATION OF OMEPRAZOLE AND DOMPERIDONE BILAYER TABLETS[52,53,54]

7.7 Post-Compression Parameters:

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, dimensions (diameter and thickness), weight variation, hardness, friability, assay and drug content.

7.7.1 Appearance:

The tablet should be free from cracks, depressions, pinholes etc. The colour and the polish of the tablet should be uniform on whole surface. The surface of the tablets should be smooth.

7.7.2 Dimensions:

The dimensions of the tablets are thickness and diameter. The tablets should have uniform thickness and diameter. The manufacturer normally states these. Thickness and diameter of a tablet were measured using vernier calipers. These values were checked and used to adjust the initial stages of compression.

7.7.3 Weight Variation test:

Take 20 tablets and weighed individually. Calculate average weight and compare the individual tablet weight to the average. The tablet pass the U.S.P. test if not more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table No.17 Limits of Weight Variation as per USP

S.No.	Average weight of tablet (X mg)	Maximum % difference allowed
1.	130 mg or less	10
2.	130 mg to 324 mg	7.5
3.	More than 324 mg	5

% Maximum positive deviation = $(W_H - A / A) \times 100$

% Minimum negative deviation = $(W_L - A / A) \times 100$

Where,

W_H = Highest weight in mg.

W_L = Lowest weight in mg.

A = Average weight of tablet in mg.

7.7.4 Hardness test:

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets.

7.7.5 Friability test:

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It is being rotated at a rate of 25 rpm. Take a sample of whole tablets corresponding as near as possible to 6.5gm and placed in the chamber of the friabilator. In the friabilator, the tablets are exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4 minutes), the tablets are taken out from the friabilator and intact tablets are again weighed collectively. Permitted friability limit is 1.0%. The percentage friability was measured by using the following formula

$$\% F = \{1-(W / W_o)\} \times 100$$

Where,

%F = friability in percentage

W_o = Initial weight of tablet

W = Weight of tablets after revolution.

7.7.6 Content uniformity:

A sample of 30 tablets are randomly seleced and 10 of them are individually assayed.9 of the 10 tablets must contain >85% and <115 of drug content. The tenth tablet must contain <75% and >125% of the labeled content.If these conditions are not met,the remaining 20 tablets are assayed individually and none must fall outside the 85%-115% range.

7.7.7 ASSAY PROCEDURE[63,64]:

Chromatographic Condition

Column	:	Phenomenex C_{18} (250x4.6 i.d., 5µm particle size)
Flow Rate	:	1.0 ml/min
UV Wave Length	:	295nm
Injection Volume	:	10µ L
Temperature	:	25˚C±2˚C
Run Time	:	10 minutes.

Preparation of Mobile phase:

Prepare a filtered and degassed mixture of pH6.5 Ammonium acetate buffer: methanol: acetonitrile in the ratio of 40:30:30 v/v/v and pH was adjusted to 7.44±0.02 with acetic acid/ammonia.

Preparation of Solutions:

Standard preparation:

Weigh accurately and transfer 20.0 mg of Omeprazole and 20.0 mg of Domperidone in to a 100 mL volumetric flask, dissolved in and diluted to mark with methanol. 1 ml of this solution was further diluted to 50 mL with mobile phase.

Sample preparation:

Weighed and finely powdered 20 tablet and transfer a portion of the resulting powder equal to the weight of respective tablet to 100 mL volumetric flask. Add 60 mL of methanol and sonicated for 15 min with occasional shaking and made the volume up to volume with methanol. Filtered the solution through 0.45µ filter. Pipette out 2.0 mL of the filtered solution and diluted to 100 mL with Mobile phase.

Procedure:

Separately inject equal volume of Mobile phase (blank), standard preparation and test preparation, record the chromatograms, and measure the areas for the Omeprazole and Domperidone. Calculate the quantity of Omeprazole and Domperidone.

CALCULATION:

% Of Omeprazole:

$$\frac{\mathbf{TA}}{\mathbf{SA}} \mathbf{x} \frac{\mathbf{SW}}{\mathbf{100}} \mathbf{x} \frac{\mathbf{1}}{\mathbf{50}} \mathbf{x} \frac{\mathbf{100}}{\mathbf{TW}} \mathbf{x} \frac{\mathbf{2}}{\mathbf{100}} \mathbf{x\ Avg.\ Wt\ x} \frac{\mathbf{P}}{\mathbf{100}} \mathbf{x} \frac{\mathbf{100}}{\mathbf{LA}}$$

Where,

SA = peak area due to Omeprazole in standard preparation.

TA = Peak area due to Omeprazole in sample preparation

SW = Weight of Omeprazole working standard, in mg.

P = Purity of Omeprazole working standard.

LA = Labeled amount of Omeprazole, in mg.

TW = weight of sample taken in mg

Ave. wt. = Average weight of tablet.

% of DOMPERIDONE:

$$\frac{\mathbf{TA}}{\mathbf{SA}} \mathbf{x} \frac{\mathbf{SW}}{\mathbf{100}} \mathbf{x} \frac{\mathbf{1}}{\mathbf{50}} \mathbf{x} \frac{\mathbf{100}}{\mathbf{TW}} \mathbf{x} \frac{\mathbf{2}}{\mathbf{100}} \mathbf{x\ Avg.\ Wt\ x} \frac{\mathbf{P}}{\mathbf{100}} \mathbf{x} \frac{\mathbf{100}}{\mathbf{LA}}$$

Where,

SA = peak area due to Domperidone in standard preparation.

TA = Peak area due to Domperidone in sample preparation

WS = Weight of Domperidone working standard, in mg.

P = Purity of Domperidone working standard.

LA = Labeled amount of Domperidone, in mg.

TW = weight of sample taken in mg

Ave. wt. = Average weight of tablet.

7.8 GASTRIC RESISTANT FOR OMEPRAZOLE[56,63,64]:

Dissolution Condition

Medium	**:**	0.1 M HCl 750mL
Apparatus	**:**	USP Type-2 (paddle)
Speed	**:**	100 RPM
Time interval	**:**	2 hrs
Temperature	**:**	37± 0.5° C

Chromatographic Condition

Column	**:**	Phenomenex C_{18} (250x4.6 i.d., 5µ m particle size)
Flow Rate	**:**	1.0 ml/min
UV Wave Length	**:**	301nm
Injection Volume	**:**	20µ L
Temperature	**:**	25°C±2°C
Run Time	**:**	10 minutes.

Preparation of Mobile phase:

Prepare a filtered and degassed mixture of pH6.5 Ammonium acetate buffer: methanol: acetonitrile in the ratio of 40:30:30 v/v/v and ph was adjusted to 7.44±0.02 with acetic acid/ammonia.

Preparation of 0.1M Hydrochloric acid(pH 1.2) :

Measure 8.5 ml of Hydrochloric acid is mixed well and dissolved in 1000 ml of water to produce required 0.1M Hydrochloric acid**.**

Standard Preparation:

Weigh accurately 20mg of omeprazole into dry, stoppered test-tube, add 20.0 ml of 0.1 M sodium hydroxide, shake vigorously for 5 minutes and dilute 1.0 ml of the solution with the mobile phase to produce 50.0 ml.

Sample Preparation:

Tablets were placed in each dissolution baskets which contains 750 ml of 0.1 N HCl. Then run the dissolutions apparatus as per the above mentioned dissolution parameters. After 2 hours drain the solution without losing of any granules. Transfer them to a 100ml volumetric flask, add 20ml of 0.1M NaOH, and mix with the aid of ultrasound. Dilute to volume with 0.1M NaOH, centrifuge about 15ml for 15min and dilute 5ml of the clear supernatanant liquid to 50ml with mobile phase.

Then the value was subtracted from the initial assay value. Then we can get the % drug released from the tablet.

Procedure:

Separately inject equal volume of Mobile phase (blank), standard preparation and test preparation, record the chromatograms, and measure the areas for Omeprazole.

Calculation:

% OF OMEPRAZOLE:

$$\frac{\mathbf{TA}}{\mathbf{SA}} \mathbf{x} \frac{\mathbf{SW}}{\mathbf{20}} \mathbf{x} \frac{\mathbf{1}}{\mathbf{50}} \mathbf{x} \frac{\mathbf{100}}{\mathbf{WT}} \mathbf{x} \frac{\mathbf{5}}{\mathbf{50}} \mathbf{x\ Avg.\ Wt\ x} \frac{\mathbf{P}}{\mathbf{100}} \mathbf{x} \frac{\mathbf{100}}{\mathbf{LA}}$$

Where,

SA = peak area due to Omeprazole in standard preparation.

TA = Peak area due to Omeprazole in sample preparation

SW= Weight of Omeprazole working standard, in mg.

P = Purity of Omeprazole working standard.

LA = Labeled amount of Omeprazole, in mg.

WT = weight of sample taken in mg

Ave. wt. = Average weight of tablet

7.9 PROCEDURE FOR DISSOLUTION TESTING[56,57,63,64]:

Dissolution Condition

Medium	:	pH 1.2 HCl 750 mL, pH6.8 phosphate buffer 1000mL
Apparatus	:	USP Type-2 (paddle)
Speed	:	100 RPM
Temperature	:	37± 0.5° C

Chromatographic Condition

Column	:	Phenomenex C_{18} (250x4.6 i.d., 5µ m particle size)
Flow Rate	:	1.0 ml/min
UV Wave Length	:	295nm
Injection Volume	:	20µ L
Temperature	:	25°C±2°C
Run Time	:	10 minutes.

Dissolution Medium Preparation:

Preparation of 0.1 N Hydrochloric Acid (pH 1.2):

Measure 8.5 ml of concentrate hydrochloric acid was taken and diluted with distilled water up to 1000 ml.

Preparation of pH6.8 Phosphate buffer:

After 2 hours of operation in 0.1 N hydrochloric acid add to the fluid in the vessel 250 mL of 0.20 M tribasic sodium phosphate that has been equilibrated to 37 ± 0.5 . Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.

Preparation of Mobile phase:

Prepare a filtered and degassed mixture of pH6.5 Ammonium acetate buffer: methanol: acetonitrile in the ratio of 40:30:30 v/v/v and ph was adjusted to 7.44±0.02 with acetic acid/ammonia.

Preparation of Solutions:

Standard Preparation:

Weigh accurately and transfer 20.0 mg of Omeprazole and 20.0 mg of Dmperidone in to a 100 mL volumetric flask, add sufficient amount of dissolution medium, sonicate to dissolve and make up to volume with dissolution medium.From this 1ml is taken and is diluted to 100ml and inject the solution directly in HPLC.

Sample Preparation:

Acid Stage:

Place one tablet in each of six vessels containing 750 mL of pH1.2 HCl medium that has been equilibrated to 37˚C± 0.5˚C. Take care to exclude air bubbles from the surface of the tablet, and immediately operate the apparatus with prescribed instrument condition for 2hrs. In every 30 min interval of dissolution, withdraw 5mL of sample solution from a zone midway between the surface of dissolution medium and the top of the rotating paddle, not less than 1 cm from the vessel wall and filter through 0.45µ filter, and inject the solution directly in HPLC.

Buffer Stage:

After 2 hours of operation in 0.1 N hydrochloric acid add to the fluid in the vessel 250 mL of 0.20 M tribasic sodium phosphate that has been equilibrated to 37 ± 0.5 . Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 10hrs. For every 10min time interval of dissolution, withdraw 5mL of sample solution for omeprazole drug release up to 1hr and there after for every 1hr from a zone midway between the surface of

dissolution medium and the top of the rotating paddle, not less than 1 cm from the vessel wall and filter through 0.45µ filter, and inject the solution directly in HPLC.

Procedure:

Separately inject equal volume of Mobile phase, Blank (Dissolution medium) standard (Five replicate injection) and test preparation, record the chromatograms, and measure the areas for the Omeprazole and Domperidone. Calculate the quantity of Omeprazole and Domperidone.

CALCULATION:

% of Omeprazole:

$$\frac{TA}{SA} x \frac{SW}{100} x \frac{1}{100} x \frac{1000}{LA} x \frac{10}{1} x \frac{P}{100} x 100$$

Where,

SA = peak area due to Omeprazole in standard preparation.

TA = Peak area due to Omeprazole in sample preparation

SW = Weight of Omeprazole working standard, in mg.

P = Purity of Omeprazole working standard.

LA = Labeled amount of Omeprazole, in mg.

% of Domperidone:

$$\frac{TA}{SA} x \frac{SW}{100} x \frac{1}{100} x \frac{1000}{LA} x \frac{10}{1} x \frac{P}{100} x 100$$

Where,

TA = Peak area due to Domperidone in sample preparation

SA = peak area due to Domperidone in standard preparation.

SW = Weight of Domperidone working standard, in mg.

P = Purity of Domperidone working standard.

LA = Labeled amount of Domperidone, in mg.

7.10 RELEASE KINETICS[57,58]:

7.10.1 Dissolution Profile Modelling:

Over recent years, the in vitro dissolution has been recognized as an important tool in drug development. In vitro dissolution has been recognized as an important parameter in quality control and under certain conditions, it can be used as a surrogate for the assessment of bio-equivalence or prediction of bioequivalence. Guidance recommends USP dissolution equipment is satisfactory. However modification of current dissolution equipment or completely new designs may be needed to accommodate new release mechanisms. Generally, methods of agitation, changing the media, and holding the dosage form in the media without interfering with the release mechanism of dosage form as well as the physical chemical properties of the drug will enable development of accurate dissolution tests.

An appropriate drug release test is required to characterize the drug product and ensure batch-to-batch re-reducibility and consistent pharmacological/biological activity and to evaluate scale up and post approval changes such as manufacturing site changes, component and composition changes. The release of the drug from a sustained release formulation is controlled by various factors through different mechanisms such as diffusion, erosion or osmosis. Several mathematical models are proposed by many researchers to describe the drug release profiles from various systems. In order to characterize the kinetics of drug release from dosage forms several model dependent methods are reported by various researchers. The model dependent methods all rely upon a curve fitting procedure. Different mathematical functions have been used to model the observed data. Both the linear and non-linear models are being used in practice for dissolution modeling. Linear models include Zero order, Higuchi, Hixson-Crowell, where as the nonlinear models include first order, Weibull, Korsmeyer-Peppas, Logistc etc.

7.10.2 Mathematical models (Release Kinetics) :

To study the release kinetics of the drug from the reservoir tablets, the release data were fitted to the following equations:

a) Zero order equation

$$Qt = k_0.t \quad (1)$$

Where Q_t is the percentage of drug released at time t and k_0 is the release rate constant; the zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration.

b) First order equation

$$\mathbf{In\ (100\text{-}Q_t) = In\ 100 - k_1.t} \quad (2)$$

Where k_1 is the release rate constant;

The first order Eq. (2) describes the release from system where release rate is concentration dependent.

The release of drug from matrix based pharmaceutical systems has been given great interest over the last 20 years. These devices have been extensively used for the delivery of drugs over an extended period of time. Significant experimental and theoretical work has been performed to accurately model drug transport and reveal the mechanisms of drug release from these systems. Basically three main mathematical approaches were used for the drug release through matrix systems: Higuchi's model, Korsmeyer and Peppas model and Hixson Crowell cube root law.

c) Higuchi's Model

$$Q_t = k_H.t^{1/2} \quad (3)$$

Where k_H is the Higuchi release rate constant;

Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). According to this model the fraction of drug released is proportional to the square root of time. The basic assumption

for the derivation of Eq. (1) is that the initial concentration of the drug in the system, C_0, is much higher than drug solubility, Cs and diffusion is the sole mechanism of drug release. The Higuchi's model basically gives an idea of only the mechanism of diffusion through a matrix based system which is generally for the water soluble drugs. When the mechanism of diffusion as well as erosion is involved another model came into picture which gives an idea of the erosion mechanism also involved.

d) Hixson-Crowell model

$$(100-Q_t)^{1/3} = 100^{1/3} - k_{HC}.t \quad (4)$$

Where k_{HC} is the Hixson-Crowell rate constant.

Hixson-Crowell model (Equation 4) describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets.)

e) Korsmeyer - Peppas Model *(*Mechanism of Drug Release)

To evaluate the mechanism of drug release, the **Korsmeyer-Peppas** model was applied:

$$Q_t/Q_\infty = k_{KP}.\ t^n \quad (5)$$

Where Q_t/Q_∞ is the fraction of drug released at time t, k_{KP} a constant compromising the structural and geometric characteristics of the device, and n, the release exponent, which is indicative of the mechanism of drug release.

Table No.18 Mechanism of drug release

Diffusion Exponent(n)	**Release**
$0.45 \leq n$	Fickian diffusion
$0.45 < n \leq 0.89$	Anomalous(Non-Fickian) diffusion
$n = 0.89$	Case II transport (swelling-controlled drug release)
$n > 0.89$	Super Case II transport

The mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case II relaxational release (swelling-controlled drug release) are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-11 relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. The rate controlling step in Case II transport kinetics is the swelling which occurs at the internal moving boundary. Anomalous transport kinetics indicates a combined mechanism of pure diffusion and Case II transport. Super Case II transport mechanism could result from increased plasticization at the relaxing boundary (gel layer).

7.10.3 Determination of kinetics of release from dosage form:

The mathematical modelling of drug release is of great importance in pharmaceutical science and engineering because the idealized but key transport mechanisms can be studied in the mathematical model and the model itself can be used to predict the effects of the composition and geometry on drug release profiles, which is very helpful to the design of new drug delivery system. The mechanism study of drug release via a swellable and dissoluble hydrophilic polymer matrix is not as extensive as for purely diffusion, swelling or polymer dissolution controlled drug release systems since all these processes are coupled, thus making the models more intricate and difficult to solve.

Generally, in swelling controlled matrix systems of controlled formulations, there are two major factors which control the rate of release of the drug from the matrix. One is the rate of aqueous medium infiltration into the matrix followed by a relaxation process (hydration, gelation or swelling) and the other is the rate of erosion of the matrix. As a result of these simultaneous processes, two fronts are evident, a swelling front (glassy polymer/gel interface) and an eroding front (gel/medium interface). The distance between the two fronts (diffusion layer thickness) depends on the relative rates at which the swelling and eroding fronts move in relation to each other. There have been several mathematical models proposed to describe the system. The mathematical approaches

most frequently used to describe the mechanism of drug release are those of Higuchi and Hixson Crowell cube root law.

The selection of particular model for release is based on regression coefficient of release profile obtained from its slope. The regression value (r^2) approaching towards 1 shows best fit for particular model. Hence the model for which release profile shows the regression coefficient value close to 1 was chosen for determination of release of drug from dosage form.

7.11 SIMILARITY FACTOR AND DISSIMILARITY FACTOR CALCULATION[59,60]

The similarity factor (f2) was defined by CDER, FDA, and EMEA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference release profiles".

Dissimilarity or difference factor (f1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves. The percent error is zero when the test and reference release profiles are identical and increases proportionally with the dissimilarity between the two profiles.

There are several methods for dissolution profile comparison. f2 is the simplest among those methods. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f1 & f2.

$$f1 = \{ [\sum_{t=1}^{n} | R_t - T_t |] / [\sum_{t=1}^{n} R_t] \} . 100$$

$$f2 = 50. \log \{ [1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100\}$$

Where 'R_t' and 'T_t' are the cumulative percentage dissolved at each of the selected n time point of the reference & test product respectively. The factor f1 is proportional to the average difference between the two profiles, where as factor f2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. The similarity factor f2 and its significance is shown in the following table.

Table No.19 Similarity factor f2 and its significance

S. No.	Similarity factor (f2)	Significance
1.	<50	Test and reference profiles are dissimilar.
2.	50 -100	Test and reference profiles are similar.
3.	100	Test and reference profiles are identical.
4.	>100	The equation yields a negative value.

7.12 STABILITY STUDY[61,64]

Stability studies are an integral part of the drug development program & are one of the most important areas in the registration of Pharma products. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity & light & enables recommended storage conditions, re-test periods and self half lives to be established. Stability assessment starts with studies on the substance to determine degradation products degradation pathway. In these types of studies the product is analyzed at intervals for various parameters which may include assay of active ingredient, measurement of known degradation products, hardness, dissolution time, appearance, etc., Omeprazole and Domperidone Bilayer tablets were packed in HDPE containers and evaluated for accelerated stability studies at 40ºC/75% RH conditions.

Storage conditions: 40±2°C/75±5%RH.

Chapter 8

RESULT S& DISCUSSION

8. RESULTS AND DISCUSSION

8.1 Organoleptic Properties:

Table No.20 Organoleptic Properties for Omeprazole

Test	**Specification / limits**	**Observations**
Colour	White or almost white powder	White or almost white powder
Taste	Bitter	Bitter
Odour	Characteristic odour	Characteristic odour

Table No.21 Organoleptic Properties for Domperidone

Test	**Specification / limits**	**Observations**
Colour	White or almost white powder	White or almost white powder
Taste	Bitter	Bitter
Odour	Characteristic Odour	Characteristic Odour

8.2 Angle Of Repose:

Table No.22 Angle of repose for Omeprazole

S. No.	**Material**	**Angle of repose**	**Average angle of repose**
1.	Omeprazole	38.37°	$38.56^{\circ}\pm0.54$
2.		39.17°	
3.		38.14°	

Table No.23 Angle of repose for Domperidone

S. No.	**Material**	**Angle of repose**	**Average angle of repose**
1.	Domperidone	38.34°	$38.66^{o}\pm0.52$
2.		39.27°	
3.		38.38°	

8.3 Determination of Bulk density and Tapped density:

Table No.24 Bulk Density and Tapped Density for Omeprazole

S.No.	Material	Bulk Density (gm / ml)	Average Bulk Density (gm / ml)	Tapped Density (gm / ml)	Average Tapped Density (gm /cc)
1	Omeprazole	0.364	0.359± 0.01	0.531	0.533± 0.01
2.		0.358		0.536	
3		0.357		0.532	

Table No.25 Bulk Density and Tapped Density for Domperidone

S.No.	Material	Bulk Density (gm / ml)	Average Bulk Density (gm / ml)	Tapped Density (gm / ml)	Average Tapped Density (gm / ml)
1	Domperidone	0.346	0.346± 0.01	0.526	0.521± 0.01
2.		0.344		0.516	
3.		0.348		0.523	

8.4 Powder Compressibility and Hausner ratio

Table No.26 Compressibility Index and Hausner ratio

Materials	Compressibility index	Hausner ratio
Omeprazole	32.64	1.48
Domperidone	33.58	1.51

The organoleptic characters of the bulk products namely Omeprazole and Domperidone comply with monograph specifications of USP and IP respectively. The flow properties, poured density, tapped density, compressibility index, Hausner ratio also complies with the above said specifications revealing that the former exhibits poor flow and the latter exhibits very poor flow with the exception that Hausner ratio value of metoprolol implies very poor flow.

8.5 LOD studies:

The Loss on drying for Omeprazole was 0.12% and for Domperidone it was 0.17%. It complies with in the limit.

8.6 Solubility:

The following table illustrates the results of solubility studies

Table No.27 Solubility of Omeprazole

Quantity of Metoprolol Succinate	**Quantity of solvents**	**Inference**
100 mg 100 mg 100 mg	100 ml of water 100 ml of 95 % ethanol 100 ml methanol	Slightly soluble Freely soluble Freely Soluble

Table No.28 Solubility of Domperidone

Quantity of Ramipril	**Quantity of solvents**	**Inference**
100 mg 100 mg 100 mg 100 mg	100 ml of water 100 ml of 95 % ethanol 100 ml of methanol 100ml of dimethylformamide	Very slightly soluble Sparingly soluble Slightly Soluble Sprangly soluble

The solubility studies of Domperidone reveals that drug belongs to BCS class II. These facts imply the necessity to choose a high viscous grade hydrophilic polymer to retard the drug release of Domperidone for formulating as a extended release layer.

8.7 Analytical method development for Omeprazole and Domperidone

Absorption Maxima Scan of Omeprazole and Domperidone:

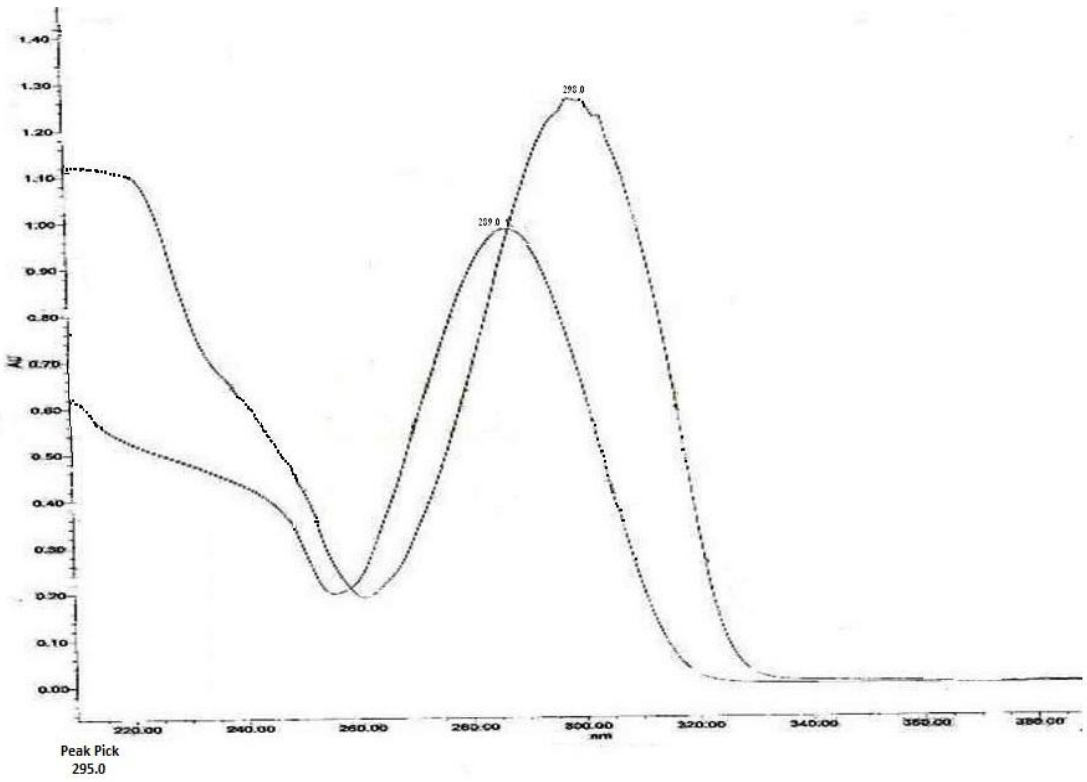


Fig No.4 λ_{max} Scan of Omeprazole and Domperidone

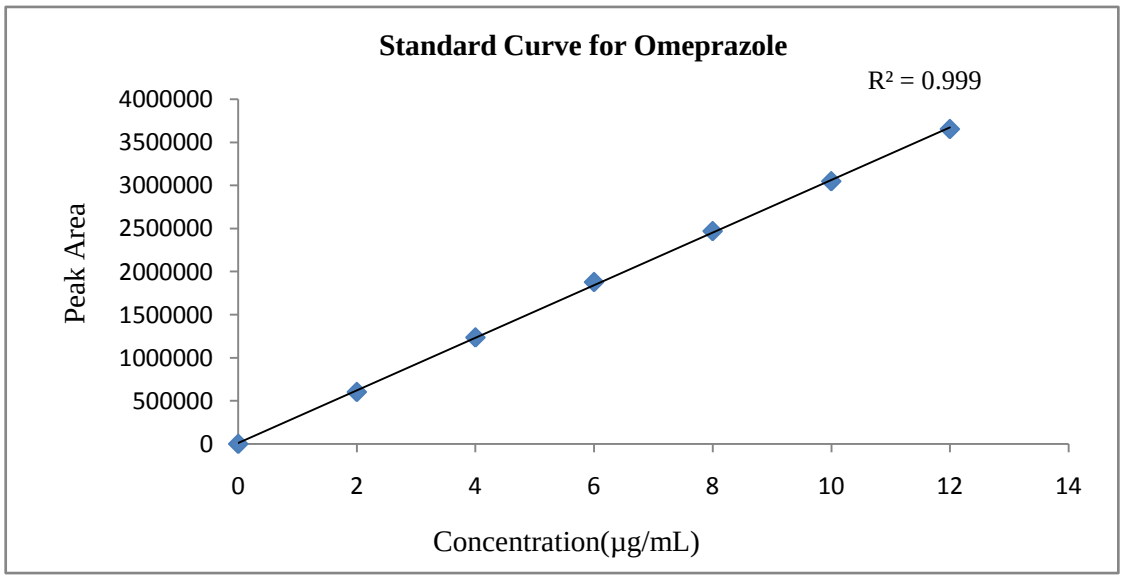
A spectrum of the working standards is obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λ_{max} is found to be 295.0nm. Hence standard curve and dissolution testings are being carried out at the same wavelength.

8.7.1 Calibration curve for Omeprazole

The standard calibration curve is plotted by preparing various concentrations of the Omeprazole in phosphate buffer of pH 6.8.

Table No.29 Preparation of Standard graph for Omeprazole

S.No	Conc.(µg/mL)	Peak Area
1	0	0
2	2	602545
3	4	1235841
4	6	1878547
5	8	2469874
6	10	3048752
7	12	3654781



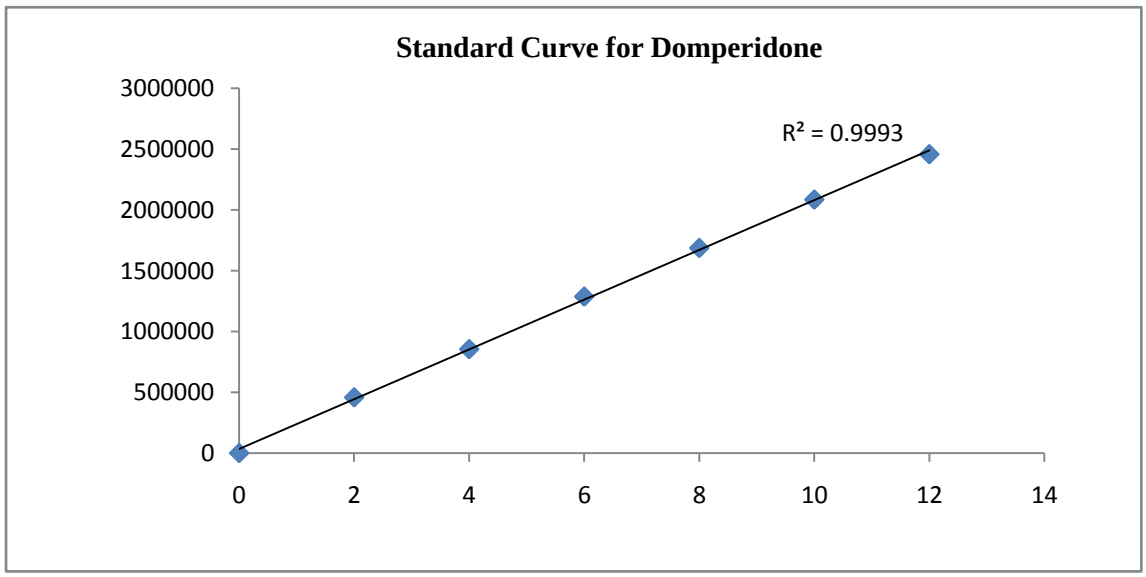
Graph No.1 Standard curve for Omeprazole

8.7.2 Calibration curve for Domperidone

The standard calibration curve is plotted by preparing various concentrations of Domperidone in phosphate buffer of pH 6.8.

Table No.30 Preparation of Standard graph for Domperidone

S.No	Conc.(µg/mL)	Peak Area
1	0	0
2	2	458421
3	4	854782
4	6	1287425
5	8	1687450
6	10	2085478
7	12	2458745



Graph No.2 Standard curve for Domperidone

8.8 Drug-Excipient compatibility study at 40° C / 75 % RH

The various drug excipient mixtures are subjected to compatibility studies by keeping the blends under accelerated conditions, 40° C / 75 % RH for a period of 4 weeks. After 4 Weeks of study physical appearance of these compositions were made and compared with the initial observations. These observations are recorded in Table

Table No.31 Excipients compatibility studies for Omeprazole

S.No	Composition	Ratio	Physical Appearance				
			Initial	1st week	2nd week	3rd week	4th week
1.	Omeprazole		A white or almost white crystalline powder	NCC	NCC	NCC	NCC
2.	Omeprazole + Mannitol	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
3	Omeprazole + $NaHCO_3$	1:0.5	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
4.	Omeprazole + Povidone	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
5.	Omeprazole + Avicel PH102	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
6	Omeprazole + Aerosil	1:0.25	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
7.	Omeprazole + Mg. stearate	1:0.5	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
8.	Omeprazole + Talc	1:0.5	A white or almost white crystalline powder	NCC	NCC	NCC	NCC

*** NCC – No characteristic change**

Table No.32 Excipients compatibility studies for Domperidone

S.No	Composition	Ratio	Physical Appearance				
			Initial	1st week	2nd week	3rd week	4th week
1.	Domperidone		A white or almost white crystalline powder	NCC	NCC	NCC	NCC
2.	Domperidone + HPMC K4	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
3	Domperidone + HPMC K15	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
4.	Domperidone + Lactose monohydrate	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
5.	Domperidone + Avicel pH101	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
6.	Domperidone + Magnesium stearate	1:0.5	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
7.	Domperidone + Talc	1:0.5	A white or almost white crystalline powder	NCC	NCC	NCC	NCC

*** NCC – No characteristic change**

After the storage, the samples were observed physically for liquefaction, caking and discoloration. It shows that there is no significant difference in the colour and appearance of the mixtures after 4 weeks at 40°C / 75% RH. Hence the selected excipients are likely to be suitable for the preparation of the bilayer tablets.

8.9 PARTICLE SIZE ANALYSIS OF API

Table No.33 Size Analysis of Omeprazole & Domperidone

Sieve number	Arthimatic mean size opening(µm) (A)	Omeprazole		Domperidone	
		% weight retained(B)	Weight size(A*B)	% weight retained(B)	Weight size(A*B)
50	300	1.2	360	0.7	210
70	212	7.4	4473.2	12.6	2671.2
100	150	11.7	1755	20.7	3105
150	125	21.6	1262.5	13.7	1712.5
170	90	18.6	1476	17.9	1611
200	75	19.6	1470	10.7	802.5
Pan	-	19.3	0	23.4	0
Total		99.4	9527.8	99.7	10112.2

Average Particle size of Omeprazole=9527.8/99.4=95.8531µm

Average Particle size of Domperidone=10112.2/99.7=101.42µm

Particles in the above size ranges are found to pose no serious problems like charge development. Therefore it was decided to use the API as it can be used without any further processing (like milling to decrease the particle size or adsorption or removal of fine to decrease cohesive forces).

8.10 DRUG –POLYMER COMPATIBILITY STUDIES BY FTIR:

The FTIR spectra of Omeprazole, and the combination of drug and excepients shows no significant interaction between drug and excepients.

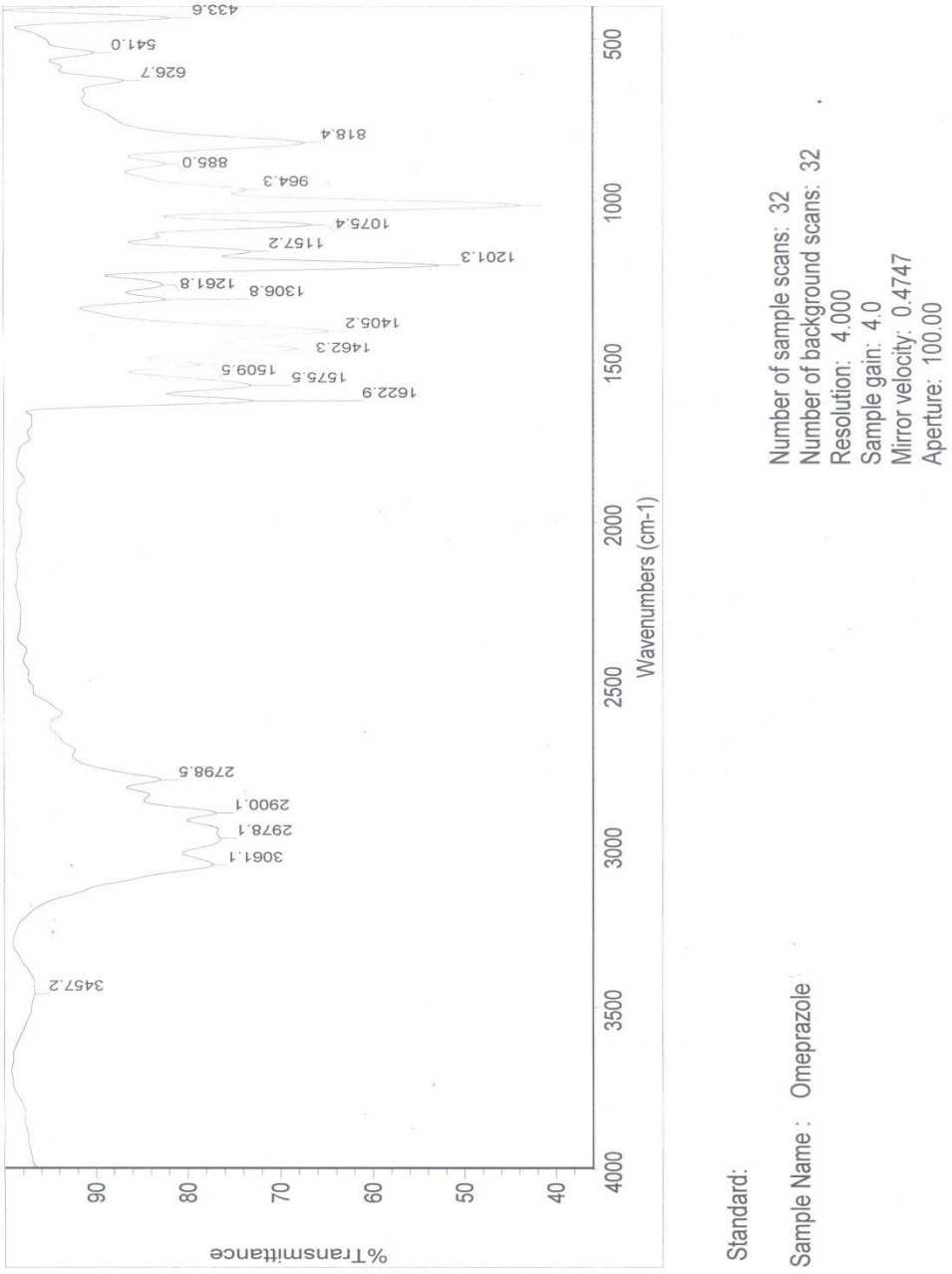


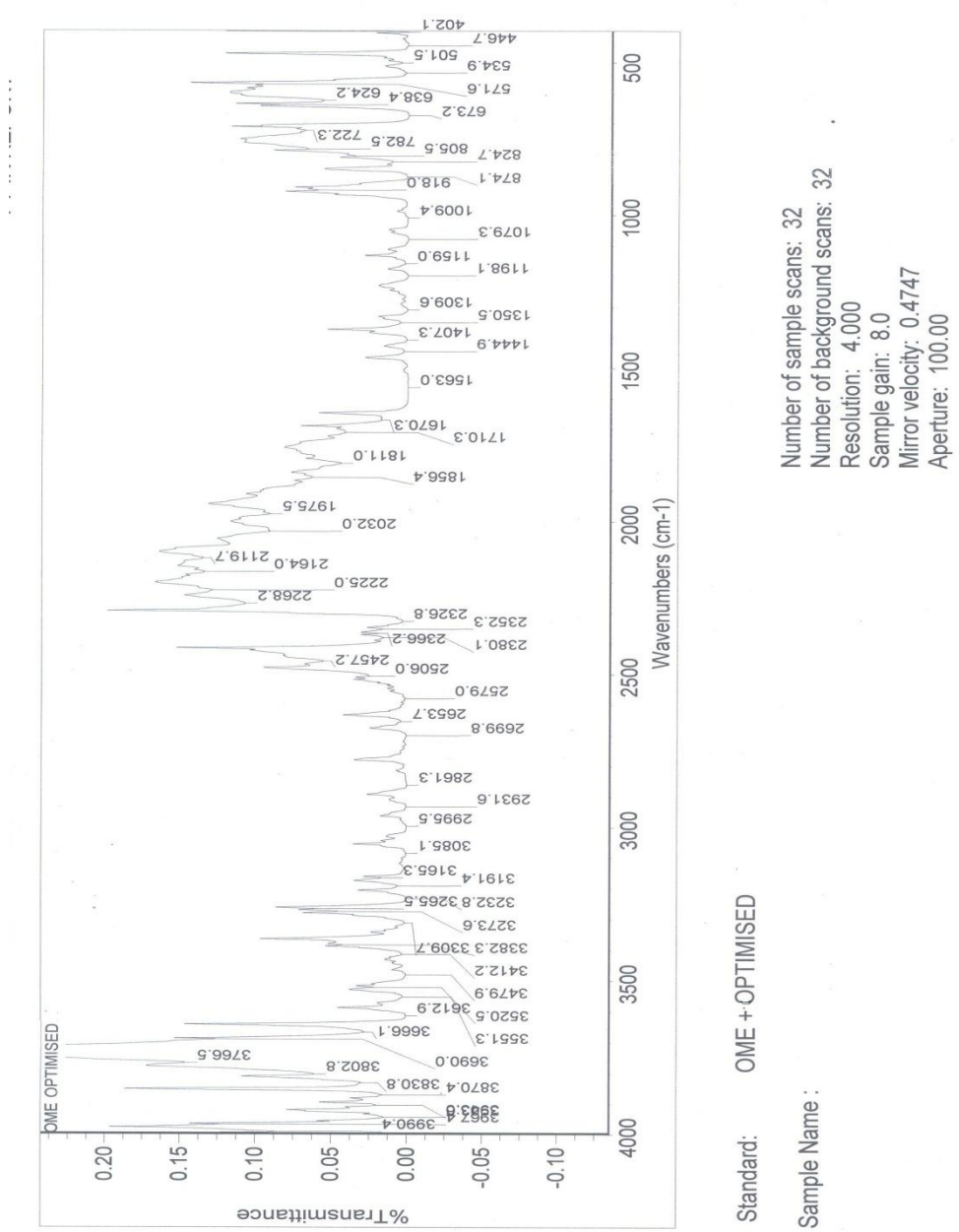
Fig No.5 FTIR Spectra of Omeprazole Drug.

Table No.34 Interpretation values of Omeprazole Spectra

S.No	Functional Group	Assessment of peak(cm^{-1}) of pure drug	Range of Groups
1.	N-H Stretching	3457.2	3509-3450
2.	CH_3- Alkyl Stretching	2978.1	3032-2953
3.	C=C Stretching	1575.5	1590-1560
4.	C-C Aromatic stretching	1509.5	1500-1510
5.	S=O Stretching	1306.8	1300-1350
6.	C-N Stretching	1261.8	1350-1280
7	C-O Stretching	1157.2	1160-1060

IR spectral analysis of Omeprazole showed the peaks at wave numbers of 3457.2 (N-H Asymmetric stretching), 2978.1 (CH_3 Alkyl Stretching)1575.5 (C=C Stretching), 1509.5,1462.3 (C-C Aromatic stretching), 1306.8(S=O Stretching), 1261.8 (C-N Stretching), 1157.2 (C-O Stretching) confirming the purity of drug with standard respectively.

Fig No.6 FTIR Spectra Omeprazole Optimised Formulation.



In the physical mixture of Omeprazole with excepients the major peaks of Omeprazole are present. However, additional peaks were observed in physical mixtures which could be due to presence of excepients and indicated that there was no chemical interaction between Omeprazole and other excipients.

FTIR absorption spectra of Domperidone and all the polymer used like HPMC K4M, HPMC K15M shows no significant interaction between drug and polymers. The graphs obtained were shown in the following FTIR spectras .

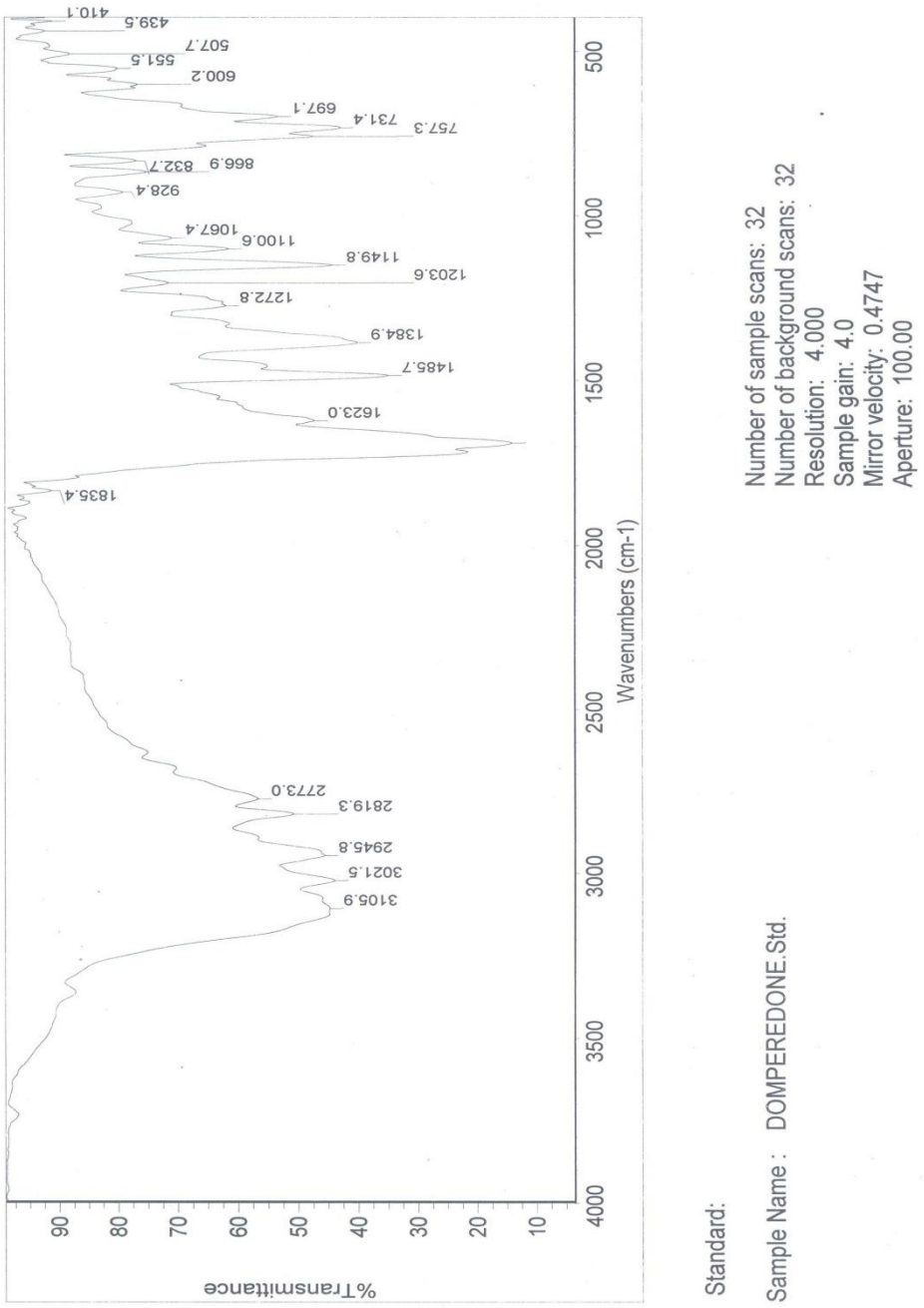


Fig No.7 FTIR Spectra of Domperidone.

Table No.35 Interpretation values of Domperidone Spectra

S.No	Group Assigned	Assessment of peak(cm^{-1}) of pure drug	Range of groups
1.	C-H Stretching Aromatic Ring	3021.5	3030-3020
2.	C=O Stretching	1835.4	1850-1790
3.	N-H Bending	1623.0	1650-1590
4	C=C Stretching	1485.7	1470-1520
5.	C-H Bending	1384.9	1380-1390
6.	C-N Stretching	1272.8	1340-1250

IR spectral analysis of Domperidone showed the peaks at wave numbers of 3021.5 (C-H Stretching Aromatic Ring) 1835.4(C=O Stretching) 1623.0(N-H Bending) 1485.7(C=C Stretching) 1384.9 (C-H Bending) 1272.8(C-N Stretching) confirming the purity of drug with standard respectively.

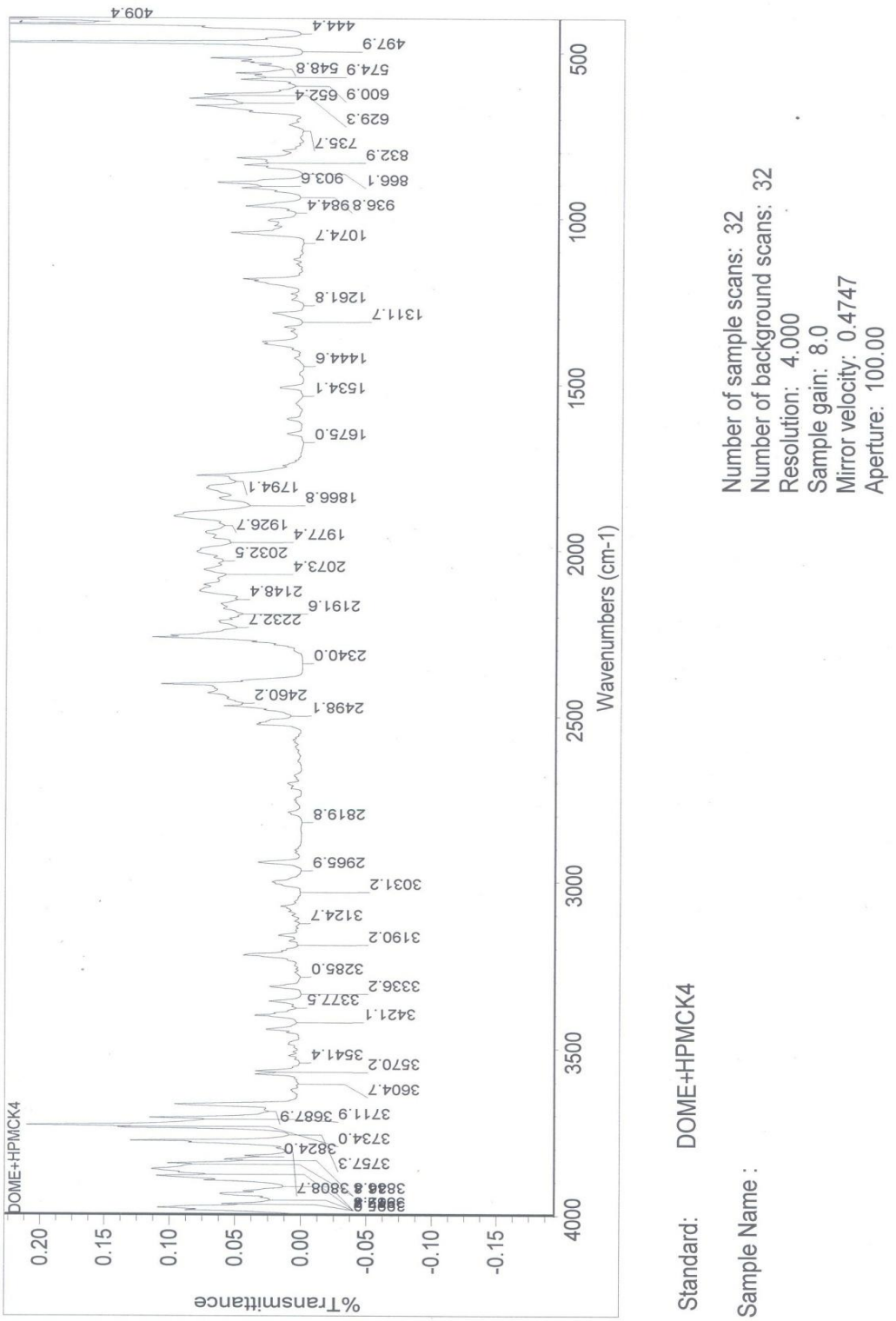


Fig No.8 FTIR Spectra of Domperidone+HPMC K4

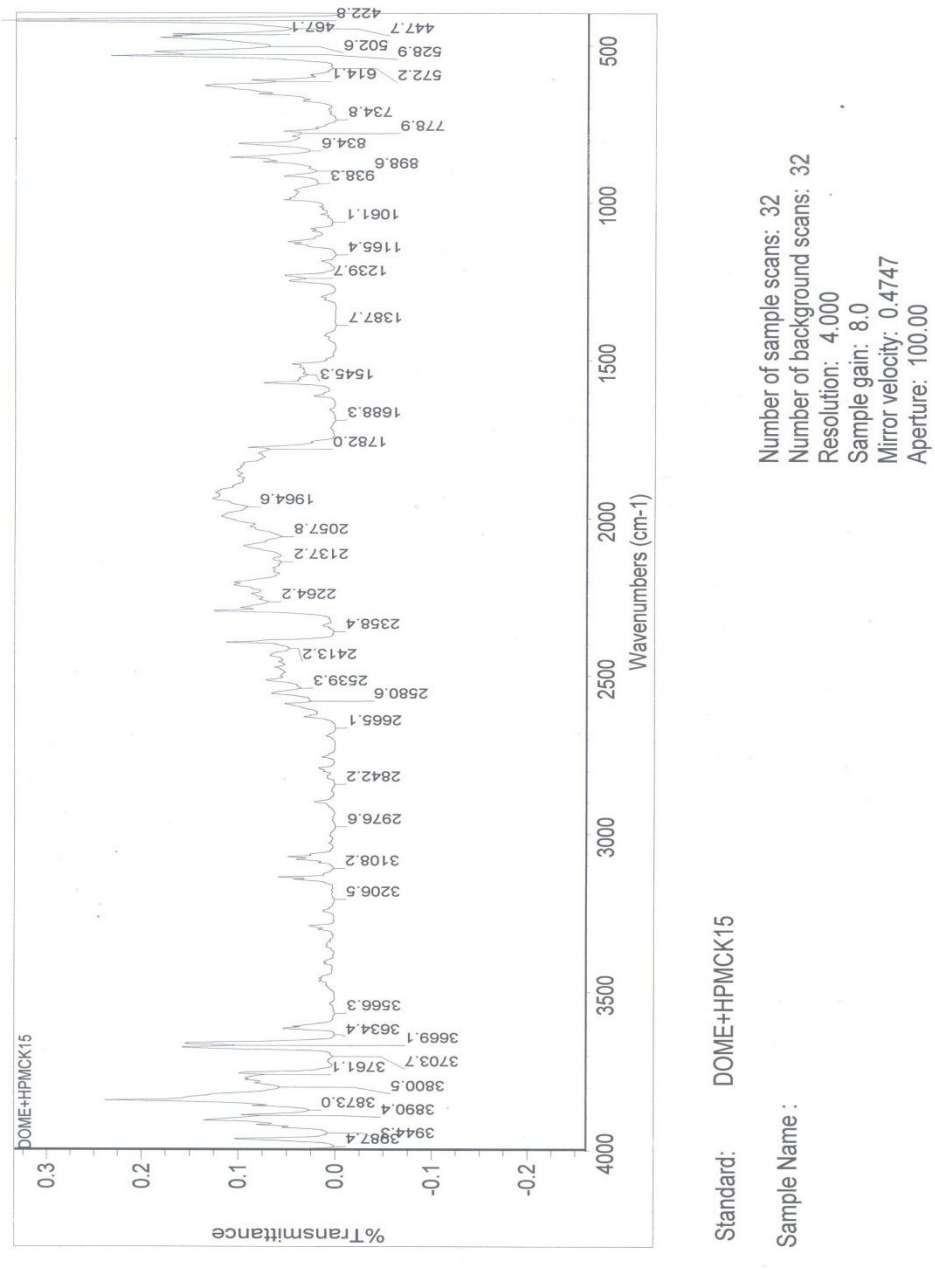


Fig No.8 FTIR **Fig No.9** FTIR**.**Spectra of Domperidone + HPMC K15

In the physical mixture of Domperidone with Hydroxy propyl methyl cellulose K4M and K15M the major peaks of Domperidone are present. However, additional peaks were absorbed in physical mixtures which could be due to presence of polymers and indicated that there was no chemical interaction between Domperidone and other excipients.

8.11Characterization of tablets

8.11.1 Pre-compression parameters

The derived properties of the formulated blends are studied at ambient conditions using standard protocols and the data is tabulated in the tables.

Table No.36 Pre-compression parameters of Omeprazole batches F1 to F6

Batch	Derived Properties			Flow Properties		
	Bulk Density (gm/ml)	**Tapped Density (gm/ml)**	**Loss on Drying**	**Angle of Repose (°)**	**Compressability Index**	**Hausner's Ratio**
F1	0.34±0.002	0.39±0.006	1.34±0.07	28.33±0.31	13.52±0.86	1.15±0.011
F2	0.34±0.003	0.39±0.001	1.34±0.07	29.05±0.13	11.28±0.42	1.12±0.005
F3	0.35±0.01	0.38±0.003	1.47±0.10	29.15±0.20	8.16±3.44	1.08±0.041
F4	0.33±0.008	0.37±0.005	1.52±0.05	31.83±0.22	10.84±3.58	1.12±0.045
F5	0.35±0.010	0.40±0.003	1.40±0.16	28.41±0.26	12.87±2.96	1.14±0.039
F6	0.32±0.006	0.35±0.004	1.36±0.08	27.72±0.13	9.62±1.10	1.10±0.013

Table.No.37 Pre-compression parameters of Domperidone batches F1 to F7

Batch	Derived Properties			Flow Properties		
	Bulk Density (gm/ml)	**Tapped Density (gm/ml)**	**Loss on Drying**	**Angle of Repose (º)**	**Compressibility Index**	**Hausner's Ratio**
F1	0.34±0.005	0.39±0.004	1.47±0.07	31.6±0.34	10.81±0.48	1.12±0.006
F2	0.36±0.004	0.41±0.002	1.38±0.14	30.7±0.13	12.42±1.58	1.14±0.020
F3	0.37±0.004	0.41±0.004	1.43±0.05	32.71±0.12	10.34±1.67	1.11±0.020
F4	0.37±0.006	0.44±0.008	1.51±0.12	31.63±0.36	15.87±2.31	1.18±0.032
F5	0.38±0.005	0.45±0.005	1.46±0.08	29.52±0.28	14.11±1.39	1.16±0.018
F6	0.39±0.009	0.46±0.003	1.38±0.13	27.81±0.25	15.12±1.81	1.17±0.025
F7	0.35±0.005	0.38±0.001	1.42±0.06	28.14±0.14	9.32±1.19	1.10±0.014

The angle of repose (Θ) is a characteristic of the internal friction or cohesion of the particles and the value of the angle of repose will be high if the powder is cohesive and low if the powder is non cohesive.

The range of angle of repose for all the Omeprazole formulations is 27.7° to 31.83°which indicates that flow of the granules ranges from excellent to good. Formulations F4 showed angle of repose above 30°, indicating that the formulation have good flow properties and the rest of the formulations showed excellent flow properties.

The range of angle of repose for all Domperidone the formulations is 27.81° to 32.71°which indicates that flow of the granules ranges from excellent to good. Formulations F5, F6 and F7 showed angle of repose in between 25° and 30°, indicating that these formulations have excellent flow properties and the rest of the formulations showed good flow properties.

Powders showing Carr's index (%) up to 21 are considered of acceptable flow properties[101].The range of Carr's index for the Omeprazole formulations is 8.16% to 13.52% which indicates that the granules have excellent to fair flow. The Carr's index for the optimized formulation, F6 is 9.62%

Powders showing Carr's index (%) up to 21 are considered of acceptable flow properties. The range of Carr's index for the Domperidone formulations is 9.32% to 15.87% which indicates that the granules have excellent to fair flow. The Carr's index for the optimized formulation, F7 is 9.32%.

In addition to Carr's index, Hausner found that the ratio D_{Bmax}/D_{Bmin} was related to the inter particle friction, so, he showed that powders with low inter particle friction, had ratios of approximately 1.25 indicating good flow. The range of Hausner's ratio for all the Omeprazole formulations is 1.08 to 1.15. The optimized formulation, F6 has Hausner's ratio of 1.10 indicating that the the flow is excellent

In addition to Carr's index, Hausner found that the ratio D_{Bmax}/D_{Bmin} was related to the inter particle friction, so, he showed that powders with low inter particle friction, had ratios of approximately 1.25 indicating good flow. The range of Hausner's ratio for all the Domperidone formulations is 1.10 to 1.18. The optimized formulation, F7 has Hausner's ratio of 1.10 indicating that the the flow is excellent

8.11.2 Post compression parameters:

Table No.38 Post compression Parameters of Omeprazole and Domperidone Bilayer tablet

Batch	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability (%)	Content uniformity (%)	
					OME	DOM
F1	8.25±0.05	2.97±0.04	359.1±1.9	0.43±0.02	97.77±0.38	98.73±0.32
F2	8.28±0.03	3.02±0.01	358.7±1.5	0.53±0.03	98.58±0.19	97.96±0.35
F3	8.25±0.04	3.03±0.01	359.0±1.6	0.59±0.04	101.67±0.6	98.50±0.62
F4	8.27±0.03	3.02±0.07	361.8±3.1	0.48±0.03	98.47±0.68	98.60±0.62
F5	8.26±0.01	2.99±0.02	358.1±1.9	0.48±0.01	99.52±0.39	98.23±0.30
F6	8.27±0.06	2.93±0.10	360.8±2.2	0.51±0.02	100.66±0.4	98.80±0.50
F7	8.29±0.08	2.99±0.13	361.5±3.4	0.61±0.03	97.30±0.05	97.76±0.89

All the formulations are tested for the post compression parameters like hardness, friability, thickness and weight variation.

The hardness of all the formulated tablets are maintained at a constant value of 8 kg / cm^2 .Since the quantity of drug varies in both the layers weight variation is also an important parameter which needs to be checked. The weight variation for all the formulations is in par with the criteria mentioned in the USP.

The thickness of the tablets ranges from 2.93 to 3.03 and are within the limits of the standard deviation. Uniform distribution of the drug is another key aspect which directly relates to the efficacy of the tablet. The range of the content uniformity for Omeprazole varies from 97.3 % to 101.67% and for Domperidone aries from 97.76% to 98.8%. All the values are in par with the USP criteria.

8.12 *IN-VITRO* RELEASE PROFILES OF THE FORMULATIONS

Table No.39 *In-vitro* release profiles of Omeprazole formulations F1 to F6

S.No	Time (min)	Cumulative % of drug release					
		F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	**0**	0	0	0	0	0	0
2	**120**	18.65	16.75	11.95	7.54	10.67	6.21
3	**130**	47.18	41.69	40.65	37.58	44.72	39.05
4	**140**	59.84	58.21	51.95	49.95	56.02	54.10
5	**150**	74.36	69.54	66.36	63.84	69.20	64.62
6	**165**	89.23	83.70	78.65	72.25	84.74	79.65
7	**180**	97.65	99.58	98.62	92.98	97.50	98.68
8	**195**	_	_	_	101.36	_	_

Drug release criteria according to USP

No individual value should exceed 10% when dissolved in the acidic phase after 2hrs of operation and not less than 75% should be released in buffer solution after continuous operation of the apparatus for 45min.

Omeprazole granules are coated with cellulose and methacrylic enteric coating polymers and are studied for their capacity to withstand the compression force during compression into a tablet form.

Formulations which obey the above specifications are generally treated as the best formulations.

In formulations F1, the Omeprazole granules are coated with 6% HPMC P enteric coating and plasticized with 2% PEG. Even the drug release in 45min is more than 75% , it does not met the specification in acid phase. Increase in enteric coating to 8% in F2 formulation does not met the specifications in acid phase.

This is because of weak mechanical properties of Cellulose mechanical properties and rupture of coating layer during compression.

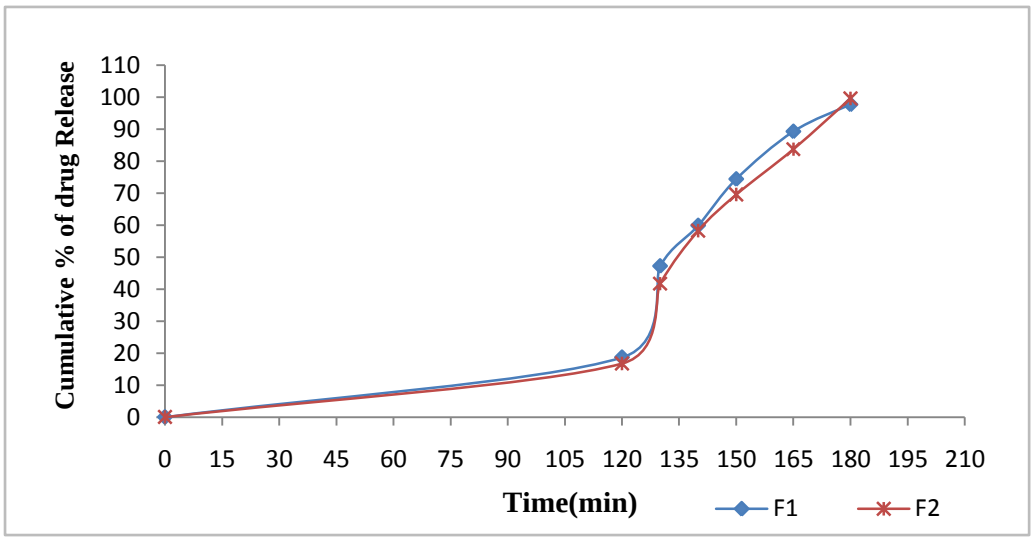
Further trials were conducted with methacrylic polymers such as Eutragit and Kollicoat.

Formulation F3 and F4 are coated with increasing Kollicoat enteric coating polymer (6 and 8%) and plasticizer (2%). An F3 formulation does not met the recommendations in Acid phase but acceptable drug release in acid phase when compared to cellulose polymers. Still increase in enteric and plasticizer ratios in F4 formulation met the recommendations of USP in Acid phase and but not in Buffer phase.

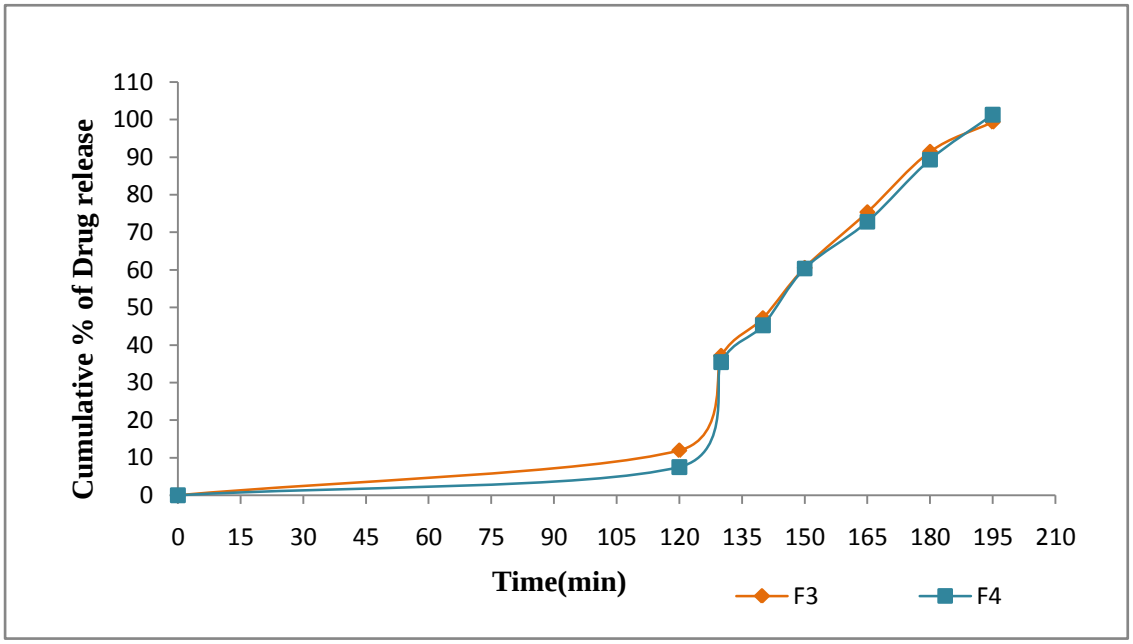
Further trials are done with Eutragit polymer for finding out the best formulation to the above specifications. Formulations F5 and F6 are coated with Eutragit and plasticized with PEG.

Formulation F5 does not met the acid phase specifications, but F6 met the USP specifications of both in Acid phase and buffer phase.

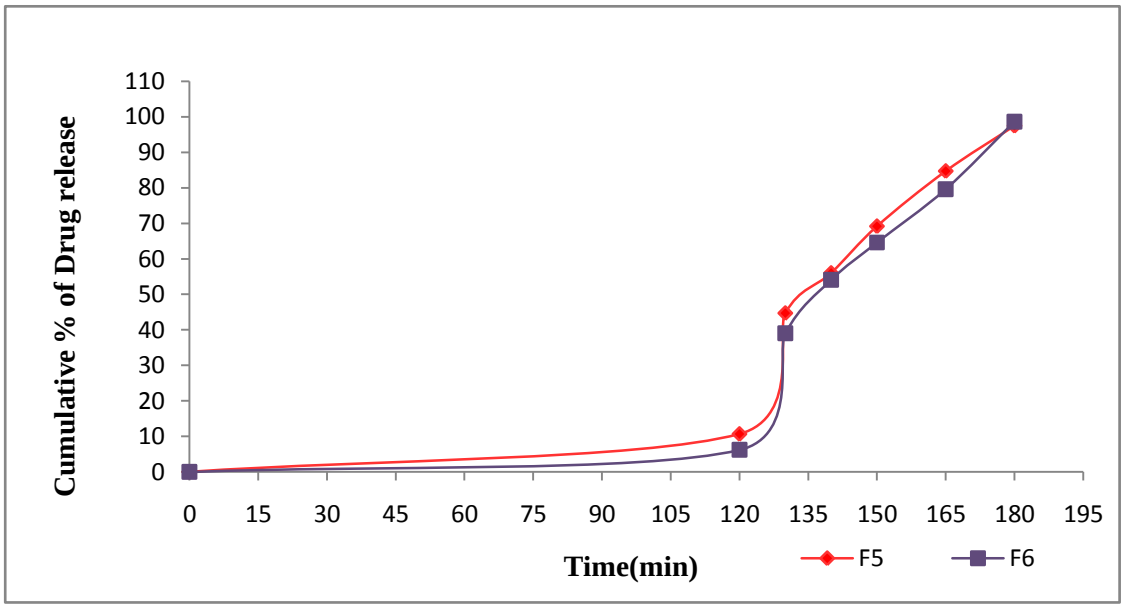
None of the formulations other than F6 passed the above criteria and hence is selected as the best formulation .Hence the above formulation has been optimized and has been further proceeded to the stability studies.



Graph No.3 Comparitive *Invitro* drug release data for Omeprazole F1&F2 formulations



Graph No.4 Comparitive *Invitro* release data for Omeprazole F3 & F4 formulations



Graph No.5 Comparitive *Invitro* release data for Omeprazole F5 & F6 formulations

Table No.40 *In-vitro* release profiles of Domperidone formulations F1 to F7

S.No	Time (hrs)	Cumulative % of drug release						
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
1	**0**	0	0	0	0	0	0	0
2	**0.5**	10.36	8.69	7.32	5.02	7.68	7.30	12.06
3	**1.0**	18.35	15.06	12.06	10.32	14.36	15.40	20.22
5	**2**	33.54	31.85	24.65	20.76	30.36	27.26	38.39
7	**4**	53.98	49.96	36.25	32.02	46.96	41.32	58.32
9	**6**	73.12	67.32	49.36	46.62	61.36	53.06	70.65
11	**8**	90.37	83.69	64.25	59.68	77.36	65.32	81.36
13	**10**	98.74	98.21	78.02	73.98	92.39	76.12	91.46
14	**11**	_	99.36	84.12	80.36	98.93	82.69	96.56
15	**12**	_	_	90.68	85.02	_	87.36	98.95

Different viscosity grades of the polymer like K4M and K15M at different concentrations have been done to study their effect on the release profile of Domperidone.

According to the USP, the amount of Domperidone release at different time points is given below

Table No.41 Drug release criteria according to USP

S. No	Time (hours)	Amount released
1.	1	Between 10% and 30%
2.	2	Between 30% and 55%
3.	4	Between 55% and 80%
4.	8	Not less than 80%

Formulations which obey the above specifications are generally treated as the best formulations.

Three different concentrations of HPMC K4M are subjected to the drug release studies for formulations F1 and F2

F1 formulation at HPMCK4M concentration of 20% releases about 98% of the drug in 10hrs when compared with the other formulations i.e, F2 at concentrations of 30% which releases 99% in 11 hrs

Further trials were conducted with HPMC of grade K15M to observe the release characteristics at the same concentrations to the formulations F3 and F4.

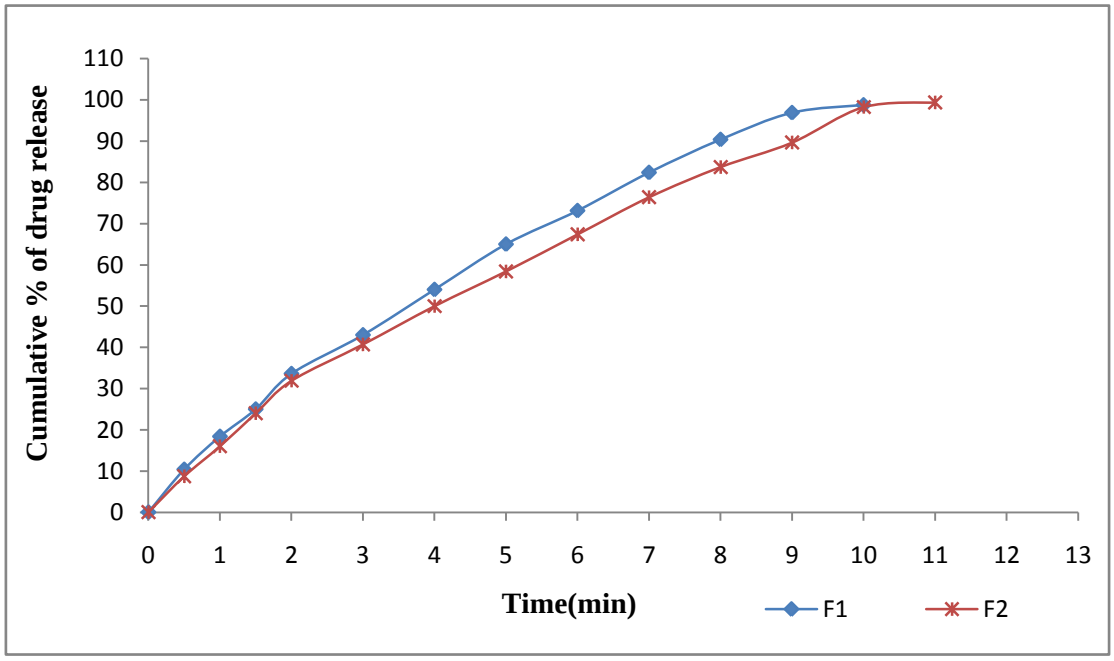
Similar trials are conducted with the grade K15M and all the above formulations failed to meet the USP criteria of drug release. Increasing the concentration of the polymer in the above cases also retarded the drug from getting released

Further trials have been conducted with combination of HPMC K4M and K15M to study its effect on the release of the drug.

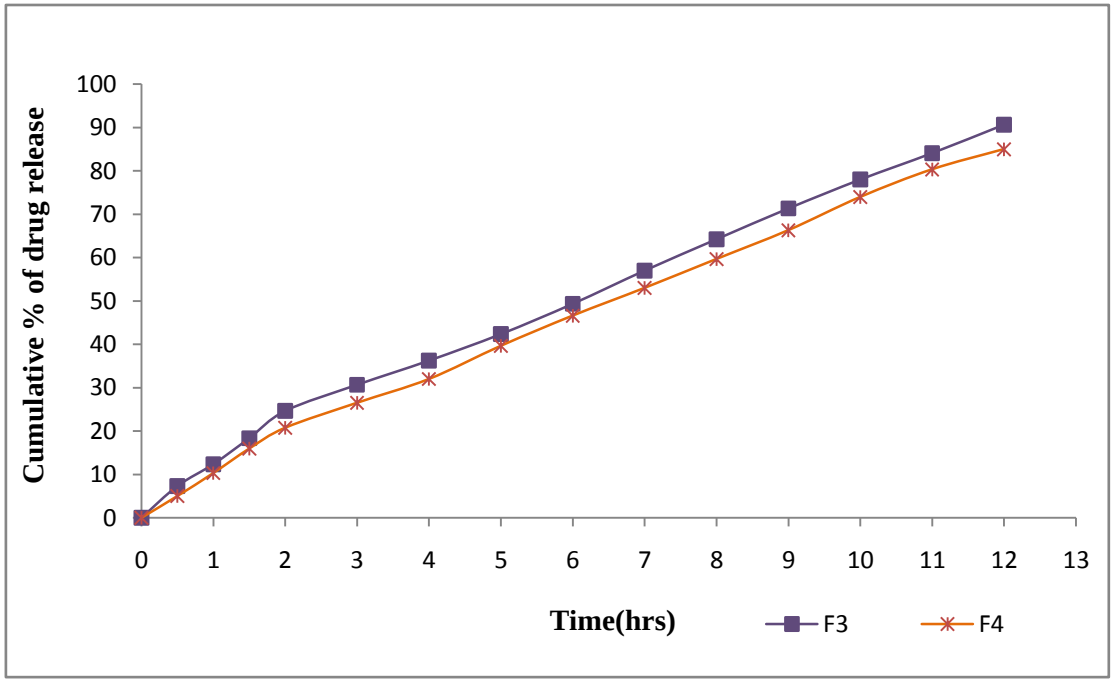
Formulations F5-F7 are formulated by the combination of HPMC K4M and K15M. On increasing the HPMC K15M the drug release was retarded. At polymer concentration of 10% of HPMC K4M and 20% of HPMC K15M proved to be effective in meeting the USP criteria of drug release.

According to the USP the drug release for Domperidone by the end of the eighth hour should not be less than 80% and the entire drug should be released within the 12 hours.

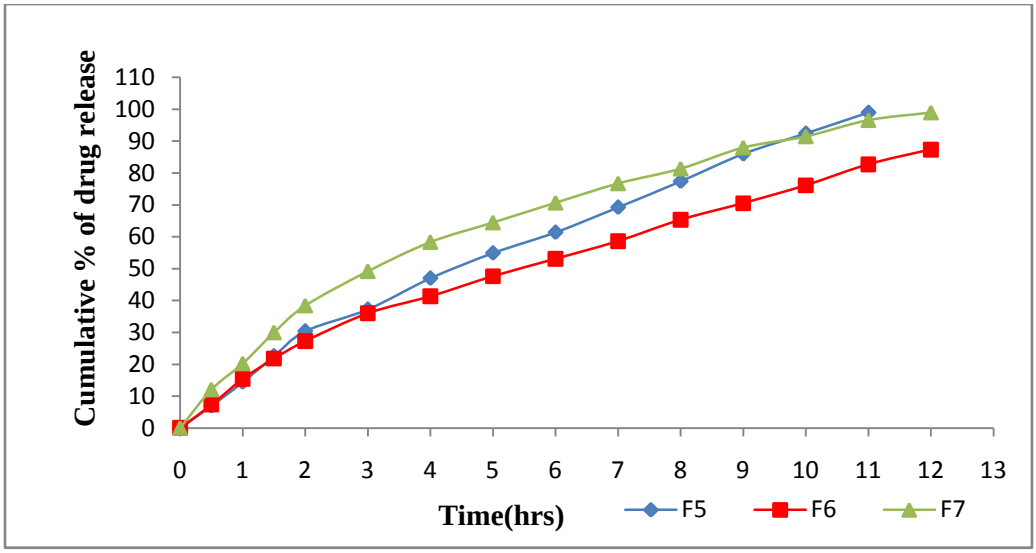
None of the formulations other than F7 passed the above criteria and hence is selected as the best formulation .Hence the above formulation has been optimized and has been further preceded to the stability studies.



Graph No.6 Comparitive *Invitro* release data for Domperidone F1 & F2 formulations



Graph No.7 Comparitive *Invitro* release data for Domperidone F3 & F4 formulations



Graph No.8 Comparative *Invitro* release data for Domperidone F5, F6 & F7 formulations

8.13 RELEASE KINETICS

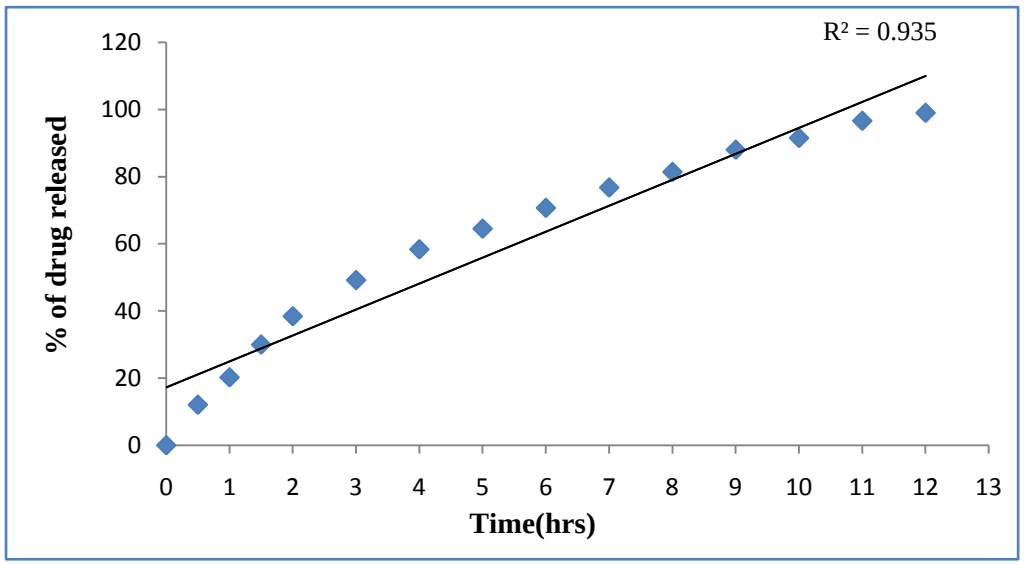
Table No.42 Kinetics of release data of different Domperidone batches

S.No	Batch No	Zero order	First order	Higuchi	Korsmeyer Peppas		Hixson crowell
					R^2	n	
1	**F1**	0.976	0.887	0.995	0.953	0.744	0.975
2	**F2**	0.978	0.839	0.996	0.947	0.749	0.955
3	**F3**	0.993	0.932	0.981	0.965	0.768	0.975
4	**F4**	0.996	0.956	0.980	0.951	0.823	0.983
5	**F5**	0.985	0.798	0.993	0.931	0.763	0.942
6	**F6**	0.976	0.967	0.995	0.929	0.670	0.989
7	**F7**	0.935	0.894	0.995	0.931	0.605	0.983

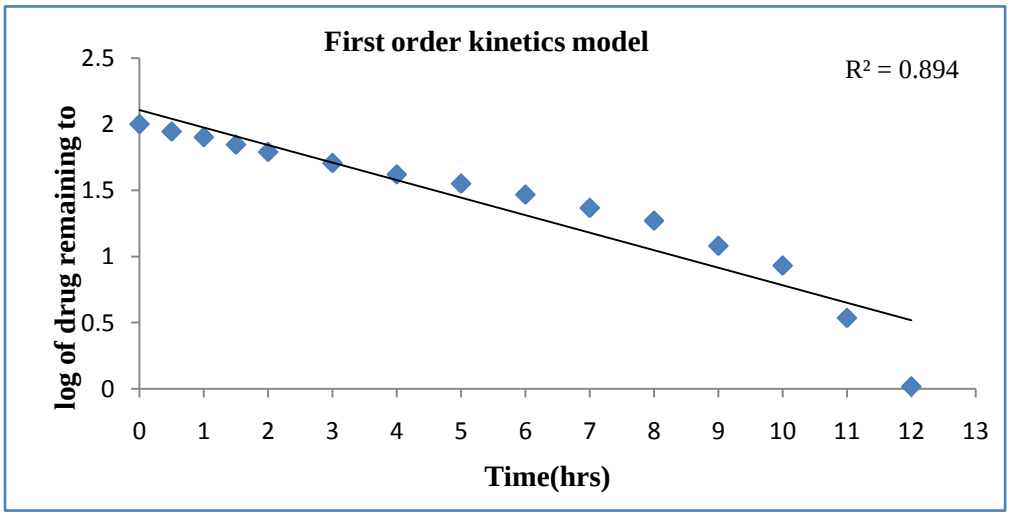
All the formulations are tested for their release properties. The kinetics of all the formulations is illustrated above.

F1, F2, F5, F6 and F7 follow Higuchi kinetics whereas F3 and F4 of the formulations followed zero order.

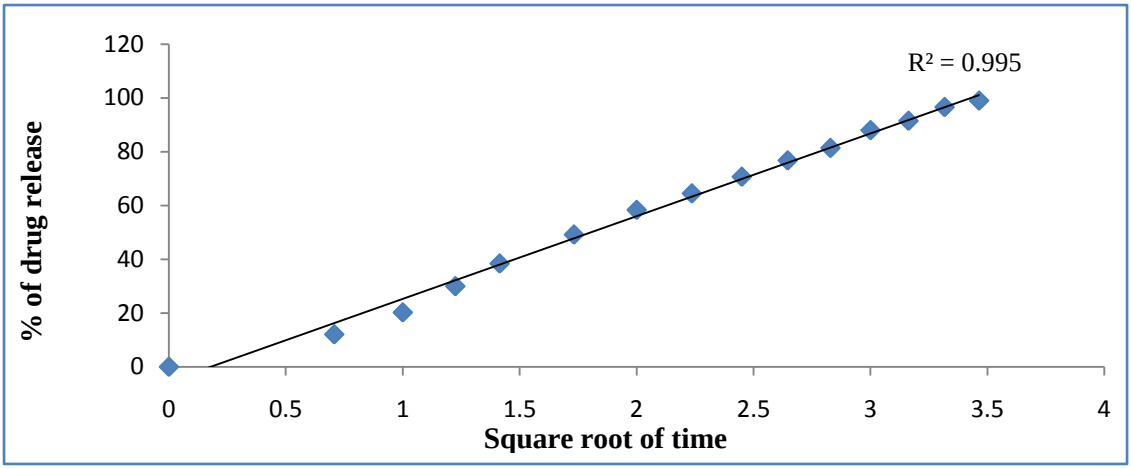
All formulations show n value greater than 0.45 and less than 0.89 indicating that the drug release follows follows Non-Fickian transport.



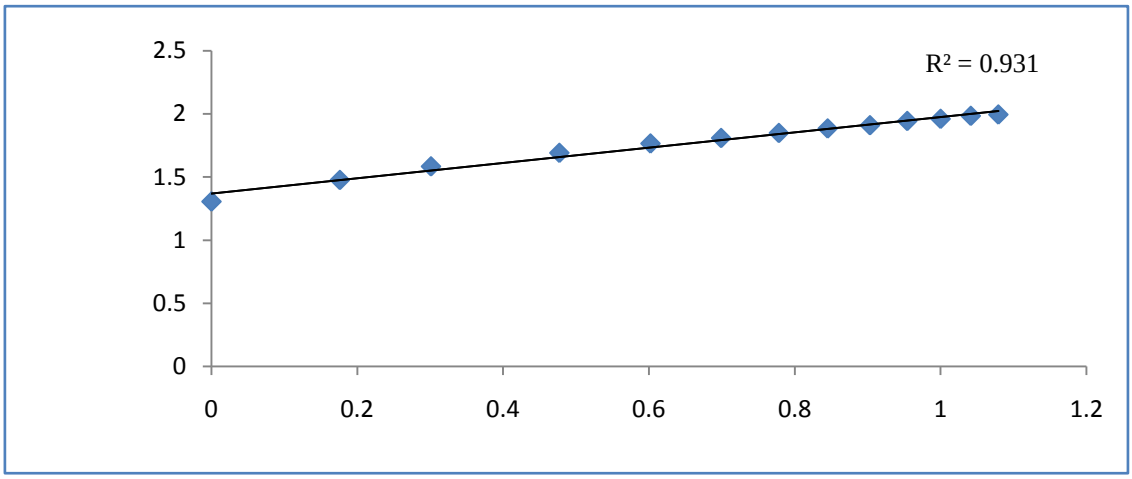
Graph No.9 Zero order kinetics for Domperidone Optimized Formulation



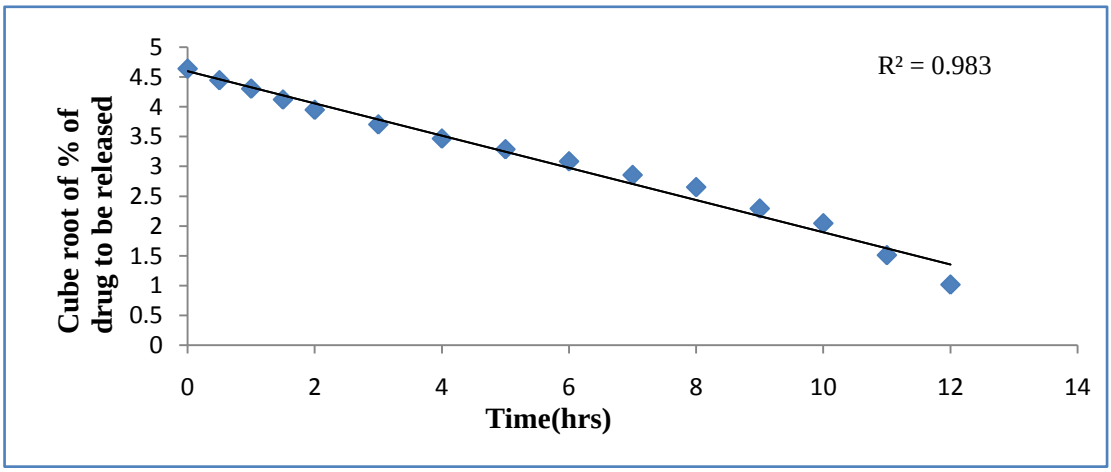
Graph No.10 First order kinetics for Domperidone Optimized Formulation



Graph No.11 Higuchi Model for Domperidone Optimized Formulation



Graph No.12 Korsmeyer-peppas Model for Domperidone Optimized Formulation

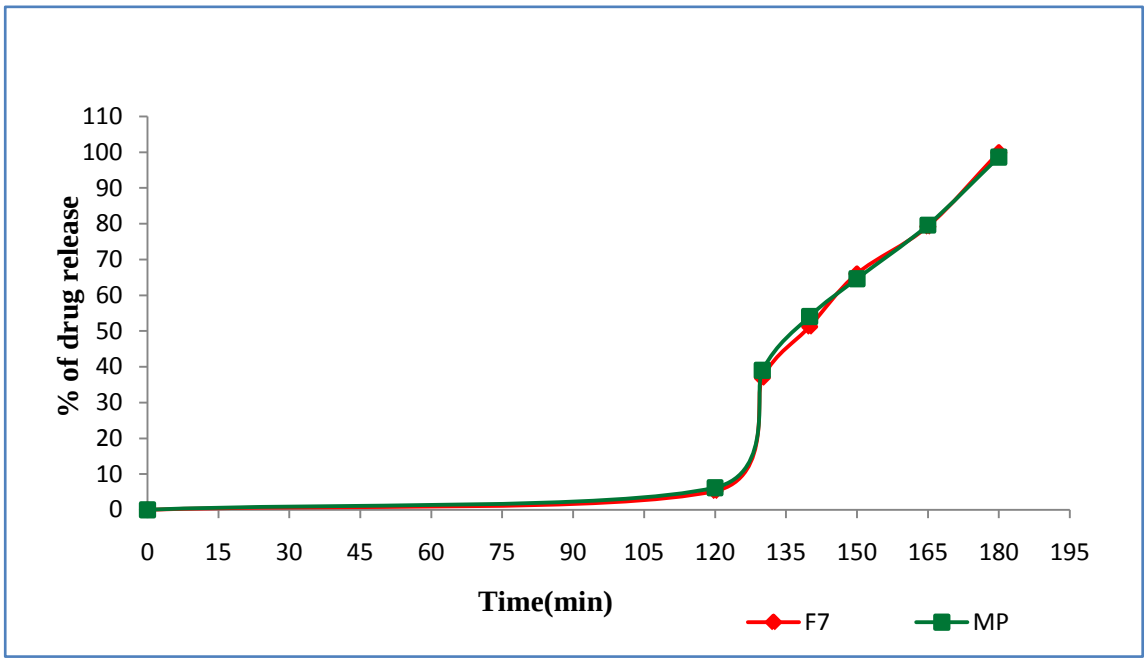


Graph No.13 Hixson crowell Kinetcs plot for Domperidone Optimized Formulation

8.14 Comparison of the Best formulation with Marketed product

Table No.43 Comparison of the *in-vitro* release profiles of Omeprazole F7 and marketed product

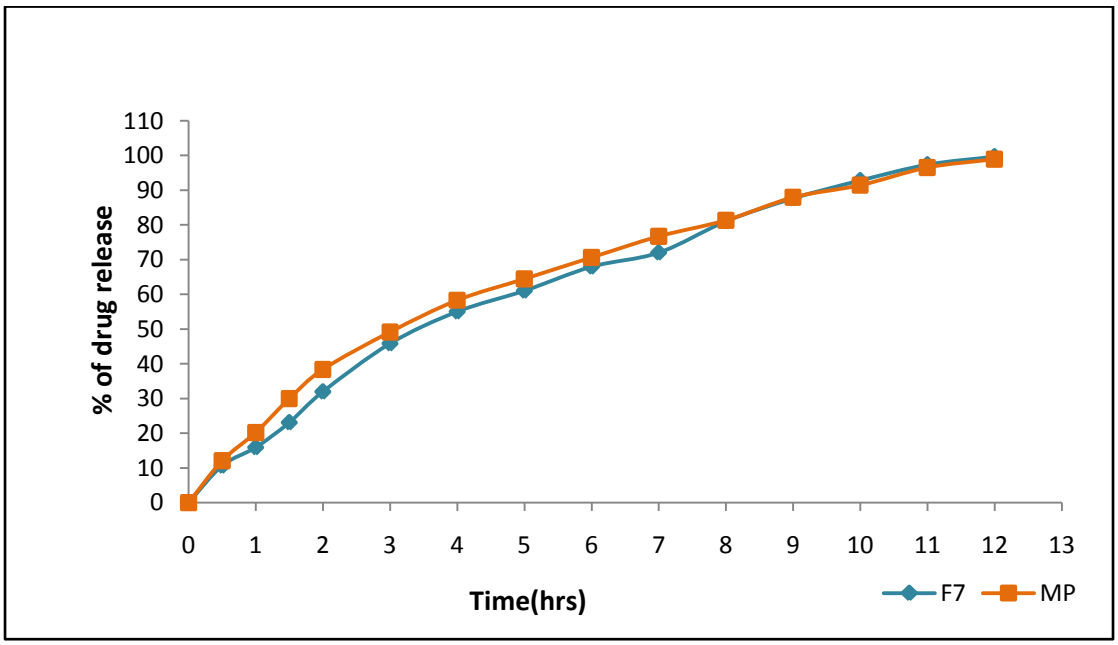
S.No	Time(min)	Marketed	F7
1	**120**	5.26	6.21
2	**130**	36.95	39.05
3	**140**	51.25	54.10
4	**150**	66.02	64.62
5	**165**	79.25	79.65
6	**180**	99.95	98.68



Graph No.14 Comparison of the *In-vitro* release profiles of Omeprazole F7 and marketed product

Table No.44 Comparison of the *in-vitro* release profiles of Domperidone F7 and marketed product

S.No	Time(hrs)	Marketed	F7
1	**1**	15.91	20.22
2	**2**	31.96	38.39
3	**4**	55.02	58.32
4	**8**	81.05	81.36
5	**12**	97.68	98.95



Graph No.15 Comparitive *In-vitro* release profiles of Domperidone F7 and marketed product

8.15 Similarity factor and difference factor assessment

Table No.45 Similarity factor and difference factor assessment

S.No	Formulations	Omeprazole		Domperidone	
		F1 factor	**F2 factor**	**F1 factor**	**F2 factor**
1	**F1**	18.79	45.93	17.97	21.23
2	**F2**	14.24	51.17	11.61	28.56
3	**F3**	9.09	59.88	20.80	43.12
4	**F4**	12.70	53.95	26.93	38.07
5	**F5**	13.29	52.95	17.04	28.41
6	**F6**	1.07	85.31	18.01	45.58
7	**F7**	1.07	85.31	4.06	71.73

The range for all the Omeprazole formulations for Difference factor 1.07 to 18.79 and the range for similarity factor is 45.93 to 85.31 .Difference factor of 1.07 and similarity factor of 85.31 of the optimized formulation, F7 corresponds to marketed products infering that the *in-vitro* dissolution profile is matching the latter.

The range for all the Domperidone formulations for Difference factor 4.06 to 28.05 and the range for similarity factor is 21.23 to 71.73 .Difference factor of 4.06 and similarity factor of 71.73 of the optimized formulation, F7 corresponds to marketed products infering that the *in-vitro* dissolution profile is matching the latter.

The release profile is found to be more or less similar with the marketed product.

8.16 STABILITY STUDIES

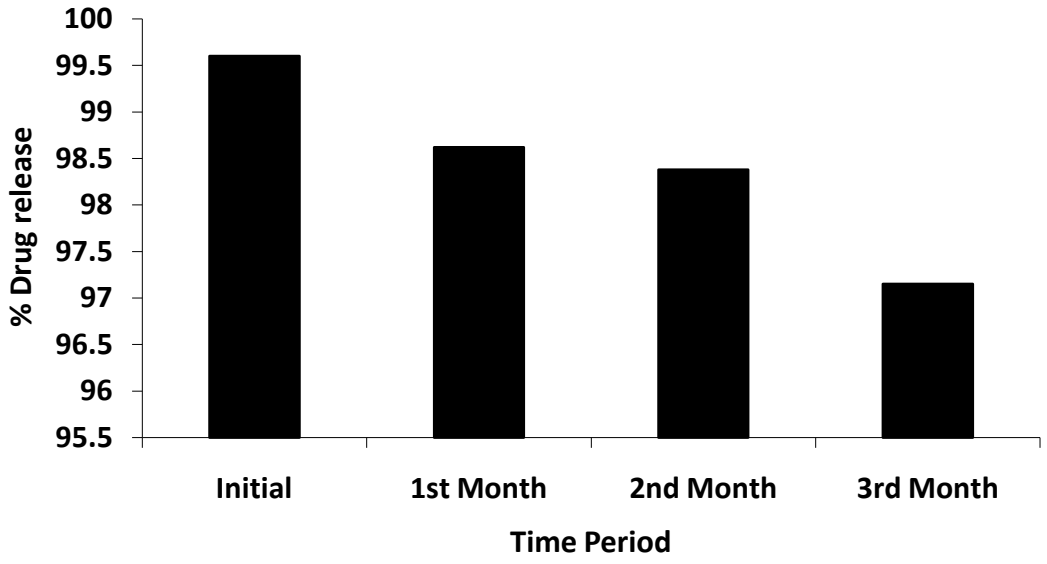
The formulation is stored at Accelerated conditions like 40°C and 75% RH for a period of three months. For stability study, the tablets were sealed in HDPE containers. Sampling is done every month and the tablets are tested for any liable changes in the hardness, friability, drug content and *in-vitro* dissolution.

Table No.46 Characteristics of the tablets during stability studies

Evaluation Parameters	**Storage condition 40°C / 75 % RH**			
	Initial	**1st month**	**2nd month**	**3rd month**
Description	White and red color round shape	complies	complies	complies
Hardness (kg/cm^2)	8.4±0.4	8.3±1.2	8.3±0.6	8.3±0.8
Thickness (mm)	3.04±0.01	3.02±0.02	2.93±0.01	3.03±0.03
Weight Variation(mg)	362.4±0.45	360.2±0.12	361.3±0.07	360.2±0.13
Friability (%)	0.654	0.554	0.754	0.654
Assay(%) **Omeprazole Layer** **Domperidone Layer**	99.24±0.11% 98.68±0.08%	98.56±0.05% 98.15±0.12%	97.86±0.06% 98.26±0.16%	97.26±0.14% 97.54±0.08%

Table No.47 Drug release of the Omeprazole optimised formulation during stability studies

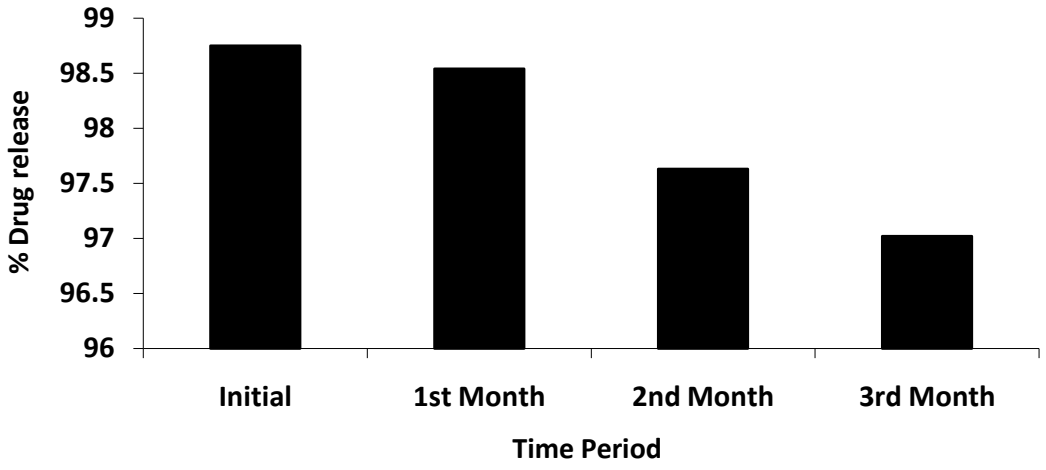
Time in min	Initial	After 1st Month	After 2nd Month	After 3rd Month
0	0	0	0	0
120	6.21	6.58	6.02	6.72
130	39.05	38.86	39.24	38.54
140	54.10	53.96	54.24	52.68
150	62.62	63.18	62.05	61.88
165	79.65	80.09	79.68	78.09
180	99.68	98.62	98.38	97.15



Graph No.16 Drug release of the Omeprazole optimised formulation during stability studies

Table No.48 Drug release of the Domperidone optimised formulation during stability studies

Time in hrs	Initial	After 1st Month	After 2nd Month	After 3rd Month
0	0	0	0	0
1	20.22	21.52	19.54	20.36
2	37.58	38.54	36.58	37.54
4	57.34	58.69	57.64	56.26
8	81.65	80.68	80.24	79.65
12	98.75	98.54	97.63	97.02



Graph No.17 Drug release of the Domperidone optimized formulation during stability studies

The stability studies are carried out for the optimized formulation F7. The release kinetics is unaltered and there are no significant changes in the physical characteristics of the tablets, which indicate that the optimized formulation is stable at the stress conditions induced.

Chapter 9

SUMMARY AND CONCLUSION

9. SUMMARY AND CONCLUSION

SUMMARY

In the present study an attempt has been made to Formulate and evaluate the multiparticulate delayed release Omeprazole as one layer and sustained release Domperidone as another layer.

Omeprazole is a PPI which is mainly used in the treatment of GERD. During GERD, the LES(lower esophagus sphinter) pressure tone decreases and causes backflow of acid from stomach to esophagus causing heartburn and possible injury to the esophagus. So, to increase the LES pressure Domperidone is given along with Omeprazole which acts as anti-emetic and increases the LES pressure and prevents efflux of stomach contents.

Omeprazole has long time binging affinity to the parietal H+/K+ ATPase enzyme. As the drug is instable in acidic pH, it is formulated as delayed release form. Domperidone has half life of 7hrs and hence it is formulated in SR form.thus the therapeutic concentrations of both drugs can be maintained for longer period of time i.e., up to 24hrs. Thus one daily dose of Omeprazole and Domperidone bilayer tablet was formulated and evaluated.

In the formulation of Bilayer tablet, Omeprazole compressible enteric coated granules were prepared by using different enteric coated polymers such as HPMC Phthalate,Eudragit NE30D and Kollicoat MAE30DP with different ratios and plastisized with PEG. Two different grades of HPMC polymer are used to study the release of Domperidone.

The prepared tablets were evaluated for hardness, weight variation, friability, drug content uniformity and *in-vitro* dissolution studies.F7 formulation showed good evaluation and drug release studies. The dissolution profiles of all the formulations are compares with innovator by calculating the f2 values. F7 has obtained the highest f2 value, hence F7 is considered to be the optimised formulation. Stability studies were carried out for F7 formulation and the values were with in the permissible limits.

CONCLUSION

In this present study nine formulations of enteric coated Omeprazole granules and Domperidone are formulated into a bilayer tablet.

The Omeprazole compressible enteric coated granules were prepared by using different enteric coated polymers such as HPMC Phthalate, Eutragit NE30D and Kollicoat MAE30DP with different ratios and plasticized with PEG. The Omeprazole granules which are coated with 8% Eutragit and plasticized with 2%PEG meet the USP criteria in drug release. From the above data it is evident that the formulation F7 shows satisfactory drug release both on acid phase and buffer phase and complies with all the pharmacopoeial limits before and after the stability studies and is the most suitable composition for the delayed release of Omeprazole.

Two different grades of HPMC polymer are used to study the release retarding activity. Different concentrations of polymer are used in the sustained release layer and their effect on the release of Domperidone is explored. The formulation F7 is found to be the best formulation since it meets the USP criteria in the drug release. HPMC of grade K4M and K15M at a concentration of 20% and 10% releases the drug as per the USP specifications. The cumulative drug release at the end of twelfth hour is 100%.From the above data it is evident that the formulation F7 shows satisfactory sustained release and complies with all the pharmacopoeial limits before and after the stability studies and is the most suitable composition for the sustained release of Domperidone.

Finally I conclude that F7 formulation shows the best release in both the layers (Omeprazole and Domperidone) and that may fulfils the objective of the study.

The stability studies were performed according to in-house specifications for the optimized formulation. The tablets were kept at accelerated condition ($40\pm2^{\circ}$ C/ 75±5% RH) for a period of three months. The obtained results were within the specifications.

Chapter 10

REFERENCES

10.REFERENCES

1. Ding X, Alani AWG, Robinson JR. Extended release and targeted drug delivery systems. In : The Science and Practice of Pharmacy. 2005; (Remington, Ed.), Twenty first edition, volume 1, pp. 939-964 ; Lippincott Williams and Wilkins.
2. Karande A.D., Dhoke S.V., Yeole P.G. Formulation and evaluation of bilayer tablets with antihypertensive drugs having different release patterns. Indian Drugs, 2006; 43(1): 44-50.
3. R.Nagaraju and Rajesh Kaza. Formulation and evaluation of bilayer sustained release tablets of Salbutamol and Theophylline. International Journal of Pharmaceutical Sciences and Nanotechnology, 2009; 2(3): 638-646.
4. Shailesh kumar, Venkata Bala Krishna Rao, N.Kannapan, Amitsankar Dutta. Formulation and evaluation of Atorvastatin calcium and Nicotinic acid in a bilayer tablets. Journal of Pharmacy Research, 2009; 2(7): 1256-1258.
5. Pharmaceutics, The science of dosage form design, Aulton M.E, 2nd edition, 1998, 1, 289-306, 412.
6. Modern Pharmaceutics, Gilbert S.Banker Christopher T.Rhodes, 4th edition, 2006, 121, 501-514.
7. The Theory and practice of Industrial Pharmacy, Leon Lachamnn., Herbert A.Liebermann., Joseph L.Kanig, 2nd edition, 2003,1, 330-331.
8. Martino Fusca, Dagmer Farber, Heppinheim, Patented on Multilayer tablets, 2001 Patent No. US 6,254,886 B1
9. Sachin S. Kale, Viraj S. Saste, Prajkta L. Ughade, Dheeraj T. Baviskar. Review article on Bilayer Tablets. International Journal of Pharmaceutical Sciences Review and Research.2011, Volume 9, Issue 1: 25-30
10. Jitendra R. Amrutkar, Mohan G.Kalaskar,Varsha G.Shrivastav, P.G.Yeole. Bilayer tablets of Metformin hydrochloride and Glilclazide. A Novel approach in treatment of diabetes, international Jour of Pharm Research and Development,2009; 1(2).
11. Wen H, Park K. Fluid bed coating and granulation for CR delivery In : Oral controlled release formulation design and drug delivery: theory to practice. 2010:. 115-121 ; John Wiley and Sons.

12. Brahmankar DM, Jaiswal BS. Controlled release medication. In: Biopharmaceutics and Pharmacokinetics a treatise. 1995: pp. 335-371, Vallabh Prakashan
13. Sansom LN. Oral extended release products. Aust Prescr. 1999 ; 22: 88-90.
14. Richards JH. Role of polymer permeability in the control of drug release. In: Polymer permeability. 1985; (Comyn J, Ed.,), pp : 220-256; Springer
15. Chinam Niranjan Patra, Arethi Bharani Kumar, Hemat Kumar Pandit, Satya Prakash singh, Meduri vimala devi. Design and evaluation of Sustained Release Bilayer tablets of propronalol hydrochloride. Acta Pharm; 2007; 57: 479-489.
16. Physical Pharmacy, Martin's, P.S Patrick J. 5th edition, 2006, 1, 337-354, 553-558.
17. Ding X, Alani AWG, Robinson JR. Extended release and targeted drug delivery systems. In : The Science and Practice of Pharmacy. 2005; (Remington, Ed.), Twenty first edition, volume 1, pp. 939-964 ; Lippincott Williams and Wilkins.
18. Rane M, Parmar J, Rajabi-Siahboomi. Hydrophilic matrices for oral extended release: influence of fillers on drug release from HPMC matrices. Pharma Times. 2010 ; 42: 41-45.
19. Brahmankar DM, Jaiswal BS. Controlled release medication. In: Biopharmaceutics and Pharmacokinetics a treatise. 1995: pp. 335-371, Vallabh Prakashan.
20. Qiu Y. Rational design of Oral modified release drug delivery systems. In: Developing solid oral dosage forms Pharmaceutical theory and practice. 2009; (Qiu, Y , Chen, Y,and Zhang, GZ,Eds.,), pp. 469-499, Elsevier.
21. Sanjahan Abdul, Anil V. Chandewar, Sunil B. Jaiswal, A flexible technology for Modified-Release drugs, J. Of Controlled release, 147 (2010) 2-16.
22. V.S.N. Murthy, and J.Vijaya Ratna, Key formulation variables in Tabletting of Coated Pellets, Indian J.of Pharmaceutical Sciences, 2008, pp.555-564
23. Ann Debunne, Chris Vervaet, Debby Mangelings, Jean-Paul Remon, Compaction of enteric-coated pellets: influence of of formulation and process parameters on tablet properties and *invivo* evaluation, European J. Of Pharmaceutical sciences, 22(2004): 305-314.
24. A.Dashevsky, K.Kolter, R.Bodmeier,Compression of pellets coated with various aqueous polymer dispersions, International J.of Pharmaceutics 279(2004): 19-26
25. G.Sailesh, T.E.G.K.Murthy, Pavan kumar sm, Compression of coated Multiparticulates from Pharmainfo.net.

26. Mangesh E. Bhad, Shajahan Abdul, Sunil B. Jaiswal, Anil V. Chandewar, Jayesh M. Jain, Dinesh M. Sakarkar, MUPS Tablets-A brief Review, International Journal of PharmTech Research, 2010 Vol.2 :pp 847-855
27. Vogeleer J. Bilayer tablets-why special technology is required. Powder pharmaceutical technology division. Niro pharma systems
28. Mehul P. Challenges in the formulation of bilayered tablets. International journal of Pharma.Research and Development. 2010 ; 2: 30-42.
29. Patel Mehul, Ganesh Nanjan, Kavitha, Tamizh Mani, Challenges in the formulation of Bilayer tablets:A review, International J. Of Pharma. Research and Development, 2005: pp 30-42.
30. www.nih.gov/medlineplus/druginfo/meds/a 693050.html.
31. www.medicinenet.com/gerd/page6.html
32. NIH Publication No 0-0882 June 2003
33. PDSP Ki Database(http//pdsp.med.unc.edu/pdsp.php)
34. http:/ / www. drugbank. ca/ cgi-bin/ show_drug. cgi?CARD=APRD00446
35. http:/ / www. nlm. nih. gov/ cgi/ mesh/ 2009/ MB_cgi?term=57808-66-9& rn=1
36. http:/ / www. drugbank. ca/ cgi-bin/ show_drug. cgi?CARD=APRD00418
37. Swann IL, Thompson EN, Qureshi K (November 1979). "Domperidone or metoclopramide in preventing chemotherapeutically inducednausea and vomiting" British medical journal **2** (6199): 1188.
38. Journal of Pediatrics 2008 (http:/ / www. ncbi. nlm. nih. gov/ pubmed/ 18589449?dopt=Abstract)
39. Rossi S, editor. Australian Medicines Handbook 2006. Adelaide: Australian Medicines Handbook; 2006.
40. http://eudragit.evonik.com/product/eudragit/en/products-services/eudragit-products/sustained-release-formulations/ne-30-d/pages/default.aspx
41. Volker Buhler, Functional polymers for pharmaceutical Insustry, BASF, 2007 pp 69-97
42. Raymond C Rowe, Paul J Sheskey,Sian C Owen Hand book of Pharmaceutical excipients Fifth edition.
43. Stedman CA, Barclay ML (August 2000). "Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors". *Aliment Pharmacol Ther* **14** (8): 963–78

44. R. Baselt, *Disposition of Toxic Drugs and Chemicals in Man*, 8th edition, Biomedical publications, Foster City, CA, 2008: 1146-1147
45. Collett J, Moreton C. Modified release peroral dosage forms. In: Pharmaceutics: The science of dosage form design. 2002; (Aulton, ME.,Ed.) Second edition:pp. 289-305, Churchill Livingstone.
46. Duphar BV, Weesp. Design for drug excipient interaction studies. Drug development and Industrial pharmacy. 1983; 9 : 43-55.
47. Meyers RA. Interpretation of IR spectra, a practical approach. Encyclopedia of analytical chemistry. 2000 : 10815 – 10837.
48. Indian pharmacopeia volume-2 2007
49. Huanjo kim.reza fassihi. Pharma Resea,vol.14(10).1997 :1415-1421
50. Mamajek RC, Moyer ES. Drug dispensing device and method. US Patent 4 207 890. June 17, 1980.
51. Rakesh patil, ashok bariaijps vol.1 issue 2, 2009 31-32.
52. Leon Lachman et.al; The Theory and Practice of Industrial Pharmacy, 3rd edition, Page. No: 293- 345
53. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified-Release Drug Products, Pg 515 Fifth Edition, 2004
54. Chapter 905, Uniformity of Dosage Units and Chapter 1151, Pharmaceutical Dosage Forms, United States Pharmacopoeia, 2008
55. V. Jannin, E.Pochard and O. Chambin, Influence of poloxamers on the dissolution performance and stability of controlled-release formulations containing Precirol ATO 5, PubMed, 2005
56. FDA guidance on "Dissolution Testing of Immediate Release Solid Oral Dosage Forms
57. Korsmeyer RW, Gurny R, Doelker E, Buri P. Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm*. 1983
58. Chien Y.W., Controlled- and modulated-release drug-delivery systems. Encyclopedia of pharmaceutical technology. New York, Dekker, pgs 281-313, 1992.
59. FDA guidance on "Dissolution Testing of Immediate Release Solid Oral Dosage Forms".
60. Acetazolamide, USP Monograph and Acetazolamide Tablets, USP Monograph, United States Pharmacopoeia, 2008

61. Korsmeyer RW, Gurny R, Doelker E, Buri P. Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm*. 1983

62. F. S´anchez Rojas., Analytical methodologies for the determination of omeprazole: An overview Journal of Pharmaceutical and Biomedical Analysis 44 (2007) :831–844
63. Bhavesh Patela; Madhabhai Patel., Simultaneous Determination of Omeprazole and Domperidone in Capsules by RP-HPLC and Densitometric HPTLC Journal of Liquid Chromatography & Related Technologies*w*, 30: 1749–1762, 2007
64. Ajit Kulkarni and Manish Bhatia **"**Development and evaluation of regioselective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile" Iranian Journal of Pharmaceutical Research. 2009; 8 (1): 15-25.
65. Chien Y.W., Controlled- and modulated-release drug-delivery systems. Encyclopedia of pharmaceutical technology. New York, Dekker : 281-313, 1992.

66. Jung AD. Gastroesophageal reflux in infants and children.