DESIGN, DEVELOPMENT AND IN-VITRO EVALUATION OF PRAZOSIN HYDROCHLORIDE DONUT SHAPED FLOATING TABLETS

Thesis submitted in partial fulfillment for the requirements of the degree of

MASTER OF PHARMACY,
FACULTY OF ENGINEERING AND TECHNOLOGY JADAVPUR UNIVERSITY

By

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2019

Dedicated.....

To my family, my guide Dr Ketousetuo Kuotsu and all well-wishers.

CERTIFICATE

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This is to certify that the research work entitled **"DESIGN, DEVELOPMENT AND IN-VITRO EVALUATION OF PRAZOSIN HYDROCHLORIDE DONUT SHAPED FLOATING TABLETS"** *has been carried out by* ***ANJALI MONDAL, B.Pharm,*** *having Examination Roll No:* ***M4PHA19010*** *and Registration No:* ***140834 of 2017-18*** *under my supervision in the Department of Pharmaceutical Technology, Jadavpur University. She has incorporated her findings into this thesis of the same title, being submitted by her in partial fulfillment of the requirements for the degree of* ***Master of Pharmacy*** *of* ***Jadavpur University****. She has carried out this research work independently and with proper care and attention to my entire satisfaction.*

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Declaration of Originality and Compliance of Academic Ethics

I do hereby declare that this thesis entitled " **DESIGN, DEVELOPMENT AND IN-VITRO EVALUATIONOF PRAZOSIN HYDROCHLORIDE DONUT SHAPED FLOATING TABLETS***"* *is a record of literature survey and original research work done by me as a part of my* ***Master of Pharmacy (Pharmaceutics)*** *studies at* ***Jadavpur University****. All information in this document have been obtained and presented in accordance with academic rules and ethical conduct. I also declare that as required by these rules and conduct, I have fully cited and referenced all materials and results that are not original to this work.*

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PREFACE

A rapid onset of pharmacological action is often desired from drugs, especially in the treatment of acute disorders. This can be effectively achieved by parenteral administration, but this method may not always be convenient for the patient. Therefore, there is a growing interest in developing newer drugs, non-parenteral reliable and convenient dosage forms using different administration routes where drugs are rapidly absorbed into the systemic circulation. The present research work entitled "*Design, Development and Evaluation of Oral Floating Donut Shaped Prazosin hydrochloride Tablets*" was designed to formulate controlledrelease dosage form of prazosin hydrochloride, a selective alpha-adrenergic receptor blocking agent widely as antihypertensive agent which release the drug at a constant rate i.e. zero order fashion in the stomach.

Prazosin hydrochloride has wonderful clinical effectiveness in the treatment of essential hypertension. It is extensively used in antihypertensive therapy. However, single dose of prazosin hydrochloride can maintain the lowering of blood pressure upto 6-8 hrs. Hence, repetitive medication is required in a day to maintain the blood pressure. This necessitates the development of controlled release formulation to maintain relatively constant blood levels for longer duration of time. In addition, oral route is one of the most potential and convenient mode of administration of pharmaceutical dosage forms for the delivery of drugs through the gastro-intestinal tract. In spite of many dosage forms available in the market administered through oral route, tablet has achieved maximum attention due to its accurate administration of drug that can be absorbed through the gastro-intestinal tract. Hence, the aim of this work is the development of controlled release tablet dosage form of prazosin hydrochloride, which would stay in the stomach for long duration to promote the maximum absorption of prazosin hydrochloride in that region.

In the present research work, donut shaped tablets were prepared using Prazosin hydrochloride as model drug. Here different binders were used including of hydroxypropyl methyl cellulose and xanthan gum in different ratio. The tablets were fabricated by direct compression using hydroxyl propyl methylcellulose and xanthan gum as release retarding polymers. Efforts has been made by recent researches to establish the application of natural as well as synthetic polymers to form a gellified hydrocolloid layer capable of entrapping CO_2 making buoyancy unity for the purpose of effective floating of the tablets.

This thesis is divided into various chapters describing fundamentals, methodologies, results and discussion, summary and conclusion and future scope.

Chapter 1 describes the fundamentals related to floating drug delivery system, gastrointestinal tract physiology. Chapter 2 describes the materials, methodologies including drug profile and properties of different components of the tablets. Chapter 3 contains all the tables and graphs. Chapter 4 includes the results and discussion of the present work. Chapter 5 includes the summary and conclusion. Chapter 6 describes the future scope and Chapter 7 facilitates references of the present work.

CONTENTS

CHAPTER I

CHAPTER 1: INTRODUCTION

1. Introduction

1.1 Oral Route and Tablet dosage form

In drug discovery and development process, numerous dosage forms such as solids, liquids, semisolids, etc and their routes of administration were invented with a view to alleviate diseases. Among all routes of administration, oral route is one of the most promising and convenient mode of administration of pharmaceutical dosage forms for the delivery of drugs through the gastro-intestinal tract. It does not cause any unfavorable conditions during administration of dosage form such as through parenteral route. In addition, it overcomes irratic drug absorption from other routes such as topical route especially depending the site condition (hydrated or dehydrated) and place (skin because thickness varies from one region to another). There are many dosage forms available in the market administered through oral route. Both solid dosage forms (powders, tablets, capsules) and liquid dosage forms (solutions, elixirs, syrups, emulsions, mixtures etc.) can be given orally. Tablet and Capsule form has achieved maximum popularity among all these dosage forms due to its accurate dosage in delivering therapeutic substances that can be absorbed through the gastro-intestinal tract. It also bears the advantage in ease of administration where delivery of this dosage form by skilled personnel is not required, easy to pack and can be transferred from one place to another [1]. A major disadvantage of capsule over tablets is their higher cost. The drugs which are hygroscopic are not suitable for filling into such capsules. They will absorb the water present in capsule shell rendering the shell brittle and ultimately may lead to crumble into pieces. Furthermore, tablets dosage form has the best physical, chemical and microbiological stabilities compared to other formulations put all together [2].

1.2 Modified release of tablet dosage form

Conventional oral tablet though has a promising scenario however it may show irrational release pattern with certain drugs whereby the concentration may fall steeply once the tablet is completely dissolved. Therefore, multiple administrations are required to accomplish drug concentration more than minimum effective

concentration level. Today, there has been a growing interest in developing reliable and convenient dosage form with a steady state release characteristics for an extended period. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting. The target in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. There is little difference between terminologies "*sustained release*" and "*controlled release*". The former provides medication over an extended time. On the other hand, controlled release indicates some actual therapeutic control, whether this is of temporal or spatial nature or both. In other words, the system attempts to control drug concentrations in the target tissue [3]. In general, the target of novel drug delivery is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain *zero-order* release from the dosage form. Zero-order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (Fig 1).

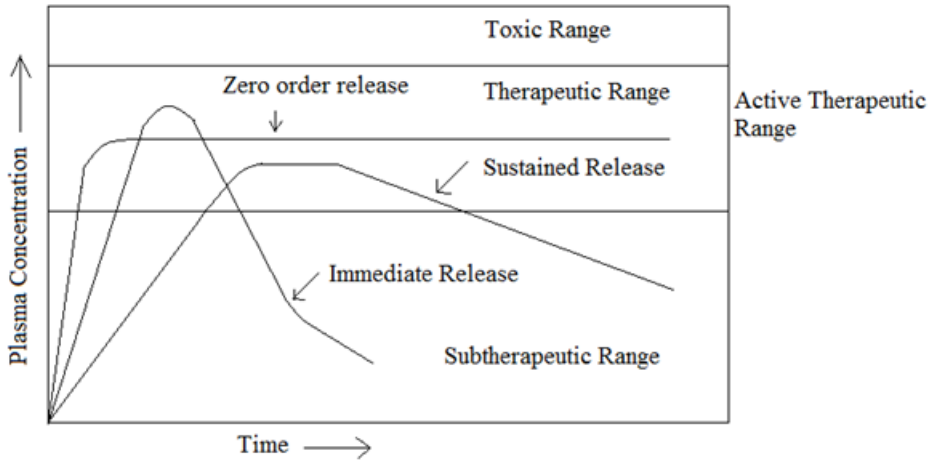


Fig 1: Time vs. drug plasma concentration curve of different release order

There are many extended release pharmaceutical dosage forms, e.g. monolithic matrices, membrane reservoirs, swellable polymers, erodible polymers, ion exchange resins etc. Some of these systems do not show zero-order release Pharmacokinetics or are not suitable for large-scale manufacturing processes. For instance, monolithic matrices, which are fabricated from water-insoluble polymers, a drug, and excipients, exhibit first-order release Pharmacokinetics or square root of time Pharmacokinetics (Higuchi Release Pharmacokinetics) [4]. Long drug diffusion time and decrease in releasing surface area with time are the causes behind this phenomenon [5].

1.2.1 The concept of geometrically modified tablets- Donut Shaped Tablet:

Hence, a novel way of ensuring approximately zero order drug release from the matrix is the modification of the geometry of tablet. This approach has been explored by keeping the surface area constant which results in semi-hemispheric, frustrum-shaped, pie-shaped, multi-holed device and device with a coaxial hole (donut-shape or doughnut shape) [6]. Except donut shaped tablet, other geometrically modified devices are not suitable for large scale commercial production. In this, there is a constant ratio between the inner and outer tablet surface area; thereby the mechanism of drug release from the delivery system is predominantly erosion i.e. upon dissolution surface area is directly proportional to the release of drug from the tablet. This ratio remains constant even when the tablets undergo dissolution. As the upper and lower portions of the tablet are coated with hydrophobic coating, the release of the drug only takes place from the outer and inner sides of the tablet. Therefore, effective surface area for release of drug remains constant. This is made possible due to the reason that as there is a decrease in the outer surface area of the tablet with progressing time of tablet dissolution, there is concomitant increase in the inner surface area [7].It is mathematically proved in the following equations (Fig 2).

Suppose, Initial outer radius of the tablet = r, inner radius of the tablet = a and width = D, after time‘t’ radius change from both sides is ‘l’ due to erosion.

So, outer radius after time t = (r - l),

Inner radius after time t = (a + l),

And total effective surface for drug release (T_e)

$$T_e=2\ \{(r - l) + (a + l)\}D, = 2\ (r + a)D.$$

At time zero effective surface area for drug release (T_0)

$$T_0 = 2\ (r + a)\ D$$

2r = outer diameter,
2a = inner diameter,
L = width of the tablet.

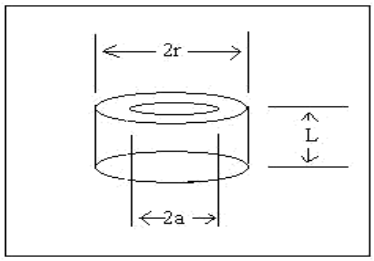


Fig 2: Donut-shaped tablet

According to Noyes-Whitney equation, the rate of dissolution is proportionately related to surface area [8]. From this point of view, it is assumed that the total effective surface area for dissolution will theoretically remain constant during the whole period. It bears not only the advantages of the controlled release dosage forms but it is easy to manufacture and the cost is also low with respect to other novel drug delivery systems. Controlled release, although resulting in a zero-order delivery system, may also incorporate method to promote localization of the drug at an active site [9, 10].

1.3. Gastric Retentive Drug Delivery [GRDD] – scope and means for achieving it:

Orally administered drugs tend to be short acting owing to the variations of gastric transit and emptying. Under these circumstances, prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit [11]. Another factor that affects the effective drug absorption from the gastrointestinal tract is the existence of absorption windows in the proximal small intestine for many important drugs [12]. These problems may be solved by increasing the residence of drug formulations at or above the absorption window.

Controlled drug delivery systems consist of three major components: a drug, a delivery module and a platforms, it is important to develop such platforms that allow extension of the effective life time of these dosage forms by overcoming the limitations set by the physiology of the gastrointestinal tract [13]. Scientists throughout the world have adopted different strategies by designing suitable platforms in order to increase the residence time of the oral controlled release dosage forms. These systems are collectively called as gastro-retentive dosage forms. It has the ability to remain in the gastric region for several hours and is expected to give better bioavailability and reduce drug degradation or its side effects.

The ideal gastro-retentive drug delivery system must have to its credit a spectrum of optimum characteristic features [14]. Some of the main characters that such a system must possess include:

1. It must be retained in the stomach.
2. Its intake must be convenient and hazard-free.
3. It must have the capacity to carry the therapeutic amounts of drugs without any change in its physicochemical properties.
4. It must release the drug at a predetermined rate.
5. It must be completely degraded in the body.
6. It must have no effect on gastric motility and emptying.
7. It must have a prolonged shelf life.
8. It must be convenient for industrial manufacturing condition

1.3.1 Basic Gastrointestinal Tract Physiology

The GIT resembles a tube of about nine meters length that starts from the mouth and ends with the anus. The anatomy of this tract is almost similar in most of its length except some local variations in each region. Since most of the drugs are absorbed in the upper small intestine, it will be beneficial to develop the dosage forms that reside in that region. As there is no specific systems that specifically reside in the upper GIT, the system that reside in the stomach for longer periods and release the drug in small intestine at regular

intervals has come to the limelight. The GIT can be conveniently divided into different functions. The variables in each segment are mentioned in Table 1.

Table 1. Specification of different parts of GIT

Segment	Length (cm)	Diameter (cm)	Surface area (m^2)	pH	Function	Transit time	
						Solid	Liquid
Stomach	20	15	3.5	1-3.5	Digestion	<30min	<3hrs.
Duodenam	20-30	3-5	2	4-6.5	Neutralization of acids, absorption of digested foods	<600sec	<60sec
Jejunam	240	3-5	180	5-7	Absorption of digested foods	3±1.5hrs.	4±1.5hrs.
Ileum	360	3-5	280	6-8	Absorption of digested foods	-	-
Colon	90-125	3-9	1.3	6-8	Absorption of water	-	20-50hrs

1.3.1.1 The Stomach

The stomach (Figure 3) is a muscular, J-shaped organ in the upper part of the abdomen. It is part of the digestive system, which extends from the mouth to the anus. The size of the stomach varies from person to person, and from meal to meal.

The stomach is approximately 25cm long and can expand to hold up to 4L of food and drink, although its empty volume is only 50ml. it has an extra muscle layer in addition to those lining the rest of the GI tract – an oblique layer that allows the stomach to distend in order to store food [15].

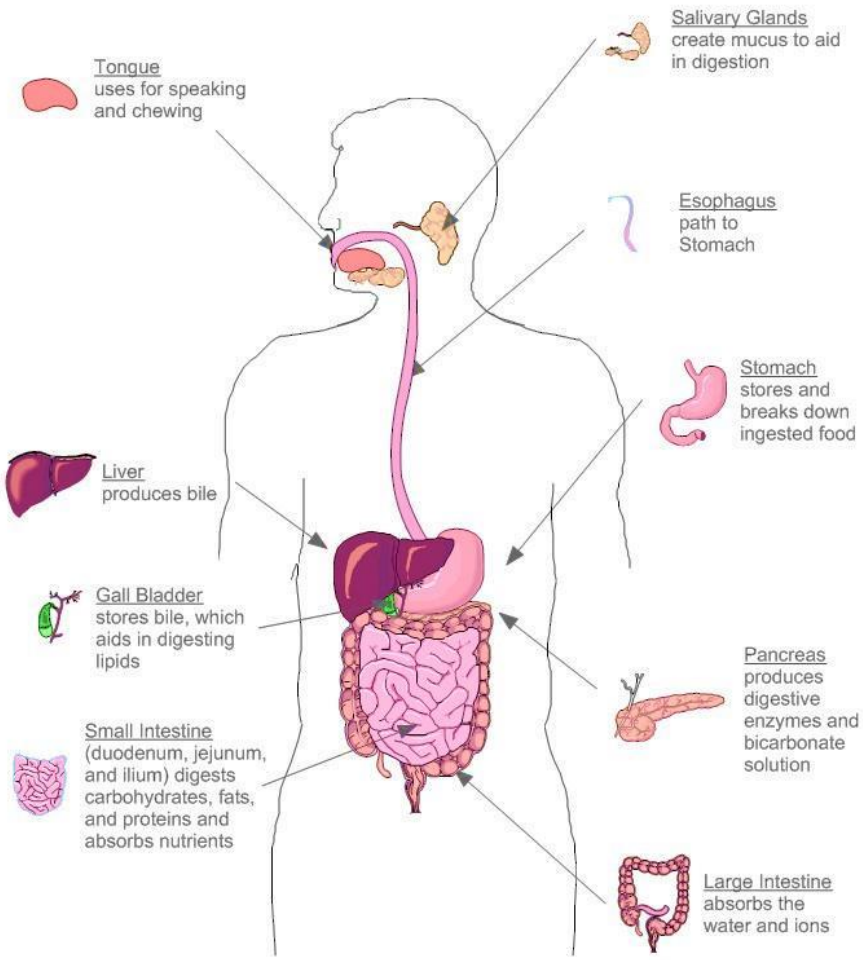


Figure 3. The parts of the digestive system.

1.3.1.2 Functions of the stomach

The stomach performs a number of important functions including:

1. **Food reservoir:** We are able to eat large meals spaced many hours apart because of the stomach's ability to expand and hold food. The contents are released slowly due to the action of the strong pyloric sphincter.
2. **Absorption:** Foodstuffs are only partially broken down by the time they reach the stomach and the molecules are too big to cross the gastric wall. Most of the digestive activity takes place in the pyloric region but only a small amount of absorption occurs in the stomach – some water is absorbed and some drugs,

especially aspirin and other non-steroidal anti-inflammatory drugs, which are mildly acidic. These drugs can cause gastric irritation and bleeding.

3. **Mucus secretion:** This is particularly important in the stomach as its prevents the stomach digesting itself. The enzyme pepsin, which digests protein, is produced in the stomach and would erode the stomach walls if it came into contact with them. The stomach mucus acts as a gel. It is made of a protein (mucin) and glycoproteins, and is spread in a layer about 1mm thick that adheres to the rugae of the stomach. Mucus in the stomach also contains some bicarbonate, which helps to neutralize the stomach acids. Mucus also helps to lubricate food in the stomach.
4. **Gastric juice secretion:** Gastric juice is a mixture of the secretions from two types of cell within the stomach. The billion or so parietal cells in the adult stomach secrete intrinsic factor and hydrochloric acid (HCl), while the chief cells secrete an enzyme pepsinogen. Together they produce 2-3L of gastric juice a day, which is highly acidic (pH 1.2-3.5). However it has a numerous functions:
    - It stops the proliferation of bacteria in the stomach
    - It inactivates salivary amylase, mixed with the food in the mouth
    - It curdles milk to prepare it for digestion
    - It tenderizes proteins (by denaturing them)
    - It converts the pepsinogen produced by chief cells into pepsin, which starts to digest protein
5. **Churning food:** Foods that enters the stomach is mixed with and diluted by the gastric secretions into a thick soup-like substance called chyme. The chyme is churned by waves of peristalsis. Each wave lasts about half a minute and ‘flows’ from the top of the stomach to the bottom.
6. **Production of intrinsic factor:** The parietal cells of the human stomach are responsible for producing intrinsic factor, which is necessary for the absorption of cyanocobalamin (vitamin B_{12}). Vitamin B_{12} is used in cellular metabolism and is necessary for the production of red blood cells, and the functioning of the nervous system.[16,17]

1.3.1.3 Gastrointestinal transit time and emptying of food:

First, there is considerable normal variability among healthy people and animals in transit times through different sections of the gastrointestinal tract. Second, the time required for material to move through the digestive tube is significantly affected by the composition of the meal. Finally, transit time is influenced by such factors as psychological stress and even gender and reproductive status [18].

A meal is typically a mixture of chemically and physically diverse materials and some substances in this mixture show accelerated transit while others are retarded in their flow downstream.

An example of how ingested substances spread out in the digestive tube rather than travel synchronously is shown in the figure 4. These data were obtained from a human volunteer [19] that ingested a meal containing ^{111}Indium-labeled pellets, then measuring the location of the radioactive signal over time by scintigraphy. It is clear that parts of the meal are entering the colon at the same time that other parts are still in the stomach.

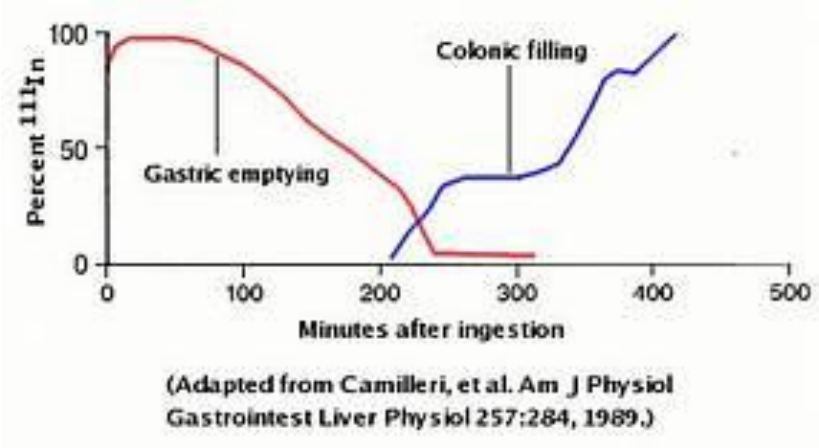


Figure 4: Gastro intestinal transit

The proximal part of stomach made of fundus and body acts as a reservoir for undigested material, whereas the antrum is main site for mixing motions and act as a pump for gastric emptying by propelling action [20]. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours [21]. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into 4 phases as described by Wilson and Washington [22].

1. Phase I (Basal Phase): This phase lasts about 30-60 min with rare contraction.
2. Phase II (Preburst Phase): This phase lasts about 20-40 min with intermittent action potential and contraction that moderately increase in intensity and frequency as the phase progresses. Later in this phase, there is gastric discharge of fluids and small particles.
3. Phase III (Burst phase): This phases lasts about 10-20 min, with intense and large, regular contractions that last for a short period of 4-6 min. This results in "sweeping" (moving) the undigested materials out of the stomach and down into the small intestine. Thus, these contractions are also known as the "housekeeper wave."
4. Phase IV: This phase lasts for a very brief (transitory) period of about 0-5 min in which the contraction between phase III and phase I disperses. This is the transitory period between two different cycles.

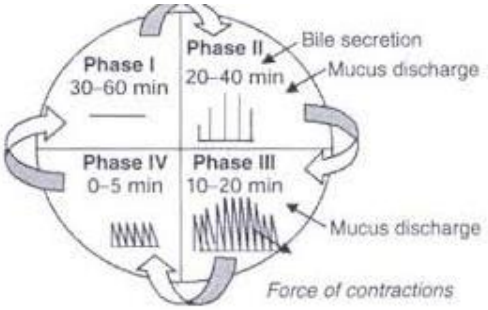


Figure 5: Representation of MMC

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continue contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed [23] resulting is slowdown of gastric emptying rate [24].

Several techniques [25] have been used to measure transit times in humans and animals. Various estimates have been reported depending on the techniques used include:

a) ***Radiography following a barium-labelled meal:*** Sequential radiographs can be used to determine when the front of the barium label reaches different regions of

the digestive tube. Such meals are not very physiologic and the technique exposes the patient to repeated exposure to radiation.

b) ***Breath hydrogen analysis:*** A number of carbohydrates are very poorly digested or absorbed in the small intestine. Fermentation liberates hydrogen gas, which diffuses into blood and is exhaled in breath, where it can be readily measured [26]. Thus, after consumption of a meal containing a non-absorbable carbohydrate (lactulose or, more commonly, baked beans), there is a large increase in exhaled hydrogen when the carbohydrate reaches the large intestine. This provides an estimate of pre-colonic (stomach plus small intestine) transit time.

c) ***Scintigraphic analyses:*** Meals containing pellets or colloids labeled with a small amount of radionuclide (^{99}Technetium, ^{113}Indium, etc.) are consumed, and the position of the radioactive label is sequentially monitored using a gamma camera [27, 28].

1.4 APPROACHES TO GASTRIC RETENTION

Various approaches have been paused to increase the duration of oral dosage form in the stomach [29, 30, 31], including floating systems, swelling and expanding system, modified shape system, high density systems and other delayed gastric emptying devices.

- **High density system**

It includes sinking systems that can be retained at the bottom of the stomach. In this system density of pellets/tablets is greater than density of stomach fluid shown in Fig 6. Gastric contents have a density close to water (≈1.004 g/cm3).The GI transit time prolonged for an average of 5.8 h to 25 h. Barium sulfate, iron powder, titanium oxide, and zinc oxide are incorporated in the formulation to increase the density of the dosage form. Increased dose size required to achieve that high density is one of the major drawbacks of this kind of system.[32]

- **Swellable and Expandable System**

In this type, the size of the gastro retentive system expands to a size bigger than the diameter of the pyloric sphincter so that it can remain logged within the stomach. Alternatively, the system is named as ‘plug type systems’ due to their

pyloricsphincter blocking attribute. Once the polymer came in contact with the gastric fluid, it absorbed water and swelled shown in Fig 6. The selection of a suitable polymer (or combination of polymers) with an appropriate molecular weight/viscosity grade and swelling properties enabled the dosage form to attain sustained-release characteristic. Further advancements of such kind of dosage form has taken place with the introduction of novel polymers with super-porous nature, causing them to swell to an equilibrium size within a minute. This characteristic rapid swelling property (swelling ratio is 1:100 or more) of the polymer with an average pore size of more than 100 μm occurs due to capillary wetting through several interrelated open pores when the dosage form comes in contact with GI fluid.[33]

- **Bioadhesive and Mucoadhesive System**

Bioadhesive or mucoadhesive drug delivery system is another approach to gastroretentive systems. Bioadhesion, the state in which two materials, amongst which one is biological in nature, adhere to each other for extended periods of time with the help of interfacial forces, provides an attractive strategy to overcome the hurdles of conventional drug delivery systems including first pass metabolism, and localized delivery of biomolecules including proteins, peptides and oligonucleotides.

Mucoadhesive systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site specific manner. This approach involves the use of mucoadhesive polymers, which can adhere to the epithelial surface in the stomach shown in Fig 6.Some of the most promising excipients that have been used commonly in thesesystems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc.

There are five theories of mucoadhesion-electronic, absorption, wetting, diffusion, fracture theory.

a) **Wetting theory:-**This theory describes the ability of a mucoadhesive polymer to spread on biological surfaces thus it gives an account of "spreadability" of active drug delivery system. According to this, the adhesive component when comes in contact with mucosa penetrates surface deformations, get hardens and attaches to the surfaces due to change in surface and interfacial energies.

b) **Electronic theory:-** This theory is based on electronic differences in structure; it describes that bonding occurs due to electron transfer between polymeric system and the mucus membrane epithelium. As a result of this a bi-layer of electronic charges formed at the mucus and mucoadhesive system interface. Ultimately this is responsible for the formation of attractive force amongst the two surfaces via electronic double layer.

c) **Adsorption theory:-** There exists two types of chemical bonds for adhesive interactions i.e. hydrogen bond and van der Waals' forces. After an initial contact amongst inter-surfaces; the mucoadhesive substance adheres due to the surface forces acting between the molecules of two surfaces. According to the chemisorption theory, interaction across the interface occurs as a result of strong covalent bonding.

d) **Fracture theory:-**The "fracture theory" relates the force for polymer detachment from the mucus to the strength of their adhesive bond. The work fracture has been found to be greater when the polymer network strands are longer or the degree of cross-linking within system is reduced. This theory allows the determination of fracture strength (σ) following the separation of two surfaces via its relationship to Young's modulus of elasticity (E), the fracture energy (ε) and the critical crack length (L) through following equation: $\sqrt{E+\varepsilon})/L$

e) **Diffusion theory:-**The diffusion theory states that interpenetration and entanglement of both polymer and mucin chains are responsible for mucoadhesion. The more structurally similar a mucoadhesive to the mucosa, the greater is the mucoadhesion. [38, 39]

- **Magnetic system**

Magnetic dosage forms with extra-corporal magnetic guidance represent a novel approach to optimize the rate and extent of absorption of drugs. This system is based on a simple idea: the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach shown in Fig 6. Using the external magnetic field (extracorporeal magnet) the gastric residence time of the dosage form can be enhanced for a prolonged period of time though is

not readily available for practical use. Ferrite is generally used in this formulation. [36,37]

- **Floating system**

This is based on buoyancy (floating) property of any dosage form experienced in GI fluid. The bulk density of the dosage form attains less than the density of gastric fluid (1.004 to 1.010 g/ml) after a certain lag time (Fig 6). This lag time depends on the rate of swelling of the polymer used in the formulation, which again depends on the type, viscosity grade, presence of wicking agent or swelling enhancers, etc. The said parameters of the formulation also determine the duration of floating as well as in vitro drug release rate. The efficacy of the floating behavior also depends on the physiological conditions of the patients, like fed-state or fasting state, amount of gastric fluid, etc. After the required drug release, the used dosage form is emptied out from the stomach. One additional attribute such as effervescence was incorporated within this swelling-based floating delivery system to improve the floating behavior (floating lag time as well as floating duration), as shown below. Various effervescent components (e.g. sodium bicarbonate, tartaric acid and citric acid) were mixed within the dosage form. When these components come in contact with the gastric con-tents, carbon dioxide (CO_2) is liberated as a result of a chemical reaction and it becomes trapped within the gellified hydro-colloid system. These combinations of effervescence and swelling help the dosage form achieve effective density less than the gastric fluid and result an upward motion onto a dosage form which maintains the buoyancy for a prolonged period of time. [38]

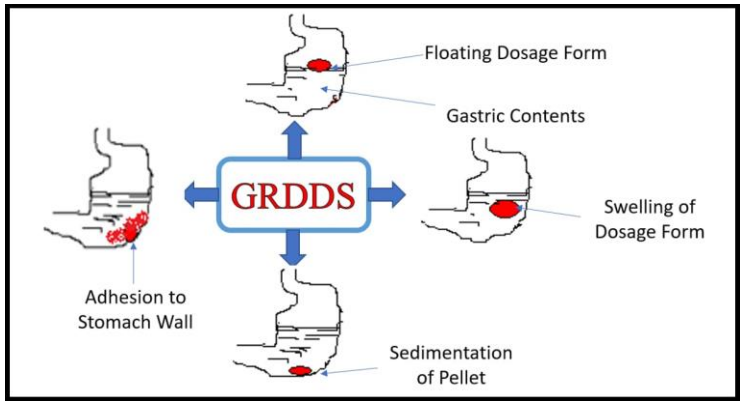


Fig 6: Different approaches of Gastric retention

1.5 Mechanism of Floating System:

Floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for a prolong period [Fig 7]

F = F buoyancy - F gravity = (Df - Ds) gv

Where, F= total vertical force (upward or downward), g = acceleration due to gravity

Df = Gastric fluid density, Ds = object density (dosage form), and v = volume of fluid

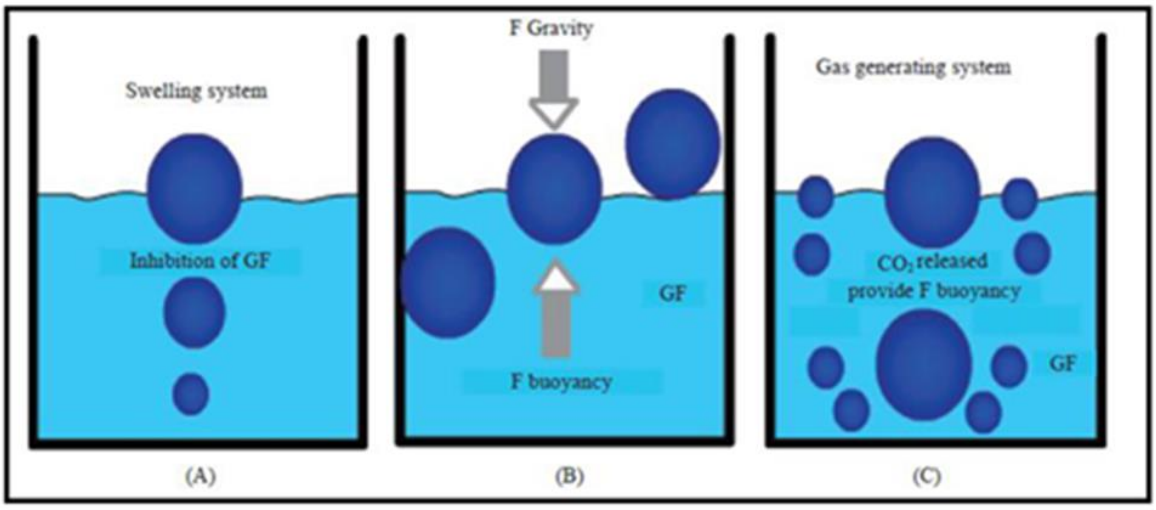


Figure 7: Mechanism of Floating system

For Floatation of Tablet in Gastric fluid,

F (Total Vertical Force) must be positive for upward movement of tablet, so that

Df (Gastric fluid density) >> Ds (Tablet density).

1.5.1 CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM BASED ON MECHANISM OF BUOYANCY

A. Single Unit Floating Dosage Systems

Single unit dosage forms are easiest to develop but suffer from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they

may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract.[39]

a) Effervescent systems or gas generating systems:

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. [40]

b) Non effervescent Systems:

One or more gel forming, highly swellable, cellulose hydrocolloids (e.g.hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methyl cellulose [HPMC] and sodium carboxy methyl cellulose, polysaccharides, or matrix forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) are incorporated in higher concentration (20-75% w/w) to tablets or capsules. For the preparation of these types of systems, the drug and the gel forming hydrocolloid are mixed thoroughly. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of less than 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. [41]

B. Multiple Unit Floating Dosage Forms

In spite of extensive research and development in the area of Hydro-dynamically Balanced System (HBS) and other floating tablets, these systems suffer from an important drawback of high variability of the gastrointestinal transit time, when orally administered, because of their all-or-nothing gastric emptying nature. In order to overcome this, multiple unit floating systems were developed, which reduce the inter-subject variability in absorption and lower the probability of dose-dumping.

Reports have described the development of both non-effervescent and effervescent multiple unit systems. [42]

a) Non-effervescent systems

Though this system has not been explored so much till date; few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit Hydro-dynamically Balanced System (HBS) containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudateis cut and dried. Chitosan hydrates float in the acidic media, and the drug release could be obtained by modifying the drug-polymer ratio. [43]

b) Effervescent systems

A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. [40]

C. Raft forming system

The raft forming system is one of the approaches which involve the formulation of effervescent floating liquid with *In situ* gelling properties. Moreover, the gels so formed *In situ* remained intact for more than 48 h to facilitate sustained release of drugs .The mechanism of the raft forming system involves the formation of continuous layer called a raft. The system involves the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The layer of the gel floats on the gastric fluid because it has bulk density less than the gastric fluid, as low density is created by the formation of CO_2. So the system remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time .The gel formed from *In situ* gelling, being lighter than gastric fluid, floats over the stomach contents or adheres to the gastric mucosa due to the presence of a mucoadhesive nature of the polymer and prevents the reflux of gastric content into the

esophagus by acting as a barrier between the stomach and the esophagus. Thus it produces retention of dosage form and increases gastric residence time (GRT) resulting in prolonged drug delivery in gastrointestinal tract. When the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of the drug, the residual system is emptied from the stomach. This results in an increased gastro retention time and a better control of the fluctuations in plasma drug concentration. [32]

1.5.2 FACTORS AFFECTING GASTRIC RETENTION TIME (GRT):

- **VOLUME OF MEAL:** Larger the bulk of the meal, greater is the stretching of stomach wall. Distension of the stomach triggers long (vagally mediated) & short (intrinsic neural plexus mediated) reflexes leading to strong peristalsis waves and increased rate of gastric emptying. [44]
- **PHYSICAL STATE AND VISCOSITY OF MEAL:** Liquid meal takes less than an hour to empty whereas solid meal takes 6-7 hours. Viscous materials empty at a slow rate than less viscous.[41]
- **COMPOSITION OF MEAL:** In general carbohydrates> proteins> fats but it does not matter whether the food has high carbohydrate, protein or fat content as long as the caloric content is same. Increase in caloric value slows down gastric emptying.[42]
- **TEMPERATURE OF MEAL:** The temperature should be near to body temperature or otherwise there might be reduction in the gastric emptying rate.
- **ELECTROLYTES AND OSMOTIC PRESSURE:** Water, isotonic solutions & solutions of low salt concentration empty the stomach rapidly whereas a higher electrolyte concentration decreases gastric emptying.[42]
- **GASTROINTESTINAL pH :** Gastric emptying is retarded at low stomach pH & promoted at higher or alkaline pH.
- **PSYCHOLOGICAL AND PHYSICAL STRESSORS:** Fear, mental stress, head injury, physical trauma, and exhaustive exercise delays gastric emptying.

- **DISEASES STATE:** Disease states like gastroenteritis, gastric ulcer, diabetes, hypothyroidism retard gastric emptying. Gastreotomy, duodenal ulcer and hyperthyroidism promote gastric emptying rate.
- **GENDER AND AGE:** Women have slower gastric emptying time than do men. Low gastric emptying time is observed in elderly than do in younger subjects. Elderly people, especially those over 70 years have a significantly longer GRT.[61]
- **DRUGS:** Poorly water soluble drugs like antacids (Aluminium Hydroxide), anticholinergics (Atropine), Tricyclic antidepressants (Imipramine, Amitriptyline) retard gastric emptying whereas Metoclopramide, Domperidone and Cisapride stimulate gastric emptying. [62]

a) FORMULATION FACTOR:

- **SIZE OF TABLET:** Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves.
- **DENSITY OF THE TABLET:** The density should be less than density of the gastric fluid to be floatable (<1.0 g/ml).In such case the dosage form will remain away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.
- **SHAPE OF THE TABLET:** Gastric residence time is also influenced by shape of the dosage form. Six shapes (ring, tetrahedron, cloverleaf, disk, string, and pellet) were screened in vivo for their gastric retention potential. The tetrahedrons (each leg 2 cm in length) exhibited 91-100% retention at 24 hr. The rings (3.6-cm diameter) provided 100% retention at 24 hrs.
- **VISCOSITY GRADE OF POLYMER:** The decrease in the release rate is observed with an increase in the viscosity of the polymeric system. Eg Polymer with lower viscosity (HPMC K100LV) is beneficial than higher viscosity polymer (K4M) in improving the floating properties of GFDDS.

b) IDIOSYNCRATIC FACTORS:

- **UPRIGHT POSITION:** An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size.
- **SUPINE POSITION:** This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units show significant reduction in GRT compared with upright subjects due to peristaltic movement.[48]

1.6 Formulation of Floating Drug Dosage Form (FDDS)

Following types of the ingredients can be incorporated in to FDDS Dosage form:

- **Hydrocolloids: -** They are gel forming, which swells in contact with gastric fluid and maintains a relative integrity of shape and bulk density less than the gastric content. Example HPMC 1000, HPMC 4000, Sodium alginate, Polyox, Acrylic Polymers.
- **Inert fatty materials:-** Edible, pharmaceutical inert fatty materials having specific gravity less than 1 can be used to decrease hydrophilic property of formulation and hence increase the buoyancy. Example Fatty acids, Long chain fatty alcohols, Beeswax, Gelucires 39/01.
- **Release rate accelerants:-**The release rate of the medicament from the formulation can be modified by including excipients like Lactose/ Mannitol (5-60) %.
- Release rate retardants:-Insoluble substances such as Calcium Phosphate, Talc, and Magnesium Stearate decreased the solubility and hence retard the release rate of the medicament.
- **Effervescent agents:-**They react with the acid and produce Carbon-di-oxide. Example Sodium bicarbonate, Citric acid, Tartaric acid, Nitroglycerine, Di-sodium glycine.
- **Buoyancy increasing agents:-**Ethyl Cellulose having bulk density less than one can be used for increasing the buoyancy of the formulation.
- **Miscellaneous: -** Pharmaceutically acceptable adjuvants like preservatives, stabilizers, and lubricants can be incorporated in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.[49,50,51]

Table 2. List of Drugs Formulated as Single and Multiple unit Forms of Floating Drug Delivery Systems

Dosage forms	Drugs		
Tablets	Theophylline[52], Furosemide[53], Chlopheniramine maleate[54],	Diltiazem[55], Captopril[56], Ampicillin[57],	Ciprofloxacin[58], Verapamil[59], Sotalol[60]
Capsules	Nicardipine[61], Diazepum[62],	Propranolol[63], Misoprostal[64],	Furosemide[65], L-Dopa[66]
Microspheres	Ketoprofen[67], Verapamil[68],	Tranilast[69], Terfenadine[70],	Ibuprofen[71], Aspirin[72]
Granules	Indomethacin [72], Diclofenac sodium [73],Prednisolone[74]		
Films	Cinnarizine[75]		
Powders	Several basic drugs[76]		

Table 3: Marketed Preparations of Floating Drug Delivery Systems

Product	Active Ingredients	Ref. no.
Madopar	Levodopa and benserzide	[66]
Valrelease	Diazepam	[52]
Topalkan	Aluminum magnesium antacid	[69]
Almagateflatcoat	Antacid	[70]
Liquid gavison	Alginic acid and sodium bicarbonate	[71]

1.7 Merits of floating drug delivery system (FDDS):-

- The Floating systems are advantageous for drugs meant for local action in the stomach. E.g. antacids
- Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
- Administration of prolonged release floating dosage forms such as tablet or capsules will result in dissolution of the drug in the gastric fluid, and it would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even from the intestine.
- Gastric retention provides advantages such as the delivery of drugs with narrow absorption window in the small intestinal region. [77]
- When there is a vigorous intestinal movement and a short transit time as might occur in certain type of disease state such as diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
- By formulating floating drug delivery system of a drug, the dose of drug can be reduced.[78]
- Minimized adverse activity at the colon asretention of the drug in GRDF (Gastroretentive Dosage Form)at stomach minimizes the amount of drugs that reaches the colon and hence prevents the degradation of drug that degraded in the colon.
- Receptor activation selectivity is improved.
- Slow release of the drug into the body minimizes the counter activity leading to higher drug efficiency.
- The bioavailability of some drugs (e.g. riboflavin and levodopa) CR-GRDF (Controlled Release–Gastroretentive Dosage Form) is significantly enhanced in comparison to administration of non-GRDF CR polymeric formulations.

- The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented.
- The drugs having short biological half-life, a sustained and slow input from FDDS may result in a flip-flop pharmacoPharmacokinetics and it reduces the dose frequency. This feature is associated with improved patient compliance and thus improves the therapy. [79, 80]

1.8 Limitations of Floating Dosage Form

- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
- It is not suitable for drugs that have solubility or stability problem in GIT.
- Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- Drugs which are irritantto gastric mucosa are also not desirable for this type of system.
- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the system.
- The dosage form should be administered with a full glass of water (200-250 ml).
- These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.[81,82]

1.9 Application of floating drug delivery system

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

1. **Enhanced Bioavailability:**

   The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug

in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.[83]

2. **Sustained drug delivery:**

   Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited.[84]

3. **Site specific drug delivery systems:**

   These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine .The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. Eg: Furosemide and Riboflavin.[85]

4. Absorption enhancement:

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.[86]

5. **Minimized adverse activity at the colon:**Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented.[87]
6. **Reduced fluctuations of drug concentration:**

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index. [88]

Objective and scope of this work

1.10 Objective

The prime target of any drug delivery is to provide therapeutically active agent at a site with maximum efficacy and minimum side effects. To achieve this drug delivery is designed in such a manner that it should deliver drug at a predetermined rate required by the body over the specified period. The basic objective of designing dosage has to control the release of drug in the face of uncertain fluctuation in the *in vivo* environment in which drug release takes place.

The main purpose of this project was to design and develop floating donut shaped tablet using Prazosin hydrochloride, an alpha-Adrenergic Blocker as a drug for the treatment of acute disorder in hypertension. Optimization process will be performed at pH 1.2. α_1-blocker Prazosin hydrochloride has been used as a model drug for this project. Short biological half-life, requirement of multiple administrations during acute disorders, good bioavailability and water solubility of the drug are suitable criteria for designing of such controlled release tablets.

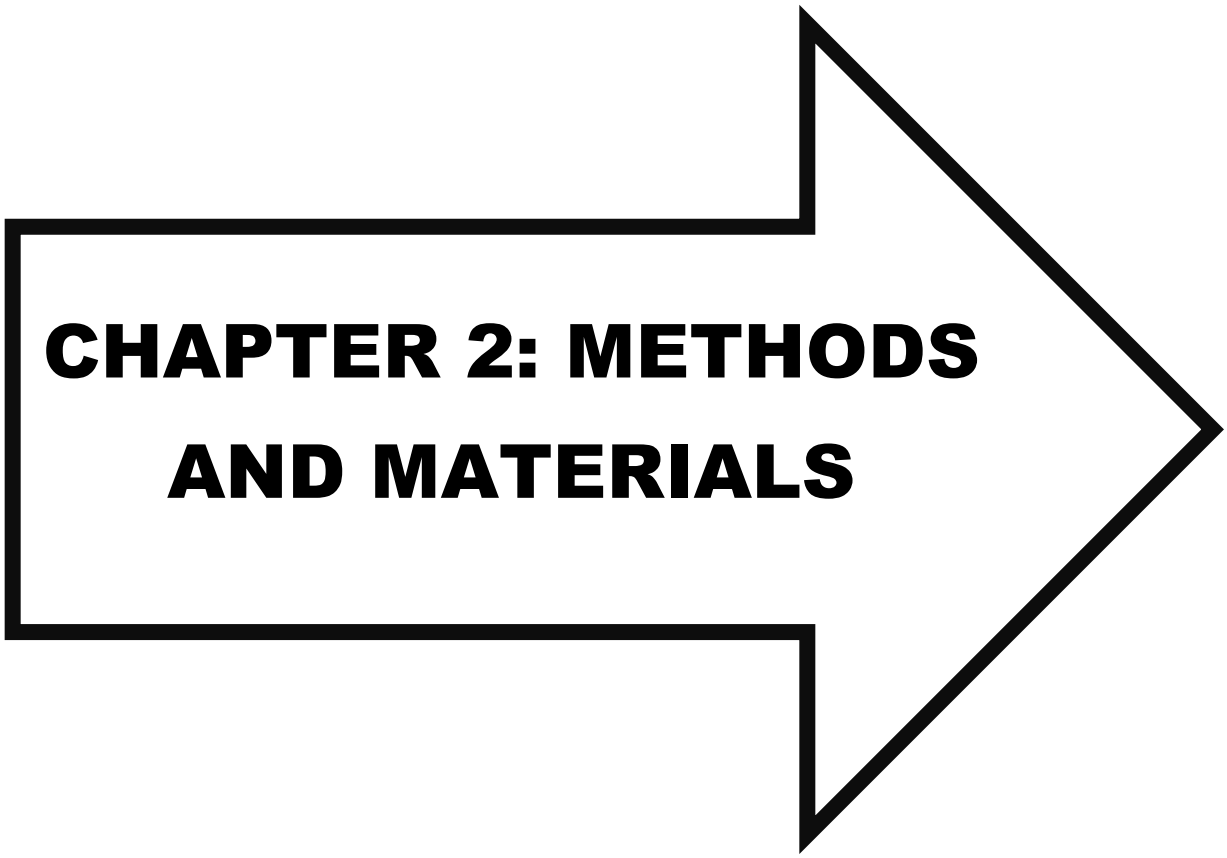
The present study - "Design, Development and Evaluation of Oral Novel Floating Donut Shaped Prazosin hydrochloride Tablets" was particularly designed to improve the therapeutic efficacy and to meet the body requirements during an early morning surge in blood pressure.

The following experimental protocols were therefore intended to allow a systematic approach to the study:

- Determination of Absorbance Maxima and development of calibration curves of Prazosin HCl at pH 1.2, pH 6.8 and Milipore water using UV spectrophotometer
- Determination of Melting point of Prazosin HCl
- Identification of functional groups present in pure drug using FTIR
- Drug-excipients compatibility studies using FTIR, DSC and XRD

- Preparation of Prazosin hydrochloride powder blend
- Study of physical properties of the powder blend such as as bulk density , tap density , Carr's index, Angle of Repose
- Preparation of tablets by direct compression method using concave face punches having a coaxial hole (inner diameter : 4mm, outer diameter : 10mm)
- Study of physical properties of the prepared prazosin Hydrochloride floating tablet like size (thickness, diameter), hardness, friability, weight variation, content uniformity.
- Evaluation of the parameters for floating tablets like swelling index, floating lag time, total floating time
- *In vitro* release study of the prepared tablets using USP-II apparatus
- Analytical studies of prepared prazosin hydrochloride tablet formulation.
- Stability Study of the optimized formulation

CHAPTER II



2.1 Materials:

Prazosin hydrochloride was obtained as a gift sample from MacLeod Pharmaceuticals Pvt. Ltd., India. $NaHCO_3$, Talc and Magnesium Stearate were obtained from Loba Chemicals Pvt. Ltd, India. Hydroxypropyl methyl cellulose (HPMC) of viscosity grade K4M and Xanthan gums were purchased from Noveon Chemicals, Bangalore. Citric acid was obtained Finar Reagents Pvt. Ltd, India. Sodium Hydroxide, Methanol (Analytical Grade) and Hydrochloric Acid was purchased from S.D Fines Chemical, Mumbai. All reagents used were of analytical grade.

INSTRUMENTS

Compression machine (10 stations)	Redmi Rotary, Mumbai
Digital Weighing Balance	Electrolab, Mumbai
Dissolution Test System (USP-II)	Veego, Mumbai
Friabilator, EF-2 (USP)	Electrolab, Mumbai
Hardness Tester	Sartorius, Switzerland
pH- Meter	Lab India, Baroda
Stability Chamber	Thermolab, Mumbai
Tap Density Tester (USP)	JEL, Ahemadabad
Vernier Caliper	Mahr Instruments, Ahmedabad
UV Spectrophotometer	Jasco V-550
ATR-FTIR Spectrophotometer	Burker Alpha-E Germany
DSC	Perkin Elmer
XRD	Ultima III, Japan

2.1 MATERIALS

2.1.1 Drug Profile

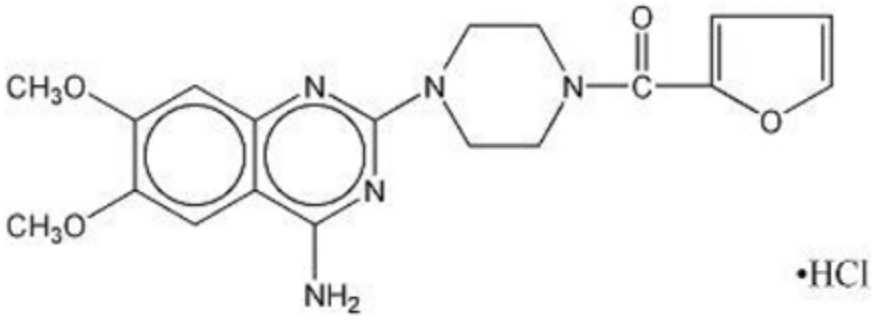


Figure 11: Structure of Prazosin hydrochloride

CHEMICAL NAME: [4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl](furan-2- yl)methanone; hydrochloride.[89]

PHYSICAL PROPERTIES:

Appearance, odour, taste: Prazosin hydrochloride is a white to off-white powder, slight sulfurous odor, bitter in taste.[90]

Solubility: It is soluble in methanol, ethanol, acetone and slightly soluble in water at ambient temperatures.[91]

Molecular Formula: $C_{19}H_{22}ClN_5O_4.HCl$

Molecular Weight: 419.866 g/mol

Melting Point: 278-280^0 C

Half Life: 2-3hour

LogP (Partition coefficient): 1.3

pKa: 6.54

Storage: Prazosin hydrochloride should be stored in well closed, light resistant containers at 15-30°C. [92]

Mechanism of action:

Alpha-adrenergic receptors are responsible for the regulation of blood pressure in humans. Two types of alpha receptors, alpha 1 and alpha 2, both play a role in regulating blood pressure. Prazosin is an α_1-blocker that acts as an inverse agonist at alpha-1 adrenergic receptors. These receptors are found on vascular smooth muscle, where they are responsible for the vasoconstrictive action of norepinephrine. [93]

Prazosin inhibits the postsynaptic alpha-1 adrenoceptors. This inhibition blocks the vasoconstricting (narrowing) effect of catecholamines (epinephrine and norepinephrine) on the vessels, leading to peripheral blood vessel dilation. [94]

INDICATION:

- This drug is indicated for the treatment of hypertension (high blood pressure). Prazosin can be given alone or given with other blood pressure-lowering drugs, including diuretics or beta-adrenergic blocking agents
- Prazosin does not negatively impact lung function, and therefore may be used to manage hypertension in patients who are asthmatic or patients with chronic obstructive lung disease (COPD)
- Benign Prostatic Hyperplasia (BPH)
- Raynaud's Phenomenon
- Disturbed sleep/nightmares [95]

SIDE EFFECT:

Common (4–10% frequency) side effects of prazosin include dizziness, headache, drowsiness, lack of energy, weakness, palpitations, and nausea. Less frequent (1–4%) side effects include vomiting, diarrhea, constipation, edema, orthostatic hypotension, dyspnea, syncope, vertigo, depression, nervousness, and rash.

Use in pregnancy

There are no adequate and well-controlled studies determining the safety of prazosin use during pregnancy. It is considered a pregnancy category C drug. Prazosin should be used during pregnancy only in cases where the benefit outweighs the possible risk to the mother and fetus Label. In specific cases where blood pressure control was emergent

during pregnancy, prazosin has been used and no effects on the fetus or neonate were reported. [96]

DRUG INTERACTION:

Acemetacin	The therapeutic efficacy of Prazosin can be decreased when used in combination with Acemetacin
Aceclofenac	The therapeutic efficacy of Prazosin can be decreased when used in combination with Aceclofenac.
Acebutolol	The serum concentration of Acebutolol can be increased when it is combined with Prazosin.
Apomorphine	The therapeutic efficacy of Prazosin can be increased when used in combination with Apomorphine
Verapamil	Prazosin may increase the orthostatic hypotensive, hypotensive, and antihypertensive activities of Verapamil
Food Interactions	Avoid alcohol. Avoid natural licorice.[96]

PHARMACODYNAMICS:

Effects on blood pressure

The pharmacodynamic and therapeutic effect of this drug includes is a decrease in blood pressure as well as clinically significant decreases in cardiac output, heart rate, blood flow to the kidney, and glomerular filtration rate. The decrease in blood pressure may occur in both standing and supine positions. [97]

Many of the above effects are due to vasodilation of blood vessels caused by prazosin, resulting in decreased peripheral resistance. Peripheral resistance refers to the level

resistance of the blood vessels to blood that flows through them. As the blood vessels constrict (narrow), the resistance increases and as they dilate (widen), and peripheral resistance decreases, lowering blood pressure. [98]

Effects on sleep disturbance related to post-traumatic stress disorder (PTSD)

Some studies have suggested that this drug improves sleep in patients suffering from insomnia related to nightmares and post-traumatic stress disorder, caused by hyperarousal. This effect likely occurs through the inhibition of adrenergic stimulation found in states of hyperarousal. [99]

PHARMACOPHARMACOKINETICS:

Absorption

After administration of an oral dose, peak plasma concentrations are attained at approximately 3 hours. [100]

Half life

The plasma half-life is about 2-3 hours.

Volume of distribution

About 0.6 L/kg 11. [100]

Protein binding

Highly bound to proteins with 97% binding to albumin and alpha 1-acid glycoprotein.Prazosin is thought to be mostly (about 80-90%) bound to albumin. [101]

Metabolism

In animals, prazosin hydrochloride is heavily metabolized. This occurs through liver demethylation and conjugation Label. Some studies in humans or human cells in vitro show similar prazosin hydrochloride metabolism. [102]

Route of elimination

This drug is mainly excreted in the bile and the feces. [103]

2.1.2 Hydroxypropylmethylcellulose (HPMC K4M)

1. Nonproprietary Names

• BP: Hypromellose

• JP: Hydroxypropylmethylcellulose

• PhEur: Hypromellosum

• USP: Hypromellose

2. Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; *Methocel*; methylcellulose

Propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Tylopur*.

3. Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

4. Empirical Formula and Molecular Weight

The PhEur 2005 describes hypromellose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the types of hypromellose stated in Table I. Molecular weight is approximately 10 000–1 500 000. The JP 2001 includes three separate monographs for hypromellose: hydroxyl propylmethylcellulose 2208, 2906, and 2910, respectively.

5. Structural Formula

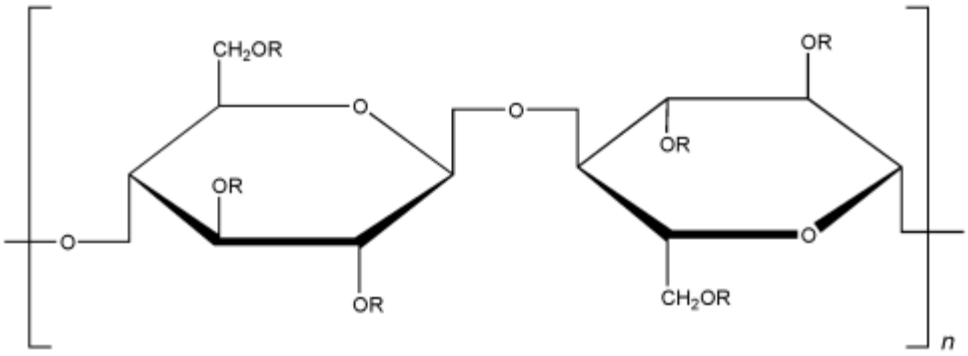


Fig 9: Structure of HPMC

6. Applications in Pharmaceutical Formulation or Technology

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

In oral products, hypromellose is primarily used as a tablet binder,in film-coating,and as a matrix for use in extended-release tablet formulations.Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of filmcoating materials that are commercially available include *AnyCoat C*, *Spectracel*, and *Pharmacoat*.

Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be

added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topicalgels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

7. Melting point:

Browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.

8. Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions.Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be re-dispersed on cooling by shaking.[104,105]

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

2.1.3 Xanthan Gum

1. Nonproprietary Names

• BP: Xanthan gum

• PhEur: Xanthani gummi

• USPNF: Xanthan gum

2. Synonyms

Corn sugar gum; E415; *Keltrol*; polysaccharide B-1459; *Rhodigel*; *Vanzan NF*; *Xantural*.

3. Chemical Name and CAS Registry Number

Xanthan gum [11138-66-2]

4. Empirical Formula and Molecular Weight

$(C_{35}H_{49}O_{29})_n$ Approximately 2 × 106

The USPNF 23 describes xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

5. Structural Formula

Each xanthan gum repeat unit contains five sugar residues: two glucose, two mannose, and one glucuronic acid. The polymer backbone consists of four β-D-glucose units linked at the 1 and 4 positions, and is therefore identical in structure to cellulose. Trisaccharide side chains on alternating anhydroglucose units distinguish xanthan from cellulose. Each side chain comprises a glucuronic acid residue between two mannose units. At most of the terminal mannose units is a pyruvate moiety; the mannose nearest the main chain carries a single group at C-6. The resulting stiff polymer chain may exist in solution as a single, double, or triple helix that interacts with other xanthan gum molecules to form complex, loosely bound networks.

6. Functional Category

Stabilizing agent; suspending agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and

emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range; Xanthan gum gels show pseudoplastic behavior, the shear thinning being directly proportional to the shear rate. The viscosity returns to normal immediately on release of shear stress.

When xanthan gum is mixed with certain inorganic suspending agents, such as magnesium aluminum silicate, or organic gums, synergistic rheological effects occur. In general, mixtures of xanthan gum and magnesium aluminum silicate in ratios between 1 : 2 and 1 : 9 produce the optimum properties. Similarly, optimum synergistic effects are obtained with xanthan gum: guar gum ratios between 3 : 7 and 1 : 9.

Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets. Controlled-release tablets of diltiazem hydrochloride prepared using xanthan gum have been reported to sustain the drug release in a predictablemanner and the drug release profiles of these tablets were not affected by pH and agitation rate. Xanthan gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin, thereby helping in the prolonged retention of the dosage form in the precorneal area. Recent studies have revealed that xanthan gum can also be used as an excipient for spraydrying and freeze-drying processes for better results. Xanthan gum can be used to increase the bioadhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems. Xanthan gum is also used as a hydrocolloid in the food industry, and in cosmetics it has been used as a thickening agent in shampoo.

8. Description

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

9. Viscosity (dynamic):

1200–1600 mPa s (1200–1600 cP) for a 1% w/v aqueous solution at 25°C.

10. Stability and Storage Conditions

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (Ph 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60°C. [106,107]

The bulk material should be stored in a well-closed container in a cool, dry place.

2.2 ANALYTICAL METHODS

2.2.1. PREPARATION OF REAGENTS

- **Preparation of 0.1 N Hydrochloric acid**

8.5 ml of concentrated hydrochloric acid was diluted with distilled water to produce 1000ml.

- **Preparation of Phosphate Buffer pH 6.8 USP**

13.872gm Potassium dihydrogen phosphate and 35.084 gm disodium hydrogen phosphatewas dissolved in 1000ml distilled water in beaker. pH was adjusted to 6.8 using a pH meter with 0.1N NaOH solution.

- **Preparation of Milipore Water**

Milipore water was be prepared using Ultrapure MiliQ Integral laboratory water purification system (Milli-Q IQ 7005). The system's comprehensive and optimized sequence of water purification and monitoring technologies allows ultrapure water with 18.2MegOhm.cm at 25°C to be produced directly from potable tap water in a single unit.

2.2.2 DETERMINATION OF λ_{MAX} OF PRAZOSIN HYDROCHLORIDE IN DIFFERENT MEDIA (pH 1.2, MILIPORE WATER, pH 6.8) AND DEVELOPMENT OF CALIBRATION CURVE:

Standard Prazosin Stock Solution (100µg/ml): A stock solution of Prazosin hydrochloride was prepared by accurately weighing 2.5mg of prazosin hydrochloride in an analytical balance and dissolving in different media (pH 1.2, milipore water, pH 6.8) in a 25ml volumetric flask. This stock solution (100µg/ml) was further diluted with respective media to obtain solution of 2-10µg/ml.

This stock resulting solution was scanned on a JASCO V-550 double beam spectrometer using same buffer solutions as blank. The ultra violet spectrum of Prazosin hydrochloride was obtained using a 1cm cell and by scanning the solution from 400nm to 200nm at a scan speed of 400nm/min. Absorbance of each diluted solution was measured at 246nm

using JASO V-550 double beam spectrometer and media solutions referred as standard. The standard calibration curve was generated for the entire range from 2-10mcg/ml.

2.2.3 COMPATIBILITY STUDIES

Drug with individual excipient, all excipients together were kept in closed containers under 40^0C and 75% relative humidity in a Humidity Chamber (Remi, India) for 1 month at an interval of 7, 14, 21, 30days to inspect the following study under this condition. The physical properties (colour change, physical state) were monitored at regular intervals.

a) Drug – Excipient compatibility study

b) Excipient – Excipient compatibility study

2.2.3.1 DRUG-EXCIPIENTS COMPATIBILITY STUDIES (CHEMICAL INTERACTION) BY ATR-FTIR

A proper design and formulation of a dosage form requires considerations of thephysical, chemical and biological characteristics of both drug and excipients used in fabrication of the product. Compatibility must be established between the activeingredient and other excipients to produce a stable, efficacious, attractive and safe product. Hence, before producing the actual formulation, compatibility of Prazosin hydrochloride with different polymers and other excipients was tested using ATR-FTIR spectroscopy.

All the samples were scanned over the wave number region 4000-400 cm-1. The ATR-FTIR Spectra of samples were given in next chapter “Results (Fig 22) and Discussion”.

2.2.4 DIIFFERENTIAL SCANNING COLORIMETRY (DSC):

DSC measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. DSC thermogram of pure drug, blank formulation and optimized formulation were carried out using Perkin Elmer instrument (Model: DSC 8000) which was calibrated against indium. Each Samplewas accurately weighed and kept into open pans, pan type used is Tzero aluminium in a hermetically sealed condition and heated at a scan speed of 10°C/min over a temperature range of 20-300 °C in a nitrogen atmosphere having a flow rate of 150ml/min.DSC analysis of pure Prazosin, all excipients and prazosin with excipients was performed to identify the drug melting point peakand polymer glass transition temperature (T_g) shown in [Fig 37, 38, 39]

2.2.5 ATTENUATED TOTAL REFLECTANCE [ATR-FTIR]:

ATR-IR spectrum of pure Prazosin hydrochloride, the physical mixture of the excipients with prazosin hydrochloride of the optimized batch and physical mixture of optimized batch without prazosin hydrochloride were performed in order to notice any interaction between drug and excipients. The spectra were recorded from 4000cm^{-1}-400cm^{-1} with scanning speed 2mm/sec and resolution 4cm^{-1} using Bruker Alpha I. [Fig 40,41,42]

2.2.6 X-RAY POWDER DIFFRACTION (XRPD):

An important technique for establishing the batch-to-batch reproducibility of a crystalline form is x-ray powder diffraction. Random orientation of a crystal lattice in a powder sample causes the x-rays to scatter in a reproducible pattern of peak intensities at distinct angles (q) relative to the incident beam. Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound. An amorphous form does not produce a pattern. Single-crystal X-ray analysis provides a precise identification and a description of a crystalline substance. Qualitative XRD studies of pure drug, blank formulation and drug-loaded formulation were performed using a wide angle X-ray diffractometer (Ultima III, Model: D/Max 2220, Rigaku Corporation, Japan). Each sample was scanned from 0 to 80 degree at a diffraction angle of 2θ range under the following conditions: source, Ni-filtered Cu-Kα (λ=1.54) radiation; voltage 40kV; current 30 mA; speed 5°/min. The area of the peaks at 2θ value had been considered as the representative peaks for the calculation of the calculation of relative degree of crystalline (RDC) as the other peaks of pure drug were merged in case of drug loaded formulation. The RDC was determined by comparing the representative peak intensity at different 2θ value in the diffraction pattern of pure drug with optimized formulation by using the following equation:

$RDC = I_F/I_{Drug} X\ 100$

Where I_F is the peak intensity of the drug loaded optimized formulation under investigation and I_{Drug} is the peak intensity at the same angle (2θ) for pure drug.[Fig 43,44,45]

2.2.7 DETERMINATION OF FLOW PROPERTIES OF THE PREPARED POWDER BLEND:

Preformulation may be described as a phase of the research and development processwhere the formulation scientist characterizes the physical, chemical and mechanicalproperties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the preformulation phase begins early in the discovery processsuch that the appropriate physical and chemical data is available to aid the selection of new chemical entities that enter the development process. During this evaluation,possible interaction with various inert ingredients intended for use in final dosage form is also considered in the present study.

Direct compression is defined as a process by which tablets are compressed directlyfrom powder blends of the active ingredients and suitable excipients, which flow uniformly into a die cavity from hopper and form firm compact.

Before employing direct compression as a method of preparation of tablets, thepowder properties of the ingredients should be assessed to ascertain their stability for direct compression. The powder of polymer and drugs were characterized by angle of repose, bulk density, tapped density and carr's index and hausner's ratio. The flow properties of powders have a great impact on tableting because it requires the flow ofmaterials from a storage container (hopper) to filling stations in a compression machine.

A. Bulk Density (B_b)

The bulk density of a powder is dependent on particle packing and changes as thepowder consolidates. A consolidated powder is likely to have a greater arch strengththan a less consolidated one and may be therefore be more resistant to powder flow.The ease with which a powder consolidates can be used as an indirect method ofquantifying powder. Apparent bulk density (gm/mL) was determined by pouring bulkpowder into a graduated cylinder via a large funnel and measuring the volume andweight. Bulk density can be calculated by the following formula,

Bulk Density of the powder is calculated by $D_b = M/ V_b$

Where, M and V_b are the mass and volume of the powder respectively. [110]

B. Tapped Density (D_t)

It is the ratio of the total mass of the tapped volume of powder. Volume was measured by tapping the powder for 750 times and the tapped volume was recovered if the difference between these two is less than 2% and if the difference is more than 2% tapping is continued for 1250 times and tapped volume is noted. The tapping was continued until the difference of the volume is less than 2 %. It is expressed n g/ml and is given by

$D_t = M / V_t$

Where M and V_t is the mass and volume of the powder respectively [110]

C. Angle of Repose

Funnel method was used to measure the angle of repose of powder. The accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powders were allowed to flow through the funnel freely onto the surface [110]. The diameter of the powder cone was measured and angle of repose was calculated using following equation:

$$\textbf{Angle of repose } \theta = \tan^{-1} H/R$$

Where, H = height of heap,
R = radius of heap

Angle of Repose	Type of flow
< 25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

D. Hausner's Ratio

Hausner's ratio is an indirect index for determination of flow properties of powder [110]. It is calculated by using following formula

Hausner's Ratio = Tapped Density/ Bulk Density

E. Compressibility Index

Present compressibility of the powder mix was determined by Carr's compressibility index calculated by

Carr's Index = $[(D_t - D_b) \times 100] / D_t(\%)$

Carr's Index (%)	Type of Flow
5-15	Excellent
15-18	Good
18-23	Fair to passable
23-35	Poor
35-38	Very Poor

2.2.8 PREPARATION OF TABLETS BY DIRECT COMPRESSION

Accurately weighed quantities of polymers were taken in a mortar and mixed thoroughly, to this mixture required quantity of Prazosin hydrochloride was added and mixed with pestle. Accurately weighed quantity of citric acid was taken separately in a mortar and powdered with pestle. The powder is passed through seive# 80 and mixed with the drug blend. To whole mixture was collected in a plastic bag and mixed for 5 minutes, to this mixture Magnesium stearateand talc was added and mixed again for 5 minutes. The mixtures were homogeneously blended and subsequently compressed into tablets using 10 station curved face punch.

Tablets have been prepared at 300 mg scale using 10 station Remi Rotary compression machine concave face punches having a coaxial hole of prazosin hydrochloride as model drug (3.33%), sodium bicarbonate as effervescent agent (15%), citric acid as acidifier(5-20%), talc as Glidant (2%), Magnesium stearate as Lubricant (2%). The binders utilized were HPMC K4M (35-50%), Xanthan gum (20%). The combination of HPMC K4M and Xanthan gum was used. The formulations were optimized with different binders to excipients ratios shown in Table 4.Hardness of the tablets was kept within 4-6 kg/cm2.External diameter and internal diameter were fixed at 10 mm and 4 mm respectively.

2.2.9 PHYSICAL PARAMETER EVALUATION OF PREPARED PRAZOSIN HYDROCHLORIDE FLOATING TABLETS:

- **Thickness:**

The thickness of tablet is important for uniformity of tablet size. The thickness of the tablets was determined using a Digital Vernier Calliper (MODEL: 500-196-20) at three different positions. Three tablets from each batch was evaluated. [111]

- **Hardness (Crushing strength):**

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. The hardness of the tablet was determined on three tablets to get an average hardness expressed in It is expressed in kg/cm^2.[111]

- **Weight Variation:**

Twenty tablets were weighed individually. Average weight tablet was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits [111]. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight)/ Average weight X 100

Table 4: Weight Variation deviation as per Indian Pharmacopoeia

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

- **Drug Content Uniformity Study:**

Twenty tablets were weighed individually and powdered. The powder equivalent to 2.5 mg of Prazosin Hydrochloride was weighed and dissolved in pH 1.2. The volume was made to 25 with pH 1.2. From this stock solution, 10 µg/ml dilution of the drug was prepared. The drug contents of the resulting solution were calculated using UV spectrometer at a wavelength of 246nm. [111]

- **Friability:**

Tablet hardness is not an absolute indicator of the strength, therefore another measure of a tablet's strength, its friability. Roche friabilator is the equipment which is used for the determination of friability. This device, subjects a number of tablets to the combined effects of abrasion and shock by utilizing a transparent synthetic polymer chamber with an initial diameter between 283 and 291 mm and a depth between 36 and 40 mm that revolves at 25±1 rpm. It is expressed in percentage. The initial weight of the tablets ($W_{initial}$) was noted. Tablets were placed in a plastic chamber which revolves at 25 rpm and they are subjected to tumbled from a distance of six inches at each turn of the drum by a curved projection in the friabilator for about 100 revolutions. Then measure the weight of the tablet (W_{final}) and observe any weight difference before tablet and after the friabilator processing. [111]

Limits: A maximum mean weight loss from the three samples of not more than 1.0%is generally considered as acceptable for compressed tablets.

F= {(W initial)- (W final)/ (W initial)}×100

- ***In vitro* buoyancy / floating study [112]:**

In vitro buoyancy studies were performed for all theformulations. The randomly selected tablets from each formulation batch were kept in a 100 ml beaker containing simulated gastric fluid, pH1.2 as per USP.The time taken for the tablet to rise to the surfaceand float was taken as Floating Lag Time (FLT). The duration of time the dosage form remained on the surface of medium was determined as the Total Floating Time (TFT).

- **Swelling Index[113]:**

The swelling behavior of a dosage unit was measuredby studying its weight gain. The swelling index oftablets was determined by placing the tablets in thebasket of dissolution apparatus using dissolution medium pH 1.2 buffers at 37±0.5º C. After 0.5, one,two, three, four, and up to six hours, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to removethe excess water and weighed on the analytical balance and the swelling index was calculated.

2.2.10 *IN VITRO* DISSOLUTION STUDY:

In vitro dissolution test of the prepared tablets was performed and optimized using USP II Dissolution Testing Apparatus (Electrolab TDT-08L) containing pH 1.2 as the Stomach gastric fluid (SGF) and the paddle was rotated at a speed of 50 rpm to mimic the peristalsis movement in the body. 900 ml of 0.1N hydrochloric acid solution was maintained at 37 ± 0.5^0C for 10 hrs dissolution study. 5 ml of samples were withdrawn at different time intervals and those amounts were replaced with corresponding dissolution mediums. The samples were filtered and assayed spectrometrically at 246 nm. Formulations were then optimized on the basis of drug release. Cumulative percentage of release of drug was calculated using various pharmacoPharmacokinetic approaches.

2.2.11 DRUG RELEASE PHARMACOKINETICS STUDY OF PRAZOSIN HYDROCHLORIDE TABLETS:

Taking the data obtained from dissolution and permeation study of Prazosin hydrochloride tablet, the drug release Pharmacokinetics studies were calculated.

For Zero-order model, Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Q_t = K_0 t$$

whereQ_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time. To study the release Pharmacokinetics, data obtained from *In Vitro* drug release studies were plotted as cumulative amount of drug released versus time.

For First order model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order Pharmacokinetics can be expressed by the equation: dC/dt = - Kc

Equation can be expressed as: $\log C = \log C_0 - Kt / 2.303$

where C_0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining vs. time.

For Diffusion release study (Higuchi Plot), the data obtained were plotted as cumulative percentage drug release versus square root of time.

For KorsmeyerPeppas Plot, to study the release Pharmacokinetics, data obtained from *In Vitro* drug release studies were plotted as log cumulative percentage drug release versus log time.

For Hixon Crowell Plot, to study the release Pharmacokinetics, data obtained from *In Vitro* drug release studies were plotted as cube root of drug percentage remaining in matrix versus time. [114,115]

2.2.12 STABILITY STUDIES OF FLOATING PRAZOSIN TABLETS

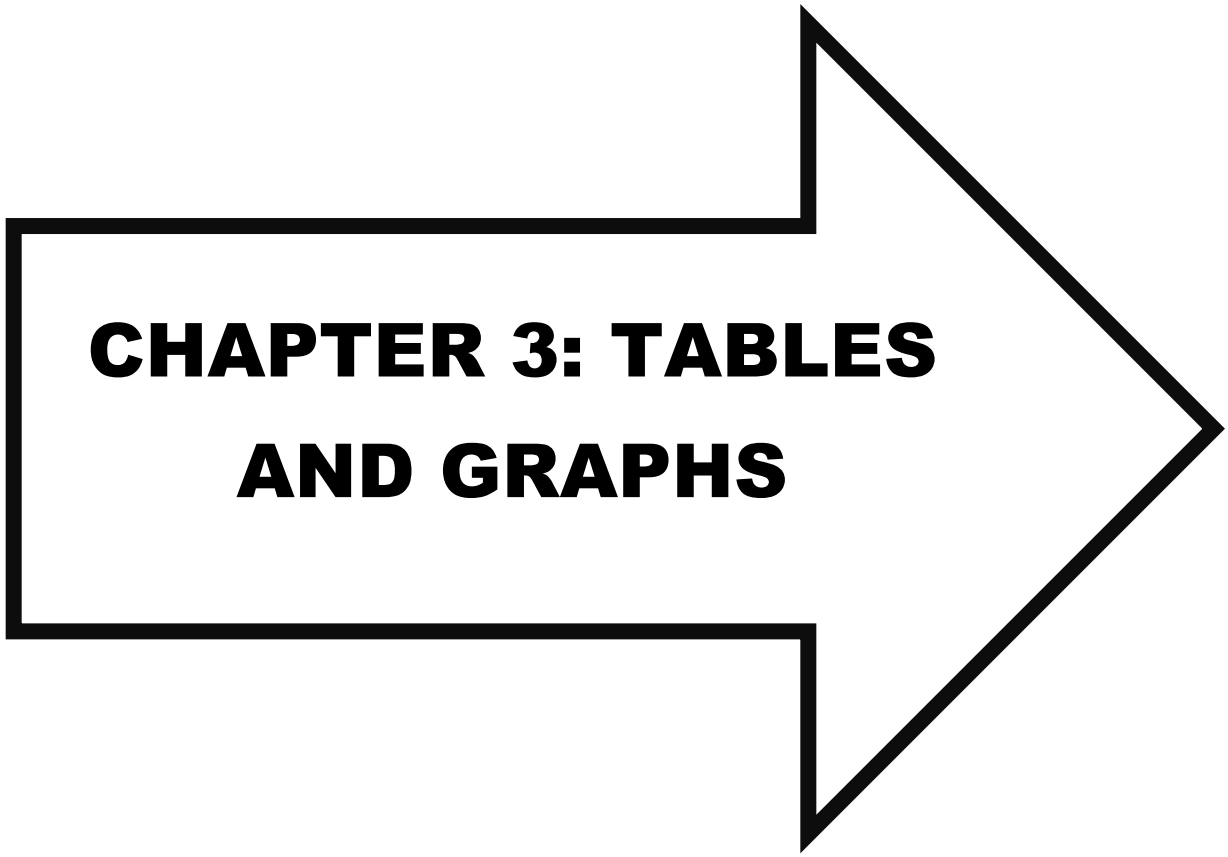
In any rational design and evaluation of dosage forms for drugs, the stability of theactive component must be a major criterion in determining their acceptance orrejection.Stability of a formulation can be defined as the time from date of manufacture of theformulation until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciablyor deleteriously.The purpose of stability testing is to provide evidence on how the quality of a drugsubstance or drug product varies with time. Under the influence of a variety ofenvironmental factors such as temperature, humidity and light, enablingrecommended storage conditions, re-test periods and shelf lives.Generally, the observation of the rate at which the product degrades under normalroom temperature requires a long time. To avoid the undesirable delay, the principlesof accelerated stability studies are adopted.The international conference on harmonization (ICH) Guidelines titled “stability ofnew drug substances and products” (QIA) describes the stability test requirements fordrug registration application in the European Union, Japan and United States ofAmerica. ICH specifies the length of study and storage conditions.Stability studies were carried out for the selected formulation according to ICHguidelines. An optimize formulation were sealed in aluminium packaging coated inside with polyethylene, and samples were kept in

humidity chamber (Remi, India) at40°C and 75 % RH for one month. At the end of the period, samples were analyzedfor drug content, floating characteristics and hardness studies.

2.2.13 STATISTICAL ANALYSIS:

Statistical Analysis perform include ANOVA study to determine P and F –Value from study Cumulative percentage release using Microsoft program (2010, version1). The one-way analysis of variance (ANOVA) is used to determine whether there are any statistically significant differences between the means of three or more independent (unrelated) groups. The one-way ANOVA compares the means between the groups you are interested in and determines whether any of those means are statistically significantly different from each other.

CHAPTER III



3. FIGURES AND GRAPHS:

3.1 Determination of absorption maxima (λ_{max}) in different media:

3.1.1 Determination of λ_{max} of Prazosin hydrochloride in Acidic Solution (pH 1.2)

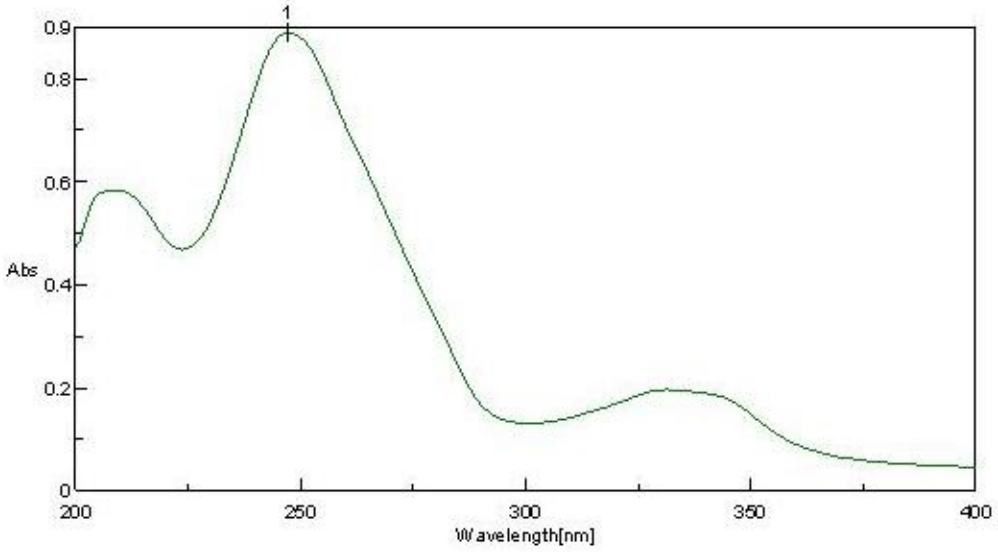


Fig 10: Determination of λ_{max} of Prazosin hydrochloride in Acidic Solution (pH 1.2)

3.1.2 Determination of λ_{max} of Prazosin hydrochloride in Milipore Water

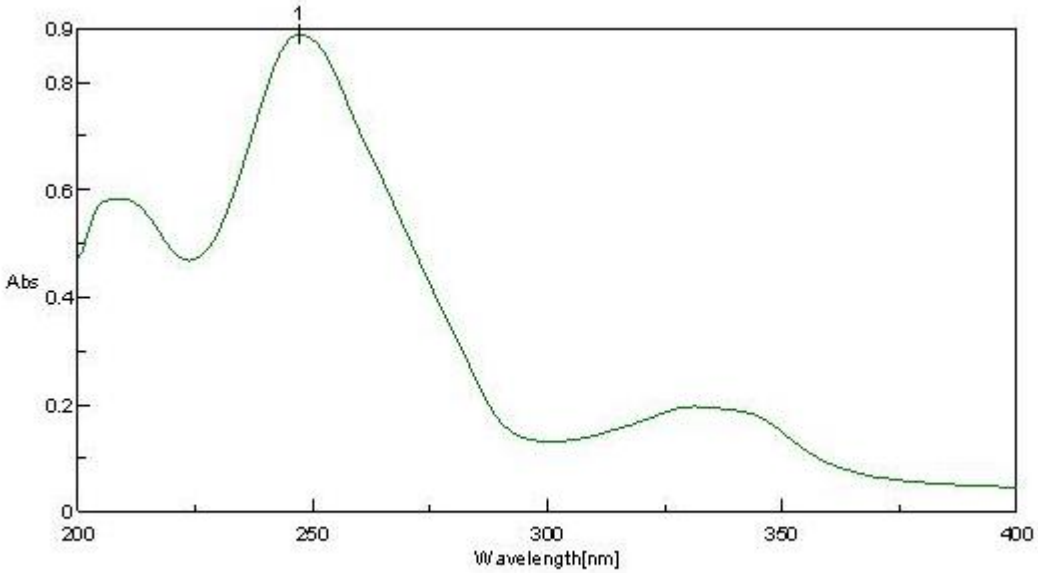


Fig 11: Determination of λ_{max} of Prazosin hydrochloride in Milipore water

3.1.3 Determination of λ_{max} of Prazosin hydrochloride in Phosphate Buffer (pH 6.8):

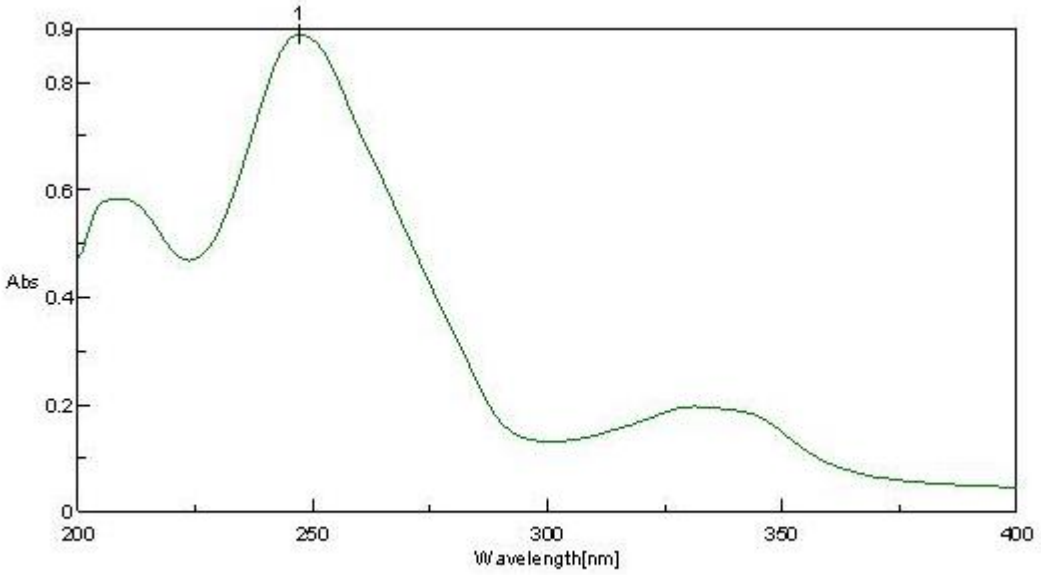


Fig 12: Determination of $\lambda_{max}$of Prazosin hydrochloridein Phosphate Buffer (pH 6.8)

3.2 Estimation of Calibration Curve in different media:

3.2.1 Absorbances at different concentrations of Prazosin hydrochloride in 0.1N HCl (pH 1.2) at 246nm.

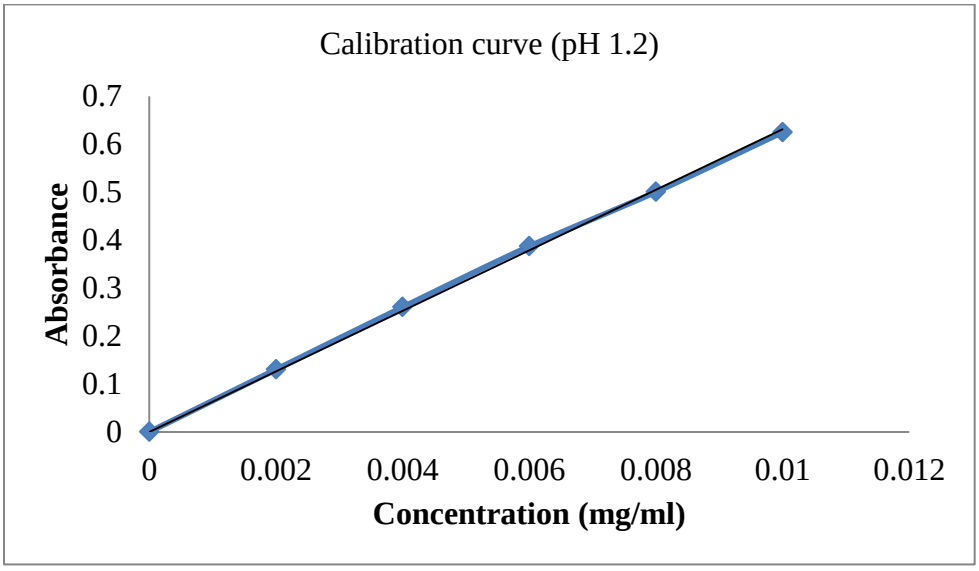


Fig 13: Calibration Curve of of Prazosin hydrochloride in 0.1N HCl (pH 1.2) at 246nm.

3.2.2 Absorbances at different concentrations of Prazosin hydrochloride in Phosphate Buffer (pH 6.8) at 246nm.

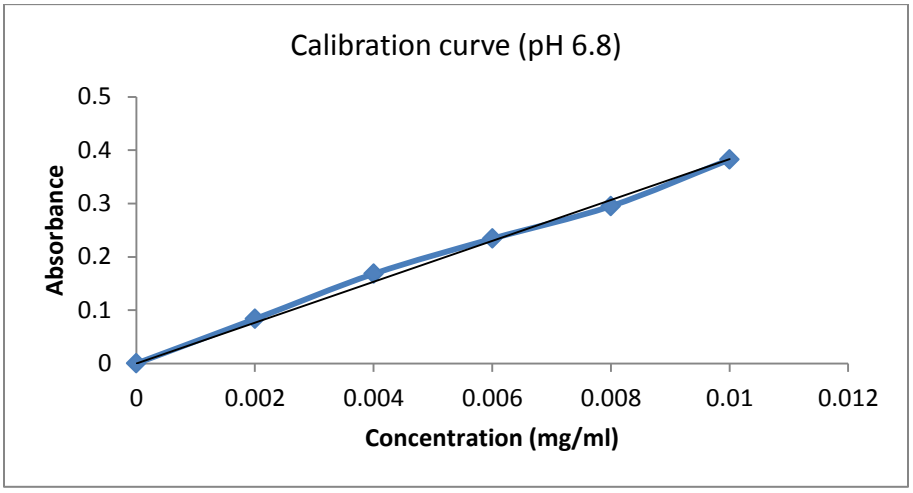


Fig 14: Calibration Curve of of Prazosin hydrochloride in Phosphate Buffer (pH 6.8) at 246nm.

3.2.3 Absorbances at different concentrations of Prazosin hydrochloride in Milipore water at 246nm.

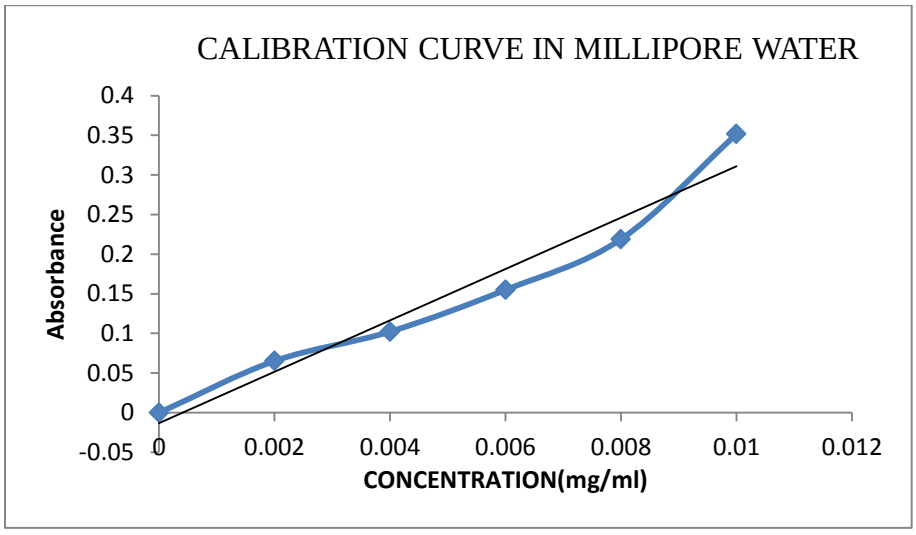


Fig 15: Calibration Curve of ofPrazosin hydrochloride in Millipore Water at 246nm.

3.3 Determination of Melting Point:

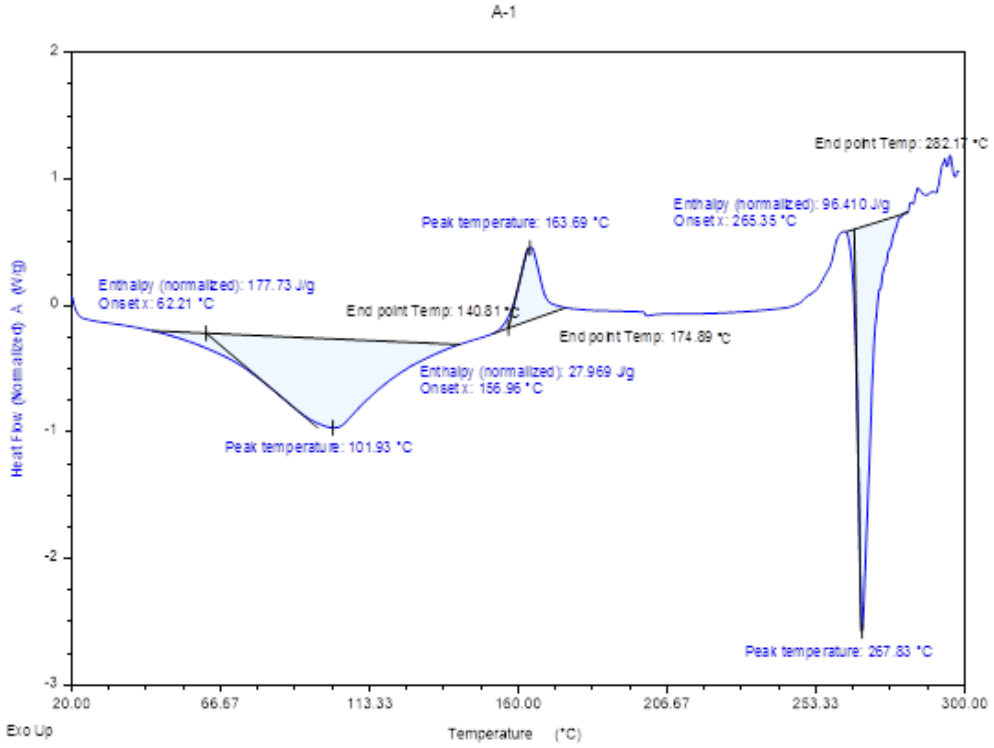


Fig 16: Melting Point of Prazosin hydrochloride

3.4 Identification of Chemical moieties:

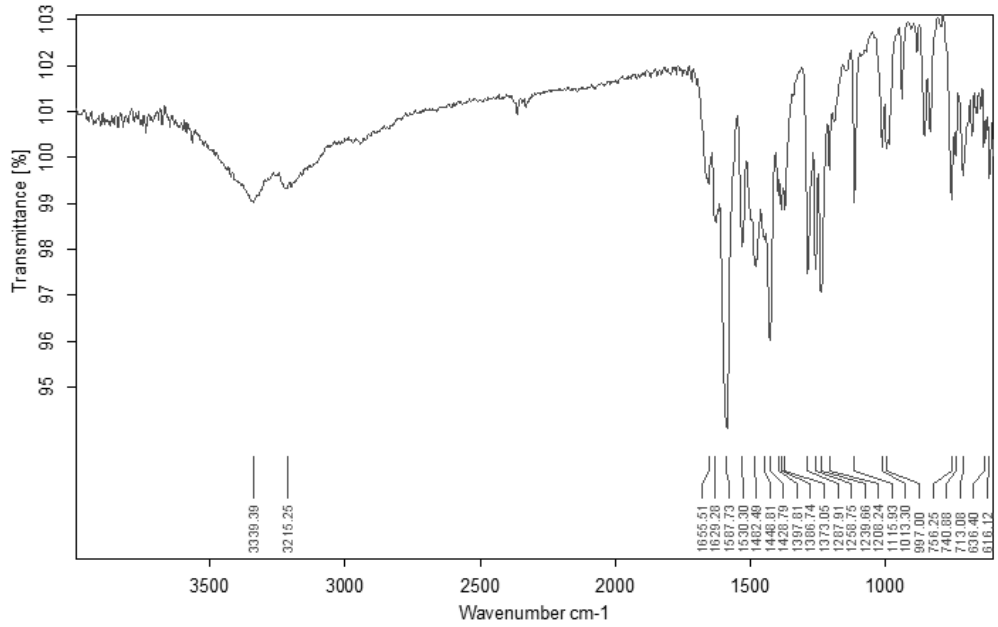


Fig 17: FTIR of Prazosin hydrochloride (pure drug)

Table 5: ATR-FTIR Peaks of Prazosin hydrochloride

Observed Value Peaks(cm^{-1})	Standard Value Peaks(cm^{-1})	Spectrum of Prazosin hydrochloride Assignment	Pure Drug
3339.39	>3000	=CH aromatic ring	Yes
1655.51	1750-1680	C=O stretching	Yes
1629.28	1560-1650	N-H bending	Yes
1287.91	1000-1320	C-O stretching	Yes

3.5 Drug – Excipients Compatibility Study:

Table 6: Visual Inspection in appearance after keeping 1months under 40^0C and 75% RH

D = Prazosin hydrochloride		**Change of Colour**			
MATERIAL	**INITIAL COLOR**	**7DAYS**	**14DAYS**	**21DAYS**	**1MONTH**
D+HPMC	WHITE	NO	NO	NO	NO
D+CARBOPOL	WHITE	NO	NO	NO	NO
D+MCC	OFF WHITE	NO	NO	NO	NO
D+NaHCO3	WHITE	NO	NO	NO	NO
D+CITRIC ACID	WHITE	NO	NO	NO	NO
D+PVP K30	OFF WHITE	NO	NO	NO	NO
D+MAGNESIUM STEARATE	WHITE	NO	NO	NO	NO
D+TALC	WHITE	NO	NO	NO	NO
D+XANTHAN GUM	OFF WHITE	NO	NO	NO	NO
D+MANNITOL	WHITE	NO	NO	NO	NO
D+LACTOSE	WHITE	NO	NO	NO	NO
D+DCP	WHITE	NO	NO	NO	NO
ALL EXCIPIENTS	WHITE	NO	NO	NO	NO

3.5.1. FTIR Spectrum of different drug –excipient mixture:

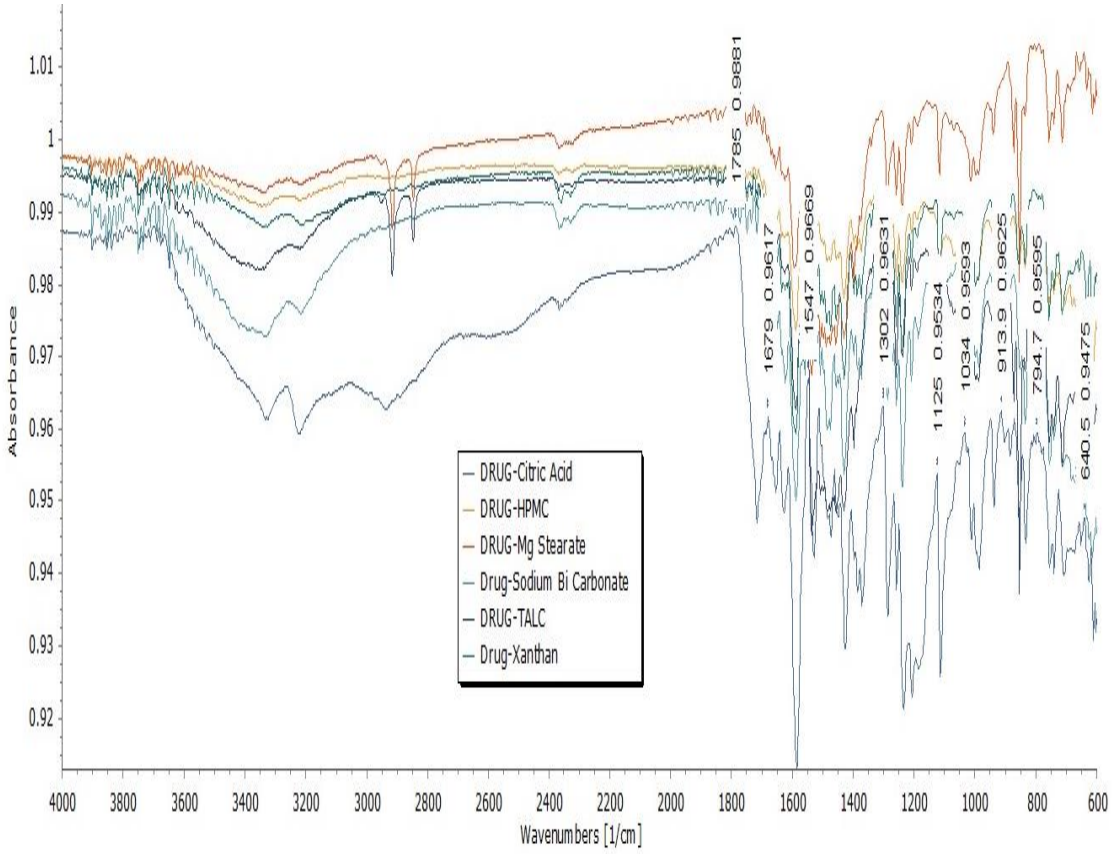


Fig 18: ATR-FTIR Curve of Drug with excipients mixtures

3.7 Optimization of HPMC and $NaHCO_3$ Prazosin hydrochloride in Floating Tablets

Table 7: Formulation details during primary development and optimization using HPMC K4M and Citric Acid:

Formulation Code	PERCENTAGE OF DIFFERENT INGREDIENTS	
	HPMC K4M	CITRIC ACID
F-1	52.67	5
F-2	50.17	7.5
F-3	47.67	10
F-4	45.17	12.5
F-5	42.67	15
F-6	40.17	17.5
F-7	37.67	20
F-8	35.17	22.5

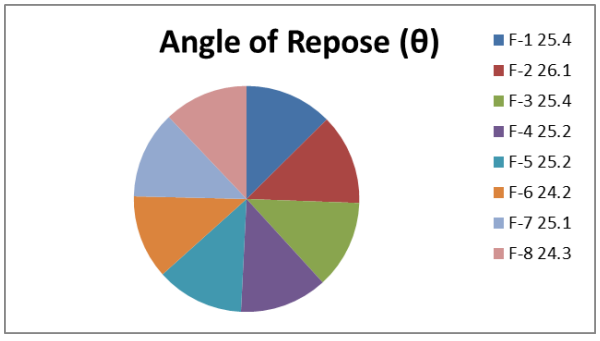
3.7 Table 8: Formulations of Different Batches of Optimized Floating Prazosin hydrochloride Tablets:

Formulation Code	DRUG (mg)	HPMC (mg)	$NaHCO_3$ (mg)	XANTHAN GUM (mg)	CITRIC ACID (mg)	TALC (mg)	Mg STEARATE (mg)
F-1	10	158.0	45	60	15.0	6	6
F-2	10	150.5	45	60	22.5	6	6
F-3	10	143.0	45	60	30.0	6	6
F-4	10	135.5	45	60	37.5	6	6
F-5	10	128.0	45	60	45.0	6	6
F-6	10	120.5	45	60	52.5	6	6
F-7	10	113.0	45	60	60.0	6	6
F-8	10	105.5	45	60	67.5	6	6

3.8 Determination of flow properties of the prepared Powder blends:

3.8.1 Table 9: Study of Flow properties for different batches [F1-F8] [mean ±SD, n=3]

BLEND FORMULATION CODE	ANGLE OF REPOSE	COMPRESSIBILITY INDEX	HAUSNER'S RATIO
F-1	25.4± 0.1	13.0±0.44	1.14±0.02
F-2	26.13333±0.057	15.7±1.62	1.18±0.02
F-3	25.36667±0.057	16.2±0.78	1.19±0.01
F-4	25.26667±0.057	14.1±1.52	1.16±0.02
F-5	25.26667±0.057	12.7±1.3	1.15±0.01
F-6	24.16667±0.056	13.7±0.67	1.18±0.05
F-7	25.16667±0.056	14.5±0.76	1.16±0.02
F-8	24.33333±0.057	15.3±0.44	1.17±0.01



- **Fig 19:**Graphical representation of Angle of repose for different batches [F1-F8]

3.8.1 Table 10: Study of Density (gm/cc) for different batches [F1-F8] [mean ±SD, n=3]

FORMULATION CODE	DENSITY (mean±SD),n=3	
	BULK (gm/cc)	TAPPED (gm/cc)
F-1	0.6394±0.009	0.71273±0.01
F-2	0.6472±0.007	0.71663±0.01
F-3	0.663033±0.01	0.76143±0.01
F-4	0.638267±0.011	0.7152±0.01
F-5	0.6587±0.009	0.74053±0.02
F-6	0.664267±0.02	0.74427±0.02
F-7	0.662167±0.03	0.73403±0.01
F-8	0.678933±0.01	0.7658±0.01

3.9 Evaluation of Prazosin hydrochloride Floating tablets (post compression evaluations):

3.9.1 Table 11: Weight Variation Study for different batches [F1-F8] [mean±SD, n=3]:

FORMULATION CODE	AVERAGE WEIGHT (mg)	% WEIGHT VARIATION
F-1	300.6±1.35	0.910301954
F-2	299.3±0.85	0.589609523
F-3	301.2333±0.85	1.615580392
F-4	298.9667±0.71	0.357182721
F-5	301.1333±1.19	0.32100952
F-6	300.9±1.74	0.398803589
F-7	299.5±2.1	0.701168614
F-8	300.3667±1.18	0.410609255

3.9.2 Table 12: Friability and Thickness of the tablets for different batches [F1-F8]:

Formulation Code	Friability (%) maen±SD(n=3)	Thickness (mm)	
		Mean±SD[n=3]	% Variation
F-1	0.7766±0.015	5.13±0.02	0.4542
F-2	0.6666±0.015	5.13±0.01	0.1949
F-3	0.4233±0.025	5.14±0.01	1.6666
F-4	0.8266±0.02	5.15±0.005	0.6666
F-5	0.8666±0.03	5.13±0.01	0.1949
F-6	0.75±0.02	5.15±0.01	0.1941
F-7	0.68±0.03	5.15±0.01	0.1941
F-8	0.7733±0.04	5.13±0.015	0.2595

3.9.3 Table 13: Diameter (inner and outer) of the tablets for different batches [mean±SD] (n=3):

FORMULATION CODE	DIAMETER(mm)			
	INNER		OUTER	
	Mean ±SD	% Variation	Mean ±SD	% Variation
F-1	3.85±0.008	0.2597	10.01±0.01	0.0999
F-2	3.87±0.012	0.3439	10.013±0.005	0.0665
F-3	3.84±0.009	0.3466	10.016±0.011	0.1331
F-4	3.86±0.004	0.0862	10.023±0.005	0.0665
F-5	3.85±0.008	0.2597	10.02±0.01	0.0998
F-6	3.85±0.124	0.3457	10.013±0.005	0.0665
F-7	3.85±0.008	0.2597	10.013±0.005	0.0665
F-8	3.85±0.009	0.3457	10.023±0.011	0.0665

3.9.4 Table 14: Hardness (kg/cm^2) of the tablets for different batches [F1-F8]:

FORMULATION CODE	HARDNESS(kg/cm^2)(mean±SD)[n=3]
F-1	4.9±0.1
F-2	5.866667±0.11
F-3	4.666667±0.15
F-4	4.866667±0.32
F-5	4.133333±0.11
F-6	5.066667±0.05
F-7	5.333333±0.05
F-8	4.833333±0.05

3.9.5 Table 15: Drug Content Uniformity of the tablets for different batches [F1-F8] [mean±SD] (n=3):

FORMULATION CODE	% Drug Content [Mean±SD]
F-1	98.61±0.2
F-2	98.53±0.1
F-3	96.06±0.2
F-4	98.56±0.6
F-5	98.42±0.7
F-6	98.62±1.1
F-7	98.56±0.6
F-8	98.49±0.7

3.9.6 Table 16: Swelling Index of gastroretentive floating tablets of Prazosin hydrochloride [F1-F8]:

FORMULATION CODE	0 HOUR	2 HOUR	4 HOUR	6 HOUR
F-1	0	25.4	35.5	46.2
F-2	0	29.3	41.9	52.6
F-3	0	31.5	42.9	59.8
F-4	0	34.4	47.6	58.7
F-5	0	36.2	48.2	60.1
F-6	0	38.8	49.8	61.2
F-7	0	32.3	45.2	57.4
F-8	0	32.5	46.5	58.4

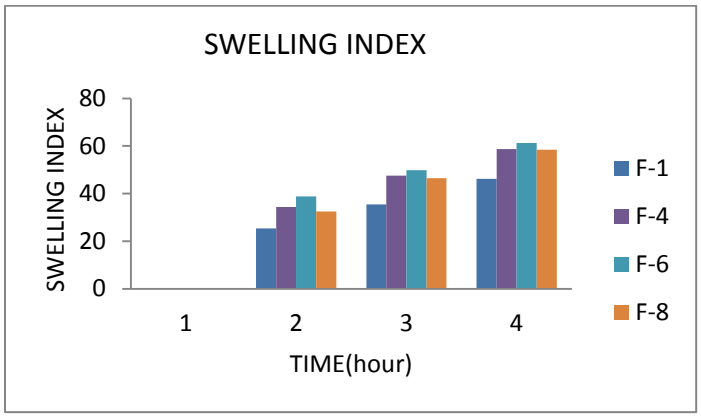


Fig 20: Comparative Swelling Index of Prazosin Hydrochloride for different batches [F1, F4, F6, F8]

3.9.7 Table 17: *In Vitro* Buoyancy Study: Tablet density, buoyancy lag time and total floating time of floating tablet of Prazosin Hydrochloride

FORMULATION CODE	Floating Lag Time(seconds) (Mean±SD)[n=3]	Total Floating Time (Hours)	Tablet Density (gm/cm^3)
F-1	12±0.02	>8	0.9
F-2	15±0.07	>8	0.86
F-3	11±0.04	>8	0.73
F-4	12±0.02	>8	0.86
F-5	10±0.01	>8	0.76
F-6	14±0.05	>8	0.69
F-7	12±0.07	>8	0.77
F-8	11±0.02	>8	0.78

Fig 32 (a): After 0 second

Fig 32 (b): After 5 seconds

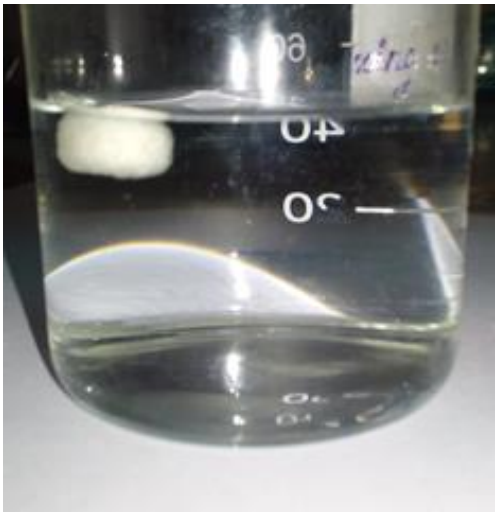


Fig 32(c): After 4 hours

3.10 *In Vitro* Release Study for different batches using USP-II Apparatus [F1-F8]:

3.10.1 Release Pharmacokinetic Study for Formulation F-1

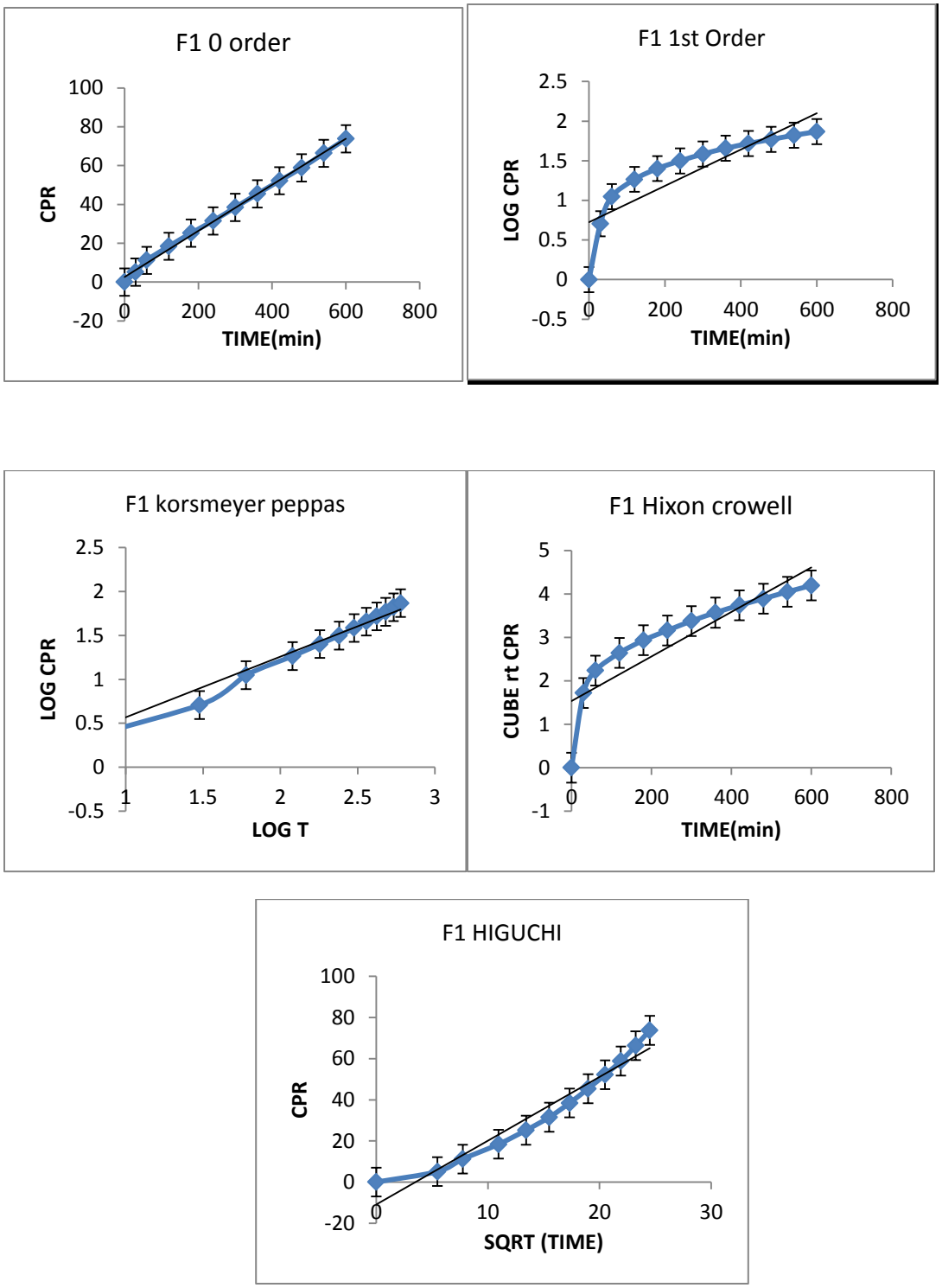


Fig 21(a-e): Different release Pharmacokinetics of Prazosin hydrochloride tablets [Formulation F-1]

3.10.2 Release Pharmacokinetic Study for Formulation F-2

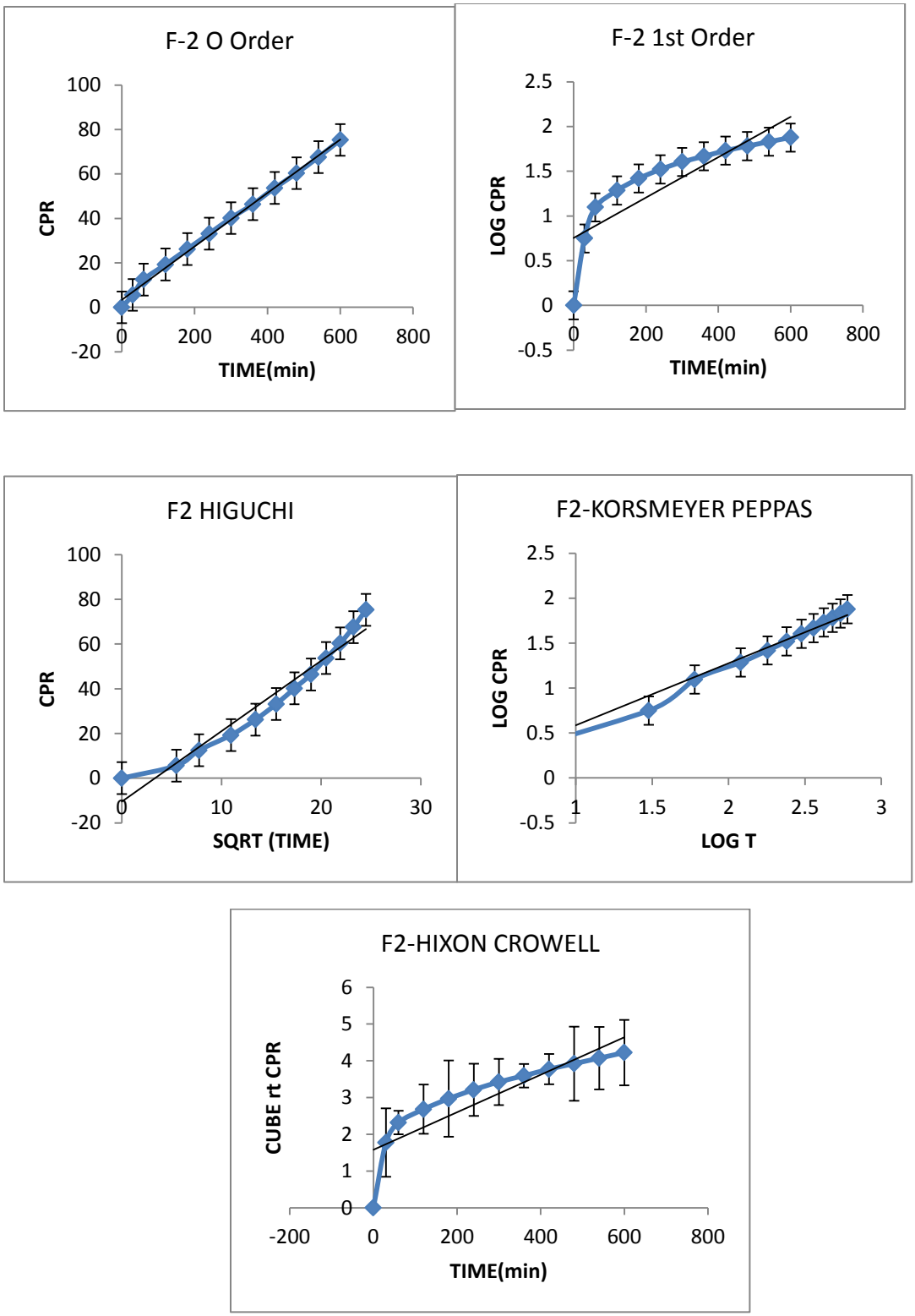


Fig 22(a-e): Different release Pharmacokinetics of Prazosin hydrochloride tablets [Formulation F-2]

3.10.3 Release Pharmacokinetic Study for Formulation F-3

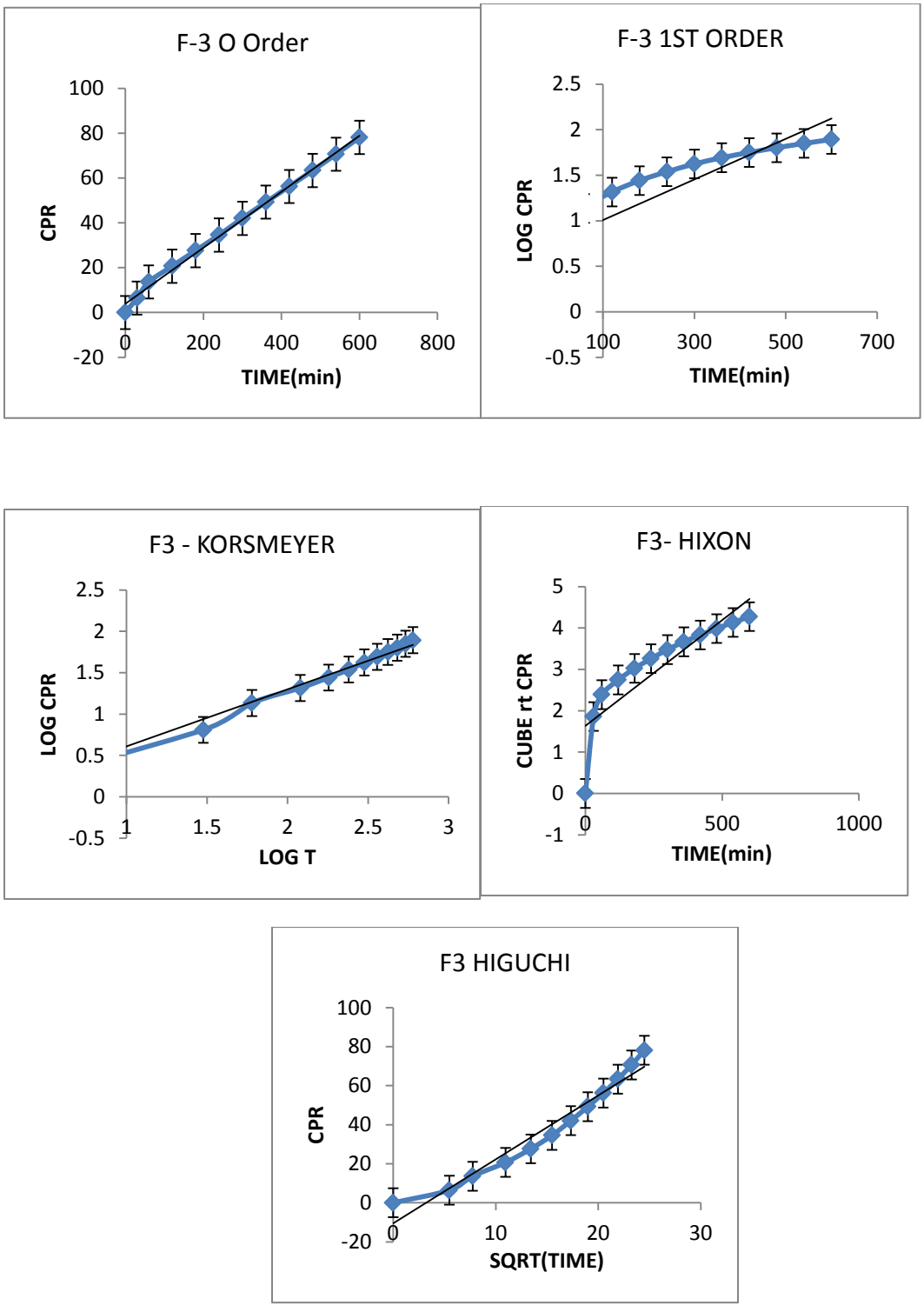


Fig 23(a-e): Different release Pharmacokinetics of Prazosin hydrochloride tablets [Formulation F-3]

3.10.4 Release Pharmacokinetic Study for Formulation F-4

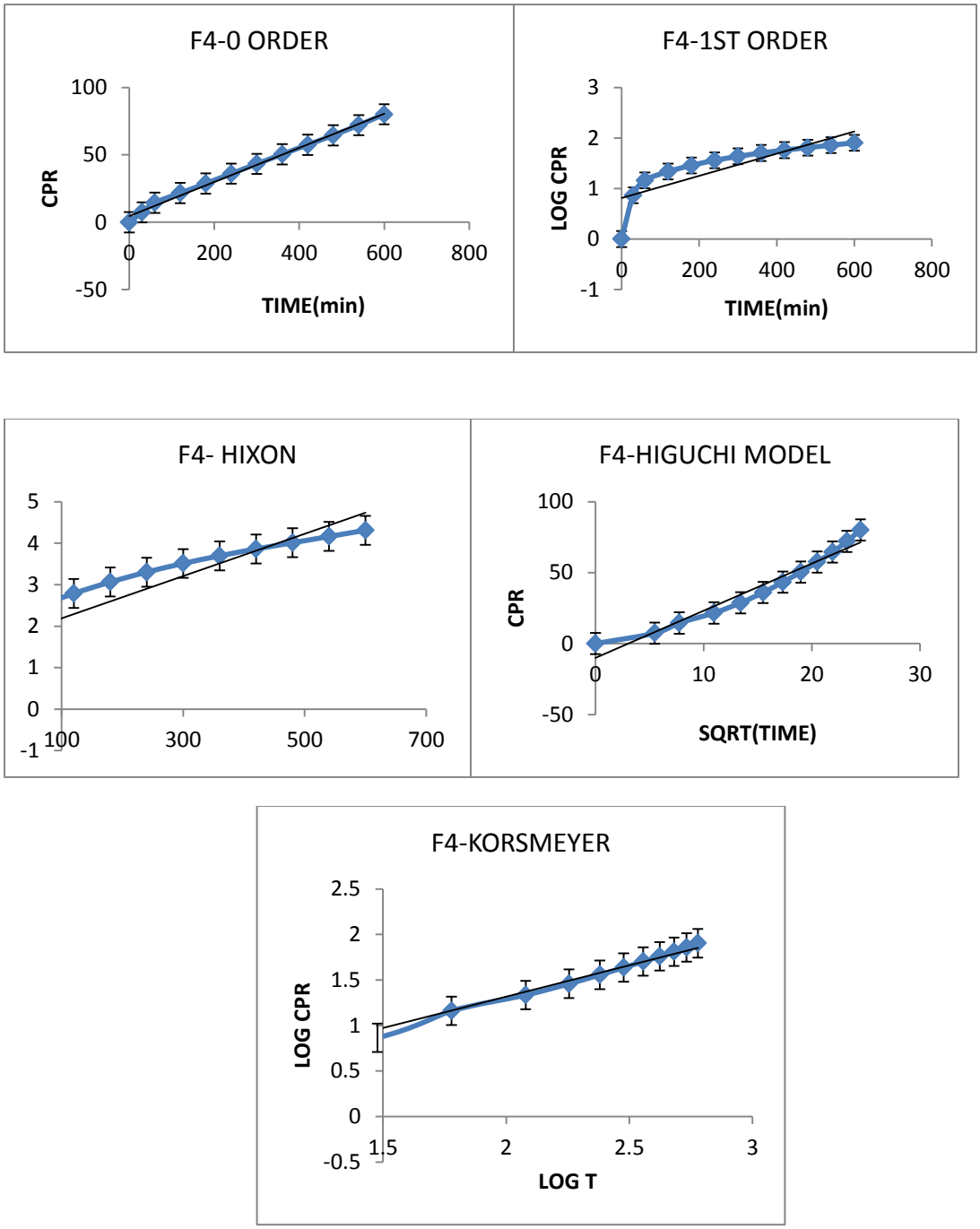


Fig 24(a-e): Different release Pharmacokinetics of Prazosin hydrochloride tablets [Formulation F-4]

3.10.5 Release Pharmacokinetic Study for Formulation F-5

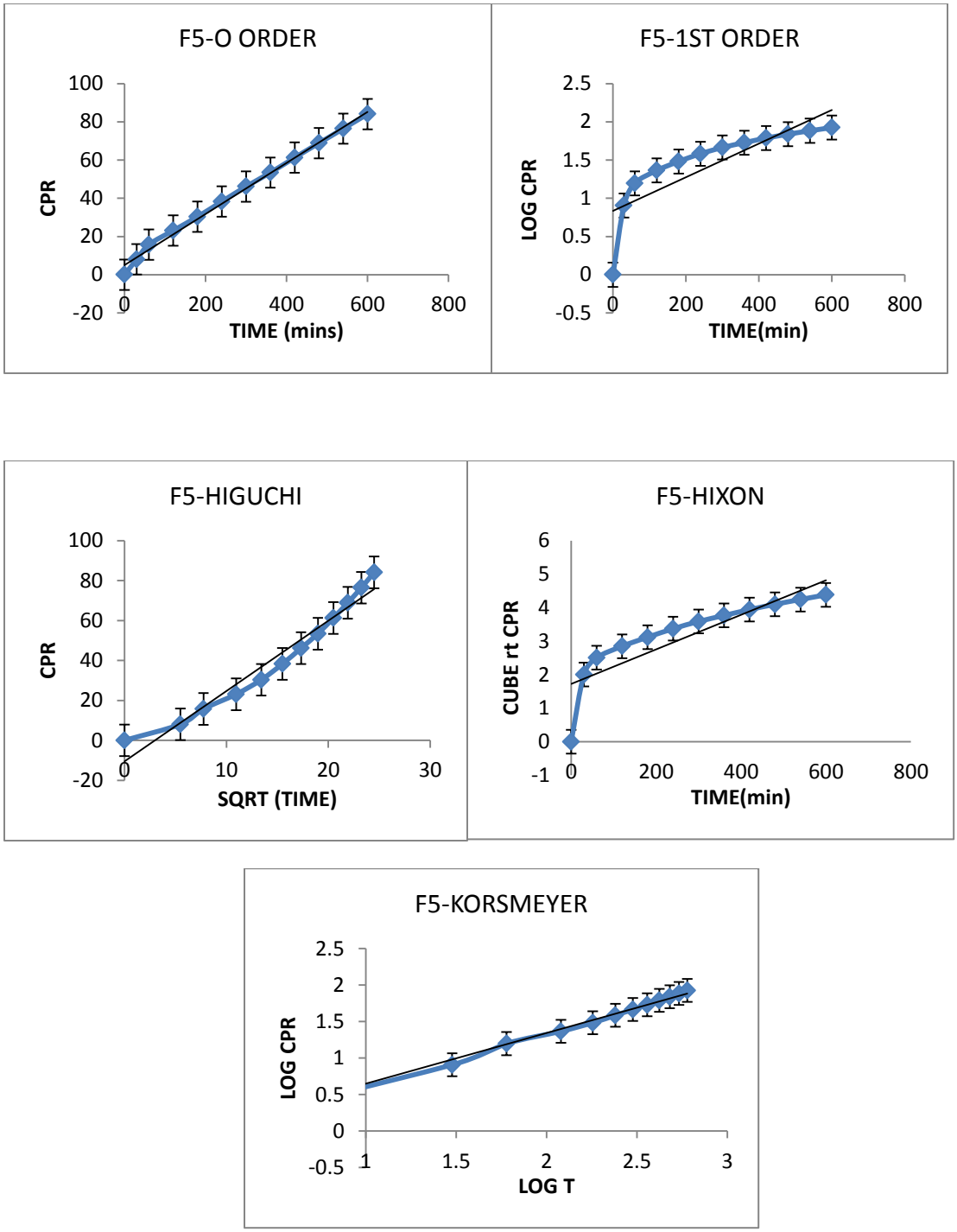


Fig 25(a-e): Different release Pharmacokinetics of Prazosin hydrochloride tablets [Formulation F-5]

3.10.6 Release Pharmacokinetic Study for Formulation F-6

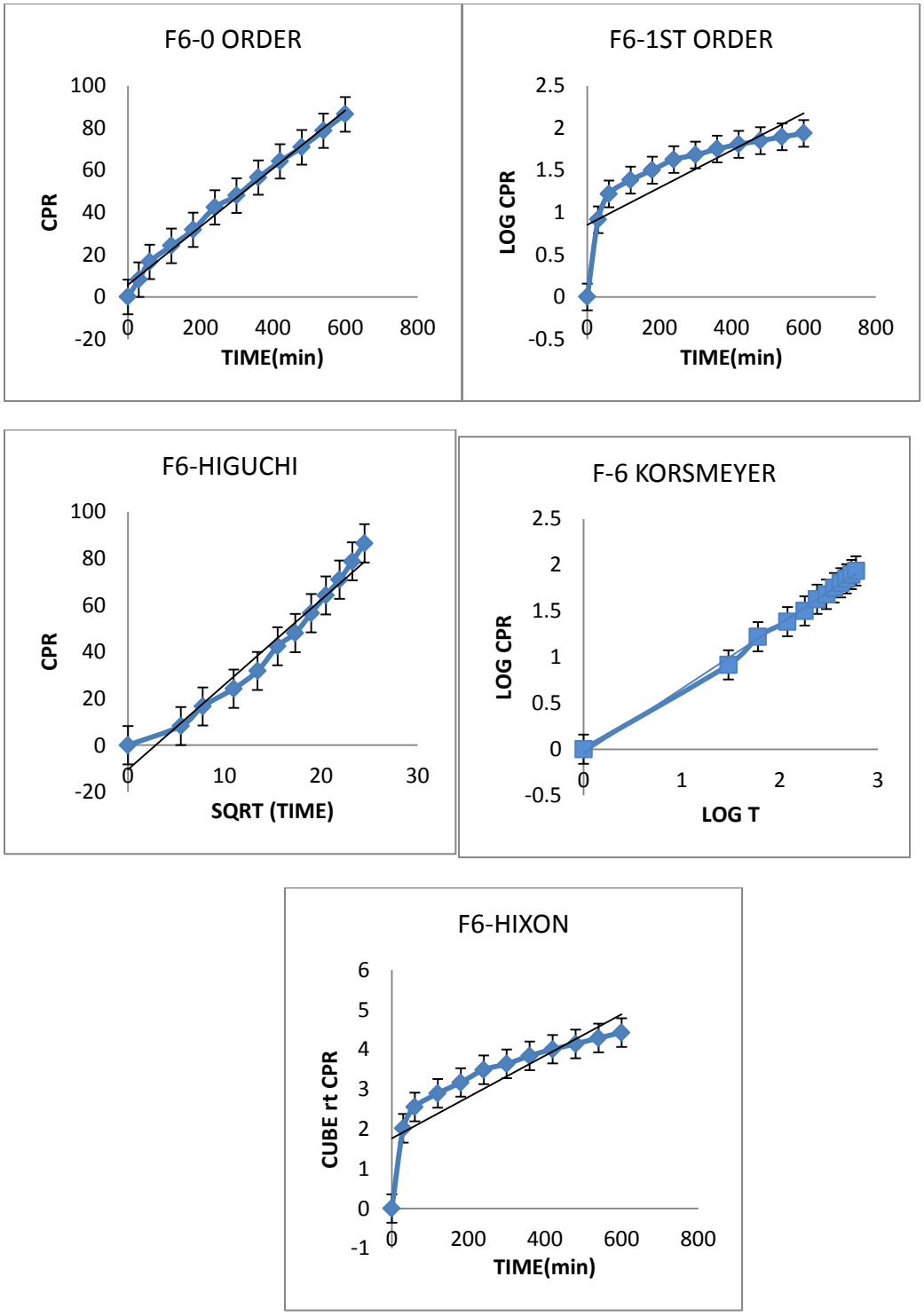


Fig 26(a-e): Different release Pharmacokinetics of Prazosin hydrochloride tablets [Formulation F-6]

3.10.7 Release Pharmacokinetic Study for Formulation F-7

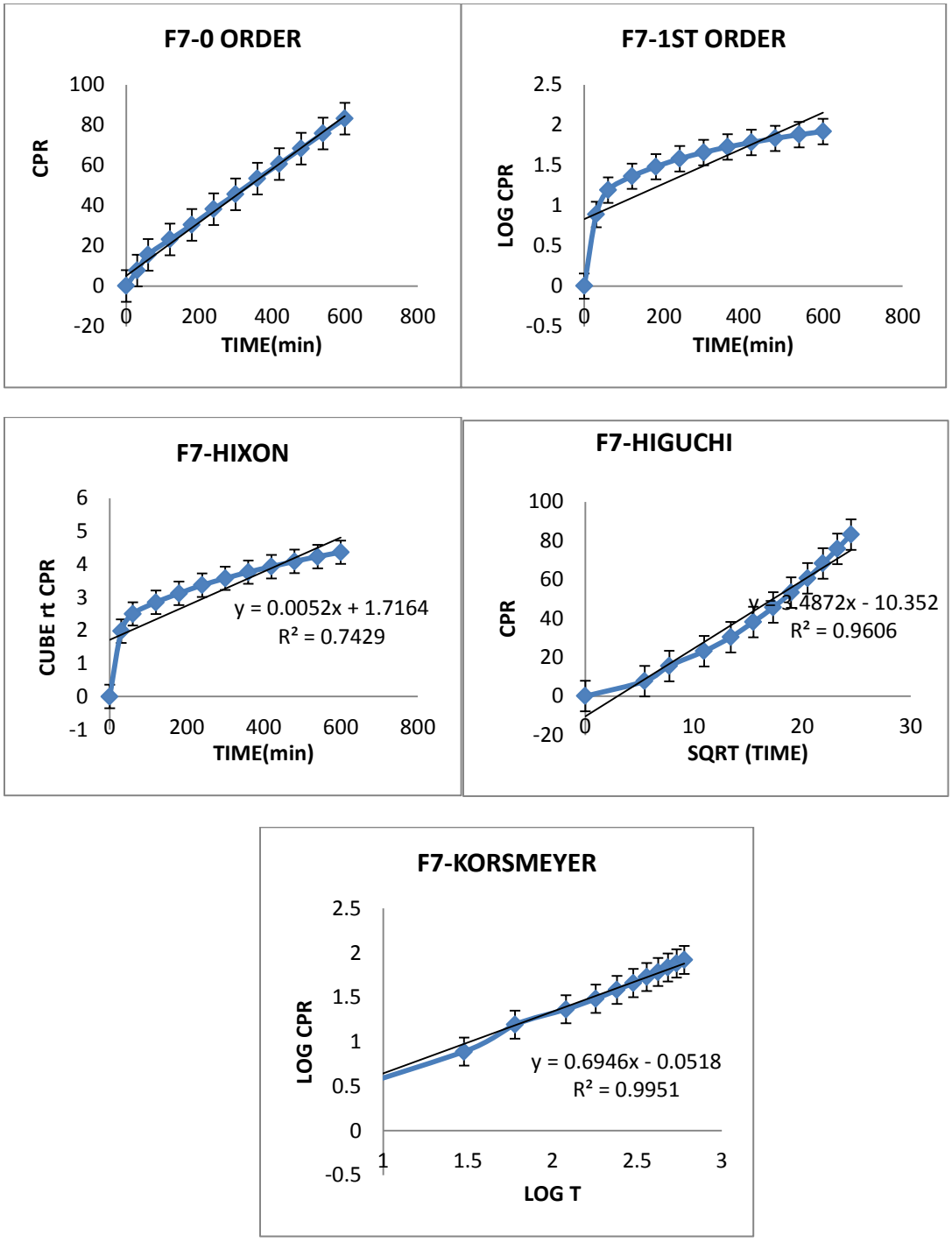


Fig 27(a-e): Different release Pharmacokinetics of Prazosin hydrochloride tablets [Formulation F-7]

3.10.8 Release Pharmacokinetic Study for Formulation F-8

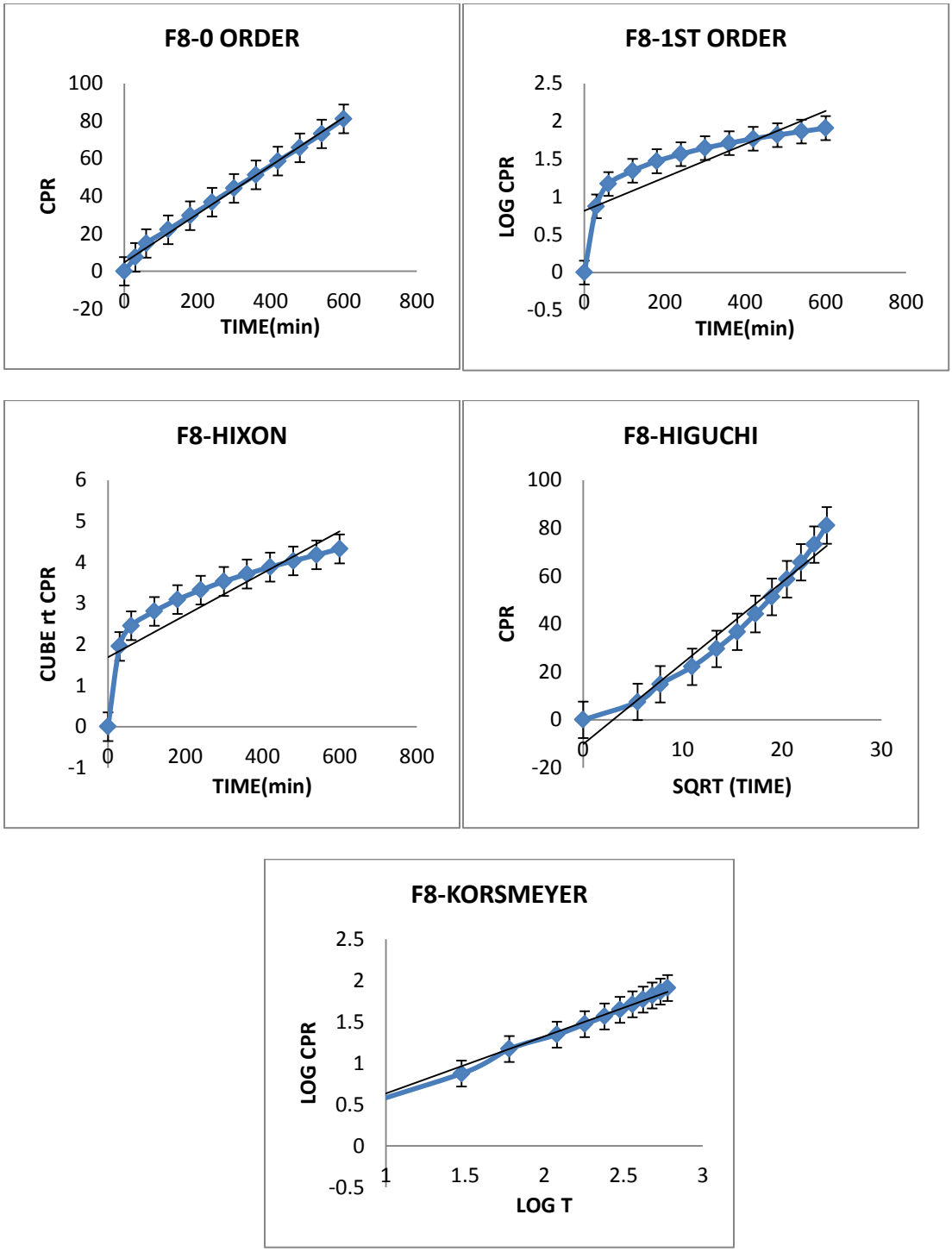
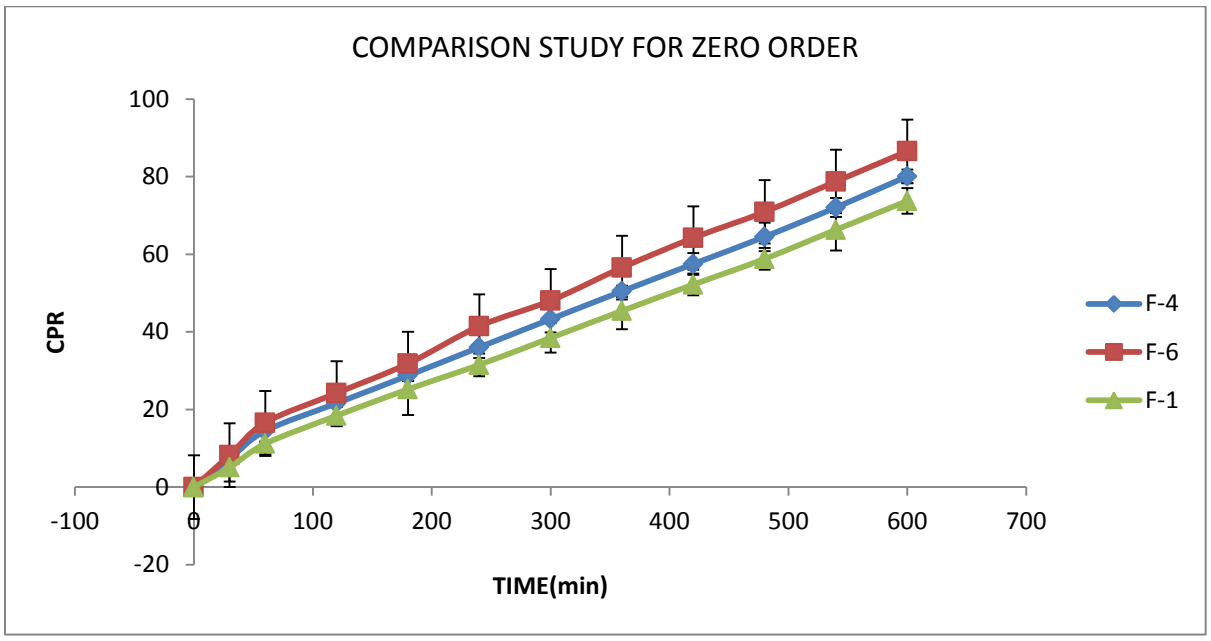
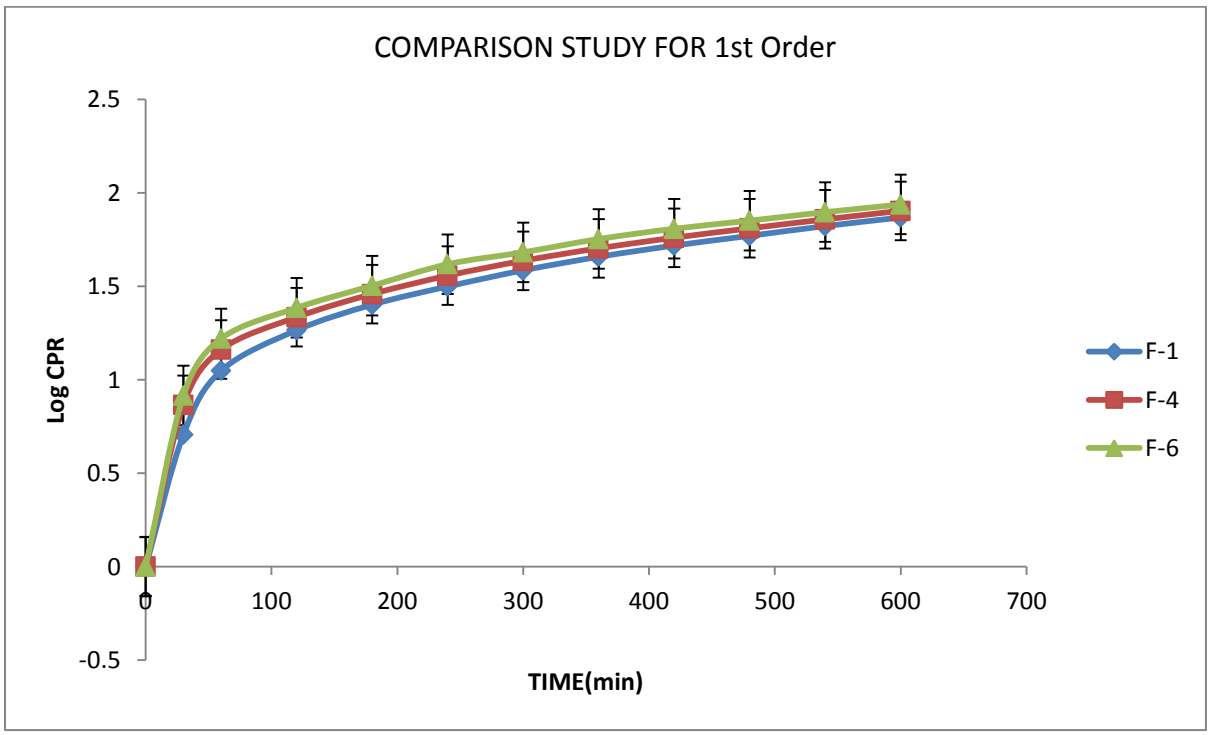
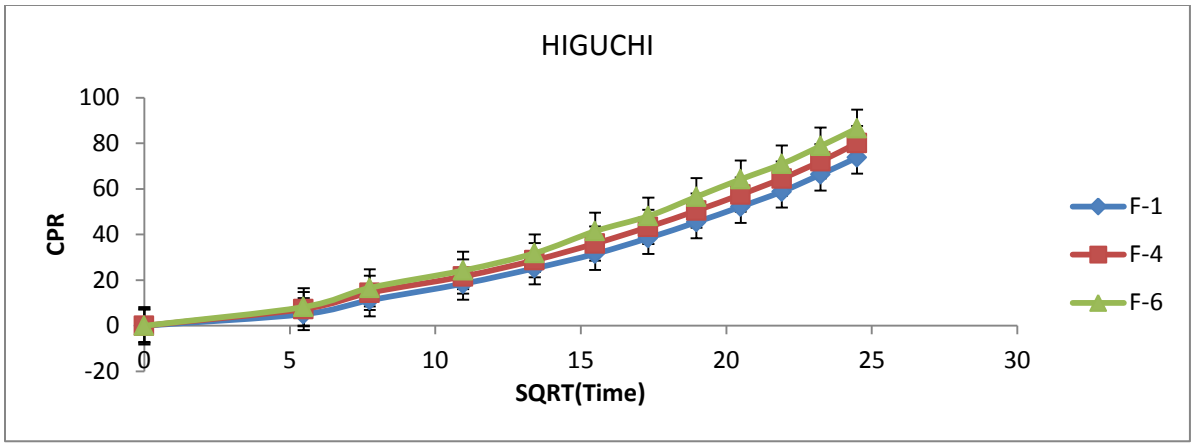


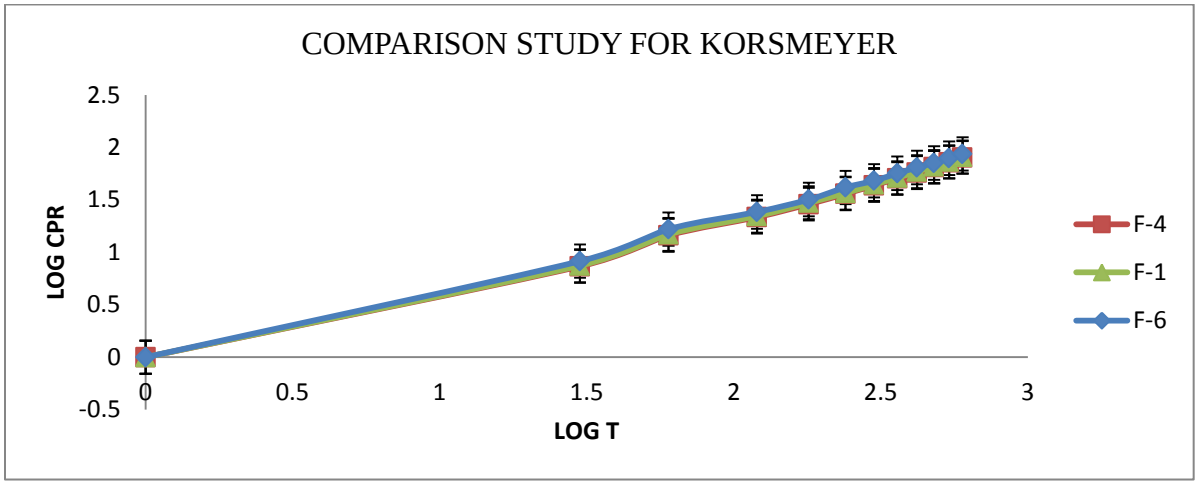
Fig 28(a-e): Different release Pharmacokinetics of Prazosin hydrochloride tablets [Formulation F-8]

3.11 29(a-e) Comparison Release Study of Donut shaped Prazosin hydrochloride Floating tablets:






HIGUCHI
CPR
100
80
60
40
20
0
-20
0
5
10
15
20
25
30
SQRT(Time)
F-1
F-4
F-6


COMPARISON STUDY FOR KORSMEYER
LOG CPR
2.5
2
1.5
1
0.5
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1
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LOG T
F-4
F-1
F-6

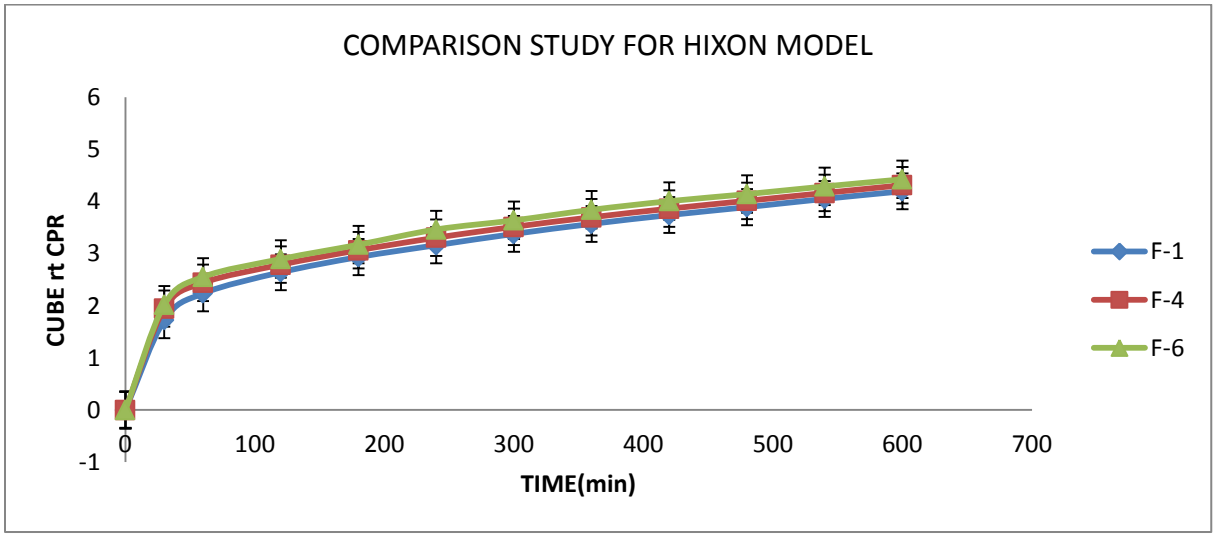

COMPARISON STUDY FOR HIXON MODEL
CUBE rt CPR
6
5
4
3
2
1
0
-1
0
100
200
300
400
500
600
700
TIME(min)
F-1
F-4
F-6

Table 18: Cumulative percentage release (mean±SD) of prazosin hydrochloride tablets at pH 1.2 (n=3)[F-1 to F-4]:

TIME (mins)	F-1 (mean±SD)	F-2(mean±SD)	F-3(mean±SD)	F-4(mean±SD)
30	5.2588±0.48	5.93662±1.15	6.651408±2.67	7.989437±1.12
60	11.30634±0.67	12.47007±0.93	13.33099±0.78	14.084507±2.78
120	18.19366±1.12	19.03873±1.32	20.12148±1.56	21.461268±0.96
180	25.85915±0.69	26.21303±0.67	27.52641±3.76	28.83275±1.39
240	31.60211±1.61	33.27465±2.34	34.83627±0.93	36.7993±0.68
300	38.88028±2.92	40.03345±0.71	42.27641±1.27	43.40669±0.82
360	45.0088±0.81	46.15317±2.03	49.2993±2.71	50.75176±1.45
420	52.31866±0.72	53.20775±0.32	56.18134±0.84	57.58275±2.78
480	58.88028±2.81	60.0581±1.41	63.31338±0.91	64.99472±3.67
540	66.80986±1.79	67.09683±3.01	70.72359±0.36	72.33803±2.46
600	**74.63732±2.36**	**75.73415±2.85**	**78.08275±2.82**	**80.46127±1.78**

Table 19: Cumulative percentage release (mean±SD) of prazosin hydrochloride tablets at pH 1.2 (n=3) [F-5 to F-8]:

TIME (mins)	F-5	F-6	F-7	F-8
30	8.401408±2.04	8.955986±4.45	7.128521±1.09	7.353873±1.74
60	15.096831±1.14	16.128521±1.42	15.5493±0.98	14.955986±1.12
120	23.74296±0.91	24.91549±1.23	23.14613±2.57	22.56338±0.08
180	30.61092±1.72	31.23944±3.73	30.73415±1.12	29.68662±2.32
240	38.76585±2.27	42.15669±2.44	38.22007±2.67	36.91901±0.98
300	46.88732±4.02	48.78873±1.08	45.64613±4.85	44.01056±0.56
360	53.68486±2.29	56.04577±0.56	53.08627±0.94	51.76761±1.34
420	61.67782±1.36	63.82042±0.64	60.46127±2.39	58.18486±3.67
480	68.46831±2.31	70.26761±2.96	68.72887±1.89	65.72887±2.21
540	76.54577±4.14	78.90669±3.17	75.67606±3.69	73.73239±1.89
600	**84.80634±2.38**	**86.10211±0.48**	**83.75±0.13**	**81.23415±3.03**

Table 20: Correlation coefficients (r^2) of the prepared Prazosin hydrochloride tablets of various formulations coded F1-F8

FORULATION CODE	ZERO ORDER	FIRST ORDER	HIGUCHI	KORSE MEYER	HIXON CROWELL
F-1	**0.9977**	0.7351	0.9483	0.9789	0.0.7761
F-2	0.9966	0.7196	0.9526	0.9844	0.7648
F-3	0.996	0.706	0.9552	0.9898	0.7569
F-4	0.9952	0.6923	0.9576	0.9939	0.7474
F-5	0.9948	0.6822	0.9592	0.9956	0.7437
F-6	0.9921	0.6713	0.9655	0.9963	0.736
F-7	0.9943	0.6825	0.9606	0.9951	0.7429
F-8	0.9947	0.6881	0.9593	0.9944	0.745

3.12 DSC ANALYSIS:

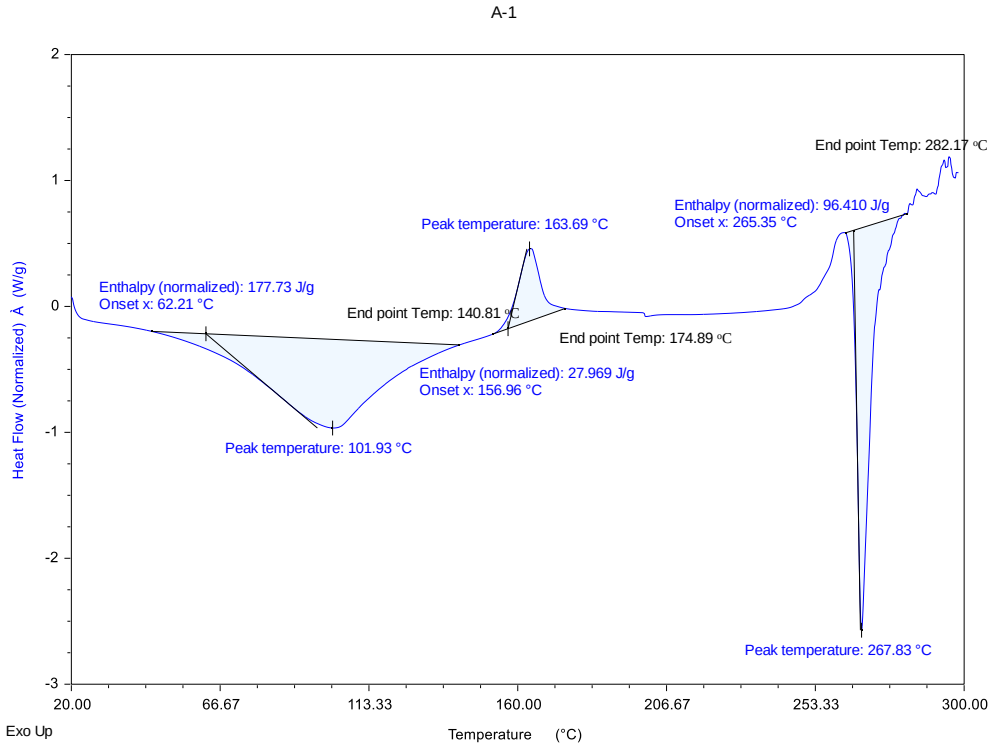


Fig 30: Differential Scanning Colorimetry (DSC) result of Prazosin hydrochloride

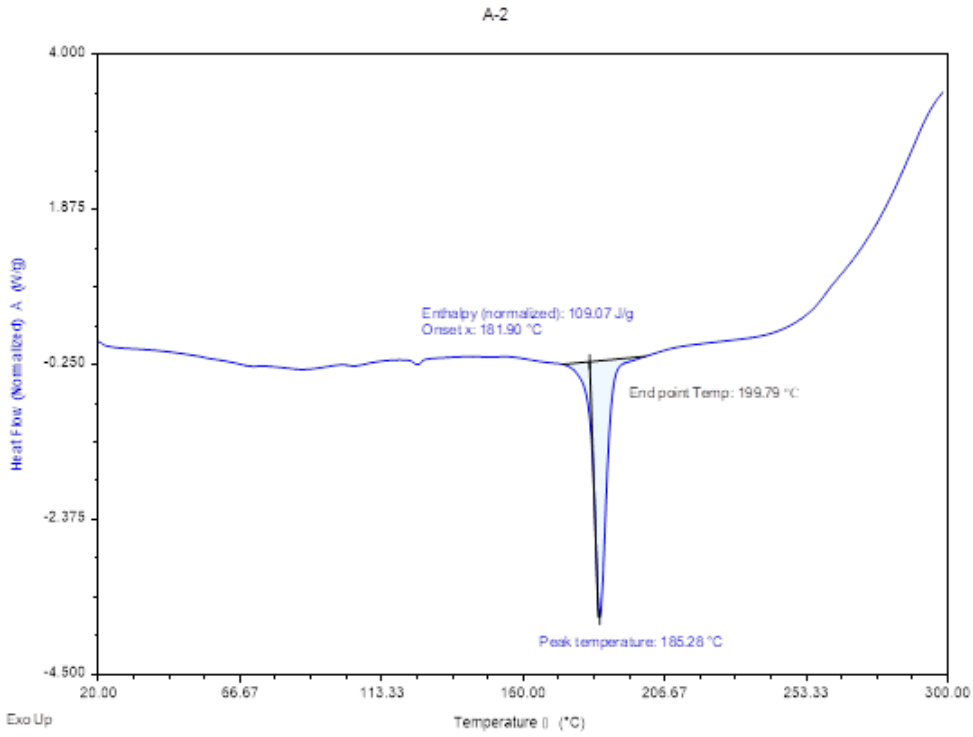


Fig 31: Differential Scanning Colorimetry (DSC) result of optimized formulation

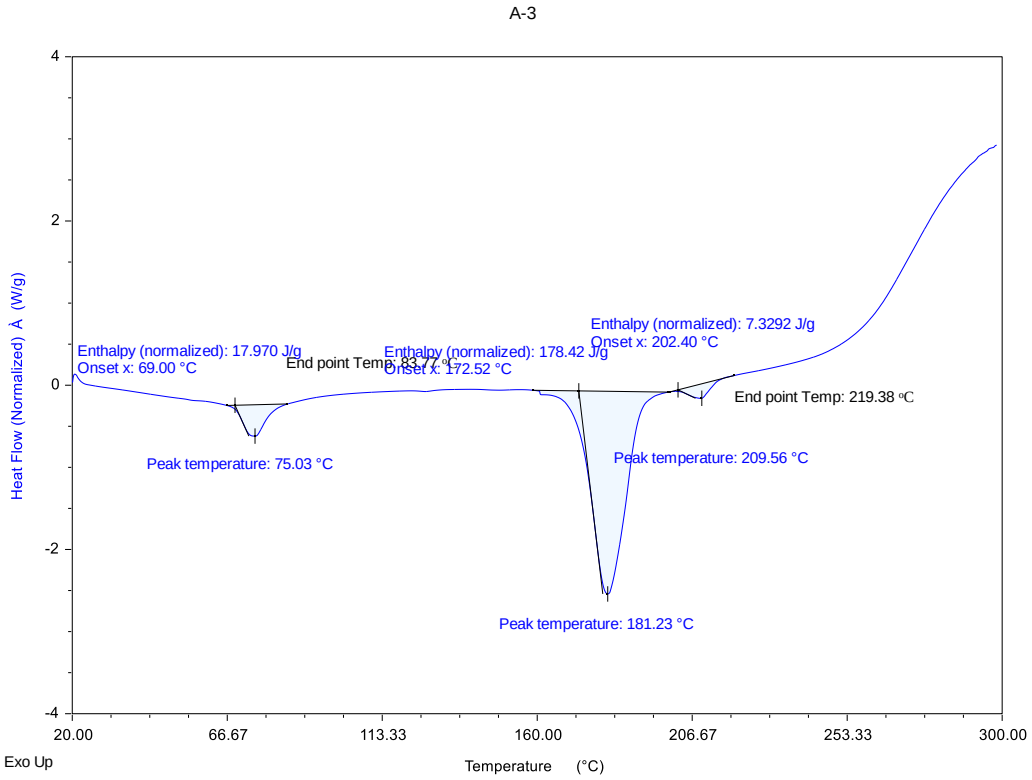


Fig 32: Differential Scanning Colorimetry (DSC) result of formulation without drug

3.13 ATR-FTIR SPECTRUM:

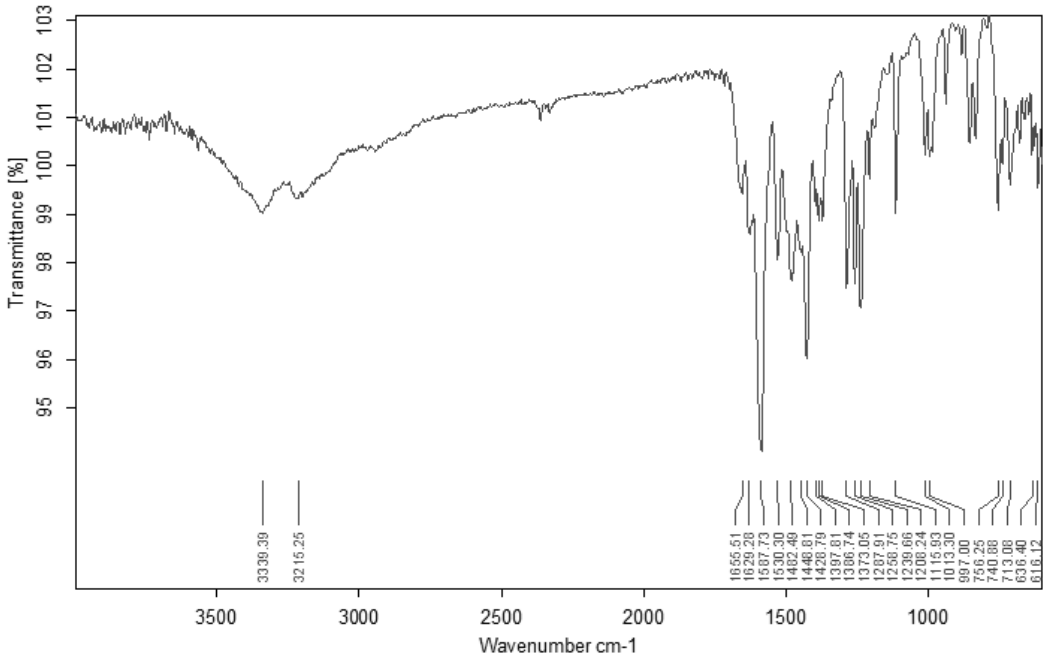


Fig 33: ATR-FTIR result of Prazosin hydrochloride

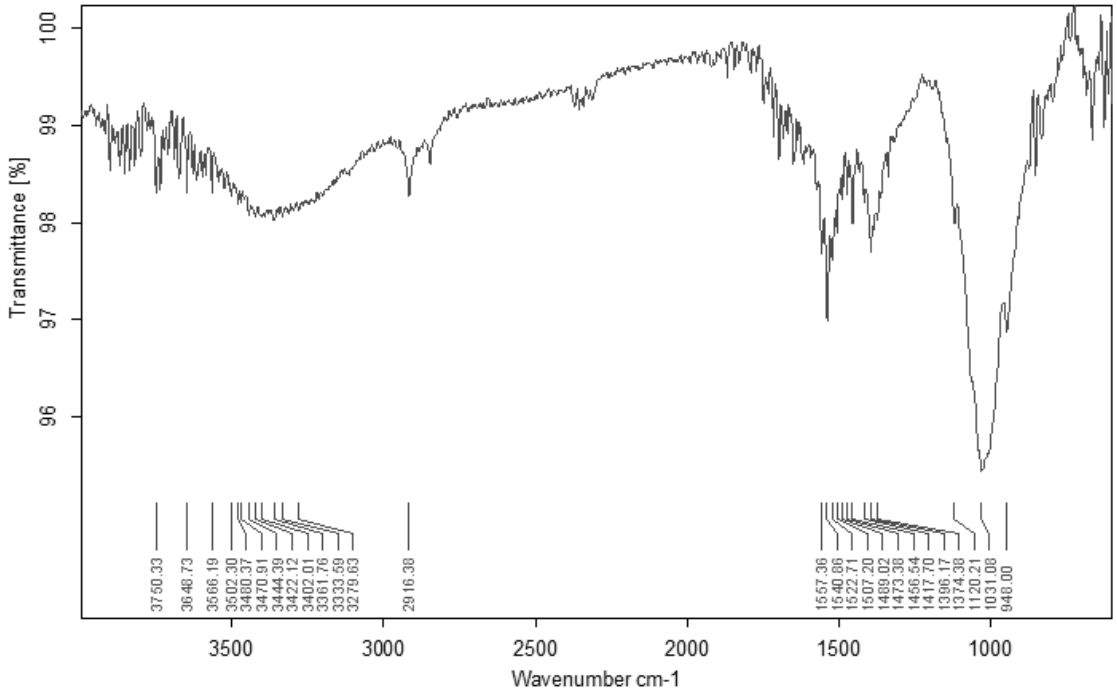


Fig 34:ATR-FTIR result of formulation (all excipients) without drug

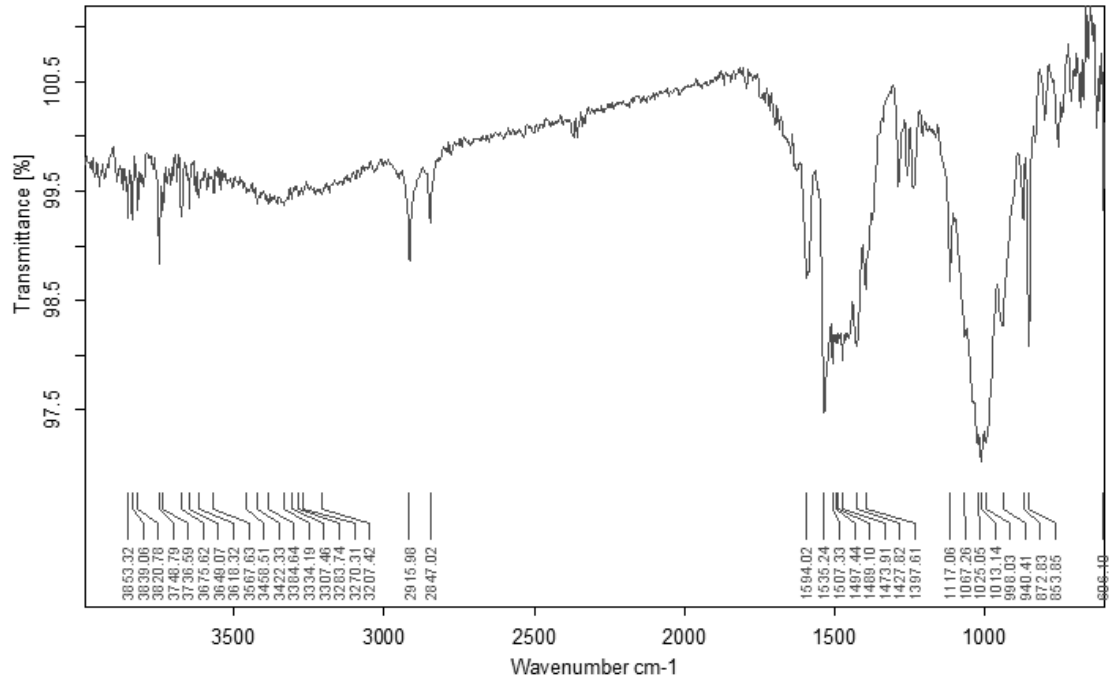


Fig 35: ATR-FTIR result of optimized formulation

3.14 X-RD ANALYSIS:

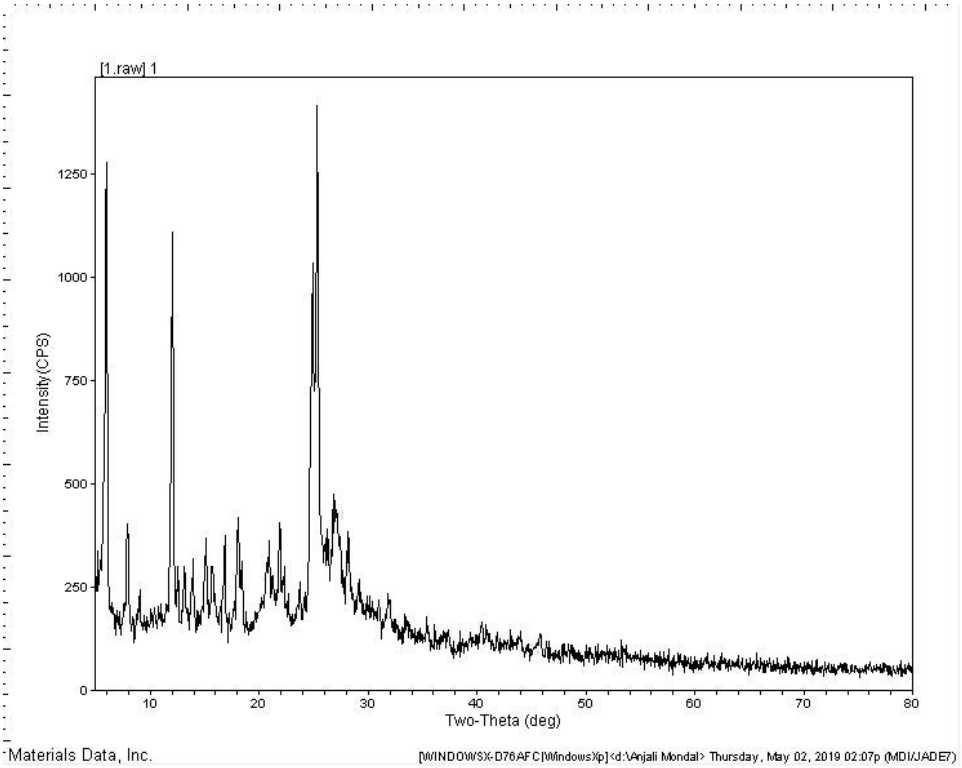


Fig 36: X- RD result of Prazosin hydrochloride

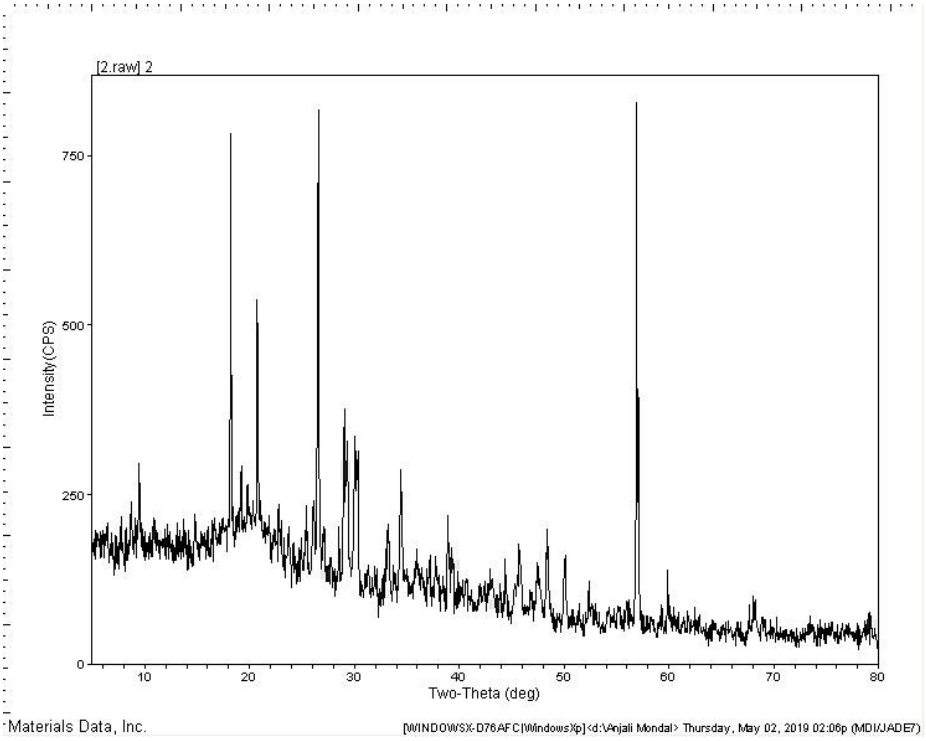


Fig 37: X- RD result of optimized formulation

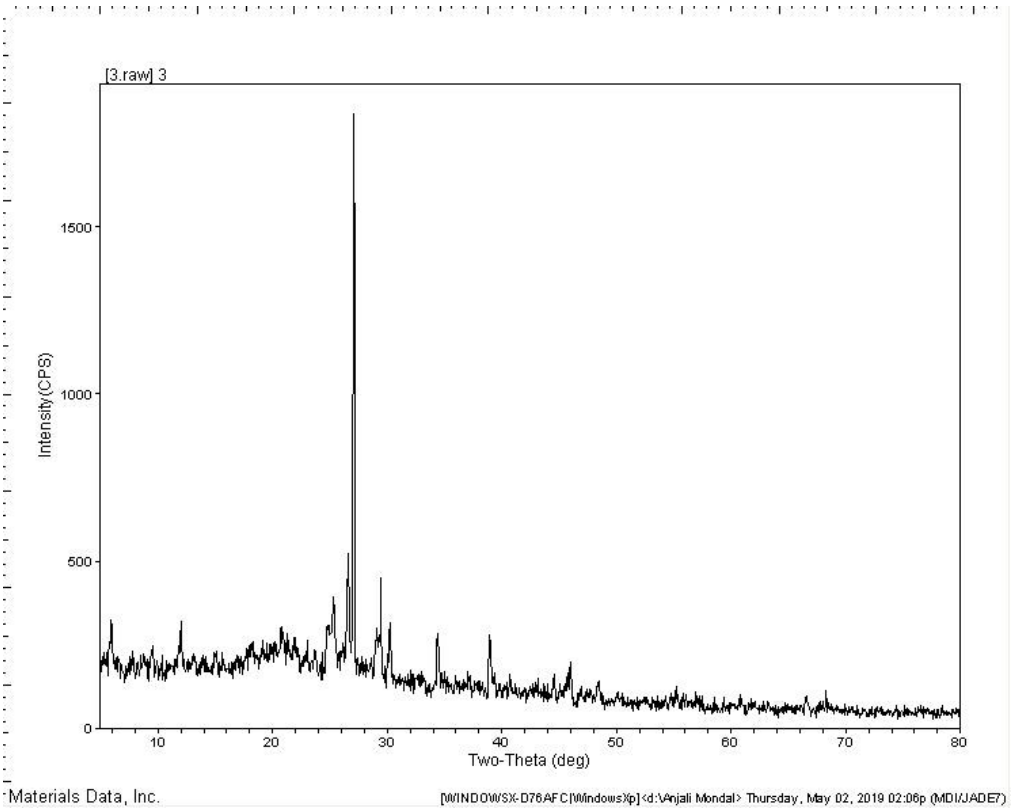


Fig 38: X- RD result of optimized formulation without drug

3.15 STATISTIC ANALYSIS:

1. CONSTANT HPMC VARYING CITRIC ACID and HAEDNESS:

Anova: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
VARYING CITRIC ACID	3	127.5	42.5	693.75
HARDNESS	3	15	5	1
CPR AT 10HOURS	3	253.875	84.625	2.332708

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	9520.906	2	4760.453	20.48732	0.002084	5.143253
Within Groups	1394.165	6	232.3609			
Total	10915.07	8				

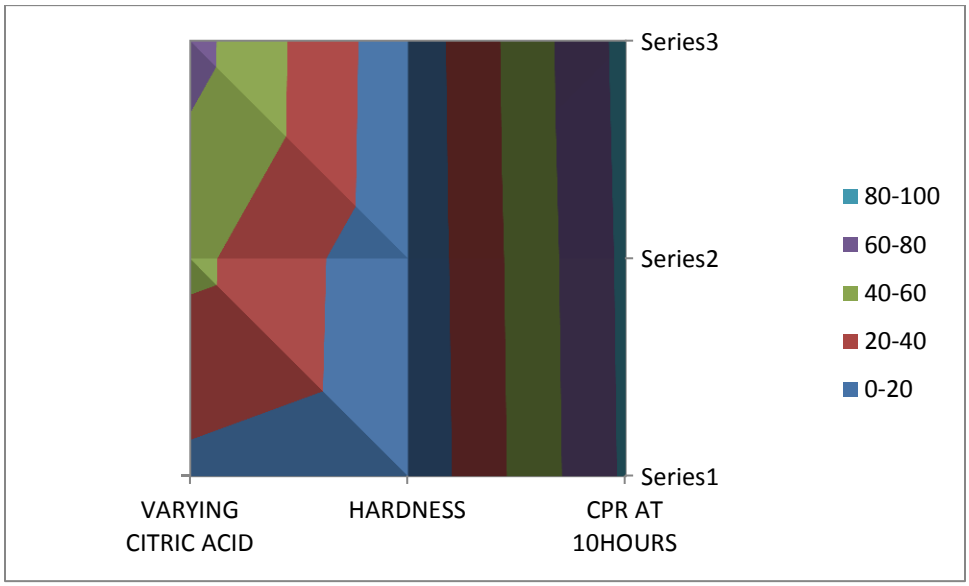


Fig: 39 Contour plot showing the effect of different levels of ingredient (Citric acid) and hardness on the cumulative percentage drug release.

2. CONSTANT CITRIC ACID VARYING HPMC and HARDNESS:

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
VARYING HPMC	3	399	133	693.75
HARDNESS	3	15	5	1
CPR AT 10HOURS	3	253.875	84.625	2.332708

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	25064.28	2	12532.14	53.93395	0.000146	5.143253
Within Groups	1394.165	6	232.3609			
Total	26458.45	8				

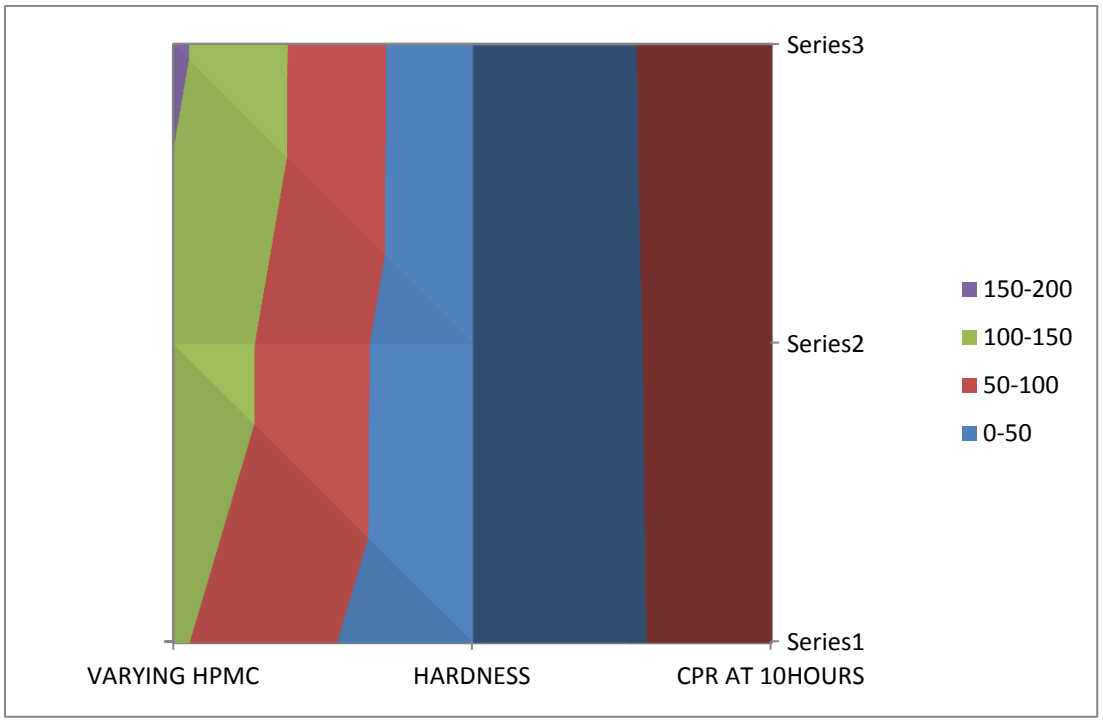


Fig: 40 Contour plot showing the effect of different levels of ingredient (HPMC) and hardness on the cumulative percentage drug release.

3. CONSTANT HARDNESS VARYING HPMC and CITRIC ACID:

Anova: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
VARYING HPMC	3	399	133	693.75
VARYING CITRIC ACID	3	127.5	42.5	693.75
CPR AT 10HOURS	3	253.875	84.625	2.332708

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	12304.90625	2	6152.453125	13.28027414	0.006257	5.143253
Within Groups	2779.665416	6	463.2775693			
Total	15084.57167	8				

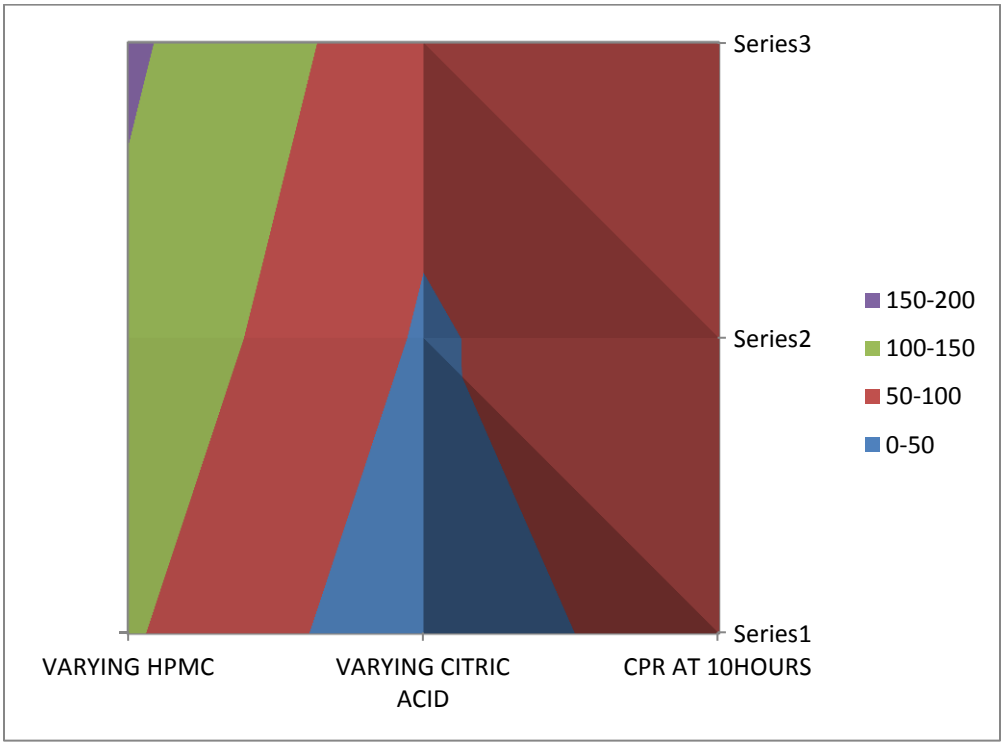
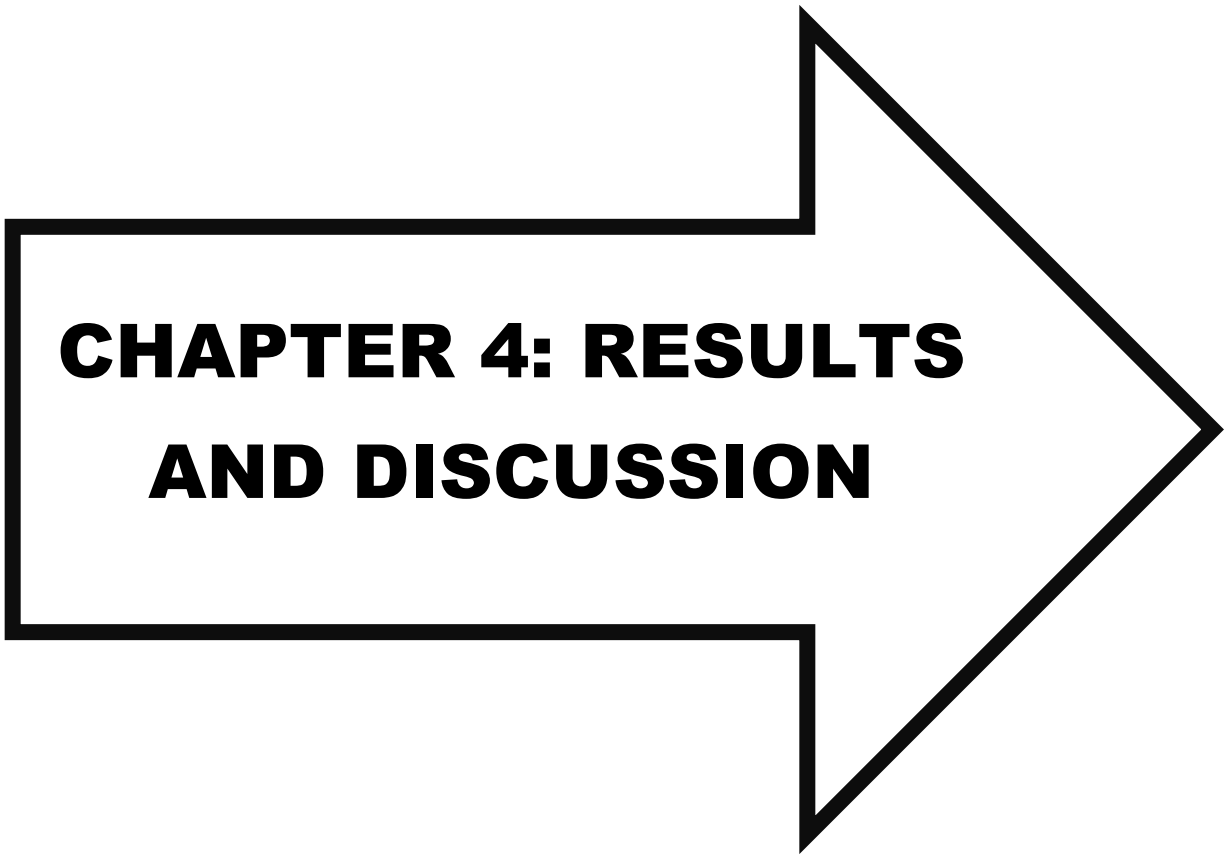


Fig: 41 Contour plot showing the effect of different levels of ingredient (HPMC, citric acid) on the cumulative percentage drug release.

CHAPTER IV



4.1 DETERMINATION OF λ_{MAX} OF PRAZOSIN HYDROCHLORIDE:

Maximum absorbance of Prazosin hydrochloride were measured at pH 1.2 (hydrochloric buffer), pH 6.8 (phosphate buffer) and Milipore water using JASCO V-550 double beam UV/Vis spectrophotometer. Figure 10, 11 and Figure 12 (chapter 3) exhibits the U.V. Spectrum of Prazosin hydrochloride scanning from 400nm to 200nm at a scan speed of 400nm/min as described in the chapter 2. The absorbance spectra are characterized by maxima at 246nm in both acidic and phosphate buffer (Milipore water, pH 1.2 and pH 6.8 medium), shows similar absorbance maxima as mentioned in Indian Pharmacopoeia. This confirms that prazosin hydrochloride under study was in pure form.

4.2 ESTIMATION OF CALIBRATION CURVE FOR PRAZOSIN HYDROCHLORIDE:

Fig 13, Fig 14 and Fig 15 shows the calibration curves of prazosin hydrochloride, which was obtained when concentration of Prazosin hydrochloride in mcg/ml was plotted against absorbance at 246nm using JASCO V-550 double beam UV/Vis spectrophotometer. It exhibited a linear path that passes through the origin in pH 1.2, Milipore water and pH 6.8 mediums. The correlation coefficient determined was found to be 0.9993(pH 1.2), 0.953(Millipore Water) and 0.9958(pH 6.8) respectively. Thus the UV spectral responses were found to be linear over an analytical range of 2-10 mcg/ml. pH 1.2 hydrochloric media was produced the maximum linearity which indicates that the drug was most stable in the acidic environment.

4.3 DETERMINATION OF MELTING POINT OF PRAZOSIN HYDROCHLORIDE USING DSC:

DSC thermogram of Prazosin hydrochloride was obtained according to the procedure give in the chapter 2. As per Indian Pharmacopoeia, the melting point of the prazosin hydrochloride is 279-280°C, which nearly fits in my case as the DSC thermogram (Fig 16) of untreated drug shows an endothermic peak at 274.5^0C, which is related to melting point of prazosin hydrochloride. This confirms that prazosin hydrochloride is in pure form.

4.4 IDENTIFICATION OF CHEMICAL MOIETIES:

ATR-FTIR Spectral analysis was done and the drug shows (Fig 17) similar data as mentioned in Indian Pharmacopoeia. By FTIR analysis of pure prazosin hydrochloride showed characteristic peaks at 33339.39 cm^{-1}, 1655.51 cm^{-1}, 1629.28 cm^{-1}, 1287.91 cm^{-1} (responsible for aromatic ring, C=O Stretching, N-H bending, C-O Stretching), these are almost same as reported in the monograph for Prazosin hydrochloride (Table 5). This confirms that the drug under study was in pure form.

4.5 DRUG- EXCIPIENT COMPATIBILITY STUDY:

a) Visual inspection of drug-excipient compatibility study:

Prazosin hydrochloride was mixed with different proportions of all excipients to be used in formulation in different ratios and kept at 40°C±5, 75% RH±2 for four weeks. The physical properties (colour change) were monitored at an interval of 7days, 14days, 21days, and 30days. The visual inspection of colour change of drug excipients mixture was shown in Table 6. Initially the mixtures of drug with different excipients (like HPMC, $NaHCO_3$, Citric acid, Magnesium stearate, Talc, Xanthan gum) shown white to off white in colour and placed in humidity chamber for 30days, there was no visual colour change was observed. That helps to determine no chemical interaction drug with excipients by visual inspection.

b) Drug-excipients compatibility observed in Molecular level:

ATR-FTIR Studies of drug excipients mixture were done separately to investigate the drug-excipients interactions. The spectrum of different mixtures is presented in Fig 18. By ATR-FTIR analysis of pure prazosin hydrochloride showed characteristic peaks at 33339.39 cm^{-1}, 1655.51 cm^{-1}, 1629.28 cm^{-1}, 1287.91 cm^{-1} (responsible for aromatic ring, C=O Stretching, N-H bending, C-O Stretching). The ATR-FTIR Spectra of drug and excipients revealed that, the major frequencies of functional groups of pure drug remain intact in the mixture containing different excipients. Hence there is no interaction between the drug and excipients used in the study.

4.6 PREPARATION OF FLOATING PRAZOSIN TABLETS:

4.6.1 OPTIMIZATION OF POLYMERS

In the design of floating tablet, Xanthan Gum (20 %) was used as polymer to control the release of Prazosin hydrochloride. It failed to provide total floating time for more than 6 hrs. It may be due to low polymer concentration as well as low viscosity which cannot sustain the drug release from the polymer-drug matrix. Further batches were prepared with HPMC K 4M (30-40%) which gave total floating time more than 12 hrs but having floating lag time more than 2 min. So combination of HPMC K 4M and Xanthan Gum were selected for optimize formulation. For optimization of polymer concentration eight batches (F-1 to F-8) were prepared with the combination of polymer shown in Table 7. The batches provided total floating time of almost 10 hrs having floating lag time less than 1 minute.

4.6.2 OPTIMIZATION OF EFFERVESCENT MIXTURE

Trial batches were evaluated for parameters such as buoyancy lag time, floating duration. Formulations containing 10 % of sodium bicarbonate alone did not show any significant floating whereas formulation containing 25 % sodium bicarbonate along with 25 % citric acid showed immediate floating but failed to give sustained release effect in spite of presence of HPMC K4M and Xanthan Gum at 8 h due to burst effect imparted by excess amount of citric acid and sodium bicarbonate. Also fail for matrix integrity after few hrs. So formulation containing 15 % sodium bicarbonate along with 5 %citric acid was selected which gave significant floating characteristic (floating lag time <1min and floating duration more than 8 h).

4.7 DETERMINATION OF FLOW PROPERTIES OF THE PREPARED POWDER BLENDS (MICROMERITIC PROPERTIES):

For direct compression of material, it is required to possess good flow and compacting properties. The preformulation studies of prepared powder blend were evaluated for various physical properties individually and the values are presented in the Table 9 and 10.

Bulk density and tapped density of the powder blend of the different batches [F1-F8] were determined as per the procedure described in Chapter II. It was found from the results (Table 10) that bulk densities of all batches examined varied in the range between 0.62 to 0.69 g/ml and the tapped densities values were between 0.70 to 0.80 g/ml.

The flow ability of the powder was also indicated by compressibility index and Hausner's Ratio. The value of Compressibility index below 15% usually gives rise to good flow characteristics, the reading above 25% indicate poor flow ability. The compressibility index of the different batches (F1-F8) was found the range in between 12-16% (Table 9) which is also within the acceptable limit.

Hauser Ratio which is obtained as a ratio between tapped density and bulk density was found to fall in the range 1.14-1.19 (Table 9), indicating that the powders have free flowing properties.

The value of angle of repose for formulations (F1-F5, F7) between 25 to 30 indicated good flow property and F6, F8 showed below 25 indicates very good flow. This may be attributed due to the reduction in the concentration of HPMC in F-6 and F-8.

4.8 THICKNESS AND DIAMETER:

Thickness and Diameter is necessary not only for consumer requirement but also for packaging. Usually ±5% variation is permissible. The thickness and diameter of the floating tablets were tested by the method described in Chapter II. It was observed that thickness of all tablets within range between 5.13 to 5.15 as shown in Table 12 and 13, as well diameter range 3.84 to 3.87 mm (inner) and 10.01-10.02mm (outer).

4.9 HARDNESS:

The hardness of all Prazosin hydrochloride tablet batches (n=3) was tested for all the prepared batches (F1-F8) by the method described in Chapter II. It was found that hardness of the prepared prazosin hydrochloride tablets varied between 4-6 kg/cm^2 for all the batches (Table 14) which is sufficient to produce a conventional tablet.

4.10 FRIABILITY TEST:

During the compression of the powder, sufficient force must be applied to get the final hardness of the tablet of around 4-6kg/cm^2 hardness. However the tablet hardness is not an absolute indicator of tablet strength. Friability test is done to ascertain whether the tablets are resistant to chipping during handling or subsequent processing. Weight loss should be less than 1% for good tablets. This test was performed on all the batches of tablets as per the procedure given in Chapter II. The loss % for all the batches was found to fall within the range of 0.42 to 0.82% (Table 12) which indicated that all the batches prepared was within the specified limits.

4.11 WEIGHT VARIATION TEST:

The maximum percentage weight variation that can be allowed for tablets according to Indian Pharmacopoeia as given in Table 4 was followed. Accordingly, if the tablet weight was 300mg, hence the maximum % deviation allowed is ±5 (Table 11) shows the weight variation of the different batches (F1-F8). The % weight variation ranged between 0.3 to 1.70 % and no tablets were found to be outside this range. So, the tablets were statistically significant with respect to weight.

4.12 CONTENT UNIFORMITY:

This is an important test to ascertain the uniformity of tablets with respect to drug content. The % variarion of drug content should be within ±15%. In all the prepared batches content uniformity tests were carried out, the % drug content of various batches [F-1to F-8] was found to be 96.06% - 98.62% (Table 15), F-6 show highest drug content (98.62%). so that all batches are within the compendia limits.

4.12 SWELLING STUDY:

Swelling is an inherent property of a polymer to prevent from getting submerged in water. Swelling profile of all the formulations of batches F1-F8 were shown in Table 16 and Fig 20. Formulation of batch F3 containing 47% HPMC K4M exhibited a much slower rate in swelling which extended up to 8hrs. Surface polymer of the matrix formed stronger gel immediately in contact with dissolution media which delayed further liquid

permeation to the inner cores and subsequently slowed down swelling process. It was observed that the concentration of HPMC played a major role in controlling swelling profile in the matrices F1, F2, F3. These matrices contained 5-10% citric acid and varying concentration of HPMC K4M ranging from 45-50%. Batches F-1, F-2 and F-3 showed increasing swelling with an increase in the concentration of HPMC in the matrices; however it did not swell as the other batches. This may be attributed due to the reduction in Citric acid. On the other hand increasing the concentration of citric acid (15-20%) and reducing HPMC concentration (35%) as shown in Fig 20 exhibited a much faster rate in swelling. The fast water uptake and high swelling ability of citric acid is attributed due to ability to quickly hydrate and produce gels upon water uptake.

4.13 *IN VITRO* BUOYANCY STUDY AND TABLET DENSITY

To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric fluid contents (1.004 g/cm^3). All the batches showed density below than that of gastric fluid (1.004). When tablet contacts the test medium, it expanded (because of swellable polymers) and there was liberation of CO_2 gas(effervescent agents, sodium bicarbonate and citric acid). Here, citric acid acts a dual action of effervescent agent as well as it maintains the pH of the environment. It was observed that the gas generated is trapped and protected with in the gel formed by hydration of polymer (HPMC K4M and Xanthan Gum), thus decreasing the density of the tablet below 1 and tablet becomes buoyant (Table 17) up to 8hrs.

4.14 DIFFERENTIAL SCANNING CALORIMETRY (DSC) OF THE OPTIMIZED TABLETS:

Differential Scanning Colorimetric (DSC) measurements provide qualitative and quantitative information about physical and chemical changes of a compound that involve endothermic and exothermic processes, or changes in heat capacity. The thermal

behaviours of the pure drug prazosin, excipient mixture, optimized formulation were shown in Fig30-32. The DSC curve showed that a sharp endothermic peak appearred at about 274.54°C for prazosin, corresponding to its melting point and indicating its crystalline nature. Absence of peak in the analyzed excipient mixture was the indication of its amorphorus nature. Furthermore a sharp endothermic peak corresponding to the drug at about 267.83°C which indicated crystalline nature of the drug in optimized formulations. DSC thermogram showed that there was no any major difference in onset temperature and peak temperature, when compared with pure drug thermogram. Hence, it was confirmed that there was no incompatibility between drug and the excipients under study.

4.15 ATR-FTIR STUDY:

ATR-FTIR Spectral analysis of the pure prazosin, physical mixture of prazosin-excipients, all excipient was done and the drug shows (Fig 33) similar data as mentioned in Indian Pharmacopoeia. By FTIR analysis of pure prazosin hydrochloride showed characteristic peaks at 3339.39 cm^{-1}, 1655.51 cm^{-1}, 1629.28 cm^{-1}, 1287.91 cm^{-1} (responsible for aromatic ring, C=O Stretching, N-H bending, C-O Stretching), these are almost same as reported in the monograph for Prazosin hydrochloride (Table 8). These bands are of indicative value to elucidate drug polymer interaction. The principle peaks of prazosin appeared unchanged in the physical mixture, formulation. Drug-excipient interaction study by ATR-FTIR for pure drug, excipients showed that there were no significant change in the position of the characteristic peaks of drug when mixed with excipients (Fig 33, Fig 34 and Fig 35 represent pure prazosin hydrochloride, optimized batch without drug, and optimized formulation) which indicated the absence of chemical interaction between prazosin and other formulation excipients.

4.16 XRD ANALYSIS:

The powder X-ray diffractometry patterns of pure durg, excipients and optimized tablets were carried out to determine whether the drug has changed any form. The XRD diffraction pattern of Prazosin Hydrochloride showed intrinsic peaks at the diffraction angles, showing a sharp peak indicating that the drug is crystalline nature (Fig 36), while physical mixtures of all excipients showed blunts peaks indicating its amorphous nature (Fig 37,Fig 38). In optimized formulation showed characteristic crystalline peaks for prazosin with reduced intensities. Thus, the results of PXRD analysis supported DSC study and confirmed that prazosin hydrochloride was present in an unchanged crystalline state in the formulation.

4.17 ANALYSIS OF *IN VITRO* DRUG RELEASE STUDIES USING VARIOUS PHARMACOKINETIC MODELS:

In vitro drug release studies of floating matrix tablets of Prazosin hydrochloride was carried out in 0.1N HCl pH 1.2 to mimic the condition of the physiological stomach gastric fluid system. Cumulative drug release of Prazosin hydrochloride was calculated on the basis of drug content of Prazosin hydrochloride present. The results obtained inthe *In vitro* drug release for the formulations F1 to F8 is shown in Table 18, 19 and percentage of their corresponding drug release versus time (t) was plotted as depicted as shown in Figure 21-28.

In formulation F-1, produced a maximum drug release of 74.63 % in 10 hours. This may be attributed to the lower concentration of citric acid in the formulation. Similarly F-2, F-3, F-4, F-5, F-7 and F-8 showed a released characteristic with a maximum drug profile of 75.73, 78.08, 80.46, 84.80, 83.75 and 81.23respectively. it was also observed that with increase in citric acid the release of the drug was higher. This may be due to the inherent character of the citric acid which is freely soluble in water thereby producing a higher amount of CO_2 release when it interacts with $NaHCO_3$. The maximum release of the drug was found to be F-6 with 86.20% at 10hrs. From the above data it was confirmed that increase in citric acid concentration lead to the increase

in the total drug release however it reaches a saturation point after which the effect of citric acid did not give any exponential release of the drug.

Various Pharmacokinetic models were fitted to identify the nature of drug release from the HPMC K 4M and Xanthan gum blended floating tablets using dissolution data derived from the USP–II Apparatus at pH 1.2 dissolution media. Model fitting was performed using the excel software program and most suitable model was chosen on the basis of correlation coefficient (r^2) values which were nearest to 1 (Table20) and mechanism of drug release is non fickian diffusion. Hixon crowell model failed to satisfy the drug release Pharmacokinetics of all the formulations. Here formulation code F-1 to F-8 followed zero order release (which does not depend on the concentration) Pharmacokinetic as these plots showed the highest linearity.

4.18 STATISTICAL ANALYSIS (ANOVA):

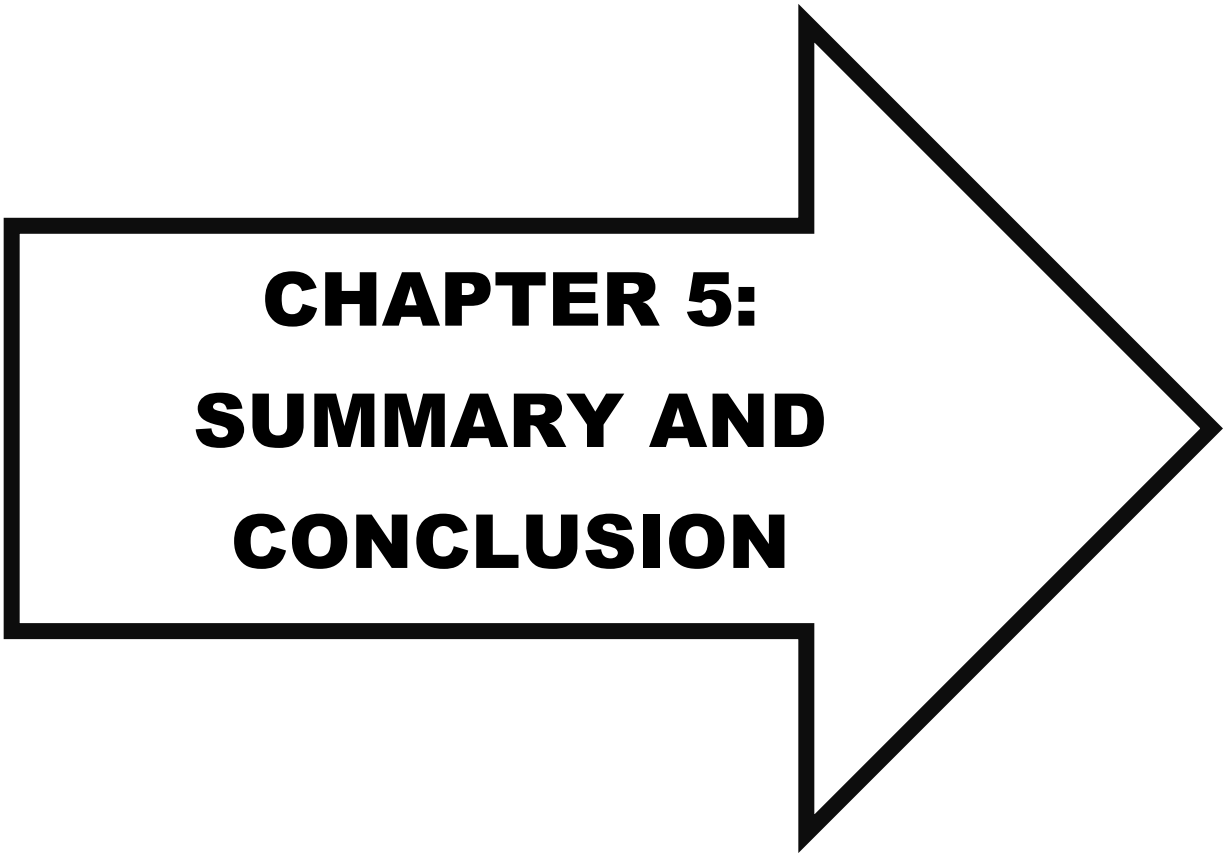
Statistical Analysis perform include ANOVA study to determine P and F-value from study Cumulative Percent Release (CPR) using Microsoft excel 2010 version 1. In the formulation variable factor HPMC and Citric acid with hardness is performed, variables factors are significant or not on CPR checked by ANOVA one way study.

If HPMC constant, citric acid and hardness of tablets are variable factors: ANOVA is an one way test of the release data obtained with using different level of citric acid and Hardness, obtained P= 0.002 which is effectively lesser than 0.05 ($P<0.05$) hence provided data is significant.

If CITRIC ACID constant, HPMC and hardness of tablets are variable factors: ANOVA is an one way test of the release data obtained with using different level of hardness and HPMC, obtained P= 0.00014 which is effectively lesser than 0.05 ($P<0.05$) hence provided data is significant.

If HARDNESS constant, HPMC and CITRIC ACID of tablets are variable factors: ANOVA is an one way test of the release data obtained with using different level of citric acid and HPMC, obtained P= 0.0062 which is effectively lesser than 0.05 ($P<0.05$) hence provided data is significant.

CHAPTER V



5. SUMMARY AND CONCLUSION

The main purpose of this project was to design and develop floating donut shaped tablet using Prazosin hydrochloride, an alpha-adrenergic Blocker as a drug for the treatment of acute disorder in hypertension.

From the above research, it can be concluded that floating tablet of an anti-hypertensive drug prazosin hydrochloride can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability. Among the polymers used to improve the gastric residence time, combination of cellulose polymers (HPMC K4M) and Xanthan gum showed most favourable drug release pattern for an extended period of time.

Formulated tablets gave satisfactory result for various physicochemical evaluations for tablets like hardness, weight variation, and content uniformity total floating time, floating lag time, swelling index and *in-vitro* drug release.

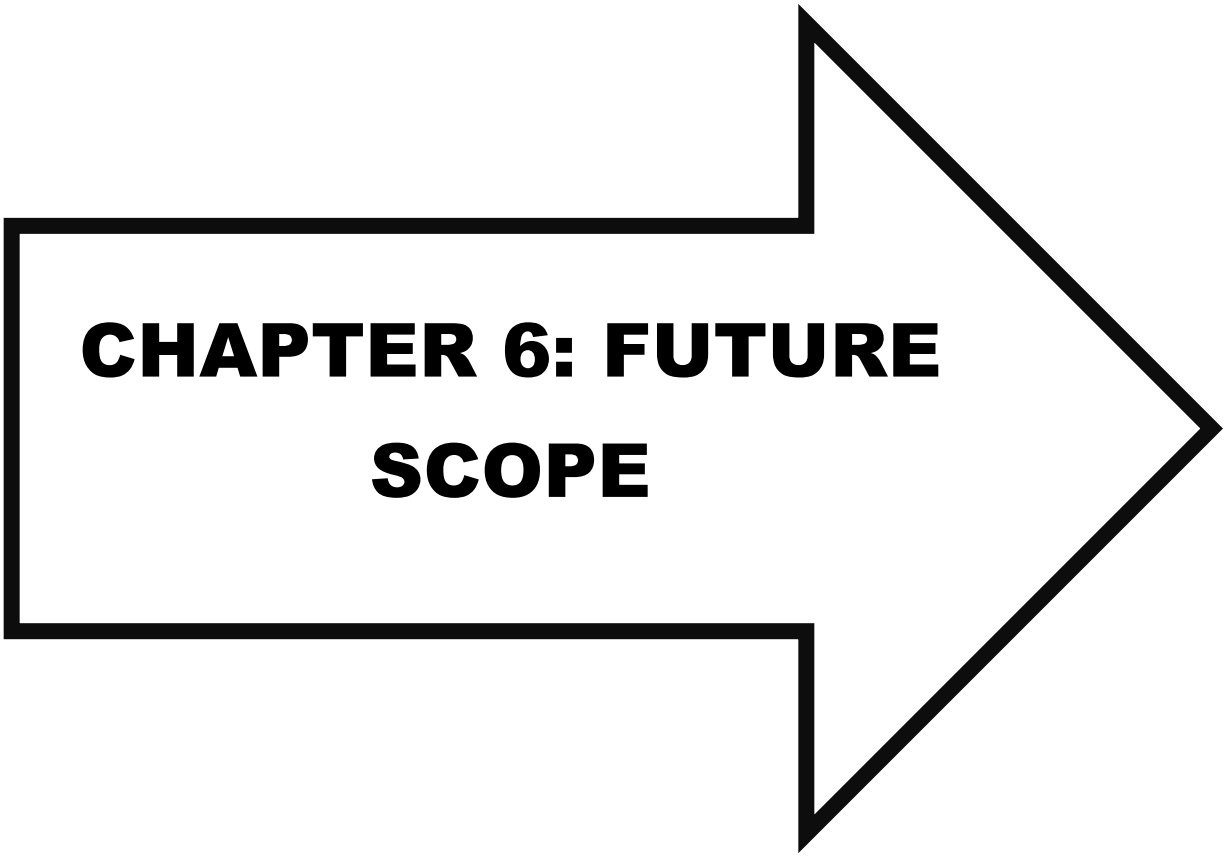
The addition of gel forming polymer HPMC K4M and CO_2 generating agent sodium bi carbonate were essential to achieve *in vitro* buoyancy. Addition of citric acid, to achieve buoyancy under elevated pH in the stomach. A number of combination concentrations of HPMC K4M and Xanthan gum were used in formulation, which sustained the release of prazosin hydrochloride for 10hrs. The reason behind choosing these polymers was because of its low density hydrocolloid system which facilitates floating time

Tablets prepared with HPMC K4M and Xanthan Gum mixture became buoyant within 1minute with appropriate resistance to breakage or disintegration.

Of the eight formulations prepared (F1-F8), F-6 gave best controlled drug release in comparison to other prepared formulation. From the *in vitro* release studies at pH 1.2 the release formulation of prazosin hydrochloride specifically followed the design criteria of more than 80% w/v release within 10hr (zero-order release).

Zero-order release was made possible due to modifying shape of the floating tablets which thus provides constant release and desirable release profile.

CHAPTER VI



6. FUTURE SCOPE

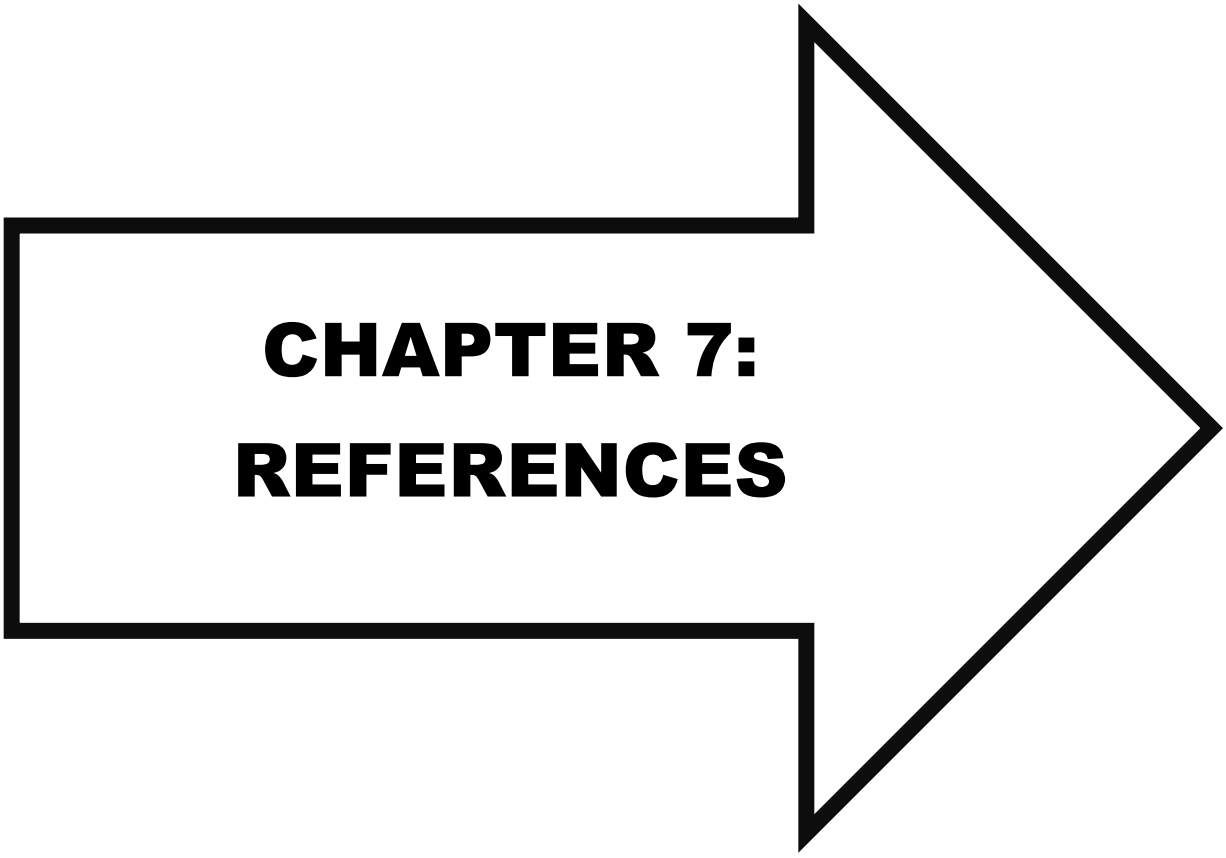
Pharmaceutical industry always keeps on searching and invests on newer drug delivery system. Despite having numerous routes oral route is still the most convenient way of administration. Of the different types of dosage from available, tablets have gained maximum attention because of its effectiveness and patient compliance. It also provides lower manufacturing cost in compared to other delivery systems - liposomes, nanoparticles and microspheres etc. Tablets can have efficiency towards packing and transferring from one place to another. This dosage form claimed to have best stability when compared to other dosage forms.

Conventional tablets often suffer with fall in concentration and irrational release profile until the tablet dissolves .Extended release delivery system omits the challenges of conventional tablets by maintaining concentration over minimum effective concentration for an extended period time. Some of these systems are devoid of zero ordrer Pharmacokinetics and sometimes create problem during large scale manufacture in industry

Donut shaped tablets have been successfully developed in controlled release formulation along with the modification such as floating it extends the release for appreciable amount of time. In last decade interest in developing with donut shaped tablet whereby if facilitates a zero order Pharmacokinetics pattern of release. When it is combined with floating the bioavailability of the increases and gives good therapeutic effect with minimum dose.

There are no hindrances for large scale production of donut shaped tablet from industrial stand point. Beside this, preparation is cost effective as compared to other controlled release drug delivery system. Hence, this tablet will definitely throw a new limelight for researchers who are interested to deign modified sustained release dosage in cost effective manner.

CHAPTER VII



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