A STRATEGIC FRAMEWORK OF NATURAL GUM BLEND MATRIX TABLETS IN ORAL SUSTAINED DELIVERY OF METOPROLOL SUCCINATE – AN EFFORT TO CONSTRUCT A MORE PATIENT-CENTRIC SAFE MEDICATION: DESIGN, DEVELOPMENT AND *in-vitro* COMPARATIVE EVALUATION

THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

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BY

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2023

To my Parents

For their endless love and constant support

CERTIFICATE

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This is to certify that the thesis entitled **"A STRATEGIC FRAMEWORK OF NATURAL GUM BLEND MATRIX TABLETS IN ORAL SUSTAINED DELIVERY OF METOPROLOL SUCCINATE – AN EFFORT TO CONSTRUCT A MORE PATIENT-CENTRIC SAFE MEDICATION: DESIGN, DEVELOPMENT AND *in-vitro* COMPARATIVE EVALUATION"** submitted to the Department of Pharmaceutical Technology, Jadavpur University in partial fulfilment of the requirements for completion of the degree of Master of Pharmacy is a record of original research work carried out by **Ms. Naureen Afrose** under my guidance and supervision in Department of Pharmaceutical Technology.

I further certify that neither this thesis nor any part of it has been submitted to any other University or Institute for award of any degree or diploma. I am pleased to forward to forward this thesis for evaluation.

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DECLARATION OF ORIGINALITY AND COMPLIANCE OF ACADEMIC ETHICS

I hereby declare that the thesis entitled **"A STRATEGIC FRAMEWORK OF NATURAL GUM BLEND MATRIX TABLETS IN ORAL SUSTAINED DELIVERY OF METOPROLOL SUCCINATE – AN EFFORT TO CONSTRUCT A MORE PATIENT-CENTRIC SAFE MEDICATION: DESIGN, DEVELOPMENT AND *in-vitro* COMPARATIVE EVALUATION"** is a bonafide and genuine research work carried out by me under the supervision of **Dr. Ketousetuo Kuotsu**, Associate Professor, Department of Pharmaceutical Technology, Jadavpur University. All information in this document have been obtained and presented in accordance with the 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

This thesis is presented in the partial fulfillment of the degree of Master of Pharmacy. The current research work, titled ***"Design, preparation, and in vitro evaluation of natural gum blend matrix tablets for oral sustained delivery of metoprolol succinate,"*** has focused on using natural gum as release rate-retardants to develop sustained release matrix tablets to deliver once-daily dose in hypertensive patients and prevent nocturnal attacks by bypassing the side-effects of the synthetic polymers being used in existing marketed formulations.

Hypertensionis a cause of morbidity and mortality.Metoprolol succinate,a cardio-selective β-adrenoceptor antagonist being used as a relevant anti-hypertensive agent has a stronger affinity for β1 receptors than for the β2 receptor subtype.It works in a competitive manner to inhibit the effects of both endogenous and exogenous β-adrenoceptor agonists.It is widely used to treat hypertension and prevents nocturnal attacks.It is a classic example of Biopharmaceutical Classification System (BCS class 1 type) drug. It has a 50% bioavailability after oral administration and a 3–7 hour half-life. Since the drug's half-life is shorter, frequent dosing is necessary, which interferes with patient compliance and increases the need for a sustained-release formulation. The highest level of patient compliance is enhanced by sustained-release tablets helping with once-daily administration.

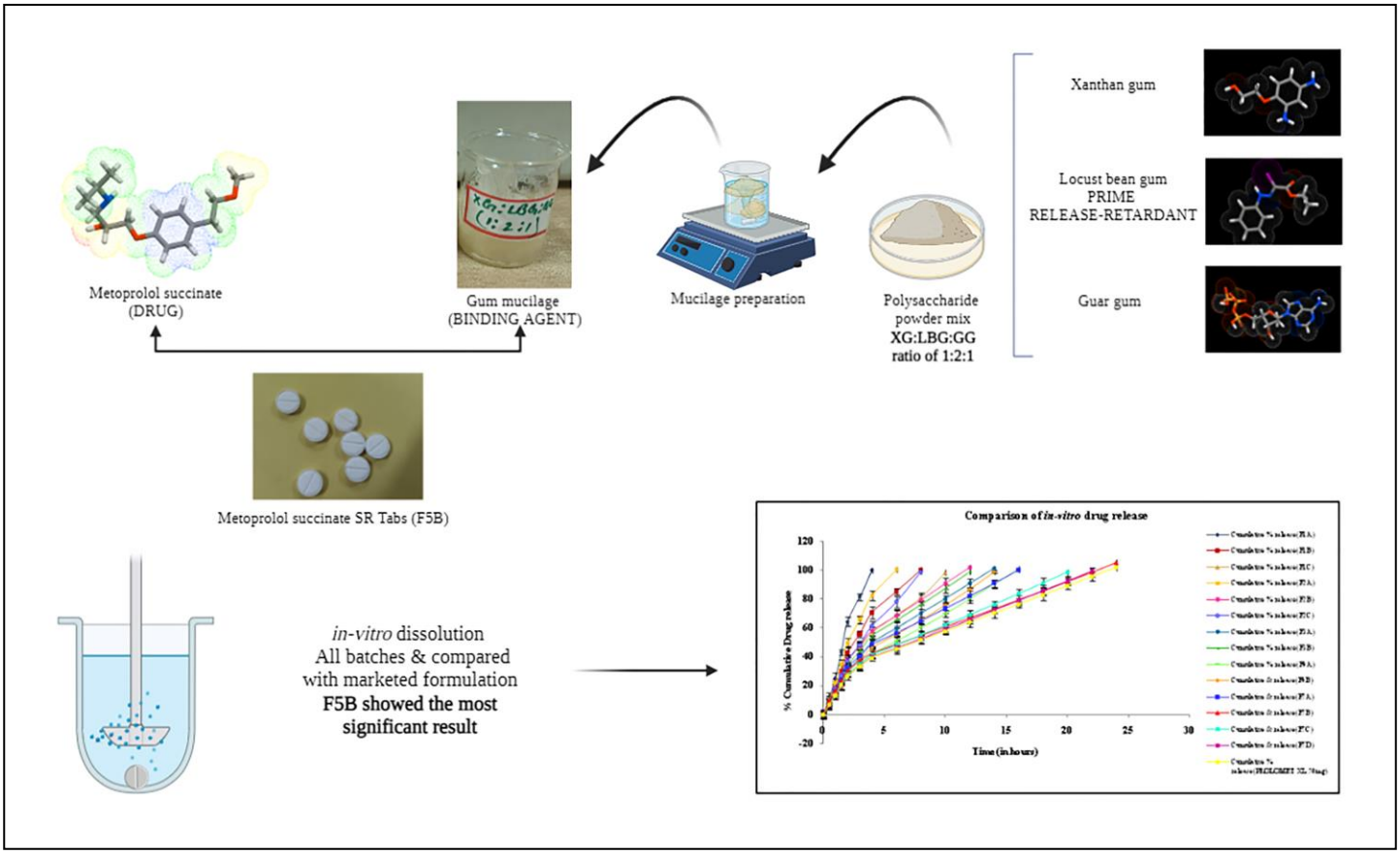
Metoprolol succinate sustained release tablets available in markets are prepared using various release-retarding polymers which are synthetic or semi-synthetic in nature. Patients intended to take such medications ingest a lot of synthetic materials daily. Such polymers have a harmful effect that much outweighs any therapeutic benefits. It would be noteworthy to replace it with natural polymers, which degrade quickly and have minimal adverse effects.Natural polymers were studied and the focus was to determine the level of release-retarding activity of these gums in order to calculate the ideal ratio for creating a natural polymer blend that would be used as a release-retardant for maintaining the release of metoprolol succinate over a 24-hour period.

This thesis is divided into eleven chapters describing the fundamentals, methodologies, results, discussions, conclusion and reference. Chapter 1 depicts the abstract. Chapter 2 is the introductory chapter that deals with the sustained release formulations for BCS class 1 type model drug metoprolol succinate using natural gums. Chapter 3 is about the literature review on various other works that have been done in this field. Chapter 4 discusses the aim, objective and the plan of work of this research project. Chapter 5 discusses study design and strategy. Chapter 6 contains the materials and methodologies used in this research work. It describes the drug, natural polymer and the excipients profile, the development and the evaluation methods of the formulation. Chapter 7 illustrates the tables and the graphs whereas, chapter 8 discusses the results obtained through various evaluations. Chapter 9 contains the conclusion section giving a brief outline of the entire work done and the results so obtained. Chapter 10 discusses the future scope in this field of work. Finally, chapter 11 enlists the references that have been used to successfully complete this thesis work.

CONTENTS

Chapter 1: ABSTRACT

The purpose of this study is to design and evaluate metoprolol succinate sustained release (SR) matrix tablets using a natural gum blend as the rate-retarder. The development of a tablet matrix utilizing the three natural gums locust bean gum (LBG), xanthan gum (XG), and guar gum (GG) was done to facilitate metoprolol succinate release over a 24-hour period and help in once-daily dose, minimizing nocturnal episodes in anti-hypertensive patients. Attempts were made to generate a synergistic effect by combining two regularly used natural gums, XG and GG, with LBG, which functioned as the principal release-retardant. Because metoprolol succinate is one of the most commonly used antihypertensive drugs, we focused on developing a formulation using natural polymers to save patients from ingesting significant amounts of synthetic polymers on a regular basis. Various polymer blend ratios were used to determine the best approach to formulate the tablet. The same polymer mix was utilized as the binding agent in the wet granulation process for developing tablets. The formulations were characterized using weight, thickness, hardness, content homogeneity, in-vitro drug release, erosion, and water uptake. Stability tests and further drug-excipient compatibility testing were carried out. An XG:LBG:GG ratio of 1:2:1 was discovered to yield the best results, exceeding commercial formulations. A relationship between gum concentration and the release rate retarding impact was additionally established. The gum concentration of 3.33% demonstrated the best sustained release effects. As a result, it can be stated that the manufactured SR metoprolol succinate tablets may be one of the best preparations for hypertensive patients because it not only serves therapeutic purposes but also values the patients' concern for minimizing side effects in the long run use of the drug.



Graphical Abstract

Chapter 2: INTRODUCTION

2.1 ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM:

Each drug delivery system seeks to quickly achieve and then sustain the required drug concentration by delivering a therapeutic amount of medication to the targeted place in the body. The kind of delivery system, the ailment being treated, the patient, the duration of therapy, and the qualities of the drug are only a few of the linked and significant factors that affect the design of oral sustained release delivery systems. Any drug delivery system that achieves delayed drug release over an extended period of time is a sustained release (SR) system. The least complex sustained action dosage form with the least processing variables that uses conventional facilities and can handle high doses of medication is thought to be matrix tablets. With the advent of extended release matrix tablets, sustain release has shown to be a useful technique for drug release control without requiring complicated production processes [1-3]. A therapeutically effective concentration in the systemic circulation can be attained over an extended period of time using the sustained release approach, improving patient compliance. Given the shortcomings of the conventional drug administration system (repeated dosing and dosage variability), the following objectives are accomplished with sustain release:

i) Consistent drug release over an extended length of time.

ii) Less frequent dosing.

iii) Less erratic blood plasma concentration.

Principle of SR formulations:

The principle involved in SR formulations states that the active ingredients are released into an absorption pool immediately after administration in conventional dosage forms [2]. The absorption pool represents a solution of the drug at the site of absorption, Kr, Ka, and Ke - first-order rate- constant for drug release, absorption, and overall elimination, respectively. Immediate drug release from a conventional dosage form implies that Kr >> Ka. For non-immediate release dosage forms, Kr << Ka, i.e., the release of drug from the dosage form is the rate-limiting step. The drug release from the dosage form as shown in ***Figure 1***should follow zero-order kinetics, as shown by the following equation:

Kr° = Rate In = Rate Out = Ke Cd Vd

Where, Kr°: Zero-order rate constant for drug release- Amount/ time, Ke: First-order rate constant for overall drug elimination-time, Cd: Desired drug level in the body – amount/volume, and Vd: volume space in which the drug is distributed in liter.

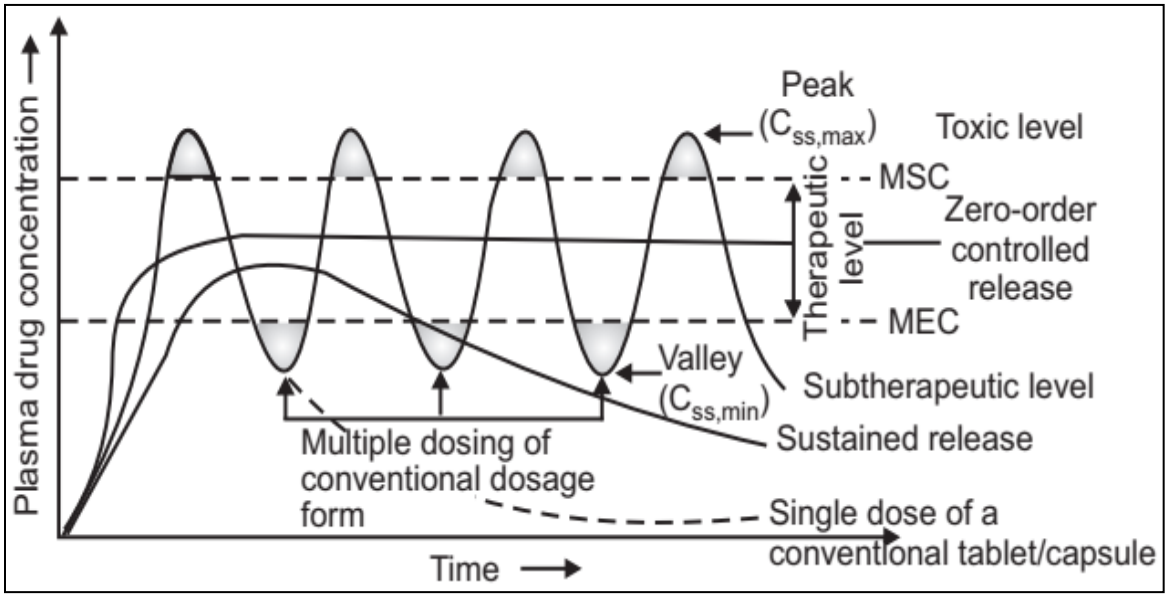


Figure 1: Release pattern of SR dosage form in comparison with conventional dosage form

Need of Sustained release drug delivery system

Oral conventional dosage forms have the following limitations. In order to overcome those sustained release formulations have been developed [4]. The following points denote the limitations of the oral conventional dosage forms:

- Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication in narrow therapeutic index drug.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition impossible

Advantages of Sustained release drug delivery system

- Reduced dosing frequency.
- Dose reduction.
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose
- . Reduces the fluctuation of peak valley concentration.
- Night time dosing can be avoided.

Factors of drug selection for SR formulation:

There are a few physicochemical factors *[Refer Table 1]* to consider when choosing a drug to formulate in a sustained release dosage form, most notably, the knowledge of the drug's molecular weight, solubility at different pHs, apparent partition coefficient, and method of absorption from the gastrointestinal (G.I.) tract as well as its general absorbability [4,5].

Other pharmacokinetic factors *[Refer Table 2]* that influence drug selection include the drug's elimination half-life, total clearance, absolute bioavailability, potential first-pass effects, and the desirable steady concentrations for peak and trough [5].

Most distinctly these are the factors that need to be considered. A drug's half-life is a measure of how long it stays in the body. The dosage form may include an excessive amount of the drug if the substance has a short half-life (less than 2 hours). On the other hand, a sustained release drug delivery system is typically not required when a drug has an elimination half-life of eight hours or more because it is sufficiently sustained in the body when taken in conventional dosage form. The drug's half-life should ideally be 3–4 hours.

Another consideration is that, drugs with low therapeutic indices should not be included in sustained-release formulations. Dose dumping could happen in the body if the system fails, which could be lethal.

The appropriateness of a drug as a candidate for sustained release is severely weakened if the dosage is high in the conventional dosage form. This is mostly due to the fact that a unit dose sustained release formulation would grow too large to administer easily [6].

Poorly water-soluble drugs may have dissolution rate restrictions on absorption. Therefore, it would be unreasonable to include such compounds in sustained-release formulations, which

could lower overall absorption efficiency. In such cases solubility enhancement of the drug must be done before preparing for the sustained release formulations.

Certain drugs, when administered orally, are absorbed only from a specific part of the gastrointestinal tract. That area is known as "absorption window". Drugs exhibiting such an absorption window, if formulated as sustained release dosage forms, are unsuitable.

It has been also observed that administering drugs in sustained release forms to those that undergo considerable hepatic first-pass metabolism seriously impairs their ability to reach the body in the optimal quantities.

Formulation Strategy for Oral Sustained Release Drug Delivery System

There are in general six main strategies to formulate sustained release formulations namely as follows:

A.Diffusion sustained system

Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. Two systems are there in this category.

- **Diffusion reservoir system**
  A drug core is covered by a polymeric substance that is water-insoluble in this arrangement. The drug will interchange with the fluid surrounding the particle or tablet after partitioning into the membrane. More drugs will enter the polymer, diffuse to the periphery, and interact with the media there. The diffusion process is used for drug release as shown in ***Figure 2(A)***.

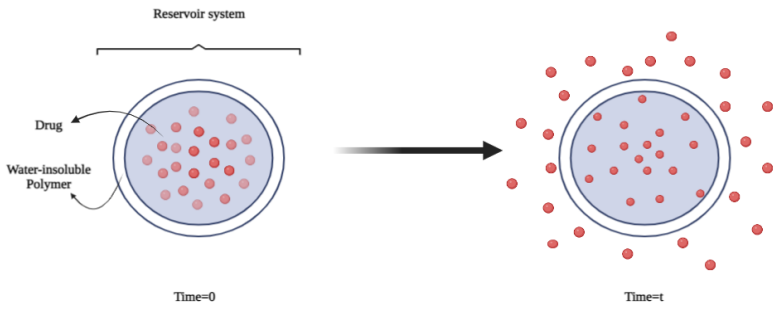


Figure 2(A): Diffusion reservoir system

- **Diffusion matrix system**

The term "matrix system" refers to a well-combined mixture of one or more than one drug and a gelling agent, such as hydrophilic polymers. For maintaining the release rate, matrix methods are frequently utilized. The release system is what delays and regulates the drug's distributed or dissolved release [7, 8]. The rate of drug release is influenced by drug diffusion, not solid dissolution because a solid drug is disseminated in an insoluble matrix. ***Figure 2(B)*** depicts the diffusion-type matrix system. The matrix system can be divided into three categories depending on the types of retarding agents or polymeric materials.

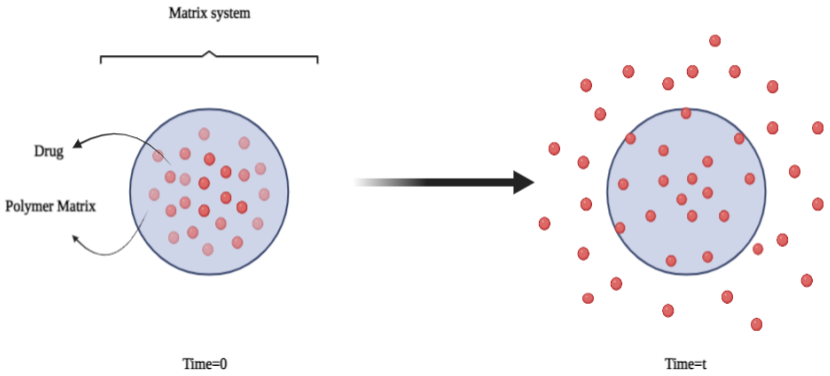


Figure 2(B): Diffusion matrix system

Hydrophobic matrix system: Although insoluble polymers can be utilized, this is the sole method in which the use of polymer is not required to achieve sustained drug release. As the name implies, the key rate-controlling components of a hydrophobic matrix are insoluble in water. Waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose, and acrylate copolymer are among the constituents. To modify drug release, soluble substances such as lactose may need to be included in the formulation. The presence of insoluble ingredients in formulations aids in the preservation of the physical dimensions of the hydrophobic matrix during drug release. The release mechanism is the diffusion of active component from the system, and the related release characteristic can be represented by the Higuchi equation, also known as the square root of time release kinetic [9].

Hydrophilic matrix system: Polymers that swell when in contact with aqueous solution and create a gel layer on the system's surface are the key rate limiting elements of hydrophilic matrix. The solvent penetrates the free spaces between macromolecular chains when the releasing medium is thermodynamically compatible with the polymer. Due to the tension of the penetrated solvent, the polymer may relax, causing the polymer chains to become more flexible and the matrix to swell. This permits the encapsulated drug to diffuse out of the matrix more quickly. On the other hand, because matrix swelling lengthens the diffusion

path, the drug would take longer to diffuse out of the matrix. It is well understood that swelling and diffusion are not the sole elements that influence drug release rate. Polymer dissolution is another significant process that can vary drug delivery rate in dissolvable polymer matrix. While either swelling or dissolving may be the most important component for a certain type of polymer, drug release kinetics is usually the consequence of a combination of these two mechanisms. The main polymers used in hydrophilic matrices are hydroxy propyl methyl cellulose (HPMC) and Hydroxy propyl cellulose (HPC), Xanthan gum, Carbopol and Alginates [10,11].

Fat-wax matrix system: By spray congealing in air or blending congealing in an aqueous media with the drug, the drug can be integrated into fat wax granulations or without the use of surfactants or spray drying processes. The drug is released from a melt of fats and waxes through leaching and/or hydrolysis, as well as fat dissolution under the effect of enzymes and pH changes in the gastrointestinal tract. Surfactants in the formulation can affect both the drug release rate and the fraction of total drug that can be incorporated into a matrix [12].

B. Dissolution sustained systems

A drug with a slow dissolving rate is inherently sustained, and pharmaceuticals with high water solubility can be reduced dissolution through suitable salt or derivative production. These systems are most typically used in the manufacturing of enteric coated dosage forms. It is utilized a covering that dissolves in natural or alkaline media. This prevents the drug from being released from the dose form until it reaches the higher pH of the intestine. In most situations, enteric coated dosage forms are not genuinely sustaining in nature, but they do serve a useful function in directing drug release to a specific region. The similar method can be used for compounds that are degraded by the severe conditions found in the stomach.

- **Soluble reservoir system**
  The drug is coated with a predetermined thickness coating in this technique, and it is slowly dissolved in the contents of the gastrointestinal tract by alternating drug layers with rate-controlling coatings, as demonstrated in ***Figure 3(A)***.
- **Soluble matrix system**
  It can be either a drug-impregnated sphere or a drug-impregnated tablet that will be slowly eroded. ***Figure 3(B)*** depicts the most common kind of dissolving sustained dose form [13,14].
- **Dissolution- sustained pulsed delivery system**
  Hydrophilic matrix technology is the most extensively used technique in sustained release formulations. A hydrophilic matrix tablet is made up of a drug, polymer, and excipients

(filler/diluents and other excipients) created in the matrix by a hydrophilic polymer. For release rate control, formulators frequently select from a variety of hydrophilic polymers, either alone or in combination with other polymers [15,16].

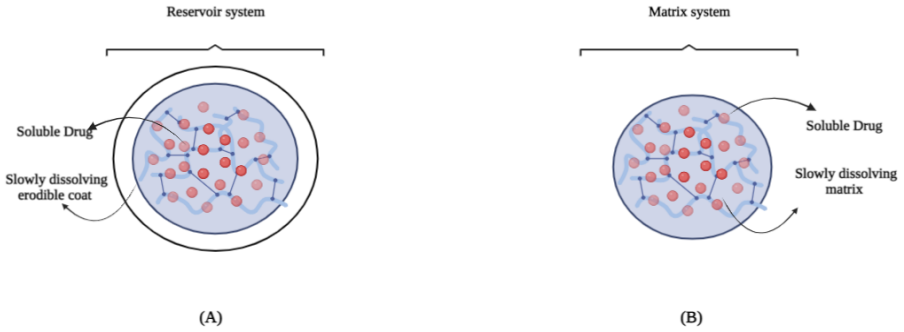


Figure 3: (A) Soluble reservoir system, (B) Soluble matrix system

C. Ion exchange resins sustained release

Ion exchange resins are water-insoluble cross-linked polymers with ionisable functional groups. The resins have been used in a variety of pharmaceutical applications. Taste masking and controlled release systems are two of the most common applications. Because of their swelling ability, ion exchange resins have been used as disintegrants in tablet formulations. When ionisable medications are exposed to the resin for an extended period of time, they form an irreversible compound. When suitable ions come into contact with ion-exchanged groups, a resin bound medication is removed.

D.Methods using osmotic pressure

The osmotic pressure differential between the compartment and the external environment is the release controlling factor that must be optimized in this procedure. Maintaining a saturated solution of osmotic agent in the compartment is the simplest and most predictable technique to create consistent osmotic pressure. This method allows for zero order release of hydrophilic drugs.

E. pH Independent formulations

The majority of drugs are either weak acids or weak bases. Sustained release formulations' release is pH-dependant. Buffers, such as amino acid salts, citric acid, phthalic acid, phosphoric acid, or tartaric acid, can be added to the formulation to help maintain a steady pH, allowing for pH independent drug release. A buffered formulation is made by combining a basic or acidic drugs with one or more buffering agents, granulating it with appropriate pharmaceutical excipients, and coating it with a gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid passes through the membrane, the buffering agents adjust the fluid inside to a stable pH, resulting in a consistent rate of drug release [8].

F. Altered density formulations

Several ways have been developed to increase the duration that a drug delivery system spends in the gastrointestinal tract. The delivery system remains at the absorption site until most, if not all, of its drug substance is discharged. The density of the pellets in the high density approach must be more than that of typical stomach content, which should be at least 1-4g/cm^3.

2.2 SUSTAINED RELEASE MATRIX TABLETS:

Since tablets represent the most affordable method of sustained and controlled release solid dosage forms, matrix tablets are a potential strategy for the implementation of extended-release medication therapy. The "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which functions as release rate retardants" is what matrix tablets are, according to one definition. These systems employ diffusion- and dissolution-controlled mechanisms to continuously release the drug.

A new development in the realm of pharmaceutical technology is the introduction of the matrix tablet as a sustained release (SR) drug delivery mechanism. During manufacturing, sophisticated production processes like coating and pelletization are not included, and the kind and concentration of polymer used in the preparations largely determines how quickly the drug is released from the dosage form. One of the least complicated techniques to the fabrication of sustained release dosage forms is the direct compression of blend of drug, retardant material and

additives to make a tablet in which the drug is embedded in a matrix of the retardant. The drug and retardant mixture is also granulated before compression in another method.

Based on Retardant Material Used Matrix tablets can be divided into 5 types.

i. Hydrophobic Matrices (Plastic matrices):

In this technique, the drug is combined with an inert or hydrophobic polymer and compressed into a tablet to achieve prolonged release from an oral dosage form. The medication that is dissolving has diffused through a network of channels that are present between compressed polymer particles, resulting in sustained release.

Polyethylene, polyvinyl chloride, ethylcellulose, and acrylate polymers and their copolymers are a few examples of materials that have been employed as inert or hydrophobic matrices. In these formulations, liquid penetration into the matrix serves as the rate-controlling step. Diffusion is a potential medication release mechanism in these types of tablets. In the presence of water and gastrointestinal fluid, certain types of matrix tablets become inactive [17].

ii. Lipid Matrices:

These matrices were created using lipid waxes and associated substances. Drug release from these matrices happens via pore diffusion as well as erosion. As a result, release properties are more sensitive to the nature of the digestive fluid than to a polymer matrix that is completely insoluble. Carnauba wax, in combination with stearyl alcohol or stearic acid, has been utilised for a retardant basis for numerous sustained-release formulations [16,17].

iii. Hydrophilic Matrices:

The versatility to achieve a desired drug release profile, cost-effectiveness, and broad regulatory acceptability, makes hydrophilic polymer matrix solutions being frequently utilised in oral controlled drug delivery. The term "matrix" refers to a well combined mixture of one or more drugs and a gelling agent (hydrophilic polymer). Three major categories can be utilised to classify the polymers used in the creation of hydrophilic matrices. Methylcellulose,

hydroxyethylcellulose, hydroxypropylmethylcellulose (HPMC), 25, 100, 4000, and 15000 cps; and sodium carboxymethyl-cellulose are all derivatives of cellulose.

Natural or semi-synthetic non-cellulose polymers include agar-agar, carob gum, alginates, molasses, mannose- and galactose-containing polysaccharides, chitosan, and modified starches. Carbopol-934, the most common type of acrylic acid polymer [5].

iv. Biodegradable Matrices:

They are composed of polymers with unstable backbone linkages made up of monomers connected to one another by functional groups. They are biologically eroded or decomposed into oligomers and monomers that can be metabolised or expelled by enzymes produced by the living cells in the vicinity or by nonenzymatic mechanisms. Examples include modified natural polymers, synthetic polymers such aliphatic poly (esters), and poly anhydrides. Natural polymers include proteins and polysaccharides [8,15].

v. Mineral Matrices:

They are made up of polymers that come from different kinds of seaweed. Alginic acid is one such substance. This hydrophilic carbohydrate is produced from various brown seaweed species by using diluted alkali [18].

General mechanism of drug release from matrix:

Active agents can be released from a SR delivery system via three main processes, namely diffusion, degradation and swelling.

- **Diffusion**
  Diffusion happens when an active substance, such as a drug, travels through the polymer that makes up the controlled-release matrix. When a drug diffuses, it moves from the polymer matrix into the surrounding medium. With this kind of mechanism, the release rate often declines over time as the active agent has to travel progressively farther and needs more time

for diffusion before it can release. The bioactive agents and polymer matrices chosen in these systems must permit the drug to diffuse through the pores or macromolecular structure of the polymer upon introduction of the delivery system into the biological environment without causing the polymer to alter in any way [7,18].

- **Degradation**
  The necessity to remove a drug delivery system once the active ingredient has been released is eliminated by biodegradable polymers, which disintegrate naturally within the body as a result of biological processes. The majority of biodegradable polymers are made to break down into biologically acceptable and progressively smaller molecules through hydrolysis of the polymer chains.The release rate of some degradable polymers, most notably the polyanhydrides and polyorthoesters, is proportional to the surface area of the drug delivery system since the breakdown only takes place at the surface of the polymer [18].

- **Swelling**
  In swelling initially the dry polymer will absorb water or other body fluids and enlarge once inside the body. The drug can diffuse through the swelled network into the surrounding environment because the swelling increases the formulation's aqueous solvent content and polymer mesh size [18].

Polymers in sustained release tablets:

Pharmaceutical drug delivery systems are based on polymers. Because of their special qualities that no other materials have, they have been used extensively in drug delivery. Controlling the rate at which drugs are released from formulations has been made possible through the use of polymers.

Some of the key drawbacks of many drugs include short half-lives, low bioavailability, and excessive dosage frequency; as a result, these issues should be addressed during formulation creation for improved usefulness and efficacy. While developing formulations, a drug's chemical and physical instability is also a top priority. Polymers are regarded as a superior alternative to address the aforementioned issues, and their utility is growing daily as the pharmaceutical sector increases globally. In addition to their traditional uses as diluents, binders, suspending and emulsifying agents, film coating materials, etc., polymers have demonstrated their effectiveness in the creation of more modern, modified drug delivery systems.

The polymer's primary function is to offer regulated or sustained release of the drug over a longer period of time so that the frequency of dose for that drug can be reduced. Polymers can be divided into many classes according to their chemistry, pattern of degradation, and function.

Polymers can be categorised into three main groups: synthetic, semi-synthetic, and natural based on both of these factors.

i) Natural polymers

Natural polymers have recently replaced synthetic polymers as the material of choice for the development of drug delivery systems since they are more compatible and biodegradable. These polymers can be made from a variety of natural resources, including plants, animals, and microorganisms and marine organisms. A few typical examples of natural polymers used for drug delivery includes cellulose, hemicellulose, glucomannan, agar, starch, pectin, inulin, rosin, guar gum, locust bean gum, gum acacia, karaya gum, gum tragacanth, aloe vera gel, chitin, alginates, carageenans, psyllium, xanthum gum [19].

ii) Synthetic polymers

The emergence of synthetic polymers was prompted by the high degree of unpredictability in natural sources, structural complexity, and expensive and time-consuming extraction processes as some of the key drawbacks of naturally produced polymers. Moreover, it has been claimed that these polymers may prolong circulation times and fundamental pharmacokinetics, both of which are crucial for biomaterials. In the case of some particular synthetic polymers, targeting of the various organs is comparably easier. Various synthetic polymers generally used includes polyhydroxybutyrate, polylactic acid, poly(e-caprolactone), polyamide, polyglutamic acid, poly(2-hydroxyethyl methacrylate), poly(N-vinyl pyrrolidone), poly(methylmethacrylate), poly(vinyl alcohol), poly(acrylic acid), poly(ethylene glycol), 2 polymethacrylic acid (2-methyl-2-propenoic acid homopolymer), polyanhydrides etc [10].

2.3 NATURAL POLYMERS IN SUSTAINED RELEASE TABLETS:

Mucilages and natural gums are being used more frequently as excipients in pharmaceuticals. Natural plant-based materials can be found for a reasonable price, and they are also biocompatible and biodegradable. They are processed in an environmentally responsible manner and made from renewable resources. Patient compliance is higher, and there are no negative effects.

The inclusion of excipients in innovative dosage forms to fulfil necessary dosage form functions is driven by a high demand for drug delivery systems. These excipients have a direct or indirect

impact on the rate and amount of drug release as well as their absorption in the GIT. As a result, the natural and plant-based products require the substitution of these natural gums for synthetic additives. These natural gums and excipients are currently of interest to the entire world. Because they are chemically inert, nontoxic, less expensive, and biodegradable, these natural materials have several advantages over synthetic ones [19,20].

2.4 METOPROLOL SUCCINATE A BCS CLASS I TYPE DRUG:

The biopharmaceutics classification system (BCS) based on solubility and permeability is used to categorize drugs into four classes. The drugs are classified as having either high or low solubility and high or low permeability. Drugs are classified as highly soluble if the maximum dose of drug is soluble in 250 ml of water and highly permeable if drugs are more than 80% absorbed across the gastrointestinal membrane. Class I drugs are highly soluble and highly permeable. Metoprolol succinate belongs to this category.

Metoprolol succinate, a BCS Class I type drug is a selective β-1 receptor antagonist, used to treat heart failure with a low ejection fraction and mostly hypertension. It is typically taken orally, where it is absorbed in the gastrointestinal tract and extensively metabolised in the liver. It has an average half-life of 3 to 4 hours in adults and a bioavailability of about 40%, which means that half-life ($t_{1/2}$) modulation is necessary to decrease the number of daily doses [21].

Since the drug's half-life is shorter, frequent administration is necessary, which interferes with patient compliance. Changes in the standard formulations' plasma concentration lead to erratic beta-adrenoceptor blocking behaviour, which could lead to nocturnal attacks. It has been noted that the majority of β1 blockages are caused by metoprolol plasma concentrations over 300 nM, but a therapeutic threshold of β2 blockage but no further β1 blockage is evident when the concentration is between 80 and 300 nM. Higher concentrations result in more β2 blockage production but not more β1 blockage. Metoprolol succinate sustained release medications are used to reduce such fluctuations and rough behaviour and offer a β1 blockage over 24 hours [22].

2.5 METOPROLOL SUCCINATE IN HYPERTENSION:

For the treatment of hypertension, Metoprolol succinate sustained-release tablets are recommended. It could be used with other antihypertensive medications or taken alone. Metoprolol works by inhibiting β1-selective (cardioselective) adrenergic receptors. Metoprolol

also inhibits β2-adrenoreceptors, which are mostly found in the bronchial and vascular musculature, at greater plasma concentrations, indicating that this preferred action is not absolute. Metoprolol does not naturally have sympathomimetic properties, and its ability to stabilise membranes can only be seen at plasma concentrations far higher than those needed to cause beta-blockade [23]. Metoprolol reduces the sinus rate and lowers AV nodal conduction, according to research on animals and people.

Metoprolol's β-blocking activity has been confirmed by clinical pharmacology studies in humans, as evidenced by the following changes: (1) decreases in heart rate and cardiac output during rest and exercise; (2) decreases in systolic blood pressure during exercise; (3) inhibition of isoproterenol-induced tachycardia; and (4) decreases in reflex orthostatic tachycardia [21].

β-blocking agents ability to lower blood pressure has not yet been fully understood. However, a number of potential explanations have been put forth, including the following:

(1) competitive antagonistic effects of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, which result in decreased cardiac output

(2) a central effect, which results in decreased sympathetic outflow to the periphery; and

(3) suppression of renin activity.

Metoprolol succinate, β1-selective adrenergic receptor blocking agent used in the management of hypertension specifically has a relatively short half-life of approximately 4 to 6 hours and in normal course of therapy. Frequent drug administration is required every 4 to 6 hours, thus need the use of sustained release formulation for prolong action and to improve patient compliance by utilizing significant release rate retardants [23]. Sustained release formulations are necessary to provide a nearly zero-order release of this highly soluble BCS Class I model drug. A 24 hours dosing provided by the SR formulations prevents nocturnal attacks in hypertensive patients.

2.6 NATURAL GUMS USED IN THE STUDY:

- **Guar gum**

The legume Cyamopsis tetragonolobus, an annual plant that primarily thrives in dry and semiarid regions of the Indian subcontinent with some occurrences in Texas and Oklahoma, is the source of guar gum. Its seed's endosperm and germ both contain guar galactomannan, while the endosperm primarily contains protein [24,25]. Commercial guar gum is a composite that is made through a series of processes that begin with the production of seeds from various guar plant

species grown under various conditions and end with the milling of seeds by various processors, occasionally under various processing conditions. Splits with the right amount of moisture are promptly heated to 105 degrees, where the endosperm begins to become slightly elastic and durable while the seed coat is still brittle so that it may be processed into the highest-quality gum.

Guaran, the functional polysaccharide in guar gum, is made up of a chain of jß-D-mannopyranosyl units that are (1 -> 4) linked, with a single a-D-galactopyranosyl unit joining every other main chain unit on average. The molecular weight of guar gum is among the highest among all naturally occurring water-soluble polymers. In polar liquids that create potent hydrogen bonding, guar gum and its derivatives swell and/or dissolve. The rate of guar gum dissolution and viscosity development typically rises as temperature, pH, and particle size all rise. Intermolecular interaction of guar gum, other galactomannans, and specific linear polysaccharides like xanthan, agarose, and c-carrageenan is an example of viscosity synergism [26,27]. Formulations for sustained release are made using these specific properties.

- **Locust bean gum**

The refined endosperm of the carob seed, an evergreen member of the legume family with the scientific name Ceretonia siliqua L., is what is used to make locust bean (carob) gum [28]. The tree is farmed in large amounts throughout the Mediterranean region, with Spain being the region where it is grown the most extensively. About 8–10% of the weight of the pod is made up of the seeds collectively. The dark brown seed coat protects them, revealing the white endosperm underneath. The yellow germ part is located in the centre. A typical seed's weight breakdown is 40–45% endosperm, 25–30% germ, and 25–30% husk or seed coat. Like guar gum, locust bean gum is a galactomannan that has a backbone composed of 1- to 4-linked 3-D-mannopyranosyl units and side stubs made of 1- to 6-linked a-D-galactopyranosyl groups [29].

Only a small amount of locust bean gum dissolves in cold water, and dispersions need to be heated to about 85° to reach their full viscosity potential. A high-purity grade dispersion at 1% will have a viscosity of between 2500 and 3500 cp after being heated and then cooled at 25° (Brookfield at 20 rpm) [30-32]. The way locust bean gum interacts with the other ingredients—agar, carrageenan, and xanthan in the preparation of a suitable retardant for sustained release tablets is crucial. By fusing the double helices of these polymers into a continuous network while they are in solution, locust bean gum is thought to improve gelation.

- **Xanthan gum**

Xanthan gum is 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. In addition to being nontoxic and compatible with the majority of other pharmaceutical components, xanthan gum has high viscosity and stability characteristics over a wide pH and temperature range. Moreover, matrices that have been physically compressed and exhibit a high degree of swelling from water absorption and a minimal level of erosion from polymer relaxation have been made using xanthan gum. It has also been utilized to make sustained-release matrix tablets along with chitosan, guar gum, galactomannan, and sodium alginate.As xanthan gum is an anionic substance, it typically cannot be used with cationic surfactants, polymers, or preservatives without precipitation. Xanthan gum precipitates from a solution when anionic and amphoteric surfactants are present in concentrations greater than 15% w/v [33].

Chapter 3: LITERATURE REVIEW

G.Sharma*et al.* aimed to develop Metoprolol succinate sustained-release tablet by wet granulation using novel polymers Eulophiaherbacae and Remusatia vivipara tuber mucilage as release retardants. A 32 complete factorial design was employed in the formulation preparation. Two factors were examined in this study on each of three levels. Swelling index, t75 of% cumulative drug release, and drug content were chosen as the dependent factors, while the concentration of Eulophiaherbacea mucilage (X1) and Remusatia vivipara mucilage (X2) were chosen as the independent variables. Tests for weight variation, hardness, friability, swelling index, drug release, and drug content were used to evaluate the produced tablets. When compared to the reference formulation PROLOMET XL 100, the optimised tablet won. Several models were used to carry out the drug release kinetics investigation. It became clear that the formulation employed both diffusion-controlled and swelling-controlled methods of drug release, as well as an anomalous diffusion (non-fickian) pattern.

J.Wikstrand*et al*. developed an extended-release (ER) metoprolol succinate as a controlled-release formulation designed to deliver metoprolol succinate at a near constant rate for approximately 20 h, independent of food intake and gastrointestinal pH. Once-daily administration of ER metoprolol succinate 12.5-200 mg resulted in even plasma concentrations over a 24-h period, devoid of the distinct peaks and troughs typical of the immediate-release (IR) formulation. For doses up to 200 mg per day, this resulted in sustained beta1-blockade over the course of 24 hours while retaining cardioselectivity. Even in heart failure patients, pharmacokinetic investigations have shown that ER metoprolol succinate is linked to a more pronounced and even beta1-blockade throughout a 24-hour period than the IR version. A large-scale clinical trial has now shown that ER metoprolol succinate is effective and well tolerated in individuals with heart failure.

R S Harland *et al.*demonstrated that a mathematical model that predicts the amount of drug released and the thickness of the gel layer as a function of time can be used to study the swelling and dissolving behaviour of pharmaceutical systems including a drug and a polymer. It is feasible to acquire an order-of-magnitude analysis of the tablet dissolution process by approximating the values of a number of the physicochemical parameters in this model. Analysis of a subset of tablet dissolution and drug release experiments led to conclusions about the significance of drug and polymer content as well as solubility in release behaviour.

T D Reynolds *et al.* focused on matrices that contained either the polymer alone or a drug content of 25% without the addition of excipients, polymer erosion of matrices of similarly substituted hydroxypropyl methylcellulose (HPMC) polymers and drug release in terms of diffusion and erosion contributions were characterised. Separating the diffusional and erosional contributions to drug release involved an innovative method. Diffusional drug release was identified by fitting release data vs (time) 0.45, and erosion-related drug release was assessed by deducting the percent predicted for diffusional drug release from the overall drug release at each particular time point. The average molecular weight of the polymer was discovered to be a factor in the linear time-versus-drug release caused by polymer erosion.Diffusional release rates, however, were comparable across all HPMC grades examined, making them independent of the average molecular weight of the polymers under investigation. Individual polymer chains detached from the matrix surface at a higher rate compared to diffusion away from the matrix surface under stirring conditions of 10-100 rpm as well as static circumstances. According to the erosion investigation, the rate-limiting phase in polymer erosion was polymer diffusion of the HPMC polymer chains via the aqueous diffusion layer. The average molecular weight of polymers was shown to be generally inversely correlated with polymer erosion. The rate of polymer degradation was correlated with the average molecular weight of each polymer using a scaling law. Similar relationships were obtained for matrices with and without drug at a stirring rate of 100 rpm.

V D Prajapati *et al.* studied that biopolymers or natural polymers are an attractive class of biodegradable polymers since they are derived from natural sources, easily available, relatively cheap and can be modified by suitable reagent. Due to its vast use as a food additive and its well-known lack of toxicity, locust bean gum is one of those substances with a broad potentiality in medication compositions. It can be modified to meet the requirements it has for candidates in the pharmaceutical and biological fields. As rate-controlling excipients in innovative drug delivery systems or as a scaffolding material in tissue engineering, locust bean gum has several uses. In this study, they have discussed important elements of locust bean gum, its manufacturing process, physicochemical properties, and uses in various drug administration systems with careful references to the documented literature on locust bean gum.

M Tako*et al.* studied the non-Newtonian behavior and dynamic viscoelasticity of a series of aqueous mixtures of xanthan and guar gum with a rheogoniometer. At a concentration of 0.2% of total gums, gelation did not occur at room temperature but occurred at a low temperature (0°). In comparison to native xanthan, a mixture of deacetylated xanthan showed a significantly greater interaction. The 2:1 xanthan to guar gum ratio produced the highest dynamic modulus. For combinations containing native and deacetylated xanthan, the transition temperatures of dynamic viscoelasticity were found to be 25° and 30°, respectively. It was determined that the side chains

of the guar gum molecule and the side chains of the xanthan molecule do not interact with one another. At low temperatures, an intermolecular contact between the side chains of the xanthan and guar gum molecules and the backbone of the guar gum molecule may be encouraged, and dissociation occurs at the transition point.

I P Gabott*et al.* used a pharmaceutical compound to study the effect of batch wet granulation process parameters in combination with the residual moisture content remaining after drying on granule and tablet quality attributes. Using a unique limited design space and a multivariate experimental methodology, the impact of three batch wet granulation process parameters was assessed. Moisture content, granule density, crushing strength, porosity, disintegration time, and dissolution were used to characterise batches. Mechanisms for how the process factors affect the characteristics of granule and tablet quality were provided. Granule density and tablet dissolving rate were significantly affected by the amount of water applied during granulation. Tablet crushing strength was significantly influenced by mixing duration, while the distribution of tablet crushing strengths was significantly influenced by mixing speed. The strength of crushing tablets was significantly impacted by the amount of residual moisture present after granule drying. The effect of moisture on tablet tensile strength had been reported before, but not in combination with granulation parameters and granule properties, and the impact on tablet dissolution was not assessed. Correlations between the energy input during granulation, the density of granules produced, and the quality attributes of the final tablets were also identified. Understanding the impact of the granulation and drying process parameters on granule and tablet properties provides a basis for process optimisation and scaling.

R B Shah *et al.* carried out a systematic evaluation of flow of pharmaceutical powders and granules using compendial and non-compendial methods. Angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner ratios were evaluated. Moreover, a powder rheometer that uses a sensitive force transducer to track the forces produced by sample displacement was used to describe flow. Samples' crucial characteristics, including cohesivity index, caking strength, and flow stability, were identified. The samples included granules made using a variety of techniques, including slugging, high shear granulators, and fluid bed dryers, as well as several grades of magnesium stearate powder, including bovine, vegetable, and food grade. For granules lubricated with varied amounts of magnesium stearate, lubricant effectiveness was also calculated. The compendial approaches were shown to frequently make no distinction for slight differences in powder flow. The additional characterization such as cohesivity, and caking strength were helpful in understanding the flow characteristics of pharmaceutical systems. The flow stability test determined that the powders were not affected by the test conditions on the rheometer. The non-compendial tests were discriminating to even minor variations in powder flow.

P K Choudhari*et al.* developeddirectly compressible (DC) co-processed excipient capable of providing nearly zero order release with improved functionality without any chemical modification by employed various techniques such as physical mixing, high shear mixer granulation and spray drying. Co-processed excipient was developed by using release retarding polymer Eudragit RSPO, separately, in combination with different concentration of hydroxyl propyl methyl cellulose 100 cps (Methocel K100 LV, HPMC), ethyl cellulose (Ethocel N50, EC) and hydroxyl propyl cellulose (Klucel EF, HPC). The flow characteristics of each co-processed excipient were assessed using the following metrics: angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. Nine co-processed excipients out of eighteen combinations showed promising flow characteristics, were deemed suitable for direct compression, and were formed into tablets. As a model drug, the BCS Class I medication metoprolol succinate was chosen, and the formulation was created using the direct compression method. Physical characteristics like thickness, hardness, friability, uniformity of weight, and assay were assessed for the generated tablets. The formulation created employing a co-processed excipient demonstrated sustained drug release, according to an in vitro dissolution investigation. DSC, FTIR, and PXRD analyses of the optimised tablet formulation confirm that no chemical changes occurred during co-processing. The optimized formulation was kept for stability study for six months as per ICH guidelines and found to be stable. In vivo pharmacokinetic study of optimized formulation in rats showed similar pharmacokinetic behaviour as was observed with the marketed brand. Study revealed that co-processed excipient has advantage over polymers with single property and can be utilised for sustained release formulation.

M Soumya *et al.* made an effort to formulate and evaluate matrix tablets of tarogum utilizing metaprolol succinate as the model drug. Two factors were examined at three levels in 32 of the entire optimisation procedures that were used. As independent variables, taro gum content (X1) and polyvinylpyrrolidone (PVP) K30 content (X2) were chosen. The dependent variable was decided to be the amount of time needed for 90% of the medication release. Direct compression was used to create the tablets, and a number of post-compression metrics, including tablet hardness, friability, weight variation, drug content, and in vitro dissolution, were assessed. The outcomes were discovered to be within acceptable bounds. According to the concentration of natural polymer, the release exponent (n), which ranges from 0.416 to 0.584, indicates that drug release from matrix tablets may be fickian or non-fickian (anomalous).T90 was 10.70, 11.20, 12.05, 12.66 hours for B6, B7, B8 and B9 batches respectively showing overriding potential of taro gum, but still the effect of PVP K 30 was noteworthy. PVP K 30 had an indirect effect on all the factors by increasing tensile strength and making the tablet firm and intact.

J Varshosaz*et al.* prepared Metoprolol tartrate sustained-release tablets (100 mg) using xanthan/guar gums and also hydroxypropyl methyl cellulose (HPMC) carboxymethyl-Cellulose

(CMC) polymers by direct compression method. Physical characteristics of the tablets and water uptake in addition to their dissolution profiles were compared with standard (LopressoR SR) tablets. The samples were subjected to a dissolution test in phosphate buffer solution (pH 6.8) and were spectrophotometrically examined at 275.7 nm. According to dissolution tests, formulations comprising 100% guar, 20% xanthan, and 60% hpmc followed the Higuchi model while those containing 100% guar, 60% xanthan, and 60% hydroxypropylmethylcellulose followed a zero-order model. The 40% xanthan tablets were designed using the Hixon-Crowell method. In cellulose derivatives, tablets with 40% HPMC had the highest MDT and dissolving efficiency over the first eight hours (DE8%); as CMC concentration increased, drug release rate dropped, and formulations with 60 and 40% HPMC met USP dissolution criteria. While, in the gum formulations, the highest mean dissolution time and the lowest DE8% belonged to tablets with 100% xanthan, increasing the xanthan decreased the release rate of metoprolol, and formulations containing 80 and 100% xanthan had the USP dissolution standards. Results showed that natural gums are suitable for production of sustained-release tablets of metoprolol.

Laicher*et al.* manufactured Metoprolol tartrate sustained-release tablets in 2.8, 7.0 and 10.0 mm diameters. The hydrophilic cellulose polymers methylcellulose, hydroxypropylcellulose, and sodium carboxymethylcellulose were utilised either alone or in combination to provide the prolonged release of active substances. It was specifically examined if the many units of miniature tablets wrapped in hard gelatin capsules permitted the continuous release of the primary active component, which is highly soluble at an acidic pH. Whereas tablets with a diameter of 7.0 and 10.0 mm that were created using HPC and NaCMC combinations are capable of a sustained release, tablets with a diameter of 2.8 mm do not permit an acceptable control of metoprolol tartrate release during the gastrointestinal passage. Active ingredient release in the range of up to 80 % release and the tablet surface area above a minimum of approximately 300 mm2 are correlated in a linear manner.

M P Venkataraju*et al.* developed a controlled delivery system for propranolol hydrochloride (PPHCL) using the synergistic activity of locust bean gum (LBG) and xanthan gum (X). Granules of PPHCL were prepared by using different drug: gum ratios of XG, LBG alone and a mixture of XLBG (X and LBG in 1: 1 ratios). Magnesium stearate (Mg. st.) and talc were added to the granules in a 1: 2 ratio before punching to improve their flowability and compressibility as well as prevent adherence to the punch and die. An in vitro release study was conducted, and the tablets' hardness, friability, and composition were all analysed. The diffusion of drug molecules through the polymeric substance into an aqueous media is controlled by the release of PPHCL from a gelatinous swelling mass. Due to the burst effect and quick release in the case of X and LBG alone, respectively, the XLBG matrices displayed accurate controlled release as opposed to the X and LBG matrices, and FTIR testing indicated that there was no chemical interaction

between the drug and polymers in the XLBG formulation. The first-pass effect of PPHCL can be avoided by using this formulation. The XLBG matrices offer more precise results than X and LBG matrices due to the effect of a synergistic interaction between the two biopolymers and the lower average size allowing uniform tablet hydration in dissolution media.

R V Nellore *et al.* designed to develop model extended-release (ER) matrix tablet formulations for metoprolol tartrate (100 mg) sufficiently sensitive to manufacturing variables and to serve as the scientific basis for regulatory policy development on scale-up and post approval changes for modified-release dosage forms (SUPAC-MR). A variety of fillers, binders, and grades of hydroxypropyl methylcellulose (Methocel K4M, K15M, K100M, and K100LV) were investigated. Direct compression, fluid-bed, and high-shear granulation were the three granulation techniques that were examined. Tablets were squeezed on an instrumented rotary tablet press after being lubricated in a V-blender. When making tablets, direct compression formulations have issues with poor flow, picking, and sticking. High-shear granulation produced hard granules that were challenging to mill but produced high-quality tablets. Several binders were used to create fluid-bed granulations, which appeared to operate satisfactorily in terms of flow and tableting. USP equipment 2 (paddle) at 50 rpm was used to perform in vitro drug release testing in phosphate buffer at pH 6.8. At a fixed polymer level, drug release from the higher viscosity grades (K100M) was slower as compared to the lower viscosity grades (K100LV). In addition, release from K100LV was found to be more sensitive to polymer level changes. Increase in polymer level from 10 to 40% and/or filler change from lactose to dicalcium phosphate resulted in about 25–30% decrease in the amount of metoprolol release after 12 h. The results of this study led to the choice of Methocel K100LV as the hydrophilic matrix polymer and fluid-bed granulation as the process of choice for further evaluation of critical and non-critical formulation and processing variables.

C K Mylangam*et al.* targeted at researching the use of natural polymers in the delivery of pharmaceutical agents. With metoprolol succinate serving as a model medication, the investigation's goal was to assess the usefulness of badam gum (BG), which was derived from Terminalia catappa LINN, a member of the combretaceae family as a buccoadhesive polymer. The process of wet granulation was used to create the tablets. Unidirectional release buccal tablets were created using the compression coating technique with cellulose acetate acting as the impermeable backing layer. According to detachment force measurements, ex vivo residence times, and swelling investigations, the BG's muco/buccoadhesive qualities increased as polymer content increased. Based on research on the bioadhesion of the medicine and drug dissolution, MBG 2 was determined to be the best formulation.FTIR and DSC studies performed on the optimized formulation indicated no drug–polymer interaction. MBG 2 was found to be stable after accelerated stability testing for 6 months as per ICH guidelines. Pharmacokinetic studies of

the optimized formulation were performed in six healthy human volunteers in comparison with that of the commercial extended release oral tablet GUDPRESS XL-25 by estimating pharmacokinetic parameters and mean residence time (MRT). It was found that there is a significant increase in the bioavailability of metoprolol succinate from BG formulation which was evident from the high AUC and MRT values compared with the commercial formulation. The above results clearly indicated that badam gum can be used as a mucoadhesive polymer for buccal drug delivery.

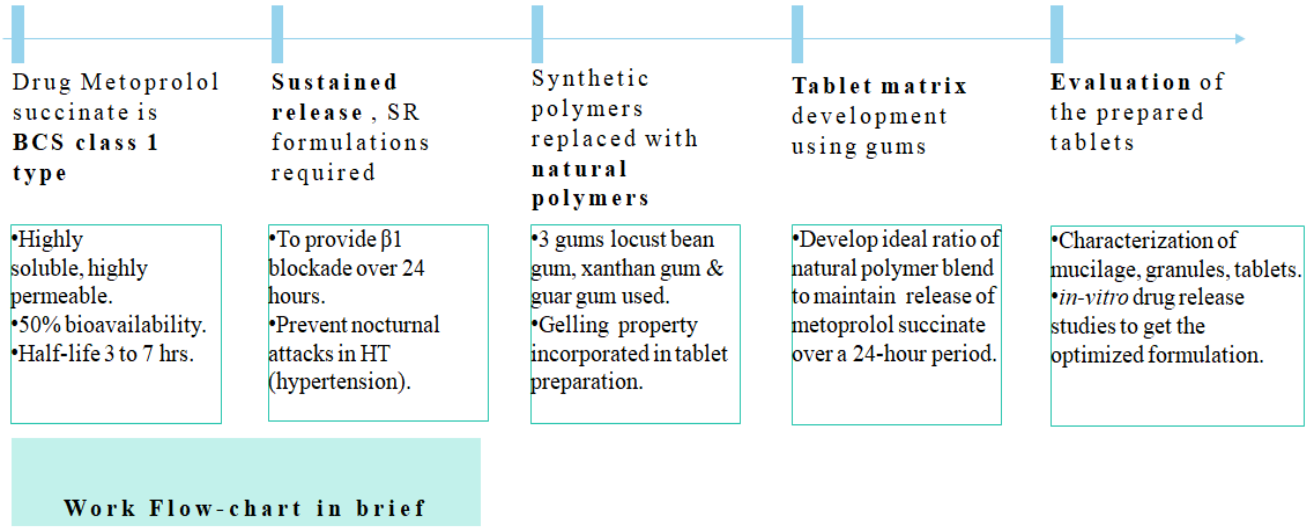
Chapter 4: AIM AND OBJECTIVE

The present work deals with the development of metoprolol succinate sustained release matrix tablets by utilising natural gums as a release-retardant. It focuses on preparing a tablet matrix with the help of three natural gums- locust bean gum (LBG), xanthan gum (XG), and guar gum (GG) to facilitate metoprolol succinate release over a 24-hour period and help in once-daily dose, minimizing nocturnal episodes in anti-hypertensive patients. It was aimed to develop such a formulation such that it could bypass the side-effects of the synthetic polymers being used in existing marketed formulations. Hypertension is a leading cause of morbidity and mortality. Metoprolol succinate sustained release tablets that are already on the market are made with a variety of release-retarding polymers that are either synthetic or semi-synthetic in origin. Patients who take such medications consume a large amount of synthetic ingredients on a regular basis. Such polymers have a negative impact that much surpasses any therapeutic benefits. In this work, attempts were undertaken to replace it with natural polymers in order to create a formulation that would provide better release results than the existing formulation, degrade quickly, and have minimal adverse effects.

The main objectives of this work are:

1. To characterize the drug Metoprolol Succinate.
2. To prepare the calibration curve of Metoprolol Succinate.
3. To characterize the matrix former -natural gums.
4. To determine the perfect gum concentration required for sustaining the drug for over 24 hours.
4. To prepare mucilages of different gum combinations and ratios.
5. To prepare the different batches of SR tablets.
6. To characterize the prepared SR Metoprolol Succinate tablets:
    - Physical characterization
    - Drug-excipient compatibility studies
    - *in-vitro* drug release comparison to determine the best formulation
    - Erosion and water uptake study
7. To compare the prepared formulations with the existing marketed formulation.
8. To perform stability studies of the optimized formulation.

Chapter 5: STUDY DESIGN AND STRATEGY



Work Flow-chart in brief

- Determination of absorbance maxima and development of calibration curve of metoprolol succinate.
- Characterization of the gums- locust bean gum, xanthan gum and guar gum.
- Determination of the gum concentration to be used in the study.
- Development of the mucilages (binding agent) of different ratios.
- Granule preparation (wet-granulation).
- Preparation of metoprolol succinate SR tablets.
- Physical characterization.
- Drug-excipient compatibility studies.
- *in-vitro* drug release studies.
- Erosion and water uptake study
- Development of relationship between gum concentration and sustained-release effect.
- Comparison with marketed formulation.
- Stability study.

Chapter 6: MATERIALS AND METHODOLOGY

6.1 MATERIALS

Chemicals and Reagents used

Metoprolol succinate was collected as a gift sample from Dr. Reddy's Laboratories, Maharashtra, India. Analytical grade samples of xanthan gum, guar gum were obtained from SRL Laboratories Pvt. Ltd., (Maharashtra, India). Food quality grade locust bean gum was purchased from Urban platter (Istore Direct Trading Pvt. Ltd.). Other tablet excipients used were microcrystalline cellulose (MCC) (SRL Laboratories Pvt. Ltd., Maharashtra, India), magnesium stearate (LobaChemiePvt. Ltd., Mumbai, India), talc (NICE chemical Pvt. Ltd., Kerala, India). Analytical grade reagents used in buffer preparations were di-potassium hydrogen orthophosphate (potassium phosphate dibasic), potassium di-hydrogen orthophosphate (potassium phosphate monobasic), tri-sodium phosphate (NICE chemical Pvt. Ltd., Kerala, India), hydrochloric acid (Merck Ltd., Mumbai, India). All other minor chemicals used were of reagent grade.

Analytical Facilities and Equipments used

- Electronic balance (Precisa XB 600 M-C, readability of 0.001 g)
- pH meter (Eutech Instruments)
- Magnetic Stirrer (Tarsons)
- Digital vernier callipers
- Brookfield viscometer Model TV-10 (Toki Sangyo Co. Ltd., Tokyo, Japan)
- Rimek Mini Press-I tablet compression machine (10 stations)
- Tablet hardness tester (Erweka, TBH 125, Germany)
- Roche's friability tester (Electrolab)
- JASCO V-550 UV-Vis Spectrophotometer
- USP Type-II (paddle-type) dissolution apparatus (LABINDIA DS-8000)
- Shimadzu FT-IR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan)
- X-Ray Diffraction Analyzer (Rigaku corporation)
- DSC analysis instrument (Perkin Elmer, USA)
- Stability chamber (Osworld)

Instruments and Equipments that were used in this study are shown below*[Figure 5(A) –(K)]:*

(5A) Electronic balance

(5B) pH meter

(5C) Magnetic Stirrer

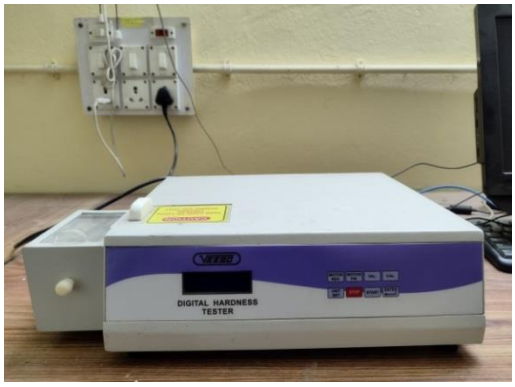
(5D) Brookfield viscometer

(5E) Millipore water

(5F) UV-Vis Spectrophotometer

5(G) Tablet compression machine

5(H) Roche's friability tester



5(I) Tablet hardness tester

5(J) USP Type-II dissolution apparatus

5(K) Stability chamber

6.2 DRUG PROFILE

Metoprolol Succinate, a cardioselective competitive beta-1 adrenergic receptor antagonist with antihypertensive qualities and no intrinsic sympathomimetic activity, is the succinate salt form of metoprolol. Metoprolol succinate inhibits beta 1-adrenergic receptors in the myocardium, which results in a decrease in cardiac output by slowing and/or blocking myocardial contraction. This substance may also lessen renin secretion, which would reduce angiotensin II levels and lessen sympathetic activation, including vasoconstriction and aldosterone release [34]. ***Figure 6*** shows the structure of metoprolol succinate.

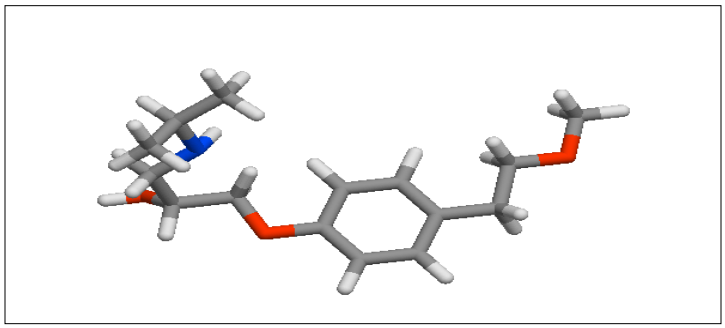


Figure 6: Structure of metoprolol succinate

IUPAC Name: Butanedioic acid;1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-ylamino)propan-2-ol

Therapeutic Class:β-blockers, anti-hypertensive.

Pharmacological Class: β1-selective (cardioselective) adrenoceptor blocker.

Molecular Formula: $C_{34}H_{56}N_2O_{10}$

Molecular weight:652.8

Solubility: It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptanes [35].

Appearance: Metoprolol succinate is a white crystalline powder

pK_a Value:9.7

log P Value: 1.76

$t_{1/2}$: 3-7 hrs

Pregnancy Risk Category:US FDA Category C

Melting Point:138°C

Storage temperature:15 to 30°C

Pharmacology:

Metoprolol is a β1-selective (cardioselective) adrenoceptor antagonist. However, this preferential effect is not absolute; at higher plasma concentrations, metoprolol also inhibits β2-adrenoreceptors, which are primarily found in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity can only be seen at plasma concentrations substantially higher than those required for β-blockade. Experiments on animals and humans show that metoprolol reduces the sinus rate and decreases AV nodal conduction. Clinical pharmacology studies in humans have confirmed metoprolol's β-blocking activity, as evidenced by (1) decreased heart rate and cardiac output at rest and during exercise, (2) decreased systolic blood pressure during exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) decreased reflex orthostatic tachycardia [36].

Various studies have established metoprolol's relative β1-selectivity: (1) Metoprolol is unable to reverse the β2-mediated vasodilating effects of epinephrine in normal people. This is in contrast to the impact of nonselective β-blockers, which entirely counteract epinephrine's vasodilating effects. (2) In asthmatic patients, at equal β1-receptor blocking doses, metoprolol lowers FEV1 and FVC considerably less than propranolol, a nonselective beta-blocker.

Pharmacokinetics

Plasma levels after oral delivery of typical metoprolol tablets, on the other hand, approximate 50% of levels after intravenous administration, indicating approximately 50% first-pass metabolism. Metoprolol passes through the blood-brain barrier and has been found in the CSF at 78% of the simultaneous plasma concentration. Following oral administration, plasma levels are highly variable. Only a small percentage of the drug (approximately 12%) is bound to human serum albumin. Metoprolol is largely metabolized by CYP2D6 and is a racemic mixture of R- and S -enantiomers. When taken orally, it exhibits stereoselective metabolism that is influenced by the oxidation phenotype. The liver is primarily responsible for elimination, and the plasma half-life ranges from 3 to 7 hours [37]. Less than 5% of an oral dose of metoprolol is recovered intact in urine; the remainder is eliminated by the kidneys as metabolites with no β-blocking activity. The urine recovery of unaltered metoprolol after intravenous injection is around 10%.

Metoprolol is mostly metabolized by CYP2D6, an enzyme that is missing in approximately 8% of Caucasians (poor metabolizers) and approximately 2% of most other groups. A variety of drugs can inhibit CYP2D6. Concurrent use of inhibitory medicines in poor metabolizers raises blood pressure. Metoprolol levels were increased severalfold, reducing metoprolol's cardioselectivity [36,37].

Indications and Usage

- **Hypertension:** Metoprolol succinate extended-release tablet is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.
- **Angina Pectoris:** Metoprolol succinate extended-release tablet is indicated in the long-term treatment of angina pectoris.
- **Heart Failure:** Metoprolol succinate extended-release tablet is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, metoprolol succinate extended-release tablet decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure [37].

Contraindications

Metoprolol succinate extended-release tablet is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome and in patients who are hypersensitive to any component of this product [36].

- **Ischemic Heart Disease:** Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol succinate extended-release tablets, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, metoprolol succinate extended-release tablet administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken [34]. Patients should be warned against interruption or discontinuation of therapy without the physician’s advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue metoprolol succinate extended-release tablet therapy abruptly even in patients treated only for hypertension
- **Bronchospastic Diseases:** Patients with bronchospastic diseases should, in general, not receive beta-blockers. Because of its relative beta1-selectivity, however, metoprolol succinate extended-release tablet may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta1- selectivity is not absolute, a beta2-stimulating agent should be administered

concomitantly, and the lowest possible dose of metoprolol succinate extended- release tablets should be used [34,37].

- **Major Surgery:** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. Metoprolol succinate extended-release tablet, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol [37]. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.
- **Diabetes and Hypoglycemia:** Metoprolol succinate extended-release tablets should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected [36].
- **Thyrotoxicosis:** Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism [37]. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.
- **Peripheral Vascular Disease:** Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals [34,36,37].
- **Calcium Channel Blockers:** Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly [36].

Precautions

In patients with compromised hepatic function, metoprolol succinate sustained-release tablets should be used with caution. In patients with pheochromocytoma, an alpha-blocking drugs should be started before any beta-blocking agent is used. During the up-titration of metoprolol succinate sustained-release tablets, cardiac failure may worsen. If these symptoms appear, diuretics should be increased, and the dose of metoprolol succinate sustained-release tablets should not be raised until clinical stability is achieved. Metoprolol succinate sustained-release tablet dosage may need to be reduced or discontinued temporarily. Such events do not impede successful titration of metoprolol succinate sustained-release tablets in the future [36,37].

Drug Interactions

When used with beta-blocking drugs, catecholamine-depleting pharmaceuticals (e.g., reserpine, monoamine oxidase (MAO) inhibitors) may have an additive impact. Patients taking metoprolol

succinate sustained-release tablets in combination with a catecholamine depletor should be continuously monitored for signs of hypotension or significant bradycardia, which can cause vertigo, syncope, or postural hypotension. Metoprolol concentrations are likely to rise when taking CYP2D6 inhibitors such as quinidine, fluoxetine, paroxetine, and propafenone. Beta-blockers may aggravate the rebound hypertension that might occur after clonidine discontinuation. If the two drugs are taken together, the beta blocker should be stopped several days before the clonidine. If a beta-blocker drug is used to replace clonidine, beta-blockers should be started several days after clonidine has been withdrawn [34,37].

Dosage

Metoprolol succinate sustained-release tablets are intended for once daily administration. For treatment of hypertension and angina, when switching from immediate release metoprolol to metoprolol succinate sustained -release tablet, the same total daily dose of metoprolol succinate sustained -release tablet should be used. Dosages of metoprolol succinate sustained -release tablets should be individualized and titration may be needed in some patients. Metoprolol succinate sustained -release tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed. In hypertension the usual initial dosage is 25 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied [34,36]

Adverse Reaction

Most adverse effects have been mild and transient [34,36,37].

- **Central Nervous System:** Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported.
- **Cardiovascular:** Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients.
- **Respiratory:** Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients.
- **Gastrointestinal:** Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, and heartburn have been reported in about 1 of 100 patients.

- **Hypersensitive Reactions:** Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.
- **Miscellaneous:** Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido, and tinnitus have also been reported. There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculo-mucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

6.3 POLYMER PROFILE

Three natural polymers were used in the study:

- **Locust bean gum**

Description: Carob bean gum is a natural product obtained from the endosperm of milled seeds from the fruit pod of *Ceratonia siliqua*. Carob bean gum is obtained from the macerated endosperm of the seeds of the fruit pod of the carob tree. This endosperm, comprising 42 to 46% of the kernel, contains virtually all of the galactomannan present in the seed. Galactomannan is not found in the kibble. Carob bean gum is used as a food stabilizer and thickener, a flavor and/or flavor modifier, an emulsifier, a texturizer and a solvent/ carrier/encapsulating agent [28,32].

Chemical Formula:$C_{10}H_{11}ClN_2O_2$

Structure: The chemical structure consists of a polymeric mannose chain branched with galactose units. The main chain consists of (1-4) linked beta-D mannose residues and the side chain of (1-6) linked alpha-D galactose [29,31,32] as shown in ***Figure 7***.

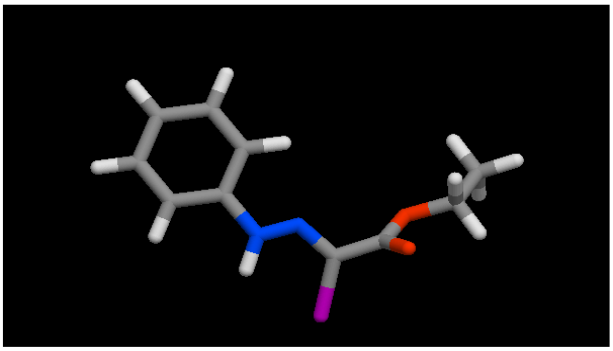


Figure 7: Structure of Locust bean gum

Molecular Weight: 226.65954

Form: Solid

Color: Off-White to Light Beige

Solubility: Ceratonia is dispersible in hot water, forming a sol having a pH 5.4–7.0 that may be converted to a gel by the addition of small amounts of sodium borate. In cold water, ceratonia hydrates very slowly and incompletely. Ceratonia is practically insoluble in ethanol [29].

Viscosity:1200-2500mPas for a 1% w/v aqueous dispersion at 25°C

Melting Point:>200°C

Pharmaceutical Uses: Ceratonia is a naturally occurring material generally used as a substitute for tragacanth or other similar gums. A ceratonia mucilage that is slightly more viscous than tragacanth mucilage may be prepared by boiling 1.0–1.5% of powdered ceratonia with water. As a viscosity-increasing agent, ceratonia is said to be five times as effective as starch and twice as effective as tragacanth.

Ceratonia has also been used as a tablet binder and is used in oral controlled-release drug delivery systems approved in Europe and the USA. Ceratonia is widely used as a binder, thickening agent, and stabilizing agent in the cosmetics and food industry. In foods, 0.15–0.75% is used. Therapeutically, ceratonia mucilage is used orally in adults and children to regulate intestinal function [28-32].

Storage: The bulk material should be stored in a well-closed container in a cool, dry place. Ceratonia loses not more than 15% of its weight on drying.

Incompatibilities: The viscosity of xanthan gum solutions is increased in the presence of ceratonia. This interaction is used synergistically in controlledrelease drug delivery systems [30].

- **Xanthan Gum**

Description: Xanthan Gum is a high molecular weight gum produced by a pure-culture fermentation of a carbohydrate with *Xanthomonas campestris*, then purified by recovery with Isopropyl Alcohol, dried, and milled. 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. It yields NLT 4.2% and NMT 5.0% of carbon dioxide, calculated on the dried basis, corresponding to NLT 91.0% and NMT 108.0% of Xanthan Gum [26].

Chemical Formula:C8H14Cl2N2O2

Structure: β-1,4-glycosidic bond-linked main chain and a trisaccharide side chain successively containing mannose, glucuronic acid, and mannose. ***Figure 8*** depicts the structure of Xanthan gum.

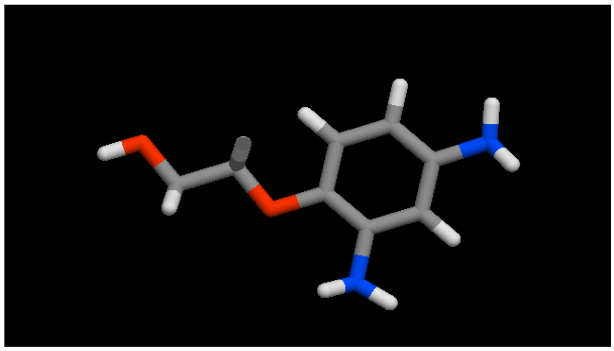


Figure 8: Structure of Xanthan gum

Molecular Weight:241.11496

Form: Solid

Color: Off-White to Pale Yellow

Solubility: Soluble in water giving a highly viscous solution, practically insoluble in organic solvents.

Viscosity:viscosity of 1% solution 1,200-1,600 mPas

Melting Point:64.43 °C

Pharmaceutical Uses: 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. Xanthan gum has been used as a suspending agent for conventional, dry and sustained-release suspensions. When xanthan gum is mixed with certain inorganic suspending agents, such as magnesium aluminum silicate, or organic gums, synergistic rheological effects occur. Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets. Xanthan gum has also been used to produce directly compressed matrices that display a high degree of swelling due to water uptake, and a small amount of erosion due to polymer relaxation. It has also been used in combination with chitosan, guar gum, galactomannan, and sodium alginate to prepare sustained-release matrix tablets. Xanthan gum has been used as a binder, and in combination with Konjac glucomannan is used as an excipient for controlled colonic drug delivery. Xanthan gum has also been used with guar gum for the development of a floating drug delivery system. It has also has derivatized to

sodium carboxymethyl xanthan gum and cross-linked with aluminum ions to prepare microparticles, as a carrier for protein delivery. 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 pre-corneal area [26,33].

When added to liquid ophthalmics, xanthan gum delays the release of active substances, increasing the therapeutic activity of the pharmaceutical formulations.Xanthan gum can be used to increase the bioadhesive strength in vaginal formulations. Xanthan gum alone or with carbopol 974P has been used as a mucoadhesive controlled-release excipient for buccal drug delivery. Xanthan gum can also be used as an excipient for spray-drying and freeze-drying processes for better results. It has been successfully used alone or in combination with agar for microbial culture media.
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. Polyphosphate with xanthum gum in soft drinks is suggested to be effective at reducing erosion of enamel.

Storage: 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.

Incompatibilities: Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives, as precipitation occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of xanthan gum from a solution. Under highly alkaline conditions, polyvalent metal ions such as calcium cause gelation or precipitation; this may be inhibited by the addition of a glucoheptonate sequestrant. The presence of low levels of borates (<300 ppm) can also cause gelation. This may be avoided by increasing the boron ion concentration or by lowering the pH of a formulation to less than pH 5. The addition of ethylene glycol, sorbitol, or mannitol may also prevent this gelation. Xanthan gum is compatible with most synthetic and natural viscosity-increasing agents, many strong mineral acids, and up to 30% inorganic salts. If it is to be combined with cellulose derivatives, then xanthan gum free of cellulase should be used to prevent depolymerization of the cellulose derivative. Xanthan gum solutions are stable in the presence of up to 60% water-miscible organic solvents such as acetone, methanol, ethanol, or propan-2- ol.

However, above this concentration precipitation or gelation occurs.
The viscosity of xanthan gum solutions is considerably increased, or gelation occurs, in the presence of some materials such as ceratonia, guar gum, and magnesium aluminum silicate. This effect is most pronounced in deionized water and is reduced by the presence of salt. This interaction may be desirable in some instances and can be exploited to reduce the amount of xanthan gum used in certain formulations.Xanthan gum is incompatible with oxidizing agents, some tablet film-coatings, carboxymethylcellulose sodium, dried aluminum hydroxide gel, and some active ingredients such as amitriptyline, tamoxifen, and verapamil [38-40].

- **Guar Gum**

Description: Guar gum, like locust bean gum, is a galactomannan derived from the seed of a leguminous plant. The source of guar, Cyamopsis tetragonolobus, is widely grown in Pakistan and India as cattle feed, and was introduced to the United States as a cover crop in 1903. The U.S. is now also a producer. It was not until 1953, however, that guar gum was produced on a commercial scale, primarily as a replacement for locus bean gum in the paper, textile and food industries. The most important property of guar is the ability to hydrate rapidly in cold water to attain a very high viscosity. In addition to the food industry, guar is used in the mining, paper, textile, ceramic, paint, cosmetic, pharmaceutical, explosive, and other industries. The guar is a hardy and drought-resistant plant which grows three to six feet high with vertical stalks. The guar pods, which grow in clusters along the vertical stems, are about six inches long and contain 6 to 9 seeds, which are considerably smaller than locus bean seeds. As in the case of locust bean gum, the endosperm, which comprises 35-42% [31,33].

Chemical Formula: $C_{10}H_{14}N_5Na_2O_{12}P_3$

Structure: Consists of the high molecular weight polysaccharides of galactomannans which are linear chain of (1 → 4)-linked β-D-mannopyranosyl units with (1 → 6)-linked α-D-galactopyranosyl residues [33] as side chains as shown in ***Figure 9***.

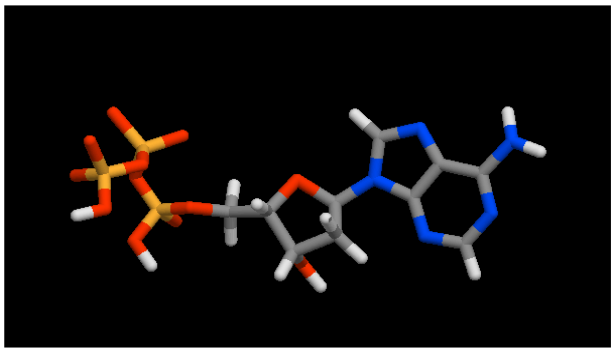


Figure 9: Sructure of Guar gum

Molecular Weight: 535.145283

Form: Free Flowing Powder

Color: Yellow-white

Solubility: It yields a mucilage of variable viscosity when dissolved in water, practically insoluble in ethanol (96 per cent).

Viscosity: 350 to 700 mPa-s(1 %, H2O, 20 °C, calcd.on dried substance)

Melting Point: >220°C

Pharmaceutical Uses: Guar gum is a galactomannan, commonly used in cosmetics, food products, and pharmaceutical formulations. It has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose. In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant; in oral and topical products as a suspending, thickening, and stabilizing agent; and also as a controlled-release carrier. Guar gum has also been examined for use in colonic drug delivery. Guar-gum-based three-layer matrix tablets have been used experimentally in oral controlled-release formulations.Therapeutically, guar gum has been used as part of the diet of patients with diabetes mellitus. It has also been used as an appetite suppressant, although its use for this purpose, in tablet form, is now banned in the UK[31,33,41].

Storage: Aqueous guar gum dispersions have a buffering action and are stable at pH 4.0–10.5. However, prolonged heating reduces the viscosity of dispersions.The bacteriological stability of guar gum dispersions may be improved by the addition of a mixture of 0.15% methylparaben and 0.02% propylparaben as a preservative. In food applications, benzoic acid, citric acid, sodium benzoate, or sorbic acid may be used.
Guar gum powder should be stored in a well-closed container in a cool, dry place [31].

Incompatibilities: Guar gum is compatible with most other plant hydrocolloids such as tragacanth. It is incompatible with acetone, ethanol (95%), tannins, strong acids, and alkalis. Borate ions, if present in the dispersing water, will prevent the hydration of guar gum. However, the addition of borate ions to hydrated guar gum produces cohesive structural gels and further hydration is then prevented. The gel formed can be liquefied by reducing the pH to below 7, or by heating.Guar gum may reduce the absorption of penicillin V from some formulations by a quarter [33,41].

6.4 METHODOLOGY

CHARACTERIZATION OF THE DRUG SAMPLE

Solubility

5 mg of the drug sample was added to 500 µl of different solvents (distilled water, buffer systems, methanol, ethanol and acetone) and it was subjected to vortex for 5 min to check the solubility of the drug.

Determination of absorption maxima and calibration curve of Metoprolol succinate

1. Determination of λ_{max}

5 mg of metoprolol succinate was dissolved in 50 ml of pH 1.2 acidic buffer and pH 6.8 phosphate buffer respectively to check λ_{max} in both the solvents. The UV-Spectrophotometric analysis was carried for the determination of absorption maxima (λ_{max}) in the range of 200 to 400 nm using JASCO V-550 UV-Vis Spectrophotometer. The observed λ_{max} was compared with the reference value [42].

2. Preparation of pH 1.2 acidic buffer

To prepare 1 liter of pH 1.2 acidic buffer, 3.7 g of potassium chloride and 7 ml of hydrochloric acid was taken in a 1000 ml volumetric flask and volume was made up to 1 liter with distilled water.

3. Preparation of pH 6.8 phosphate buffer

To prepare 1 liter of pH 6.8 phosphate buffer, 7.956 g of di-potassium hydrogen orthophosphate (potassium phosphate dibasic) and 7.394 g of potassium di-hydrogen orthophosphate (potassium phosphate monobasic) were taken in a 1000 ml volumetric flask and volume was made up to 1 liter with distilled water.

4. Metoprolol succinate stock solution (pH 1.2 acidic buffer)

Standard stock solution of metoprolol succinate (100 µg/ml) was prepared by dissolving 5 mg of the drug in 50 ml of pH 1.2 acidic buffer.

5. Metoprolol succinate stock solution (pH 6.8 phosphate buffer)

Standard stock solution of metoprolol succinate (100 µg/ml) was prepared by dissolving 5 mg of the drug in 50 ml of pH 6.8 phosphate buffer.

6. Development of standard calibration curve in pH 1.2

The stock solution prepared (100 µg/ml) was further diluted to get solutions of various concentrations ranging from 5 to 30 µg/ml. The absorbance was measured at 222 nm against pH 1.2 acidic buffer as blank.

7. Development of standard calibration curve in pH 6.8

The stock solution prepared (100 µg/ml) was further diluted to get solutions of various concentrations ranging from 5 to 30 µg/ml. The absorbance was measured at 222 nm against pH 6.8 phosphate buffer as blank.

PREPARATION OF MUCILAGE

The use of the polysaccharide powders included using each separately, in pairs, and in various ratios. Mucilage was prepared by gradually adding distilled water to the polysaccharide powder while stirring it with a magnetic stirrer. 3.33% polysaccharide powder of total tablet weight was used to prepare the mucilage. Various concentrations and ratios of the physical mixtures of the gums were used*[Refer Chapter 7; Table 3]*.***Figure 10*** depicts the mucilage prepared.

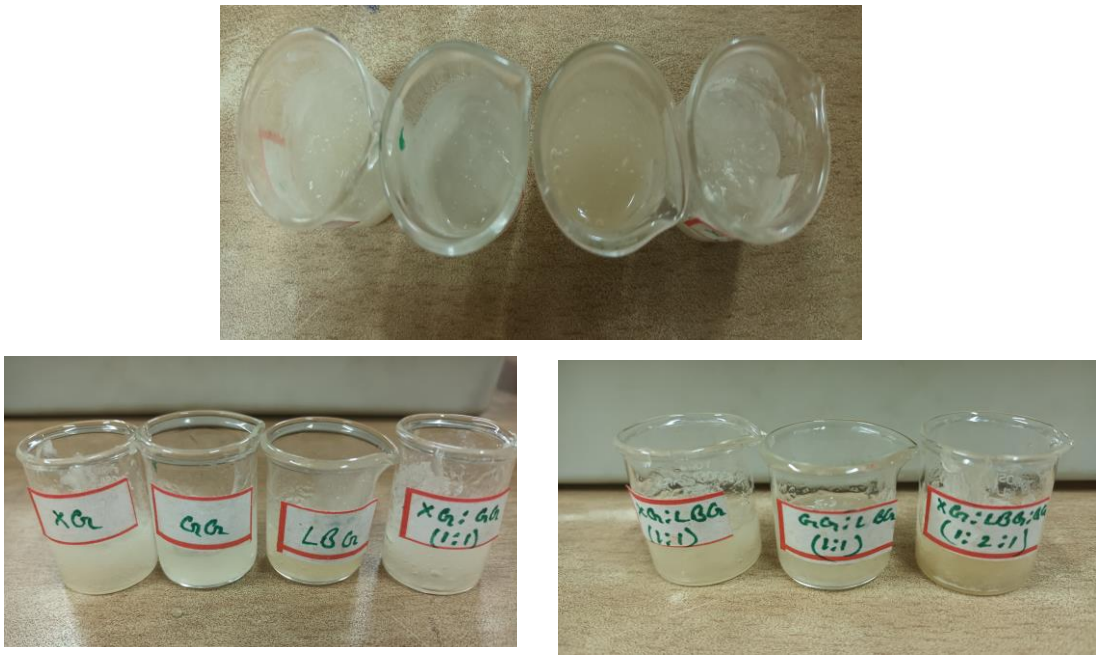


Figure 10: Various concentrations and ratios of mucilages prepared

CHARACTERIZATION OF MUCILAGE

The viscosity of the gum mucilage was determined using Brookfield viscometer Model TV-10 (Toki Sangyo Co. Ltd., Tokyo, Japan) spindle no.M2 (21) at rpm 60 in cgs unit in triplicate (n=3). The test was done at standard conditions. Here standard conditions referred to RT (room temperature of 25°C) and 1 atm (atmospheric pressure).

PREPARATION OF GRANULES

The granules were prepared by the wet granulation technique. The prepared mucilage served as the binding agent. The active ingredient metoprolol succinate was mixed properly with MCC used as diluent. The aforementioned mixture was used to prepare a wet mass or dough by using the previously prepared mucilage as binding agent. The dough was then passed through sieve #20 to obtain a uniform size of granules and dried at 40°C for 30 mins in a tray dryer keeping the moisture content around 1% [43]. The dried granules were then lubricated with talc and magnesium stearate and mixed for about 10 mins.

CHARACTERIZATION OF GRANULES

The granules prepared were subjected to evaluation by the angle of repose, compressibility index (CARRs index) and Hausner's ratio to understand the flow properties of the granules [44-46]. Bulk density and tapped density were used to determine CARRs index and Hausner's ratio. The angle of repose was determined by fixed funnel method [47].

1. Bulk density

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in grams per mL (g/mL) although the international unit is kilograms per cubic meter (1 g/mL = 1000 kg/m3) because the measurements are made using cylinders [44,46]. It may also be expressed in grams per cubic centimeter (g/cm3) and is given by:

$$D_b = M/V_b$$

Where M and V_b are mass of powder and bulk volume of the powder respectively.

2. Tapped density

Tapped density of a powder is the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time. The tapped density of a powder represents its random dense packing [47]. The tapped density is also expressed in grams per mL (g/mL) although the international unit is kilograms per cubic meter (1 g/mL = 1000 kg/m3) because the measurements are made using cylinders [46,47]. It may also be expressed in grams per cubic centimeter (g/cm3) and is given by:

$$\mathbf{D_{t=} M/V_t}$$

Where M and V_t are mass of powder and tapped volume of the powder respectively.

3. Hausner's ratio

Hausner's ratio is an ease of index of powder flow *[Refer Table 4]*. It is calculated by using the following formula:

Hausner's ratio= Tapped density/Bulk density

4. Compressibility index

Compressibility index of the powder is determined by Carr's index *[Refer Table 5]* and is given by:

$$\mathbf{Carr'sindex(\%)= \{(D_t- D_b)/ D_t\} x 100}$$

DRUG EXCIPIENTS COMPATIBILITY STUDIES

To ascertain whether any sort of interaction is occurring or not, chemical compatibility tests between the drug, gums, and excipients were performed. Fourier transforms infrared spectrophotometer (FTIR) analysis, X-ray diffraction (XRD) analysis and Differential scanning calorimetry (DSC) were used to examine the drug-excipient compatibility.

1. Fourier transforms infra-red spectrophotometer (FTIR) analysis

FTIR analysis were done on Shimadzu FT-IR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan) by using potassium bromide (KBr) pellet technique and scanned in the wavelength range 500-4500 cm^{-1}.Small amount (1-2 mg) of powdered pure drug, physical mixes of pure drug,

gums, and excipients before and after granulation were used and combined in a 1:6 ratio with KBr (sample: KBr). This was then put into a tiny die and maintained there for five minutes under mechanical pressure of roughly five tonnes to create KBr pellets. The resulting pellets were then scanned in the designated range.

2. X-ray diffraction (XRD) analysis

XRD analysis was done using X-Ray Diffraction Analyzer (Rigaku corporation). The sample was examined with a scanning speed of 5°/min over a 2θ range of 0-70°. XRD analysis is based on the principle of constructive interference of monochromatic X-rays and indicates the crystalline or amorphous nature of the compound.

3. Differential Scanning Calorimetry (DSC) analysis

DSC analysis (Perkin Elmer, USA) was carried out to characterize the thermal behaviour of the drug and the polymers in the final formulation. Ultrahigh purity nitrogen gas was purged at a flow rate of 20 ml/min. Approximately 3 mg of the sample was used to carry out the analysis. A heating rate of 10°C/min was maintained from 25 to 250°C for the study.

PREPARATION OF SUSTAINED RELEASE MATRIX TABLETS

Sustained release metoprolol succinate tablets were prepared by wet granulation technique as shown in ***Figure 11***. The granules prepared by wet granulation technique were compressed using Rimek Mini Press-I tablet compression machine (10 stations).The average weight of each tablets formed were 300 mg with hardness of 7.5 kg/cm^2. Biconvex punch of 10 mm was used in the process. *[Refer Chapter 7; Table 6 & 7]* for the summary of the composition and the different formulations prepared respectively.

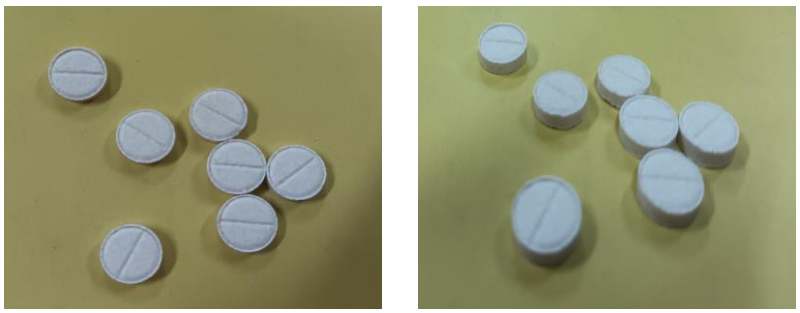


Figure 11: Metoprolol succinate SR tablets prepared

EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS

Physicochemical evaluations were done as per the standard protocols. To assess the homogeneity of the formulations, drug content was performed. To obtain the ideal release profile, in-vitro dissolution tests that mimicked the gastro-intestinal tract (GIT) environment were conducted. An understanding of the drug's release mechanism from the formulation was provided by water-uptake analysis. Finally stability studies were conducted to check the degradation compatibility with time.

1. Physical characterization

Diameter and thickness of the tablets were determined by Digital vernier callipers. USP method using tablet hardness tester (Erweka, TBH 125, Germany) was used to test the hardness of the tablets taking n=10 tablets in random. A set of 20 tablets from each formulation of the metoprolol succinate SR tablet were weighed using a digital precision balance (Precisa XB 600 M-C, readability of 0.001 g), and the weight variation test was carried out in accordance with the official technique, taking a weight variation limit of ±5% into consideration [43,48]. 20 tablets of metoprolol succinate SR tablets were taken and weighed (W1), and they were rotated in a Roche's friability tester (Electrolab) at speed of 25 rpm for 4 min. Then, the tablets were reweighed and noted as W2. The weight difference in percentage was noted and expressed as a percentage as [48]:

$$[(W1 - W2)*100/W1]$$

2. Drug content

Content uniformity of the prepared metoprolol succinate SR tablets was examined by using UV-Vis spectroscopy method. A set of 10 (n=10) tablets from each formulation were taken in random and triturated using mortar pestle. The powdered form was then transferred to a 100 ml volumetric flask containing 50 ml of pH 1.2 acidic buffer. The contents were filtered through a 0.45µ filter and then washed with a pH-1.2 acidic buffer to bring the volume up to the desired level. Additionally, the sample was appropriately diluted before being evaluated spectrophotometrically at 222 nm (λ_{max} of metoprolol succinate) using a JASCO V-550 UV-Vis Spectrophotometer in comparison to a blank (pH 1.2 acidic buffer). In line with USP 905 [49,50], acceptance values were evaluated.

3. *in-vitro* dissolution studies

The *in-vitro* drug release was done using USP Type-II (paddle-type) dissolution apparatus (LABINDIA DS-8000). 900 ml of acidic buffer (pH 1.2) was employed as the dissolution medium for the first 2 hrs followed by phosphate buffer (pH 6.8) for the rest 24 hrs at a paddle speed of 75 rpm. The buffer step was brought to pH 6.8 using tri-sodium phosphate. Temperature of the medium was maintained at 37±0.5°C. Sample aliquots of 5 ml were withdrawn at required intervals. Test was continued over 24-hour duration with samplings done at intervals of 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24. The samples withdrawn were analyzed spectrophotometrically at 222 nm for metoprolol using a JASCO V-550 UV-Vis Spectrophotometer in comparison to a blank of pH 1.2 acidic buffer for the samples upto 2 hrs and pH 6.8 phosphate buffer for the remaining samples.

4. Erosion and water-uptake of tablets

The swelling behaviour of the metoprolol succinate SR tablet played the main role in determining the release mechanism of the drug. Swelling of the gum indicated the rate of water uptake by the formulation, erosion of the matrix and drug release. Percentage of water uptake by the tablets prepared was tested separately for the formulations F5B, F5C and F5D in triplicate. Dry weight was taken before starting the test. The tablets were subjected to 100 ml of medium (pH 1.2 acidic buffer and pH 6.8 phosphate buffer) under the condition same as described for dissolution testing. After the specified intervals of time the tablets were removed, patted with tissue paper and weighed to get the wet weight. The following equation was used to determine the percent water uptake.

% water uptake = [(Wet tablet weight – dry tablet weight)*100/ wet tablet weight]

STABILITY STUDY

According to the International Conference on Harmonization's guidelines, stability studies were conducted. Drug along with the excipients and polymersutilised were placed within a sealed 40 ml HDPE container with a child-resistant cap inside a stability chamber (Osworld, India) under controlled temperature conditions at 40°C±0.5°C/75±5% RH for 6 months. At certain intervals (2 month, 4 months, and 6 months), the sample was removed and its composition and *in-vitro* release assessed. Analysis of the variances and comparison with the formulationsF5B, F5C and F5D were done.

DRUG RELEASE KINETICS MODEL

The release kinetics of metoprolol succinate from the prepared metoprolol succinate SR tablets was determine by finding the best fit of the curve (% release against time) to distinct models [51].

Zero-order Kinetics

The pharmaceutical dosage forms following zero-order kinetics, release the same amount of drug per unit time and it is ideal method of drug release in order to achieve a prolonged pharmacological action. For this model, a graph of percent drug release versus time will be linear i.e. the drug release is independent of it's concentration in the system. The following relation can express this model is a simple way:

$$\mathbf{Q_t = Q_0 + K_0 t}$$

Where, Q_t is the amount of drug released in time=t, Q_0 is the initial amount of drug in the solution (most timesQ_0=0) and K_0 is the zero-order release rate constant.

First-order Kinetics

The pharmaceutical dosage forms following this kinetics profile, such as those containing water soluble drugs in porous matrices release the drug in a way that is proportional to the amount of drug released by unit of time diminishes. This model can be expressed as:

$$\mathbf{\ln Q_t = \ln Q_0 - K_1 t}$$

Where, Q_t is the amount of drug released in time=t, Q_0 is the initial amount of drug in the solution and K_1 is the first-order release rate constant.

Higuchi Model

In 1963 Higuchi developed several theoretical models to study the release of water soluble and poorly soluble drugs incorporated in semi solid and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. In a general way, Higuchi model may be expressed as:

$$\mathbf{Q = K_h t^{1/2}}$$

Where, Q is the amount of drug released in time=t per unit area, K_h is the Higuchi dissociation constant.

This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms.

Korsemeyer-Peppas Model

In 1983 Korsemeyer*et al.* developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time=t, which can be described as,

$$\ln (Q_t/Q_\infty) = \ln K + n \ln t$$

Where, Q_t/Q_∞ is the fraction of drug released at time=t and K is the rate constant comprising the structural and geometric characteristics of the formulation and n is the release exponent. For the determination of exponent n the portions of the release of pharmaceutical dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved.

n=0.45 indicates Fickian diffusion, $0.45<n<0.89$ indicates Anomalous transport or non-Fickian diffusion (both diffusion and erosion), n=or >0.89 indicates Case-II transport (erosion of the polymeric chain).

Chapter 7: TABLES AND GRAPHS

7.1 TABLES

Table 1: Physicochemical factors of drug selection for SR formulation

Parameter	Preferred value
Molecular weight/size	< 1000 Daltons Solubility
Solubility	> 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

Table 2: Pharmacokinetic factors of drug selection for SR formulation

Parameter	Comment
Elimination half-life	Preferably between 2 to 8 hrs
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution (Vd)	The larger Vd and MEC, the larger will be the required dose size
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration (Css)	The lower Css and smaller Vd, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Table 3:Mucilage content in ratios and description

Sl. No.	Mucilage code	Ratio	Gum concentration
1	M1A	-	3.33% GG of total tab wt.
2	M1B	-	3.33% XG of total tab wt.
3	M1C	-	3.33% LBG of total tab wt.
4	M2A	1:1 of GG:XG	1.667% GG & XG of total tab wt. each
5	M2B	1:1 of LBG:XG	1.667% LBG & XG of total tab wt. each
6	M2C	1:1 of GG:LBG	1.667% GG & LBG of total tab wt. each
7	M3A	1:3 of XG:LBG	0.833% XG, 2.5% LBG of total tab wt.
8	M3B	1:3 of LBG:XG	0.833% LBG, 2.5% XG of total tab wt.
9	M4A	1:5 of XG:LBG	0.557% XG, 2.777% LBG of total tab wt.
10	M4B	1:5 of LBG:XG	0.557% LBG, 2.777% XG of total tab wt.
11	M5A	1:1:1 of XG:LBG:GG	1.11% of total tab wt.
12	M5B	1:2:1 of XG:LBG:GG	0.833% XG & GG, 1.667% LBG of total tab wt.
13	M5C	1:2:1 of LBG:XG:GG	0.833% LBG & GG, 1.667% XG of total tab wt.
14	M5D	1.5:1.5:1 of XG:LBG:GG	1.25% XG & LBG, 0.833% GG of total tab wt.

Table 4:Hausner's ratio and flow character

Hausner Ratio	Flow Character
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

Table 5:Carr's index and flow character

Compressibility index	Flow Character
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

Table 6: Composition of the Metoprolol succinate SR tab

Composition	Amount (mg) per tablet	Percentage (%) per tablet
Metoprolol succinate[#]	47.5	15.83
Gums	10	3.33
MCC	234	78
Mg Stearate	3.5	1.67
Talc	5	1.67
Total	300	100

[#] 47.5 mg Metoprolol succinate is equivalent to 50 mg of Metoprolol tartrate

Table 7: Different formulations of metoprolol succinate matrix based tablets using natural gum mucilage

Formulation code	F1A	F1B	F1C	F2A	F2B	F2C	F3A	F3B	F4A	F4B	F5A	F5B	F5C	F5D
Mucilage used	M1A	M1B	M1C	M2A	M2B	M2C	M3A	M3B	M4A	M4B	M5A	M5B	M5C	M5D

Table 8: Measured viscosities of the various gum combinations (at RT=25°C and 1 atm)

Mucilage code	Viscosity (mPa.S) mean±SD[*]	
M1A	473±2.65	Individual gum
M1B	766±4.58	
M1C	850±2.00	
M2A	511±1.73	Gum pair ratio 1:1
M2B	1156±3.61	
M2C	771±4.58	
M3A	1230±2.00	Gum pair ratio 1:3
M3B	1189±3.46	
M4A	1399±2.65	Gum pair ratio 1:5
M4B	1274±4.36	
M5A	1421±3.61	Blend of 3 gums in ratios 1:1:1, 1:2:1, 1.5:1.5:1
M5B	1869±3.61	
M5C	1765±2.65	
M5D	1790±2.65	

[*] n=3, values are expressed as mean±SD (Standard deviation)

Table 9: Characteristics of the granules

Formulation code	Angle of repose(θ°) mean±SD*	Bulk density(g/cm^3) mean±SD*	Tapped density(g/cm^3) mean±SD*	Carr's Index (%)	Hausner's ratio
F1A	23.72±0.121	0.369±0.023	0.425±0.006	13.18	1.15
F1B	25.95±1.186	0.382±0.082	0.489±0.004	21.88	1.28
F1C	26.99±0.366	0.428±0.006	0.526±0.005	18.63	1.23
F2A	25.23±0.289	0.367±0.008	0.463±0.007	20.73	1.26
F2B	27.82±0.861	0.489±0.028	0.577±0.004	15.25	1.18
F2C	24.55±0.284	0.356±0.013	0.462±0.004	22.94	1.30
F3A	27.89±0.540	0.466±0.016	0.592±0.006	21.28	1.27
F3B	26.43±0.095	0.396±0.031	0.472±0.004	16.10	1.19
F4A	25.34±0.815	0.381±0.007	0.477±0.004	20.13	1.25
F4B	26.22±0.833	0.87±0.008	0.432±0.004	10.42	1.12
F5A	26.58±0.105	0.487±0.009	0.591±0.012	17.60	1.21
F5B	27.29±0.296	0.498±0.019	0.566±0.003	12.01	1.14
F5C	26.25±0.824	0.379±0.075	0.458±0.008	17.25	1.21
F5D	26.89±0.141	0.469±0.025	0.549±0.006	14.58	1.17

* n=3, values are expressed as mean±SD (Standard deviation)

Table 10: Physical tableting properties of SR metoprolol succinate tablets

Formulation code	Diameter (mm) mean±SD*	Thickness (mm) mean±SD*	Friability (%) (n=20) mean±SD*	Hardness (kg/cm^2) (n=10) mean±SD*	Weight variation (mg) (n=20) mean±SD*
F1A	10.02±0.05	2.75±0.02	0.13±0.09	6.58±0.03	301±2.65
F1B	10.01±0.02	2.77±0.03	0.11±0.01	7.5±0.02	299±2.65
F1C	9.99±0.01	2.74±0.01	0.16±0.05	6.69±0.03	299±1.00
F2A	10.01±0.01	2.75±0.03	0.14±0.05	7.12±0.02	298±1.73
F2B	10.03±0.01	2.75±0.04	0.15±0.03	6.79±0.04	302±1.00
F2C	9.98±0.02	2.74±0.03	0.11±0.03	6.99±0.05	301±2.00
F3A	10.01±0.04	2.74±0.03	0.11±0.04	7.02±0.10	297±4.00
F3B	10.01±0.01	2.74±0.04	0.13±0.04	7.06±0.04	297±2.65
F4A	9.99±0.04	2.76±0.03	0.17±0.02	7.29±0.04	299±3.46
F4B	10.02±0.03	2.75±0.04	0.15±0.03	6.85±0.03	299±2.00
F5A	10.01±0.01	2.77±0.03	0.14±0.03	7.45±0.03	298±2.65
F5B	10.01±0.03	2.77±0.02	0.12±0.05	7.5±0.02	297±5.00
F5C	9.99±0.01	2.75±0.03	0.13±0.04	7.63±0.04	301±3.00
F5D	10.01±0.01	2.75±0.03	0.11±0.03	7.28±0.03	302±3.00

* n=3, values are expressed as mean±SD (Standard deviation)

Table 11: Assay of the prepared SR metoprolol succinate batches

Formulation Code	Assay%mean±SD*
F1A	99.64±0.72
F1B	101.32±3.17
F1C	101.32±2.12
F2A	97.42±2.64
F2B	100.68±0.79
F2C	97.11±4.20
F3A	102.11±3.66
F3B	98.23±3.35
F4A	102.03±1.39
F4B	97.99±1.55
F5A	100.36±1.53
F5B	101.75±1.66
F5C	101.51±1.63
F5D	99.31±1.37

* n=3, values are expressed as mean±SD (Standard deviation)

Table 12: Cumulative % release of significant formulations and marketed formulation

Time (inhrs)	Cumulative % release(F5B)	Cumulative % release(F5C)	Cumulative % release(F5D)	Cumulative % release(PROLOMET XL 50mg)
0	0	0	0	0
0.5	9.57±2.85	6.67±2.18	6.54±2.18	6.77±2.24
1	16.69±2.95	13.54±2.61	13.25±2.78	13.58±2.91
1.5	23.43±3.19	20.58±3.46	20.09±2.09	20.35±2.73
2	30.22±2.91	27.80±1.92	27.02±5.20	27.12±2.51
3	37.20±2.64	34.37±2.78	33.22±2.92	33.17±4.60
4	42.38±2.55	41.07±2.02	39.55±2.45	39.25±2.88
6	48.49±3.38	47.88±4.21	45.94±3.11	45.33±1.83
8	54.56±2.96	54.79±3.71	52.39±2.29	51.44±3.01
10	60.64±2.47	61.75±3.53	58.90±2.21	57.59±4.02
12	66.84±3.16	68.81±2.57	65.47±2.82	63.76±4.49
14	72.87±2.48	75.97±2.84	72.13±2.75	69.96±3.20
16	79.26±2.66	83.27±2.29	78.82±1.56	76.20±2.39
18	85.50±2.70	90.70±3.83	85.54±3.02	82.49±2.16
20	91.77±3.89	98.27±2.61	92.33±1.92	88.82±2.18
22	98.35±2.77		99.20±2.79	95.18±3.52
24	104.99±2.55			101.56±1.55

Table 13: Stability and compatibility study

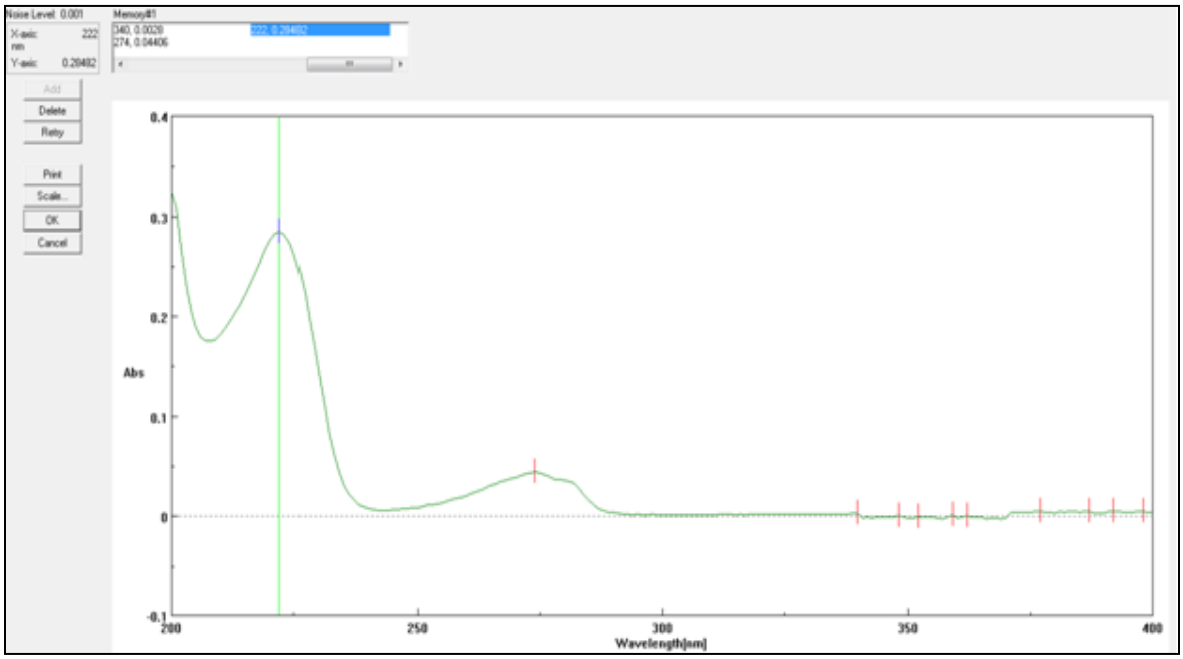
Sample	Physical Appearance	Initial condition	Time Period		
			After 2 months	After 4 months	After 6 months
Drug+ LBG	Nature Colour	Solid, powder Light beige	No change	No change	No change
Drug+ XG	Nature Colour	Solid, powder Off-white	No change	No change	No change
Drug+ GG	Nature Colour	Solid, powder Pale-yellow	No change	No change	No change
Drug+ MCC	Nature Colour	Solid, powder White	No change	No change	No change
Drug+ Mg Stearate	Nature Colour	Solid, powder White	No change	No change	No change
Drug+ Talc	Nature Colour	Solid, powder White	No change	No change	No change
F5B	Nature Colour	Solid, tablet Off-White	No change	No change	No change
F5C	Nature Colour	Solid, tablet Off-White	No change	No change	No change
F5D	Nature Colour	Solid, tablet Off-White	No change	No change	No change

Table 14: Correlation coefficient (R^2) values of different release kinetics

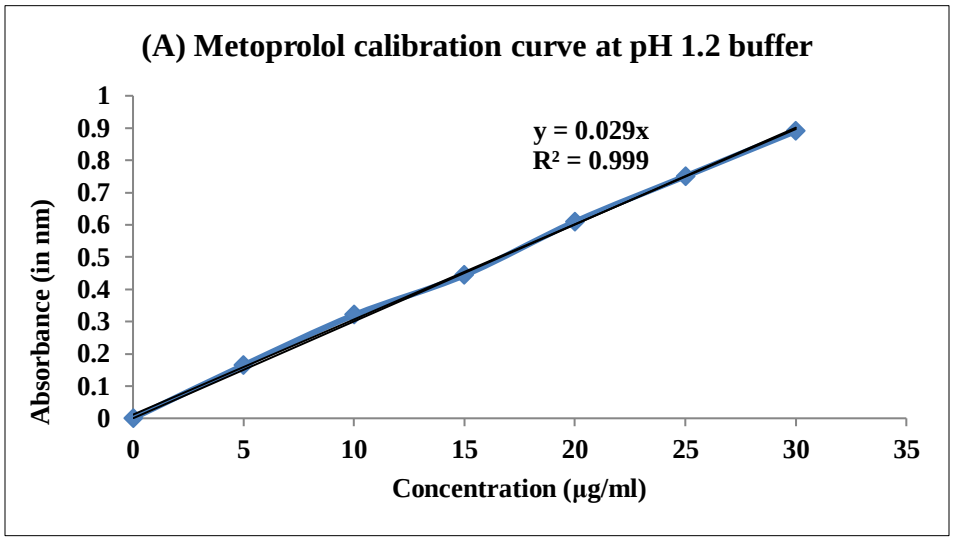
Formulation code	Correlation coefficient (R^2)				
	Zero-order	First-order	Higuchi	Korsemeyer-Peppas	Hixson-Crowell
F5B	0.951	0.808	0.992	0.982	0.837
F5C	0.956	0.815	0.991	0.973	0.839
F5D	0.958	0.815	0.991	0.974	0.840
PROLOMET XL	0.958	0.813	0.992	0.975	0.842

7.2 GRAPHS

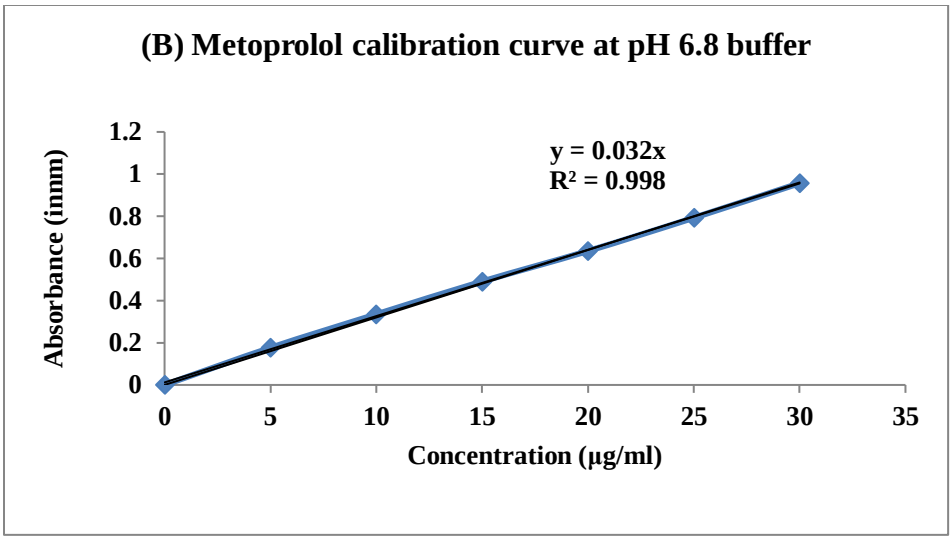
Graph 1: λ_{max} of Metoprolol Succinate



Graph 2: Standard calibration curve at pH 1.2 and 6.8 buffer respectively

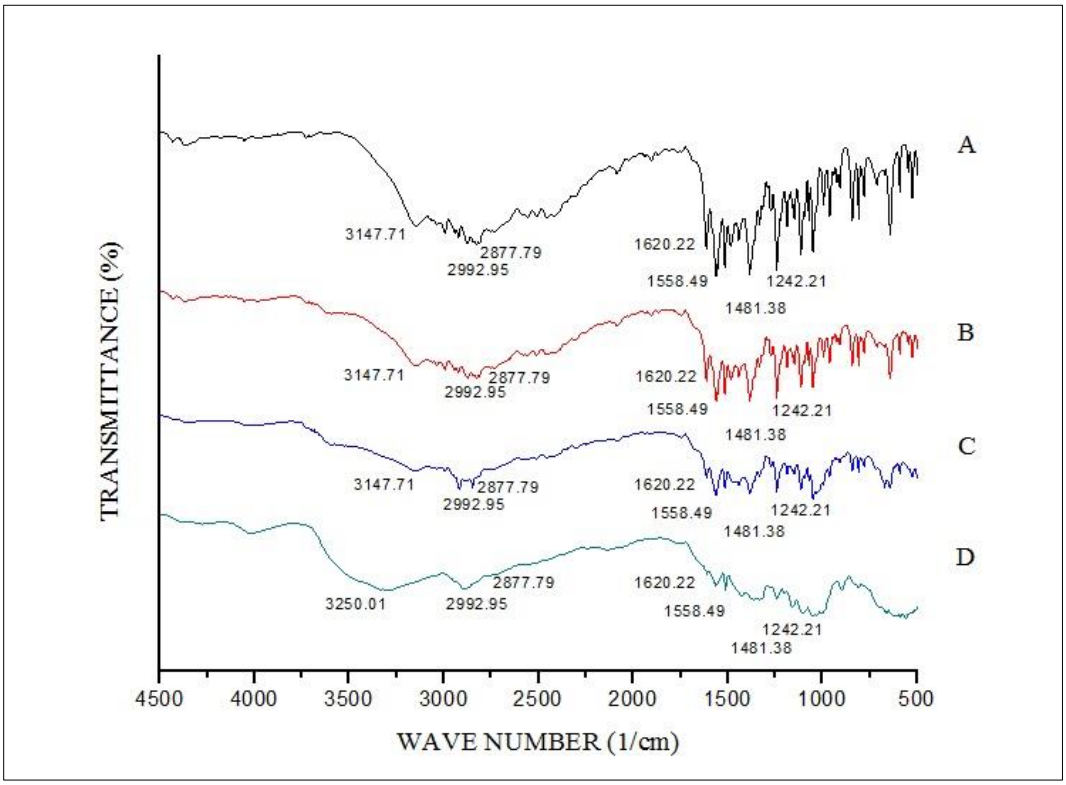


Conc. (µg/ml)	Absorbance (in nm)
5	0.1642
10	0.3201
15	0.4437
20	0.6095
25	0.7505

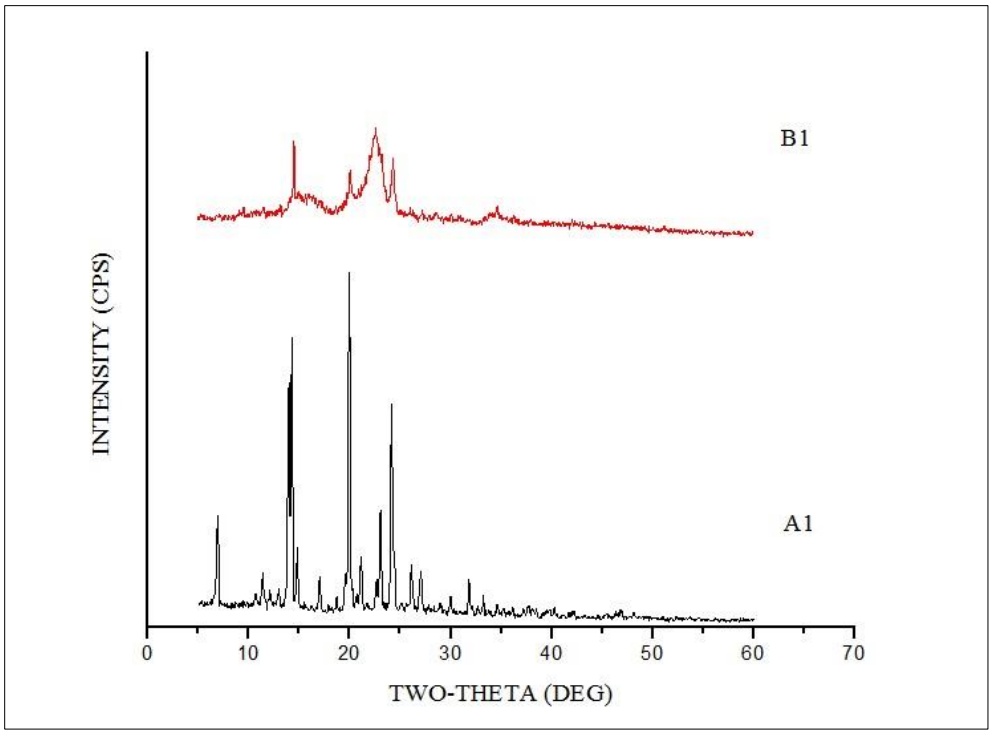


Conc. (µg/ml)	Absorbance (in nm)
5	0.1761
10	0.3348
15	0.4906
20	0.6352
25	0.7926

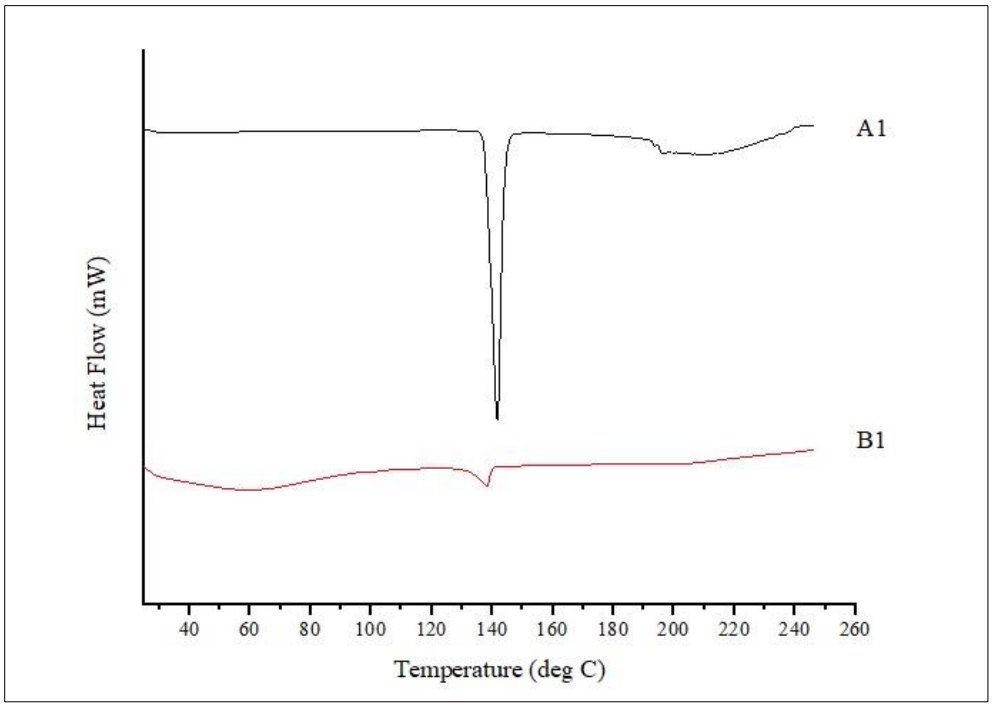
Graph 3: FTIR spectra of (A) pure drug (B) pure drug+XG, GG, LBG, (C) pure drug+gums+tablet excipients before granulation, (D) pure drug+gums+tablet excipients after granulation (optimized formulation F5B)



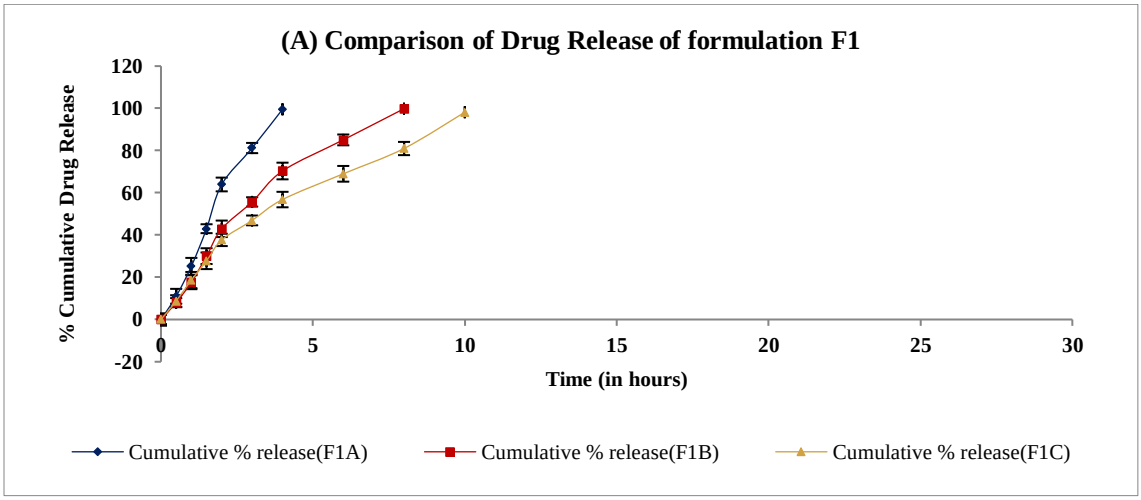
Graph 4: XRD spectra of (A1) pure drug and (B1) optimized formulation F5B

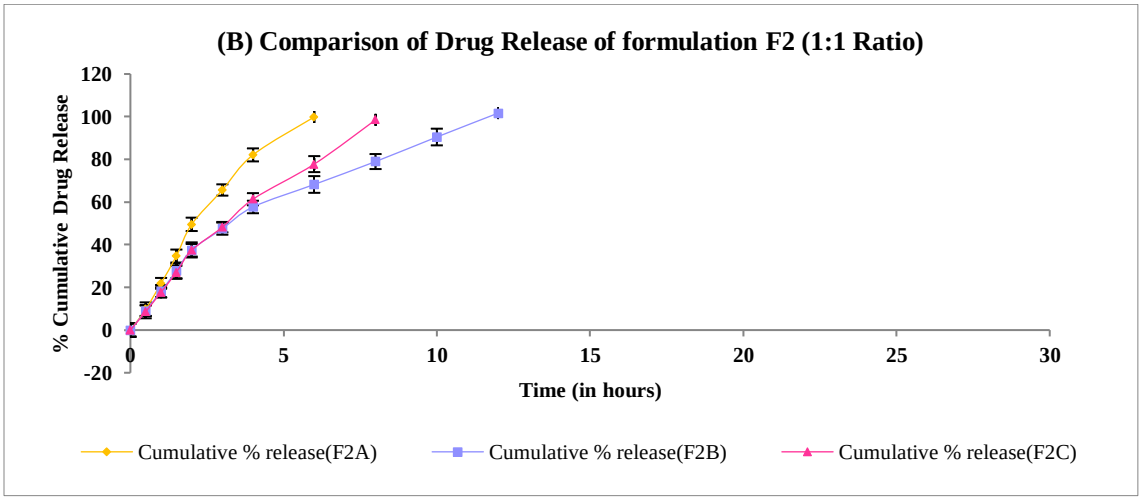


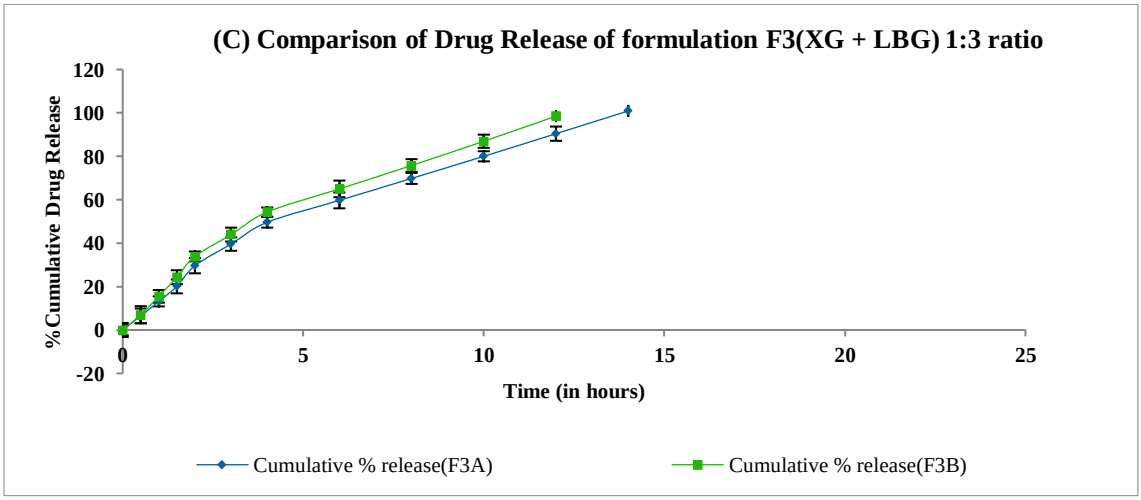
Graph 5: DSC thermograms of (A1) pure drug and (B1) optimized formulation F5B

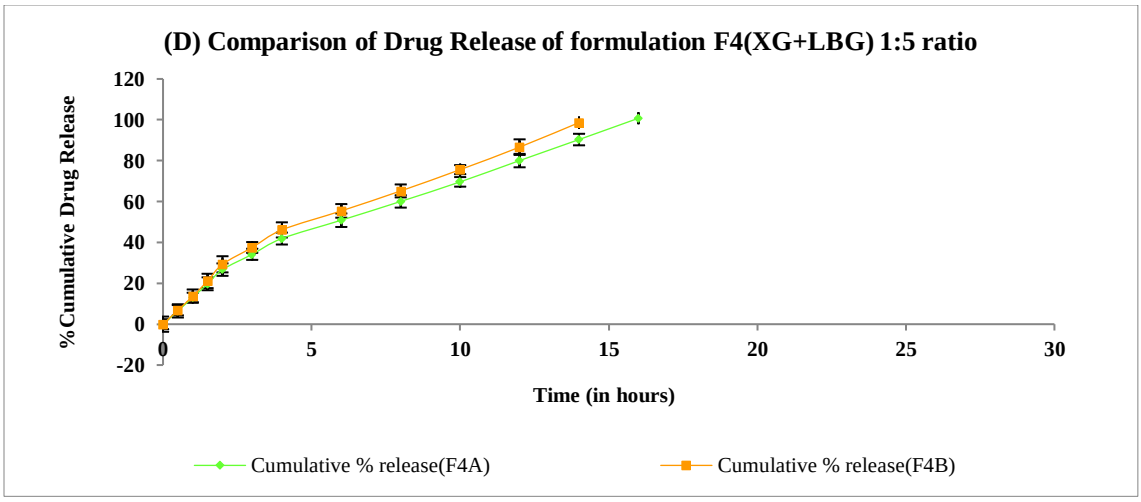


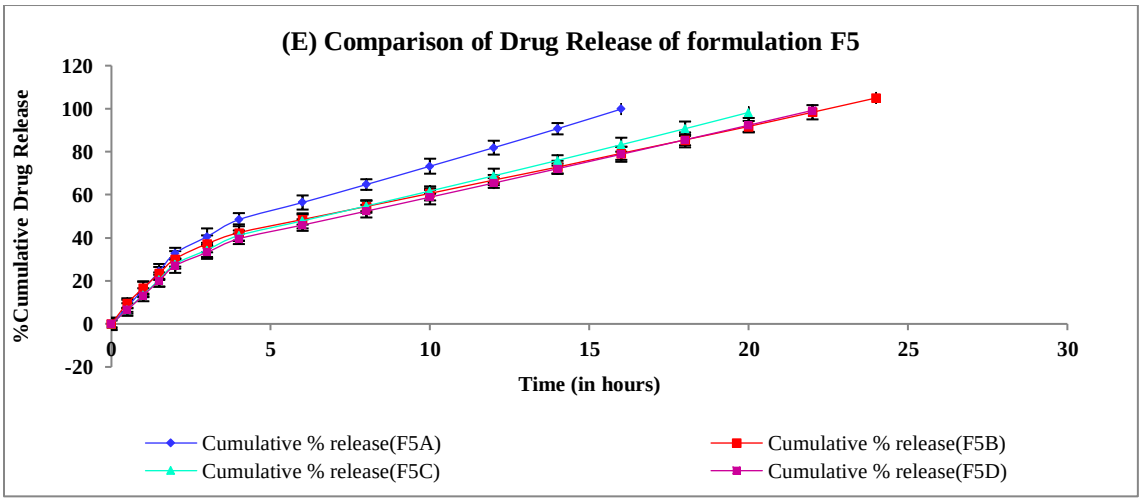
Graph 6: *in-vitro* drug release profile of SR metoprolol succinate (A) batch F1 (B) batch F2 (C) batch F3 (D) batch F4 (E) batch F5 (F) comparative view of all the batches

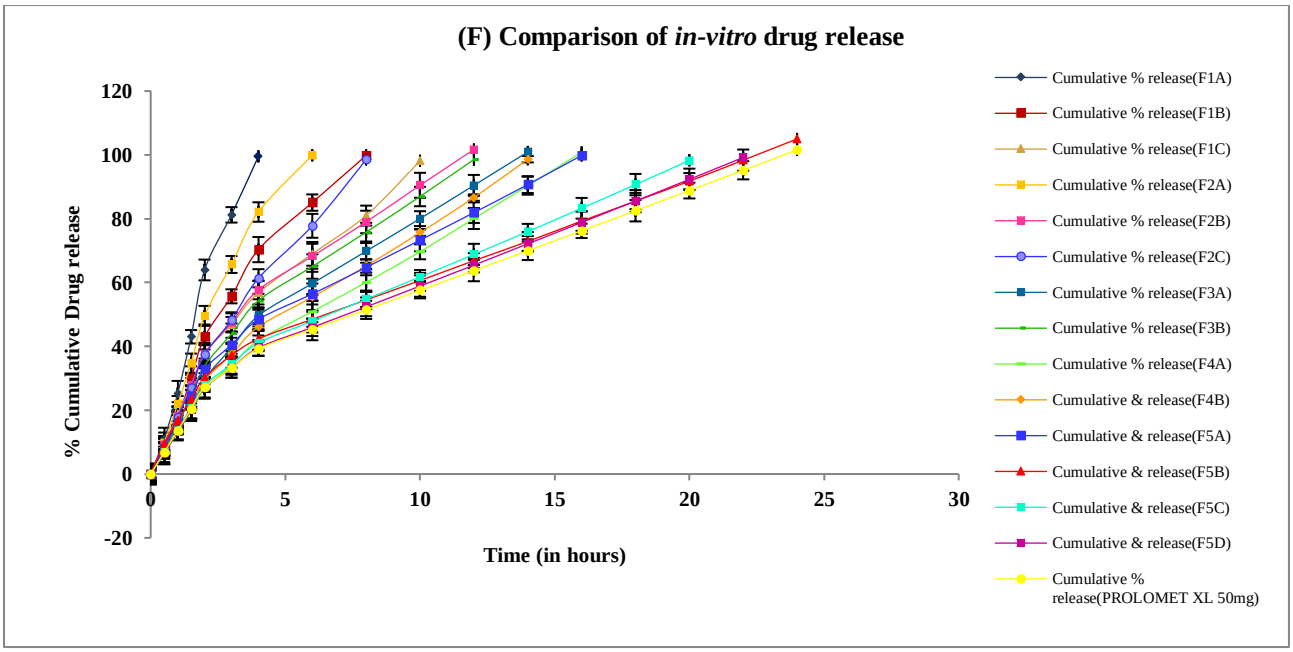




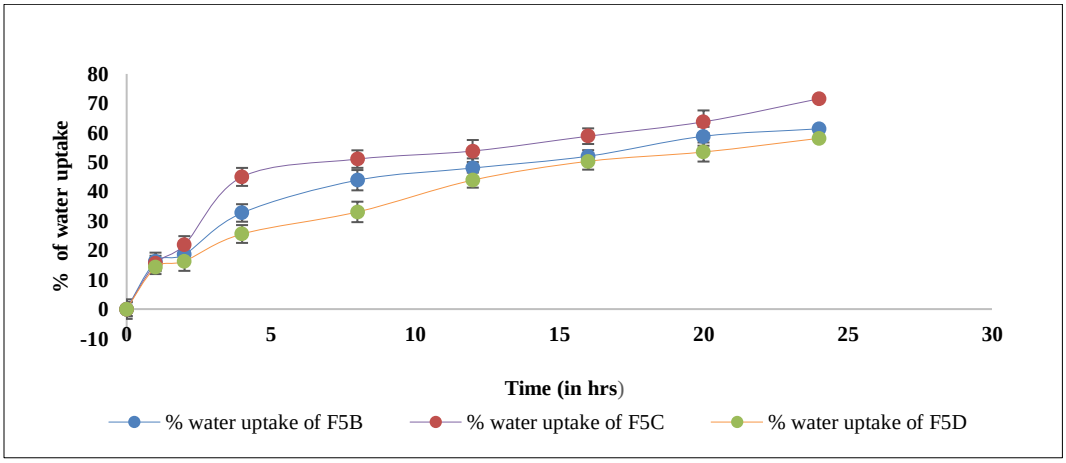



(D) Comparison of Drug Release of formulation F4(XG+LBG) 1:5 ratio
%Cumulative Drug Release
Time (in hours)
Cumulative % release(F4A)
Cumulative % release(F4B)

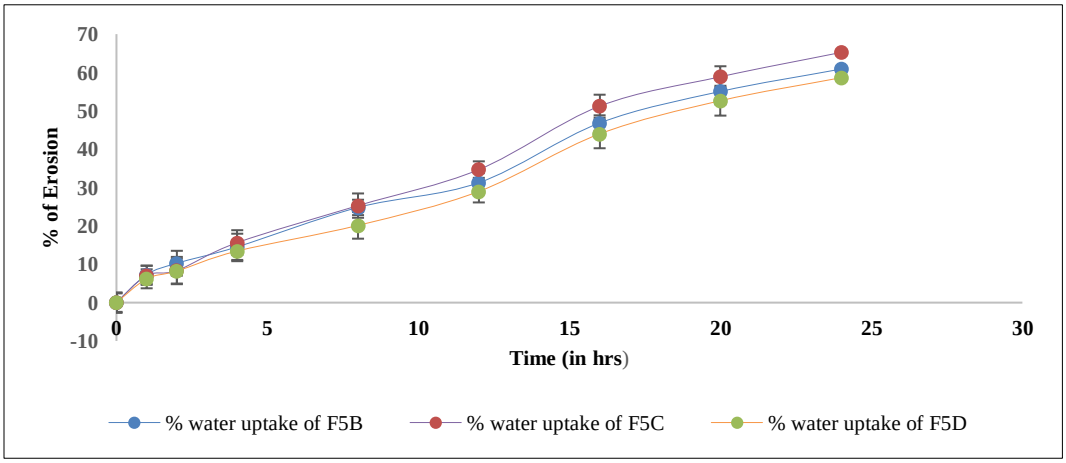

(E) Comparison of Drug Release of formulation F5
%Cumulative Drug Release
Time (in hours)
Cumulative % release(F5A)
Cumulative % release(F5B)
Cumulative % release(F5C)
Cumulative % release(F5D)


(F) Comparison of *in-vitro* drug release
% Cumulative Drug release
Time (in hours)
Cumulative % release(F1A)
Cumulative % release(F1B)
Cumulative % release(F1C)
Cumulative % release(F2A)
Cumulative % release(F2B)
Cumulative % release(F2C)
Cumulative % release(F3A)
Cumulative % release(F3B)
Cumulative % release(F4A)
Cumulative & release(F4B)
Cumulative & release(F5A)
Cumulative & release(F5B)
Cumulative & release(F5C)
Cumulative & release(F5D)
Cumulative % release(PROLOMET XL 50mg)

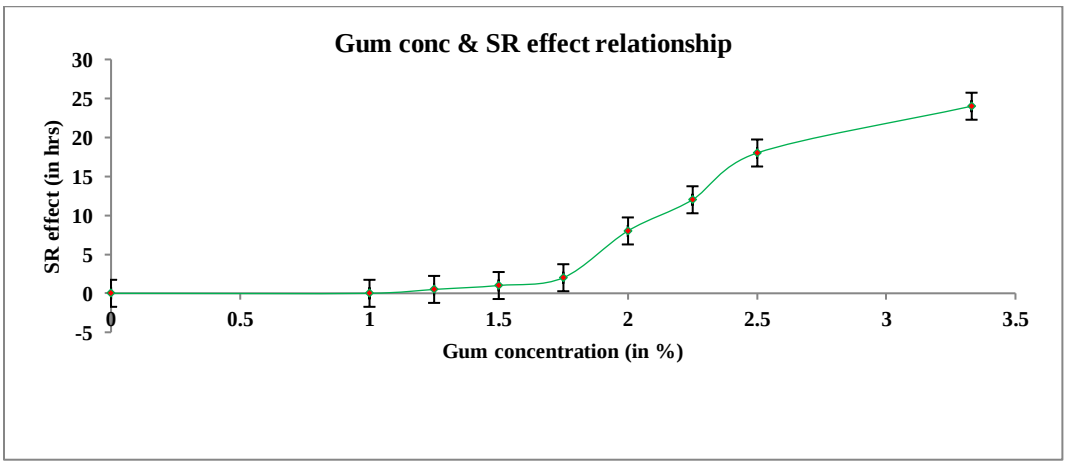
Graph 7: Water uptake percentage of metoprolol succinate SR formulations F5B, F5C and F5D



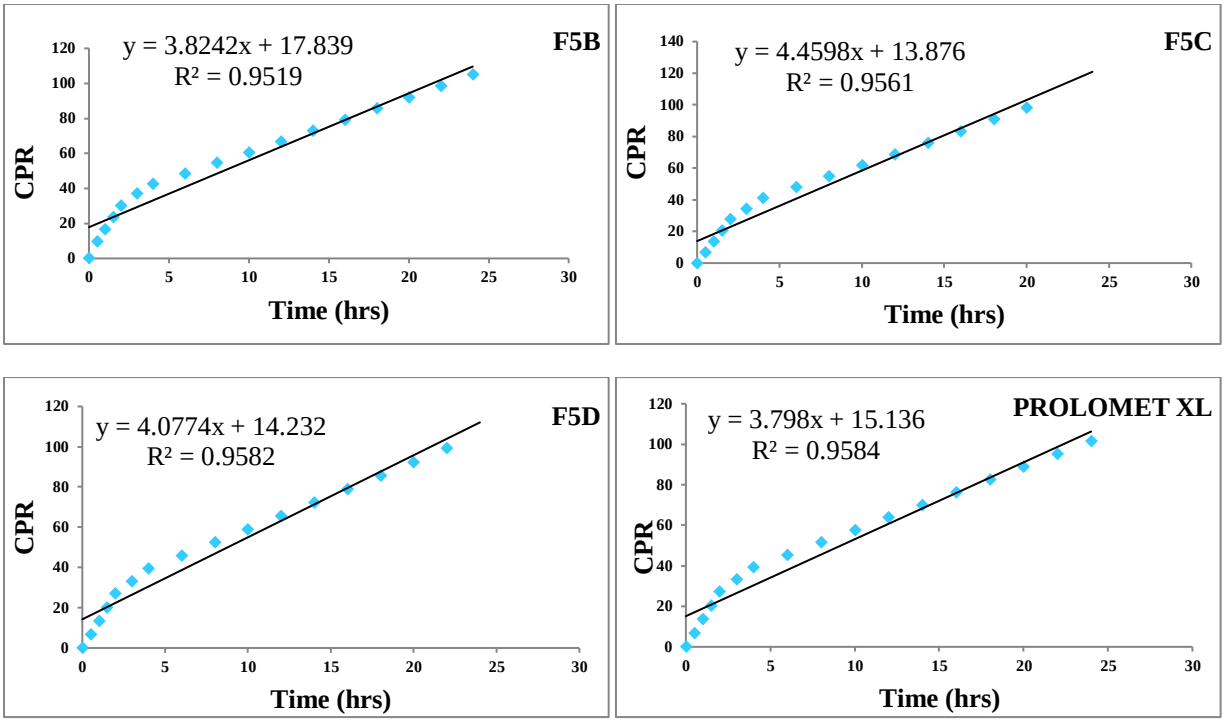
Graph 8: Erosion percentage of metoprolol succinate SR formulations F5B, F5C and F5D



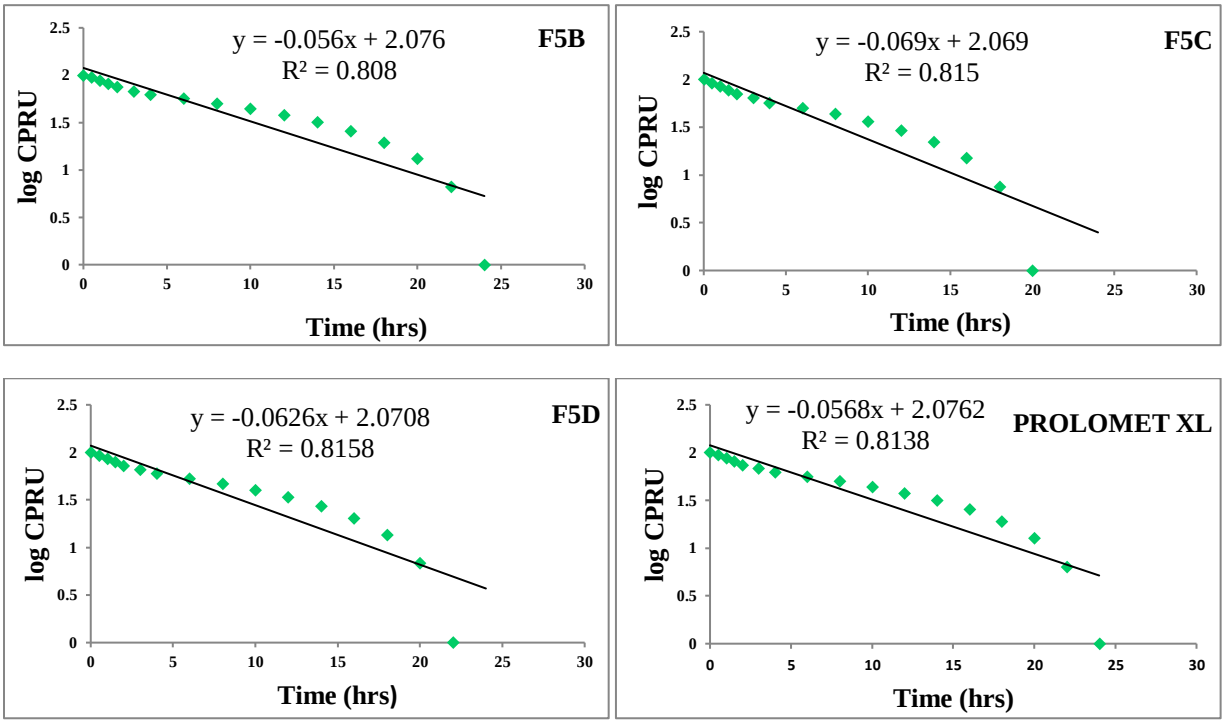
Graph 9: Gum concentration& SR effect relationship



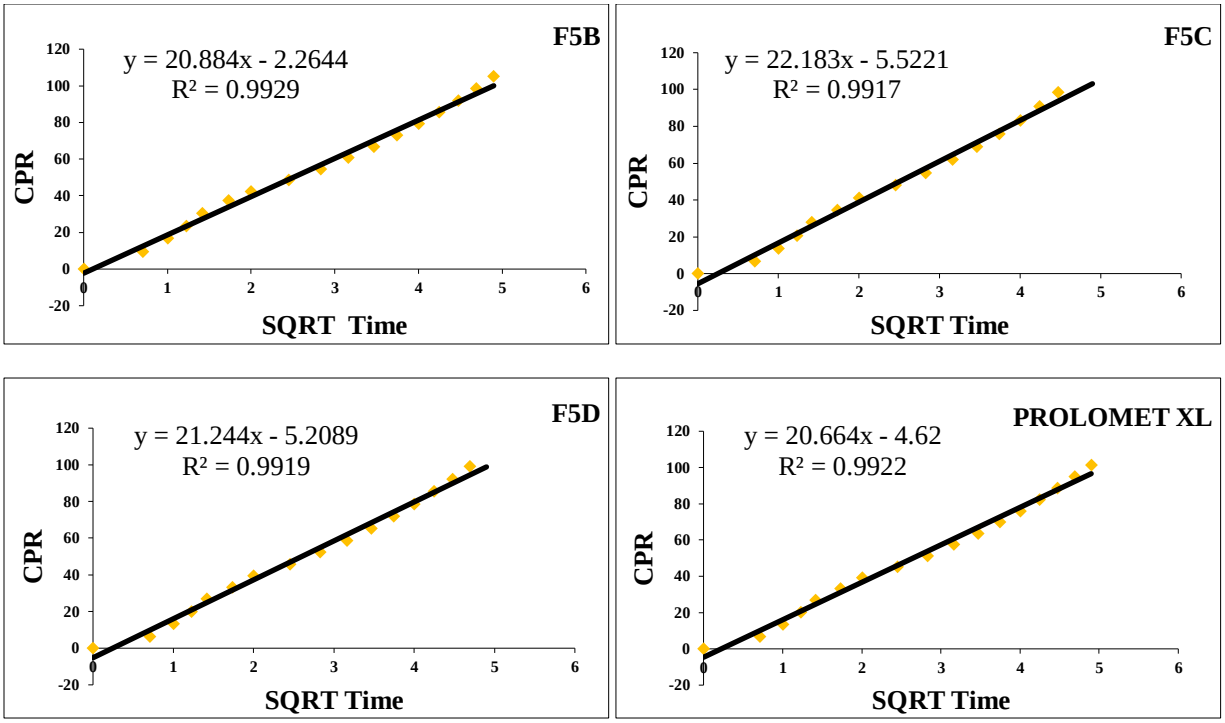
Graph 10:Zero-order kinetics



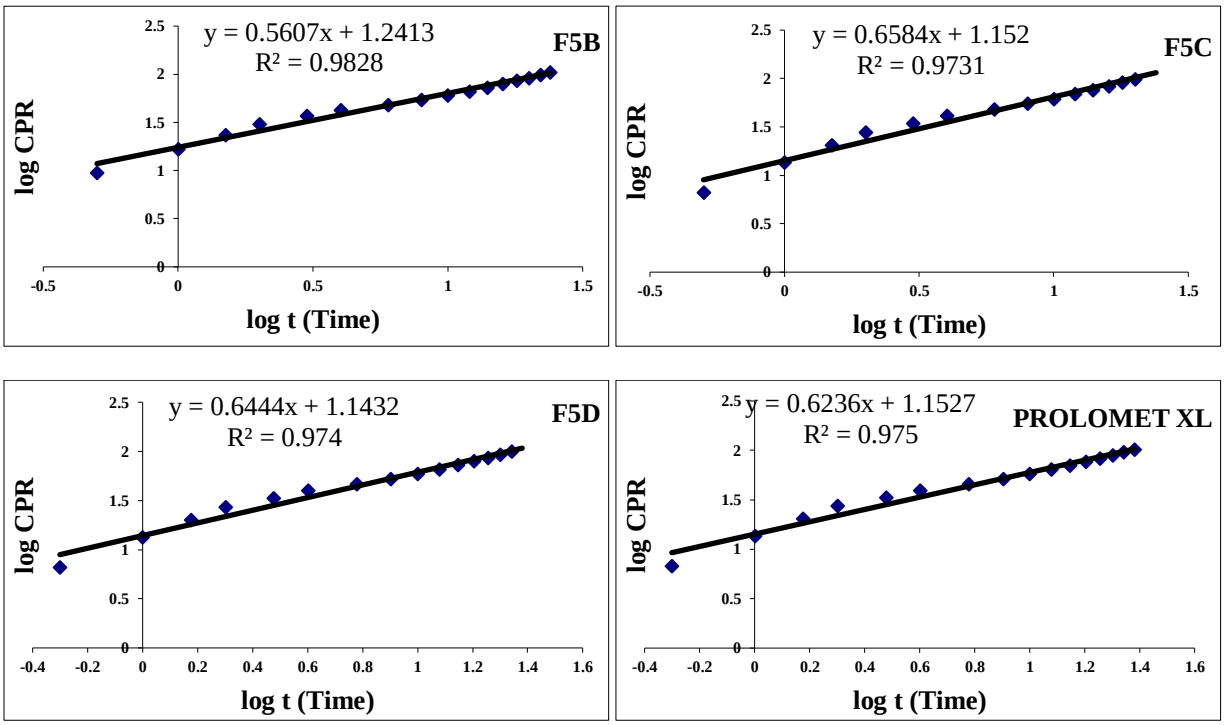
Graph 11: First-order kinetics



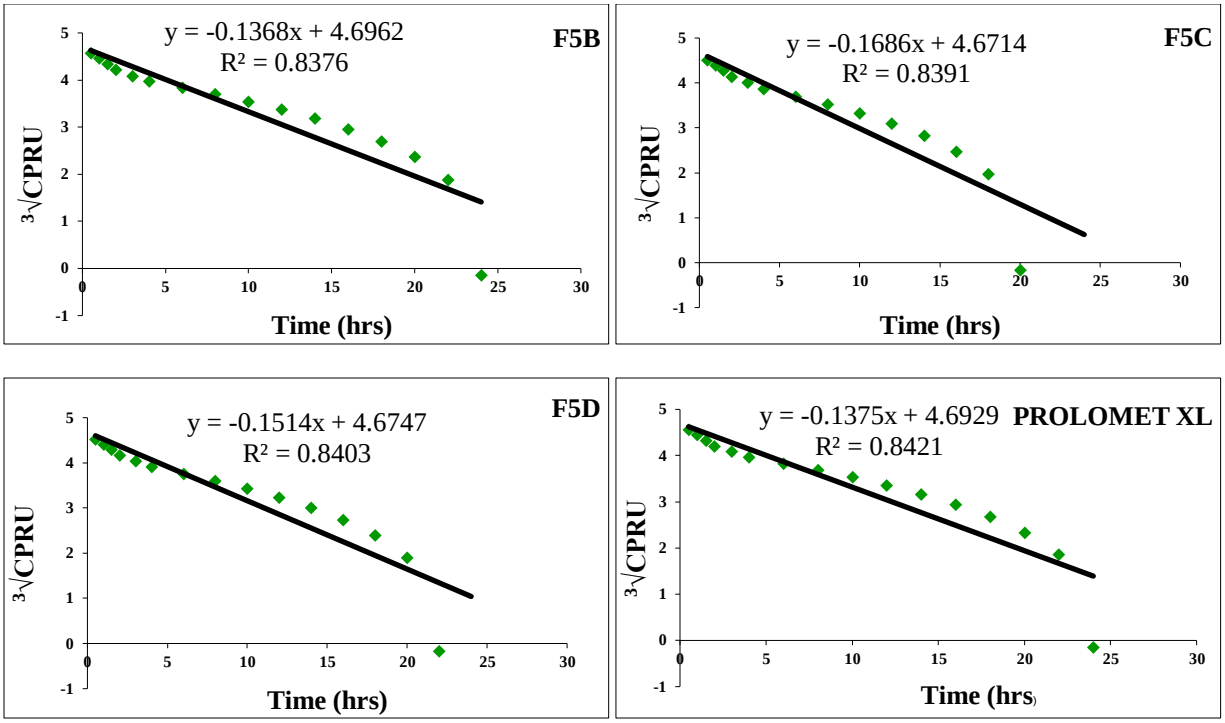
Graph 12: Higuchi plot



Graph 13: Korsemeyer-Peppas plot



Graph 14: Hixson-Crowell plot



Chapter 8: RESULTS AND DISCUSSION

CHARACTERIZATION OF THE DRUG SAMPLE

Solubility

The sample of drug was found to be freely soluble in distilled water, soluble in methanol, sparingly soluble in ethanol and practically insoluble in acetone. In the buffer systems used pH 1.2 acidic buffer and pH 6.8 phosphate buffer it was freely soluble.

Absorption maxima and calibration curve of Metoprolol succinate

1. Determination of λ_{max}

The λ_{max} of the drug sample was reported to be 222 nm from the UV-spectrophotometric spectrum of the sample of metoprolol succinate. The obtained value was compared with the reference $\lambda_{max}$of metoprolol succinate given in reference (222 nm) [42]. The UV spectrum has been shown in Chapter 7*[Refer Chapter 7; Graph 1]*.

2. Calibration curve of Metoprolol succinate

The calibration curve was plotted using concentration 5 to 30 µg/ml of metoprolol succinate. R^2 was calculated from the calibration curve and its value was 0.998 and 0.999 at pH 1.2 and pH 6.8 respectively. The slope was found to be 0.030 and 0.032 at pH 1.2 and pH 6.8 respectively *[Refer Chapter7; Graph 2(A), 2(B)]*.

CHARACTERIZATION OF MUCILAGE

The measured viscosities of the various gum combinations showed substantial variability in the results *[Refer Chapter 7; Table 8]*. The gum's thick texture helped to prolong the release of the drug from the tablet's matrix. Mucilage held the drug molecules, releasing them more gradually over time.

The mucilages made with a single gum (M1A, M1B, and M1C) had the lowest viscosity of all when measured, with the order M1A<M1B< M1C. It was proposed that LBG and XG had a major impact. . The M2 gum combinations demonstrated that adding equal amounts of GG with XG and LBG did not result in an increase in viscosity; however, using XG and LBG did result in a modest rise. The results were significantly higher for M3 and M4 gum pairings than for M1 and M2. When all three gums were combined, M5 had the highest viscosities of any substance. A medium viscous mucilage with values between 1500 and 1900 mPa.S was the target, and M5B, M5C, and M5D achieved this.

CHARACTERIZATION OF GRANULES:

The flow properties of the granules made for each formulation were examined, and the results are presented in tabulated form *[Refer Chapter 7; Table 9]*. All of the granule batches that were prepared had acceptable flow characteristics.

DRUG EXCIPIENTS COMPATIBILITY STUDIES

Studies on the compatibility of drugs with their excipients have shown that there were no substantial compatibility problems between the drugs and the gums or other excipients.

1. Fourier transforms infra-red spectrophotometer (FTIR) analysis

The FTIR spectra of pure metoprolol succinate exhibited major peaks at 3147.71 cm^{-1} (NH-symmetric stretching) due to secondary amine, 1620.22 cm^{-1} (C=O stretching) due to succinic acid, 1481.38 cm^{-1} (ring-C=C- stretching), 1242.21 cm^{-1} (C-O-C- asymmetric stretching). Some other minor peaks were also observed at 2992.95 cm^{-1}, 2877.79 cm^{-1} and 1558.49 cm^{-1}. Pure drug+XG, GG, LBG, pure drug+gums+excipients before granulation, and pure, drug+gums+excipients after granulation all showed the same typical peaks in the same positions with a minor increase in wavelength in one of the cases. The aforementioned data unequivocally demonstrated that there was no chemical interaction between the drug, gum, or any other excipients utilised in tablet preparation. The FTIR spectrum of the optimised formulation is represented is labelled as (D) *[Refer Chapter 7; Graph 3]*.

2. X-ray diffraction (XRD) analysis

To investigate the crystalline changes of the drug during tablet preparation, XRD studies were conducted. The x-ray diffractograms of pure drug metoprolol succinate and the optimized formulation has been displayed *[Refer Chapter 7; Graph 4].*The diffraction spectrum of the pure drug metoprolol succinate was observed at 2θ angle of 6.9, 14.25, 14.3, 19.95, 20, 23.05, 24.1, 24.15. The optimised formulation F5B's diffraction spectrum revealed diminished drug peak intensities, indicating that the compression force used during tablet manufacturing had reduced the drug's crystallinity.

3. Differential Scanning Calorimetry (DSC) analysis

DSC thermogram of the pure drug metoprolol succinate showed a sharp endothermic peak at 141.69°C that indicated the melting point of the stable crystalline drug. The sample of the optimized formulation showed an endothermic peak at 138.43°C showing that that were no significant changes in melting point. *[Refer Chapter 7; Graph 5]*diplays the DSC thermograms of both the samples.

EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS

1. Physical characterization

Tableting properties of the SR metoprolol succinate tablets were evaluated that included tablet dimensions, friability, hardness and weight variation. The corresponding results are presented *[Refer Chapter 7; Table10].* 10 mm tablets of off-white colour were produced having score on one side and an average thickness of 2.75 mm. Hardness of all the batches of formulations were found to be in the range of 6.5-7.5 kg/cm^2 with an average hardness of 7.125 kg/cm^2. Friability (<1%) and uniformity of weight (±5%) were within the limits as per Indian Pharmacopoeia (IP).

2. Drug content

Drug content of each of the formulations prepared were checked in acidic buffer pH 1.2 and the assay results are depicted *[Refer Chapter 7; Table 11].* The drug content of all the batches of SR metoprolol succinate prepared were within the limits and were found to be in the range of 97.42-102.11%.

3. *in-vitro* drug release

There were a total of five batches used for the release studies of the prepared SR metoprolol succinate tablets. The data obtained from each batch were used to determine the study pattern of the next batch. The first batch included the F1 formulation, in which each gum was utilised separately to maintain the drug release. *[Refer Chapter 7; Graph 6(A)]* for the release profiles for F1. GG was utterly incapable of exerting any sustaining effect. For about 8 to 10 hours, XG and LBG released the drug. As there was no discernible effect in batch F1, the subsequent batch F2 was made using two gums in a 1:1 ratio. Results as *[Refer Chapter 7; Graph 6(B)],* showed that GG when used with XG showed no significant effect but when used with LBG a slight increase was observed. The effect was due to LBG. When combined, XG and LBG demonstrated a noticeable improvement in the release profile. Since GG had a minimal impact, it wasn't employed in batches F3(1:3) and F4(1:5), which solely used XG and LBG. As illustrated in *[Refer Chapter 7; Graph 6(C)]*XG:LBG(1:3) demonstrated the same outcome as LBG:XG(1:5), with XG:LBG(1:5) sustaining the release for up to 16 hours as shown in*[Refer Chapter 7; Graph 6(C)(D)]*. Study showed that while these two have a synergistic impact when administered together, LBG is primarily responsible for the effect. The study's intended goal of maintaining the drug release for more than 24 hours, however, was not met. GG was employed once more in batch F5 to augment the effect in order to achieve that. ***Figure 3*** displays the findings of the study, which involved three gums in various ratios as shown in *[Refer Chapter 7; Graph 6(E)]*.

Finally, it was discovered that the F5 batch, particularly F5B, F5C, and F5D, displayed favourable outcomes. Cumulative drug release of these formulations has been described *[Refer Chapter 7; Table 12]*. The duration of the drug release was 24, 20, and 24 hours, respectively. Consequently, it was demonstrated in this study that a single gum cannot support distribution. The impact of GG is minimal, however when combined with XG and LBG, desirable outcomes are attained. LBG among them was responsible for showing the most promising effect. A comparison of the overall drug release patterns of all formulations compared with marketed formulation PROLOMET XL 50 is shown in *[Refer Chapter 7; Graph 6(F)]*.

4. Erosion and water-uptake of tablets

As the in-vitro drug release profiles of the formulations F5B, F5C, and F5D produced the intended outcomes, they were employed to study the relationship between matrix erosion, water uptake, and drug release. *[Refer Chapter 7; Graph 7]* displays the water uptake of the aforementioned formulations during a 24-hour period. Percent of water uptake by F5B, F5C and F5D were 61.33%, 71.54% and 58.09% respectively. *[Refer Chapter 7; Graph 8]* depicts the erosion percentage for F5B, F5C, and F5D, which were found to be 60.89%, 65.23%, and

58.64%, respectively. The data showed that as water uptake increased gradual increase in matrix erosion was also observed.

STABILITY STUDY

Stability studies conducted for 6 months as per the ICH guidelines demonstrated that there were no changes *[Refer Chapter7; Table 13]*.

EFFECT OF GUM CONCENTRATION ON DRUG RELEASE

Natural gums used in this study namely xanthan gum, guar gum and locust bean gum have been extensively studied to develop a perfect concentration to be used as binding agent in the tablet so produced capable of sustaining the release of metoprolol succinate over 24 hours. Generally as per the monographs and various works in this field [52-54], it was found that approximately a concentration of 1.0-1.5% of gums were used to develop a binding agent in the tablets. However, in this present study it was found that the aforesaid concentration was insufficient to sustain the metoprolol succinate release according to the desired criterion. A concentration of roughly 3% and to be more precise 3.33% was capable to show the desired effect. Hence, it was found that there was a direct relationship between the gum concentration and the sustained release effect. In food industries 0.15-0.75% [55] is used as binder and in the pharmaceutical field 1.0-1.5%, but to achieve sustained effect a concentration higher that 1.5% is required.

A detailed study was carried out with formulation F5B to establish the perfect gum concentration responsible for showing the sustained release effect*[Refer Chapter 7; Graph 9]*. For the above reason, few concentrations which were prior studied in the early trial steps of the study were re-developed, and the above effect was studied. It was found that upto 1.75% no rate-retarding effect was observed and the tablets so produced released the drug within 0.5-1.0 hr. A concentration of 2.0-2.5% showed positivity in the results. Following such studies, it was established that a concentration of 3.33% was acceptable for the cause.

RELEASE KINETICS

Various kinetic models were employed to investigate drug release mechanism of the formulations using *in-vitro* release data. The *in-vitro* release data were fitted to models representing zero-order, first-order, Higuchi's square root of time and Korsemeyer-Peppas model to determine the correlation coefficient, slope and intercepts values. From the values of the correlation coefficients, the best fitted data can be predicted. The curve fitting of the release data was carried out mainly by regression analysis. To evaluate the drug release mechanism, the *in-vitro* dissolution profile was fitted into Korsemeyer-Peppasequation. Various parameters of these model equations of all formulations were tabulated *[Refer Chapter 7; Table 14]*. The plots have been shown *[Refer Chapter 7; Graph 10-14]*.

Chapter 9: CONCLUSION

Marketed metoprolol succinate sustained release formulations are widely available. However, the matrix of such tablets is made from synthetic or semi-synthetic polymers. Natural polymers are widely used in many pharmaceutical fields, and the drug delivery systems developed with them are just as effective as those produced with synthetic ones. So, in this study, natural polymers were used with the goal of developing a dosage form that may fulfil a therapeutic function while also reducing the limits of synthetic polymers.

Xanthan gum and guar gum have long been used. Their impact on numerous domains of delivery of drugs has been positive. More specifically, because this study is focused on sustained release tablets, previous studies with these two gums were thoroughly examined. It was discovered that neither of these two gums could sustain the drug for an extended period of time. Locust bean gum is a prominent binder, thickening ingredient, and stabilising agent in the food and cosmetics industries. LBG's intrinsic qualities make it a viable choice for use as a release retardant in tablets. The concept derived from it was used in the present study. The LBG used in the current study was of food grade quality, and significant benefits were seen.This has resulted in a beneficial economic outcome. Food grade quality is less expensive, hence production costs are substantially lower. Because no interactions were found between the gums, excipients, and the drug, the formulation developed was free of undesired side effects.

A concentration of 3.33% gum was found to be suitable for demonstrating a prolonged effect. Concentrations below that were ineffective since they just demonstrated a binding action with no additional benefits. The various ratios were studied, and all batches of formulations were analysed, keeping track of even little alterations. The top three formulations based on *in-vitro* drug release data were formulations F5B, F5C, and F5D. F5B, on the other hand, produced the best outcomes. The optimised formulation performed satisfactorily in all of the analytical tests, indicating that it is a promising formulation for the once-daily administration of the antihypertensive drug metoprolol succinate, reducing the risk of nocturnal attacks and offering a minimum of adverse reactions than the existing marketed formulation.

Chapter 10: FUTURE SCOPE

This study aimed to create a formulation capable of overcoming the human body's excessive use of synthetic substances. Hypertension, which is a fairly prevalent disease in today's population, has no permanent remedy. The treatment of which necessitates the regular use of anti-hypertensives. This already has an influence on the person's health because of the adverse effects. Even if only a small amount of work could be done to improve the person's well-being, it would be greatly valued. The natural gums utilized to maintain metoprolol succinate for more than 24 hours outperformed the existing marketed versions. The *in-vitro* testing yielded positive results. However, more detailed research is required to establish this strategy. However, more detailed research is required to establish this strategy. *in-vivo* testing of the generated formulations is necessary for further validation of the study. Drugs from the same BCS Class-I drug category can also be used to employ the same technique and generate safe drugs that help patients.

Chapter 11: REFERENCES

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