# FORMULATIONS FOR MONITORED ADMINISTRATION OF PROTON PUMP INHIBITORS

**Thesis**
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By

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## Declaration by the Scholar

I hereby declare that the work presented in this thesis entitled FORMULATIONS FOR MONITORED ADMINISTRATION OF PROTON PUMP INHIBITORS in fulfillment of the requirements for the award of Degree of Doctor of Philosophy, submitted in the Maharishi School of Pharmaceutical Sciences, Maharishi University of Information Technology, Lucknow is an authentic record of my own research work carried out under the supervision of Dr. A. K. S. RAWAT. I also declare that the work embodied in the present thesis

i) is my original work and has not been copied from any journal/ thesis/ book; and

ii) has not been earlier submitted by for any Degree or Diploma for any University / Institution.

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## Supervisor's Certificate

This is to certify that Mr. **Shashi Shekhar Tripathi** has completed the necessary academic turn and the swirl presented by him is a faithful record is a bonafide original work under my guidance and supervision. He worked on the topic FORMULATIONS FOR MONITORED ADMINISTRATION OF PROTON PUMP INHIBITORS under the School of Pharmaceutical Sciences, Maharishi University of Information Technology, Lucknow.

**Dr. A. K. S. RAWAT**
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## ABSTRACT

The intention & purpose of current research technique was into produce controlled (medicament) releasing formulations of drug Esomeprazole & drug Dexlansoprazole to increase bio-availability and prevent plasma variations associated into with existing innovator formulations.

In third chapter an over all overview of concept is briefed. The concepted formulation as designed would increase in the time duration action while guaranteeing proper release, would standardize medication (drug) release, its kinetics, effectively this can minimize dose (sudden) dumping, consequently it releases the API drug away from formulation at a predetermined pace of (molecule) drug liberation, locally or in systemic area and eventually reduce variation of the steady-state level. This in turn would enhance patient convenience, enhance safety, improve the health condition of the patient and increase therapeutic pharmacological efficacy. The third chapter also describes the taken overall course for the entire work.

In fourth chapter the methodology of experiments was described. Esomeprazole[API] & Dexlansoprazole were procured from different pharmaceutical companies in Bangalore and Mumbai, respectively. Esomeprazole is (an API) drug that is a proton ($H^+$) pump - inhibitor, that lessens the acid in stomach production by block and prevent the proton ($H^+$) pump as this is final step, of stomach for acid ($H^+$) production. Dexlansoprazole, is another proton ($H^+$) pump - inhibitor that can selectively inhibit the ($H^+$), $K^+$)-ATPase on the secretory membrane of stomach parietal cells. Polymer like the Eudragit®- S 100, Eudragit®- L 100, Eudragit®- RS PO, and Eudragit®- RL PO obtained from very reliable and authentic sources. Similarly, all other polymers were like Carbopol®-974 P, Pectin,

H.P.M.C - K 4M, H.P.M.C - K 100 M, and H.P.M.C - K 15 M, Xanthan-gum, Guar-gum, and Carboxymethylcellulose Sodium (USP) were procured from different companies. Later, it is elaborated on chemical assembly, molecular bulk, description and functional class of the drug, polymer and added excipients described in detail. The next portion of the chapter describes about various pre-formulation properties like repose angle, density of the bulk, density modulation, Carr's Index of consolidation and Hausner's (tapped vs bulk) ratio. Post formulation assess of the compressed tables were done for Weight fluctuation examination, Toughness, Thickness, Friability test, Determination of the drug's concentration, Dissolution investigations (in-vitro), Analysis of Dissolution Data Using Release Rate Kinetics. For the rate kinetics Kinetics of first – order rate release, Higuchi's model of release, Korsmeyer and Peppas's model of release and Hixson-Crowell model of release.

Investigations into Stability involve formulating safe, effective, and stable dosage [unit] forms for medications. Factors like storage temperature, prevalent humidity, and storage light influence conditions, re-test intervals, and product shelf life were assessed. Regarding Esomeprazole's Control led Released Tablet In-Vivo Studies, pharma-co-kinetic investigations focused on optimized tablet batch (F-6) for control led released. These studies intended to relate Esomeprazole's concentrations over time with the marketed rapid release tablets.

In fifth chapter results and discussions were detailed that included compatibility evaluation of Excipient and the Drugs, FT-IR Data Interpretation for Esomeprazole's and Dexlensoprazol and Drug compatibility testing using polymers was done. Later all details about evaluation of the physico & chemical values of Esomeprazole's and

Dexlensoprazol Control led Released Tablets, flow properties of powder blend for Esomeprazole's and Dexlensoprazol, Esomeprazole's and Dexlensoprazol Control led Released Tablet evaluation was also done and several evaluations were carried out to findout the physio & chemical properties. To estimate the drugs' release (in %) from the Esomeprazole's and Dexlensoprazol formulation in-vitro drugs' release (in %) studies utilizing standardized method was carried out. In same chapter there is mention about the In-vitro comparison of Optimized Esomeprazole's and Dexlensoprazol CR Formulation (F-6) with Innovator Product. The drugs' release (in %) data was processed for kinetics viz First ($1^{st}$) Order Kinetics, model Higuchi Kinetics and model Korsmeyer-Peppas Kinetics. Further the stability studies on the optimized dosing formulation of Esomeprazole's and Dexlensoprazol was performed and data was analyzed.

In chapter six the result and conclusion is enumerated. Gastroesophageal (in stomach) reflux disorder is treated with Proton (H+) Pump - Inhibitors such as Esomeprazole's (GERD). Only 50–68% of the drug is bioavailable, which means it has a poor therapeutic medicament index and a short half-life in body (1–1.5 hours). It was determined that Esomeprazole's was a good choice for controlled medication & delivery - systems because it met the prerequisite.

Esomeprazole's drug and excipient interactions, if any were studied in detail during pre-formulation studies. All excipients were documented and found compatible and method used was FTIR and DSC testing. Polymethacrylates polymers like as Eudragit®-L100, Eudragit®-RS PO, Eudragit®-RS 100, and Eudragit®- RL PO produced Esomeprazole's controlled - released tablets, which practically were then compressed using a direct (dry) compression method. Esomeprazole tablets in various controlled (medicament) releasing

formulations using various pure / combination polymers just such as Eudragit®- S100, L-100, RS PO, RS-100, RL-100, RL PO; as glidant talc; lubricant magnesium (salt) stearate; and diluent Di. Calcium Phosphate; via the Direct (dry) compression process. To make.

Before and after formulation, the properties of tablet blends and esomeprazole tablets were examined, including flow characteristics and weight fluctuations, the hardness, and the friability of the drug content. Within pharmacopeia's guidelines, all these measurements were within acceptable limits. Dissolution in-vitro method and release (in %), kinetics investigations was conducted using the formulations developed. In terms of (molecule) drugs' release (in %) and mechanism of pharmacological action, the F-6 formulation was shown to be the best option. An ICH-required six-month stability study was performed on this formulation, and the results verified that it is stable. Final results showed that pharma-co-kinetic parameters were predictable in rabbits, but dosage [unit] form remained in body for a longer time; additionally, pharma-co-kinetic parameters showed more controlled drugs' release (in %) and 5.6 times increased relative bio-availability. The results in in-vivo study were therefore predictable.

**Keywords:**

Drug [API] delivery , Monitored administration, Sustained release, Modified release, Controlled (medicament) releasing formulations, Drugs' release timing, Prolonged release, Proton (H+) pump - inhibitor (PPI), Esomeprazole, Dexlansoprazole, H+/K+ adenosine triphosphatase, Polymer, Eudragit®- polymer, Carbopol® - 974.P, H.P.M.C grade, Xanthan-gum, Guar-gum, Carboxy-methyl-cellulose (Na salt) (USP), Pectin, chem Analysis and chem Evaluation, Drug content, Dissolution in-vitro method testing.

## LIST OF FIGURES

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## LIST OF ABBREVIATIONS

| S. No | Abbreviation | Expansion |
|---|---|---|
| 1 | CR | Controlled Release |
| 2 | CRDD | Controlled Release Drug Delivery |
| 3 | ODDS | Oral Drug Delivery - system |
| 4 | SR | Sustained Release |
| 5 | ER | Extended Release |
| 6 | API | Active Pharmaceutical Ingredient |
| 7 | FTIR | Fourier Transforms Infrared Spectroscopy |
| 8 | DSC | Differential Scanning Colorimetry |
| 9 | UV | Ultra Violet Spectrophotometer |
| 10 | GRT | gastric retention time |
| 11 | DR | Delayed Release |
| 12 | S.D | Standard deviation |
| 13 | Ml | Millilitre |
| 14 | RPM | Revolutions per minute |
| 15 | µg | Microgram |
| 16 | $^{o}$C | Degree Celsius |
| 17 | Mg | Milligram |
| 18 | % | Percentage |
| 19 | R2 | Regression coefficient |
| 20 | Nm | Nanometer |
| 21 | Mm | Millimeter |
| 22 | Min | Minute |
| 23 | RT | Room temperature |
| 24 | T | Time |
| 25 | Kg | Kilogram |
| 26 | h / hrs | Hours |
| 27 | HCl | Hydrochloric acid |
| 28 | g/gm | Gram |
| 29 | FDA | Food and Drug Administration |

## LIST OF ABBREVIATIONS (Cont./-……)

| S. No | Abbreviation | Expansion |
|---|---|---|
| 30 | IP | Indian pharmacopeia |
| 31 | BP | British pharmacopeia |
| 32 | USP | United State pharmacopeia |
| 33 | PhEur | European pharmacopoeia |
| 34 | Mp | Melting point |
| 35 | g/cm3 | gram per centimeter cube |
| 36 | HPMC | Hydroxy Propyl Methyl Cellulose |
| 37 | KBr | Potassium bromide |
| 38 | SCMC | Carboxymethylcellulose Sodium (USP) |
| 39 | BCS | Biopharmaceutical classification system |
| 40 | PVP | Poly Vinyl Pyrrolidone |
| 41 | Vd | Volume of distribution |
| 42 | MCC | Micro Crystalline Cellulose |
| 43 | Cp | Centipoises |
| 44 | NaoH | Sodium Hydroxide |
| 45 | P | Pascal |
| 46 | F | Formulation |
| 47 | λmax | Absorbtion Maxima |
| 48 | Cm-1 | Centimeter inverse |
| 49 | Fig. | Figure |
| 50 | W/V | Weight per Volume |
| 51 | Ex. | Example |
| 52 | Conc. | Concentration |
| 53 | t/ cm2 | Ton per square centimeter |
| 54 | LBD | Loose bulk density |
| 55 | RH | Relative humidity |
| 56 | i.e | that is |
| 57 | USP-NF | United States Pharmacopoeia National Formulary |
| 58 | pH | Negative logarithm of hydrogen ion |

## LIST OF ABBREVIATIONS (Cont./-……)

| S. No | Abbreviation | Expansion |
|---|---|---|
| 59 | Ppm | parts per million |
| 60 | ICH | International Conference on Harmonization |
| 61 | Eq | Equation |
| 62 | CC | Carr's Compressibility Index |
| 63 | t1/2 | Biological half-life |
| 64 | λ | Wavelength |
| 65 | ODDS | Oral Drug Delivery - system |
| 66 | LOD | Loss on Drying |
| 67 | PK | Pharmacokinetic |
| 68 | EC | Ethyl Cellulose |
| 69 | M | Molarity |
| 70 | Cmax | Peak Plasma Concentration |
| 71 | CDDS | Conventional Drug Delivery System |
| 72 | Tmax | Time to achieve maximum measure concentration in plasma |
| 73 | SRDDS | Sustained Release Drug Delivery System |
| 74 | USFDA | United States Food and Drug Administration |
| 75 | MRT | Mean Residence Time |
| 76 | Cmin | Minimum Concentration Drug Plasma |
| 77 | ANOVA | Analysis of Variance |
| 78 | AUC | Area Under Curve |
| 79 | CP | Carbopol® |
| 80 | OD | Once daily |
| 81 | edn. | Edition |
| 82 | Kel | Elimination Rate Constant |
| 83 | Ka | Absorption rate constant |
| 84 | BA/BE | Bio availabelity and Bio equivilence |

# CONTENTS

# CHAPTER 1

## INTRODUCTION

### 1.1 Delivery Methods for Oral Drugs :

To ensure rapid and total systemic absorption, most conventional oral pharmaceutical forms, such as tablets / capsules, designed to releasing the active (API) ingredient soon after oral delivery. The onset of medication absorption and the resulting pharmacological effects are incredibly rapid with these instant release formulations. Pharma-co-kinetic (ADME) data show that medication plasma (blood) concentrations remain low even when whole absorption is done from dose form. When medication concentrations within blood drop below the minimal efficient concentration i.e MEC, therapeutic impact of (molecule) drug stays compromised, another dose is frequently administered if a lasting therapeutic effect is necessary before reaching this phase. Instead of yet another dose of medicament, there a greater advantage of providing a sustained-release dosage [unit] form. These formulations maintain drug in plasma & level above what is observed with immediate-release forms [1].

The term "controlled - released medication products" refers to pharmaceuticals that regulate the releasement of (API) active ingredients by altering the timing or the rate which they are released. A method where in time course and location of (molecule) drugs' release (in %) are chosen to achieve beneficial or comfortability purposes not accessible via normal or conventional medic formulations like ointments or solution, or promptly providing dosage [unit] forms is the definition of a modified-release dosage [unit] form. Modified-release pharmaceutical medicines come in wide & formats, some of which are listed below:

1. When compared to an instant (standard) form of the same medicine the extended - release form will allow for minimum a two-fold decrease in

frequency of dosing. Extended-release forms comprise of controlled - released and / or consistent and even long-acting pharmacological formulations.

2. A prescription form distributes a portion of (an API) drug at an interval other than shortly following administration, whilst one piece may be supplied immediately following administration. Delayed-release medication goods: Late-release dosage formulations are typically enteric-coated.
3. Any type of medicinal preparation with targeted release of medicine: a dosage-form in which the medicine is administered at the required biological location of action. It is conceivable to have a control led released dose type that is either immediate or long-lasting [2].

| Route of Administration | Drug Product | Examples | Comments |
|---|---|---|---|
| Oral drug products | Extended release | Diltiazem HCI extended release | Once-a-day dosing. |
| | Delayed release | Mesalamine delayed release | Coated for drugs' release in terminal ileum. |
| | Oral mucosal drug [API] delivery | Oral transmucosal fentanyl citrate | Fentanyl citrate is in form of a flavoured sugar lozenge that dissolves slowly in mouth. |
| Transdermal drug delivery - systems | Transdermal therapeutic system | Clonidine transdermal therapeutic system | Clonidine TTS is applied every 7 days to unbroken skin on upper arm / chest. |

| | | | |
|---|---|---|---|
| | Iontophoretic dose delivery | | Here minute electric current transfers charged drug across the skin. |
| Ophthalmic delivery of (molecule) drug | Available as an Insert | It contains pilocarpine in a controlled type of release | Shape of elliptical insert meant for continuous efflux of pilocarpine drug after placing in eye area of cul-de-sac |
| Parenteral delivery of (molecule) drug. | Drug products that are given in intra-muscular. | Injection of Depot formation | Lyophilized-microspheres that contain leuprolide acetate in suspension for depot formation |
| | | Injection that are Water immiscible | Medroxy progesterone acetate (Depo-Provera@) |
| | Subcutaneous drug products | Control led released insulin | Basulin is a controlled- release, recombinant human insulin delivery. |

**Table 1.1 Modified Methods in Drug Delivery**

Based on (an API) drug's physical, chemical, biological, and pharma-co-kinetic (ADME) features and the quality of the materials used in its dosage [unit] form, modified release medicine products are examined for alternate administration routes. Modified release medicine products are characterized by their drugs' release properties using various terms. [3]

## 1.2 Controlled Release Systems for Oral Drugs:

As a fast and efficient way to accomplish simultaneous local and systemic effects, oral administration of medication is most easy and common method for administration. Typical oral medicine delivery method have comparatively inadequate control the quantity of released medication. It's possible for achieve effective concentrations with the location by interchanging administration of grossly excessive dosages, which frequently leads to constantly transferring, unpredictable, and commonly sub or supratherapeutic plasma (blood) concentrations, which result at the observed adverse problem effects.

It's possible for administer pharmaceuticals orally with consistent and stable pharma-co-kinetic (ADME)s for an encoded duration throughout GI transit using oral CRDD and thus provide drugs in specific exact site at the tissue [body] specifically the GI tract for enhanced and the local / systemic action.

As long as the target location receives an exact and consistent amount of medication, ideal Odds shall be use over a lengthy period. A constant dose or volume of [API] drug delivered using the CR delivery method, allowing for therapeutic plasma (blood) concentrations to be maintained after absorption, reducing side [undesired] effects & administration frequency.

While CDDS has its limitations, recent technological breakthroughs have enabled its extension, which holds promise of modernizing medicine while also providing an extensive choice of therapeutic beneficial [4].

### 1.2.1 Advantage in utilizing a controlled - drug (medicine) delivery - system:

Amongst the numerous the following are benefits in employing well monitored and controlled [drug] (medicine) delivery - system:

- PDC held in very safe range & therapy to get a best and successful results.

## Introduction

- Long last and better more consistent medicinal therapeutic impact already is been documented.
- We optimized the dose-to-efficiency relationship.
- Reduce overall amount of medicine used compare using typical dosage [tablet] forms.
- I decreased the likelihood of harmful side affects.
- Frequent dose will no longer be necessary.
- It increased patient & hospital compliance.
- Improves condition control, i.e., lowers the volatility of medication pharm levels.
- Local toxic side affects are minimized or eliminated
- Prolonged dosing might be reduce number of (molecule) drug at body.
- By taking SR aspirin in evening before the bed, patient can get relief from morning arthritis pain.
- Healthcare pharma cost can reduce as result in economic factors. Reduced doses frequency, more therapeutic benefits, and fewer adverse affects contribute to a lower average treatment cost over time.

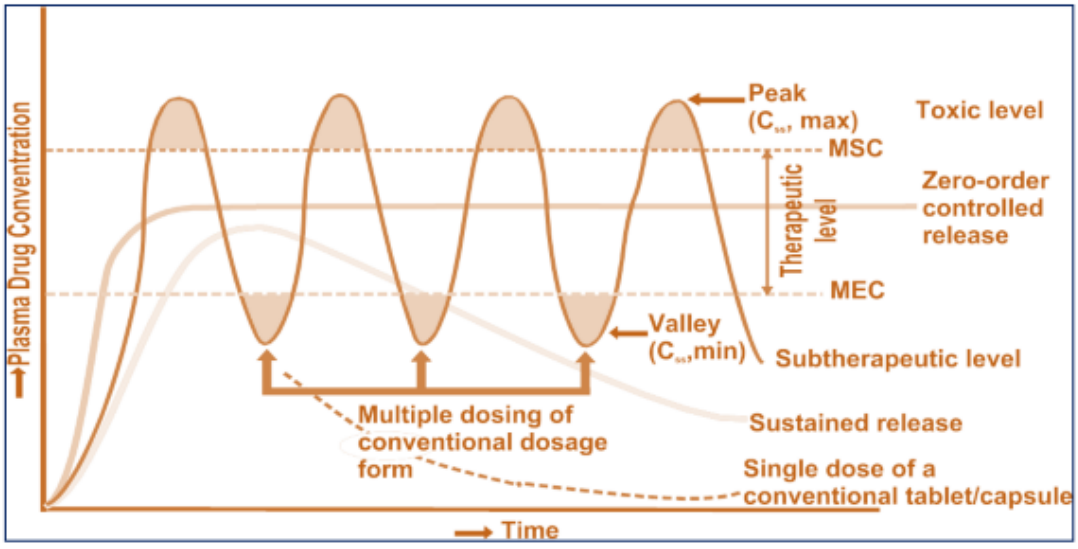



**Fig. 1.1: Conventional multiple dosing and single doses of sustained and controlled delivery formulations.**

### 1.2.2 The drawbacks of Controlled Drug (medicine) Delivery - systems:

Amongst the numerous following are / can get disadvantage of a controlled . drug (medicine) delivery type system:

- The dose and unit, the medication, it's variability has risen.
- The last final comparison between in-vitro (outside) & vs in-vivo (inside) lab experiment is low.
- The dose sudden dumping, toxicity can occur when more significant percentage of (molecule) drug is dispensed than average.
- It is difficult to retrieve a medicine in event of toxicity, poisoning, or hypersensitivity responses.
- Tolerance develops more rapidly.
- Increased patient training and counselling are required.
- Reduced possibility of dose modification for medications typically delivered in a range of strengths.

## 1.3 The Types of Oral and Controlled Release Drug (medicine) Delivery [5,6]

Diversity methods utilized to manage drug medication to mouth in precise manner. It could be a dissolution, diffusion based, or even combination of processes. These commonly use methods oral control led released (medicine) systems ought produce medication evenly release in body.

- Control led released systems based on dissolution.
- Diffusion-based [drug] delivery - system.
- Dissolution / diffusion systems.
- Release of (molecule) drug mechanism that are osmotically regulated.
- Drug [API] delivery - systems that are gastro-retentive.
- Release devices that can electrically activated.
- Resins for purpose in ion exchange.

### 1.3.1 The Controlled released type of System for Dissolved (medicine) Matter:

The numerous dosage [unit] form rate will be sustained by medicine with a slow rate at which it dissolves. Dissolution is the limiting factor in scenario. Because of this, medications can be made to last longer by reducing their breakdown rate.

It’s possible for build dissolution & controlled type system in one or two methods.

- Varying types of concentrate coating in polymers can done that impact rate of evaporation (dosage from Matrix Dissolving System).
- Giving the medicine a set beds with varied coating thicknesses is an effective maner to administer it (Encapsulated Dissolution type Systems).

It’s possible for make a matrix category dissolution type system by compressing a polymer-carrier tablet. Two methods are utilized to create wax matrices: congealing the wax or spreading the wax-drug mixture in water.

Using Encapsulated Dissolution type Systems, the beads are coated with different thicknesses, which means their release is gradual. Thinner layers deliver first dose, while thicker ones keep drug levels stable over time. An equation with Noyes-Whitney describes this dissolving process at a steady state.

$$\frac{dC}{dt} = k(C_s - C_b)$$

Where;

dc/dt = dissolution rate of the drug,

k = dissolution rate constant,

$C_s$ = concentration of drug in the stagnant layer, and

$C_b$ = concentration of drug in the bulk of the solution at time t

C = concentration of solute in the bulk solution

### 1.3.2 Systems with Control Diffusion (medicine) Release:

Here the water - insoluble polymer can determine the amount of medication released into the system. However, there are basically 2 types of diffuse devices:

#### 1.3.2.1 The Devices that can store water:

A membrane polymer surrounds drug-filled central area (reservoir device). The minute structure of this membrane can determine amount of medicine release.

Microencapsulation of (molecule) drug microscopic particles and coating of tablets containing [API] drug cores are two techniques utilized to produce reservoir type devices.

**Advantages of this system:**

- The device is capable of providing medicine in a manner that is zero-order.

**Disadvantages:**

- Physical removal of the system from implant locations is required.
- Delivering high molecular weight molecules is challenging.

### 1.3.2.2 Devices in Tab Matrix:

Materials such as insoluble plastics, hydrophilic polymers, and fatty chemicals make matrix devices. Comprised mixtures are most commonest method to administering medications to a patient. Following is explanation for how drugs' released when within a porous or granular matrix works:

$$M = (D_s.C_a.\{P/T\}.[2C_0-PC_a]t)^{1/2}$$

Where;

P = Porosity of the matrix

T = Tortuosity

$C_a$= Solubility of the drug in the release medium

$D_s$= Diffusion coefficient in the release medium

**Advantages:**

- Possibility of delivering molecules with a high weight of molecular drug.

**The Disadvantages:**

- It is ideally not possible to attain a perfect zero-order type release.
- Any implanted systems the remaining Matrix has to be removed.

### 1.3.3 Controlled Diffusion / Dissolution:

Diffusion / dissolving processes control the dissolution rate in these systems.

### 1.3.4 Release Mechanisms Under Osmotic Control:

Extensively-released medications use an osmotic pump, a relative innovation as per area. The phenomenon of dissolve leading for release in amount of medicine over unit time are methods to control any drug [API] administration, an osmotically managed device, as "push and pull" method uses water to push the medication out of an expanded osmotic compartment at a set rate. A single laser-drilled hole in tablet is utilized to administer the drug.

Nifedipine (Procardia XL) and other drugs may be taken in form of Alza Corporation's "push-pull" Gastrointestinal Therapeutic System (GITS). Osmotic and active medicinal ingredients are contained in two layers of the system's two-type core layer. Here laser holes present in dosage [unit] form allow aqueous media to enter in system. This increases osmotic pressure, drives the medicine out of system.

### 1.3.5 Drug [API] delivery - systems that Retain Drugs . in Gastrointestinal Tract:

Systems that can be kept in stomach are known as gastro retentive (GRDDS). The GRDDS system ought to enhance control of (molecule) drug [API] delivery with absorption drug window and continue releasing drug. An extended period in time of absorption is resulted, thereby this ensures the drug best bio-

availability.

High and low density (sink and float) system comprise biocompatible types and have been utilized to up come the stomach withholding of oral dose.

### 1.3.5.1 Bioadhesive Membranes:

Adhesion is the process by which macromolecules from both natural and artificial sources are anchored permanently to the body's cellular membranes. Mucoadhesion occurs actually if layer mucosal acts as the membrane substrate. For example, a bioadhesive can extend its duration at the absorption site and establish a strong concentration gradient.

### 1.3.5.2 Expanding and the Swelling Systems:

These techniques extend the time that the dosage [unit] form is in the stomach before it is expelled. To avoid being stuck in stomach, food with a diameter of more than ten microns must be swallowed whole. The type swelling of systems use hydrogels, such polymers that may expand even to 100 times their dry weight. Biodegradable hydrogels must be used.

### 1.3.5.3 Systems with a high density:

There must be at least 1.40 times the bulk density of the usual stomach in high-density systems. To develop and execute these formulations, heavy, inert ingredients like barium sulphate or titanium dioxide might be applied to the medicine's core. Pellets may be covered with diffusion-controlled membranes after they have been weighed.

### 1.3.5.4 Systems along with low resource concentration (floating):

The gastric fluids are less in density than the floating drug system that delivery drug (FDDS), as they remain floating in gastric area for a extra extended period.

this all can be done with out gastric [GIT] emptying rate. The drug is gradually absorbed whilst it floats on stomach juice. An enhanced GRT and better supervision of plasma / medication concentration changes the outcome. They are perfect for administering medications that are not dissolved or unstable in GIT.

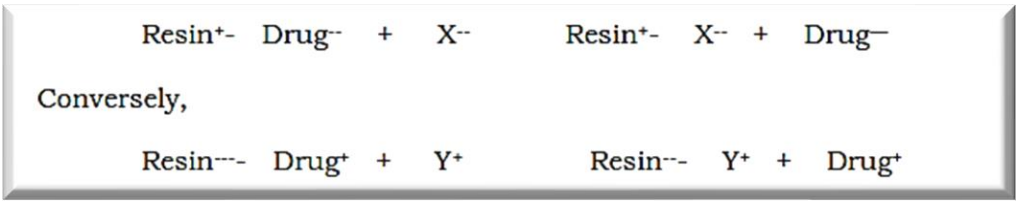
### 1.3.6 A Release Device That Is Electrically Stimulated:

When an external electrical stimulus is applied, the gels of polyelectrolyte gels expand, causing a change in pH. A pulsatile release profile can be achieved by varying the current during the release process. Optimizing medication therapy requires fine-tuning dosage and timing of (molecule) drugs' release from implanted devices. Polyelectrolyte hydrogels with electrically regulated medication release can help achieve these goals.

For example, as the fluid phase synergizes, the drug is ejected from the gel, drug diffusion occurs along a concentration gradient, charged drugs are electrophoresed toward an oppositely charged electrode, and drug liberation occurs when the gel complex erodes.

### 1.3.7 Materials Having a Capacity for Ion Exchange:

In ion exchange systems, cross-linked polymer resins generate resins that are not soluble in water. Repeated salt-forming functional organic groups, be actually found overall throughout polymer chain in (poly) these materials. Drugs are embedded in resin and released when they contact ions that are suitably charged at the ion-exchange interface.



X- and Y+ are gastro-intestinal ions, respectively. The medication is released from resin in a controlled manner. Pharmaceuticals can complexed with resins repeatedly running them through chromatography columns or prolonged contact with the resin.

Depending on amount of cross-linking employed in resin, the imbibed diffusion region, the imbibed diffusional path length, and the resin's stiffness, the imbibed diffusion amount is definite. Wax or ethyl-cellulose, are hydrophobic rate-limiting polymers and be utilized to cover the “ion-exchange” resin so that performance is better. These systems rely on a polymer coat to control the speed at which medications are made available.

## 1.4 WRITTEN STRUCTURE OF THESIS:

The Dissertation consists of Six Chapters:

- Chapter 1: clearly outlines the Introduction and concept.
- Chapter 2: elaborates on the existing Literature.
- Chapter 3 illustrates the clean concept of Theoretical Investigations
- Chapter 4 defines the clean concept of Experimental Methodology.
- Chapter 5 illustrates the clean concept of Experimental find Results and Discussion.
    - Chapter 6 defines the clean concept of Summary and Conclusion.

# CHAPTER 2

## LITERATURE SURVEY

### 2.1 Introduction:

The points in this chapter, discusses the existing literature that projects information. This topic literature data review check serves as foundation of for scholarly inquiry, providing a comprehensive understanding of Proton (H+) Pump - Inhibitors and various types of polymers that can be utilized to make desired drug [API] delivery. In thesis, we delve into, through the rich sources enlightening academic discourse, exploring themes, methodologies, and gaps in field. By critically evaluating prior work, we position our research within intellectual landscape, aiming to contribute novel insights and address unresolved questions.

### 2.1.1 Literature that is done on Proton (H+) Pump - Inhibitors:

A research by Niyaz S. Mansuri and coworkers (2018) for stomach acid-related illnesses, PPIs (Proton (H+) Pump - Inhibitors) are the most effective pharmacological treatment. There are various testified side effects connected with the long-term usage of PPIs, however they are usually regarded safe. With a ‘only’ once-daily standard dose, PPIs fail to dominate acid over 24 hours fully. It is currently increasingly challenging to overcome failure of PPIs in handling of Gastroesophageal (in stomach) reflux disorder [7].

This study prepared Esomeprazole magnesium trihydrate enteric-coated tablets to transport the medicine to the upper gastrointestinal tract. Super-disintegrants like “Ac-Di-Sol”, CP, and SSG and diluent like Pharma-tose DCL11 and Mannogem EZ were utilized for individual tablets. Acryl-EZE coating was applied to pills. Different physico & chemical values of the

medications were examined. Amount of (molecule) drug (API) content was homogeneous and predictable across all compositions as compress variable were already within acceptable ranges. [8].

The current edition intends to create and approximate the CRC.R.ablets (Ropinirole HCl). Ropinirole HCl is a pH-independent hydrophilic medication. Yet another Idiopathic Parkinson's condition is one of the problems utilized to treat. polymers were utilized to coat the tablet matrix of (molecule) drug Ropinirole, including Guar-gum, sodium [Na] alginate, & Carbopol® copolymer 940P [9].

Drug Naproxen API and drug Esomeprazole API were really combined into one tablet by Irin Dewan and her colleagues in 2017. They used a review of recent revisions to plan and practice layer after layer tableting. Drug Naproxen api and drug Esomeprazole API were really combined and applied - immediate release component across the entire coating suspension to achieve delayed onset. Lastly, the product was coated with a layer of natural colorant and buffing powder to protect the esomeprazole layer and to enhance the product's aesthetic appeal [10].

Rese.arches et al. (2017) established that gastro - retentive drug forms could be contained in Gastric tract for a prolonged period and this increases the medication oral bio-availability. The Mucoadhesive nanoparticles of (molecule) drug Esomeprazole studied after evaluation. The solvent evaporation technique was adopted to prepare all mucoadhesive microspheres. Visual Analysis with SEM was done for external dose morphology. The formulation F-14, maximum percent muco-adhesion was achieved at 14%. By observing the primary outcomes, it can, was determined that the formule F-14 produced reproducible results [11].

Using amoxicillin as an antibiotic and Esomeprazole as an anti-secrtory drug, Majeed Saad M et al. (2016) state that the current study aims to produce dual (02) therapy for stomach ulcers to maximize therapeutic benefits and patient with medicament compliance. Like the non-watery (aqueous) granulation type

method utilized to manufacture an SR layer of 500mg amoxicillin, direct (dry) compression was utilized to create an ER matrix layer of 20mg esomeprazole orally given granules [12].

In addition to Prabha Singh (2015), It was hoped that the hydrophilic polymer matrix used in in-progress modification would help maintain medicine plasma·concentration·and·boost·patient·compliance·with·the·oral·CR·once-daily·

composite tablet of Ambroxol HCl. The granules were made using a process called non-aqueous granulation, so all granules were examined. The pharma-co-kinetic (ADME)s of (molecule) drug were also studied by conducting in-vivo experiments. A stability study was also utilized to zero in on the ideal mix. This resulted in more stable & proper predictable [drug] release (in %) method for the upgraded composition. A study found that the mixture displayed CR in-vivo, which means that it can lower the frequency of dosage, resulting in better patient with medicament compliance [13].

For reduction adverse GIT effects, Nagarjuna Naik. R et al. (2014) conducted a study to design and assess enteric-coated pellets for Esomeprazole staggered release multi-particle. Fluidz - bed western technology was utilized to prepare several units with delayed-release. There is a slew of coatings to choose from, including medication coating, sealing coating, enteric coating. It was determined that this Esomeprazole was stable in its Innovator and Optimized versions. Using combination in excipients, we could minimize GI tract side effects with Esomeprazole. [14].

For instance, authors Swami Vivekananda and others in 2014, Pharmaceutical grade Ingredients (API’s) and other excipients were made into pellets, small powders, or granules. Compaction & medication stacking are 02 of the used ways for producing pellets. The main goal of study was the oral benzimidazole anti-ulcer drug EMT's pharmacological equivalence, resilience, and DR micro pellet composition [15].

Tusher G. R et al. (2014) highlight that Esomeprazole is manufactured as DR tablets & offer desire affect the predetermined time and it is able to maintain drug viz. concentration without causing any undesirable results, and rise the bio-availability by reducing its exposure to gastric acid. The tablets were assembled using a non-aqueous approach as a substitute for direct (dry) compression due the drug's associated properties. The best tab. core were then picked for process enteric type coating with a specific base coating excipient cellulose & derivative to avoid core (small) tablet moisture absorption. They were compared to an innovator product (ESOZ)[16].

Cefpodoxime [salt] Proxetil compressed coated pills for GRDD were the intended outcome, according to N. D. Banerjee et al. (2014). The combination individual excipients in core pill ensures that it will remain in stomach for roughly 12 hours. Core pill contains half of (molecule) drug, while the protective coating holds the rest. Over a period of 15 minutes, this most out layer dissipates drug content so as to attain initial burst (load dose) release. Later, the core part of the layer releases its drug content over period of 12 hours and this ensures that plasma concentration remains within therapeutic limits throughout period [17].

M. Srinivasulu and co researchers in 2014 established Esomeprazole as proton (H+) pump - inhibitor (PPI) that utilize to get rid of dyspepsia. The purpose of this study was to associate the concentrations of natural non-synthetic polymer such as gum Xanthan, gelatin, Guar-gum and to determine the effect of components' physico & chemical values on the dissolution profiles. This study established Esomeprazole can be utilized in SRDDS formulating it with a sustained and controlled delivery - systim that gives a extended duration for drug effect within therapeutic compliance window without attaining toxic levels as with standard-dose forms [18].

According to author Govind Kishanrao et al. (in 2014), main aim in work was synthesize Esomeprazole employing direct (dry) compression and cellulose acetate phthalate as an enteric coating. Prevent drug releasing & absorption

from occurring before the dissolution sites reach the colon, CDDS must defend drugs enroute upto the colon Prevent drug releasing & absorption from occurring before the dissolution sites reach the colon, CDDS must defend drugs enroute upto the colon [19]. Amount of (molecule) drugs' release, absorption can prevented as dissolution is prevented until the colon [19].

### 2.1.2 Literature survey on polymers:

Antihypertensive Carvedilol CR tablet compositions were formulated employing H.P.M.C grades with different [thick] viscosity type grades as (an API) drugs' release rate retardant, according to Buchi N. and colleagues (2013). By compressing the tablets directly, they were tested for a varied range of physical / chemical dose properties. H.P.M.C - K4.M was selected release-retardant [20].

In a study by Shashidhar Reddy D and colleagues (2013), Desvenlafaxine matrix pellets were used to produce an ER tablet that could be associated with in-vitro medicament release (in %) to its absorption as well in-vivo. Drying by spray method of API along with H.P.M.C – K 100 M, MCC, Carboxy-methyl-cellulose (Na salt) (USP), and lactose was employed for granules. Using H.P.M.C - K 100 M at 20% conc., MCC at 26.06% conc., Carboxy-methyl-cellulose (Na salt) (USP) at 6.6% conc., lactose at 13.3% conc., and Kollidon K30 at 5% conc. as binder, the best batch of Desvenlafaxine was synthesized [21].

Soad A. Y et al. (2013) state that recent leanings indicate tablet formulations drug [API] delivery methods are particularly well-suited to achieve SR/DR oral compositions as to their minimal risk of (molecule) drug degradation, flexibility in mixing, and constant release (in %) pattern. One tactic for accomplishing this goal was to develop and produce ER oral capsules of itopride as a particularly aqua - soluble medication while increasing its GRTime [22].

According to Purohit A. et al. (2012), the ongoing study deals with expanding H.P.M.Cell. - based meds with cephalexin ER tablets via direct (dry) compression, which results in drug being released for six hours at a predetermined pace.

H.P.M.C-15cps concentrations were manipulated from low to high to proper study their potential for drugs' release (in %). The outcome of ER pill composition F-5, which contains 13.3 percent HPM C 15 centi poise in addition to medicine, indicates that drug is released at a predetermined rate in 06 hours, in comparison to other five formulations [23].

Esomeprazole dissolution rates at Bangladesh were determined in work by Shimul Halder et al. (2012). Testing was done with USP type dissolving [paddle] equipment at 1.2 pH for 15 minutes, then at pH 6.8 for the last 30 minutes (Paddle type-II). There was no brand displaying pattern for delivery as the original one (E1). 03 brand (E-3, E-6, and E-7) have been found to exhibit a disintegration pattern that is quite close to that of E-3. Compared to original E-11, a branded version was supposed to be inferior. Compared to original E-11, a branded version was supposed to be inferior [24].

Accordingly Vijaya Kumar D et al. (2012), the purpose of revision was to increase the size of tablets for oral CR of Deflazacort. To provide superior treatment adherence and prolong duration in drug's release (in %) from the dose form. Excipients such as H.P.M.C - K 100 M, with synthetic ethyl polymer cellulose, with and H.P.C. were used to increase the structure of diffusion type based CR compact dispersion of Deflazacort and their variations and collection of the optimum design among them. In-vitro data of dissolution established that associated to other documents, the quantity released drug was enhanced by up to 12 hours in composition F-12. This shows that medication removed from the F-12 formulation was efficacious for a period of up to 12 hours [25].

The CR tablets, according to Izhar A. S. et al. (2012), have a diltiazem release that is nearly zero order. To better understand the kinetics with sources of (molecule) drugs' release, altered dissolution type models were applicable. To better understand the kinetics with sources of (molecule) drugs' release, altered dissolution type models were applicable. It demonstrates that non - Fickian diffusion and super in case type-II methods were utilized to release

drug from matrix tablets and multilayer tablets, respectively. D-3 and D3L3 had a mean dissolving time (MDT) of 4.17 and 16.45 hours, respectively [26].

Golam K. et al. (2012) explored the ER component in API alfuzosin, a prostatic hypertrophy antagonist for male. Alfuzosin is sold as three different layered tablet preparation that really requires specific facilities, it is more costly, takes extensive effort to formulate, and is more complex to function than ordinary direct (dry) compression. The fraction of medication released at 1, 6, 12, and 20 hours was determined to respond. most & significant like effect & response variables were quantified [27].

KENY R.R.V.t al., (2012) aimed at extend the period of once pr daily ER matrix type tablets of API Minocycline by using H.P.M.C either pure or along with carboxy-methyl-cellulose (Na salt) as the bulk material in changing quantities. The formulated pills were compared against the innovator market product. The formulated pills were compared against the innovator market product. According to the dissolution detail results, the compositions FComb - IV, FComb - V , and FComb - VI established maximum drugs' release for up to 24 hours. The innovative market product was established to increase the clearance for up to 14 hours [28].

## 2.2 Future area Scope following Research Work

Future work in field can investigate biocompatible polymers, dendrimers, natural polymers ensuring minimal toxicity & immunogenicity can give benefits. Future scope is also develop strategies for safe term use along with develop smart polymers that respond to physiological signs and drug [API] delivery for personalized treatment regimens

The, ever-evolving scene of (molecule) drug [API] delivery, biocompatible polymers have always emerged as promising allies. These versatile materials, derived from both natural and synthetic sources, have significant potential to

transform therapeutic interventions. Biocompatible polymers, as the term suggests, are highly compatible with biological systems. This ensures that patients adhere to their medication regimens for every dose and drug incorporated with these materials.

Ongoing efforts are expected to break new ground and significantly enhance patient compliance with their medications.

# CHAPTER 3

## EXPERIMENTAL TECHNIQUES

### 3.1 REASONING OF CURRENT WORK:

The actual making form controlled (medicament) releasing formulation recommends various benefits just like regulated progress in novel and new therapeutic affect in manner predetermined, monitored drug conc. of blood [in body] concentration, alleviation in adverse problem effects, decrease of time and quantum of dose and frequency, and enlarged patient with medicament compliance.

The main motto in controlled category systyem for (an API) drug can make better or augment a drug's pharma-co-kinetic (ADME), biopharmaceutical, and pharma-co-dynamic properties and take full benefit of API and give a treating to patient from disease.

Rational for Esomeprazole [20.0 mg] and Dexlansoprazole [30.0 mg] formula in Control led released manner:

- Drug availability at Moderation: A pharmaceutic preperation is prescribed to prolong with sustaining drug [in body] concentration at constant manner for long or specified quantum of duration with least adverse problem effects in manner that facilitates Esomeprazole [20.0 mg] and Dexlansoprazole [30.0 mg] tablets.
- The control led released technique is preferred, it avoids dose dump when taking immediate-release Proton (H+) Pump - Inhibitors (Esomeprazole & Dexlansoprazole). In case, Esomeprazole 20mg must released in controlled manner to ensure that that the remedy accumulation is preserved by expanding bioactivity.
- Significantly, enhance the site of action's consistent therapeutic medicament index. By selecting and guaranteeing uniformity. The

operation involving Dexlansoprazole 30mg, maintained over a specific time frame, can be completed within a single day with minimal side effects.

- The initiative led to the production of unique controlled-release tablets, now available in 20mg of Esomeprazole and 30mg of Dexlansoprazole. The objective was to maximize the release interval over a designated period, ensuring appropriate medication release.

(a) To make the most of the full interval during a period of time assuring appropriate release.

(b) Efforts to regulate medicine (drug's) release, its kinetics are understood.

(c) The dose (sudden) dumping can be effectively minimized.

(d) Already determined amount of (molecule) drug liberation, locally or systematically.

(e) Lessened difference in steady - state amount of (molecule) drug.

(f) Elevate the patient's head. (taking medication) convenience.

(g) Enhance security window for medicine as It's elevated. potency.

(h) Progresses towards innovation & improvement of chronic or acute disease state.

(i) Reducing medication costs in wide-ranging health care.

(j) Improved overall pharma therapeutic medic efficacy.

**3.2 THE PURPOSE AND ITS OBJECTIVE:**

Main motive of investigation to make controlled (medicament) releasing formulating of Esomeprazole & Dexlansoprazole Proton (H+) Pump - Inhibitors.

The investigation's primary goals below indicated:

- Esomeprazole & Dexlansoprazole calibration are constructed.
- To conduct FTIR and DSC investigation for (molecule) medicine in the polymer interactions.

## Conceptual Research

- To stable Esomeprazole formulation (tablet) with various niche controlled with released polymers, like Eudragit [S-100], Eudragit® –[L-100], Eudragit® –[RS PO], Eudragit® –[RS 100], Eudragit® –[RS 100], & Eudragit® [RL PO].

- Carbopol® - 974.P, HPMC grades for prevalence like HPMC - K4.M, HPMC - K15.M, & HPMC - K100.M; & polymers that are natural such as Xanthan-gum, Guar-gum, Carboxy-methyl-cellulose (Na salt) (USP), & Pectin via Direct (dry) conversion process can be employed towards formulation various controlled ways of forming Dexlansoprazole tablets.

- Esomeprazole & Dexlansoprazole's unit weight, tapered density, Hausner's proportion, Carr's index, and inclination of repose The repose was made known before compression.

- A variety of post-compression features, comprising percentage deviation, toughness, Testing the strength of fractures, thicknesses, percent drug, Disintegration in-vitro, were examined.
- Analyses the in-vitro dissolving properties, utilizing the USP dissolving equipment type-II, of Esomeprazole & Dexlansoprazole combination (paddle).
- To evaluate, kinetic parameters can be utilized in dissolving procedure of medicine.
- ICH-recommended stability investigations must be conducted.

### 3.3 WORK PLAN:

The work plan that was implemented in this thesis is indicated below:

- Studying of literature
- Excipients and as well as active substances.
- Pharmaceutical components & excipients are procured.
- Controlled - released tablets for Esomeprazole & Dexlansoprazole.

Experimental Work

(a) Pre-formulation Analysis:

## Conceptual Research

- Aspects of physico-chemistry

(i) Organoleptic characteristics: sensory characterstics of a substance that Our senses are the means by which we perceive. These characteristics provide understand and evaluate things like taste & smell & texture & and appearance

(ii) Solubility Profile

(iii) Loss because of drying

- Analytical techniques:

(i) Identification of Determination of λ max. the specific wavelength at a substance absorbs the more light.

(ii) Esomeprazole & Dexlansoprazole calibration curves are pure medicine were developed.

(iii) Determine the % purity of medication.

- The contact of the quality, pure medicament with pharma excipient

(i) FTIR (Fourier transform infrared) spectroscopy.

(ii) Thermal investigation via DSC

- Creating a Powder Mixture characterization.

(i) Quantity of power provide details about how power packing affects the powder's flow.

(ii) Density tapped of granules.

(iii) The Hausener's Ratio & characterization.

(iv) Carr's index's value.

(v) The angle of repose that checks flow property.

(b) Compressing powder into tablets mixtures.

(c) Tablet evaluation.

- Appearances

## Conceptual Research

- Physico & chemical values

  (i) Variation in weight

  (ii) Roughness

  (iii) Friability examination

  (iv) Thickness

  (v) The substance that makes up the drug

  (vi) Dissolution investigations conducted [in-vitro] helps us predict how medicines will work inside our bodies

- Dissolution experiments [in-vitro] to assess the kinetics governing release of (molecule) drug .
- Examination of pharma-co-kinetic identifying (ADME) properties in - vivo of better formulation prepared of Proton (H+) Pump - Inhibitors (drug Esomeprazole & Dexlansoprazole).
  - Stability (as ICH) studies about medication's Esomeprazole & Dexlansoprazole in the improved forms. Medicine would be tested under different conditions. Entire tests done in above will be processed on the medicine like appearance, chemical characterstics, and strength. The investigation purpose is to get the better and safest process of keeping of the drugs.
- Findings and Discussion. & Conclusion.

# CHAPTER 4

## THE METHODOLOGY OF EXPERIMENTS

Esomeprazole were purchased from Astra Zeneca Pharma Ltd, Bangalore & Dexlansoprazole was purchased from Zydus Takeda Pharma Ltd, Mumbai. Polymers [Eudragit® - S100] and [Eudragit® -L 100[ was prurchased from Evonik's Health Care, Germany. [Eudragit® RS PO], [Eudragit® RL PO], Carbopol®-974 P and Pectin were recieved from Yarrow Chem. Products, Mumbai. [Eudragit® RS 100[ and Eudragit® RL 100] was from S & D Fine Chem. Ltd, city: Mumbai. H.P.M.C – [K 4M] and [H.P.M.C - K 100 M] were donated by Otto Chemie Pvt. Ltd, Mumbai and H.P.M.C - K 15 M was donated by Trexchem Pvt. Ltd, Ahmedabad. Xanthan-gum (natural), Guar-gum (natural) and Carboxy-methyl-cellulose (Na salt) (USP) was purchased from Akhil Health & Care Pvt. Ltd, Gujarat

| Sr. No. | Materials | Manufacturers |
|---|---|---|
| 1 | Esomeprazole | Astra Zeneca Pharma Ltd, Bangalore |
| 2 | Dexlansoprazole | Zydus Takeda Pharma Ltd, Mumbai |
| 3 | Eudragit® -S 100 | Evonik Health Care, Germany |
| 4 | Eudragit® -L 100 | Evonik Health Care, Germany |
| 5 | Eudragit® RS PO | Yarrow Chem. Products, Mumbai |
| 6 | Eudragit® RS 100 | S.D Fine Chem. Ltd, Mumbai |
| 7 | Eudragit® [RL 100] | S.D Fine Chem. Ltd, Mumbai |
| 8 | Eudragit® RL PO | Yarrow Chem. Products, Mumbai |
| 9 | Carbopol®-974 P | Yarrow Chem. Products, Mumbai |

| | | |
|---|---|---|
| 10 | HPMC - K 4M | Otto Chemie Pvt. Ltd, Mumbai |
| 11 | HPMC - K 15 M | Trexchem Pvt. Ltd, Ahmedabad |
| 12 | HPMC - K 100 M | Otto Chemie Pvt. Ltd, Mumbai |
| 13 | Xanthan-gum | Akhil Health care Pvt. Ltd, Gujarat |
| 14 | Guar-gum | Akhil Health care Pvt. Ltd, Gujarat |
| 15 | Pectin | Yarrow Chem. Products, Mumbai |
| 16 | Carboxymethylcellulose Sodium (USP) | Akhil Health care Pvt. Ltd, Gujarat |
| 17 | Talc | Yarrow Chem. Products, Mumbai |
| 18 | Aerosil | Yarrow Chem. Products, Mumbai |
| 19 | Magnesium Stearate | Yarrow Chem. Products, Mumbai |
| 20 | Micro Crystalline Cellulose | Yarrow Chem. Products, Mumbai |
| 21 | Di calcium phosphate | Akhil Health Care Pvt. Ltd, Gujarat |

**Table 4.1: List of Materials**

For the fabrication of the formulations there were many instruments used for this work. The used instruments are enumerated below. Their make and model is also mentioned alongside the name of the instrument.

| **Sr.No** | **Instruments** | **Make** | **Model** |
|---|---|---|---|
| 1 | Tablet Compression Machine | Karnavathi | Rimek mini press I |

| | | | |
|---|---|---|---|
| 2 | FT-IR spectrophotometer | Bruker | Alpha-T- 1020 |
| 3 | Differential Scanning Calorimetry | Hitachi | 6300 |
| 4 | HPLC | Agilent Technologies | 1200 |
| 5 | UV-Visible spectrophotometer | Lab india | UV 3200+ |
| 6 | Dissolution test apparatus | Lab India | DS-8000 |
| 7 | Electronic Weighing balance | Shimadzu | ATX224 |
| 8 | Friabilator | Lab India | FT 1020 |
| 9 | Hardness tester | Monsanto | SISCO |
| 10 | Tapped (vol) density apparatus | Lab India | TD 1025 |
| 11 | Bulk density apparatus | Thermonik | PD-IOO |
| 12 | Sonicator | Ultrasonic's, | 1.51. (H) |
| 13 | Centrifuge | Remi | C -854/6 |
| 14 | Hot air oven | Universal | D-5247 |
| 15 | Sieve no's 16, 40 and 60 | Jayant Scientific | J-82 |
| 16 | Stability chamber | Cintex IC | CIC-64 AA |
| 17 | PH meter | Lab India | SAB 5000 |

**TABLE 4.2: List of Equipment**

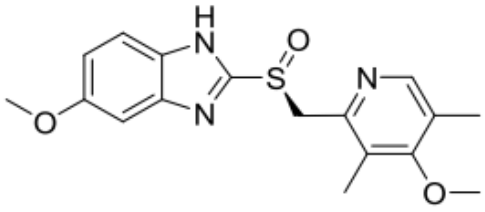
## Methodology of Experiments

### 4.1 PROFILE OF (AN API) DRUG:

### 4.1.1 ESOMEPRAZOLE:

**Description:** A highly effective inhibitor of gastric acid secretion used in the therapy of stomach ulcers and zollinger-ellison syndrome. The drug inhibits the H(+)-K(+)-ATPase (H(+)-K(+)-exchanging ATPase) in the proton pump of gastric parietal cells.

**Chemical Structure:**




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

**Molecular weight :** Average: 345.416, Monoisotopic: 345.114712179 g/mol.

**IUPAC Name:**

5-methoxy-2-[(S)-(4-methoxy-3,5-dimethylpyridin-2yl)methane sulfinyl]-1H-1,3-benzoimidazole.

**Solubility:** Soluble in methanol, DMSO (143 mg/ml at 25 °C), ethanol (143 mg/ml at 25 °C), and water (<1 mg/ml at 25 °C).

**Categories:** Proton Pump Inhibitors (PPI), Gastroesophageal reflux disease (GERD).

## Methodology of Experiments

**Pharmacokinetic Data:**

| | |
|---|---|
| Bio-Availability | : 50 to 90 % |
| Protein Binding | : 97% |
| Metabolism | : Hepatic |
| Excretion | : 80 % Renal; 20% Faecal |
| Half Life | : 1-1.5 hours |

**Effectiveness Mechanism:**

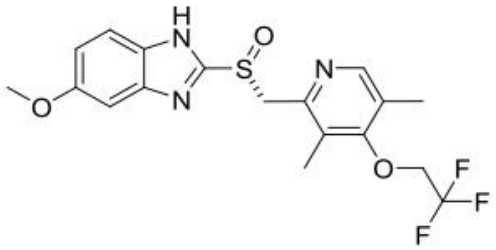
As of proton (H+) pump - inhibitor, Esomeprazole prevents parietal cell of stomach from pumping out H+/K+ ATPase. Esomeprazole reduces stomach acidity by blocking of proton ($H^+$) pump, the final step in acid preparation. [29-30].

### 4.1.2 DEXLANSOPRAZOLE:

**Description:**

Powder of Cystalline that is white or nearly white.

**Chemical Structure:**




**Molecular formula:** $C_{16}H_{14}F_3N_3O_2S$

**Molecular weight :** 369.363 g/mol.

## Methodology of Experiments

**IUPAC Name:** Sodium-[5-(difluoromethoxy)- 2-[(3,4-dimethoxypyridin-2-yl) methylsulfinyl]- 1*H*-benzoimidazole sesquihydrate

**Dissolution rate:**

A solution made up of phosphate and pH 7.4is marginally soluble; n-hexane is completely insoluble.

**Categorization:**

It is usually utilized to treat Gastroesophageal (in stomach) reflux disorder to treat peptic ulcer disease.

**Pharmacokinetic Data:**

| | |
|---|---|
| Bio-Availability | : ~60% |
| Protein Binding | : 96 to 99 % |
| Metabolism | : Rapidly metabolized in liver |
| Excretion | : 50% Renal and 47% in the Feces. |
| Half Life | : 1 to 2 hours. |

**Effectiveness Mechanism:**

The (H, K)- ATPase in the stomach parietal cell's secretory membrane is selectively inhibited by Dexlansoprazole, which falls under the substituted benzimidazole category of antisecretory medicines. A gastrointestinal proton (H+) pump - inhibitor, Dexlansoprazole, blocks acid formation from parietal cell's acid (-proton) pump enzyme. [31-33].

## 4.2 PROFILES OF EXCIPIENTS [34-37]:

### 4.2.1 POLYMETHACRYLATES:

#### 4.2.1.1 EUDRAGIT® S-100 AND EUDRAGIT® L-100:

Chemical/IUPAC name :

EUDRAGIT S-100: Poly (methacylic acid-co-methyl methacrylate) 1:2.

Description: Eudragit S-100 and Eudragit L-100is a solid substance in form of a white powder with a faint characteristic odour.

Functional Category: tablet diluents, tablet binder, Film-forming agent.

#### 4.2.1.2 EUDRAGIT® RS-100 AND EUDRAGIT® RL-100:

#### 4.2.1.3 EUDRAGIT® RS PO AND EUDRAGIT® RL PO:

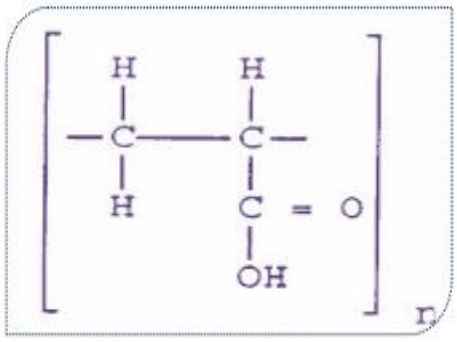
Chemical/IUPAC name :

Eudragit RLPO: Poly (ethylacrylate - co - methylmethacrylate - co - trimethyl ammonio ethyl methacrylate chloride) 1:2:0.2

Description: Eudragit RSPO and Eudragit RLPO is a white powder with a faint amine-like odour.

### 4.2.2 CARBOPOL:

The structural formula is as follows:



**Molecular mass:** 104 400 g/mol

**Characterization:**

White and Fluffy powder, contains acidic& hygroscopic taste and odor.

**Classification of the functions of a system:**

Release modifier, emulsifying and dissolving agent, tablet binders, and increasing agents all fall under the umbrella term "suspension ingredient."

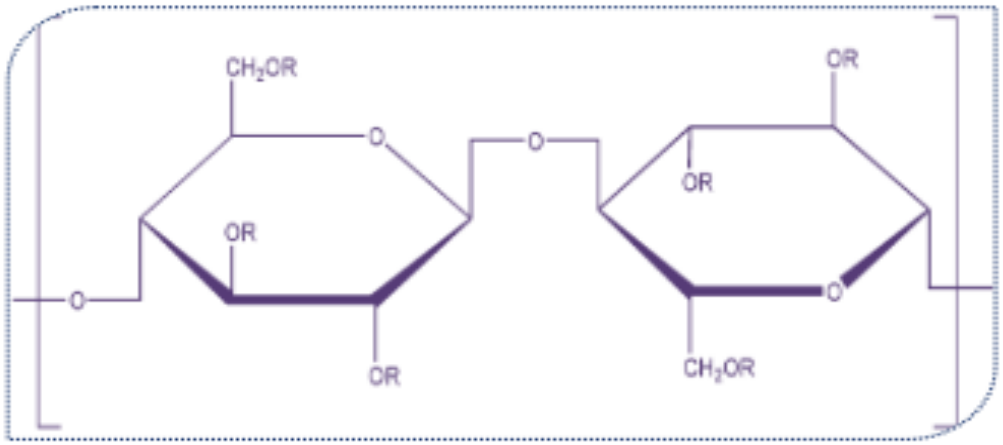
### 4.2.3 HYDROXYPROPYL METHYLCELLULOSE (H.P.M.C):

**Descriptive terms:**

Pharmacol, Methocel-E15LV, Spectral

**Chemical formula of structure:**

Chemical formula of structure is as follows:




**Molecular mass:** 10000-150000

**Characterization:**

Hydroxypropylmethylcellulose is a white powder with no odor or taste.

**Functional Classification:**

Resistance to evaporation, film-former/stabilizer/stabilizer, emulsifier/substrate raiser, tablet binder/MR agent.

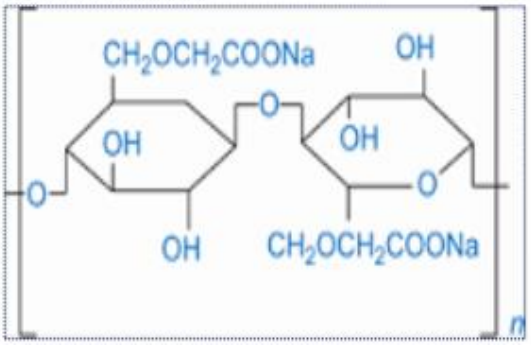
**Pharmaceutical Formulation Applications:**

Pharmaceutical compositions for oral, nasal, ophthalmic, and cosmetic delivery all use hypromellose.

### 4.2.4 Carboxymethylcellulose Sodium (USP):

Synonyms: Akucell, Carbose D, SCMC, Cethylose, Carmellosum natricum.

Structural formula:




**Molecular mass:** 262.19 g/mol.

**Characterization:**

Carboxy [Methyl] Cellulose Sodium is granular powder that is white and near to white in color, odorless, and tasteless.

**Functional Classification:**

Liquefiers for capsules and tablets, tablet binder, viscosity enhancer, and water-absorbent all fall under the umbrella term "coating agent."

**Pharmaceutical Formulation Applications:**

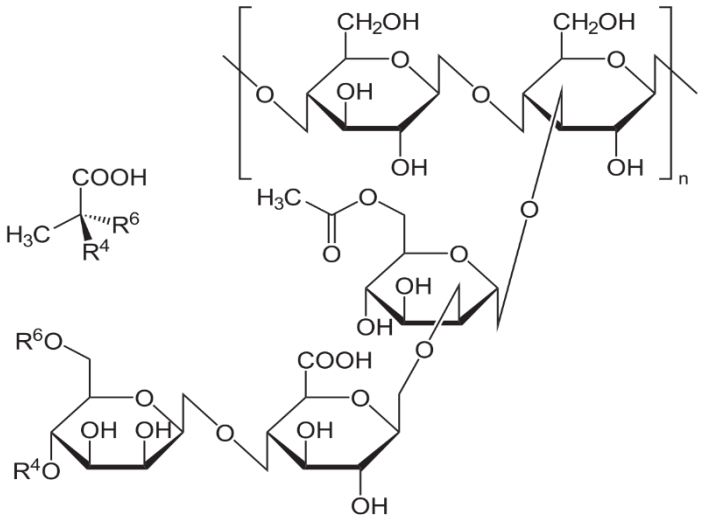
Given its ability to increase viscosity, this normally used in both oral and topical pharmaceutical formulations.

### 4.2.5 XANTHAN-GUM:

Synonyms: Corn sugargum, Keltrol, Rhodigel, Vanzan NF, Xantural.

Chemical Name: 9H-Xanthene

Structural formula:




Molecular weight: 182.2179 g/mole

Description: Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

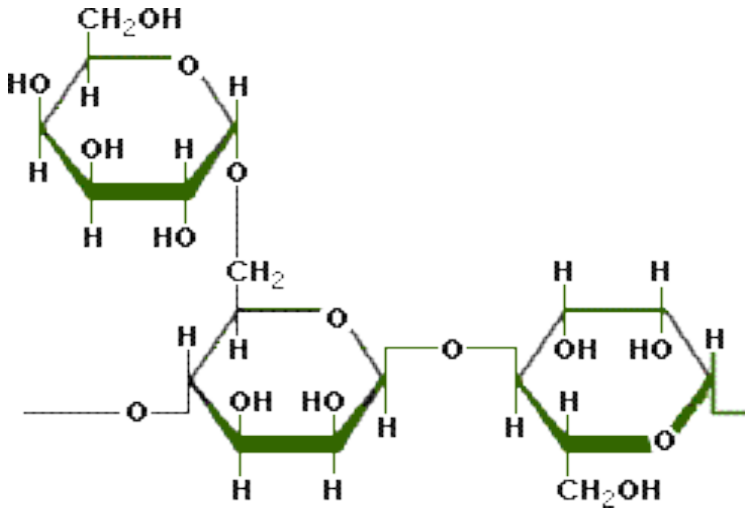
Functional Category: Stabilizing agent, suspending agent, viscosity-increasing agent.

### 4.2.6 GUAR-GUM:

Synonyms: Galactosol, gaur flour, jaguar gum, meprogat, meyprodor.

Chemical name: Galactomannan polysaccharide.

Structural formula:



Molecular weight: 50,000-8,000,000.

Description: White to yellowish-white, nearly odorless, free-flowing powder

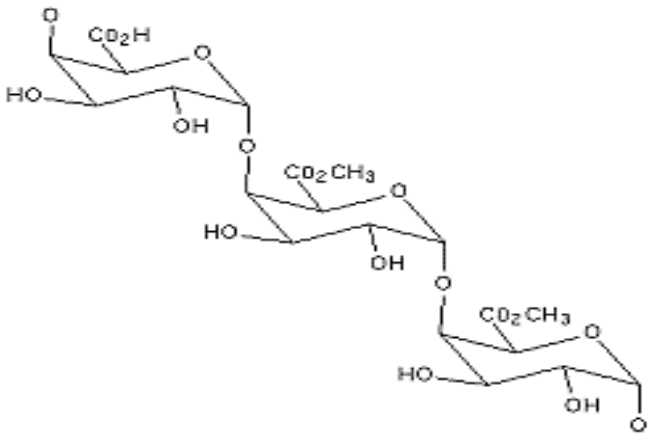
Functional Category: Thickener, Stabilizer, Emulsifier.

### 4.2.7 PECTIN:

Synonyms: D-galacturonic acid

Chemical Name: β-D-galactopyranuronic acid.

Structural formula:



Molecular weight: 60 -130,000 g/mol,

Description: White, yellowish, light grayish or light brownish powder.

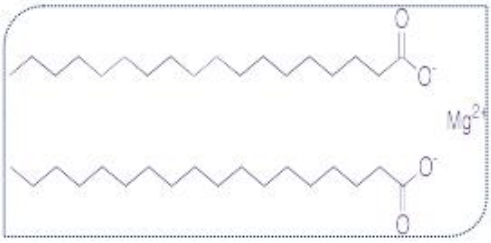
Functional Category: Gelling agent, thickener, stabilizer, emulsifier.

### 4.2.8 MAGNESIUM STEARATE:

Synonyms: Metallic stearate, Magnesium salt.

Chemical Name: Octadecanoic acid magnesium salt.

Structural formula:




Molecular weight: 591.27 g/mol.

Description: It is a fine, white, precipitated, milled powder having low bulk density. It has faint characteristic odour and taste. It is greasy to touch and readily adheres to skin.

Functional Category: Tablet and capsule lubricant, Glidant, Anti-Adherent.

### 4.2.9 TALC:

Synonyms: Altalc; hydrous magnesium calcium silicate; hydrous magnesium silicate; powdered talc

Molecular weight: 379.26568 g/mol.

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.

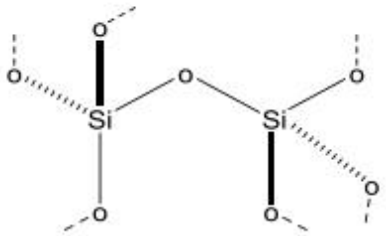
Functional Category: Anticaking agent, glidant, tablet and capsule diluents, tablet and capsule lubricant.

### 4.2.10 AEROSIL (COLLOIDAL SILICON DIOXIDE):

Synonyms: Colloidal silica, fumed silica, light anhydrous silicic acid.

Chemical Name: silicon dioxide.

Structural formula:




Molecular weight: 60.08.

Description: Colloidal silicon dioxide is sub microscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

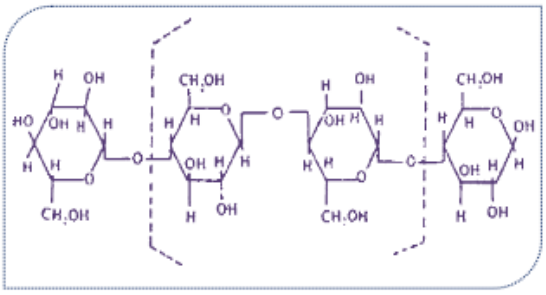
Functional Category: Adsorbent, Anticaking agent, emulsion stabilizer, Glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent.

## 4.2.11 MICROCRYSTALLINE CELLULOSE (MCC):

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

Chemical Name: Cellulose

Structural formula:



Molecular weight: 36 000

Description: Microcrystalline cellulose is purified, partially depolymerised cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Functional Category: Adsorbent, suspending agent, tablet and capsule diluents, tablet disintegrant.

## 4.3 STUDIES BEFORE YOU FORMULATE:

The pre-formulations study's objectives are as indicated:

- To explain the required physico & chemical figurines of a novel medicinal substance.
- To determine kinetic diagram of its release.
- To ascertain its eligibility to gel-up with other excipients.

Testing for qualities such as solubility, emulsibility, and melting point is part of the pre-formulations process for a medicine sample [38,39].

### 4.3.1 Parameters for pre-formulation:

Once created, physico-chemical qualities of blends generally define the goodness of tablet. Mixing contains various of formulations and functions variables, all of which can alter the purposes of the mixes created. The varied functions of mixes are expressed by Pharmacopoeia [40].

### 4.3.2 Properties of flow [41-44]:

#### 4.3.2.1 Repose Angle:

Powder flow rate can be determined by using the funnel method through it. A 2cm-high funnel attached to plane's surface received the powder. The Repose - Angle was computed by drawing pile's diameter in pencil on graph paper and then conducting a measurement by pile's base radius five times:

$$\Theta = \tan^{-1} H/R$$

Θ=angle of repose; H=height of powder cone; R=radius of powder cone

## Methodology of Experiments

The free-flowing character of the material substance is demonstrated by an Repose - Angle less than 30 degrees.

### 4.3.2.2 Density of the bulk:

The measurement of powder density is complete in gms. per cubic centimeter by dividing the volume of a powder is used to measure its mass. Particle size distribution, shape, and propensity to cling together all have a role in determining a powder's bulk compactness. Resources and blends would be handled, transported, and kept in containers with predefine bulk compactness in mind. When it comes to Equipment that blends sizes.,, That is essential. Dry 20 (TWENTY) mililitre cylinder was filled by 10 (Ten) gram of powder blend that It was sifted and then proceeded added deprived of compacting. Powder gradually The worried was leveled deprived of compacting it seeming quantity, Vo The mentioned formula were used to calculating bulk density:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

$V_o$ = apparent volume of powder

### 4.3.2.3 Density modulation:

The model was tapped using an appropriate mechanical selected (vol) density sample that could produce 100 drops per 60 second by bulk mass measurement protocol. The operation was repeated until the error between measurements was lower than 2 [two] percent to get a correct reading of the volume, V. By utilizing the method for tapped (vol) density (grams per liter), we were able to find the density:

$$Tap = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

### 4.3.2.4 Carr's index of consolidation:

The Carr index is a measure of a powder's compressibility.

This is determined using the formula.

$$C = \frac{(\rho b - \rho t)}{\rho b} \times 100$$

Where, $\rho_b$ is the bulk density

$\rho_t$ is the tapped bulk density

A Carr's index is greater than than 25 indicates bad flowability, whereas one lower than 15 indicates better flowability.

### 4.3.2.5 Hausner's ratio:

Hausner's (tapped vs bulk) ratio measures a powder's or granular material's flowability. The expression formula for calculating the Hausner's (tapped vs bulk) ratio is as follows:

$$H = \rho_{b/} \rho_b$$

Where, $\rho_b$ is the bulk density

$\rho_b$ is the tapped bulk density

Higher than 1.25 Hausner's (tapped vs bulk) ratio is believed to indicate poor

flowability.

## 4.4 TABLET FORMULATION AND DEVELOPMENT:

### 4.4.1Tablet Preparation:

### 4.4.2 Method of Direct (dry) compression:

By all means of the straight (dry) compression approach, various tablet compositions were created. All powders were run over a 60mesh sieve. The required amounts of medication and polymers were carefully combined. Lubricant magnesium stearate were added. A glidant, talc was utilized. As a diluent, microcry-stalline -cellulose was utilized. Finally, The powder mixture was squeezed into a smaller volume after uniformly mixed in polybag. Before compression, the mixes underwent a battery of tests [45-48]

## ESOMEPRAZOLE COMPOSITIONS

**Table 4.3: Compositions of Esomeprazole CR tablets (F1-F9)**

| S.No | Ingredients(mg/tab) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Esomeprazole | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| 2 | Eudragit S-100 | 20 | 40 | --- | --- | --- | --- | 20 | 20 | --- |
| 3 | Eudragit L-100 | --- | --- | 20 | 40 | --- | --- | 20 | --- | 20 |
| 4 | Eudragit RSPO | --- | --- | --- | --- | 20 | 40 | --- | --- | 20 |
| 5 | Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 6 | Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | Di.Calcium Phosphate | Qs | Qs | Qs | Qs | Qs | Qs | Qs | Qs | Qs |
| | Total Weight | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 4.4: Compositions of Esomeprazole CR tablets (F10-F19)**

| S.No | Ingredients(mg/tab) | F10 | F11 | F12 | F13 | F14 | F15 | F16 | F17 | F18 | F19 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Esomeprazole | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| 2 | Eudragit RS-100 | 20 | 15 | --- | --- | 20 | 30 | 15 | --- | --- | --- |
| 3 | Eudragit RL-100 | --- | 15 | 20 | 40 | --- | --- | 20 | 30 | 15 | 20 |
| 4 | Eudragit RLPO | --- | --- | --- | --- | --- | --- | --- | --- | 20 | 15 |
| 5 | Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 6 | Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | Di.Calcium Phosphate | Qs | Qs | Qs | Qs | Qs | Qs | Qs | Qs | Qs | Qs |
| | Total Weight | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

## DEXLANSOPRAZOLE COMPOSITIONS

**Table 4.5: Compositions of Dexlansoprazole CR tablets (F1-F12)**

| S.No | Ingredients(mg/tab) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Dexlansoprazole | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| 2 | Carbopol-974 P | 150 | 75 | 50 | 100 | 75 | 50 | 100 | 20 | --- | --- | --- | --- |
| 3 | HPMC K4M | --- | 75 | 100 | 50 | --- | --- | --- | 150 | --- | --- | --- | --- |
| 4 | HPMC K 15M | --- | --- | --- | --- | 75 | 100 | 50 | --- | 150 | 75 | 50 | 100 |
| 5 | Sodium CMC | --- | --- | --- | --- | --- | --- | --- | --- | --- | 75 | 100 | 50 |
| 6 | Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 7 | Aerosil | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 8 | MCC | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| | Total Weight | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

**Table 4.6: Compositions of Dexlansoprazole CR tablets (F13-F22)**

| S.No | Ingredients(mg/tab) | F13 | F14 | F15 | F16 | F17 | F18 | F19 | F20 | F21 | F22 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Dexlansoprazole | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| 2 | Xanthan gum | 75 | 100 | 15 | --- | --- | --- | --- | --- | --- | --- |
| 3 | Guar gum | --- | --- | 50 | 75 | --- | --- | --- | --- | --- | --- |
| 4 | Pectin | --- | --- | --- | --- | 75 | 100 | --- | --- | --- | 35 |
| 5 | HPMC K 100M | --- | --- | --- | --- | --- | --- | 50 | 75 | 100 | 50 |
| 6 | Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 7 | Aerosil | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 8 | MCC | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| | Total Weight | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

## 4.5 Assessment of post-compression variables for Tablets that have been made:

The physicochemical characteristics of compression tablets with the indicated composition were studied, including weight variation, toughness, smoothness, rheological (flow) properties, and drug contented [49-54].

### 4.5.1 Weight fluctuation examination:

A digital weighing balance was employed for the purpose of measuring individual weights of twenty pills and the sum of the weight group. Assuming the total weight of the items pills, the normal weight of a single pill was calculated. The pharmaceutical's homogeneity content The weight variation can be used to determine it test. In accompanying table, just two weights vary compared to the average by greater than 10% and none by more than double that percentage. The average and standard were determined by the process deviation. The % deviation was computed using the method below.

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

**Table 4.7: Pharmacopoeial specifications for tablet weight variation**

| Average weight of tablet (mg) (I.P) | Average weight of tablet (mg) (U.S.P) | Maximum percentage difference allowed |
|---|---|---|
| Less than 80 | Less than 130 | 10 |
| 80-250 | 130-324 | 7.5 |
| More than | More than 324 | 5 |

### 4.5.2 Toughness:

A tablet's stiffness is determined by quantity of force needed to crack it in half across its diameter. How well tablet holds up the handling and storage charges and storage transformations before the tablet's hardness governs usage. Each formulation's hardness The measurement was done using a Monsanto hardness tester, and the average and standard deviation were computed.

### 4.5.3 Thickness:

Appearance reproduction relies heavily in tablet thickness. A tablet's thickness is determined by its important factor in achieving a realistic appearance. The core & coated tablets' regular deviation and average thickness has calculated.

### 4.5.4 Friability test:

Tablets that has subject to mechanical stun or wear will show signs of wear and lamination or fracture on that surfaces. A Roche Friabilator were used to compute tablets friability (Lab India, FT 1020). There are percentages involved (percent). Initial 10 (ten) tablets were weighted and delivered towards friability. At a rate of 25 revolutions per minute for four minutes, or till 100 (hundred) revolutions per sixty second, the stabilator was running at full speed. Once more, [W (in end))] took a scale towards tablets. That was follow by calculating the % of friability:

$$F = \frac{[W(\text{initial}) - W(\text{final})]}{W(\text{initial})} \times 100$$

### 4.5.5 Determination of the drug's concentration:

The drug particlars of compression tablet was tested. One tablet for Esomeprazole was finely pulverized and weighed in a 100 (hundred) ml volume flask containing 50 (fifty)  ml of water. Drugs were allowed to liquefy in flask

by standing it up fully. The amount of mixtures was increased from adding up water. A UV observable spectrophotometer were used to compute the assimilation of solution at various concentrations. The medicine concentration were resolute using calibration-curve [55-57].

### 4.5.6 Dissolution investigations in-vitro:

Lab in India [DS 8000+], a USP class II dissolving instrument, computed the conclusion in-vitro method. A 37+0.5oC warmth and RPM of 50 were recorded. 120 minutes were spent in acid buffer (pH-1.2), 120 minutes00 in acetate- buffer (pH-4), eight hours in phosphate ($PO_4$) -buffer (pH-6.8), and twelve hours in 7.4 pH phosphate ($PO_4$) buffer. The % of statistics on drugs' discharge at various intervals was gathered [58-65].

In dissolving media, the pills were dissolved, & device was activated. It is necessary to swap out 5 ml aliquots every 1 (One), 2 (Two), 4(four), 6 (Six), 8(Eight), 10 (Ten), 12 (Twelve), 14 (Fourteen), 16 (Sixteen), 18 (eighteen), 20 (Twenty), 22 (Twenty Two), and 24 (Twenty Four) hours for fresh dissolving media kept in same temperature. Whatman filter paper was utilized to filter each aliquot of five mL. (No.41). After 120 minutes in acid buffer (pH-1.2) and 120 minutes in both acetate and phosphate ($PO_4$) - buffer (pH-4.5 and 7.4, respectively), the absorbance of solutions was examine using UV fluorescence spectroscopy. Using a regular calibration curve, the concentration of drugs at example were determined. [66-69] The statistics for releases was gathered.

### 4.6 Analysis of Dissolution Data Using Release Rate Kinetics:

The capacity of several models to appropriately explain Kinetics governing discharge of (molecule) drug were methodically tested. The gathered model was correlated towards zero-order, first-order, Higuchi, and Korsmeyer-Peppas releases models [70-76] to set-up the instrument behind dosage [unit] form's drugs' discharge rate kinetics.

### 4.6.1 Dynamics of the zero-order discharge:

Mentioned equation is utilized to analyze zero-order (drug) release, its kinetics.

$$F = K_o t$$

On time - T, 'F' specifies the quantity of medication has released, and "Ko" denotes the 0 (zero) – command rate discharge rate constant. The % of drugs discgarged after time a straight line graph.

### 4.6.2 Kinetics of first-order release:

The mentioned formulations is fitted to the statistics on discharge rates.

$$\text{Log } (100\text{-}F) = kt$$

It’s possible for obtain first - command rate release by plotting The drug's cumulative log percent remaining against time.

### 4.6.3 Higuchi's model of release:

We utilized the mentioned formulations to fit the discharge rate data to examine - Higuchi (drug) release, its kinetics.

$$F = k\, t1/2$$

Higuchi constant is denoted by 'k' in case. In Higuchi model, a plot of percentage drugs’ release vs. Time is linear in its square root.

### 4.6.4 Korsmeyer and Peppas's model of release:

The Korsmeyer-Peppas equation, which displays the log proportion of (molecule) drugs’ released versus log time, were used for determine instrument

of (molecule) drugs' release. The drugs' discharge instrument is indicated from slope of straight line with exponent of n.

$$M_t / M_\infty = K\, t^n$$

Where, $M_t / M_\infty$ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n=0.5; for zero-order release (case-II transport), n=1; and for super case-II transport, n > 1.In this model, a plot of log ($M_t / M_\infty$) versus log (time) is linear.

### 4.6.5 Hixson-Crowell model of release:

$$(100-Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

The Hixson's - Crowell models depicts how drugs are mostly liberated through erosion from an insoluble matrix. When the particle or tablet's changes occur in both surface area and diameter [77-81]

### 4.7 Investigations into Stability:

Formulation development is entire about finding a dosage [unit] form composition is safe, effective, and stable while medication's intended use.

It's possible for recognize the finer conditions for storage, re-test intervals, and shelf life depends onto various environmental factors, like The level of temperature, humidity, and light [82-86].

## 4.8 ESOMEPRAZOLE CONTROL LED RELEASED TABLET IN-VIVO STUDIES:

Pharma-co-kinetic (ADME) study about Esomeprazole optimized tablets (F-6) for controlled released are discussed in chapter. Mathematical representations of t time courses about blood Esomeprazole concentrations and comparisons includes marketed version about Esomeprazole rapid discharge tablets was key goals for animal studies. The bio-availability of new developed dosage [unit] forms can final better understood by pharma-co-kinetic (ADME) investigation medications supplied via dosage [unit] forms.

An effective regulated drug [API] delivery relies on maintaining a long-term dosage. Formulation F-6, i.e., Eudra git -RS PO compression tablets, was chosen for evaluation in-vivo(inside the body) in healthy subjects rabbits depends on [in-vitro] dissolving findings of multiple Esomeprazole control (medicament) releasing formulations briefed in next chapter 5. Esomeprazole was chosen for learning because it released the mimimum quantity of medicine in controlled manner over 24 hours. Pharma-co-kinetic (ADME) study in-vivoalso supported these results. It has decided that to verify the new version of Esomeprazole is safe and effective, current investigation would undertake [in-vivo] testing and compare them towards [in- vitro] results.

### 4.8.1 Development of an analytical method: HPLC method:

- HPLC determined The level of Esomeprazole in plasma samples. Analyzed plasma sample was utilized to draw up the determination of the requires the use of a calibration curve

Esomeprazole concentration. This findings used an acetonitrile/phosphate ($PO_4$) buffer composition of 700ml (70 percent) and 300ml (30 percent) for preparing the (HPLC) chromatographic . mobile (liquid) phase. Five minutes of US water bath degassing viewed by vacuum filtering all the way through

0.45 filter were utilized to prepare the mixer. Ultraviolet spectroscopy was used to recognize the Esomeprazole samples. When it came time for dilute the sample, the (HPLC) chromatographic . mobile (liquid) phase was employed [90, 91].

### 4.8.2 Standard solutions preparation:

The operational standard for 10 (ten) mg Esomeprazole The weight was exactly accurately measured and fully transferred to a 10 ml volumetric flask. Add 7ml of solvent to dilute powder medication, use the same method to adjust the volume solvent to get correct amount. (stock solution). The stock solution was pipetted in the 10 (Ten)ml volumetric flask, the diluent was used to achieve that outcome towards desired concentration. A filter was used to filter the preparation 0.45m filter. Multiple concentrations (1, 10, 20, 30, and 40 g/ml) were created for linearity test. The achivements were analyzed.

## 4.9 DEXLANSOPRAZOLE CONTROL LED RELEASED TABLET IN-VIVO STUDIES:

Dexlansoprazole optimized tablets (F-2) for controlled led released focus on this chapter's pharma-co-kinetic (ADME)s inquiry. In well rabbits, Dexlansoprazole concentration in blood was main goal of pharma-co-kinetic (ADME) studies. The marketed Dexlansoprazole rapid discharge tablets was comparison to these results. The bio-availability of newly developed dosage [unit] forms can final determined through pharma-co-kinetic (ADME) findings of (molecule) drugs supplied in dosage [unit] forms.

Drug [API] delivery - system can prolong the duration of medication release are essential for their efficacy. Formulation F-2, i.e., Carbopol®-974 P, HPMC - K4.M compression tablets, was recommended for in-vivo assessment in well rabbits depends on in-vitro dissolving findings of numerous Dexlansoprazole controlled (medicament) releasing formulations reported in Chapter-5. For this

findings, we picked this formulation since it show minimum quantity for Dexlansoprazole release throughout 24 hours in controlled manner. For further confirmation, pharma-co-kinetic (ADME) findings were undertaken in-vivo(inside the body). Therefore, the present study was crafted to carry out in-vivo testing and compare them with in-vitro results to setup the enhanced formulation delivers Dexlansoprazole into controlled manner [87-89].

### 4.9.1 Development of an analytical method: HPLC method:

Plasma samples were analyzed to determine the % concentration molecules of Dexlansoprazole through HPLC. Plazma sample varying quantities for Dexlansoprazole were utilized In order to determine the molecular concentration of dexlansoprazole, a calibration curve needs to be established. 300ml (30 percent) of 0.1m phosphate ($PO_4$)- buffer ph 3.35 and 700ml (70 percent) of acetonitrile was utilized to prepare the (HPLC) chromatographic . mobile (liquid) period for study. Five minutes for US water bath ultrasonic degassing follow from vacuum filtering between a 0.45 filter were utilized to prepare the mixer. Dexlansoprazole sample was detected using an ultraviolet spectrum at 297 nm. The (HPLC) chromatographic . mobile (liquid) phase were used as diluent.

### 4.9.2 Standard solutions preparation:

- The operational regulations of 10 (Ten) mg Dexlansoprazole[api] was precisely weighted & merged to a volumetric graduated flask with a quantity of 10 (ten) ml. Add 7ml of main solvent so dilute powder medication, and then modify the volume by using the very same solvent get the accurate amount. (stock solution). Thus formed stock [API] solution were pipetted in 10 (Ten) mililitre volumetric (graduated) flask, then diluted towards desired concentration using diluent. The preparation was refined utilizing a 0.45m filter. Concentration of 1 (one) to 40 g/ml was utilized for Linearity test.

# CHAPTER 5

## RESULTS AND DISCUSSION

### 5.1 ESOMEPRAZOLE:

The phosphate ($PO_4$) buffer at pH 6.8 was used to analyze Esomeprazole at 236 nm and 238 nm, respectively.

| S.No | Concentration(µg/ml) | Absorbance(nm) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 0.110 |
| 3 | 10 | 0.214 |
| 4 | 15 | 0.304 |
| 5 | 20 | 0.407 |
| 6 | 25 | 0.510 |
| 7 | 30 | 0.621 |
| 8 | 35 | 0.718 |
| 9 | 40 | 0.815 |

**Table 5.1: Observation in graph of Esomeprazole in O.1N HC1 (236nm)**

## Results and Discussion

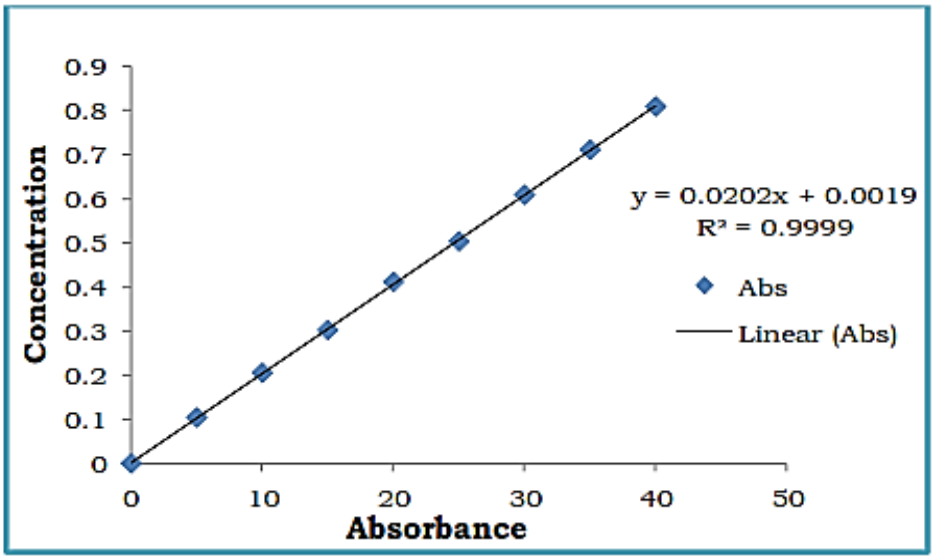



**Fig. 5.1: Standard graph of Esomeprazole in O.1N HC1 r**

| S.No | Concentration(µg/ml) | Absorbance(nm) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 0.093 |
| 3 | 10 | 0.199 |
| 4 | 15 | 0.291 |
| 5 | 20 | 0.384 |
| 6 | 25 | 0.487 |
| 7 | 30 | 0.589 |
| 8 | 35 | 0.698 |
| 9 | 40 | 0.795 |

**Table 5.2: Observation in graph of Esomeprazole In pH 6.8 phosphate ($PO_4$) buffer (238nm)**

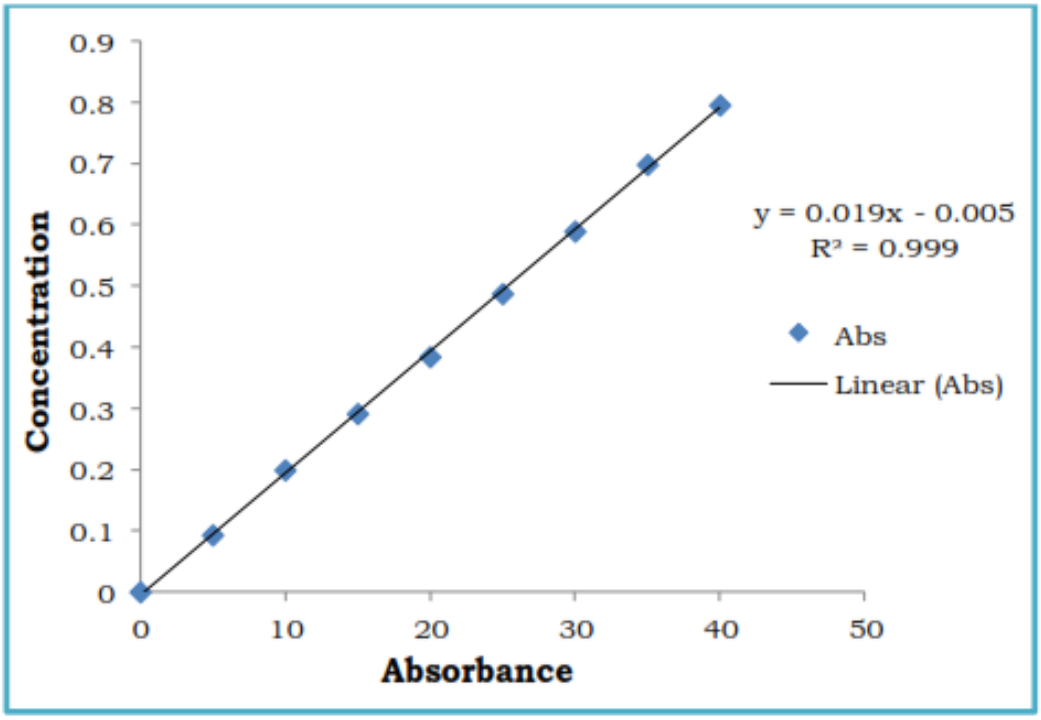



**Fig. 5.2: Standard graph of Esomeprazole pH 6.8 phosphate** ($PO_4$) **buffer**

### 5.1.1 Compatibility evaluation of Excipient and the Drugs:

#### 5.1.1.1 Infrared Fourier Transform Spectroscopy (FTIR):

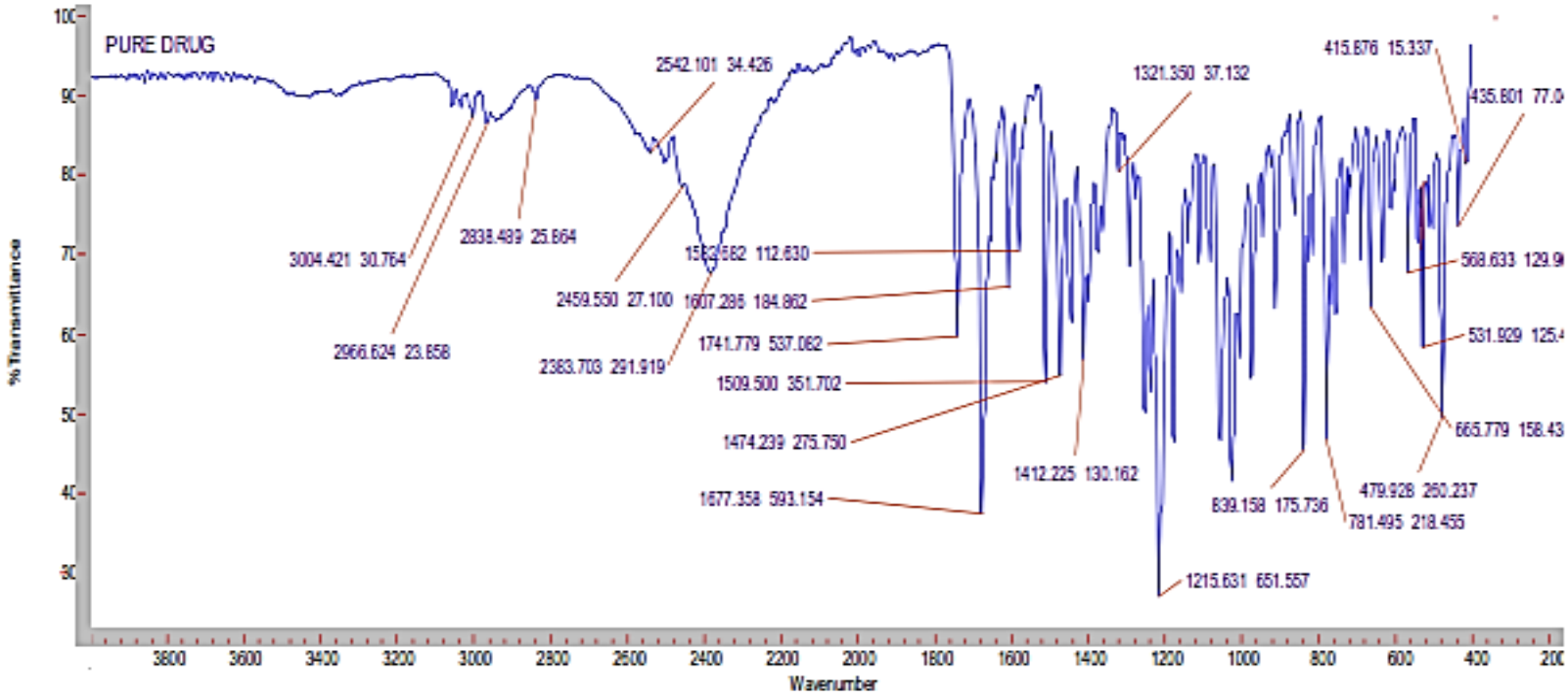



**Fig. 5.3: FTIR range (spectrum) Esomeprazol pure drug.**

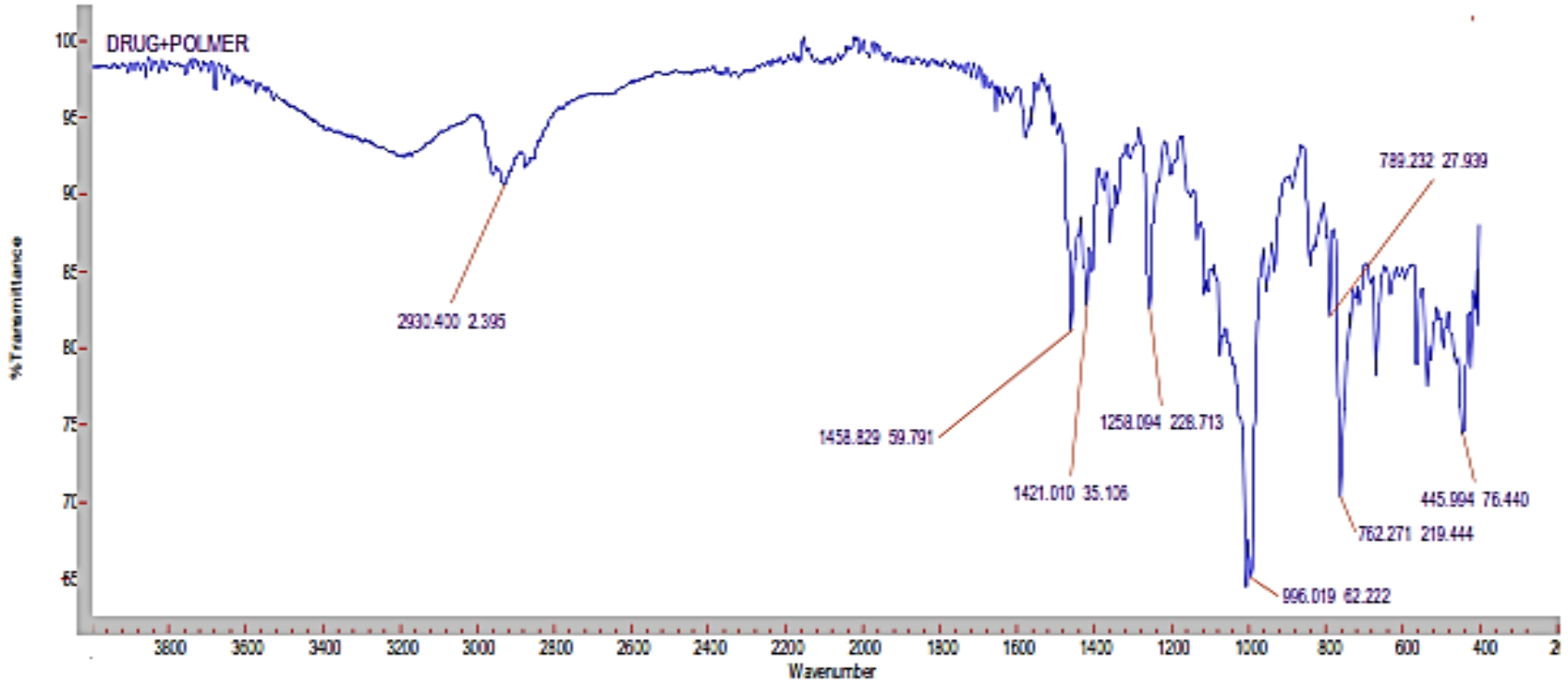



**Fig. 5.3: FTIR range (sepectrum) Esomeprazole + Eudragit® RS PO**

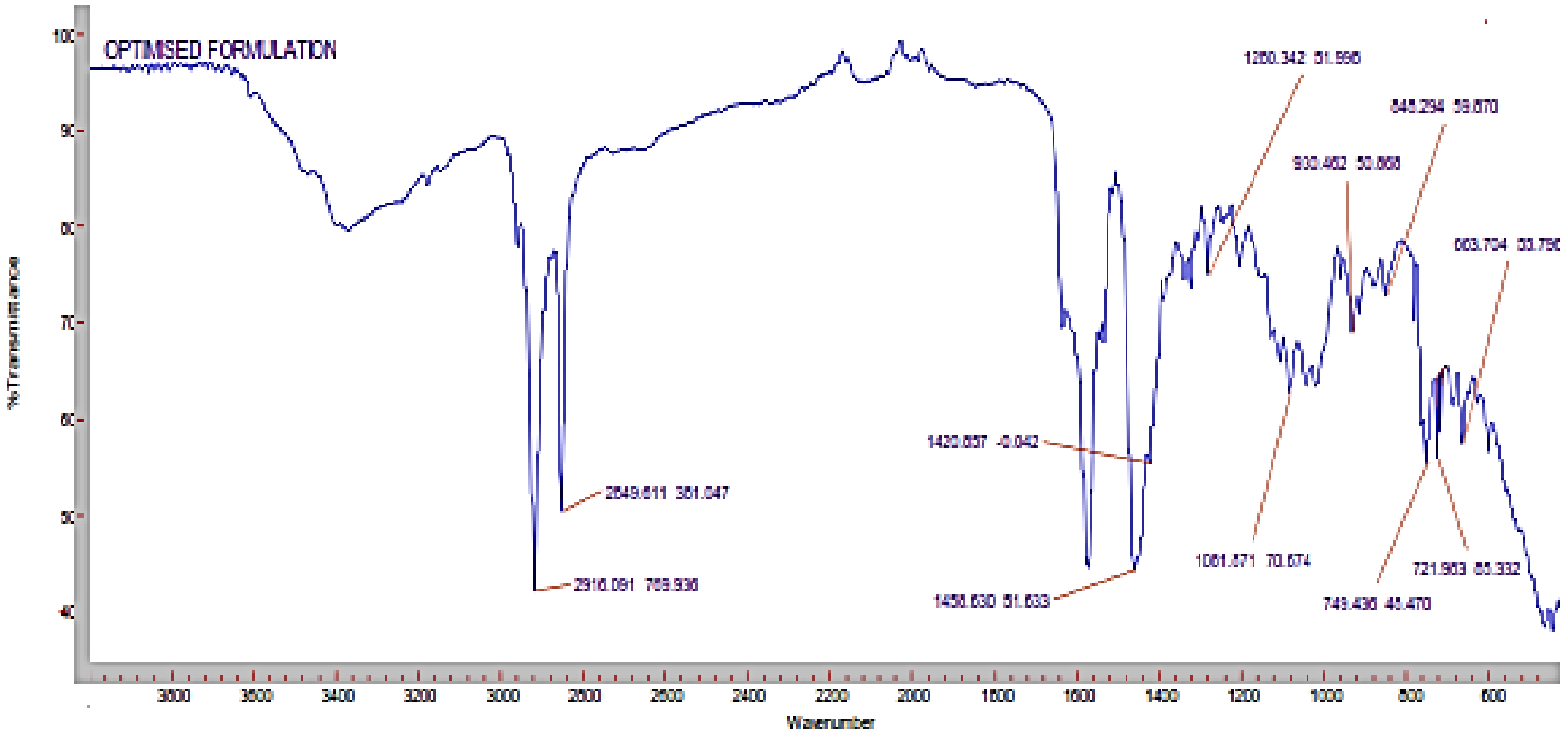



**Fig. 5.5: FTIR range (sepectrum) Esomeprazole optimized tablet formulation**

| S.NO | Wave number in formulation ($cm^{-1}$) | | | Characteristic Wave number range ($cm^{-1}$) | Bond nature and bond attributed |
|---|---|---|---|---|---|
| | Esomeprazole | Esomeprazole + Eudragit RSPO | Optimized formulation | | |
| 1 | 2966.624 | 2930.400 | 2916.091 | 3400-2400 | O-H stretching Carboxylic acid |
| 2 | 1509.500 | 1458.829 | 1458.630 | 1600-1475 | -C=C- stretching aromatic |
| 3 | 1474.239 | 1458.829 | 1420.857 | 1500-1400 | C-C stretch in ring aromatics |
| 4 | 1215.631 | 1258.094 | 1280.342 | 1350-1000 | C-N stretch amines |
| 5 | 781.495 | 762.271 | 749.436 | 910-665 | N-H $1^0$,$2^0$ amines |
| 6 | 839.158 | 789.232 | 848.294 | 900-690 | C-H out-of-plane bend aromatics |

**Table 5.3: FT-IR Data Interpretation for Esomeprazole**

### 5.1.1.2 Drug compatibility testing using polymers:

#### 5.1.1.2.1 FTIR (Fourier transform infrared) spectroscopy:

Choosing the right excipients is critical to a successful formulation. It is now in its physical condition, Esomeprazole. Eudragit® RS PO, Esomeprazole in its pure form, and Esomeprazole in polymers for the occurrence of esomeprazole Researchers used FTIR analysis to establish compatibility between Eudragit® RS PO (Eudragit®), Talc, Mg.Stearate, and Di.Calcium Phosphate and Esomeprazole (Esomeprazole). Figures 5.3, 5.4, 5.5, and Table.5.3 show the results in IR spectra.

The drug's physicochemical interaction into polymer was assessed utilizing FTIR measurements. Esomeprazole's Peaks were identified by infrared

spectral analysis wavelength range 2966.624 (O-H [stretching - carboxylic acid]), 1509.500 (-C=C- stretching aromatic), 1474.239 (C-C stretch in ring aromatics), 1215.631 (C-N stretch amines), 781.495 (N-H 10, 20 amines), and 839.158 (C-H out-of-plane bend aromatics), confirming its purity.

The drug Esomeprazole+ Eudra git RS PO had peaks at wave numbers, as indicated by an IR spectral analysis 2930.400 (O-H [stretching-carboxylic acid]), 1458.829 (-C=C- stretching aromatics), 1258.094 (C-N stretch amines), 762.271 (N-H 10, 20 amines), and 789.232 (C-H out-of-plane bend aromatics), confirming the drug's purity.

O-H [stretching-carboxylic] acid, 1458.630 (-C=C stretching aromatic), 1420.857 (C-C stretching ring aromatics), 1280.342 (C-N stretch amines), 749.436 (N-H 10, 20 amines) and 848.294 were observed in physical mixing for [Esomeprazole] with various excipients like polyethylene glycol (PEG) (C-H out-of-plane bend aromatics). Polymers were identified as a factor in absorption of additional peaks in substantial mixtures, it has find that Esomeprazole did not interact with various other polymers.

### 5.1.2 Calorimetry via Differential Scanning:

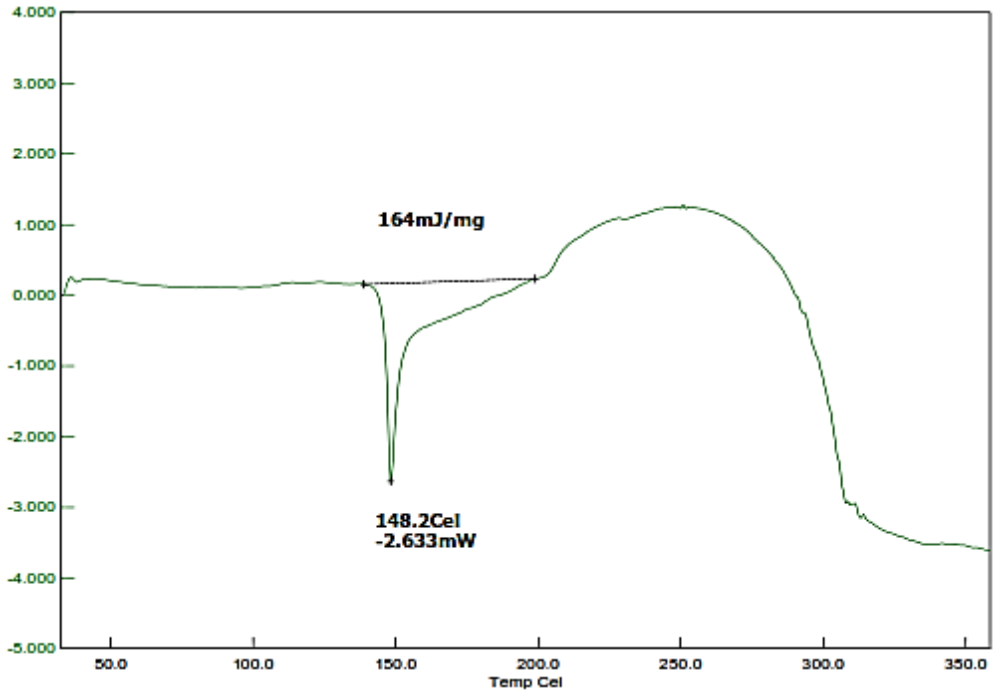



**Fig. 5.6: Differential Scanning Calorimetry analysis of Esomeprazole.**

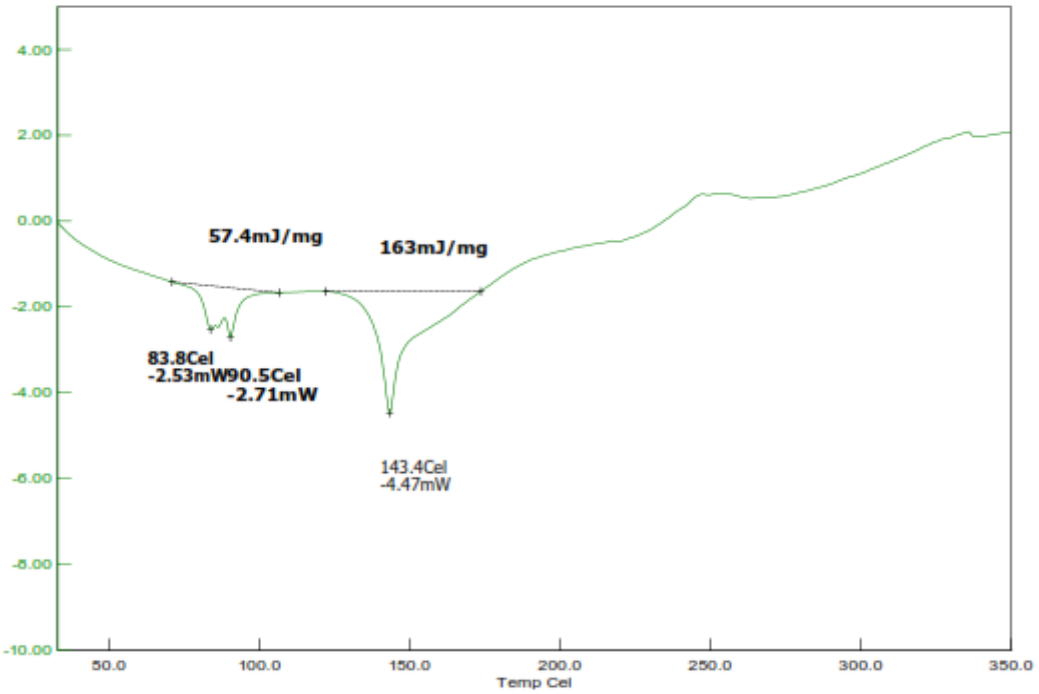



**Fig. 5.7: Differential Scanning Calorimetry analysis of Esomeprazole + Eudragit® RS PO**

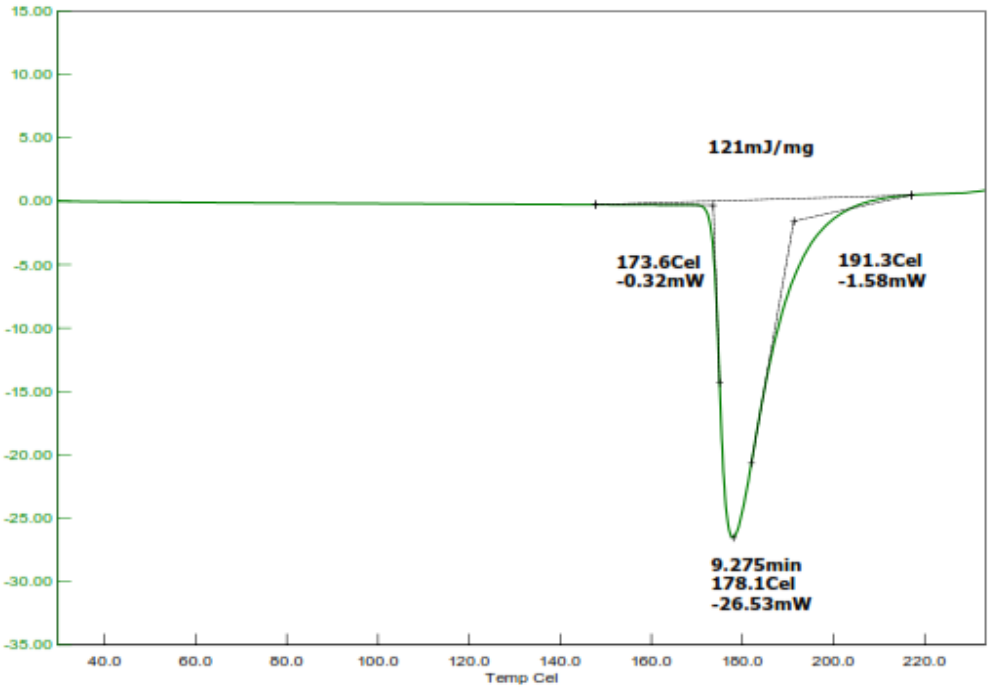



**Fig. 5.8: Differential Scanning Calorimetry analysis of Esomeprazole optimized tablet formulation**

| S.No | Name of ingredients and physical mixtures used in formulation | Temperature at which peak obtained |
|---|---|---|
| 1. | Esomeprazole | 148.2°C |
| 2. | Esomeprazole + Eudragit RSPO | 143.4°C |
| 3. | Esomeprazole + Eudragit RSPO + Talc + Mg.Stearate + Di.Calcium Phosphate | 178.1°C |

**Table 5.4: Data of DSC thermogram parameters for Esomeprazole**

• DSC was used to investigate the mutual compatibility and interactions of two medications and polymers. Figures 5.6; 5.7; 5.8; and Table 5.4 show the achievements of study, respectively. While the DSC thermograph represent that Esomeprazole had a heating point of 148.2°C, mixing Esomeprazole with Eudra-git [RS PO] yielded heating points ranging from 83.8°C to 143.4°C, and mixing Esomeprazole with Eudra-git [RS PO], Talc,

Mg.Stearate, and [Di-Calcium Phosphate] yielded heating ranging from towering of 173.6°C to a short The endothermic energy for Esomeprazole was -2.633 mW, while the endothermic energies for mixtures for Esomeprazole plus Eudra-git [RS PO] and Esomeprazole plus Eudra-git [RS PO] Plus [Talc] Plus Mg.Stearate Plus [Di-Calcium Phosphate] plus Eudra-git [RS PO] were -4.47 mW and -26.53 mW, correspondingly. The Compatibility between Esomeprazole and polymers in enhanced formulation was tested utilizing DSC analysis. Esomeprazole's heating point was not significantly different when it has blended with other polymers of optimal formulation, as per the outcomes in studies.

### 5.1.3 RESEARCHES INTO FORMULATES:

#### 5.1.3.1 Evaluation of the physicochemical properties of Esomeprazole (matrix type) Tablets - Control Release in-vitro: (Mean + SD) (n=3)

Blending parameters for tablets dust were varied. This highlights that dust has good flowability, All formulations were found to have a bulk density that was between 0.48 ± 0.07 and 0.56 ± 0.02 gm/cm 3 Repose - Angle ()*. This highlights that dust has fine flow properties, as tap (vol) The density was established as being between 0.52 ± 0.05 and 0.63 ± 0.04 for entire formulations. An outstanding flowability is indicated from Hausner’s (tapped vs bulk) ratio for between 0.94 ± 0.06 and 1.14 ± 0.08. The [Carr's] index values ranged from 11.14 ± 0.05 to 16.98 ± 0.08 of all formulations. All formulations, Repose - Angle were find to range between 23°.36' ± 0.36 and 27°.79' ± 0.79. This clear from these numbers that dust blend has excellent flow properties.

| Formulation Code | Bulk density (gm/cm3)* | Tapped density (gm/cm3)* | Hausner ratio (HR)* | Carr's index (CI)* | Angle of repose (θ)* |
|---|---|---|---|---|---|
| F1 | 0.51±0.02 | 0.53±0.03 | 0.98±0.05 | 15.96±0.08 | 24°.13'±0.64 |
| F2 | 0.50±0.03 | 0.54±0.06 | 1.03±0.06 | 16.18±0.04 | 23°.36'±0.36 |
| F3 | 0.49±0.09 | 0.57±0.04 | 1.08±0.09 | 14.68±0.07 | 24°.69'±0.62 |
| F4 | 0.52±0.07 | 0.53±0.06 | 1.01±0.03 | 16.59±0.09 | 25°.26'±0.71 |
| F5 | 0.53±0.07 | 0.58±0.05 | 1.1±0.07 | 15.84±0.06 | 24°.98'±0.58 |
| F6 | 0.54±0.02 | 0.55±0.08 | 1.10±0.08 | 14.98±0.02 | 24°.12'±0.54 |
| F7 | 0.55±0.08 | 0.58±0.03 | 0.94±0.06 | 15.98±0.04 | 23°.86'±0.87 |
| F8 | 0.56±0.02 | 0.63±0.04 | 1.14±0.08 | 14.84±0.03 | 25°.02'±0.22 |
| F9 | 0.54±0.03 | 0.53±0.04 | 1.09±0.03 | 16.98±0.08 | 24°.98'±0.35 |
| F10 | 0.49±0.01 | 0.53±0.09 | 0.98±0.07 | 13.98±0.03 | 25°.64'±0.63 |
| F11 | 0.48±0.07 | 0.52±0.05 | 1.11±0.04 | 14.54±0.06 | 27°.79'±0.79 |
| F12 | 0.50±0.02 | 0.54±0.03 | 1.12±0.06 | 15.34±0.03 | 26°.98'±0.25 |
| F13 | 0.49±0.03 | 0.61±0.07 | 1.1±0.05 | 13.52±0.02 | 24°.63'±0.11 |
| F14 | 0.47±0.08 | 0.57±0.02 | 0.99±0.03 | 12.34±0.05 | 26°.35'±0.73 |
| F15 | 0.51±0.07 | 0.59±0.04 | 1.12±0.07 | 14.63±0.02 | 27°.19'±0.59 |
| F16 | 0.50±0.05 | 0.56±0.06 | 1.14±0.06 | 11.14±0.05 | 25°.23'±0.34 |
| F17 | 0.49±0.01 | 0.59±0.09 | 1.12±0.08 | 12.34±0.03 | 26°.55'±0.27 |
| F18 | 0.50±0.06 | 0.58±0.04 | 1.11±0.06 | 13.43±0.06 | 24°.99'±0.13 |
| F19 | 0.49±0.03 | 0.55±0.07 | 0.99±0.02 | 12.39±0.01 | 25°.45'±0.45 |

**Table 5.5: Flow properties of powder blend for Esomeprazole**

**5.1.3.2 Esomeprazole (matrix type) Tablets - Control Release were evaluated in-vitro for their post-compression properties:**

## Results and Discussion

**Table 5.6: Physico Chemical Characterization of Esomeprazole Controlled Release Tablets**

| Formulation Code | Weight variation(mg) | Hardness (kg/cm²) | Friability (%) | Thickness (mm) | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 100±0.48 | 4.5±0.41 | 0.50±0.13 | 3.8±0.29 | 99.17±0.73 |
| F2 | 101.4±0.86 | 4.1±0.23 | 0.59±0.48 | 4.1±0.24 | 98.96±0.36 |
| F3 | 99.1±0.86 | 3.9±0.16 | 0.61±0.29 | 3.4±0.14 | 99.74±0.64 |
| F4 | 101.6±0.86 | 3.5±0.39 | 0.75±0.66 | 4.9±0.57 | 98.96±0.11 |
| F5 | 98.9±0.11 | 4.2±0.22 | 0.56±0.25 | 3.9±0.35 | 99.59±0.35 |
| F6 | 99.8±0.32 | 4.4±0.56 | 0.65±0.18 | 4.1±0.23 | 99.87±0.13 |
| F7 | 98.4±0.53 | 3.8±0.12 | 0.59±0.74 | 3.4±0.24 | 98.85±0.37 |
| F8 | 101.3±0.42 | 3.3±0.11 | 0.49±0.33 | 3.3±0.61 | 99.36±0.31 |
| F9 | 99.1±0.44 | 3.8±0.37 | 0.57±0.37 | 3.5±0.27 | 99.61±0.44 |
| F10 | 101±0.52 | 3.7±0.25 | 0.64±0.42 | 3.9±0.65 | 98.67±0.76 |
| F11 | 99.2±0.43 | 4.2±0.62 | 0.59±0.52 | 4.2±0.45 | 99.56±0.52 |
| F12 | 99.5±0.72 | 3.9±0.53 | 0.67±0.76 | 3.8±0.17 | 98.59±0.25 |
| F13 | 101.2±0.21 | 3.7±0.18 | 0.64±0.17 | 4.7±0.89 | 99.62±0.29 |
| F14 | 98.8±0.82 | 4.1±0.52 | 0.59±0.44 | 3.6±0.42 | 99.42±0.27 |
| F15 | 101.2±0.23 | 3.9±0.47 | 0.66±0.52 | 4.2±0.59 | 98.95±0.26 |
| F16 | 99.1±0.71 | 4.2±0.24 | 0.65±0.46 | 3.7±0.62 | 99.46±0.52 |
| F17 | 101.5±0.65 | 3.8±0.43 | 0.56±0.52 | 3.8±0.55 | 99.59±0.56 |
| F18 | 99.5±0.65 | 3.9±0.53 | 0.59±0.19 | 3.7±0.74 | 99.68±0.96 |
| F19 | 100.3±0.89 | 4.1±0.71 | 0.57±0.34 | 3.9±0.28 | 98.97±0.35 |

**Table 5.6: Physico Chemical Characterization of Esomeprazole Control led Released Tablets**

### 5.1.3.3 Esomeprazole Control led Released Tablet Evaluation:

#### 5.1.3.3.1 Appearances:

The tablets were examined in a visual manner and confirmed to devoid of flaws like topping, cracking, or lamination.

### 5.1.3.3.2 Dimensions:

Esomeprazole control ( drugs' discharge tablets from ([F1] to [F19]) were experienced for heaviness variation, stiffness, friability, depth, & drug content, and the achievement in compositions (F1 to F19) were find in limits set out to formal texts.

### 5.1.3.3.3 Weight fluctuation:

When a group of tablets was examined, the weigh change and percentage deviation for each tablet was recorded. Assuming regular weight between 98.0 ± 0.533 and 100.0 ± 0.686, the maximum allowable percentage is 7.5%. (greater than 80mg but a lesser amount of than 250mg). The weights for tablet met pharmacopeial requirements.

### 5.1.3.3.4 Tablet Durability:

The hardness of three tablets from each batch was determined by Monsanto's hardness tester. The results indicated stiffness for tablets range in 3.3 ± 0.11 and 4.5 ± 0.41kg/cm2.

This implies that the medicine is sufficiently strong.

This implies that the tablet is sufficiently strong.

### 5.1.3.3.5 % Friability:

It was determined that all formulations were within the range 0.49 ± 0.33 and 0.75 ± 0.66 percent friable. This indicates that the CR tablet that has created was simple to use.

### 5.1.3.3.6 Dimensions (Dimensions) (Diameter x Thickness):

Each product can have its own depth & span specifications. Packaging and consumer acceptance could be affected if a broad variety for tablet depth & span available. The diameter and thickness ranged from 3.3 ± 0.61 to 4.9 ± 0.57 mm for tablets for entire formulations.

### 5.1.3.3.7 Composition of the drug:

The lively component level It was determined that the formulation should be between 98.59 ± 0.25 and 99.74 ± 0.64 percent w/w, that into IP-specified range (90-110 percent w/w).

It was determined that weight fluctuation, friability, stiffness, thickness, and drug content were in acceptable ranges.

## Results and Discussion

### 5.1.4 ESOMEPRAZOLE (MATRIX TYPE) TABLETS - CONTROL RELEASE DISSOLUTION IN-VITRO METHOD STUDIES:

**Table 5.7: *In-Vitro* drug release studies of Esomeprazole Controlled Release tablets (F1-F7)**

| Time (hours) | CUMULATIVE % DRUG RELEASE | | | | | | |
|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 6.98±0.74 | 6.42±0.59 | 7.08±0.45 | 7.35±0.76 | 15.55±0.35 | 6.42±0.64 | 14.21±0.69 |
| 2 | 7.86±0.36 | 8.52±0.65 | 18.73±0.87 | 14.39±0.57 | 19.94±0.47 | 12.59±0.43 | 19.65±0.76 |
| 4 | 14.65±0.83 | 13.26±0.43 | 27.74±0.23 | 19.22±0.46 | 28.33±0.54 | 24.26±0.94 | 24.98±0.97 |
| 6 | 18.64±0.52 | 22.73±0.93 | 39.11±0.72 | 24.21±0.95 | 35.29±0.72 | 38.12±0.67 | 28.76±0.24 |
| 8 | 23.36±0.19 | 33.79±0.34 | 47.44±0.37 | 31.42±0.21 | 40.11±0.46 | 49.94±0.43 | 35.34±0.76 |
| 10 | 29.82±0.23 | 41.21±0.87 | 58.35±0.92 | 39.73±0.36 | 48.87±0.25 | 57.15±0.79 | 44.50±0.53 |
| 12 | 34.61±0.78 | 50.22±0.54 | 63.53±0.63 | 51.29±0.28 | 55.83±0.92 | 69.93±0.64 | 54.56±0.94 |
| 14 | 43.07±0.92 | 57.33±0.11 | 69.89±0.56 | 60.11±0.72 | 61.12±0.29 | 75.66±0.92 | 61.05±0.58 |
| 16 | 48.71±0.45 | 68.03±0.45 | 74.29±0.43 | 72.14±0.93 | 69.76±0.62 | 81.78±0.52 | 64.98±0.86 |
| 18 | 57.22±0.69 | 74.39±0.37 | 79.01±0.96 | 78.77±0.38 | 73.58±0.91 | 85.19±0.74 | 72.03±0.75 |
| 20 | 68.35±0.43 | 76.15±0.92 | 81.43±0.53 | 83.64±0.67 | 79.56±0.68 | 91.26±0.59 | 76.92±0.68 |
| 22 | 77.23±0.34 | 81.12±0.54 | 83.36±0.68 | 86.89±0.46 | 85.32±0.75 | 94.18±0.86 | 85.88±0.93 |
| 24 | 86.77±0.28 | 88.27±0.45 | 90.67±0.96 | 91.03±0.25 | 91.93±0.54 | 97.47±0.97 | 91.12±0.78 |

## Results and Discussion

**Table 5.8: *In-Vitro* drug release studies of Esomeprazole Controlled Release tablets (F8-F14)**

| Time (hours) | CUMULATIVE % DRUG RELEASE | | | | | | |
|---|---|---|---|---|---|---|---|
| | F8 | F9 | F10 | F11 | F12 | F13 | F14 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 10.53±0.81 | 10.11±0.67 | 8.25±0.34 | 7.52±0.36 | 7.82±0.46 | 8.15±0.73 | 7.63±0.48 |
| 2 | 19.29±0.52 | 16.74±0.73 | 11.72±0.73 | 10.16±0.73 | 10.26±0.82 | 10.61±0.62 | 9.53±0.63 |
| 4 | 29.21±0.98 | 28.37±0.22 | 18.53±0.62 | 16.56±0.51 | 17.28±0.53 | 13.72±0.81 | 16.55±0.41 |
| 6 | 36.36±0.64 | 33.44±0.87 | 25.43±0.73 | 21.62±0.98 | 24.37±0.69 | 19.28±0.63 | 20.36±0.87 |
| 8 | 41.39±0.76 | 43.45±0.53 | 33.72±0.83 | 26.22±0.42 | 35.28±0.23 | 24.11±0.92 | 26.25±0.59 |
| 10 | 49.62±0.52 | 49.34±0.82 | 42.13±0.54 | 34.75±0.61 | 44.71±0.58 | 30.79±0.67 | 31.82±0.98 |
| 12 | 58.01±0.97 | 58.11±0.98 | 54.46±0.98 | 40.17±0.49 | 53.19±0.82 | 35.27±0.85 | 36.29±0.72 |
| 14 | 65.47±0.42 | 66.94±0.43 | 63.29±0.46 | 44.34±0.76 | 61.67±0.93 | 46.09±0.98 | 48.26±0.63 |
| 16 | 73.55±0.55 | 69.38±0.32 | 75.67±0.75 | 49.25±0.21 | 73.98±0.34 | 49.27±0.43 | 48.71±0.42 |
| 18 | 77.48±0.64 | 74.14±0.82 | 83.24±0.37 | 56.71±0.73 | 80.32±0.86 | 58.99±0.81 | 57.22±0.65 |
| 20 | 80.35±0.98 | 79.76±0.63 | 87.52±0.83 | 67.23±0.64 | 84.41±0.91 | 66.45±0.79 | 69.47±0.53 |
| 22 | 84.66±0.33 | 84.88±0.58 | 91.79±0.65 | 78.76±0.82 | 88.27±0.38 | 74.32±0.66 | 78.83±0.66 |
| 24 | 90.87±0.84 | 89.98±0.97 | 93.82±0.24 | 88.29±0.34 | 92.61±0.65 | 89.13±0.43 | 90.77±0.98 |

**Table 5.9: *In-Vitro* drug release studies of Esomeprazole Controlled Release tablets (F15-F19)**

| Time (hours) | CUMULATIVE % DRUG RELEASE | | | | |
|---|---|---|---|---|---|
| | F15 | F16 | F17 | F18 | F19 |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 9.25±0.53 | 5.99±0.46 | 7.78±0.63 | 7.45±0.41 | 8.87±0.35 |
| 2 | 15.53±0.41 | 9.93±0.83 | 10.72±0.76 | 9.98±0.76 | 10.49±0.26 |
| 4 | 20.35±0.74 | 13.27±0.32 | 19.81±0.82 | 15.62±0.59 | 19.36±0.18 |
| 6 | 22.83±0.92 | 19.29±0.57 | 27.79±0.85 | 19.34±0.22 | 26.87±0.63 |
| 8 | 29.31±0.46 | 24.93±0.85 | 34.65±0.61 | 25.87±0.27 | 34.23±0.24 |
| 10 | 38.79±0.67 | 30.26±0.92 | 45.87±0.23 | 30.68±0.43 | 41.19±0.76 |
| 12 | 49.93±0.82 | 37.37±0.24 | 54.46±0.53 | 36.92±0.12 | 53.55±0.55 |
| 14 | 58.37±0.53 | 45.25±0.52 | 62.76±0.38 | 44.26±0.26 | 62.87±0.38 |
| 16 | 70.83±0.54 | 49.82±0.43 | 74.16±0.45 | 49.98±0.55 | 73.82±0.62 |
| 18 | 79.98±0.45 | 58.92±0.72 | 81.34±0.68 | 58.45±0.87 | 81.19±0.74 |
| 20 | 84.35±0.34 | 69.29±0.89 | 85.11±0.75 | 69.87±0.55 | 84.52±0.43 |
| 22 | 88.26±0.78 | 78.47±0.49 | 89.67±0.57 | 78.92±0.64 | 88.44±0.14 |
| 24 | 92.47±0.33 | 87.93±0.45 | 91.43±0.28 | 89.79±0.74 | 92.12±0.25 |

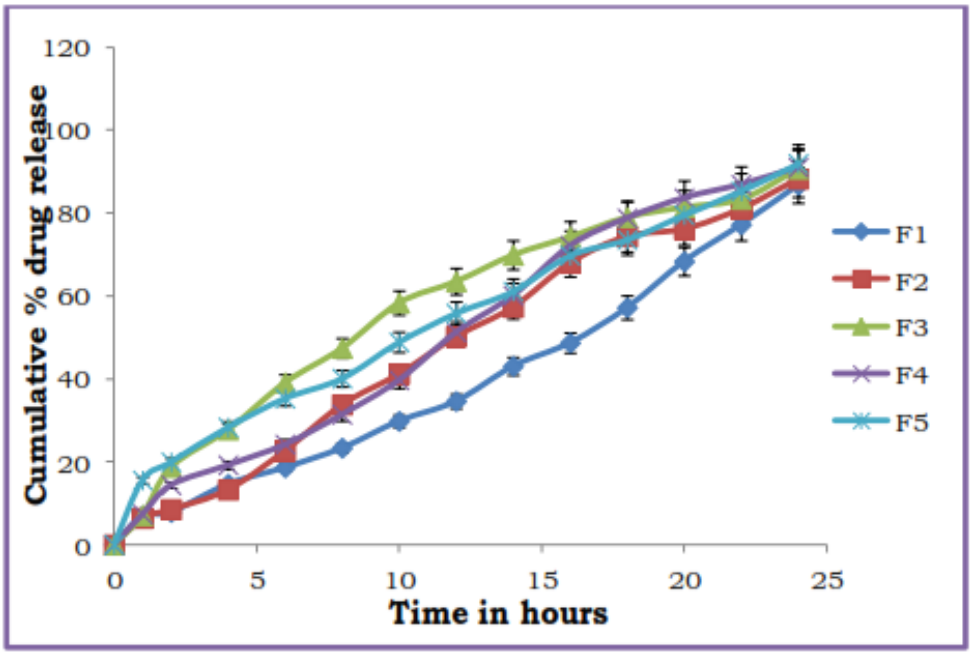



**Fig. 5.9: Dissolution graphs for the formulations F1 to F5**

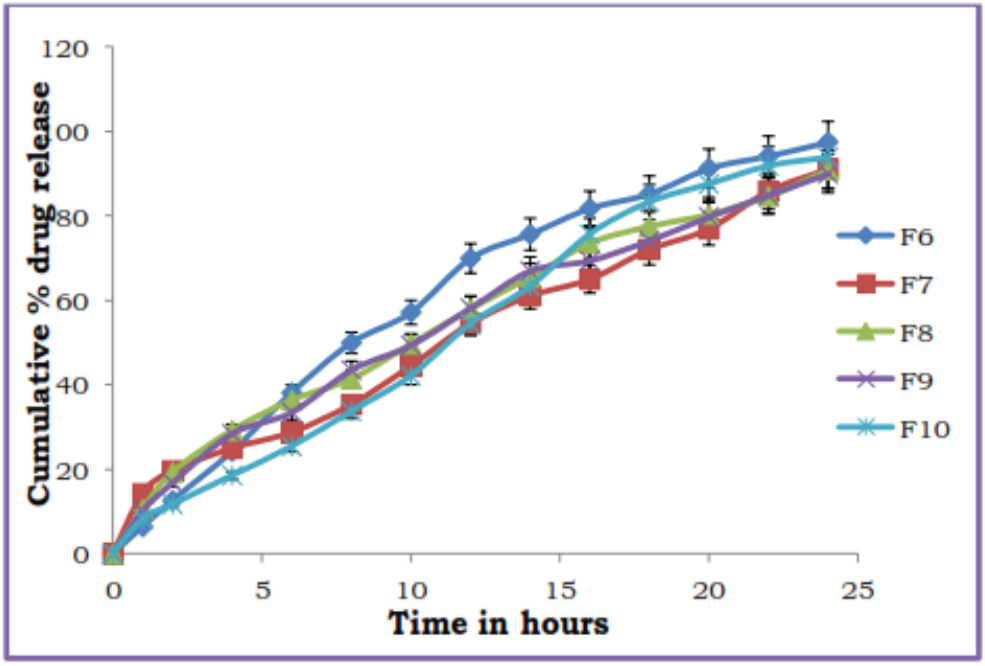



**Fig. 5.10: Dissolution graphs for the formulations F6 to F10**

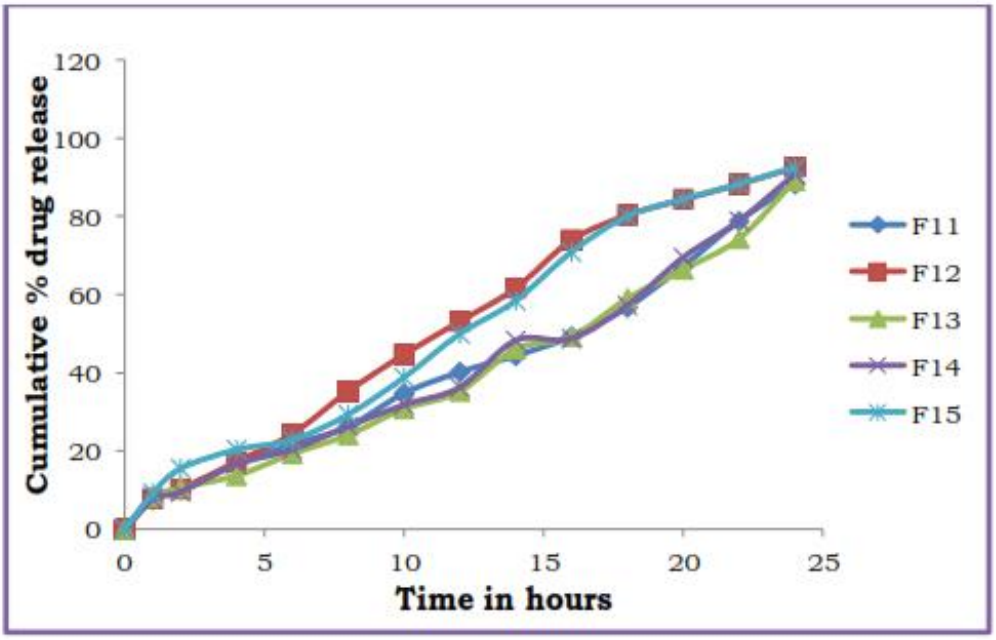



**Fig. 5.11: Dissolution graphs for the formulations F11 to F15**

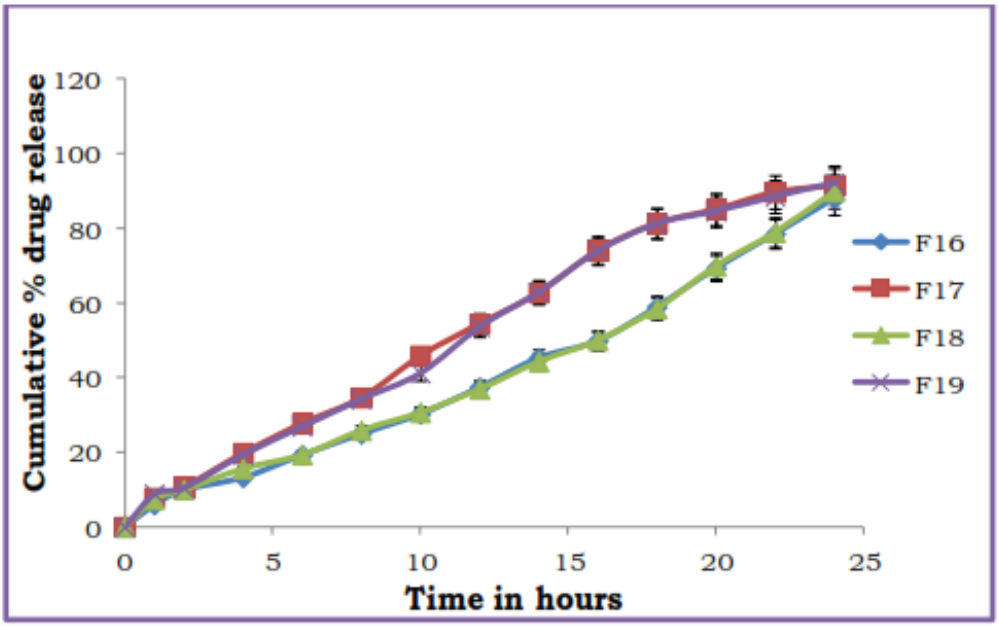



**Fig. 5.12: Dissolution graphs for the formulations F16 to F19**

## Results and Discussion

### 5.1.4.1 Esomeprazole at [in-vitro] drugs' release studies:

There viz. were four [04] different type method utilizing for testing the dissolving the Esomeprazole fabricated CR tablets that were manufactured: acidic buffers (pH-1.2), acidic buffers (pH-4.5), acetate with reagent buffer (pH-4.5), and 6.8 with pH (phosphate ($PO_4$)) buffer. Various time duration sought and utilized at determining the % drugs' release. Table 5.7 - 5.9 and Graph 5.9 - 5.12 summarise the research finding.

Esomeprazole fabricated tablets be made utilising a viz. good variety in polymers, like Eudragit® [S100], L-100, RS PO, RS 100, RL100, RL PO, magnesium (salt) stearate, and of Di salt of Calcium ion Phosphate as diluents, via the Direct (dry) compression process.

F1 and F2 formulations contain Eudragit®-S100. After 24 (twenty four) hrs in testing two, F-1 and F-2 formulations displayed percentage release (cumulative) of (molecule) drug as 86.77 ± 0.28 percent and 88.27 ± 0.45 percent, respectively. F-3 and F-4 formulations contain Eudragit®-L100. At the end of the 24th hour, formulations F-3, F-4 demonstrated a drugs' release ranged 90.67 ± 0.96 percent and 91.03 ± dev. 0.25 percent, respectively.

F-5 and F-6 formulations incorporating Eudragit®-RS PO. At the conclusion, $24^{th}$ hour, formulations F-5, F-6 demonstrated a drugs' release ranged 91.93 ± 0.54 percent and 97.47 ± 0.97 percent, respectively. Combining Eudragit®-S100 along with Eudragit®-L100 in formulation F7.

The end conclusion, $24^{th}$ hour, Formulation F7 demonstrated a 91.12 ± 0.78% drugs' release. Eudragit®-S100-containing formulation F8. At end conclusion $24^{th}$ hour, Formulation F8 demonstrated a 90.87 ± 0.84 percent drugs' release.

## Results and Discussion

Combination along Eudragit®-L100 with Eudragit®-RS PO in formulation F9. The conclusion of 24$^{th}$ hour, Formulation F9 demonstrated an 89.98 ± 0.97 percent drugs' release.

Eudragit®-RS 100 is presentwith formulation F10. At ending with 24$^{th}$ hour, Formulation F10 had drugs' cumm. release amt. of 93.82 ± 0.24%. Eudragit®-RS [100] and Eudragit®– RL [100] are mixed well in formulation labeled as F11. Towards culminating 24$^{th}$ hour interval, Formulation labeled as F11 has display release as 88.29 ± 0.34% drugs' release. Eudragit®– [RL 100] containing formulations F-12 and F-13. Towards ending the 24$^{th}$ hourly interval, two formulations F-12 and F-13 established a drugs' releasing 92.61 ± 0.65% and 89.13 ± 0.43%, respectively.

F14 and F15 formulations contain Eudragit®-RS 100. Ending the 24$^{th}$ hour, formulations F14, F15 demonstrated a 90.77 ± 0.98 percent and 92.47 ± 0.33 percent drugs' release, respectively. Combining Eudragit®- [RS 100] along Eudragit®- RL100 in formulation F-16. At the conclusion i.e 24$^{th}$ hour, Formulation F-16 demonstrated an 87.93 ± 0.45 percent drugs' release. Eudragit®- [RL100] presnt with formulation F-17. End conclusion of hour 24, Formulation F-17 demonstrated a drugs' releaseing 91.43 ± 0.28 percent.

F-18 and F-19 formulations comprise with mix, Eudragit®-RL100 & Eudragit®-RL PO. Formulations F-18, F-19 demonstrated medicine release rating of 89.79 ± 0.74 percent and 92.12 ± 0.25%, respectively, later 24$^{th}$ hour.

Controlled Esomeprazole release observed with literally every formulation, with formulation F-6 showing peak high cumulative percent drugs' release, 97.47 ± 0.97 culminating ending 24$^{th}$ hour, as plan with final formulation, even others not reaching upto time ending maximum release however, extending the release.

### 5.1.5 In-vitro comparison of Optimized Esomeprazole CR Formulation (F-6) with Innovator Product:

Table 5.10: Comparative *In-vitro* drug release studies of optimized formulation of Esomeprazole (F-6) with Innovator product

| Time (Mins) | F-6 | Innovator Product |
|---|---|---|
| 0 | 0 | 0 |
| 10 | --- | 38.25±0.78 |
| 20 | --- | 59.77±0.24 |
| 30 | --- | 76.86±0.18 |
| 45 | --- | 97.12±0.24 |
| 60 | 6.42±0.64 | |
| 120 | 12.59±0.43 | --- |
| 220 | 24.26±0.94 | --- |
| 340 | 38.12±0.67 | --- |
| 460 | 49.94±0.43 | --- |
| 580 | 57.15±0.79 | --- |
| 700 | 69.93±0.64 | --- |
| 820 | 75.66±0.92 | --- |
| 940 | 81.78±0.52 | --- |
| 1060 | 85.19±0.74 | --- |
| 1180 | 91.26±0.59 | --- |
| 1300 | 94.18±0.86 | --- |
| 1420 | 97.47±0.97 | --- |

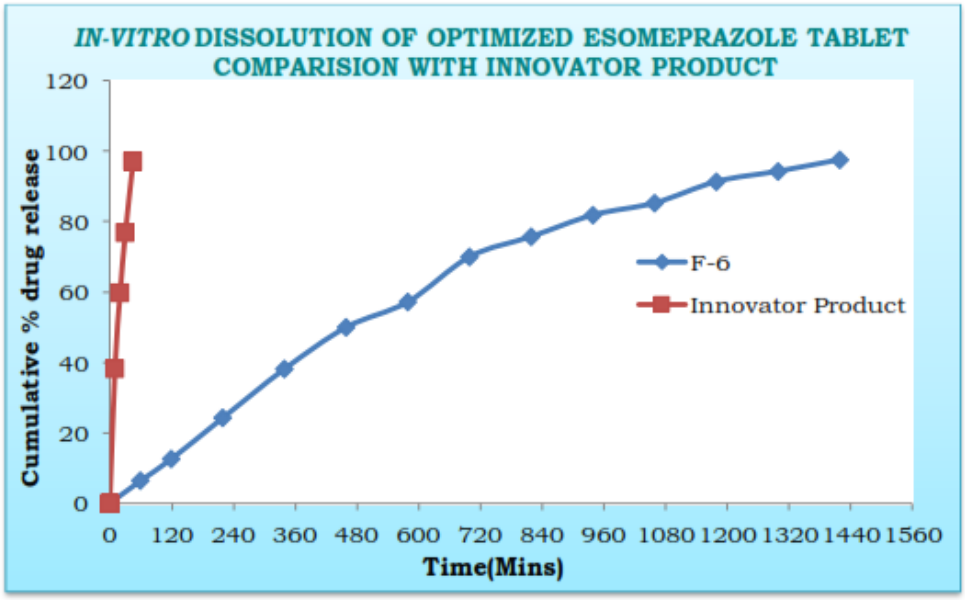



**Fig. 5.13: Comparative *In-vitro* drug release studies of optimized formulation of Esomeprazole (F-6) with Innovator product.**

**5.1.5.1 In-vitro Comparison exhibit, Esomeprazole Optimized Controlled (**medicament**) releasing formulation (F-6) with Innovator Product:**

Usual quick releaseing tablet (solid) dosage [unit] form with Esomeprazole at tab Nexium 20mg Tablets, established brand under selling of medication.

The peculiar formulation and specific ingredient in Esomeprazole (matrix type) Tablets - Control Release 20mg were optimised within purpose to increase the duration in medication release to 24$^{th}$ hour. Esomeprazole (matrix type) Tablets - Control Release 20mg in-vitro drugs' release evaluation and comparison within similar Innovators .product were performed.

Only about 97.12 ± 0.24 percent of medication in 20mg Nexium tablets ought to release after just 45 minutes, but with completed Control led Released Tablet

dose incorporating Drug - Polymer (Esomeprazole:Eudragit®-RS PO) at 1:2 ratios (F-6) was viz. released roughly 97.54 ± 7.97 % (percentage) drug at hour 24th. The best intuitive formulation established to be the one that showed zero-order / continuous drugs' release across desired time period.

In-vitro investigations displayed that in completed Control led Releasing Tablet dosage [unit] form has drugs' release time of up to 24 hours, while the commercial present Innovator produce had drugs' release duration of merely 45 minutes. Esomeprazole controlled - released tablets can delivered one each day, while innovator produce shall ggiven twice, (in 12 hr) per day, as results show.

### 5.1.6 The Usage of Release-Rate Kinetics to Analyze Dissolution Data:

The capacity of many models to appropriately explain kinetics governing release, (molecule) drug was essential thoroughly tested. For purpose of figuring out mechanism underlying kinetics governing release at (molecule) drug fro dosage [unit] form, data were fitted & release models such as zero- and first (1st) order, release with Higuchi and Korsmeyer-Peppas.

**Table 5.11: Esomeprazole Release Kinetic Parameters for Optimized Formulation**

| F. Code | Zero Order | First Order | Higuchi | Best fit | Korsmeyer-Peppas | | Release Mechanism |
|---|---|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | | $R^2$ | n-value | |
| F6 | 0.992 | 0.984 | 0.969 | Zero order | 0.991 | 0.951 | Non-Fickian (or) Anomalous Diffusion |

**Optimized Formulation (F-6) for Release Kinetics Graphs:**

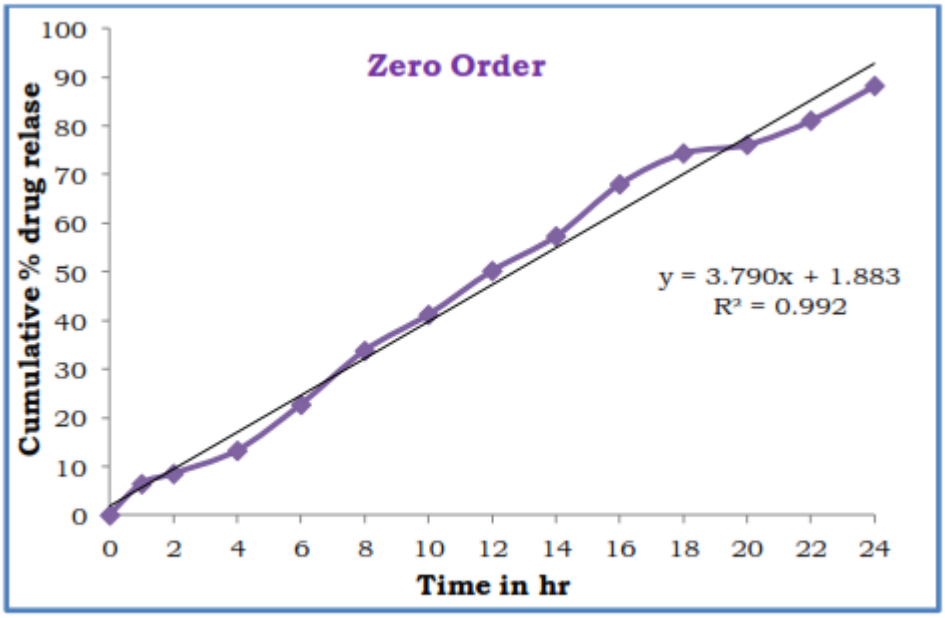



**Fig. 5.14: Zero order release kinetics of Esomeprazole optimized Formulation (F-6)**

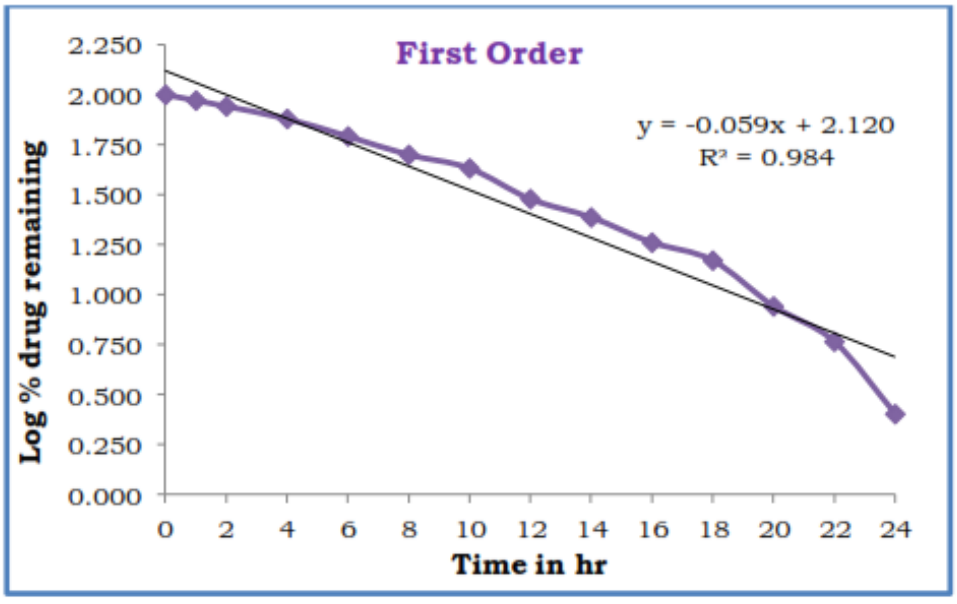



**Fig. 5.15: First order release kinetics of Esomeprazole optimized Formulation (F-6)**

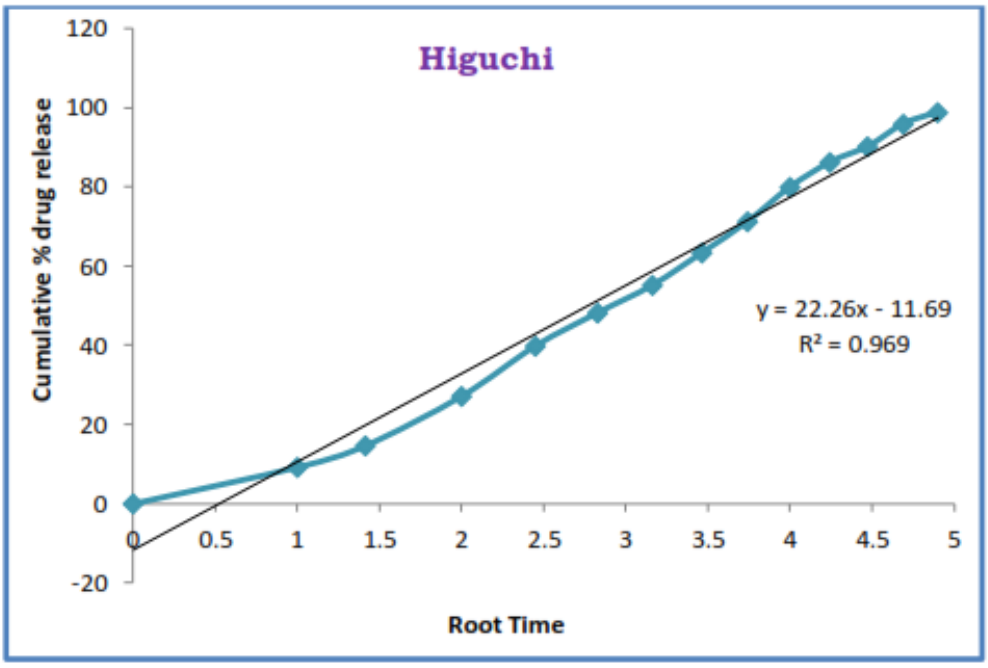



**Fig. 5.16: Higuchi model kinetics of Esomeprazole optimized Formulation (F-6)**

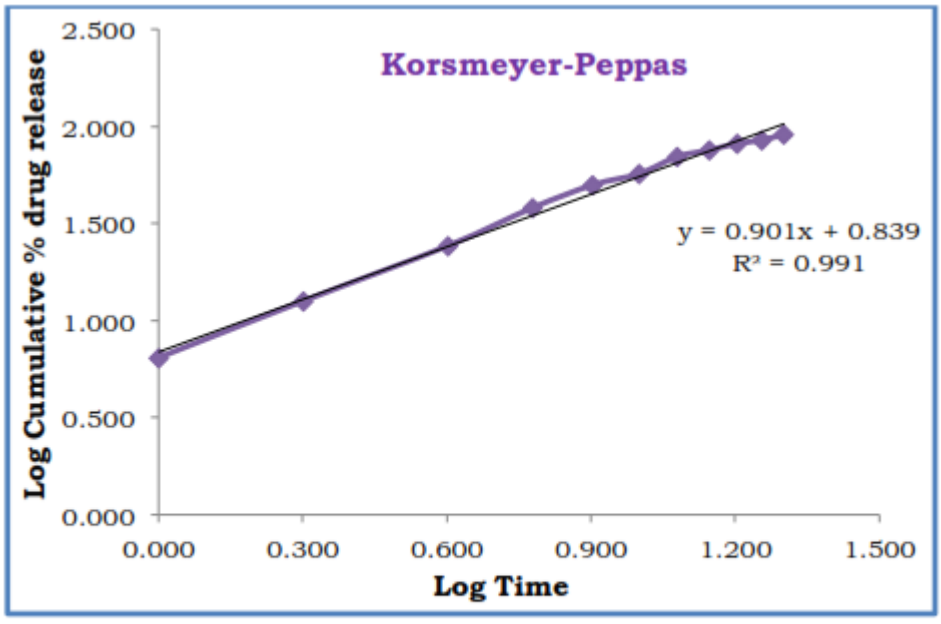



**Fig. 5.17: Korsmeyer-Peppas model kinetics of Esomeprazole optimized Formulation (F-6)**

### 5.1.7 Dissolution in-vitro method ‘Kinetics’ for Formulation Optimization:

Table.5.11 and Figure.5.14-5.17 summarise the findings that with dissolution in-vitro method kinetic viz. parameter computation at Esomeprazole with Control led Released Tablet. R2 value for zero-order drugs’ release dynamics was 0.992, and Non-Fickian (or) Anomalous Diffusion relates with proper mechanism (molecule) drugs’ release due with the ‘n’ value for Korsemeyer-Peppas being 0.95.

### 5.1.8 Stability Test & Studies on Formulation (Optimised) Esomeprazole:

With accordance, ICH guidelines, six (06) month of accelerated long stability trials carried for optimised formulation. Esomeprazole dissolution in-vitro method and weight with variation, thickness variation, hardness fluctuation, friability, drug content, in-vitro evaluation criteria have all been described. The findings are well summarised at Table 5.12. Before and after storage, there was no substantial segregation between metrics that were examined, and they found all within pharmacopoeia acceptable levels now. Tablets functioned well at 400C / 20C / 75% percent RH / 5%.

## Results and Discussion

### 5.1.8.1 Stability Test & Studies on Formulation (Improved), Esomeprazole (F-6):

The F-6 formulation ought examined for several physically attained properties upon storage; the findings are shown at Table 5.14.

**Table 5.12: Stability study of Optimized formulation (F-6) of Controlled release Esomeprazole tablets at Accelerated temperature $40^0$ C ± $2^0$ C / 75% RH ± 5%.**

| Parameter | Initial | Accelerated temperature ($40^0$ C ± $2^0$ C / 75% RH ± 5 % ) | | | |
|---|---|---|---|---|---|
| | | 1st Month | 2nd Month | 3rd Month | 6th Month |
| **Weight variation (mg)** | 99.8± 0.32 | 99.1± 0.43 | 98.9± 0.21 | 99.2± 0.48 | 99.5± 0.27 |
| **Thickness (mm)** | 4.1±0.23 | 4.1±0.25 | 3.9±0.97 | 4.1±0.42 | 4.1±0.74 |
| **Hardness(kg/cm²)** | 4.4±0.56 | 4.3±0.85 | 4.2±0.73 | 4.3±0.65 | 4.4±0.31 |
| **Friability (%)** | 0.65±0.18 | 0.64±0.73 | 0.64±0.31 | 0.64±0.42 | 0.65±0.54 |
| **Drug content (%/tablet)** | 99.87±0.13 | 99.49±0.84 | 98.63±0.61 | 99.55±0.32 | 99.41±0.64 |
| ***In-vitro* drug release at 24th hour** | 99.47±0.97 | 99.35±0.84 | 98.61±0.36 | 99.73±0.11 | 99.23±0.52 |

All the values are expressed as mean± SE, n=3

### 5.1.9 Esomeprazole Estimation from In-Vivo Samples Using HPLC:

HPLC was utilized at determining Esomeprazole specific concentration at plasma samples. To final determine Esomeprazole concentration, a calibration curve was developed by examining plasma time samples having various Esomeprazole concentrations. The (HPLC) chromatographic . mobile (liquid) phase was produced in investigation by combining 300ml (30%) 0.1M phosphate ($PO_4$) type buffer pH 3.5 and 700ml (70%) acetonitrile. The mixer was degassed in ultrasonic water bath for 5 minutes and filtered under vacuum

through 0.45 filter. The Esomeprazole samples shall identify at wavelength 297 nm in ultra violet spectrum. As diluent, (HPLC) chromatographic . mobile (liquid) phase was used.

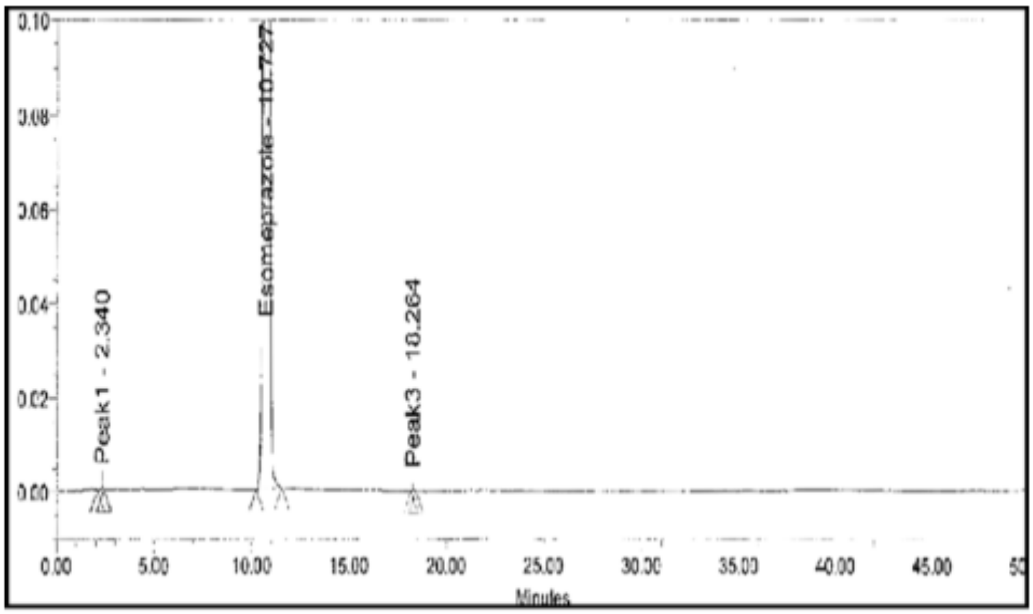



**Fig. 5.18: Chromatogram of Esomeprazole by HPLC with retention time.**

**Table 5.13: Linearity Results of Esomeprazole**

| S.No | Concentration (µg/mL) | Peak Area |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 25 | 82650 |
| 3 | 50 | 156735 |
| 4 | 75 | 235351 |
| 5 | 100 | 326267 |
| 6 | 125 | 402141 |
| 7 | 150 | 474736 |

## Results and Discussion

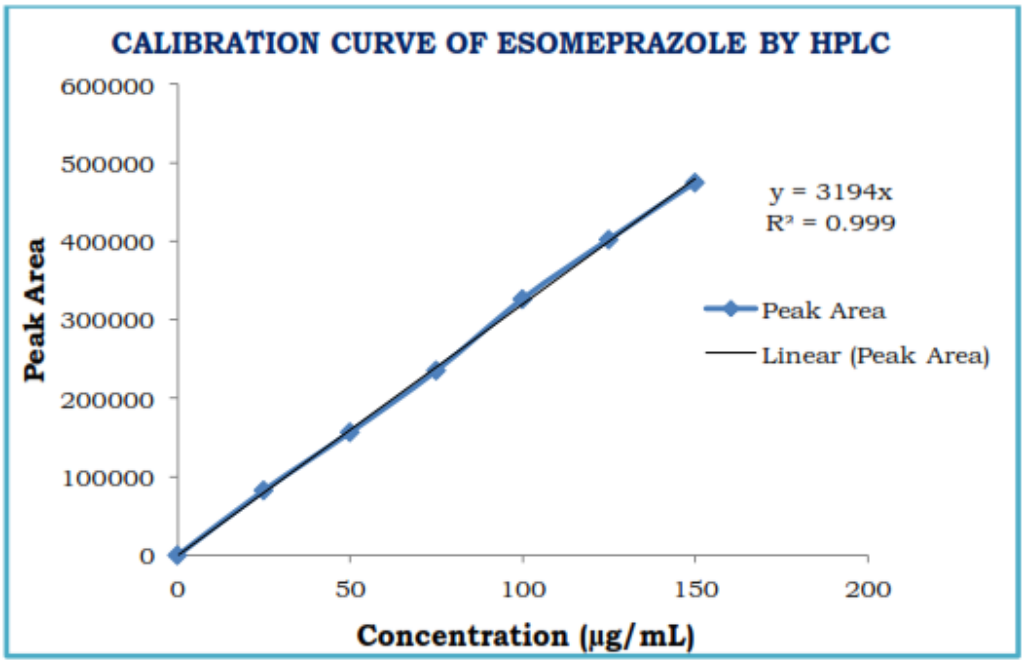



**Fig. 5.19: Calibration curve of Esomeprazole**

**Table 5.14: Plasma concentration values of Esomeprazole formulations**

| Time (hours) | Plasma Concentration (ng/mL) | |
|---|---|---|
| | Optimized Tablet | Oral Suspension |
| 0 | 0 ± 0 | 0 ± 0 |
| 0.5 | 16.54 ± 1.3 | 29.3 ± 2.1 |
| 1 | 41.5 ± 2.9 | 88.3 ± 9.7 |
| 2 | 59.2 ± 6.9 | 112.1 ± 19.3 |
| 4 | 88.7 ± 10.1 | 31.4 ± 6.2 |
| 6 | 119.6 ± 14.3 | 11.6 ± 4.8 |
| 8 | 139.4 ±20.1 | 4.3 ± 2.5 |
| 12 | 73.6 ± 11.3 | 0.7 ± 0.3 |
| 18 | 31.9 ± 8.4 | --- |
| 24 | 11.8 ± 4.5 | --- |

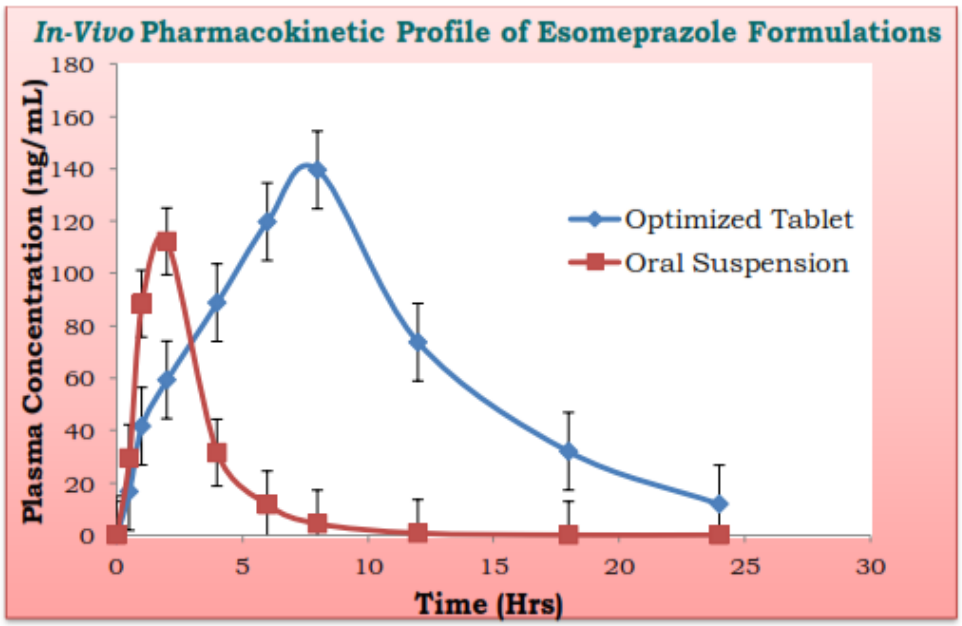



**Fig. 5.20: *In-Vivo* pharmacokinetic profile of Esomeprazole formulation**

**Table 5.15: Pharmacokinetic Parameters of Esomeprazole Formulations**

| Pharmacokinetic Parameter | Value | |
|---|---|---|
| | Optimized Tablet | Oral Suspension |
| $C_{max}$ (ng/mL) | 139.4± 9.4 | 112.1± 4.6 |
| $T_{max}$ (Hours) | 10.8 ± 1.1 hrs | 1.6 ± 0.5 hrs |
| $K_{el}$ ($hr^{-1}$) | 0.152 | 0.391 |
| $T_{1/2}$ (Hrs) | 7.28 | 1.43 |
| Ka ($hr^{-1}$) | 0.174 | 0.395 |
| MRT (Hrs) | 10.78 | 4.36 |
| AUC (ng.hr/mL) | 2377.71 ± 58.3 ng.hr/mL | 421.58 ± 16.3 ng.hr/mL |
| Relative Bioavailability | 5.64± 1.3 | |

### 5.1.10 Esomeprazole Pharmacokinetic Studies atIn-Vivo:

When optimised tablet, Esomeprazole rapidly released and swiftly permeated through GI tract compared at oral solution, pharma-co-kinetic (ADME) study in-vivoshow. Controlled - released tablet's Cmax value was meant to higher than oral suspension's (112.1 ± 4.6 ng/mL) Cmax value. Optimized tablet formulations showed greater Tmax value (11.81 – 1.11 hours) than did oral medicament solution (1.6–0.5 hours). This suggests a more control led released of medication. The extended half-life (7.28 hours) of optimised tablet that compared with oral suspension (1.43 Hrs). MRT for control led - released tablet was set higher than that for oral suspension (10.78 hrs) since tablet was completed (4.36 hrs). This shows specific control led effect at optimize tablet. There shall considerable increase in average AUC value for optimised Control led Released Tablet (2370.7 ± 15.7 ng.hr/mL) as when compared with oral medicament suspension (421.58 ± 16.3 ng.hr/mL). The bio-availability of enhanced Control led Released Tablet was increased by 5.6 times. Control led Released Tablets can successfully maintain Esomeprazole's plasma profile that documented, demonstrated by this study.

## 5.2 RESULTS AND DISCUSSION DEXLANSOPRAZOLE:

The goal of peculiar research, to develop a ranging with polymers so, make Dexlansoprazole and Control led Released Tablets. The basic physical and additionally in-vitro drugs' release analyses into all formulations.

Simulated Gastritic Fluid (pH 1.2) with pH of 6.8 i.e. Phosphate ($PO_4$) type Buffer were utilized to make graphs of Dexlansoprazol.

**Table 5.16: Observations for graph of Dexlansoprazole in 0.1N HCl (232nm)**

| S.No | Concentration (µg/ml) | Absorbance (nm) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 0.105 |
| 3 | 10 | 0.202 |
| 4 | 15 | 0.298 |
| 5 | 20 | 0.397 |
| 6 | 25 | 0.487 |
| 7 | 30 | 0.588 |
| 8 | 35 | 0.676 |

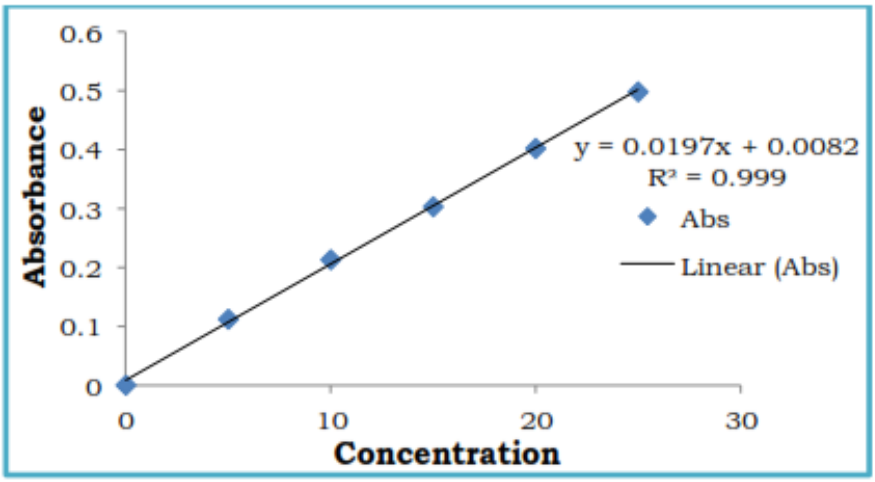



**Fig. 5.21: Standard graph of Dexlansoprazole in 0.1N HCl**

**Table 5.17: Observations for graph of Dexlansoprazole in pH 6.8 phosphate buffer (234nm)**

| S.No | Concentration (µg/ml) | Absorbance (nm) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 0.112 |
| 3 | 10 | 0.213 |
| 4 | 15 | 0.303 |
| 5 | 20 | 0.402 |
| 6 | 25 | 0.498 |

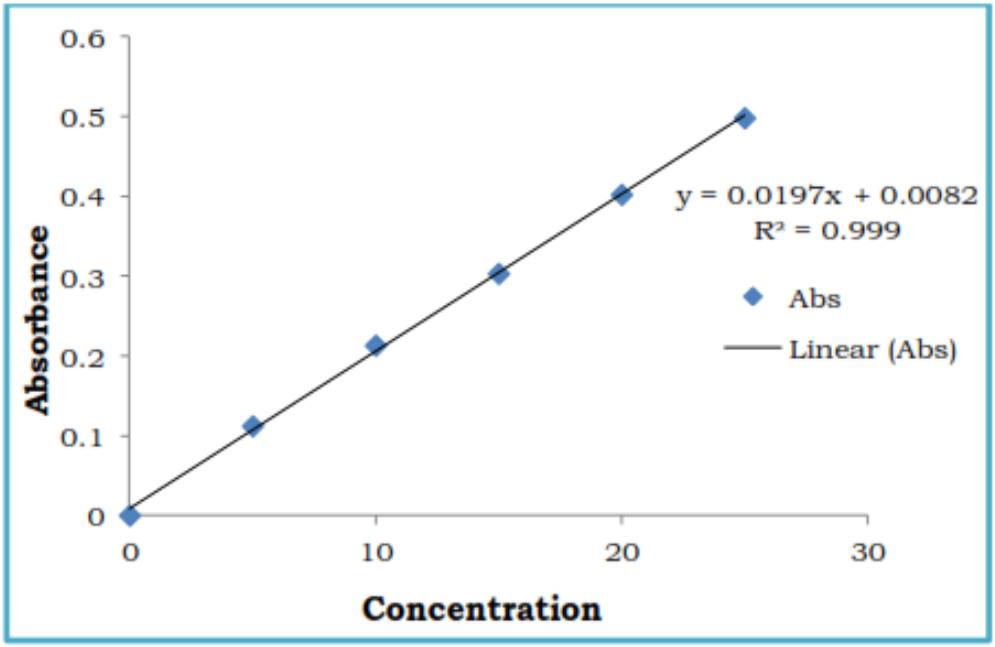



**Fig.5.22: Standard graph of Dexlansoprazole pH 6.8 phosphate buffer**

## Results and Discussion

### 5.2.1 Compatibility with Evaluation viz. Excipient and Drugs:

#### 5.2.1.1 Infrared Fourier type Transform Spectroscopy (FTIR):

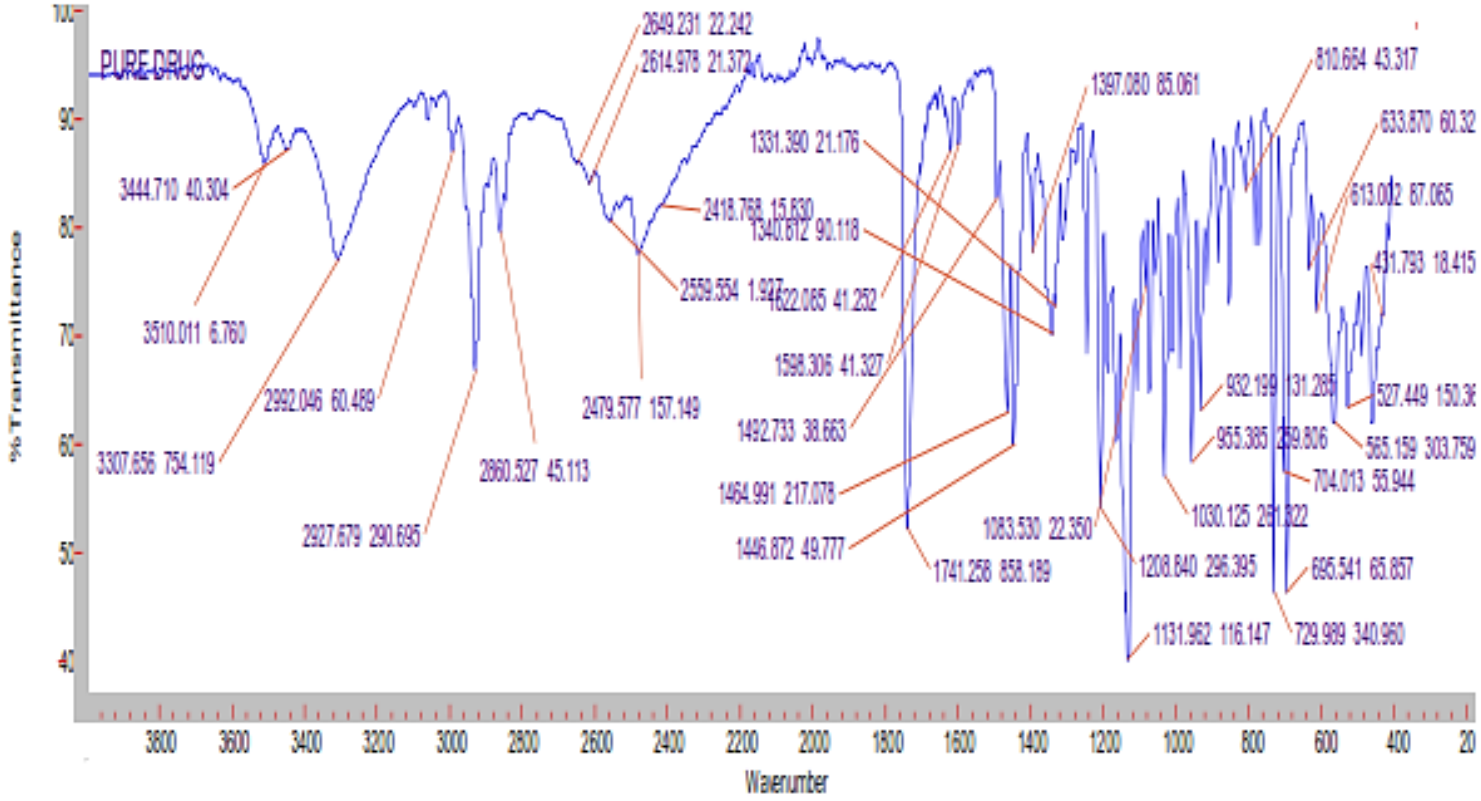


**Fig. 5.23: FTIR range (sepectrum) Dexlansoprazol pure drug.**

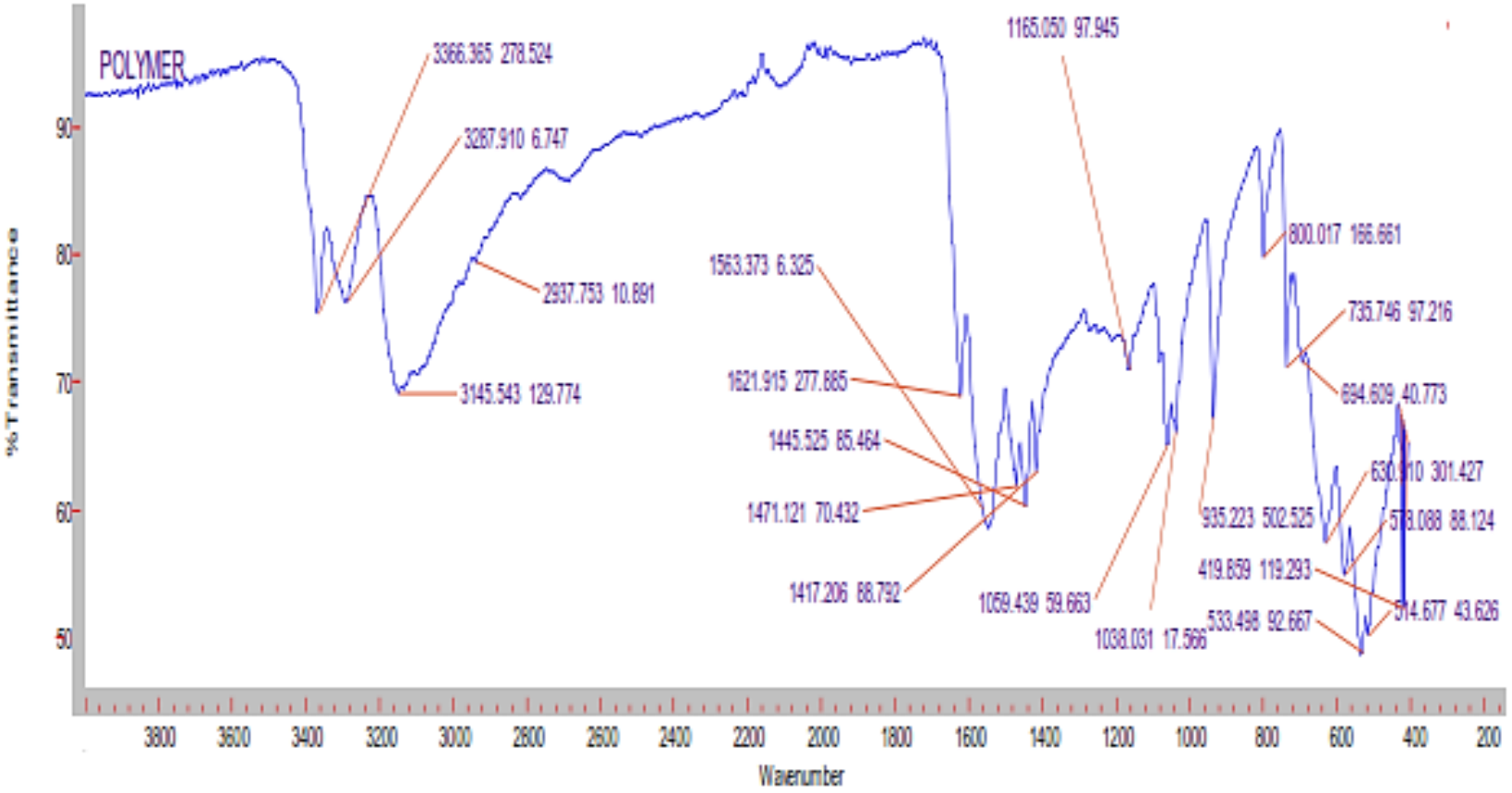



**Fig. 5.24: FTIR range (sepectrum) Carbopol® - 974.P + HPMC – K[4M]**

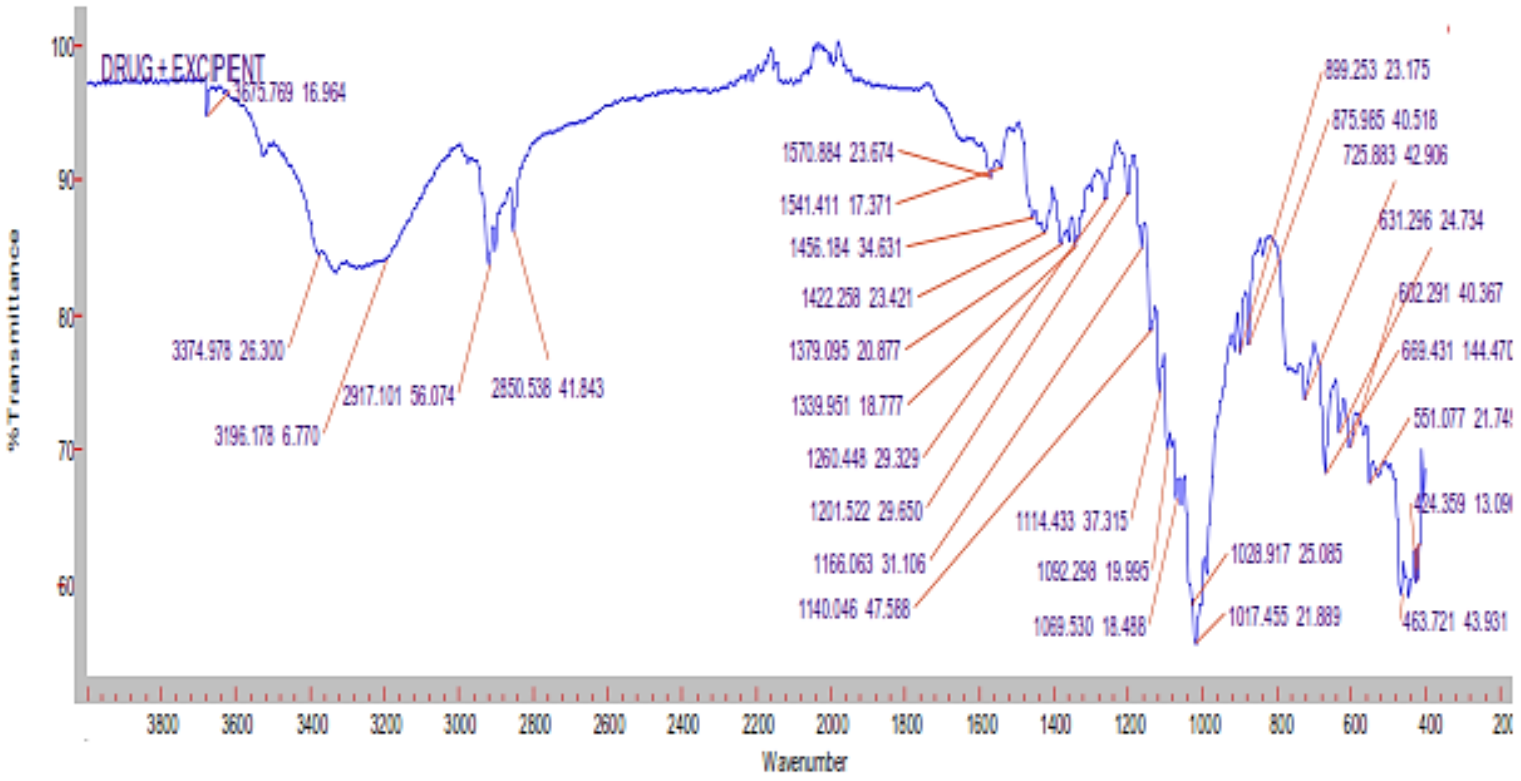



**Fig. 5.25: FTIR range (sepectrum) Dexlansoprazole optimized tablet formulation**

**Table 5.18: FT-IR Data Interpretation for Dexlansoprazole**

| S.NO | Wave number in formulation ($cm^{-1}$) | | | Characteristic Wave number range ($cm^{-1}$) | Bond nature and bond attributed |
|---|---|---|---|---|---|
| | Dexlansoprazole | Dexlansoprazole+ Carbopol-974P+ HPMC-K 4M | Optimized formulation | | |
| 1 | 2927.679 | 3145.543 | 2917.101 | 3400-2400 | O-H stretching Carboxylic acid |
| 2 | 2992.046 | 2937.753 | 2850.538 | 3000-2850 | C-H stretching Alkanes |
| 3 | 1598.306 | 1563.373 | 1570.884 | 1600-1475 | -C=C- stretching aromatic |
| 4 | 1464.991 | 1471.121 | 1456.184 | 1500-1400 | C-C stretch in ring aromatics |
| 5 | 1131.962 | 1165.050 | 1166.063 | 1350-1000 | C-N stretch amines |
| 6 | 810.664 | 800.017 | 875.985 | 910-665 | N-H $1^{o}$,$2^{o}$ amines |
| 7 | 704.013 | 735.746 | 725.883 | 900-690 | C-H out-of-plane bend aromatics |

### 5.2.1.2 Drug compatibility testing using polymers:

#### 5.2.1.2.1 FTIR (Fourier transform infrared) spectroscopy:

Choosing the right excipients is critical to successful formulation. A physical state is achieved, and as result the medication Dexlansoprazole now available. There lay three ways which Dexlansoprazole can used: as pure drug, combined with Carbopol® - 974.Pand H.P.M.C - K 4M, and polymer form. Hydroxy propyl methyl cellulose (H.P.M.C - K 4M) with magnesium sulphate Using FTIR, the drug-polymer compatibility of stearate, aerosil, and microcrystalline (MCC) cellulose ought determined. Results are presented: IR spectra (Figs. 5.23 – 5.25) and table (Table.5.18).

## Results and Discussion

The polymer's physicochemical compatibility with medication was determined perfectly using FTIR studies. Pure Dexlansoprazole's I.R. (non-visible) spectra showed peaks at all wave numbers of 2927.679 (O-H stretching carboxylic acid), 2992.046 (C-H stretching alkanes) and 1598.306 (C-C- stretching Aromatics). Dexlansoprazole+Carbopol® - 974.P+H.P.M.C - K 4M had IR spectra that showed peaks at wave numbers of 3145.543 (O-H stretching Carboxylic acid), 2937.753 (C-H stretching Alkanes) and 704.013. (C-H out-of-plane bend aromatics) Clearly, this is pure substance.

O-H stretching carboxylic acid, 2850.538 (C-H stretching alkanes), 1570.884 (-C= C- bond stretch aromatics), 1456.184 (c-c stretch in ring aromatics), 1166.063 (c-n stretch amines) and 725.883 (O-H stretching carboxylic acid) were most prominent peaks in physical spectra of chemical compounds (C-H out-of-plane bend aromatics). Polymers, however, accounted for additional peaks in substantial mixes, suggesting that Dexlansoprazole did not interact chemically with wide-range of other polymers.

## Results and Discussion

### 5.2.2 Calorimetry using Differential (range) Scanning Calorimetry:

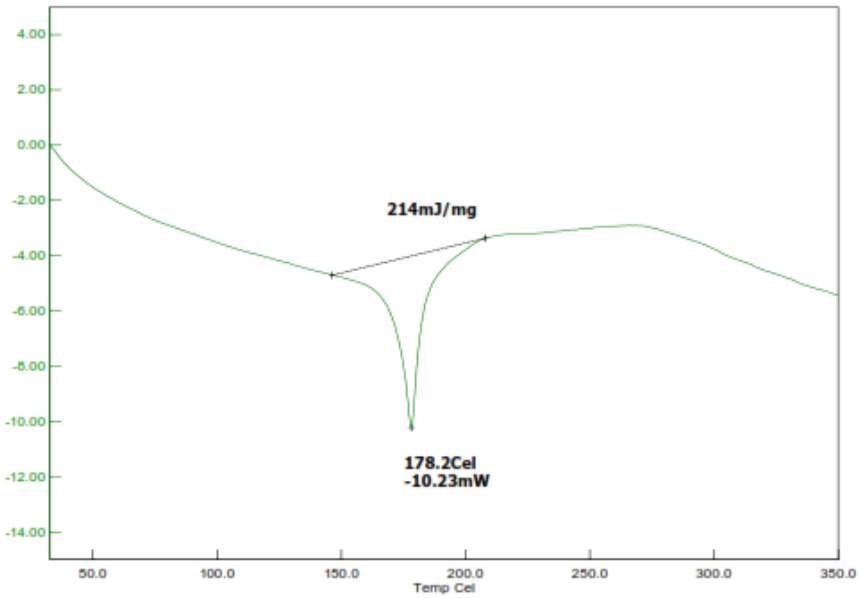



**Fig. 5.26: Differential Scanning Calorimetry analysis of Dexlansoprazole.**

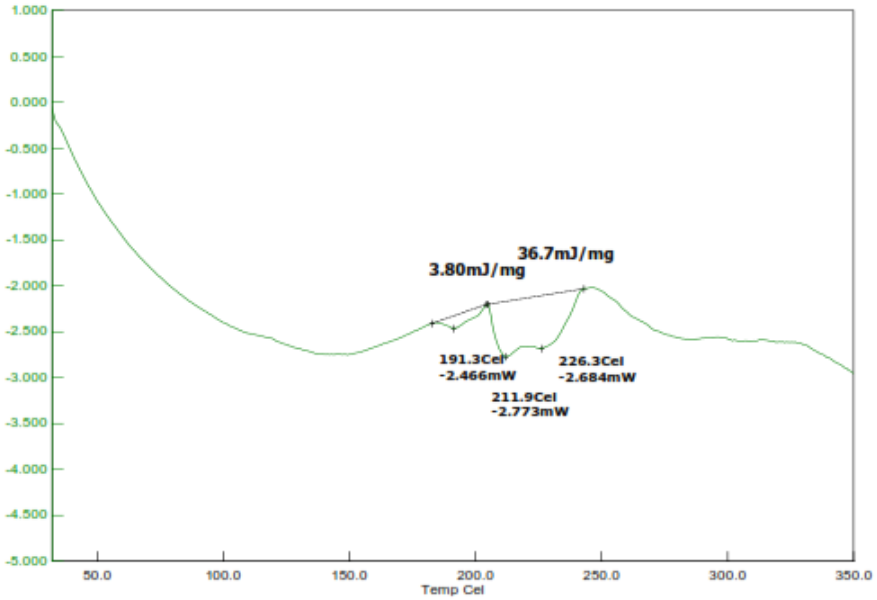



**Fig. 5.27: Differential Scanning Calorimetry analysis of Dexlansoprazole +Carbopol-974P+ HPMC-K 4M**

## Results and Discussion

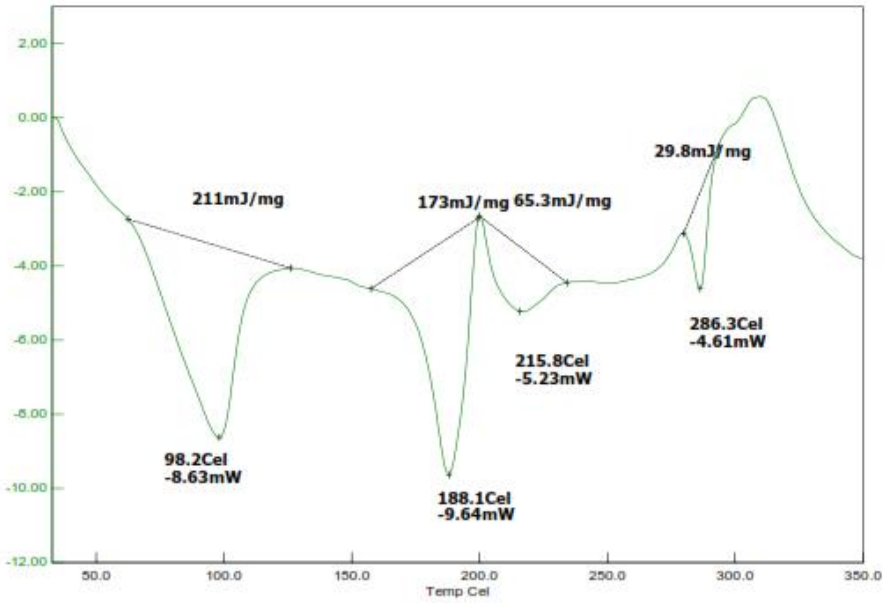



**Fig. 5.28: Differential Scanning Calorimetry analysis of Dexlansoprazole optimized tablet formulation**

**Table 5.19: Data of DSC thermogram parameters for Dexlansoprazole**

| S. No | Name of ingredients and physical mixtures used in formulation | Temperature at which peak obtained |
|---|---|---|
| 1. | Dexlansoprazole | 178.2°C |
| 2. | Dexlansoprazole+Carbopol-974P+ HPMC-K 4M | 191.3°C |
| 3. | Dexlansoprazole + Carbopol-974P+ HPMC-K 4M +Mg.Stearate +Aerosil+ MCC | 188.1°C |

## Results and Discussion

DSC was utilized to investigate the compatibility along, and interactions between drugs and polymers, shown at Figs. 5.26–5.28 and Table 5.19. The DSC thermograph for Dexlansoprazole showed melting point at 178.2°C, while the mixer for Dexlansoprazole + (polymer) Carbopol® - 974.P+ H.P.M.C – K[4M] indicated melting points range with 191.3°C to 226.3°C and Dexlansoprazole +Carbopol® - 974.P+ H.P.M.C – K[4M] +Mg.Stearate +Aerosil+ Micro Crystaline Cellulose indicated melting Dexlansoprazole and polymers at enhanced formulation subjected at testing using DSC. When Dexlansoprazole combined with some polymer of optimal formulation, the melting point does not alter much, accords the documented research.

## Results and Discussion

### 5.2.3 STUDIES ON FORMULATIONS:

### 5.2.3.1 Dexlansoprazole: its Control led Released Tablets evaluated invitro for its physicochemical properties: (Mean + SD) (n=3):

**Table 5.20: Flow properties of powder blend for Dexlansoprazole**

| Formulation Code | Bulk density ($gm/cm^3$) | Tapped density ($gm/cm^3$) | Hausner ratio (HR) | Carr's index (CI) | Angle of repose ($\theta$) |
|---|---|---|---|---|---|
| F1 | 0.48±0.01 | 0.59±0.04 | 1.3±0.25 | 14.76±0.04 | 27°.7'±0.61 |
| F2 | 0.35±0.09 | 0.61±0.07 | 1.1±0.26 | 13.63±0.86 | 25°.1'±0.30 |
| F3 | 0.47±0.07 | 0.74±0.05 | 1.13±0.01 | 13.55±0.43 | 26°.2'±0.42 |
| F4 | 0.36±0.09 | 0.69±0.06 | 1.2±0.09 | 12.18±0.97 | 25°.6'±0.18 |
| F5 | 0.42±0.04 | 0.51±0.02 | 0.9±0.29 | 11.68±0.07 | 26°.9'±1.12 |
| F6 | 0.49±0.05 | 0.64±0.09 | 0.97±0.17 | 16.36±0.34 | 29°.7'±0.79 |
| F7 | 0.34±0.06 | 0.55±0.07 | 0.9±0.36 | 12.26±0.31 | 30°.3'±0.65 |
| F8 | 0.42±0.03 | 0.62±0.04 | 1.13±0.42 | 14.68±0.88 | 26°.5'±0.69 |
| F9 | 0.38±0.08 | 0.76±0.05 | 0.89±0.69 | 15.23±0.39 | 27°.5'±1.46 |
| F10 | 0.39±0.06 | 0.52±0.05 | 0.7±0.76 | 14.87±0.53 | 28°.7'±1.20 |
| F11 | 0.46±0.03 | 0.64±0.07 | 1.14±0.53 | 14.63±0.75 | 29°.9'±0.27 |
| F12 | 0.38±0.02 | 0.63±0.04 | 0.9±0.66 | 12.55±0.59 | 26°.5'±0.24 |
| F13 | 0.43±0.05 | 0.78±0.06 | 1.1±0.49 | 13.53±0.97 | 28°.3'±0.36 |
| F14 | 0.39±0.01 | 0.74±0.06 | 1.14±0.65 | 14.87±0.76 | 29°.5'±0.71 |
| F15 | 0.44±0.02 | 0.65±0.01 | 0.9±0.66 | 12.32±0.42 | 27°.3'±0.39 |
| F16 | 0.48±0.09 | 0.69±0.05 | 1.15±0.53 | 11.89±0.87 | 24°.5'±0.65 |
| F17 | 0.36±0.05 | 0.76±0.03 | 1.16±0.42 | 13.56±0.65 | 26°.9'±0.99 |
| F18 | 0.39±0.04 | 0.69±0.06 | 1.12±0.87 | 12.72±0.43 | 29°.7'±0.43 |
| F19 | 0.43±0.05 | 0.77±0.01 | 1.1±0.58 | 14.36±0.98 | 27°.2'±0.65 |
| F20 | 0.40±0.07 | 0.60±0.09 | 1.11±0.32 | 12.75±0.46 | 25°.3'±0.98 |
| F21 | 0.46±0.08 | 0.61±0.04 | 1.15±0.24 | 11.87±0.76 | 28°.6'±0.54 |
| F22 | 0.48±0.05 | 0.68±0.09 | 0.9±0.34 | 13.42±0.54 | 29°.4'±0.76 |

## Results and Discussion

Tablet powder (with API) blend was subjected variety (different) pre-formulations conditions. It’s found, powders’ bulk density with formulations (varied) ranged 0.34 ± 0.06 to 0.49 ± 0.05 grammes per / cubic centimetre, documenting information that powder flows well. It’s found that tapped (vol) density of formulations was between 0.51 ± 0.02 and 0.78 ± 0.06. Using Hausner’s (tapped vs bulk) ratio, its seen that powder ought to have excellent flowability. All (new) formulations maintain Carr's index which range right from 11.68 ± 0.07 & 16.36 ± 0.34. All (new) formulations built an Repose - Angle ranged from 24°.5' ± 0.65 & 30°.3' ± 0.65. It’s clear with numbers that powder blend has excellent (flowability) flow properties.

### 5.2.3.1.1 Parameters for Tablet Quality Control:

Drug’s content (amount) and solubility in various media ought tested wrt accordance documented Pharmacopeia's specifications.

## Results and Discussion

### 5.2.4 In-vitro Investigations Post (after) Compression & properties: Dexlansoprazole's Control led Released Tablets:

**Table 5.21: Physico Chemical Characterization of Dexlansoprazole Controlled Release Tablets.**

| Formulation Code | Weight variation(mg) | Hardness ($kg/cm^2$) | Friability (%) | Thickness (mm) | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 249±0.74 | 4.2±0.32 | 0.58±0.25 | 3.62±0.53 | 99.81±0.08 |
| F2 | 250±0.67 | 4.9±0.89 | 0.59±0.53 | 3.98±0.71 | 99.98±0.03 |
| F3 | 251±0.75 | 3.9±0.46 | 0.62±0.61 | 3.69±0.23 | 101.2±0.07 |
| F4 | 249±0.23 | 3.9±0.72 | 0.58±0.42 | 3.25±0.97 | 99.41±0.26 |
| F5 | 249±0.05 | 4.3±0.18 | 0.79±0.15 | 4.1±0.07 | 99.24±0.75 |
| F6 | 251±0.86 | 4.1±0.52 | 0.62±0.55 | 3.24±0.53 | 101±0.12 |
| F7 | 250±0.55 | 4.3±0.63 | 0.59±0.17 | 3.59±0.62 | 99.26±0.09 |
| F8 | 249±0.77 | 4.4±0.42 | 0.67±0.82 | 3.57±0.41 | 101.1±0.62 |
| F9 | 250±0.24 | 3.8±0.74 | 0.78±0.26 | 3.11±0.26 | 100±0.25 |
| F10 | 249±0.03 | 3.9±0.79 | 0.69±0.82 | 3.27±0.67 | 99.2±0.01 |
| F11 | 248±0.75 | 4.4±0.62 | 0.65±0.16 | 3.52±0.16 | 98.13±0.02 |
| F12 | 249±0.52 | 4.1±0.14 | 0.79±0.04 | 3.78±0.97 | 99.3±0.17 |
| F13 | 250±0.51 | 3.9±0.84 | 0.67±0.43 | 3.21±0.46 | 100±0.46 |
| F14 | 248±0.35 | 4.1±0.37 | 0.55±0.84 | 3.74±0.48 | 99.1±0.74 |
| F15 | 249±0.37 | 4.4±0.52 | 0.78±0.32 | 3.7±0.03 | 100±0.45 |
| F16 | 251±0.82 | 4.3±0.43 | 0.66±0.15 | 3.55±0.64 | 98.8±0.89 |
| F17 | 250±0.47 | 3.8±0.48 | 0.81±0.54 | 4.24±0.45 | 99.5±0.54 |
| F18 | 249±0.49 | 4.2±0.23 | 0.76±0.88 | 3.55±0.76 | 98.9±0.98 |
| F19 | 249±0.98 | 3.9±0.14 | 0.55±0.53 | 3.66±0.35 | 99.3±0.87 |
| F20 | 251±0.65 | 3.6±0.34 | 0.61±0.43 | 3.37±0.79 | 100±0.98 |
| F21 | 250±0.95 | 4.1±0.53 | 0.71±0.65 | 4.3±0.64 | 99.8±0.42 |
| F22 | 249±0.95 | 4.7±0.75 | 0.62±0.88 | 3.76±0.31 | 99.6±0.65 |

## Results and Discussion

### 5.2.5 Dexlansoprazole Control led Released Tablet Evaluation:

#### 5.2.5.1 Tablet (dosage) Appearance per se:

Tablets (individual) were visually examined and confirmed to devoid of flaws like capping (02 parts), chipping (edges), or lamination (surface).

#### 5.2.5.2 Dimensions:

Control led Released Tablets (dosage form) (F1 to F22) were robust tested for weight (variation) fluctuation, hardness (strong), friability (chipping), thickness (height) and also drug content. The results in formulations (F1 to F22) all were well found within limits of official books.

#### 5.2.5.3 Variation in weight:

When aliquot batch tablets subjected & tested, the weight (in mg) variation also percentage (%) deviation against each tablet were recorded. Formulated tablet weighs between 248.0355 and 251.6086 milli-grammes on average, the allowed weight (in %) variation is only 5%. (greater than 250mg). The weights of tablets met pharmacopeial requirements.

#### 5.2.5.4 Tablet Durability:

Monsanto's hardness (strong) tester was utilized to (officially) determine hardness in three tablets from each batch. Results, indicated pass as hardness (in $kg/cm^2$) of tablets ranged between $3.6 \pm 0.34$ and $4.9 \pm 0.89 kg/cm^2$. This implies that tablet hardness ought sufficiently strong.

### 5.2.5.5 % Friability:

All formula had (%) friability percentage ranging 0.55 ± 0.53 to 0.79 ± 0.04 percent. This demonstrate that all CR (dosage) tablet that had been created was simple to use.

### 5.2.5.6 Dimensions (Dimensions) (Diameter x Thickness):

Each product can have its own thickness (in mm) & diameter (in mm) specifications. Packaging and consumer acceptance could be greatly impacted due to massive range variation effect on tablet thickness and diameter available. In prepared formulations, diameter (in mm) was basically found as 80.0 mm and thickness range between 3.1111 mm and 4.3 ± 06.4 mm.

### 5.2.5.7 Composition of Drug:

The medicament or active (API) component content of formulation was determined as between 98.13 ± 0.02 and 101.2 ± 0.07 percent w/w, as per official (IP) range specified (90-110 percent w/w).

Weight fluctuation, friability, hardness (kg/cm2), thickness (in mm), & drug (%) content were found within official acceptable possible ranges.

## 5.2.6 STUDIES FOR in-vitro (%) RELEASE: DEXLANSOPRAZOLE; CONTROL LED RELEASED TABLETS:

**Table 5.22: *In-Vitro* drug release studies of Dexlansoprazole Controlled Release tablets (F1-F8)**

| Time (hours) | CUMULATIVE % DRUG RELEASE | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 32.48±0.78 | 6.23±0.86 | 10.45±0.61 | 19.13±0.82 | 16.76±0.68 | 17.49±0.75 | 21.76±0.78 | 8.23±0.74 |
| 2 | 56.87±1.24 | 9.64±0.51 | 19.59±0.29 | 35.64±0.33 | 24.43±0.74 | 36.38±0.43 | 38.46±1.06 | 10.75±0.34 |
| 4 | 71.09±1.22 | 27.13±0.86 | 25.11±0.48 | 47.56±0.38 | 38.96±0.98 | 42.76±0.34 | 41.03±1.08 | 16.42±0.76 |
| 6 | 82.86±1.09 | 39.80±0.11 | 29.67±0.14 | 59.43±0.92 | 51.29±1.02 | 58.96±0.28 | 53.49±0.98 | 21.31±0.84 |
| 8 | 94.86±0.75 | 48.18±0.18 | 37.53±0.12 | 69.49±0.46 | 58.46±0.84 | 61.22±0.56 | 57.84±0.84 | 31.47±0.98 |
| 10 | 97.32±.68 | 55.17±0.13 | 54.22±0.18 | 84.63±0.36 | 63.86±0.98 | 64.76±0.98 | 61.98±0.68 | 41.75±0.91 |
| 12 | 98.82±.54 | 63.36±0.65 | 66.53±0.27 | 88.68±0.63 | 69.16±0.48 | 69.23±0.84 | 70.72±0.73 | 52.46±0.1 |
| 14 | 99.94±0.74 | 71.24±0.69 | 72.3±0.44 | 96.75±0.79 | 74.69±0.68 | 71.46±0.67 | 74.39±0.25 | 58.69±0.77 |
| 16 | ----- | 79.92±0.31 | 83.41±0.48 | 99.57±0.35 | 75.46±0.84 | 73.34±0.68 | 78.67±0.43 | 61.32±0.72 |
| 18 | ----- | 86.18±0.77 | 85.96±0.89 | ----- | 79.47±0.56 | 74.31±0.84 | 83.38±0.57 | 64.46±0.67 |
| 20 | ----- | 90.17±0.14 | 87.43±0.11 | ----- | 82.46±0.76 | 76.69±0.76 | 85.64±0.48 | 63.78±0.58 |
| 22 | ----- | 95.86±0.22 | 88.39±0.18 | ----- | 84.76±0.84 | 78.46±0.48 | 88.46±0.74 | 65.82±0.84 |
| 24 | ----- | 98.79±0.48 | 90.31±0.74 | ----- | 86.16±0.67 | 80.23±0.78 | 91.23±0.66 | 68.49±0.67 |

**Table 5.23: *In-Vitro* drug release studies of Dexlansoprazole Controlled Release tablets (F9-F15)**

| Time (hours) | CUMULATIVE % DRUG RELEASE | | | | | | |
|---|---|---|---|---|---|---|---|
| | F9 | F10 | F11 | F12 | F13 | F14 | F15 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 6.72±0.84 | 23.88±0.94 | 17.82±0.35 | 9.57±0.84 | 14.86±0.35 | 14.12±0.71 | 15.62±0.36 |
| 2 | 14.16±0.71 | 49.32±1.32 | 18.9±0.48 | 22.68±0.72 | 32.28±0.73 | 16.25±0.16 | 22.27±0.13 |
| 4 | 18.46±0.67 | 53.92±0.84 | 31.13±0.78 | 26.1±0.98 | 44.32±0.15 | 28.43±0.86 | 30.45±0.75 |
| 6 | 28.56±0.87 | 63.07±0.67 | 60.84±1.01 | 28.09±1.04 | 55.75±0.29 | 37.35±1.97 | 37.72±1.21 |
| 8 | 37.44±0.67 | 71.77±1.24 | 75.6±1.28 | 55.8±1.32 | 67.16±0.88 | 46.54±0.55 | 45.47±0.18 |
| 10 | 45.12±0.78 | 77.85±0.98 | 84.49±0.37 | 69.3±0.37 | 74.43±0.96 | 58.18±0.82 | 53.63±0.53 |
| 12 | 50.54±0.32 | 83.76±1.09 | 92.7±0.68 | 76.5±0.67 | 84.59±0.13 | 66.31±0.33 | 69.78±0.82 |
| 14 | 59.4±0.49 | 86.34±0.98 | 93.18±1.38 | 80.45±0.32 | 89.66±0.49 | 75.18±0.88 | 72.93±0.63 |
| 16 | 60±0.97 | 89.43±0.65 | 94.08±0.84 | 83.1±0.84 | 94.34±0.21 | 79.22±0.15 | 78.35±0.46 |
| 18 | 61.2±0.54 | 93.6±1.24 | 94.59±1.24 | 83.6±0.47 | 99.46±0.87 | 83.73±0.87 | 81.92±0.37 |
| 20 | 62.25±0.78 | 93.67±1.42 | 95±0.84 | 84.6±1.24 | ----- | 88.26±0.21 | 84.28±0.64 |
| 22 | 64.08±0.38 | 95.86±0.67 | 95.67±0.69 | 85.09±0.86 | ----- | 90.71±0.86 | 86.56±0.53 |
| 24 | 65.86±0.49 | 96.9±0.82 | 96.24±0.84 | 85.79±0.78 | ----- | 92.68±0.53 | 90.98±0.89 |

**Table 5.24: *In-Vitro* drug release studies of Dexlansoprazole Controlled Release tablets (F16-F22)**

| Time (hours) | CUMULATIVE % DRUG RELEASE | | | | | | |
|---|---|---|---|---|---|---|---|
| | F16 | F17 | F18 | F19 | F20 | F21 | F22 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 11.26±0.86 | 26.63±0.29 | 7.26±0.35 | 12.34±0.87 | 15.12±0.65 | 6.35±0.41 | 21.89±0.36 |
| 2 | 16.28±0.63 | 43.27±0.82 | 17.87±0.76 | 17.53±0.54 | 28.35±0.44 | 15.74±0.26 | 36.43±0.35 |
| 4 | 21.54±0.86 | 58.57±0.61 | 23.65±0.34 | 26.89±0.35 | 37.54±0.76 | 22.83±0.34 | 39.67±0.67 |
| 6 | 27.87±0.29 | 67.43±0.25 | 31.44±0.98 | 38.67±0.86 | 49.76±0.82 | 30.55±0.98 | 44.65±0.98 |
| 8 | 35.27±0.18 | 77.25±0.82 | 40.34±0.65 | 47.52±0.56 | 51.14±0.59 | 38.75±0.65 | 59.83±0.42 |
| 10 | 48.46±0.65 | 80.62±.14 | 48.82±0.76 | 56.89±0.87 | 59.98±0.34 | 45.97±0.76 | 64.99±0.23 |
| 12 | 56.38±0.72 | 85.82±.62 | 56.76±0.43 | 65.53±0.34 | 62.15±0.98 | 53.42±0.45 | 70.65±0.87 |
| 14 | 61.46±0.14 | 89.26±0.53 | 60.35±0.78 | 70.98±0.65 | 67.45±0.39 | 61.76±0.78 | 75.98±0.19 |
| 16 | 67.74±0.36 | 94.71±.65 | 64.55±0.57 | 76.57±0.89 | 74.68±0.62 | 67.41±0.57 | 81.76±0.54 |
| 18 | 74.55±0.81 | 99.36±0.16 | 71.36±0.34 | 80.65±0.45 | 79.25±0.45 | 74.43±0.34 | 85.33±0.21 |
| 20 | 79.37±0.92 | ----- | 77.73±0.32 | 84.25±0.32 | 80.87±0.85 | 81.76±0.32 | 89.23±0.56 |
| 22 | 86.47±0.75 | ----- | 85.13±0.87 | 86.73±0.76 | 84.54±0.56 | 88.98±0.87 | 90.54±0.87 |
| 24 | 91.04±0.14 | ----- | 92.66±0.54 | 89.36±0.45 | 87.35±0.37 | 93.56±0.54 | 92.36±0.44 |

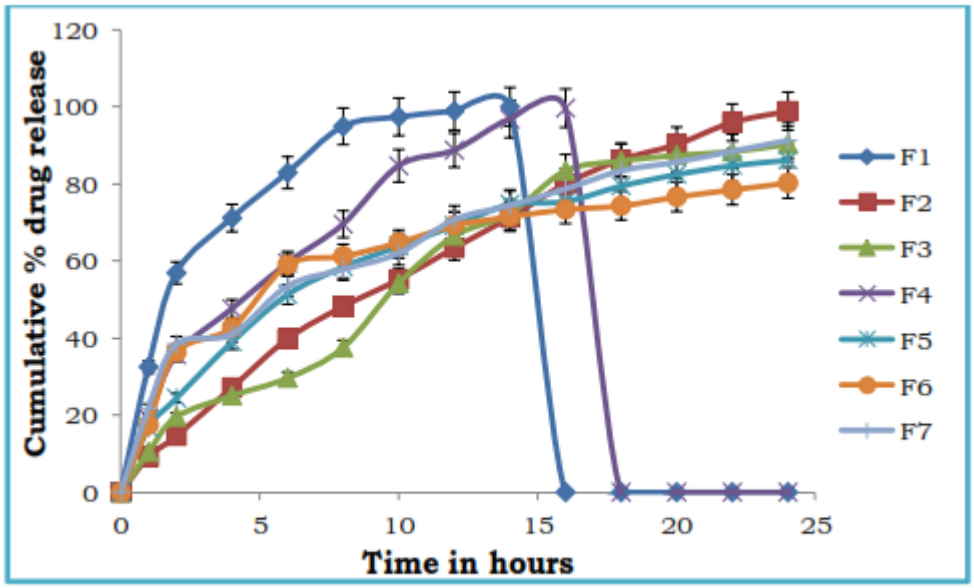



**Fig. 5.29: Dissolution graphs for the formulations F1 to F7**

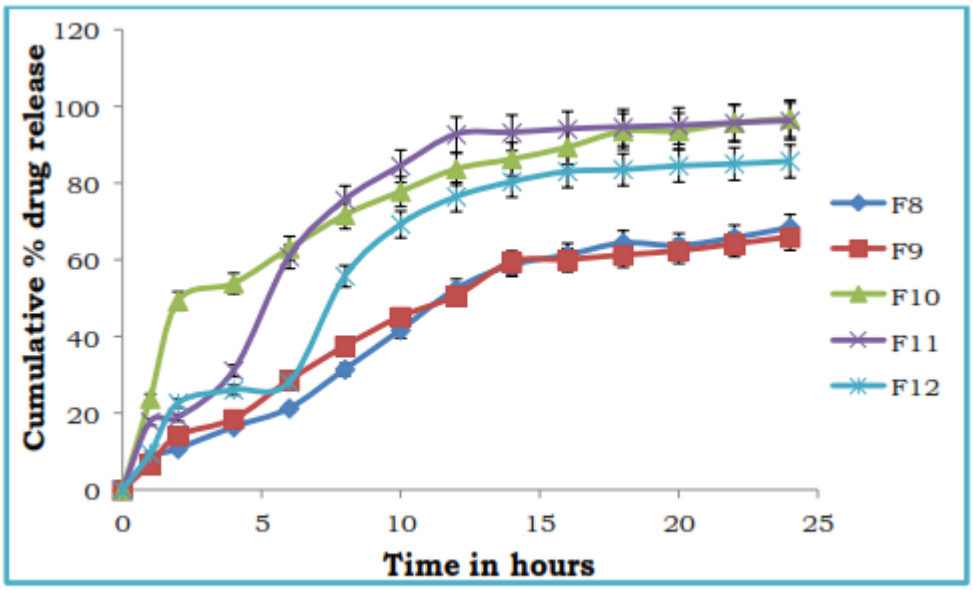



**Fig. 5.30: Dissolution graphs for the formulations F8 to F12**

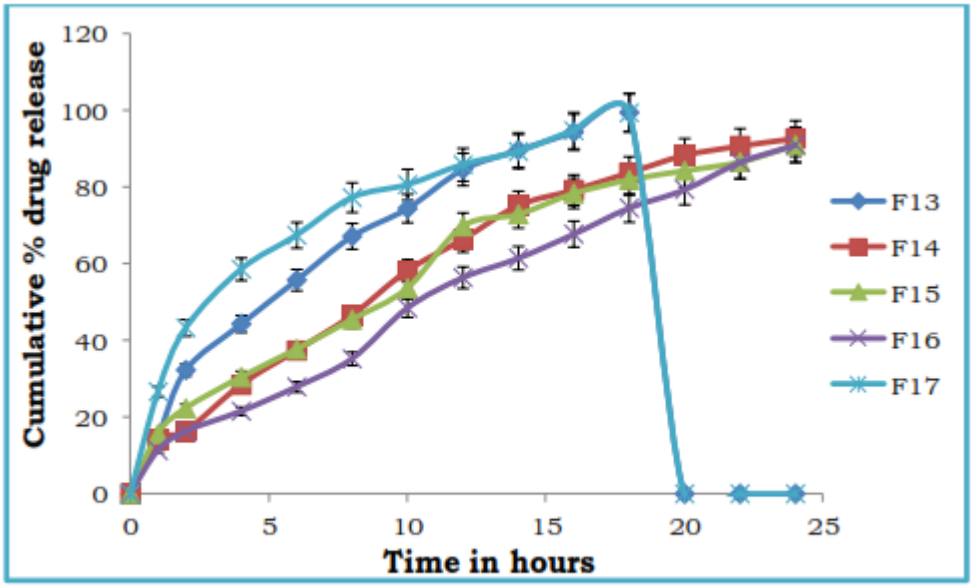



**Fig. 5.31: Dissolution graphs for the formulations F13 to F17**

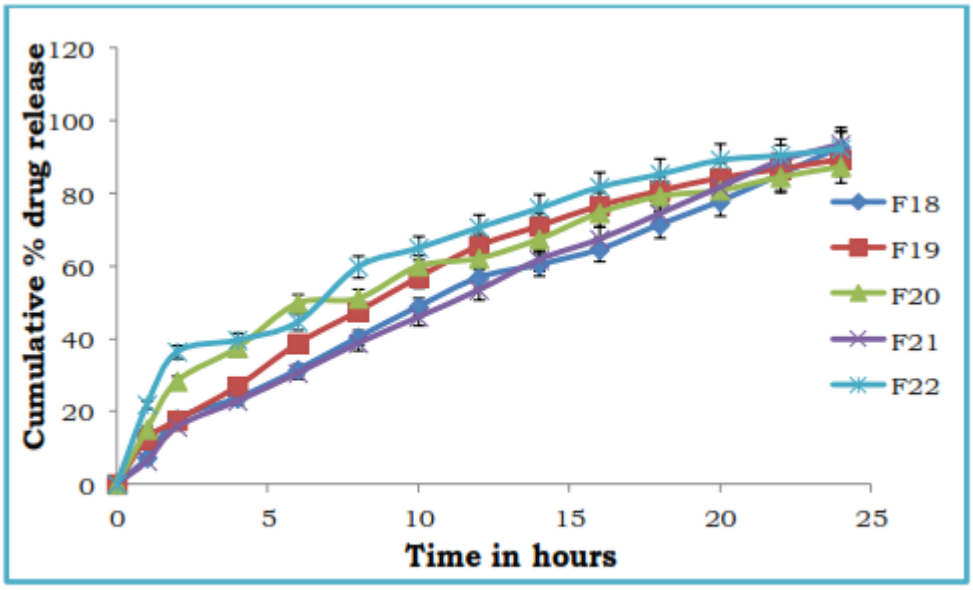



**Fig. 5.32: Dissolution graphs for the formulations F18 to F22**

### 5.2.6.1 Dexlansoprazole in-vitro drugs' release studies:

## Results and Discussion

These formula tablets once placed in (pH-1.2) acid buffer for two hours, 4.5 pH-acetate buffer for two hours, 6.8-phosphate ($PO_4$) buffer for eight hours, and 7.4-phosphoric acid buffer for twelve hours percent so as to conduct dissolving studies. The drug's release (%) rate was monitored over time. Tables 5.22-5.24 and Graphs 5.29-5.32 provide a periodic overview in findings.

To make Dexlansoprazole tablets, researchers used variety polymers, suitably, Carbopol® - 974.P, various grades of H.P.M.C for prevalence testing (H.P.M.CK4-K15-K100M), natural (plant) polymers as such, Xanthan and Guar-gums, Carboxy-methyl-cellulose (Na salt) (USP) and pectin, aerosil, magnesium (salt) stearate, and microcrystalline (MCC) cellulose as diluents.

Dependent on combination, Carbopol® - 974.Pand H.P.M.C K4M, F1, F3, & F4 are referred as F1, F3, and F4. After 14 hours, Formulation F1 released 99.94% of medicine, 98.79% after 24 hours, 90.31% after 24 hours, and 99.57% after 16 hours, all totaling to 99.94% of drug. All three specific formulations tested for 24 hours showed results with specifically, Formulation F4 at the hour $16^{th}$ with maximum release.

Formulations namely F5, F6, & F7 all contain common input and mixture Carbopol® - 974.Pand H.P.M.C K15M in them. F5 shown that 86.16 ± 0.67% of drug that is been released almost up to the duration of 24 hours. Ending the period phase of 24th hour, formula serial F6 released 80.23 ± 0.78%. During the 24th hour, Formulation F7 released 91.23 ± 0.66 percent, that’s about same as what

release is expected out of the entire drill.

Formulation F8 is made up of Carbopol®-974.Pand H.P.M.C K4M. F8 displays excellent % of 68.49 ± 0.67 percent of medicament ought to been released over hour $24^{th}$. Formulation number F9 only has H.P.M.C K15M in it. F9 has shown that over the course of $24^{th}$ hour, the cumulative (%) percentage (molecule) drugs' released was 65.86% to 0.499% and this was at the end of $24^{th}$ hour.

## 5.2.7 Optimized Dexlansoprazole CR Formulation (F-2) vs. Innovator's Product (F-1) were both tested for drugs' dissipation in-vitro:

Table 5.25: Comparative *In-vitro* drug release studies of optimized formulation of Dexlansoprazole (F-2) with Innovator product

| Time (Mins) | F-2 | Innovator Product |
|---|---|---|
| 0 | 0 | 0 |
| 10 | --- | 38.25±0.36 |
| 20 | --- | 47.34±0.69 |
| 30 | --- | 55.71±0.12 |
| 45 | --- | 66.62±0.27 |
| 60 | --- | 74.48±0.81 |
| 75 | --- | 89.87±0.65 |
| 90 | --- | 98.43±0.76 |
| 120 | 9.64±0.51 | --- |
| 220 | 27.13±0.86 | --- |
| 340 | 39.80±0.11 | --- |
| 460 | 48.18±0.18 | --- |
| 580 | 55.17±0.13 | --- |
| 700 | 63.36±0.65 | --- |
| 820 | 71.24±0.69 | --- |
| 940 | 79.92±0.31 | --- |
| 1060 | 86.18±0.77 | --- |
| 1180 | 90.17±0.14 | --- |
| 1300 | 95.86±0.22 | --- |
| 1420 | 98.79±0.48 | --- |

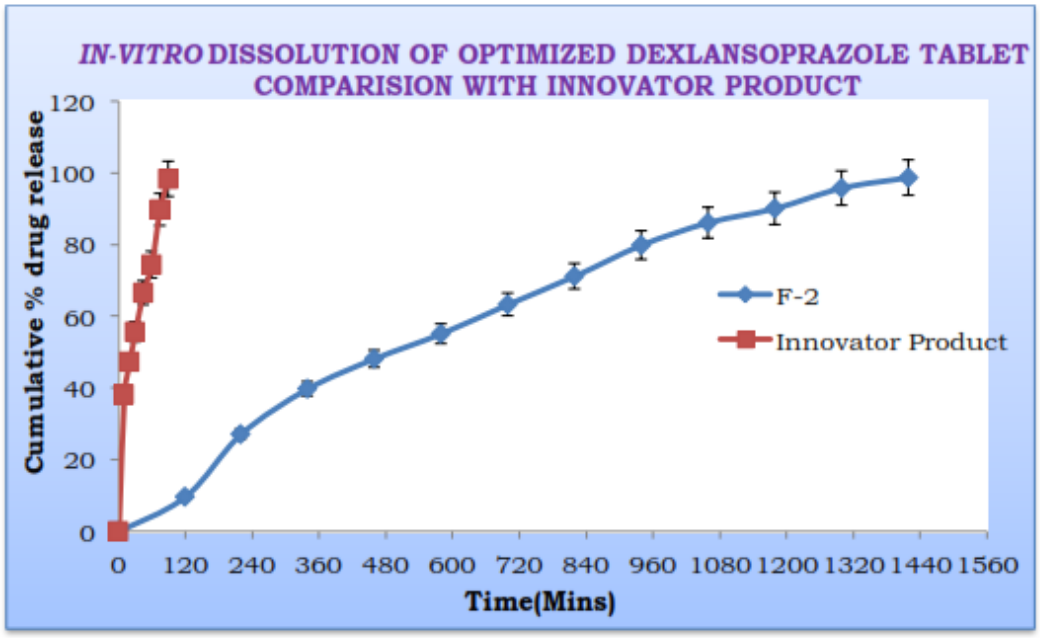



**Fig. 5.33: Comparative *In-vitro* drug release studies of optimized formulation of Dexlansoprazole (F-2) with Innovator product**

### 5.2.7.1 In-vitro Comparison of drug Dexlansoprazole Optimized Controlled (medicament) releasing formulation (F-2) with Innovator Product:

Instant-release type tablet with medicament Dexlansoprazole are sold as Dexilant 30mg Tablets.

Dexlansoprazole (API) Control led Released Tablets 30mg were subject of current study aiming effort to extend the drug's release (in %) time, reaching 24$^{th}$ hour. Optimised Dexlansoprazole (API) Control led Released Tablets 30mg were thoroughly tested in-vitro and linked to comparable Innovator product's in-vitro drugs' release.

Finalized Control led Releasing Tablet dosage including Carbopol®-974 P: H.P.M.C K4M at 1:1 ratios (F-2) showed cumulative percent drugs' release 98.79

± 0.48 after 24 hours, compared 98.43 ± 0.76 in minutes 90 for Dexilant 30mg tablets. Best type formulation always determined as one that showed zero-order / continuous drugs' release across desired time period.

After 90 minutes, the commercially viable and available product of Innovator showed about complete cumulative percentage (%) of (molecule) drugs' releasing from finished Control led Releasing Tablet dosage [unit] form, wrt, according the in-vitro type release testing. Dexlansoprazole Control led released pill capable delivery once day to maintain therapeutic concentrations, but innovative product need to administer atleast twice daily, as we go on results.

### 5.2.8 Dissolution Data Analysis Using Releasing, Rate Kinetics:

The capacity of several many models to appropriately explain kinetics governing releasing (molecule) drug thoroughly tested. For purpose to figuring out mechanism underlying kinetics governing released of (molecule) drug into media from within dosage [unit] form, data were fitted & release models for order; zero- and first - order, model Higuchi and Korsmeyer-Peppas.

**Table 5.26: Dexlansoprazole Release Kinetic Parameters for Optimized Formulation**

| F. Code | Zero Order | First Order | Higuchi | Best fit | Korsmeyer-Peppas | | Release Mechanism |
|---|---|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | | $R^2$ | n-value | |
| F2 | 0.984 | 0.874 | 0.969 | zero order | 0.997 | 0.792 | Anomalous Diffusion |

**Optimized Formulation (F-2) for Release Kinetics Graphs:**

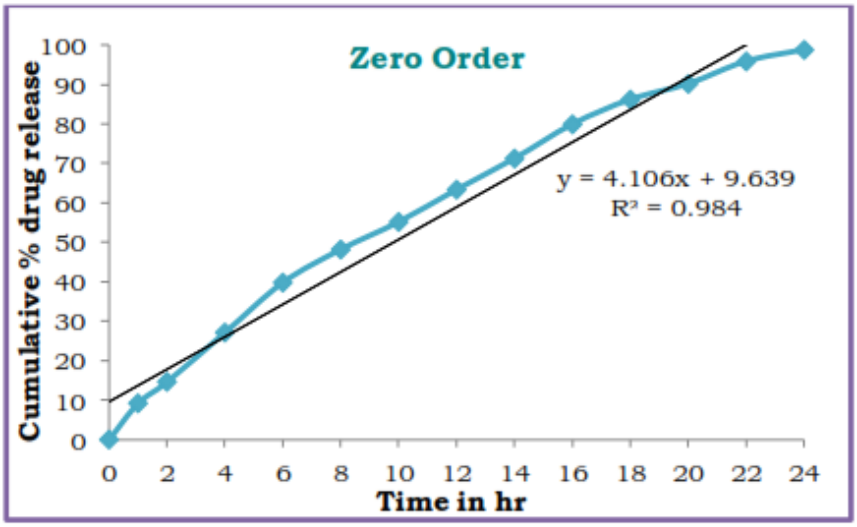



**Fig. 5.34: Zero order release kinetics of Dexlansoprazole optimized Formulation (F-2)**

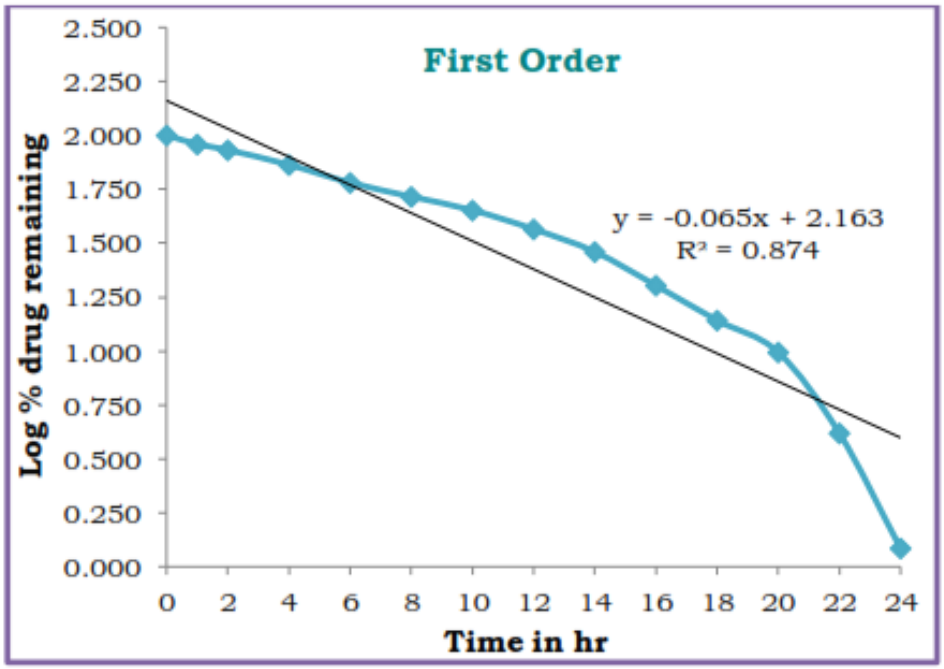



**Fig. 5.35: First order release kinetics of Dexlansoprazole optimized Formulation (F-2)**

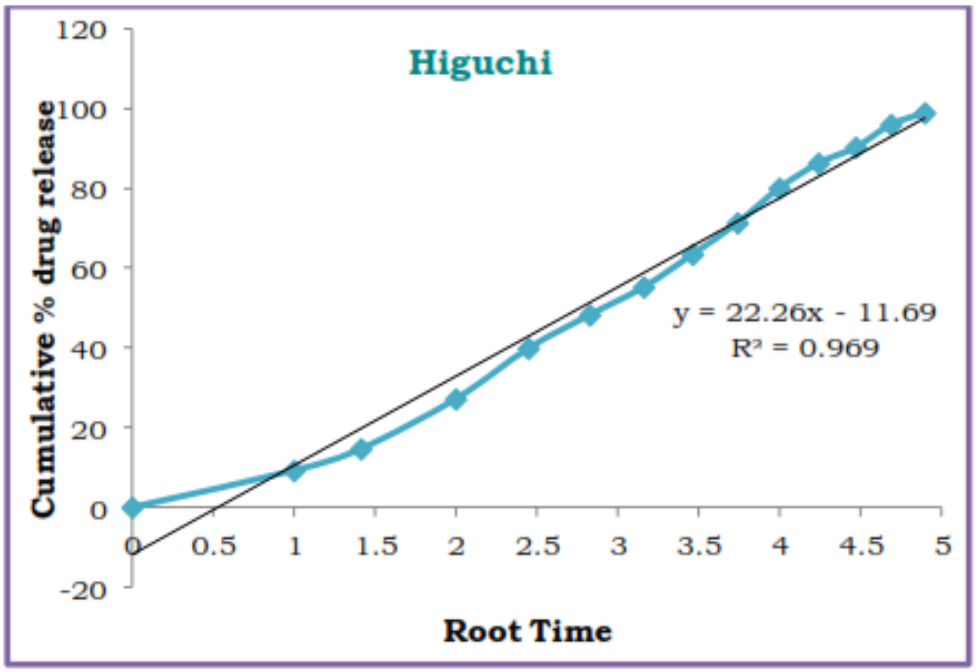



**Fig. 5.36: Higuchi model kinetics of Dexlansoprazole optimized Formulation (F-2)**

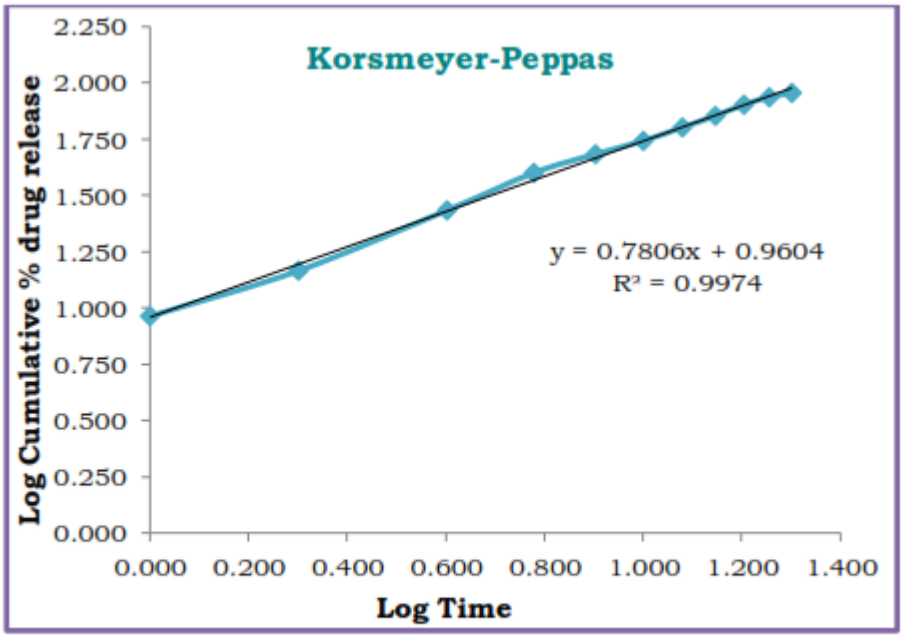



**Fig. 5.37: Korsmeyer-Peppas model kinetics of Dexlansoprazole optimized Formulation (F-2)**

### 5.2.9 Dissolution in-vitro method 'Kinetics' for Formulation Optimization:

Data of study, which show in-vitro dissolving kinetic type parameter for Dexlansoprazole (API) Control led Released Tablet, found in tables 5.26 and 5.34 and 5.35 and 5.36. Anomalous Diffusion found and deeply associated with release of medication from formulation, with important R 2 value 0.984% and a specific 'n' value 0.792 for Korsemeyer-Peppas model type dissolution.

### 5.2.10 Stability studies on improved formulation of Dexlansoprazole (F-2):

Several storage-related physical attributes (parameter) to formulation were investigated, with results presented as below Table 5.14.

**Table 5.27: Stability study of Optimized formulation (F-2) of Controlled release Dexlansoprazole tablets at Accelerated temperature $40^0$ C ± $2^0$ C / 75% RH ± 5%.**

| Parameter | Initial | Accelerated temperature ($40^0$ C ± $2^0$ C / 75% RH ± 5 % ) | | | |
|---|---|---|---|---|---|
| | | 1st Month | 2nd Month | 3rd Month | 6th Month |
| Weight variation (mg) | 250±0.67 | 249±0.45 | 248±0.23 | 249±0.55 | 250±0.29 |
| Thickness (mm) | 3.98±0.71 | 3.37±0.28 | 3.25±0.78 | 3.37±0.28 | 3.23±0.31 |
| Hardness(kg/cm²) | 4.9±0.89 | 4.8±0.79 | 4.9±0.54 | 4.8±0.62 | 4.9±0.48 |
| Friability (%) | 0.59±0.53 | 0.58±0.45 | 0.59±0.37 | 0.58±0.21 | 0.59±0.54 |
| Drug content (%/tablet) | 99.98±0.03 | 99.57±0.12 | 98.78±0.53 | 99.42±0.63 | 99.11±0.47 |
| In-vitro drug release at 24th hour | 98.79±0.48 | 98.35±0.19 | 97.98±0.25 | 98.32±0.41 | 98.43±0.24 |

All the values are expressed as mean± SE, n=3

### 5.2.10.1 Stability Studies on Optimized .Formulation- Dexlansoprazole:

Within scope and accord ICH guidelines, six (06) months of accelerated (rapid) stability trials subjected [carried] on optimised formulation. Dissolution in-vitro method at 24 Dexlansoprazole at preset time intervals, weight change, thickness (in mm), hardness (in kg/$cm^2$), friability (wt change), drug content, and dissolution in-vitro method have all been studied. The findings summarized into Table 5.27. Before and after storage, there was nil significant or major difference at any of examined parameters.

### 5.2.11 Development at analytical method: HPLC method:

HPLC was utilized in measuring plasma levels of Dexlansoprazole. Dexlansoprazole-containing plasma (from blood) samples analysed to [make] create calibration curve. An acetonitrile/phosphate ($PO_4$) buffer mixture along 700ml (70 percent) and 300ml (30 percent) was utilized to make the (HPLC) chromatographic . mobile (liquid) phase as this document study. Five minutes of

ultrasonic water bath degassing followed bypass vacuum filtering through 0.45 filter were utilized at prepare the mixer. Dexlansoprazole [API] samples detected using ultra violet spectrum at 296 nm. Accurate and precise method, (HPLC) chromatographic . mobile (liquid) phase as a diluent in experiment.

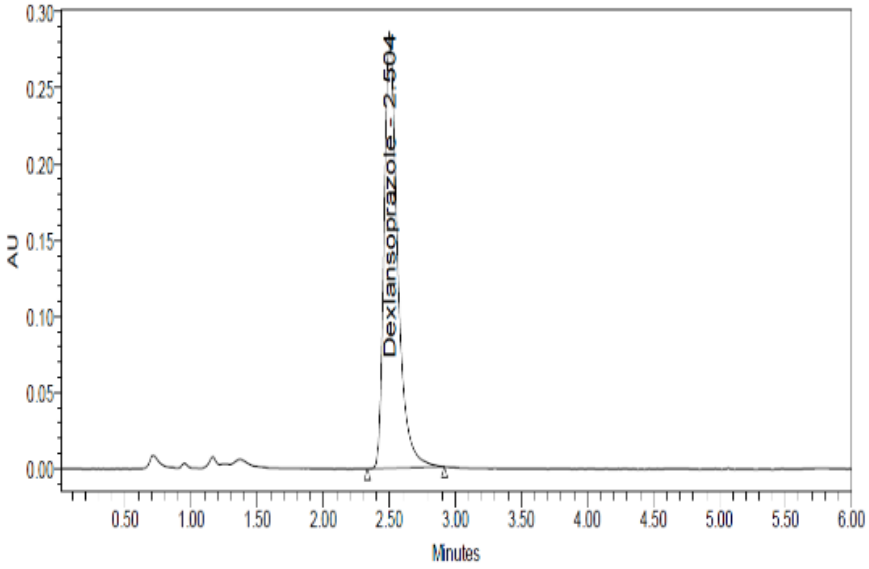



**Fig. 5.38: Chromatogram of Dexlansoprazole by HPLC with retention time of 2.50 min**

**Table 28: Linearity Results of Dexlansoprazole**

| S.No | Concentration (µg/mL) | Peak Area |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 25 | 593458 |
| 3 | 50 | 1123578 |
| 4 | 75 | 1701367 |
| 5 | 100 | 2235154 |
| 6 | 125 | 2761547 |
| 7 | 150 | 3267438 |

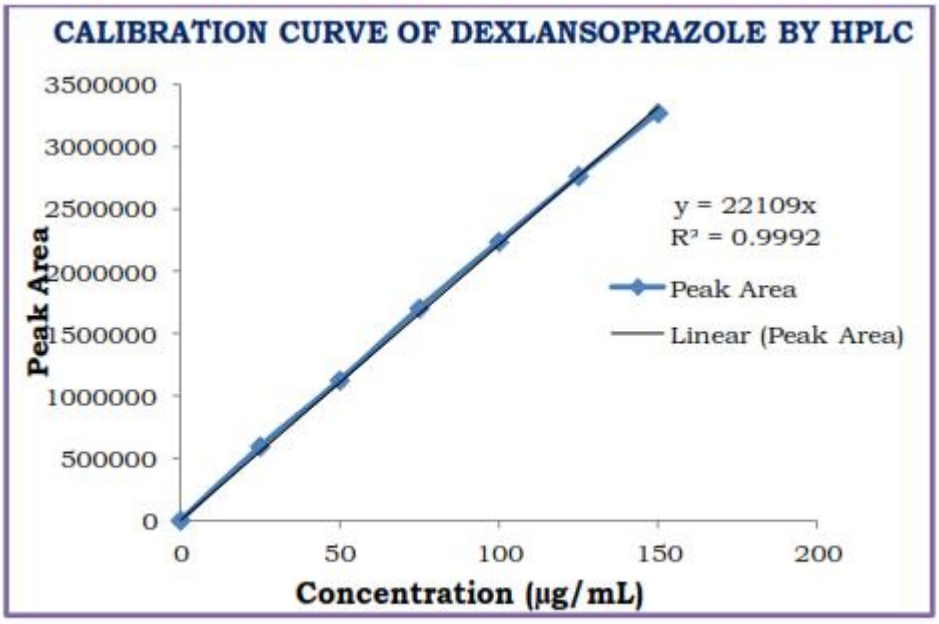



**Fig. 5.39: Calibration curve of Dexlansoprazole**

**Table 5.29: Plasma concentration values of Dexlansoprazol formulations**

| Time (hours) | Plasma Concentration (ng/mL) | |
|---|---|---|
| | Optimized Tablet | Oral Suspension |
| 0 | 0 ± 0 | 0 ± 0 |
| 0.5 | 14.17 ± 1.2 | 27.4 ± 1.9 |
| 1 | 32.8 ± 2.9 | 84.7 ± 9.4 |
| 2 | 57.1 ± 5.8 | 102.1 ± 21.5 |
| 4 | 87.5 ± 11.4 | 35.8 ± 6.5 |
| 6 | 119.6 ± 16.7 | 14.5 ± 5.1 |
| 8 | 131.1 ±21.3 | 6.3 ± 2.8 |
| 12 | 59.7 ± 13.1 | 0.9 ± 0.5 |
| 18 | 29.4 ± 9.2 | --- |
| 24 | 9.8 ± 3.8 | --- |

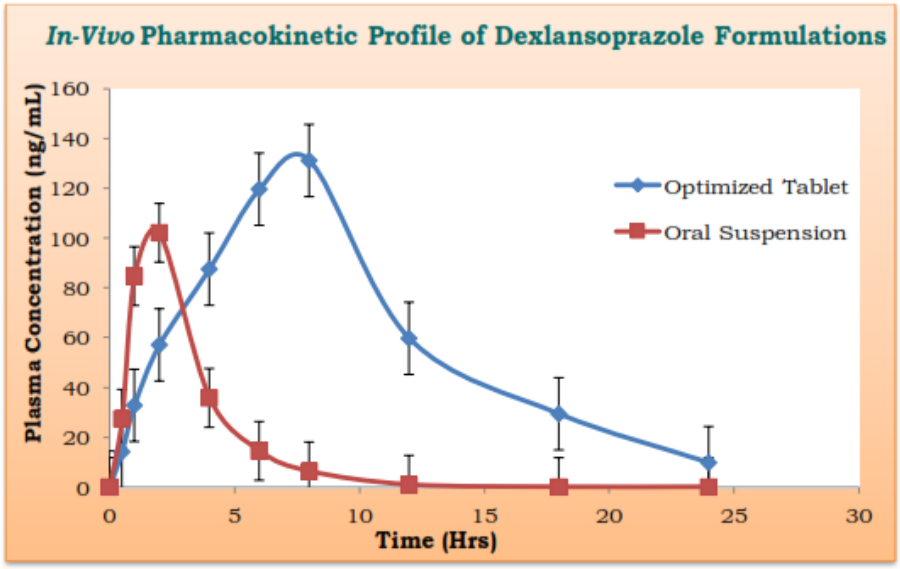



**Fig. 5.40: *In-Vivo* pharmacokinetic profile of Dexlansoprazole formulation**

**Table 5.30: Pharmacokinetic Parameters of Dexlansoprazole Formulations**

| Pharmacokinetic Parameter | Value | |
|---|---|---|
| | Optimized Tablet | Oral Suspension |
| $C_{max}$ (ng/mL) | 131.1 ± 8.2 ng/mL | 102.1 ± 3.9 ng/mL |
| $T_{max}$ (Hours) | 10.5 ± 1.3 hrs | 1.9 ± 0.6 hrs |
| $K_{el}$ ($hr^{-1}$) | 0.121 | 0.326 |
| $T_{1/2}$ (Hrs) | 7.48 | 1.79 |
| Ka ($hr^{-1}$) | 0.313 | 0.594 |
| MRT (Hrs) | 11.23 | 4.96 |
| AUC (ng.hr/mL) | 3188.78 ± 46.3 ng.hr/mL | 514.32 ± 14.9 ng.hr/mL |
| Relative Bioavailability | 6.2 ± 1.4 | |

# CHAPTER 6

## SUMMARY AND CONCLUSION

Purpose for current and existing research: to check and make controlled release formulation(s) of (molecule) drug Esomeprazole & drug Dexlansoprazole to raise and increase bio-availability so and prevent plasma variations associated that with existing innovator formulations.

### 6.1 ESOMEPRAZOLE:

- Gastroesophageal (GE) reflux problem or disease is treated with Proton (H+) Pump - Inhibitors like Esomeprazole (GERD). Only 50–68% [API] i.e. research used drug be bioavailable, which means it's poor therapeutic medicament index with short half-life in body (1–1.5 hours). Research determined that API Esomeprazole is good choice candidate for controlled medication & delivery - systems because it met all mentioned above criteria.
- Esomeprazole's excipient vs API interactions were studied in pre-formulations studies. The excipients were readily found to compatible using FTIR and DSC testing.
- Polymethacrylates e.g. Eudragit®-L100, Eudragit®-RS PO, Eudragit®-RS 100, & Eudragit®- [RLPO] produced Esomeprazole API controlled - released tablets, which when compressed by using direct (dry) compression method.
- Esomeprazole tablets at various controlled (medicament) releasing formulations using various polymers, such like Eudragit®- S100, L-100, RS PO, RS-100, RL-100, RL PO; as glidant talc; lubricant magnesium (salt)

stearate; and diluent Di. Calcium Phosphate; via the Direct (dry) compression process. To make.

- Before and after formulation, the properties in tablet blends and esomeprazole tablets (final) were examined, including flow type character with weight fluctuations, the hardness (in $kg/cm^2$), and friability (% change) of drug content. Within pharmacopeia's guidelines, all these measurements lay within officially acceptable limits.
- Dissolution in-vitro method and release, kinetics investigations will conducted using formulations developed. As terms (molecule) drugs' releasing & explained action mechanism, the F-6 formulation repeatedly was shown as best option. An ICH-required six-month (06) stability built study was performed on this formulation, and results verified that it's stable.
- Final results showed positive that pharma-co-kinetic (ADME) para-meters were predictable in rabbits, but dosage [unit] form remained in body for longer time; additionally, pharma-co-kinetic (ADME) parameters showed more controlled drugs' release i.e. 5.6 times increased relative bio-availability. Results in in-vivo type study conducted were highly precise and therefore predictable.

## 6.2 DEXLANSOPRAZOLE:

- API dexlansoprazole, chemically a proton (H+) pump - inhibitor utilized for treating heartburn associated basically with gastroesophageal type reflux. disease (GERD) and mend erosive type esophagitis (esophageal damage caused with stomach acid). API has short biological $t_{1/2}$ half-life (between 1 & 2 hours), high bio-availability (60%), with narrow therapeutic medicament index. Dexlansoprazole was chosen as good contender for

controlled medication & delivery - systems as per all mentioned above qualities.

- Pre-formulations experiments conducted on Dexlansoprazole, and polymers utilized were determined at initiate compatible based per se results in FTIR and DSC studies.
- The Direct (dry) compression type method utilized to make dexlansoprazole API controlled - released tablets utilizing opposing polymers, Carbopol® - 974.Pacrylic acid polymer & H.P.M.C grades for predominance. Carboxy-methyl-cellulose (Na salt) (USP), Xanthan-gum, Guar-gum, Pectin, H.P.M.C - K4.M, H.P.M.C - K15.M, & H.P.M.C - K100.M are all Natural Polymers.
- The physico & chemical values of produced formulations differed between pre-and post-compression stages. Formulations tested for in-vitro drugs' release, kinetics, and mechanism at (molecule) drugs' release after the values found as per official pharmacopeial limits.
- F-2 formulation made was shown as per values, the most effective in-vitro dissolving and (drug) release, its kinetics studies. Comparing optimised type formulation vs original product, there was enhancement in release profile as the delay in aliquot is most important.
- In accord with ICH guidelines, six (06) month stability experiments were undertaken on F-2, an optimized dose formulation, and stable.
- Pharma-co-kinetic (ADME) metrics showed more regulated drugs' release & higher relative bio-availability by 6.2 times following in-vivo testing in rabbits. The dosage [unit] form remained in body for more extended period.

## 6.3 Future Domain Research

Tailored Polymer Selection can incorporate inc. a broad domain wrt polymers beyond those studied as above study. This tailored polymer will aid in enhance drug profile in delivery and also will surely capable maintaining requisite amount in (molecule) drug delivered in requisite area of GIT. Along this additionally, hybrid system formulations combining synthetic polymers (e.g., Carbopol® - 974.P) along natural ones (such as Carboxy-methyl-cellulose (Na salt) (USP), Xanthan-gum, and Guar-gum) ought utilized to fabricate various drug formulations. However, it already known that one single specific polymer cannot be possessing all the properties, it of course thereby be an domain area to future research. Esp. what could be possible potential at combination of different uncommon polymer pharm blends. In area knowledge i.e. different materials especially polymers (natural/ synthetic), the combined effect attained by combine of more or min. two different sources or types, polymers opens up numerous promises. By combining binary / more typical polymers, there's potential of reaping the benefits of novel properties and applications. These synergistic system may optimize drugs' releasement profile and enhance (increase) patient hospital compliance.

This same area of pharmaceutical type research, rigorous in-vivo studyt needs proper evaluation so as validate the pharma-co-kinetic (ADME)s and therapeutic type efficacy of safe drugs. Task research can undertaken with proper patientcare and caution. In field of medical research, rigorous in-vivo type study are required, purpose, validate the pharma-co-kinetic (ADME)s and therapeutic API efficacy of safe drugs. These studies provide crucial insights onto drug behaviour within living organisms, ensuring patient end safety and informing evidence-based medical practices. Future research disclosure can be targeted at point & must approach this

task with meticulous care and caution, recognizing the ethical responsibility inherent in advancing healthcare.

Targeted delivery just to fundus will enhance GERD clinical indication symptom. Targeted proper delivery to patientt stomach and fundus can really have lot of potential for enhancing treatment effectiveness in gastrointestinal disorders. By precisely reaching the required anatomical region that responsible of clinical problem, all areas can surely be improved like drug absorption, bio-availability, and therapeutic outcomes. Furthermore, if patient centered delivery can even be generated it could personalize dosing regimens based at genetic factors or disease severity and enhance therapeutic result ending with outcomes.

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Original Article

# Spectrophotometric Determination With Anticancer Drugs, Proton Pump Inhibitors And Antihypertensive Drugs In Non Polar Medium

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## Abstract

Spectrophotometric methods for the analytical determination of organic, inorganicand biological substances are generally based on development of colour by reagents and identifying such reagents is often cumbersome and time consuming. In this respect, spectrophotometric determination of drugs may be facilitated by their ability to from coloured charge transfer complexes with electron acceptors. In the present investigation, a variety of drugs acting as electron donors e.g. anticancer drugs (Altretamine, Imatinib, Letrozole, Irinotecan) and proton pump inhibitors (Ilaprazole, Omeprazole, Rabeprazole, Lansoprazole, Pantoprazole, Ranitidine)have been used for spectrophotometric determination in a relatively non polar medium.

**Keywords:** Spectrophotometric methods, anticancer drugs, PPI, Antihypertensive drugs etc.

## INTRODUCTION

The large equilibrium constants of complex formation and the colour stability are the main advantage. A couple of neuroleptics e.g. haloperidol and droperidol have likewise been determined, in polar media, through CT interaction with $I_2$, TCNQ, DDQ, TCNE and bromanil in highly polar media [1]. While these investigations are useful, the highly polar media such as acetone and acetonitrile are likely to form CT complexes with the acceptors and so their conclusions are in doubt.

The literature survey has shown that studies for the analytical determination of drugs have mainly been focused on

- UV-Visible spectrophotometric methods where the characteristicabsorption maximum (λmax) was used for the determination of the drugs [2-35].
- UV-Visible spectrophotometric methods wherein the drug is converted to coloured species through some reaction through charge transfer complex formation,oxidation or reduction of the drug complexing with coloured species like dyes, diazotization reaction in the case of primary and secondary amine moieties containing compounds [36-47].

Most of the chromatographic methods not only allow the detection and determination of the pure drug but also the impurities present along with the drug. So, mostly chromatographic methods are being used for analysis of purity of drug andimpurities present in the drug simultaneously. All chromatographic methods are performed using costly instruments, and the running and maintenance cost are also high compared to UV-Visible

spectrophotometric method. In this respect, UV-Visible spectrophotometric methods can be used for the analysis of different drugs.

Keeping this point in view, the author developed UV-Visible spectrophotometric methods taking advantage of intense coloured charge transfer complex formation between the drug and selected acceptors. In present study examine the Spectrophotometric determination with anticancer drugs, proton pump inhibitors and antihypertensive drugs in non polar medium.

## METHODOLOGY

The selected drugs are divided into two groups, anticancer and proton pump inhibitor. The drug molecules selected for the study are presented in Table 1 to 2. All drug moleculesare referred to asdonors. The selected drugmolecules in pure form were obtained on request from quality control laboratories of Mylon Laboratories, Hetero Drugs Limited, Laurus Labs, all in Hyderabad, India and few of them werefrom sigmaAldrich, USA or E. Merck,Germany. The list of acceptors selected for the study arepresented in Table 3. All these compounds werefrom, E. Merck, Germany, SigmaAldrich, USA or British Drug House, BDH, England. The drugs & acceptors were stored in separate vacuum desiccators. HPLC grade or Spectroscopy grade solvents cyclohexane, acetonitrile, dichloromethane and boron trifluoride diethyl etherate (BF3.OEt2) are from E. Merck, Germany or Sigma Aldrich, USA, were further distilled before use after drying them over anhydrous sodium sulfate. All the drugs are of 99.8% pure or above. Majority of drugs were obtained in pure base form & remaining as hydrochloride, sodium and mesylate form. The drugs in pure base form were directly dissolved in the selected solvent. Preparation of knownconcentration of solution was done bydissolving known weight of drug in a known volumeof solvent. The drugs in hydrochloride and sodium forms, were converted to base form using the following extraction procedure.

In a separating funnel, a knownweight1 of drug hydrochloride was dissolved in 100 mL distilled water, to which 20 mL of 0.1 M sodium hydroxide solution and 20 mL of dichloromethane were added and promptly extracted. The hydrochloride medicines were extracted with dichloromethane. This extraction method was performed four times using new 20 mL of dichloromethane each time. The extracted dichloromethane was poured into a beaker. Anhydrous sodium sulphate was used to dissolve any remaining water in the solvent. A 100 mL solution of dichloromethane was prepared. The concentration of was determined using the published molar extinction coefficient at the UV-peak maximum of the specific drug molecules and the weight of the hydrochloride form of drug. A known weight of Sodium form of drugs was dissolved in 100 mL distilled water in a separating funnel to which 20mL of 0.1M hydrochloric acid solution and dichloromethane were added and extraction was carried out immediately. This extraction technique was rapidly repeated four times using fresh 20 mL of dichloromethane each time. The portions of dichloromethane extracted were transferred to a beaker. Anhydrous sodium sulphate was used to eliminate the water. A 100 mL solution of dichloromethane was prepared. Since medicines degrade in acidic or basic solutions, the extraction operation was completed in as little as 10-15 minutes. The drug concentration was determined using the weight of the dissolved Sodium form of the drug and the published molar extinction coefficient at the UV-peak maximum of that particular medication. The above approach was used to treat the drug's mesylate form.

Thermo Electronics Unicam UV-500 recording double beam spectrophotometer with a grating of 0.2 nm band width and temperature regulated cells (water peltier system) with an accuracy of + 1 0C was used to record all UV and visible spectra. The spectra were recorded using matched quartz quvettes of 1.0, 0.5, and 0.1 cm with air tight teflon lids. The $^{1}H$, $^{13}C$ and $^{11}B$ percentage (%) natural abundance of nuclei are 99.98, 1.108, 80.42 respectively. NMR spectra was recorded at NMR Research Centre, Andhra University, Visakhapatnam, using Bruker AV-400 multinuclear NMR spectrometer. The $^{1}H$ and $^{13}C$ chemical shifts (δ) were measured relative to $Me_4Si$ and $^{11}B$ shifts were with reference to $Et_2O.BF_3$ standards respectively.

**Table 1Details of the selected anticancer drugmolecules (donors)**

| Name of Compound | Structure of Compound | Molecular Formula | M.W (g/mol.) | M.P ($^{0}C$) | CAS No |
|---|---|---|---|---|---|

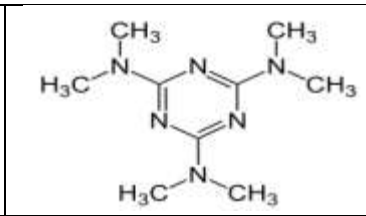
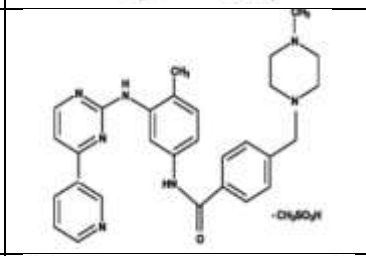
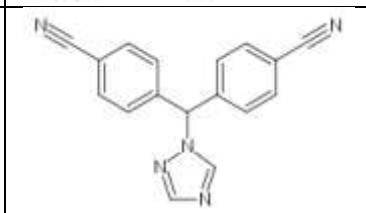
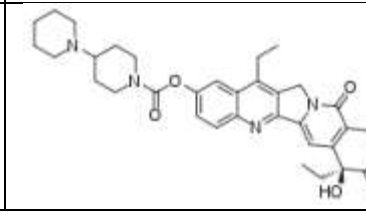
| | | | | | |
|---|---|---|---|---|---|
| Altretamine |  | C9H18N6 | 210.2 | 172-174°C | 645-05-6 |
| Imatinib mesylate |  | C29H31N7O | 589.7 | 226 °C | 220127-57-1 |
| Letrozole |  | C17H11N5 | 285.3 | 184 - 185°C | 112809-51-5 |
| Irinotecan HCl |  | C33H38N4O6 | 586.6 | 223 °C | 100286-90-6 |

**Table 2 Details of selected proton pump inhibitor drug molecules (donors)**

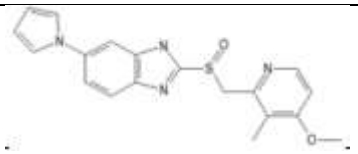
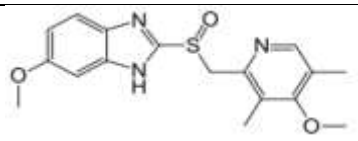
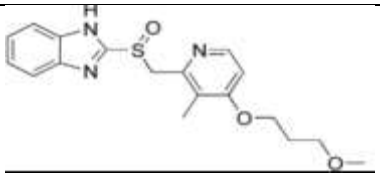
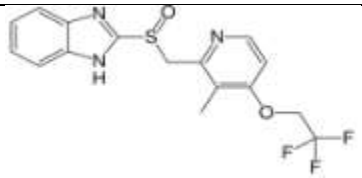
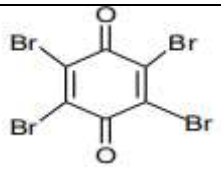
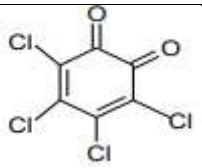
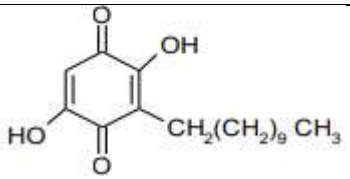
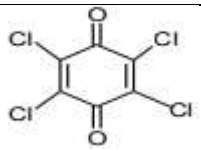
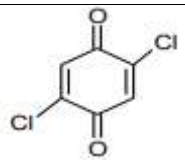
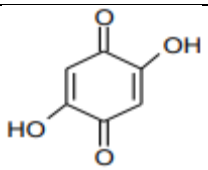
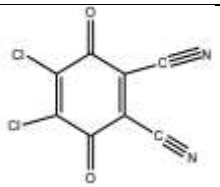
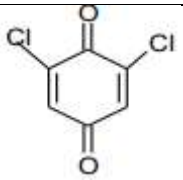
| Name of the Compound | Structure of Compound | Molecular Formula | M.W (g/mol.) | M.P ($^0$C) | CAS No |
|---|---|---|---|---|---|
| Ilaprozole |  | C19H18N4O2S | 366.1 | 150-155 °C | 172152-36-2 |
| Omeprazole |  | C17H19N3O3S | 345.4 | 156 °C | 73590-58-6 |
| Rabeprazole sodium |  | C18H21N3O3S | 359.4 | 140-141°C | 117976-90-6 |
| Lansoprazole |  | C16H14F3N3O2S | 369.3 | 178-182 °C | 103577-45-3 |

**Table 3 Details of selected acceptors**

| σ- Acceptor | | |
|---|---|---|
| S.No. | Name of compounds | Structure of compound |
| 1 | Iodine | $I_2$ |

| π-Acceptors | | |
|---|---|---|
| 2 | Bromanil |  |
| 3 | o-Chloranil |  |
| 4 | 2,5-Dihydroxy-3-undecyl-2,5- cyclohexadiene-1,4-dione(Embelin) |  |
| 5 | p-Chloranil |  |
| 6 | 2,5-Dichloro-pbenzoquinone |  |
| 7 | 2,5-Dihydroxy-pbenzoquinone |  |
| 8 | 2,3-Dichloro-5,6-dicyano-1,4- benzoquinone |  |
| 9 | 2,6-Dichloro-pbenzoquinone |  |

## RESULTS AND DISCUSSION

The experimental details are as presented in chapter II. All experiments were conducted at room temperature (27 $^{o}$C).

## ANTICANCER DRUGS

When a drug, e.g. imatinib is mixed with an acceptor 2, 5-DHPBQ in dichloromethane solvent an intense colour developed and remained stable for about ten minutes (Fig 1). The acceptor was maintained, in the all the cases, in excess of the drugs concentration to ensure a 1:1 complex. The mixture shows an absorption maximumat 486 nm. The absorbance was constant for the actual period of measurements. The new transition was not present in either donor or acceptor. No bandswere present due to formation of radical ions of the acceptor. The 485 nm band was therefore assigned tentatively to a charge transfer from the drug to an acceptor.

A plot of the absorbance with concentration of drug, imatanib is linear in the range 30-200 ppm (Fig 2)

showing the validity of Beer's law. Similar results were obtained with other anticancer drugs. The data for altretamine, imatinib and irinotecan areshown in tables 4 to 5 and 6. Since the interaction of letrozole with π-acceptors is weak no investigation has been carried out to determine letrozole by spectrophotometric method.

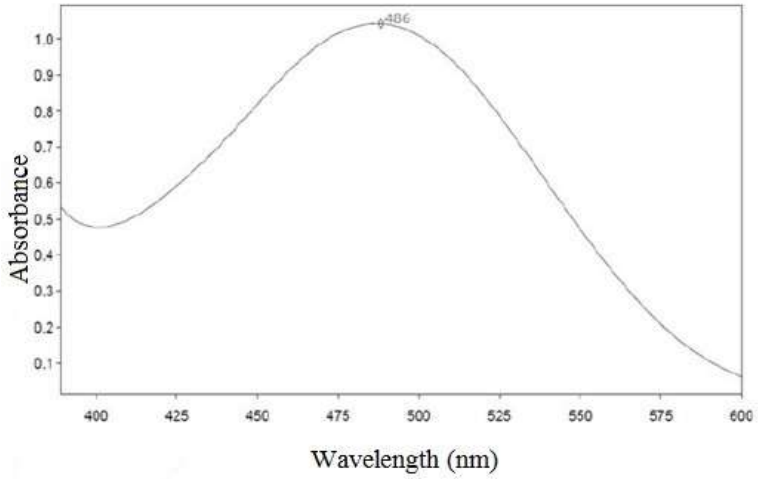



Fig 1 CT bandposition for imatinib -2, 5-DHPBQcomplex in $CH_2Cl_2$

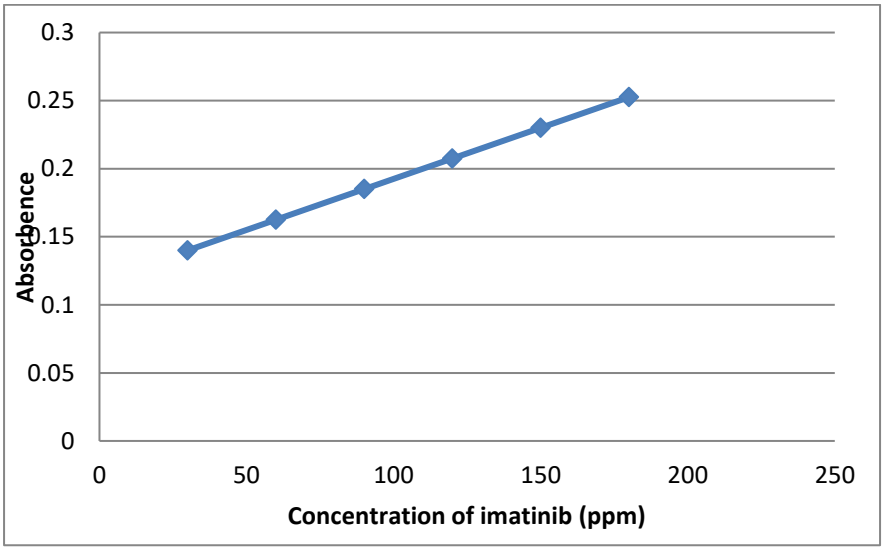



**Fig 2 Beer's law plot of imatinib with 2, 5 DHPBQ in $CH_2Cl_2$**

**Table 4 Determination of altretamine with different π-acceptors.**

| S.No. | Acceptor | λmax (nm) | LOQ (ppm) | Linear dynamic range (ppm) |
|---|---|---|---|---|
| 1 | Embelin | 463 | 82 | 82-700 |
| 2 | p-Chloranil | 518 | 196 | 196-1200 |
| 3 | Bromanil | 523 | 171 | 171-1200 |
| 4 | 2,5-DHPBQ | 483 | 51 | 51-360 |
| 5 | 2,5-DCPBQ | 467 | 62 | 62-480 |

Note: Time required for stable complex formation is: 2 to 5 minutes

**Table 5 Determination of imatinib with different π-acceptors**

| S.No. | Acceptor | λmax. (nm) | LOQ (ppm) | Linear dynamic range (ppm) |
|---|---|---|---|---|
| 1 | Embelin | 462 | 103 | 103-900 |
| 2 | p-Chloranil | 451 | 204 | 204-1200 |
| 3 | Bromanil | 460 | 162 | 162-1000 |
| 4 | 2,5-DHPBQ | 485 | 32 | 32-200 |
| 5 | 2,5-DCPBQ | 535 | 31 | 31-220 |

Note: Time required for stable complex formation is: 2 to 5 minutes.

**Table 6 Determination of irinotecan with different π-acceptors**

| S.No. | Acceptor | λmax. (nm) | LOQ\|ppm) | Linear dynamic range (ppm) |
|---|---|---|---|---|
| 1 | Embelin | 505 | 64 | 64-420 |
| 2 | p-Chloranil | 534 | 84 | 84-700 |
| 3 | Bromanil | 423 | 92 | 92-800 |
| 4 | 2,5-DHPBQ | 498 | 24 | 24-300 |
| 5 | 2,5-DCPBQ | 486 | 55 | 55-350 |

Note: Time required for stable complex formation is: 2 to 5 minutes.

It is interesting to note, that all the anti cancer drugs except letrozole with 2, 5- DHPBQ and 2,5-DCPBQ show a dynamic range in low ppm range, the haloquinone acceptors do better in the high concentration ranges.

## PROTON PUMP INHIBITORS

When a drug, e.g. ilaprazole is mixed with an acceptor embilin in dichloromethane solvent an intense colour developed and remained stable for about ten minutes Fig 3. The acceptor was maintained, in the all the cases, in excess of the drugs concentration to ensure a 1:1 complex. The mixture shows an absorption maximum at 501 nm. The absorbance was constant for the actual period of measurements. The new transition was not present in either the donor or acceptor. The 501 nm band is therefore due to a charge transfer from the drug to an acceptor. No further reaction took place.

A plot of the absorbance with concentration of drug, ilaprazole in the range 50- 450 ppm is shown in Fig 4. The plot is linear, showing the validity of Beer's law. Similar results were obtained with other Proton Pump Inhibitors. The data for ilaprazole, omeprazole, rabeprazole, lansoprazole, pantoprazole and ranitidine are shown in tables 7 to 12.

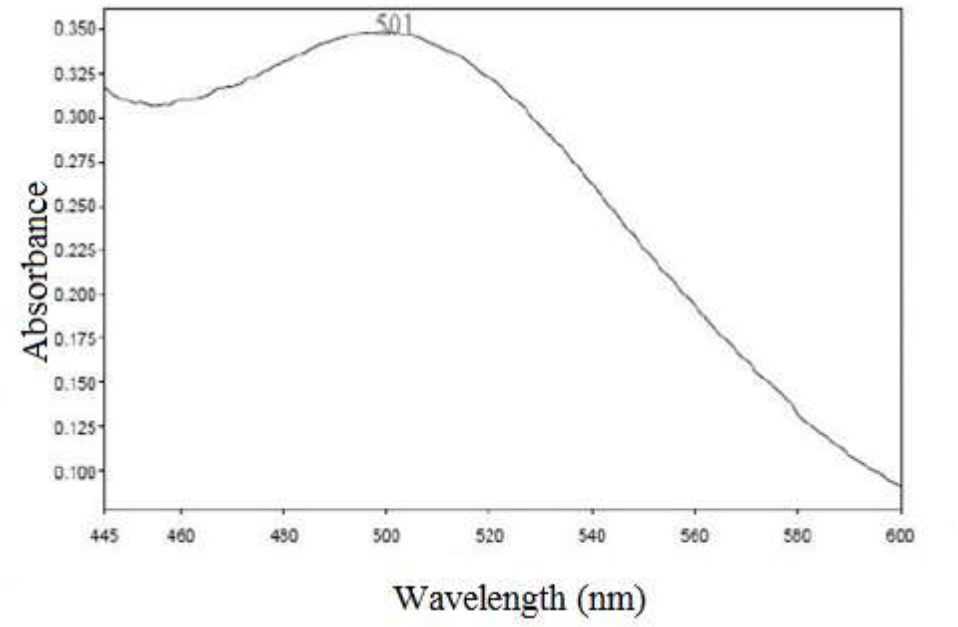



Fig 3 CT band position for ilaprazole- embilin complex in $CH_2Cl_2$

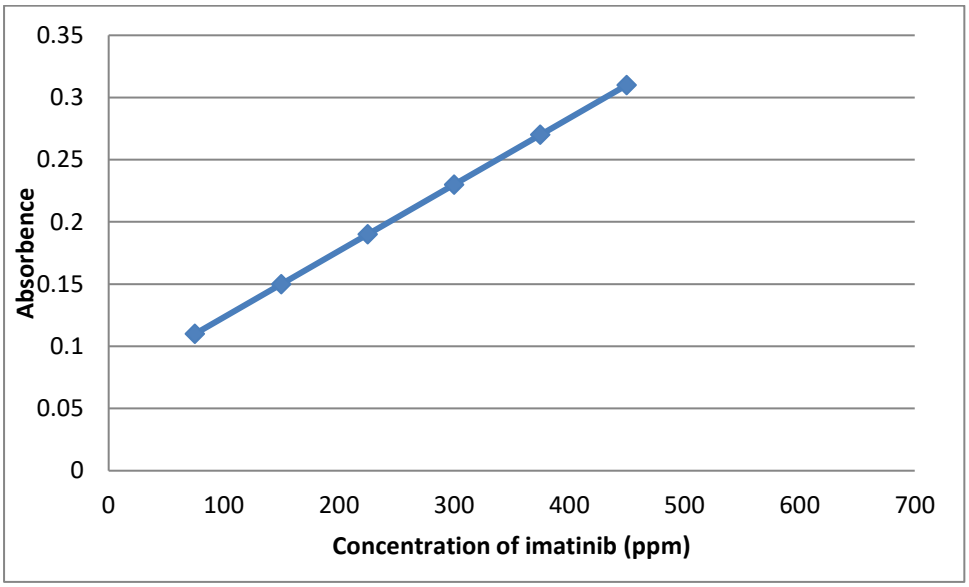



Fig 4 Beer's law graph of ilaprazole with 2, 5 DHPBQ in $CH_2Cl_2$.

**Table 7 Determination of ilaprozole with different π-acceptors.**

| S.No. | Acceptor | λmax. (nm) | LOQ (ppm) | Linear dynamic range (ppm) |
|---|---|---|---|---|
| 1 | Embelin | 502 | 41 | 41-250 |
| 2 | p-Chloranil | 524 | 85 | 85-700 |
| 3 | Bromanil | 425 | 35 | 35-200 |
| 4 | 2,5-DHPBQ | 497 | 51 | 51-480 |
| 5 | 2,5-DCPBQ | 407 | 45 | 45-200 |

Note: Time required for stable complex formation is: 2 to 5 minutes.

**Table 8 Determination of omeprazole with different π-acceptors.**

| S.No. | Acceptor | λmax. (nm) | LOQ (ppm) | Linear dynamic range (ppm) |
|---|---|---|---|---|
| 1 | Embelin | 497 | 91 | 91-600 |
| 2 | p-Chloranil | 428 | 94 | 94-700 |
| 3 | Bromanil | 414 | 52 | 52-450 |
| 4 | 2,5-DHPBQ | 485 | 45 | 45-250 |
| 5 | 2,5-DCPBQ | 477 | 35 | 35-250 |

Note: Time required for stable complex formation is: 2 to 5 minutes.

**Table 9 Determination of rabeprazole with different π-acceptors**

| S.No. | Acceptor | λmax. (nm) | LOQ (ppm) | Linear dynamic range (ppm) |
|---|---|---|---|---|
| 1 | Embelin | 513 | 55 | 55-500 |
| 2 | p-Chloranil | 514 | 96 | 96-700 |
| 3 | Bromanil | 452 | 75 | 75-600 |
| 4 | 2,5-DHPBQ | 405 | 67 | 67-550 |
| 5 | 2,5-DCPBQ | 445 | 43 | 43-300 |

Note: Time required for stable complex formation is: 2 to 5 minutes.

**Table 10 Determination of lansoprazole with different π-acceptors**

| S.No. | Acceptor | λmax. (nm) | LOQ (ppm) | Linear dynamic range (ppm) |
|---|---|---|---|---|
| 1 | Embelin | 493 | 22 | 22-140 |
| 2 | p-Chloranil | 405 | 32 | 32-200 |
| 3 | Bromanil | 431 | 23 | 23-140 |
| 4 | 2,5-DHPBQ | 406 | 24 | 24-200 |
| 5 | 2,5-DCPBQ | 448 | 13 | 13-70 |

Note: Time required for stable complex formation is: 2 to 5 minutes.

**Table 11 Determination of pantoprazole with different π-acceptors**

| S.No. | Acceptor | λmax. (nm) | LOQ (ppm) | Linear dynamic range (ppm) |
|---|---|---|---|---|
| 1 | Embelin | 488 | 18 | 18-140 |

| | | | | |
|---|---|---|---|---|
| 2 | p-Chloranil | 405 | 38 | 38-280 |
| 3 | Bromanil | 405 | 25 | 25-160 |
| 4 | 2,5-DHPBQ | 404 | 36 | 36-240 |
| 5 | 2,5-DCPBQ | 483 | 23 | 23-140 |

Note: Time required for stable complex formation is: 2 to 5 minutes

**Table 12 Determination of ranitidine with different π-acceptors**

| S.No. | Acceptor | $\lambda_{max.}$ (nm) | LOQ (ppm) | Linear dynamic range (ppm) |
|---|---|---|---|---|
| 1 | Embelin | 457 | 15 | 15-140 |
| 2 | p-Chloranil | 541 | 75 | 75-500 |
| 3 | Bromanil | 554 | 52 | 52-350 |
| 4 | 2,5-DHPBQ | 481 | 25 | 25-180 |
| 5 | 2,5-DCPBQ | 493 | 21 | 21-180 |

Note: Time required for stable complex formation is: 2 to 5 minutes

It is interesting to note, that the all proton pump inhibitors with 2, 5-DHPBQ and 2, 5-DCPBQ show a dynamic range in low ppm range, the haloquinone acceptors do better in the high concentration ranges.

## CONCLUSIONS

The author observed that irinotecan, imatinib, pantoprazole, lansoprazole, carvedilol, irbesartan and valsartan gave intense colours with all the five selected acceptors. Using this, methods havebeen developed for spectrophotometric determinationof the selected drugs. As reported earlier the interaction of letrozole and azelnidipine with π-acceptors are weak i.e., they form weak complexes. So, for their interactions high concentrations the drugs are needed. So, the author has not carried out analysis of these two drugs.

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Original Article

# Development Of Controlled release Formulations Of proton Pump Inhibitors Of Esomeprazole

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## Abstract

This study aims to develop a controlled release tablet (ECRT) dose version of Esomeprazol. Esomeprazol is a Proton Pump Inhibitor (PPI) medication used to treat gastro-esophageal reflux disease (GERD). Controlled release medication delivery systems increase patient compliance, therapeutic effectiveness, adverse effects & dosing regimen. The primary goal of paper is to create controlled release formulations of Esomeprazole Proton Pump Inhibitors. The following are the investigation's primary goals: Esomeprazole calibration curve construction for drug & polymer interaction research using FTIR and DSC. To create various controlled release formulations of Esomeprazol tablets using various polymer such as Poly-methacrylates suchas Eudra git- S100, Eudra git-L100, Eudra git-RSPO, Eudra git-RS100, Eudra git-RL100 & Eudra git RLPO through the Direct Compression technique.

**Keywords:** FTIR, DSC, Esomeprazole, Proton Pump Inhibitors

## INTRODUCTION

To achieve rapid and complete systemic medication absorption, most traditional oral drug formulations, such as tablet & capsule, are designed to release active agent soon after oral administration. These fast release medicines result in relatively quick drug absorption & commencement of accompanying pharmacological effects. Despite the fact that the medication is completely absorbed from dosage form, plasma drug concentrations refuse to rise in accordance with drug's PK profile. Eventually, plasma medication concentrations fall below minimal effective plasma concentration (MEC), resulting in therapeutic action loss. If a persistent therapeutic impact is necessary, another dosage is typically administered before this point.

An alternative to administering an extra dose isto employ a dosage form that allows for prolonged drug release, which keeps plasma drug concentrations higher than what is generally seen with immediate release dosage forms. [1]

Based on physic-cochemical, pharma-cologic & PK properties of drug, as well as qualities of materials employed in dosage form, modified release drug products are explored for alternative routes of administration. Many dissimilar terminology are currently developed to characterize the various sorts of modified release medication products depending on their drug release properties. [2]

The development of oral controlled release formulations suggests benefits such as regulated administration of therapeutic doses at the delivery rate, stable blood levels of the medication, reduced adverse effects, reduced dosage frequency, and improved patient compliance. The primary idea behind controlled release drug delivery is to optimize a medications bio-pharmaceutical, pharma-cokinetic & pharma-codynamic characteristics such that its utility is maximized and disease cure is attained. The following is the rationale behind the applicability of Esomeprazole 20 mg Controlled Release as a medication delivery system: To avoid dosage dumping of Proton Pump Inhibitors (Esomeprazole) consumption, Controlled Release is preferred, which means that in this situation, Esomeprazole 20mg must be delivered in a regulated manner, so that therapeutic concentration may be maintained by boosting bio-availability. Significantly, to improve site of action's consistent therapeutic index.

KenyR V et al., (2009) attempted to prolong once-daily ER matrix tablet of mino cycline, utilizing HPMC alone or in combination with ethylcellulose as matrix material in different amounts. The developed tablet was also compared to the innovator product. According to dissolution research results, compositions FC IV, FC V & FC VI demonstrated maxi[m] drug release up to 24 h, however innovator products were established to increase release only up to 14 h. [3]

According to Izhar Ahmed Syed etal. (2011), the CR pills exhibit near to zero order diltiazem release. In order to examine release mechanisms and kinetics, altered dissolution models were used to drug release data. It represents the type of drug release from matrix tablet & multilayer tablet, which used nonFickian diffusion & super case-II mechanisms, respectively. The mean dissolving time (MDT ) for formulations D-3 & D3L3 was 4.17 h and 16.45 h, respectively. [4]

SoadA.Yehia etal., (2012) state that dosage form drug delivery systems are particularly suitable for achieving SR/DR oral compositions due to the minimal danger of dose dumping and the flexibility of blending to generate changed release patterns with consistent results. One method to this goal was to develop and produce ER oral tablets of it opride as a highly water soluble medication while also increasing its GRT. [5]

Governor Govind Kishanrao et al., (2013) was to develop esomeprazole using a direct compression approach enteric coated with cellulose acetate phthalate. CDDS should be capable of defending medication along route to colon. Drug release and absorption should not take place in the gastrointestinal tract or small intestinal tract, and the bioactive ingredient should not be degraded at any of the dissolution sites until the system reaches the colon. [6]

The review of modern revision wasto plan & practice a mix product of naproxen & esomeprazol tablet by layer tableting technique by Irin Dewan et al., (2015). Naproxen and esomeprazole were mixed as a quick release portion that was put as a medication layer around enteric coated naproxen core throughout a coating solution to offer delayed action. Lastly, the product received a finishing touch of a coating layer with a coloring agent & polishing powder to protect the esomeprazol layer & advance the aesthetic value of product. [7]

The current study by Rajesh Kumar P et al. (2016) evaluates directly compressible esomeprazol Mg trihydrate enteric coated tablet that were primed to release medication in the upper GIT. Individual pills were made using super dis integrants such Ac-Di-Sol, CP, SSG, & diluents like Pharmatose DCL11 and Mannogem EZ. Acryl-EZE was used to enteric coat the tablets. The pills were tested for several physicochemical characteristics. The compression settings were within limitations, and the medication content in all formulations was designed to be consistent and dependable. [8]

K. Deepika et al. (2021) sought to increase bioavailability by developing controlled release formulations of Esomeprazol. Esomeprazol is a PPI that inhibits gastric acid output by targeting H+/K+-ATPase in gastric parietal cell. Weight variation, Hardness, Friability test, Thickness, Drug Content, & Invitro dissolution investigations of Esomeprazol controlled release tablets were evaluated. Assessment of the in-vitro dissolution uniqueness of all Esomeprazole formulations using the USP dissolving apparatus type II(paddle). To investigate mechanism of drug dissolution using kinetic parameters. To conduct stability studies on improved Esomeprazole formulations in accordance with ICH recommendations. [9]

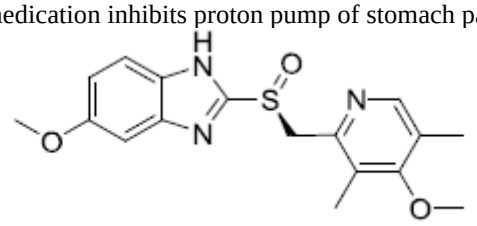
Justyna Srebro etal. (2022) outline discovery & development of PPIs, explore formulation concerns & provide current formulation options, prospects, and challenges. The review explains physico chemical features of PPIs, links them to pharmaco kinetic & pharmaco dynamic properties, & describes PPI stability, including identification of most essential variables influencing them. Moreover, options for qualitative & quantitative PPI analysis are briefly described. Their analysis includes analyzes commercial preparations containing PPIs that are accessible in US & European Union. The majority of the study focuses on state of art in development of innovative formulations containing PPIs, including nano particles, micro particles, mini tablet, pellet, bi layer, floating & muco adhesive tablet, as well as parenteral, transdermal & rectal preparations. [10]

To avoid NAB, Kwon etal. (2022) create a new esomeprazol magnesium loaded dual-release mini tablet polycap (DR polycap) with a delayed onset time & increased bio availability. The EPM minitablet core's composition resulted in fast medication release. In vitro release tests & in vivo pharmaco kinetic investigations were used to improve the mini-tablet combination. The AUC0-24h of DR polycap was equivalent to that of a comparable commercial product (Nexium®); Cmax was roughly 50% lower, and Tmax was approximately 1.7-fold longer. Finally, given of its dual-release properties, DR polycap is a better option to commercial medications in terms of NAB and dose compliance. [11]

The pharmaco kinetics and pharmaco dynamics of YPI-011 were compared to that of standard enteric-coated rabeprazole (Pariet®) by Bae S etal. (2023). The systemic exposure to rabeprazol at steady state following multiple dose treatments was likewise comparable in both dosage groups. The test treatment took less time to attain the maximal rabeprazole concentration. The PK-PD connection of PPI is well understood, & rabeprazole's quicker absorption resulted in amore rapid mode of action in acid suppression. As compared to standard enteric-coated rabeprazole, fixed dosage combination of rabeprazol with $NaHCO_3$ demonstrated quicker absorption &, as a result, more immediate stomach acid suppression with a similar systemic exposure of rabeprazol at steady state. [12]

## ESOMEPRAZOLE:

A potent inhibitor of gastric acid production used to treat stomach ulcers & zollingerellison syndrom. The medication inhibits proton pump of stomach parietal cells' H(+)-K(+)-ATPase (H(+)-K(+)-exchanging ATPase).



Molecularformula: $C_{17}H_{19}N_3O_3S$, Molecularweight: 345.416, Mono isotopic: 345.115 g/mol.
IUPAC Name: 5- methoxy -2- [(S)-(4- methoxy-3 5- dimethylpyridin-2yl) methanesulfinyl]-1H-1,3-benzoimidazol
Solubility : Soluble in methanol, DMSO (143 mg/ml at 25°C), ethanol (143 mg/ml at 25°C), & water (<1 mg/ml at 25°C).
Categories : ProtonPump Inhibitors (PPI), Gastroesophagealreflux disease (GERD).

## DISCUSSION

Graphs of Esomeprazol weretaken in Simulated Gastric fluid (pH 1.2) & in pH 6.8 phosphate buffer at 236nm & 238nm respectively.

**TABLE 1: OBSERVATIONSFOR GRAPH OF ESOMEPRAZOLEIN 0.1N HCL (236nm)**

| CONCENTRATION (MG/ML) | ABSORBANCE (nm) |
|---|---|
| 0 | .00 |
| 5 | .11 |
| 10 | .21 |
| 15 | .30 |
| 20 | .41 |
| 25 | .51 |
| 30 | .62 |
| 35 | .72 |
| 40 | .81 |

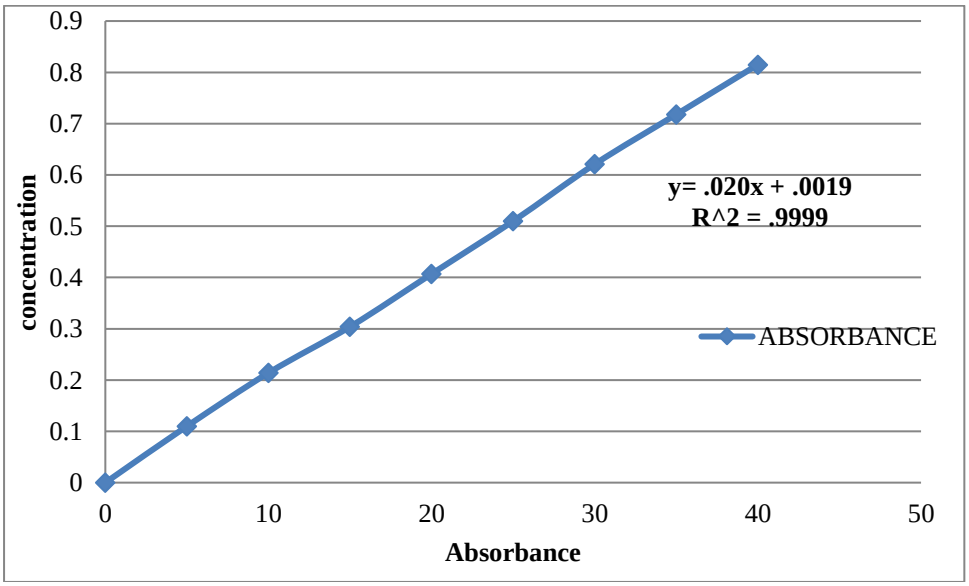


**FIG. 1: STANDARD GRAPHOF ESOMEPRAZOL IN 0.1N HCL**

**TABLE 2: OBSERVATION FORGRAPH OF ESOMEPRAZOL IN PH 6.8 PHOSPHATE BUFFER (238nm)**

| CONCENTRATION (mg/ml) | ABSORBANCE (nm) |
|---|---|
| 0 | .00 |
| 5 | .09 |
| 10 | .20 |
| 15 | .29 |
| 20 | .38 |
| 25 | .49 |
| 30 | .59 |
| 35 | .70 |
| 40 | .79 |

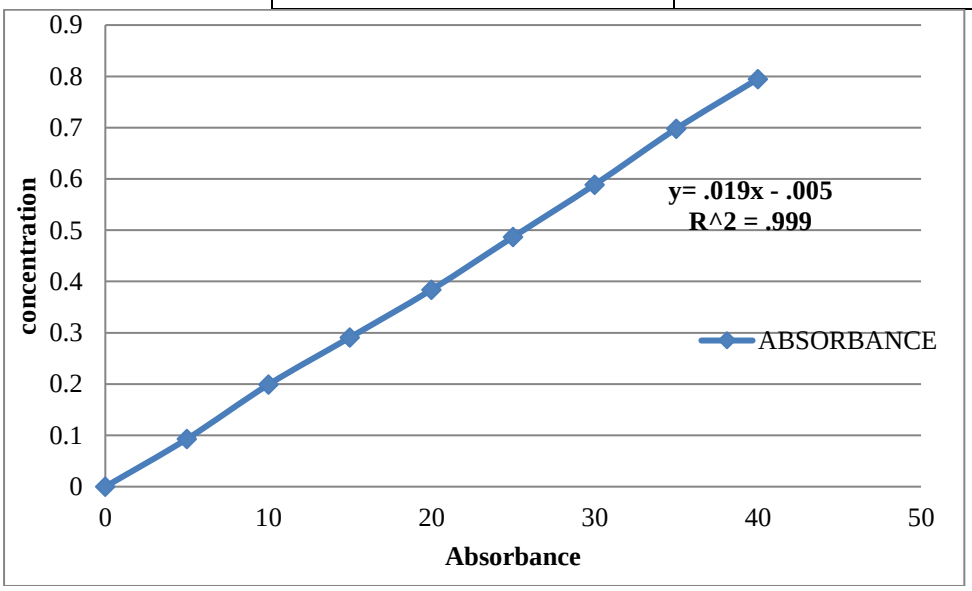



**FIG. 2: STANDARD GRAPHOF ESOMEPRAZOLE PH 6.8 PHOSPHATEBUFFER**

**DRUG - EXCIPIENTCOMPATABILITYSTUDIES:**
**FTIR**

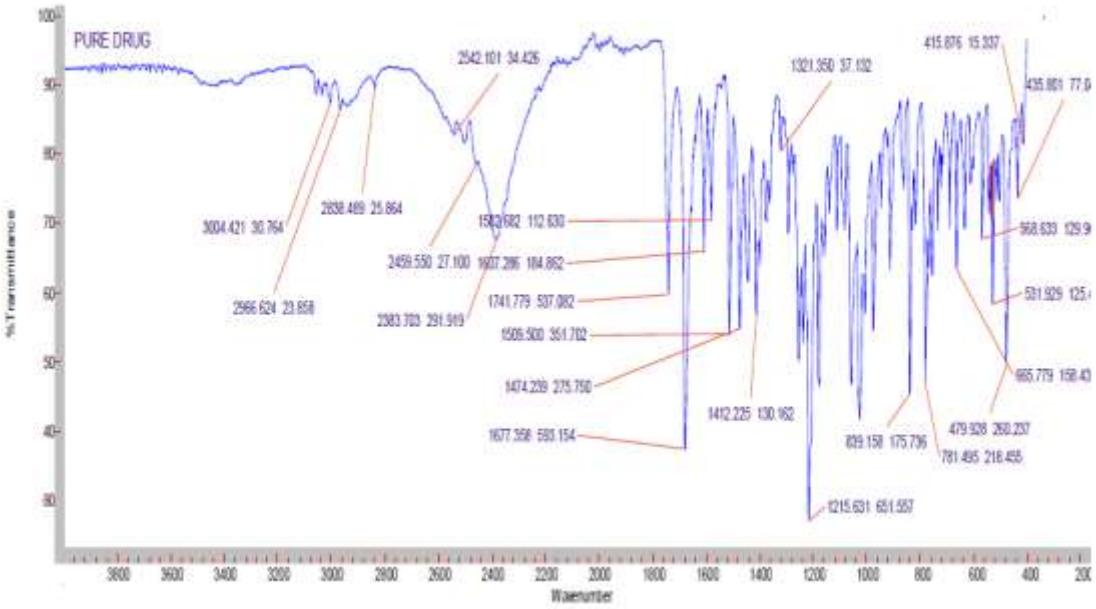



**FIG. 3: FT-TR SPECTRUMOF ESOMEPRAZOLE PURE DRUG.**


**FIG. 4: FT-IR SPECTRUMOF ESOMEPRAZOLE + EUDRAGITRSPO**

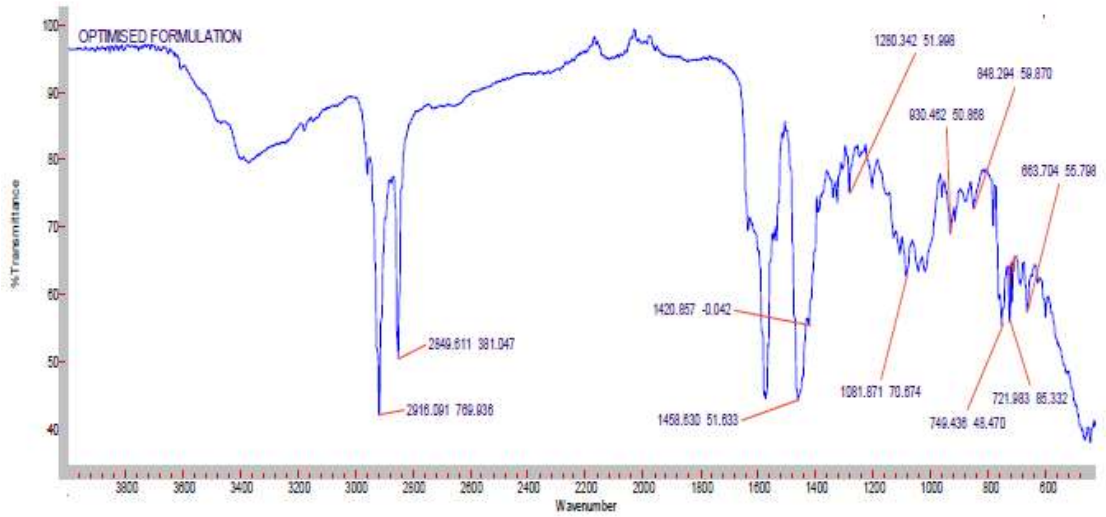



**FIG. 5: FT-IR SPECTRUM OFESOMEPRAZOLE OPTIMIZED TABLET FORMULATION**

**FORMULATION STUDIES**

**In-vitro evaluation ofEsomeprazole Controlled Release tablets for physicochemical characteristics : (Mean+SD) (n=3)**

**TABLE 4 FLOW PROPERTIESOF POWDER BLEND FOR ESOMEPRAZOL**

| FORMULATION CODE | BULKDENSITY ($gm/cm^3$)* | TAPPEDDENSITY ($gm/cm^3$)* | HAUSNER RATIO (HR)* | CARR'SINDEX (CI)* | ANGLE OF REPOSE (Θ)* |
|---|---|---|---|---|---|
| F1 | .5 ± .020 | .53 ± .030 | 0.1 ± .051 | 16.0 ± .081 | 24°.14' ± .65 |
| F2 | .5 ± .030 | .54 ± .061 | 1.0 ± .060 | 16.2 ± .042 | 23°.35' ± .35 |
| F3 | .49 ± .091 | .56 ± .041 | 1.1 ± .090 | 14.7 ± .071 | 24°.68' ± .63 |
| F4 | .52 ± .071 | .53 ± .060 | 1.0 ± .030 | 16.6 ± .090 | 25°.25' ± .72 |
| F5 | .53 ± .070 | .58 ± .051 | 1.1 ± .070 | 15.8 ± .062 | 24°.97' ± .57 |
| F6 | .54 ± .022 | .55 ± .080 | 1.1 ± .081 | 15.0 ± .020 | 24°.13' ± .55 |
| F7 | .55 ± .081 | .58 ± .031 | 0.9 ± .061 | 16.0 ± .041 | 23°.85' ± .86 |
| F8 | .56 ± .021 | .63 ± .041 | 1.1 ± .080 | 14.8 ± .030 | 25°.03' ± .23 |
| F9 | .54 ± .033 | .53 ± .040 | 1.1 ± .030 | 17.0 ± .081 | 24°.97' ± .36 |
| F10 | .49 ± .010 | .53 ± .091 | 0.1 ± .071 | 14.0 ± .030 | 25°.65' ± .64 |
| F11 | .48 ± .071 | .52 ± .050 | 1.1 ± .041 | 14.5 ± .061 | 27°.78' ± .78 |
| F12 | .5 ± .022 | .54 ± .031 | 1.1 ± .062 | 15.3 ± .030 | 26°.97' ± .26 |
| F13 | .49 ± .032 | .61 ± .071 | 1.1 ± .053 | 13.5 ± .023 | 24°.64' ± .12 |
| F14 | .47 ± .081 | .57 ± .021 | 0.1 ± .031 | 12.3 ± .050 | 26°.36' ± .74 |
| F15 | .5 ± .071 | .59 ± .041 | 1.1 ± .070 | 14.6 ± .021 | 27°.18' ± .58 |
| F16 | .5 ± .052 | .56 ± .061 | 1.1 ± .062 | 11.1 ± .050 | 25°.24' ± .35 |

| | | | | | |
|---|---|---|---|---|---|
| F17 | .49 ± .010 | .59 ± .092 | 1.1 ± .081 | 12.3 ± .032 | 26°.56' ± .26 |
| F18 | .5 ± .062 | .58 ± .040 | 1.1 ± .062 | 13.4 ± .061 | 24°.98' ± .14 |
| F19 | .49 ± .032 | .55 ± .071 | 0.1 ± .021 | 12.4 ± .012 | 25°.46' ± .46 |

Tablet powder blend was subjected to various pre formulation parameters. The bulk density of all formulations wasfound to be in rangeof .48 ± .071 to .56 ± .021 (gm/cm3) showing that powder has goodflow properties. The tappeddensity of all formulations was found tobe in range of .52 ± .050 to .63 ± .041 showing powder has good flowproperties. The hausner's ratioranging b/w .9 ± .061 to 1.1 ± .080 indicating powder hasgoodflow properties The Carr's index of all formulations was found tobe in range of 11.1 ± .050 to 17.0 ± .081. The angleof repose of all formulations was found tobe in range of 23°.35' ± .35 to 27°.78' ± .78. All thesevalue indicates that powder blend has goodflow properties.

## INIVITROIEVALUATION OF ESOMEPRAZOL CONTROLLED RELEASETABLETS FOR POSTCOMPRESSION CHARACTERISTICSI

**TABLE 5 PHYSICO CHEMICALCHARACTERIZATION OFESOMEPRAZOLE CONTROLLEDRELEASE TABLETS**

| FORMULATION CODE | WEIGHT VARIATIO(mg) | HARDNESS ($kg/cm^2$) | FRIABILITY (%) | THICKNESS (mm) | DRUG CONTEN (%) |
|---|---|---|---|---|---|
| F1 | 100.1 ± .47 | 4.6 ± .42 | .51 ± .14 | 3.7 ± .28 | 99.16 ± .74 |
| F2 | 101.5 ± .85 | 4.2 ± .24 | .58 ± .47 | 4.2 ± .25 | 98.95 ± .35 |
| F3 | 99.2 ± .85 | 3.8 ± .15 | .62 ± .28 | 3.5 ± .15 | 99.75 ± .65 |
| F4 | 101.5 ± .85 | 3.6 ± .38 | .76 ± .65 | 4.8 ± .56 | 98.95 ± .12 |
| F5 | 98.8 ± .12 | 4.3 ± .23 | .55 ± .26 | 3.8 ± .36 | 99.58 ± .36 |
| F6 | 99.7 ± .33 | 4.5 ± .55 | .66 ± .17 | 4.2 ± .24 | 99.86 ± .14 |
| F7 | 98.5 ± .54 | 3.7 ± .13 | .58 ± .75 | 3.5 ± .25 | 98.86 ± .36 |
| F8 | 101.4 ± .43 | 3.4 ± .12 | .48 ± .34 | 3.4 ± .62 | 99.35 ± .32 |
| F9 | 99.2 ± .45 | 3.9 ± .36 | .56 ± .36 | 3.6 ± .26 | 99.62 ± .45 |
| F10 | 101.1 ± .53 | 3.6 ± .26 | .65 ± .43 | 3.8 ± .66 | 98.66 ± .75 |
| F11 | 99.3 ± .44 | 4.3 ± .63 | .58 ± .53 | 4.3 ± .46 | 99.55 ± .53 |
| F12 | 99.6 ± .73 | 3.8 ± .54 | .66 ± .75 | 3.7 ± .16 | 98.58 ± .26 |
| F13 | 101.3 ± .22 | 3.6 ± .17 | .65 ± .16 | 4.6 ± .88 | 99.63 ± .28 |

## EVALUATIONOF CONTROLLED RELEASE TABLET OF ESOMEPRAZOLE:
## APPEARANCE:

The tablets were visually examined & found tobe free of defects suchas cap, chipping, & lamination.

## PHYSICAL CHARACTERISTICS:

Weight variation, hardness, friability, thickness & drug content of ECRT (F1-F19) were determined, & the results of formulations (F1-F19) were found tobe within limitations stipulated in official literature.

## WEIGHTIVARIATION:

Tablets of each batch were subjected to weight variation test, difference in weight & percent deviation were calculated foreach tablet. Average wt of tablet is approximatelyin range of 98.5 ± .54 to 101.5 ± .85, so permissible limit is ±7.5% (more than 80mgLess than 250mg). Thetablet wts were within Pharma copoeial specifications.

## TABLETIHARDNESS:

The hardness of 3 tablets from each batch was tested using a Monsanto hardness tester. The findings revealed that hardness of tablets ranged from 3.4 ± .12 to 4.6 ± .42 kg/cm$^2$. This shows that the tablet is of high quality.

## PERCENTFRIABILITY:

The friability of all formulations was determined to be between .48 ± .34 to .76 ± .65 %. This stated that the produced CR pill was easy to handle.

## DIMENSIONI(DIAMETER ANDTHICKNESS):

Individual product thickness & dia parameters are possible. Extreme variance in tablet thickness and diameter might cause packaging and customer acceptability issues. The dimension (diameter) of all formulations' tablets was determined to be 6.1 ± 0.1 mm, with thickness ranging from 3.4 ± .62 to 4.8 ± .56.

## DRUGCONTENT:

The active component content in the formulation was determined to be b/w 98.58 ± .26 to 99.75 ± .65 % w/w, which is within IP limit (i.e. 90.0 – 110.0% w/w). Weight fluctuation, friability, hardness, thickness & drug content were all determined tobe within limits.

## INVITRO DISSOLUTION STUDIES OF ECRT:

**TABLE 6 IN-VITRO DRUGR ELEASE STUDIES OF ECRT (F1-F7)**

| TIME (HOURS) | CUMULATIVE % DRUG RELEASE | | | | | | |
|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 6.97±0.75 | 6.43±0.58 | 7.07±0.46 | 7.36±0.75 | 15.56±.35 | 6.42±0.64 | 14.21±0.69 |
| 2 | 7.86±0.36 | 8.52±0.65 | 18.73±.87 | 14.39±0.57 | 19.94±.47 | 12.59±0.43 | 19.65±0.76 |
| 4 | 14.65±0.83 | 13.26±0.43 | 27.74±.23 | 19.22±0.46 | 28.33±.54 | 24.26±0.94 | 24.98±0.97 |
| 6 | 18.64±0.52 | 22.73±0.93 | 39.11±.72 | 24.21±0.95 | 35.29±.72 | 38.12±0.67 | 28.76±0.24 |
| 8 | 23.36±0.19 | 33.79±0.34 | 47.44±0.37 | 31.42±0.21 | 40.11±.46 | 49.94±0.43 | 35.34±0.76 |
| 10 | 29.82±0.23 | 41.21±0.87 | 58.35±0.92 | 39.73±0.36 | 48.87±.25 | 57.15±0.79 | 44.50±0.53 |
| 12 | 34.61±0.78 | 50.22±0.54 | 63.53±0.63 | 51.29±0.28 | 55.83±.92 | 69.93±0.64 | 54.56±0.94 |
| 14 | 43.07±0.92 | 57.33±0.11 | 69.89±0.56 | 60.11±0.72 | 61.12±.29 | 75.66±0.92 | 61.05±0.58 |
| 16 | 48.71±0.45 | 68.03±0.45 | 74.29±0.43 | 72.14±0.93 | 69.76±.62 | 81.78±0.52 | 64.98±0.86 |
| 18 | 57.22±0.69 | 74.39±0.37 | 79.01±0.96 | 78.77±0.38 | 73.58±.91 | 85.19±0.74 | 72.03±0.75 |
| 20 | 68.35±0.43 | 76.15±0.92 | 81.43±0.53 | 83.64±0.67 | 79.56±.68 | 91.26±0.59 | 76.92±0.68 |
| 22 | 77.23±0.34 | 81.12±0.54 | 83.36±0.68 | 86.89±0.46 | 85.32±.75 | 94.18±0.86 | 85.88±0.93 |
| 24 | 86.77±0.28 | 88.27±0.45 | 90.67±0.96 | 91.03±0.25 | 91.93±.54 | 97.47±0.97 | 91.12±0.78 |

**TABLE 7: INVITRO DRUG RELEASE STUDIES OF ECRT (F8 to F14)**

| Time (hours) | CUMULATIVE % DRUG RELEASE | | | | | | |
|---|---|---|---|---|---|---|---|
| | F8 | F9 | F10 | F11 | F12 | F13 | F14 |
| **0** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **1** | 10.54±.82 | 10.12±.66 | 8.26±.35 | 7.53±.35 | 7.83±.45 | 8.15±0.73 | 7.63±0.48 |
| **2** | 19.27±.53 | 16.75±.74 | 11.73±.74 | 10.15±.74 | 10.25±.83 | 10.61±0.62 | 9.53±0.63 |
| **4** | 29.22±.97 | 28.36±.23 | 18.54±.63 | 16.55±.52 | 17.27±.54 | 13.72±0.81 | 16.55±0.41 |
| **6** | 36.35±.65 | 33.45±.86 | 25.44±.74 | 21.63±.97 | 24.36±.68 | 19.28±0.63 | 20.36±0.87 |
| **8** | 41.38±.75 | 43.46±.54 | 33.73±.84 | 26.23±.43 | 35.27±.24 | 24.11±0.92 | 26.25±0.59 |
| **10** | 49.63±.53 | 49.35±.83 | 42.14±.55 | 34.76±.62 | 44.72±.57 | 30.79±0.67 | 31.82±0.98 |
| **12** | 58.02±.96 | 58.12±.97 | 54.45±.97 | 40.16±.48 | 53.18±.83 | 35.27±0.85 | 36.29±0.72 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **14** | 65.46±.43 | 66.95±.44 | 63.28±.45 | 44.35±.75 | 61.66±.94 | 46.09±0.98 | 48.26±0.63 |
| **16** | 73.56±.56 | 69.37±.33 | 75.66±.74 | 49.26±.22 | 73.97±.35 | 49.27±0.43 | 48.71±0.42 |
| **18** | 77.47±.65 | 74.15±.83 | 83.25±.36 | 56.72±.74 | 80.33±.85 | 58.99±0.81 | 57.22±0.65 |
| **20** | 80.36±.97 | 79.75±.64 | 87.53±.84 | 67.24±.65 | 84.42±.92 | 66.45±0.79 | 69.47±0.53 |
| **22** | 84.66±.34 | 84.87±.57 | 91.78±.64 | 78.75±.83 | 88.26±.37 | 74.32±0.66 | 78.83±0.66 |
| **24** | 90.86±.85 | 89.97±.96 | 93.83±.25 | 88.28±.35 | 92.62±.64 | 89.13±0.43 | 90.77±0.98 |

**TABLE 8 INVITRO DRUG RELEASE STUDIES OF ECRT (F 15 - F 19)**

| **TIME (HOURS)** | **CUMULATIVE % DRUG RELEASE** | | | | |
|---|---|---|---|---|---|
| | **F15** | **F16** | **F17** | **F18** | **F19** |
| **0** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **1** | 9.26±.54 | 5.98±.45 | 7.77±.64 | 7.46±.42 | 8.86±.36 |
| **2** | 15.54±.42 | 9.94±.84 | 10.73±.75 | 9.97±.75 | 10.48±.25 |
| **4** | 20.36±.75 | 13.26±.33 | 19.82±.83 | 15.63±.58 | 19.35±.17 |
| **6** | 22.84±.93 | 19.28±.56 | 27.78±.86 | 19.35±.23 | 26.86±.64 |
| **8** | 29.32±.45 | 24.94±.86 | 34.66±.62 | 25.86±.26 | 34.24±.25 |
| **10** | 38.78±.66 | 30.25±.93 | 45.86±.24 | 30.67±.44 | 41.18±.75 |
| **12** | 49.94±.83 | 37.36±.25 | 54.45±.54 | 36.93±.13 | 53.56±.56 |
| **14** | 58.36±.54 | 45.26±.53 | 62.75±.37 | 44.25±.25 | 62.86±.37 |
| **16** | 70.84±.55 | 49.83±.44 | 74.15±.46 | 49.97±.56 | 73.83±.63 |
| **18** | 79.97±.46 | 58.93±.73 | 81.35±.67 | 58.46±.86 | 81.18±.75 |
| **20** | 84.36±.35 | 69.28±.88 | 85.12±.76 | 69.86±.56 | 84.53±.44 |
| **22** | 88.25±.77 | 78.46±.48 | 89.66±.56 | 78.93±.65 | 88.45±.15 |
| **24** | 92.46±.34 | 87.94±.46 | 91.44±.27 | 89.78±.75 | 92.13±.26 |

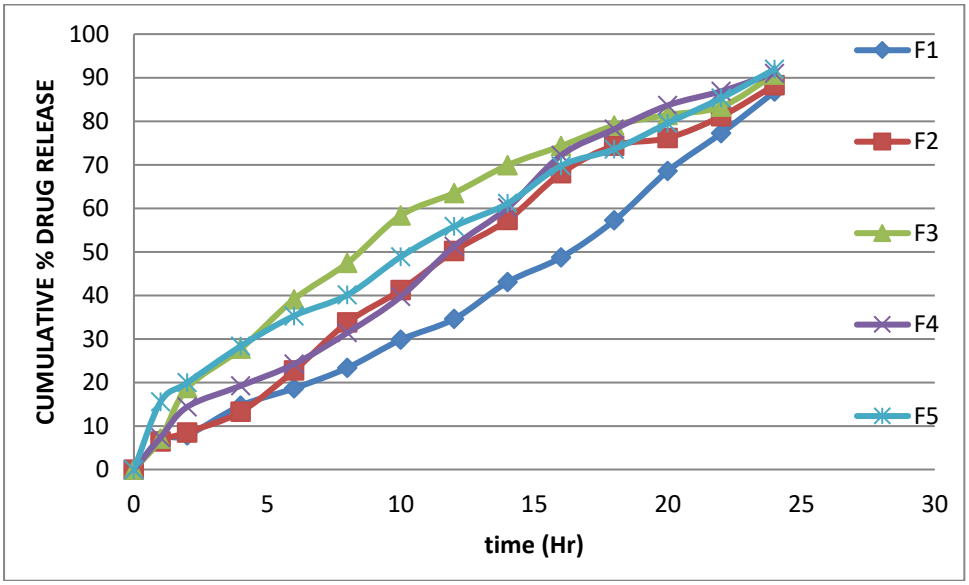



**FIG. 6 DISSOLUTIONGRAPHS FOR THEFORMULATIONS F1-F5**

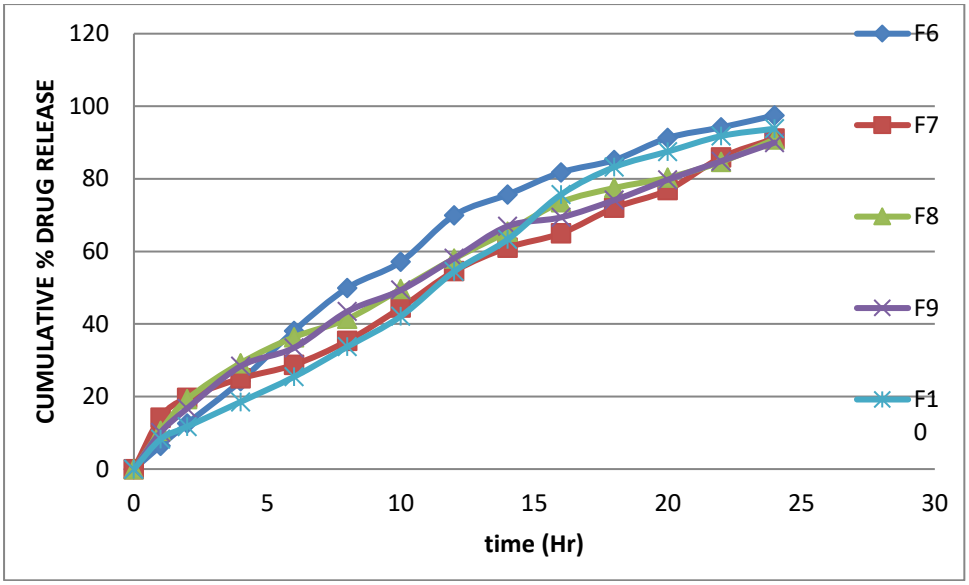



**FIG. 7 DISSOLUTIONGRAPHS FOR THE FORMULATIONSF6 TO F10**

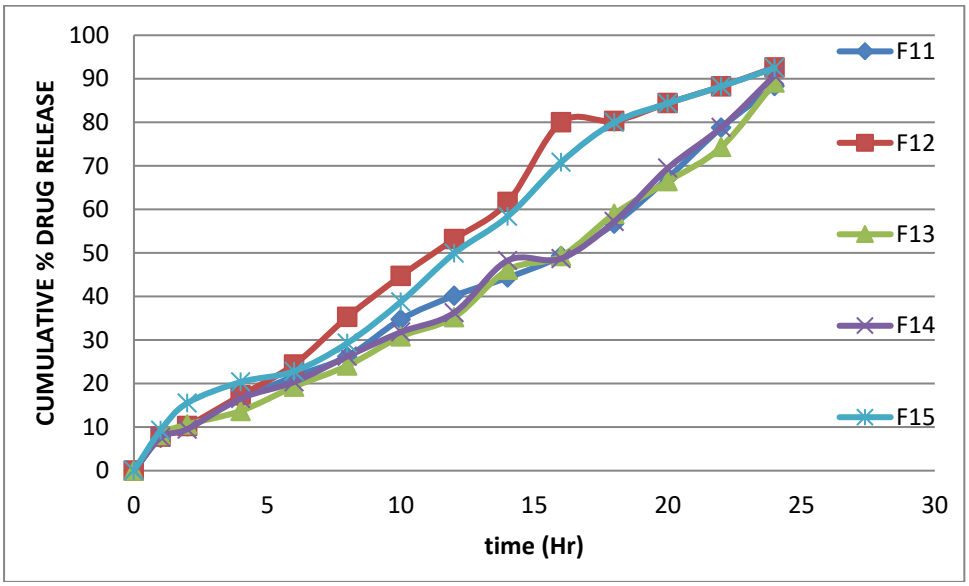



**FIG. 8 DISSOLUTIONGRAPHS FOR THE FORMULATIONSF11 TO F15**

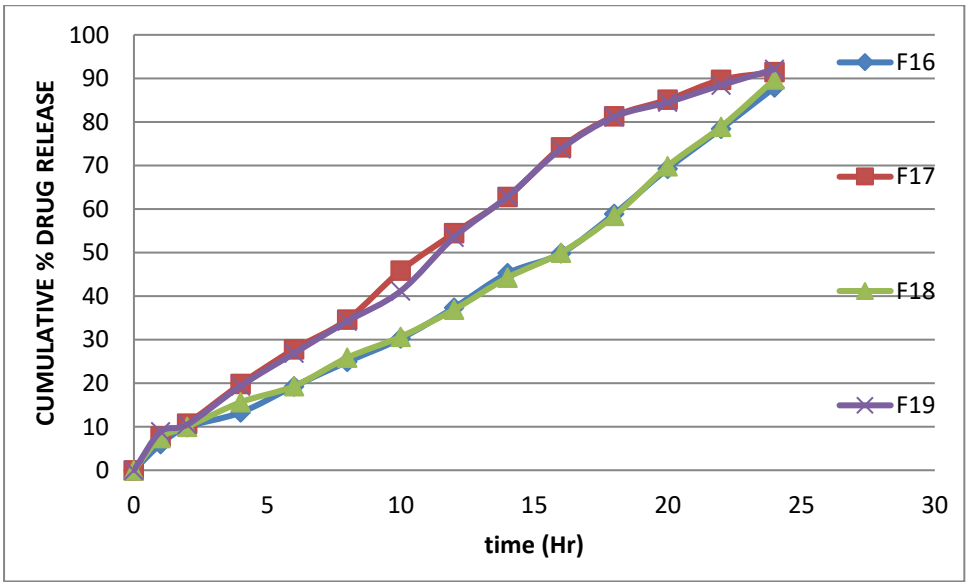


**FIG. 9 DISSOLUTIONGRAPHS FOR THEFORMULATIONS F16 TO F19**

## IN-VITRODRUG RELEASESTUDIES OF ESOMEPRAZOL:

The prepared ECRT were evaluated for dissolution studies inacid buffer (pH-1.2) for 2 hrs, 4.5 pH acetate buffer for2 hrs, 6.8 pH phosphatebuffer for 8 hrs & 7.4 pH phosphatebuffer for 12 hrs % drug release was calculated atvarious timeintervals. The results were shown in Table. 6 to 8 and Fig.6 to 9.

To prepare different controlled release formulations of Esomeprazol tablet with differentpolymers like Polymethacrylatessuch as EudragitS100, L100, RSPO, RS100, RL100, RLPO & Talc is glidant, magnesiumstearate is lubricant & Dicalcium Phosphate was used as diluents by Direct compression method.

Eudragit-S100-containing formulations F1 and F2. At the conclusion of the 24th hour, the cumulative% drug release for Formulations F1 and F2 was 86.76±.27 % and 88.26±.46 %, respectively. EudragitL100-containing formulations F3 and F4. At the conclusion of the 24th hour, the drug release rates for Formulations F3, F4 were 90.66±.95 %, 91.04±.26 %, respectively.

F5 and F6 formulations contain Eudragit-RSPO. At the conclusion of the 24th hour, the drug release rates for Formulations F5, F6 were 91.94±.55 %, 97.46±.96%, respectively. Formulation F7 is a mix of EudragitS100 and EudragitL100. At the conclusion of the 24th hour, Formulation F7 demonstrated drug release of 91.13±.77 %. Formulation F8 with EudragitS100.

At the conclusion of the 24th hour, the drug release from Formulation F7 was 90.86±.85%. Formulation F9 is a mix of EudragitL100 and EudragitRSPO. The medication release rate in Formulation F9 was 89.97±.96% at the conclusion of the 24th hour.

Formulation F10 with EudragitRS100. The medication release rate in Formulation F10 was 93.83±.25% at the conclusion of the 24th hour. F11 has a mixture of EudragitRS100 and EudragitRL100. The medication release rate in Formulation F11 was 88.28±.35% at the conclusion of the 24th hour. F12 and F13 formulations include Eudragit-RL100. At the conclusion of the 24th hour, the drug release rates for Formulations F12 and F13 were 92.62±.66%, 89.14±.44%, respectively.

F14 and F15 formulations incorporating EudragitRS100. At the conclusion of the 24th hour, the drug release rates for Formulations F14 and F15 were 90.76±.97%, 92.46±.34%, respectively. Formulation F16 is a mix of EudragitRS100 and EudragitRL100. The medication release rate in Formulation F16 was 87.94±.46%at the conclusion of the 24th hour. F17 formulation with EudragitRL100. At the conclusion of the 24th hour, the drug release in Formulation F17 was 91.44±.27%%.

F18 and F19 include a mixture of EudragitRL100 and EudragitRLPO. The drug release rates for Formulations F18 and F19 were 89.78±.75%, 92.13±.26%, respectively, at the end of the 24th hour.

Results of drug release shown that Esomeprazol wasreleased in acontrolled behaviour from all formulations where formulation F-6 showed maximum cumulative % drug release i.e. 97.46±.96 at end of 24th hr which was intent of finalized formulationwhile others being not reached to time point of maximum release still extending release.

## CONCLUSIONS

Esomeprazol is a PPI used for treatment of GERD. It has a short bio logical halflife (1–1.5 hrs), low bio availability (50–68%), & a limited therapeutic index. Esomeprazol was identified as a good choice for controlled medication delivery systems based on all of these features. Preformulation tests for Esomeprazole were conducted to identify drug excipient interactions utilizing FTIR and DSC investigations, which revealed that the excipients were compatible. Esomeprazol controlled release tablets were made using the direct compression method and several poly methacrylates, including Eudragit -S 100, Eudragit -L100, Eudragit RSPO, EudragitRS 100, EudragitRL 100, & Eudragit - RLPO. The Direct Compression method was used to prepare different controlled release formulations of Esomeprazol tablets with different polymers such as Poly methacrylates such as Eudragit -S 100, L -100, RSPO, RS -100, RL -100, RLPO & Talc as glidant, magnesium stearate as lubricant, & Dicalcium Phosphate as diluents. Before and post formulation features of esomeprazole manufactured tablet mix and tablets were evaluated, including flow qualities & weight fluctuation, hardness, friability, & drug content. All of these criteria yielded results that were within pharma copoeial limitations. Formulations developed are intended for invitro dissolution & release kinetic investigations. Based on results, the F6 formulation was selected as the best of all formulations in terms of drug release & mechanism.

This formulation was preserved for a 6-month stability study in accordance with ICH rules, and the findings confirmed that the improved one is stable.

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