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Physicochemical characterization of metoprolol tartrate loaded by hydroxypropyl cellulose microparticles used for drug delivery systems

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بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

ABSTRACT

Metoprolol tartrate (MT) is a selective beta-1 blocker that is employed as an antihypertensive. To enhance its bioavailability and target delivery, the metoprolol tartrate microparticles loaded by hydroxypropyl cellulose (HPC) were prepared using the freeze-drying technique. The obtained microparticles were evaluated by various physicochemical characteristics and in-vitro drug release. The percentage yield, encapsulation efficiency, and drug loading of microparticles loaded by hydroxypropyl cellulose (MTMPs) were 77.48%, 99.84%, and 42.01% respectively. The particle size ranged from 5 μm to 50μm. Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and X- ray diffraction (XRD) analyses illustrated the interaction between metoprolol tartrate and hydroxypropyl cellulose which confirmed the coating effects of MT as well as the importance of HPC as a carrier in drug delivery systems.

ملخص

ميتوبرولولول طرطرات (MT) هو حاصرات بيتا 1 الانتقائية التي تستخدم كمضاد لخفض ضغط الدم. ولتعزيز التوافر البيولوجي والتوصيل المستهدف، تم تحضير الجسيمات الدقيقة للميتوبرولولول طرطرات المحملة بهيدروكسي بروبيل السليلوز (HPC) باستخدام تقنية التجفيف بالتجميد. تم تقييم الجسيمات الدقيقة التي تم الحصول عليها من خلال الخصائص الفيزيائية الكيميائية المختلفة وإطلاق الدواء في المختبر. وبلغت النسبة المئوية للإنتاجية وكفاءة التغليف وتحميل الدواء للجسيمات الدقيقة المحملة بهيدروكسي بروبيل السليلوز 77.48% و99.84% و42.01% على التوالي. تراوح حجم الجسيمات من 5 ميكرومتر إلى 50 ميكرومتر. أوضحت تحاليل التحليل الطيفي بالأشعة تحت الحمراء (FTIR)، والمسعر المسحي التفاضلي (DSC) وتحليلات حيود الأشعة السينية (XRD) التفاعل بين الميتوبرولولول طرطرات وهيدروكسي بروبيل السليلوز الذي أكد تأثيرات الطلاء للميتوبرولول وكذلك أهمية هيدروكسي بروبيل السليلوز كحامل في أنظمة توصيل الدواء.

الكلمات المفتاحية: ميتوبرولولول طرطرات، هيدروكسي بروبيل السليلوز، تقنية التجفيف بالتجميد، الجسيمات الدقيقة.

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DEDICATION

بسم الله الرحمـٰن الرحيم

(وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ) التوبة /105

صدق الله العظيم

All praise is due to Allah, by whose grace no effort is completed and no endeavor is sealed except by His permission, and we have not reached this point except by His guidance.

To the one who conveyed the message, fulfilled the trust, and advised the nation, the Prophet of Mercy and the Light of the Worlds, our Prophet Muhammad, peace be upon him.

To those who sacrificed their precious lives, the owners of pure blood, our righteous martyrs.

To the land of prophets and the second Qiblah of the Arabs, the blessed land of Palestine.

To the one who taught me that life is a struggle and success is patience and perseverance, my support and source of strength, my companion on the path (my beloved father).

To my paradise and the light that illuminates my path, to the one whose prayers were the secret of my success and whose tenderness was the balm of my wounds (my dear mother).

To my steadfast pillar that never sways, to the ones who strengthened my resolve, my brothers (Ibrahim, Nour Elddine, and Ismail).

To the great ones, my sisters, whom Allah has blessed me with (Hadjar and Nour Elhouda).

To my companion on the journey, my friend (Amira).

I ask Allah to grant me success in my endeavors and to guide my steps on the path of righteousness.

Peace be upon you and the mercy of Allah and His blessings.

SARA

DEDICATION

{ الْحَمْدُ لِلّهِ الَّذِي هَدَانَا لِهَـذَا وَمَا كُنَّا لِنَهْتَدِيَ لَوْلا أَنْ هَدَانَا اللهُ }

الأعراف: 43

I dedicate this work to

whose face is characterized by reverence

To the one whose name I bear with pride

To the one who paved my path to success

.My dear father

To the one to whom the Prophet commanded us three times

To the one under whose feet is paradise

.My beloved mother

To my laughter and smile in life

.my sisters

To those who support me in life

.My brothers

To my father's grandchildren, whom I pray to God to help them reach what I have reached.

To my classmate, my best friend

.SARA

To every friend or acquaintance who helps me in my search, even a little

AMIRA

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NOMENCLATURE

API	Active pharmaceutical ingredient
BC	Bacterial cellulose
CDDs	Controlled drug delivery systems
CMC	Cellulose microcrystal
CMC	Carboxymethyl cellulose
CMF	Cellulose microfibrils
DDs	Drug delivery systems
DSC	Differential scanning calorimetry
EC	Ethyl cellulose
FDI	Food and drug administration
FTIR	Fourier transform infrared
HEC	Hydroxyethyl cellulose
HPMC	Hydroxypropyl methyl cellulose
HPC	Hydroxypropyl cellulose
MC	Methyl cellulose
MC	Micro cellulose
MDDs	Micro drug delivery systems
MTMPs	Metoprolol Tartrate microparticles
MT	Metoprolol Tartrate
MPs	Microparticles
NDDs	Noval drug delivery systems
NPs	Nanoparticles
PLA	Poly lactic acid
PLGA	Poly lactic -co-glycolic acid
$ScCO_2$	Supercritical carbon dioxide
SCF	Supercritical fluids
SDDSs	Smart drug delivery systems
SEM	Scanning electron microscopy analysis

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Chapter I

INTRODUCTION

1.1 Background of study

Hypertension is known as "the silent killer" due to its lack of signs until serious consequences arise. Hypertension is a common and serious illness that can cause several health issues or complications. Furthermore, hypertension significantly increases the risk of cardiovascular death and morbidity. Hypertension is linked to an increased risk of renal failure, stroke, angina, early death, and heart failure due to cardiovascular cause (Pálsson & Patel, 2014) . The World Health Organization (WHO) considers hypertension to be a leading cause of premature death. The relative risks of stroke and heart disease are significantly linked to blood pressure. People aged 80–90 had a 33% reduced risk. People aged 50–59 had a 62% risk of stroke. Although, High blood pressure poses a risk for various disorders, including heart disease, stroke, and renal disease (Mazhar et al., 2023).

Metoprolol ((2R,3R)-2,3-dihydroxybutanedioic acid; bis(1-[4-(2-methoxyethyl)phenoxy] -3-[(propan-2-yl)amino] propan-2-ol)) is a selective beta-1 blocker that is employed as an antihypertensive (*Metoprolol Tartrate | DrugBank Online*, n.d.) Also, it was the first systemic b-blocker admitted for clinical use in the USA. Metoprolol is often sold as a succinate or tartrate salt; the two formulations have different release forms, but the metoprolol cation and the dicarboxylate anion are present in a 2:1 ratio in each. The b-adrenergic blocking is caused by the S-isomer in this racemic mixture of drugs (Ciciliati & Cavalheiro, 2019). The structure formula of metoprolol tartrate is:

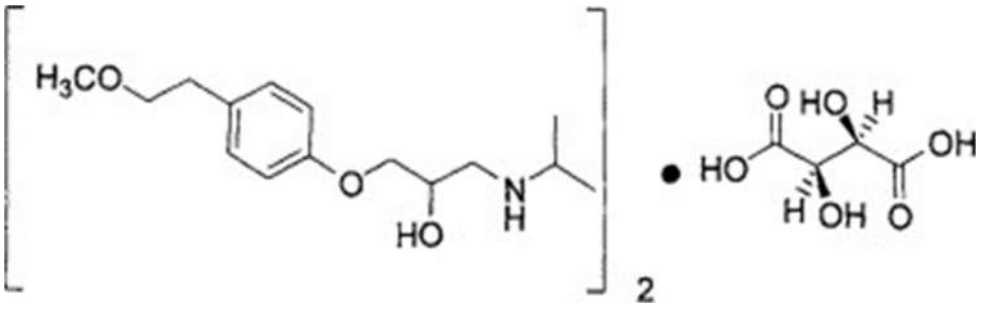


Figure I.1: Metoprolol tartrate structure

Metoprolol is mostly lipophilic, and its distribution is typical for a basic lipophilic medication. There is considerable hepatic first-pass elimination, with approximately 50% of the oral dosage reaching the systemic circulation. Metoprolol has a half-life of 3 to 4 hours in most people when taken as non-extended-release tabs. The kidneys are the primary organs that excrete metoprolol (Morris et al., 2024).

The medication is composed of pharmaceutical active compounds and excipients. Excipients are inactive compounds used in pharmaceutical compositions alongside active drugs. These compounds are added to pharmaceutical products for a variety of reasons, including improved stability, improved bioavailability, assisting in the manufacturing process, improving appearance or taste, and enabling administration or transport of the active ingredient. Excipients are often pharmacologically inactive, meaning they have no therapeutic effects on their own. Instead, they serve to formulate and deliver the active pharmaceutical ingredient (API) to the patient (Li, 2023).

One of the common excipients is hydroxypropyl cellulose (HPC), which is a polymer that possesses biodegradable and biocompatible properties. It exhibits the ability to self-repair as well as shape memory and undergoes a distinct hydrophilic/hydrophobic transition in response to various external stimuli, including pH, temperature, pressure, light, and magnetic or electric fields. HPC has been employed in the fabrication of

thermo-responsive hydrogels for the purpose of controlling the release of hydrophilic drugs (Ciolacu et al., 2020). The synthesis of hydroxypropyl cellulose (HPC) involves the reaction of propylene oxide with alkali cellulose on its anhydrous glucose chain.

HPC demonstrates solubility in a variety of organic solvents, as well as in cold water. This characteristic makes HPC an effective thickening agent or tablet binding agent for drug release systems (B. Sun et al., 2019).

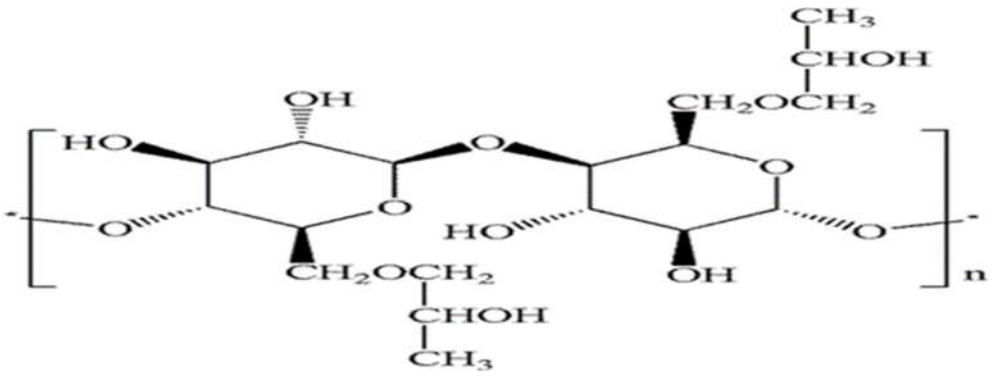


Figure I.2: Hydroxypropyl cellulose structure

Targeted drug delivery is a technique used to administer medication to a patient in a manner that enhances the concentration of the medication in certain areas of the body compared to others. The objective of targeted drug delivery is to concentrate the medication in the desired tissues while reducing its concentration in the remaining tissues. This approach enhances the effectiveness of the medication while minimizing the occurrence of side effects. Drug targeting refers to the administration of drugs to specific receptors, organs, or other specific parts of the body. The therapeutic index of a drug, which is determined by its pharmacological response and safety, depends on the drug's ability to access and selectively interact with its target receptor, while minimizing its interaction with non-target tissue. The desired distribution of the drug through targeted delivery would spare the rest of the body and substantially decrease overall toxicity, while still maintaining its therapeutic benefits. The targeted or site-

specific delivery of drugs is an appealing objective, as it represents one of the most promising approaches to enhancing the therapeutic index of drugs (Manish & Vimukta, 2011).

Sustained delivery systems offer a variety of beneficial properties that serve to improve the overall effectiveness and efficiency of drug delivery. One such advantage lies in the ability to reduce dosing frequency, which proves particularly beneficial in reducing the burden on patients and healthcare providers alike. By minimizing the need for repeated administration, sustained delivery systems effectively minimize the occurrence of potential side effects, thereby ensuring a higher level of patient safety and well-being. In addition, these innovative systems contribute to a significant improvement in patient compliance, as the extended drug delivery eliminates the need for the patient to strictly adhere to rigid dosing schedules. In addition, sustained delivery systems allow greater control over the concentration of the therapeutic drug in the patient's body, a critical aspect in ensuring optimal treatment outcomes. This increased level of control gives healthcare professionals the ability to precisely regulate medication dosage and tailor it to the specific needs of each patient. Finally, the implementation of sustained delivery systems in the treatment of chronic diseases holds tremendous promise for reducing manufacturing costs, as prolonged drug release reduces the total amount of drugs needed. This not only benefits healthcare providers through optimized resource allocation, but also helps reduce the financial burden on patients, thereby ensuring more sustainable care (B. Sun et al., 2019).

Advances in the field of pharmaceuticals and related disciplines require the targeted delivery of drugs, vaccines, genes, and various other biomolecules. Additionally, addressing the stability and safety concerns associated with these agents in the manufacture and storage of advanced marketed products can present significant

challenges in the effective treatment of diseases. Extensive research has been conducted on new drug delivery formulations and their applications, with particular emphasis on microparticle systems and their advantages. The term “microparticle” refers to a spherical particle with a size of 1 μm to 2 mm that encloses a core substance in one or more membranes or shells. Based on their internal structure, microparticles can be further classified into microspheres or microcapsules. Microspheres typically consist of a homogeneous matrix in which it is not possible to distinguish between a core and a membrane, while the active pharmaceutical ingredient (API) is dispersed in the polymer matrix either as small clusters or at the molecular level. Microcapsules, on the other hand, consist of a central liquid, solid or semi-solid core that contains the active ingredient alone or in combination with excipients and is surrounded by a membrane or a continuous polymer coating. Expanding the definition of a microcapsule, it is possible to include not only membrane-encased particles or droplets, but also solid matrix dispersions without an outer membrane (Vlachopoulos et al., 2022).

Essentially, microencapsulation is a process or technique with which thin coatings can be reproducibly applied to small solid particles, liquid droplets or dispersions, thereby creating microcapsules. It can be easily distinguished from other coating processes by the size of the particles involved; These are between several tenths of a micrometer and 5000 μm in size. A number of microencapsulation processes are discussed in the literature. Some are based on chemical processes and involve a chemical or phase change; others are mechanical and require special equipment to create the required physical change in the system. The microencapsulation process provides solutions to problems such as masking the taste of bitter drugs, a means of formulating longer-acting dosage forms, a means of separating incompatible materials, a method of

protecting chemicals from moisture or oxidation, and a means of modifying the physical properties of a drug Material properties for easy handling in formulation and manufacturing (Garg et al., 2018).

1.2 Problem statement

There are various limitations in the current techniques used to administer conventional drugs via tablets or liquids, such as low solubility and limited drug efficacy.

Metoprolol tartrate suffers from low bioavailability, which is only available as an immediate-release tablet, thus it must be taken many times a day. This can cause central nervous system (CNS) (Shah et al., 2020) and gastrointestinal side effects. Due to their non-toxic, biodegradable, and bioavailability properties, the drug-loaded microparticles with lower therapeutic drug dosages protect healthy cells in our bodies.

Therefore, polymeric microparticle delivery systems with lower drug dosages can improve the solubility, bioavailability, and targeting properties of Metoprolol. The unique properties of microparticles (e.g., large surface-to-volume ratio) enhance the therapeutic effectiveness of components with specific shapes and sizes. Hydroxypropyl cellulose (HPC) microparticles were discovered as popular drug delivery carriers due to their biocompatibility and controlled release characteristics.

1.3 Research objectives

The study aims to develop drug-loaded, polymeric microparticles MPs for effective drug delivery. The specific objectives are as follows:

- Preparation of Metoprolol tartrate microparticles loaded with hydroxypropyl cellulose.

- Physicochemical characterization and determination of the properties of MTMPs.
- In-vitro evaluation of the obtained microparticles.

Chapter II

LITERATURE REVIEW

II.1 Introduction

The application of microtechnology in drug delivery has changed the landscape of the pharmaceutical and biotechnology industries in the 21st century (Sun et al., 2020). Microencapsulation is a promising technique in drug development (Singh et al., n.d.). In that sense, microencapsulation is defined as the process in which small quantities of an active ingredient are packed inside a capsule with a size in the micrometer range to avoid potential harmful chemical and physical reactions and to protect the active ingredient from its surrounding environment (Razavi et al., 2021).

II.2 Drug delivery systems (DDS)

Drug delivery system is a method for delivering medication to a patient that targets it to particular parts of the body (Adepu & Ramakrishna, 2021). The main goal of drug delivery system is to liberate the drug at the right time in a right amount of concentration at a specific target site (Bheemidi, 2011), thereby increase therapeutic efficacy and reduce off-target accumulation in the body (Ezike et al., 2023).

The physicochemical properties of the therapeutic agent and bio-barriers such as skin and organ membranes typically define the requirements for efficient medication delivery. Drug characteristics can vary widely depending on size, chemical makeup, hydrophilicity, and capacity to bind specific receptors, even when treating the same symptoms. Many medications have low bioavailability due to their insolubility in physiological fluids and the low permeability of various human organs. Thus, the therapeutic performance is not only dependent on the activity of the applied medicament, Evidence indicates that it is equally important to consider bioavailability on the target side (Laffleur & Keckeis, 2020).

II.2.1 Conventional drug delivery systems

Traditional methods of delivering drugs involved fast-acting and simple compounds that are taken in different forms, such as tablets, pills, capsules, creams, liquids, aerosols, suppositories, injectables, or ointments (Bheemidi, 2011; Laffleur & Keckeis, 2020). These conventional DDSs provide several benefits. The main advantage is convenience that are easy for patients to use. They are also typically non-invasive. Additionally, conventional systems come in pre-measured doses, ensuring patients receive the correct amount of medication each time. This accuracy, along with a higher shelf life, contributes to better patient compliance. Furthermore, conventional systems can be formulated to accommodate variations in patients, such as age or weight. This flexibility allows doctors to adjust dosages as needed for optimal cure. Finally, conventional DDSs are generally less expensive to produce and administer (Adepu & Ramakrishna, 2021).

However, conventional DDSs have limitations despite their benefits. The major issue is the low absorption; the drug may not be up taken fully, thereby losing the medication. In addition, traditional DDSs suffer from no targeted site, leading to side effects. Another issue is the repeated doses that cause poor availability. (Adepu & Ramakrishna, 2021 ; Ezike et al., 2023).

Advantages of conventional DDSs	**Disadvantage of conventional DDSs**
Convenience in administration	Poor absorption from the site of administration
Non-invasive and better IVIVC	No target specificity
Accurate and measured unit dosage form	Premature excretion from the body
Higher shelf-life Premature metabolism of	

the drug	Premature metabolism of the drug
Accommodate patient variation	Poor bioavailability
Flexibility for physician to dose adjustment	Repeated dosing
Low cost)	Poor patient compliance

Table II.1: Advantages and disadvantages of conventional DDSs

II.3 Microparticles as a drug delivery system

Delivering the therapeutic compound to the target site is a major problem in the treatment of many diseases. Initial work in this area focused mainly on developing drug delivery systems to the target site to improve bioavailability and increase the concentration of therapeutic agents in diseased tissues (Wilczewska et al., 2012).

In recent years, the use of microparticles as carriers to deliver drugs to the target site in the body has received attention due to their distinctive properties of encapsulating the drug and increasing its effectiveness in target cells and tissues, which maximize the therapeutic effect of drugs and reduce dosage and side effects, in addition to enhancing the solubility of some poorly soluble compounds in water and enhancing their bioavailability (Bale et al., 2016).

The above-mentioned benefits enable the use of targeted therapeutic microparticles in a variety of medical specialties, for example:

II.3.1 Cardiovascular diseases and hypertension

Hypertension is one of the leading causes of death around the world and is associated with an increased risk of cardiovascular disease. Studies have shown a correlation between high blood pressure and heart disease, as patients with high blood pressure

levels increase their risk of cardiovascular disease by more than 10% (Oparil et al., 2018).

Although many innovative therapeutic methods have been developed, such as gene delivery and cell transplantation, to reduce the risk of hypertension and heart disease, they remain traditional methods to eliminate disease aggravation (Yetisgin et al., 2020). It has now been suggested in this area to design nanoparticles that carry therapeutic agents with the aim of improving biological availability and delivering medicines in a targeted way to re-expand blood vessels (Yetisgin et al., 2020).

Phosphatidylcholine and cholesterol were combined to produce lipid particles that were then coated with chitosan and loaded with small serolimus. It has been demonstrated that the resulting liposomal sirolimus greatly inhibits vascular restenosis (Yetisgin et al., 2020).

II.3.2 Cancer

Chemotherapy is a common treatment for many types of cancer, and cancer is one of the leading causes of mortality. On the other hand, chemotherapeutic drugs have poor tumor selectivity, dose-dependent toxicity, and poor water solubility. Another problem with chemotherapy is multidrug resistance, which is mostly brought on by increased efflux pumps, which are in charge of removing anti-cancer drugs from cell membranes, nowadays, the majority of therapeutic nanoparticles that have received FDA approval are created by repurposing combinations of chemotherapeutic medications with nanoparticles.

As an illustration, super-paramagnetic iron oxide microparticles (SPIOMs) are frequently utilized in clinics as contrast agents for magnetic resonance imaging due to their high magnetic susceptibility. Similarly, super-paramagnetic qualities enable

steady therapeutic drug transport to the body or cell and appropriate tissue accumulation, offering a reliable and secure therapeutic strategy.

Magnetic hyperthermia, which metallic nanoparticles can induce when exposed to an alternating magnetic field, makes them useful for tumor ablation in cancer treatment (Yetisgin et al., 2020).

II.4 Advantage of micro drug delivery systems (MDDS)

Due to the complex cellular network of the body, it is difficult for the drug molecule to reach diseased tissues, so new drug delivery systems have been (Manish & Vimukta,2011).

Targeted drug delivery is a modern technique for delivering therapeutic agents and increasing their concentration in specific parts of the body, thus minimizing the side effects of the drug (Manish & Vimukta, 2011). One of the latest drug delivery systems is microencapsulation due to its specific characteristics required in medical technology, including biocompatibility, standardized encapsulation , better compliance, controlled and sustainable release patterns responsible for reducing toxicity and dose frequency (Bale et al., 2016), and among the most important advantages of microparticles in drug delivery systems: Protecting the encapsulated drug from the external environment and aiding in the sustained and controlled release of the drug (Bale et al., 2016). Therefore, release the drug at the right time and the right concentration at the target site (Laffleur &Keckeis,2020) can improve bioavailability and enhance the solubility of poorly soluble drugs (Bale et al., 2016). It can also minimize toxicity due to repeat dosing while maintaining the therapeutic benefits of the drug and, thus, higher treatment efficiency (Manish & Vimukta, 2011). Hence, this can help masking undesirable drug

odor and taste for patients (Bale et al., 2016) and encapsulating different molecules of the drug (Vlachopoulos et al., 2022).

II.5 Microparticles uptake mechanisms

Scientists have adopted the development of microparticles in the pharmaceutical industry due to their properties in drug delivery and improving the efficiency of treatment, and the most important interactions that occur between the body and microparticles are those at the cellular level, which determines their harmful or beneficial effects on the body. The cell consists of internal components and an outer membrane consisting of a bilayer of lipids with hydrophilic heads and hydrophobic tails. This membrane plays the role of a shield that protects the internal components of the cell from the surrounding environment and maintains cellular balance and ion concentration, as it controls the entry and exit of charged small molecules and nutrients. Microparticles aim to deliver specific factors (genes and drugs) to the cytosol, nucleus, or other specific intracellular sites (Behzadi et al., 2017).

The cellular uptake of microparticles is through the process of endocytosis, which occurs at the level of the cell membrane first, where the interaction between the microparticles and the outer cell membrane and its penetration form intracellular vesicles, which are then transported to specialized intracellular vesicles to be sorted in sorting compartments (Behzadi et al., 2017).

Endocytosis can be classified into several types:

- Phagocytosis.
- Clathrin-mediated endocytosis (CME).
- Caveolae-dependent endocytosis.
- Clathrin/caveolae independent endocytosis.

- Macropinocytosis (Behzadi et al., 2017).

Although endocytosis is the main mechanism of microparticle internalization, there are other mechanisms of cellular uptake including:

Passive diffusion, hole formation, direct microinjection, and electroporation (Behzadi et al., 2017).

II.6 Effect of the physicochemical properties of microparticles on their cellular uptake

There are some physicochemical properties of microparticles that affect their cellular uptake, including:

Effects of size and shape: The size of microparticles plays an important role in cellular uptake as the smaller diameter allows the microparticles to adhere to cells faster and stronger, and the shape (spheres vs. elliptical disks) also plays an important role as spherical particles were collected more quickly, while disks spread in the blood for a longer time (He & Park, 2016).

Surface charge effect: Since the cell membrane is negatively charged, positively charged particles are expected to have strong adhesion to the cell membrane due to electrostatic attraction (He & Park, 2016).

Effect of hydrophobicity: The in vitro study showed that more hydrophilic particles exhibited higher cellular uptake efficiency (He & Park, 2016).

II.7 Microcellulose

Cellulose, the most abundant, sustainable, and naturally occurring polymer, is gaining significant attention in its micro cellulose (MC) forms including cellulose microcrystals (CMC), cellulose microfibrils (CMF), and bacterial cellulose (BC)

(Omran et al., 2021). Their physicochemical and mechanical properties, biodegradability and biocompatibility, become microcellulose a promising material for drug administering drugs. However, microcellulose has low solubility in water and several solvents. To overcome this limitation, researchers can synthesize derivative celluloses (e.g. hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC), and hydroxyethyl cellulose (HEC)) by chemical modifications such as sulfonation, esterification, etherification, silylation, or amidation (Ciolacu et al., 2020).

II.8 Preparation of MPs

Several studies have been carried out to develop microparticle manufacturing techniques for drug delivery applications that are classified into physicochemical methods (emulsion solvent evaporation), chemical methods (polymerization), and mechanical methods (spray drying, microfluidics) that have led to a wide variety of shapes and sizes (Ciolacu et al., 2020).

II.8.1 Physicochemical methods

Emulsion solvent evaporation methods are the most common method of encapsulation in which a polymer is dissolved in a selected organic solvent, usually chloroform or dichloromethane, in an aqueous continuous phase with an emulsion, for example, poly (vinyl alcohol), by mechanical agitation until the solvent partitions into the aqueous phase and is removed by evaporation as micron-sized drops are formed. Microparticles are then recovered by centrifugal or filtration and lyophilized. This technique is simple, fast, and low-cost, and it allows for particle size adjustment by changing the viscosity of organic and aqueous stages, homogenization speed, and emulsion concentration. This method is divided into two techniques: single-oil emulsion in water and double-emulsion technology. The first technique is used for the encapsulation of hydrophobic or poorly water-soluble active ingredients. For double-

emulsion technology, it is used for the encapsulation of hydrophilic drug molecules. This technique is commonly used, but the large quantities of organic solvents required limit their use at the industrial level (Ciolacu et al., 2020).

II.8.2 Chemical methods

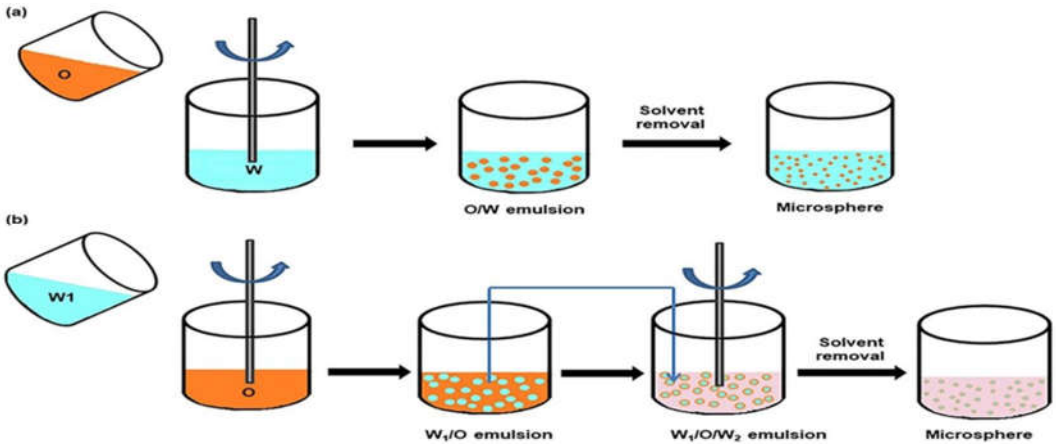


Figure II.1 : Schematic of MPs prepared via (a) single emulsion and (b) double emulsion

Polymerization is a chemical method for the manufacture of microparticles, divided into 4 different types: suspension polymerization, emulsion, bulk, and interfacial polymerization. The appropriate method of polymerization must be used based on the nature of the drug (hydrophilic or hydrophobic) to ensure optimal packaging of therapeutic agents, allowing control of their release rate (Bale et al., 2016).

II.8.3 Mechanical methods

Supercritical fluids are an emerging technique for the production of microparticles where the process is performed in a T-shaped microfluidic device containing micron-sized channels that inject the continuous, unmixable phase (such as a pharma copolymer solution) through one channel while the dispersed phase flows through another. The two channels are perpendicular to each other, and the exact drop is formed at the intersection of the channels. This technique is characterized by a simple preparation process, the production of micro-single dispersion particles and adjustable structures, and high encapsulation efficiency. This technique also allows the chemical composition of droplets to be controlled according to the change in the component fluid, as well as the size of the droplet according to the flow rate of different stage (Su

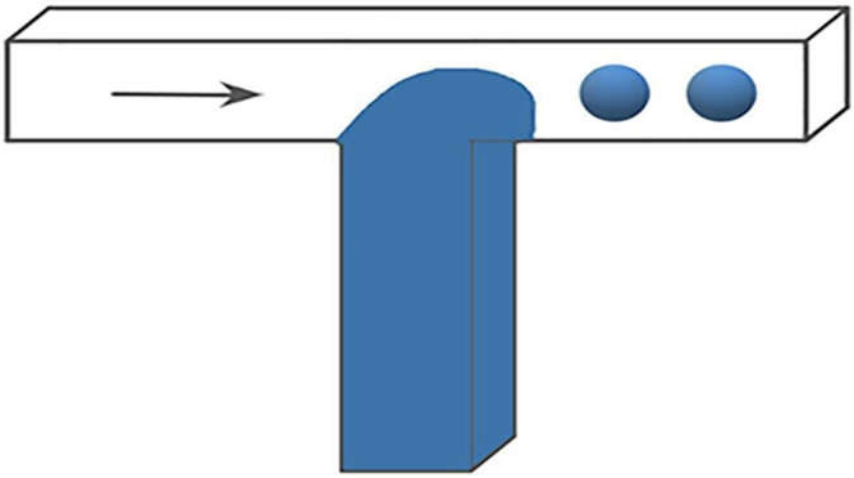


Figure II.2 : T-Junction Microfluidic device

et al., 2021).

Recently, supercritical liquids (SCF) were widely adopted to prepare fine particles, and the use of supercritical carbon dioxide (scCO2) is most commonly used as a green substitute for organic solvents with its relatively low critical temperature (31.1 ◦C) and its critical pressure, estimated at 73.8 bar. The process depends on the formation of particles by rapid pressure relief caused by the low pressure of the polymer solution

(dissolved polymer in scCO2) through a nozzle in a low-pressure environment. Pressure, nozzle diameter, solution concentration, and temperature can affect the properties of the final particles (Vlachopoulos et al., 2022).

Spray drying is a modern strategy for the microencapsulation of active compounds. Drugs and polymer solutions are disinfected and injected into hot air (Su et al., 2021). The process includes four stages: to dissolve and mix droplets, solvent volatility, and product separation. This method is adopted in the preparation of inhalable formulations suitable for the delivery of pulmonary drugs. The final MP size can be adjusted by adjusting the strength of the electrostatic field, solution flow rate, and concentration. This method generates particles quickly and continuously, eliminating the need for separate drying operations. It is suitable for packaging proteins, peptides, DNA, and small molecules (Vlachopoulos et al., 2022).

II.9 Advantages of Hydroxypropyl Cellulose (HPC) for Drug Delivery

Hydroxypropyl cellulose has several benefits as a material for the encapsulation of drugs in microparticles and as a carrier agent. These microparticles can be used as an excipient and loaded with an active pharmaceutical ingredient to create a controlled release system.

Improved solubility: HPC can improve the solubility of poorly water-soluble drugs, making them more and better bioavailable for absorption by the body (Martin-Pastor & Stoyanov, 2020).

Enhanced bioavailability: the active pharmaceutical ingredient can be optimized by HPC microparticles, leading to increased bioavailability and reduced side effects (Bale et al., 2016).

Drug safety: HPC can protect the encapsulated drug from external factors such as temperature fluctuations and stomach acidity, possibly improving drug stability and effectiveness (Bale et al., 2016).

Taste masking: HPC can help cover up the unpleasant taste and smell of drugs, leading to improved patient compliance (Bale et al., 2016).

Targeted drug delivery: HPC microparticles enhance the concentration of the medication in certain areas of the body compared to others (Bale et al., 2016)

Controlled Release: HPC allows for precise control over the rate of drug release. This can be particularly advantageous for drugs that require sustained or slow release to maintain therapeutic efficacy (Kamel et al., 2008).

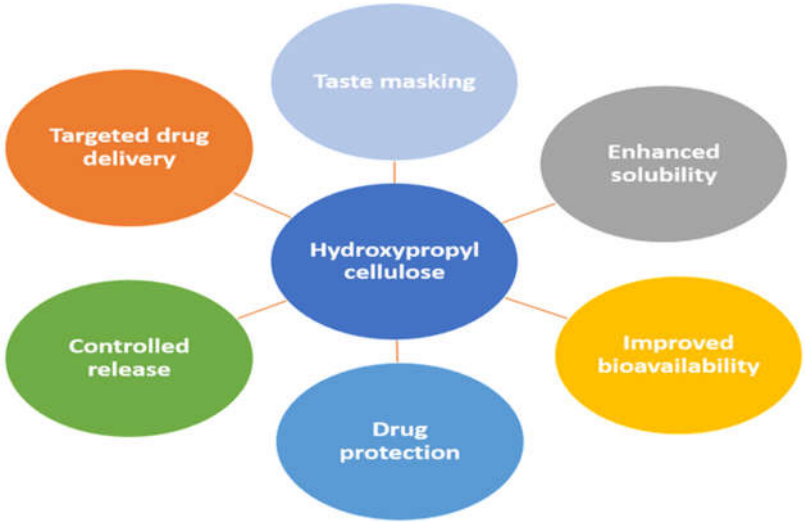


Figure II.3: Advantages of HPC

II.10 Application of hydroxypropyl cellulose (HPC) in medicine

After its application in medication delivery, HPC is an agent with many other uses in medicine. Here advantages:

- Used for artificial tears and treating medical conditions like keratoconjunctivitis sicca, corneal erosions, decreased corneal sensitivity, exposure, and neuroparalytic keratitis (Lavanya et al., 2011).
- Lubricant for artificial eyes (Lavanya et al., 2011).
- Used as a thickener, low-level binder, and emulsion stabilizer (Lavanya et al., 2011).
- Used in pharmaceuticals as a disintegrant and binder in tablets (Lavanya et al., 2011).
- Used as a sieving matrix for DNA separations via capillary and microchip electrophoresis (Lavanya et al., 2011).
- Used in treating oral mucosal disorders like canker sores (Kamel et al., 2008).
- Used in thickening agents, tablet binding, modified release, and film coating (Kamel et al., 2008).

II.11 Distinctive features of microparticle

Microparticles have become commonly used in many industrial, medical, and pharmaceutical fields and have gained importance in medical and pharmaceutical applications due to their distinctive properties, which are: Drug delivery to the target site and easy absorption at the cellular level due to their small size, optimal packaging of therapeutic agents, improving efficiency and enhancing bioavailability, which contribute to reducing the dose given and reducing the toxicity of some treatments such as anti-cancer drugs, as well as turning liquid substances into solids and hiding the taste and odor of the drug (Katekar et al., 2023).

II.12 Controlled and Sustained release

A recent review of the literature on the subject of drug delivery has found that the sustainable and controlled launching matrix-type drug delivery system plays an

important role in releasing the drug for a specified period of time, maintaining a steady level of the drug, and increasing its therapeutic effectiveness so that harmful effects are avoided (Ciolacu et al., 2020).

II.12.1 Controlled release

The term “pulsatile release” refers to the delivery of a drug product that is designed to release certain amounts of drug at predetermined time intervals (Kamel et al., 2008). The incorporation of some poorly water-soluble drugs into microparticles has produced controlled-release formulations for up to 22–24 days (Ciolacu et al., 2020).

Controlled-release drugs are categorized based on the drug release mechanism into dissolution-controlled, diffusion-controlled, water penetration-controlled (swelling control), chemical-controlled, and nanoparticle-based systems (Adepu & Ramakrishna, 2021).

The goal of controlled-release formulations is to minimize side effects, variability in plasma levels, and frequency of administration while increasing patient compliance.

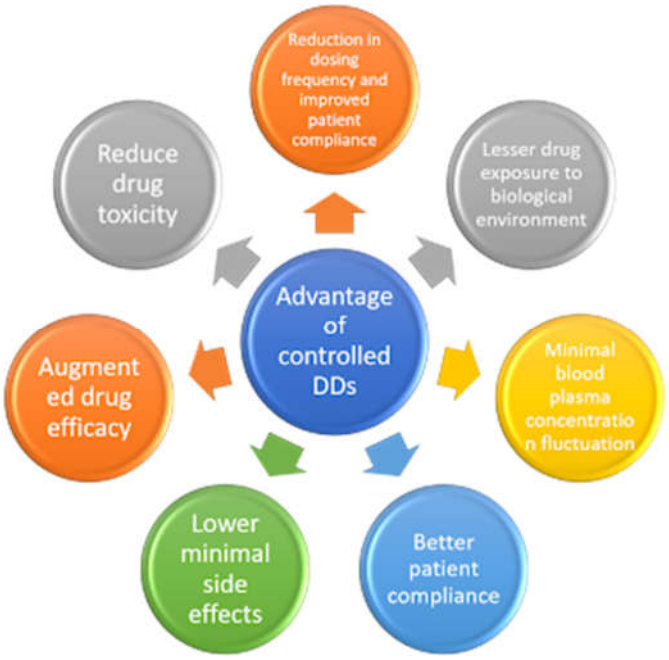


Figure II. 4: Advantages of controlled DDS

II.12.2 Sustained release

Extended-release dosage form: is a dosage form that delivers one or more medications systemically or locally to a specific target over a definite period of time in a predetermined pattern, In order to maintain the therapeutic range of the medication in blood plasma. (Kamel et al., 2008)

Polymers such as methylcellulose (MC), cellulose ethyl (EC), hydroxypropyl cellulose (HPC), and hydroxypropyl methyl cellulose (HPMC) are hydrophilic compounds that can form a gel in the presence of a high amount of water. They are biodegradable and biocompatible, have suitable properties for targeted and continuous release of the drug over a long period of time, and have the ability to deliver the drug even in the presence of a particular environmental catalyst. In addition to using Poly (lactic acid) (PLA) and poly (lactic-co-glycolic acid) (PLGA)-based microscopic molecules in the field of sustainable release of therapeutics recently, a prominent area of research due to their excellent biodegradability and biocompatibility, the methods

available to manufacture these systems proved to be versatile. In this direction, enhanced drug release behaviors, different particle size and structure properties, and loading capabilities can be achieved by modifying some experimental variables related to the preparation process (Ciolacu et al., 2020).

The ideal drug delivery system must administer the right amount of the drug at the right site of action and at regular intervals.

So, reducing dosage, delivering consistent medication administration, and minimizing dosing frequency are the objectives of creating a sustained release drug delivery system. This approach is typically utilized when a single dose is needed for the course of treatment, which may be days or weeks, such as in the case of an infection, diabetes, or hypertension. Sustained release medication delivery systems are highly beneficial in improving dosage efficiency, dosage safety, and patient compliance. These days, the oral route of administration for sustained release drug delivery systems has drawn increased interest since it offers greater patient compliance, reduced frequency of dosage, and more flexibility. The physical-chemical characteristics of the drug, the kind of delivery system, the disease being treated, the patient's condition, the length of the treatment, the presence of food, gastrointestinal motility, and the coadministration of other medications are some of the factors that influence the design of an oral sustained release drug delivery system. From the explanation above, we can deduce that, in addition, the oral sustained release drug delivery system's affordable price has made it easier for it to enter the market and replace oral traditional drug delivery systems (Kamel et al., 2008).

II.13 Burst release

The initial burst release is one of the main problems in the development of controlled release formulations, including drug-loaded nanoparticles and nanoparticles that occur in the first minutes of dose contact from the external medium (Hasan et al., 2007), and this burst release is due to the leakage of the drug located near the surface of the particles. This explosive release may be useful in the case of dermal applications, but continuous release is important for toxic active drugs at high concentrations or those that need to be present over a long period of time (Hasan et al., 2007).The burst release mechanism occurs in three phases, starting with the propulsive release to focus the drug on the surface, followed by a slow release rate until the polymeric microparticle matrix decomposes, and finally a rapid final drug is released again .When the initial batch is released, a large proportion of the encapsulated drug occurs quickly within a short period of time, immediately after administration (Vlachopoulos et al., 2022). This initial rush of the drug is undesirable because it shortens the total duration of the therapeutic effect of the drug and may even cause toxicity that can have side effects on the patient (Yoo & Won, 2020). In this study, strategies have been developed to reduce the drug's initial impulse from microparticles (PLGA), which is one of the most widely used means of delivering polymeric medicines. There are approximately 20 commercialized medicines using PLGA as a swag in more than half of these formulations. PLGA is used in the form of microparticles (sizes ranging from 60 nm to 100 micrometers) (Yoo & Won, 2020). The primary role of PLGA is to control the kinetics of the drug's release towards achieving a sustainable release of the drug, but PLGA molecules still face the problem of explosive release. Several studies have been conducted to improve the release of the drug and eliminate the effect of explosion by altering the distribution of the drug within the polymer matrix or by

developing more sophisticated drug delivery systems (Hasan et al., 2007). Some scientists have suggested encapsulating the drug with micro-particles prepared with a mixture of polymers characterized by viscosity, molecular weight, and various swelling properties that may also modify the release of the drug compared to micro-particles prepared from a single polymer. This experiment was applied to ibuprofen, which was encased in a combination of ethyl cellulose and polystyrene, which was prolonged over a 24-hour period with a low explosion compared to the microscopic pellets prepared from ethyl cellulose alone (Hasan et al., 2007).

Differents	**Controlled release**	**Sustained release**	**Burst release**
Release rate	Regulated	Consistent	High then slow
Release' s duration	Extended	Extended	Short
Applications	Several drugs	Drugs need consistent blood level	Sites need high initial dose
Advantages	Reduce toxicity, Lower side effects and better patient compliance	Reduce dosage, deliver consistent medication administration, and minimize dosing frequency.	Useful for dermal applications
Disadvantages	Complex to design	Not suitable for all drugs	Must lead by sustained release

Table II. 2: Comparison among release forms

II.14 Kinetic modeling on drug release

A drug of high-water solubility dissolve in water or gastrointestinal fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a

sharp increase in the blood drug concentration compared to less soluble drug, The maximal half-life for absorption should be roughly 3–4 hours if we assume that dose forms transit through the absorptive regions of the GI tract in 8–12 hours. If not, the dose form will exit absorptive areas before the whole amount of medicine is released (Kamel et al., 2008).

II.15 Metoprolol tartrate

II.15.1 Physical properties

The physical properties of metoprolol tartrate are:

- White in color
- Crystalline powder
- Solubility: very soluble in water, freely soluble in methylene chloride, in chloroform, and in alcohol, slightly soluble in acetone and insoluble in ether
- Melting point: 124°C
- Molecular weight: 684.82 g/mol
- Chemical formula: $(C_{15}H_{25}NO_3)_2 . C_4H_6O_6$
- λ_{max}: 223 nm (Metoprolol Tartrate | DrugBank Online, n.d.).

II.15.2 Synthesis of metoprolol tartrate

The general process involves three steps:

Step 1: Synthesis epoxide by reacting 2-(methoxyethyl)phenol with epichlorohydrin. Three times of washing the organic phase are conducted using water with a pH between 7 and 8.

Step 2: To produce metoprolol base, react epoxide with isopropyl amine.

Step 3: The metoprolol base is reacted to produce a metoprolol tartrate (*ORGANIC SPECTROSCOPY INTERNATIONAL: Metoprolol Tartrate,* 2016)(Choubey et al., 2005)

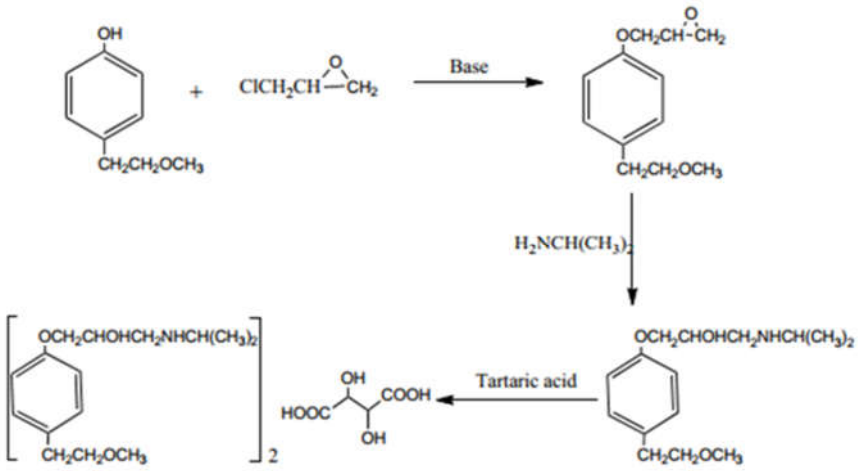


Figure II.5 : Synthesis of metoprolol tartrate

II.15.3 Pharmacokinetic properties of metoprolol tartrate

Absorption: Oral bioavailability of Metoprolol is about 50% as pre-systemic metabolism occurs which can be stopped with the increase of the dose.

Distribution: Volume of distribution of Metoprolol is 3.2 to 5.6 L/kg. About 10% of Metoprolol in plasma binds with the serum albumin. It crosses the placenta and blood brain barrier. It is also found in breast milk. It does not bind with P-glycoprotein.

Metabolism: Metoprolol is a racemic mixture of R- and S- enantiomer and after administration it shows stereoselective metabolism. This metabolism is dependent on oxidation phenotype. Metoprolol Tartrate is primarily metabolized by the CYP2D6 which is absent in about 8% Caucasians and about 2% of most other populations (poor metabolizers). People having no CYP2D6 enzyme system shows several fold higher plasma concentrations than those who have this enzyme.

Elimination: The elimination half-life of Metoprolol is 3-4 hours but in poor metabolizers it may be 7-9 hours. 5% of oral dose and 10% of intravenous dose are excreted through urine as unchanged state in normal subjects. In poor metabolizers, the excreted unchanged amount of drug increase to 30% of oral dose and 40% of intravenous dose (*Metoprolol*, n.d.).

II.15.4 Adverse reactions and Side effects of conventional MT

Central Nervous System: Tiredness and dizziness, Mental confusion and short-term memory loss, Headache, nightmares, and insomnia.

Cardiovascular: Shortness of breath and bradycardia, cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension.

Respiratory: Wheezing (bronchospasm) and dyspnea, rhinitis.

Gastrointestinal: Diarrhea, nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn.

Hypersensitive Reactions: Pruritus or rash and very rarely, photosensitivity and worsening of psoriasis.

Miscellaneous: Peyronie's disease, musculoskeletal pain, blurred vision, and tinnitus (*Metoprolol*, n.d.).

II. 15.4 Existing methods for MT deliver

In 2011, Bharti D. Adi., et al formulated metoprolol tartrate microspheres with chitosan. The prepared microspheres were prepared by ionic precipitation and chemical cross-linking methods and evaluated for particle size, surface morphology,

entrapment efficiency, in vitro drug release, and infrared spectroscopy (Adi et al., 2012).

In 2012, Khan, et al. prepared an intranasal in situ gel with increased nasal residence time in order to improve bioavailability of metoprolol tartrate using Carbopol and Hydroxypropyl methyl cellulose K4M and K15M in different concentrations. The obtained gel was characterized for viscosity, rheological behavior, gelation behavior, gel strength, and mucoadhesion (Khan et al., 2012).

In 2016, Malipeddi., et al aimed to prepare and evaluate controlled release microspheres of metoprolol tartrate with ethyl cellulose and polyethylene glycol-6000. The microspheres were prepared by solvent evaporation method with varying concentrations of a mixture containing ethyl cellulose and polyethylene glycol-6000. The prepared microspheres were evaluated for the percent yield, drug content, efficiency encapsulation and in drug release and characterized by Fourier transform infrared spectroscopy (FTIR) and the differential scanning calorimetry (DSC) (Malipeddi et al., 2016).

In 2018, yildiz, et al aimed to design metoprolol tartrate loaded chitosan microparticles to obtained modified drug release. Chitosan microparticles produced via ionic gelation with tripolyphosphate as a crosslinking agent. Prepared formulations were characterized and metoprolol tartrate was loaded into the optimal blank microspheres. The entrapment efficiency, drug loading, cell viability assay and in vitro drug release were investigated. Optimum formulation was spherical and had 81% of yield and 75.373±7.384µm particle size. 16 mg of metoprolol tartrate could be loaded into microparticles and drug release could be maintained for 48 hours (Demirbolat et al., 2018).

In 2020, Mohan., et al worked to optimize different immediate and sustained release formulations of metoprolol tartrate, immediate release layer was prepared by using Sodium Starch Glycolate and Crospovidone as super disintegrants and Sustained release layer was prepared by using HPMC K100M and HPMC K15M as release retardant polymers (Mohan et al., 2020).

In 2022, the study developed thermosensitive liquid suppositories (LSs) carrying the model antihypertensive drug metoprolol tartrate (MT) for the first time. The suppositories were based on biodegradable nanoparticles synthesized by ring opening polymerization. The drug was released over 12 hours, with 66-91% released depending on the concentration. The LSs were then evaluated for their mechanical and rheological properties. The study found that the diffusion process was dominant, and the MT release profile was governed by the rheological and mechanical properties (Bialik et al .,2022).

Chapter III

METHODOLOGY

III.1 Introduction

Microparticles are widely employed in drug delivery systems, providing several benefits due to their structural and functional abilities, and their application is suitable for convenient and tolerable drug administration (Lengyel et al., 2019).

To enhance the release rate of metoprolol tartrate, hydroxypropyl cellulose was used in the formulation of microparticles due to its properties, such as being biodegradable, non-toxic, and biocompatible.

Synthesize of metoprolol tartrate microparticles was performed by controlling the weight ratio of the active compound and polymer based on minimum particle size. For easy preparation, an HPC/MT ratio of 2:1 displayed a minimum particle size (Hassani et al., 2019).

However, before the preparation of MTMPs should determine the physical and chemical properties of MT alone to effective, state, and safe dosage form.

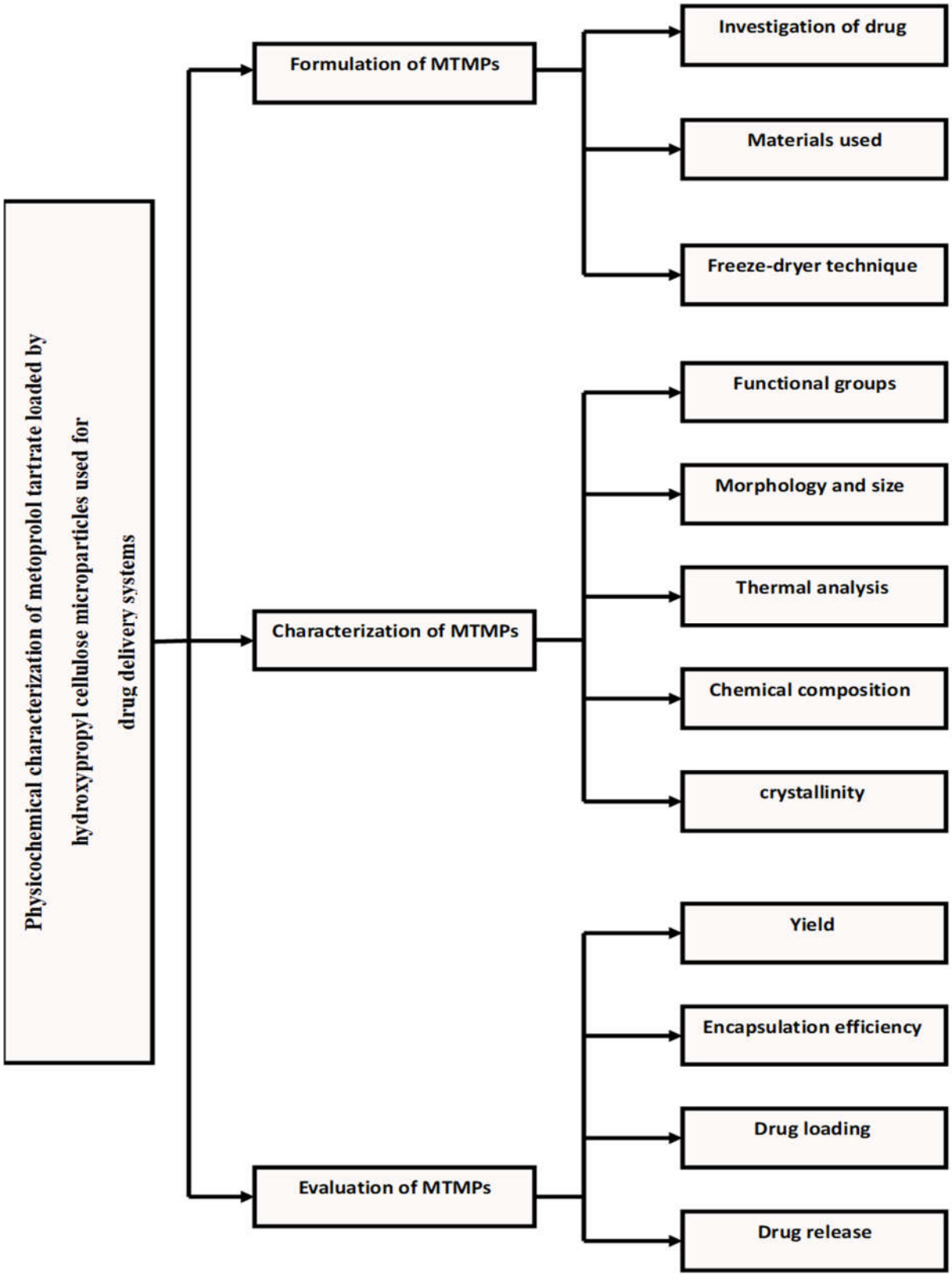


Figure III.1: The flowchart of study

III.2 Materials and Equipment

III.2.1 Materials

The materials were obtained as indicated in the table below:

S.No	Ingredients	Sources
1	Metoprolol Tartrate (P=99%)	Sigma-Aldrich company
2	Hydroxypropyl cellulose (P=99.8%)	Sigma-Aldrich company
3	Distilled water	Laboratory (kasdi Merbah Ouargla)
4	Hydrochloric acid	Laboratory (kasdi Merbah Ouargla)
5	Buffer solution pH 7	Laboratory (CRAPC Ouargla)
6	Buffer solution pH 4	Laboratory (CRAPC Ouargla)

Table III. 1: List of materials with sources

III.2.2 Equipment

The following table shows the equipment used:

S.No	Equipment	Model
1	Electronic balance	OHAUS AX324
2	Ultra Thorax	IKA T-18
3	Freez-dryer	CHRIST ALPHA2-4 LCBASIC
4	Magnetic stirrer	
5	Digital pH meter	YINMIK YK-P01
6	UV spectrophotometer	AGILENT Cary 100
7	FTIR spectrophotometer	AGILENT Cary 630

8	Scanning electron microscope	CARLSEIZZ Zeiss evo 15
9	X-Ray Diffraction patterns	
10	Differential Scanning Calorimeter	Mettler Toledo
11	Shaker	IKA KS 3000 I C C

Table III. 2: List of equipment with model

III.3 Methods

III.3.1 Pre-Formulation studies

III.3.1.1 melting point test

Melting point was determined by melting point equipment.

III.3.1.2 Standard curve of metoprolol tartrate

100 mg of metoprolol tartrate was dissolved in a small amount of hydrochloric acid solution and the volume was adjusted to 100 ml, the same solution having a concentration of 1000 µg/ml. 10 ml of this solution is taken and diluted to 100 ml with HCl solution to obtain 100 µg/ml. Aliquots of 1, 2, 3, 4, 5, and 6 mL of the final solution were transferred to 10 mL volumetric flasks and the final volume was made up to 10 mL with HCl solution to obtain 10 to 60 µg/ml. The absorption values of these solutions were measured against blank HCl at... nm using a UV-visible spectrophotometer.

III.3.2 Formulation of metoprolol tartrate microparticles (MTMPs)

Freez-drying technique was employed to prepare microparticles. Experiment was carried out in a weight ratio 2:1(W/W). 0.5 g metoprolol tartrate was dissolved in 50

ml of distilled water at room temperature, hydroxypropyl cellulose solution was prepared by dissolving 1g of HPC in 200 ml of distilled water at 50 °C under stirring**.**

The MT solution was added dropwise in the HPC solution under agitation at room temperature for 72h. The obtained mixture was mixed by using Ultra Thurrax at room temperature for 7 min and frozen at - 80 °C, and subsequently freeze-dried for 120h.

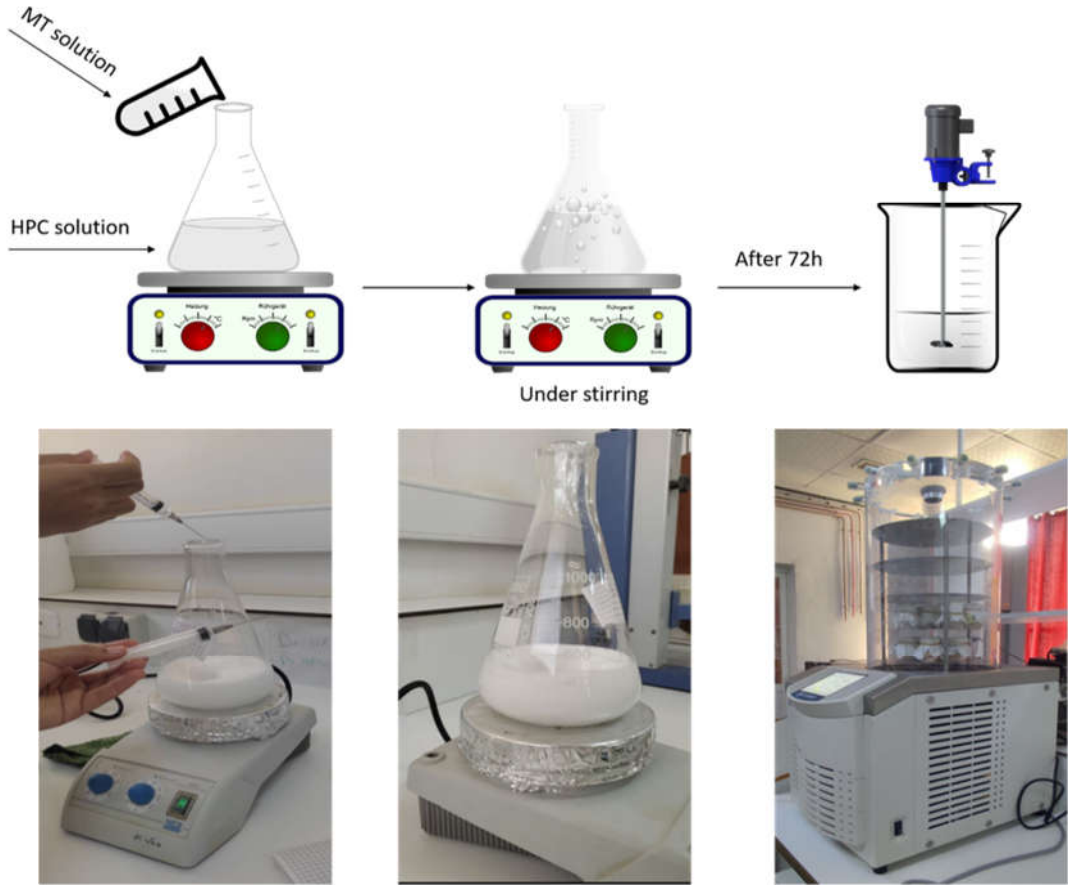


Figure III.2: Preparation of MTMPs

III.3.3 Preparation of physical mixture

The physical mixture of HPC\MT in the 2:1 weight ratio as the MTMPs were prepared. The active pharmaceutical ingredient and the polymer were admixed for 5 min to form a homogeneous powder using a pestle and mortar.

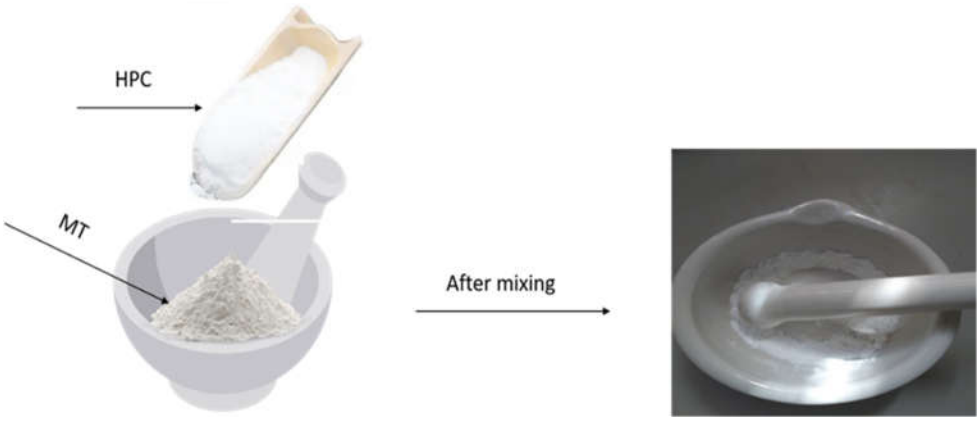


Figure III.3 : Preparation of physical mixture

III.3.4 Physicochemical characterization

III.3.4.1 UV-visible Absorption Spectroscopy

The UV-visible absorption spectrums of MT, HPC, MTMPs, and physical mixture were performed using an UV-visible spectrophotometer.

III.3.4.2 Fourier transform infrared spectroscopy (FTIR)

Fourier transform infrared spectroscopy study was carried out to show complex formation and identify functional groups of molecules, interpreted from infrared spectrum. In this way, absorption characteristics and wavenumbers of functional groups were exhibited. FTIR spectra of HPC, MTMPs, and physical mixture were recorded using FTIR spectra. The samples are placed directly in the sample holder.

The analysis was carried out via the KBr disc method which involves pressing 1% of the compound in 200 mg of potassium bromide at room temperature over the range of 4000-400 cm^{-1} and the resolution of 4 cm^{-1}.

III.3.4.3 Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry analysis is a technique used to study thermal behavior of a material by analyzing the heat flow changes. DSC were recorded by using 5 mg of samples on a Mettler Toledo instrument with heating rate of 30°C/min from 25°C to 500°C under nitrogen atmosphere (N_2) flow rate (50ml/min).

III.3.4.4 X-Ray diffraction Powder (XRD)

To deliver the structure crystallinity of resulting microparticles, MT, HPC, and physical mixture in this study, patterns were recorded using Cu K α radiation 30 KV at the range of 2-60°analysis of samples was carried out with dwell time of 2°per minute.

III.3.4.5 Scanning electron microscopy with energy dispersive X-ray spectroscopy (SEM/EDX)

The surface of morphology and chemical composition of dried MTMPs were examined in ZEISS SEM/EDX. Vacuum dried small amount of prepared MTMPs samples were kept on an SEM stub using double-sided adhesive. Afterwards, the stub containing the sample was placed in the scanning electron microscopy (SEM) Chamber. The photomicrograph was taken at an acceleration voltage of 10 KV.

III.3.5 Evaluation of metoprolol tartrate microparticles

III.3.5.1 Yield percent

The dried MTMPs were weighed, and the percentage yield of the prepared microspheres was calculated by using the following formula:

$$\textbf{Percentage yield} = \frac{\textbf{Weight of MTMPs}}{\textbf{Weight of HPC + MT}} \times \textbf{100}$$

III.3.5.2 In-Vitro release Study

To evaluate the quality of a drug product, the test was carried out by dissolving 10 mg of MTMPs in 30 ml of buffer solution at pH 4 and 7 under stirring by a shaker at 37°C. The absorbance was measured at interval times on a spectrophotometer at λ_{max} = 273 nm.

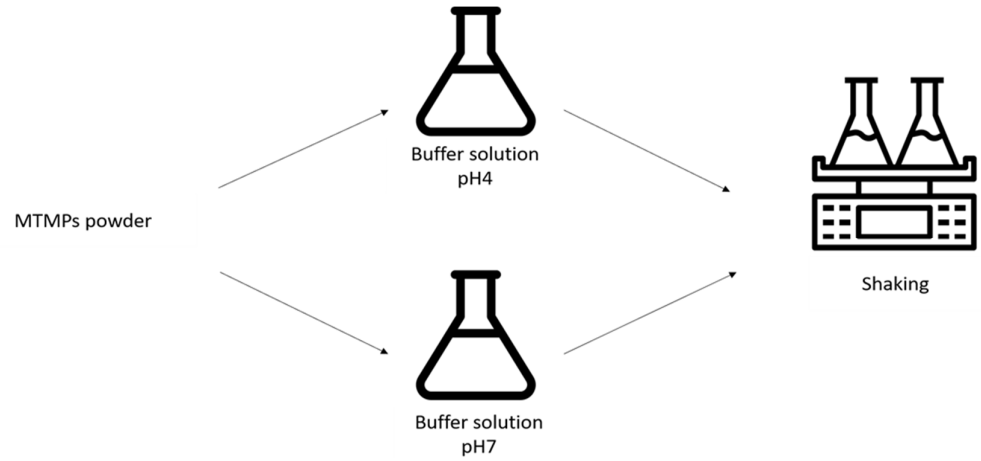


Figure III.4 : In-vitro drug release experience

III.3.5.3 Drug loaded (DL)

10 mg of the obtained microparticles were dissolved in 30 ml of 100 µg/ml HCl solution. The concentration of MT loading in MPs was calculated using standard curve. The percentage of drug loading was calculated as per the following formula:

$$\textbf{DL \%} = \frac{\textbf{The amount of MT in MTMPs}}{\textbf{The amount of MTMPs}} \times \textbf{100}$$

III.3.5.4 Encapsulation efficiency (EE)

The encapsulation efficiency of microparticles prepared by freeze-drying technique was determined using by UV-spectrophotometer at 273 nm. The amount of MT non-

encapsulated was calculated by standard curve. The encapsulation efficiency was calculated using following formula:

$$\mathbf{EE\%= \frac{Initial\ amount\ of\ MT - free\ amount\ of\ MT}{Initial\ amount\ of\ MT} \times 100}$$

Chapter IV

RESULTS AND DISCUSSION

IV.1 Characterization of microparticles

IV.1.1 The UV-visible Absorption Spectrum of metoprolol tartrate (MT), hydroxypropyl cellulose (HPC), and metoprolol microparticles (MTMPs):

The absorption spectrums of metoprolol tartrate (MT), Hydroxypropyl cellulose (HPC), and (MTMPs) are shown in Figures 4.1, Figure 4.2 and Figure 4.3, respectively. The purpose of UV-Visible measurement is to confirm the λ_{max} absorption of MT, HPC and MTMPs. The UV-Visible spectrum of MT and HPC showed a broad absorption bands intensity at 273nm, 205 nm, and in Figure 4.1 and Figure 4.2.

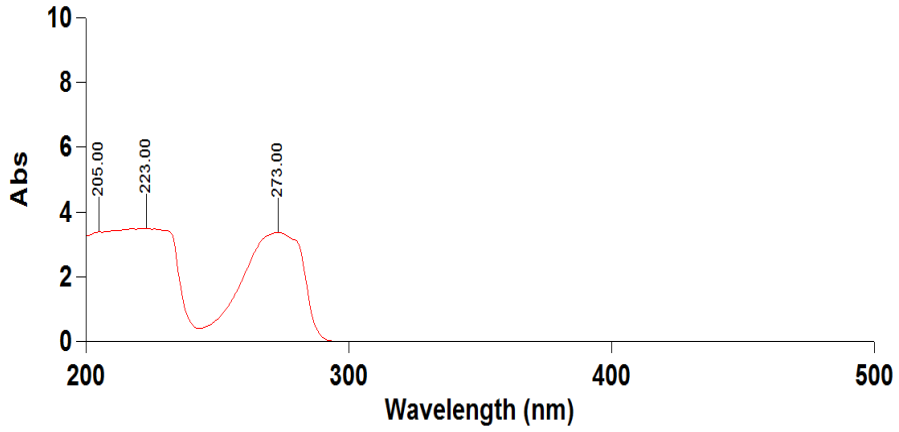


Figure IV. 1: The UV-Vis spectrum of metoprolol tartrate

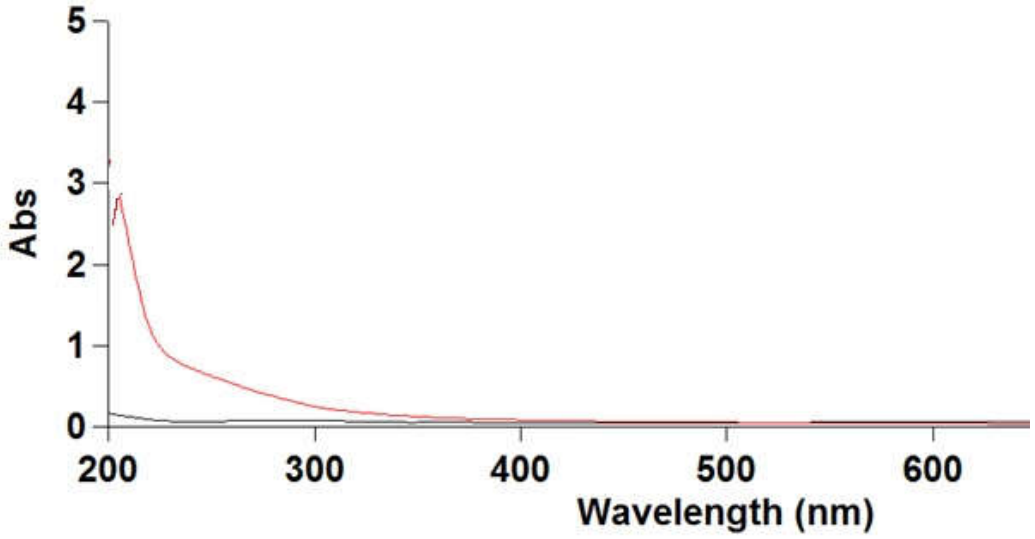


Figure IV. 2: The UV-Vis spectrum of hydroxypropyl cellulose

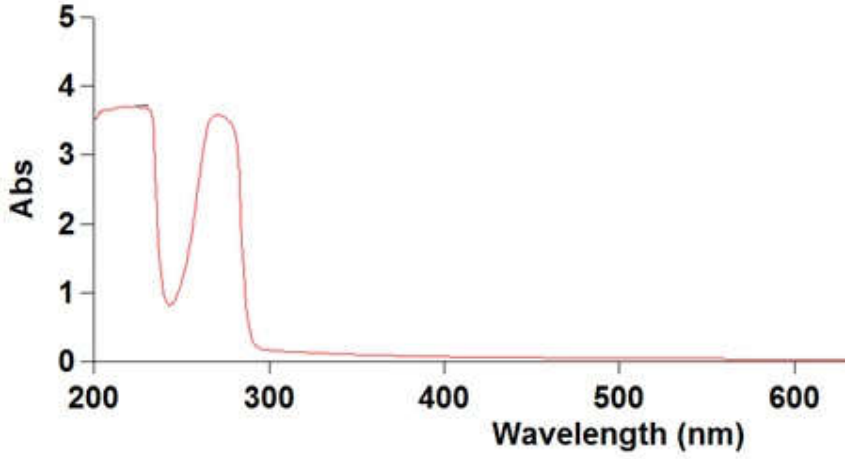


Figure IV. 3: UV-Vis spectrum of MTMPs

The absorption spectrums of MTMPs in Figure 4.3 mentioned the presence of two broads' absorption intensity of HPC at 205 nm and MT at 273nm.

IV.1.2 FTIR spectrums of (a) MT, (b) HPC, (c) Physical mixture, (d) MTMPs

The FTIR analysis was performed to demonstrate the formation of complexes and identify the functional groups of compounds that were resulted from the infrared spectrum.

The FTIR spectra of MT, HPC, Physical mixture and MTMPs are shown in Figure 4.3. The spectrum of MT with band characteristics is presented in Figure (4.3.a.)

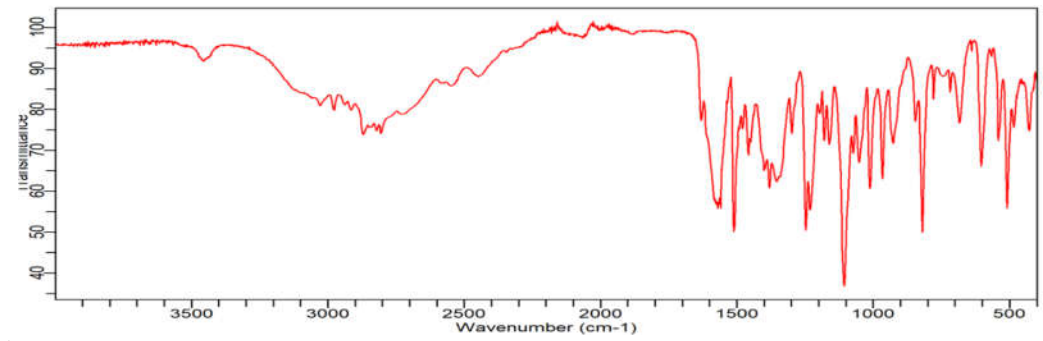
FT-IR spectrum of metoprolol tartrate shows the characteristic functional groups of this organic molecule. The hydrogen-bonded O–H band is a broad peak between 3,350 to 3,450 cm^{-1}. An alkane chain is evidenced by several C–H bands between 2,700 to 2900 cm^{-1}. An aromatic character in the sample is evidenced by several bands. A weak C–H stretching band is observed at 3,030 cm^{-1} and two strong C=C stretch bands at 1,480 and 1,607 cm^{-1}. The para-substitution is indicated by a strong C–H bending at 800 cm^{-1}. The phenyl alkyl ether character of the sample is evidenced by two strong bands at 1,280 and 1,110 cm^{-1} due to the two kinds of C–O bonds. Since this pharmaceutical compound is a carboxylate salt, two strong bands are observed at 1,590 and 1,340 cm^{-1} due to asymmetric and symmetric stretching of this carboxylate. A secondary amine presents a NH stretch at 2,990 cm^{-1} and a broad band at 2,066 cm^{-1}.

Fourier transform infrared (FT-IR) absorption spectra for HPC was shown in Figure (4.3.b.). Absorption band at 3431 cm^{-1} is due to hydroxyl group in the pyranose unit of HPC. Absorptions band at 2810 cm^{-1} and 2932 cm^{-1} is due to CH_2 and CH stretching vibration. Absorption band at 1079 cm^{-1} is due to C-O-C stretching vibration.

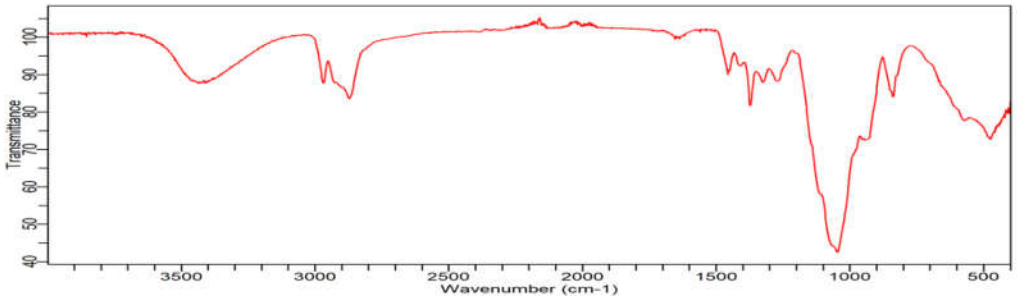
However, various peaks of HPC appeared to shift slightly towards the lower frequency range in the spectrum of the MTMPs (Figure 4.3.d), which were

accompanied by the disappearance of most peaks of MT. The differences in characteristic absorptions peaks can be explained by the interaction occurred between MT and HPC. Various peaks of MT and HPC were presented in the physical mixture spectrums Figure 4.3.c with no considerable changes, signifying the absence of any interactions.

a-



b-



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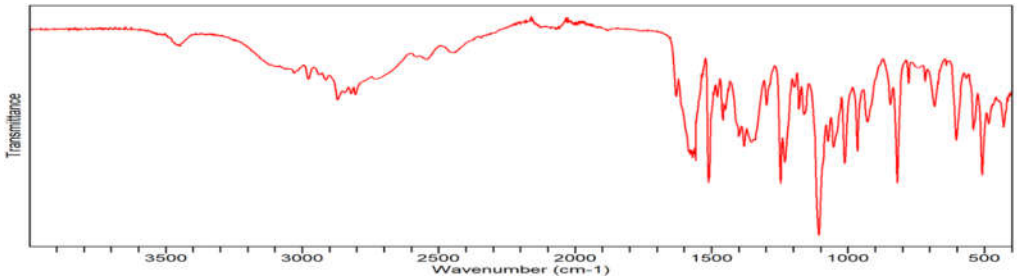


d-

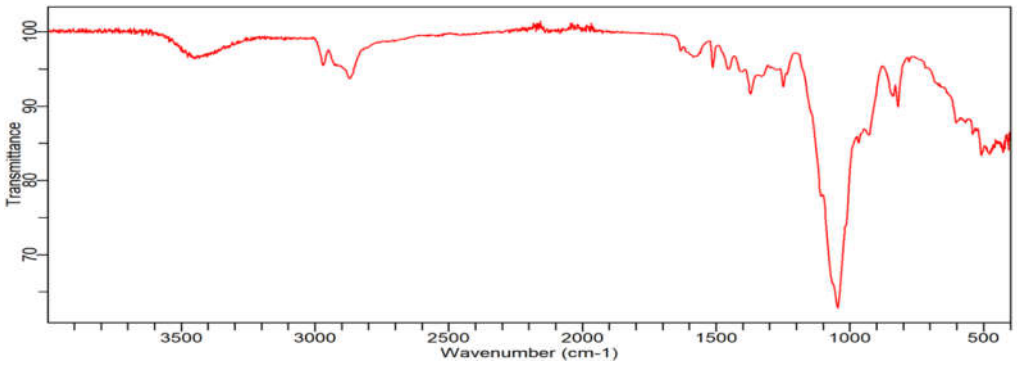


Figure IV. 4: FTIR spectrum of (a) MT, (b) HPC, (c) Physical mixture, (d) MTMPs

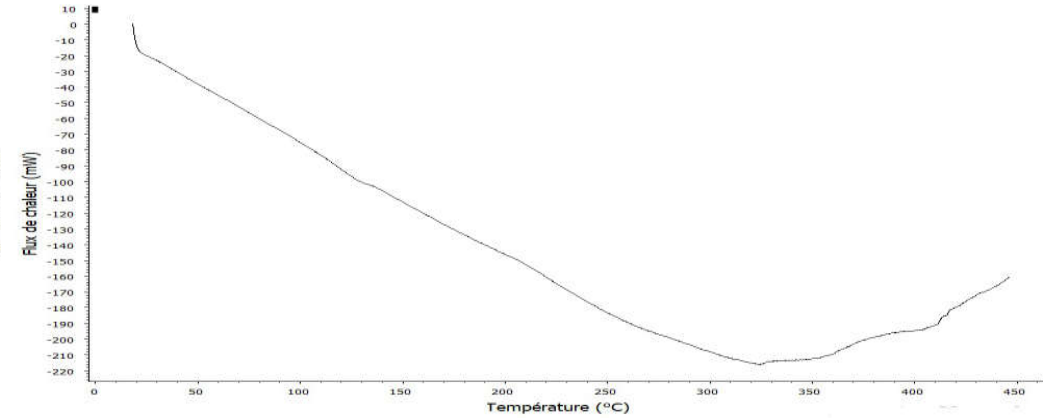
IV.1.3 Thermal study

The differential scanning calorimetry is usually used to examine the physical state and decomposition of compounds Figure 4.5 presents the differential scanning calorimetry DSC profile of MTMPs, HPC, pure compound, and physical mixture.

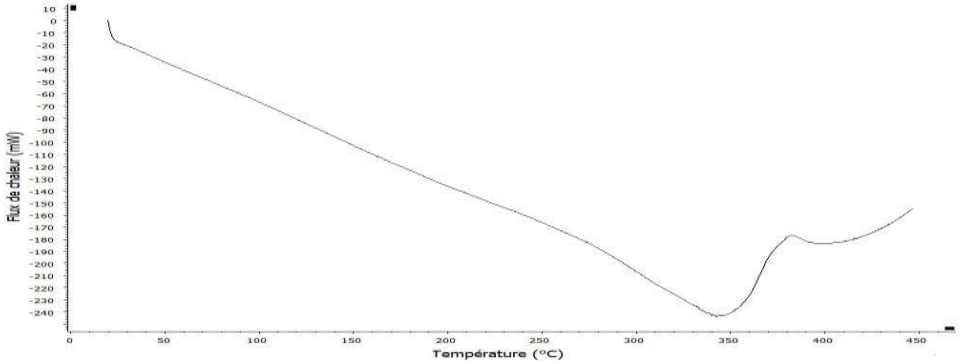
As shown in Figure 4.5 (a), the DSC profile of MT demonstrated an endothermic peak at 125.2°C, which corresponded to the melting point of MT. The endothermic peak of MT vanished completely in the DSC pattern of MTMPs (Figure 4.5.d).

The DSC results of HPC indicated an endothermic peak at 345.11°C mentioning the melting point of HPC (Figure 4.5.b). Furthermore, the DSC pattern of MT in the physical mixture (Figure 4.5.c) showed an endothermic peak with lower intensity at 130°C. These marked changes related to the masking of MT melting endotherm or the fusion between MT melting and HPC decomposition which may attributed to the overlapping of the vicinity of both effects.

a-



b-



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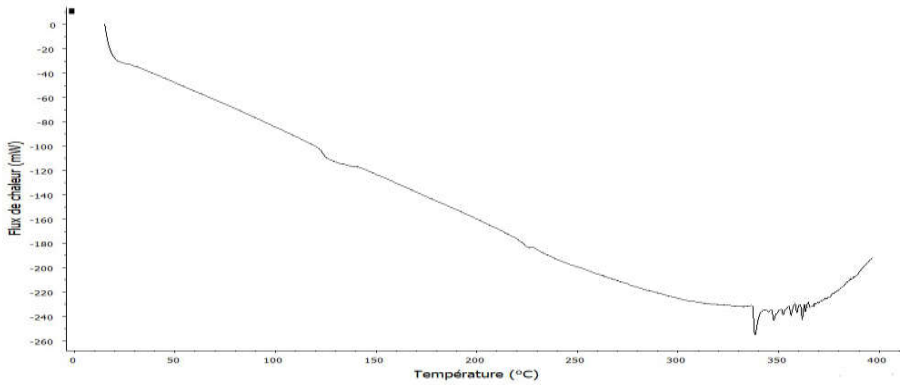


d-

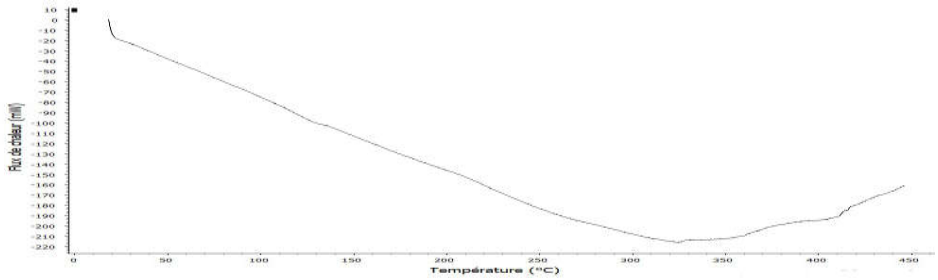


Figure IV. 5: DSC spectrum of (a) MT, (b) HPC, (c) Physical mixture, (d) MTMPs

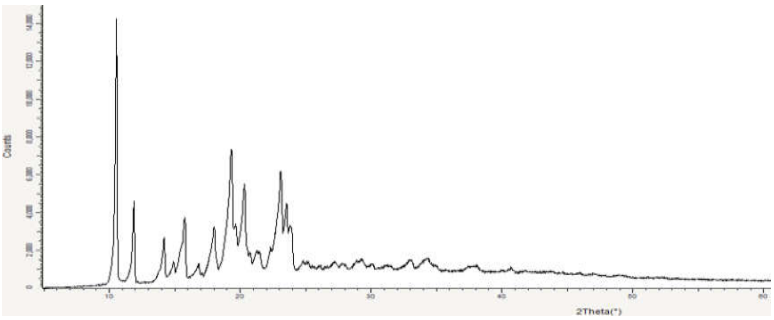
IV.1.4 X-ray diffraction analysis

X-ray diffraction analysis was performed to assess the complexation and amorphous states of MT and HPC. The XRD patterns of MTMPs was further revealed and confirmed via the characteristic peaks recorded in the XRD spectra as depicted in the Figure IV.6. The diffractograms in Figure IV.6 present the patterns of MT, HPC, physical mixture, and MTMPs.

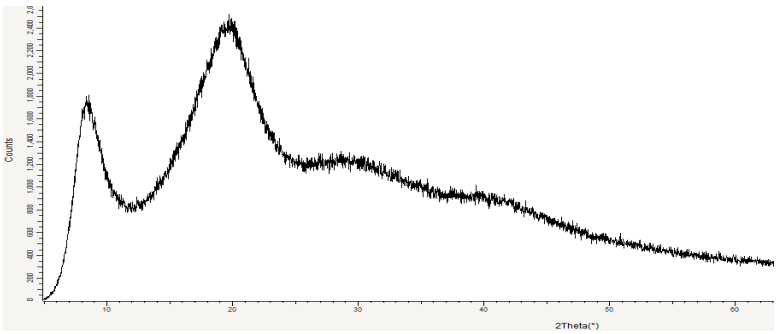
Figure IV.6(a), the X-ray diffractogram of MT revealed sharp diffraction peaks at different diffraction angles of 10.5°, 11.84°, 14.32°, 15.6° 18.3°, 19.4°, 20.3° and 23.80°.

The diffractogram depicts the crystalline nature of MT with no detectable impurities recorded as well. The same diffraction peaks appeared in the physical mixture pattern by reduction of intensity (Figure IV.6.c). However, the MTMPs (Figure IV.6.d). revealed only two small peaks at 9.2° and 19.5°, while the majority of diffraction diffractograms were totally diffused, which shows its amorphousness. As shown in Figure IV.6(b), the HPC pattern revealed only two no obvious peaks at 8.2° and 19.1° as evidenced by the disappearance of diffraction peaks. This diffraction indicated that HPC was presented as an amorphous material.

a-



b-



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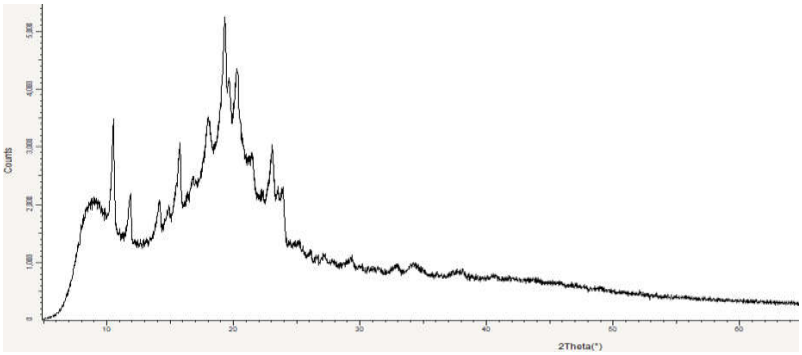

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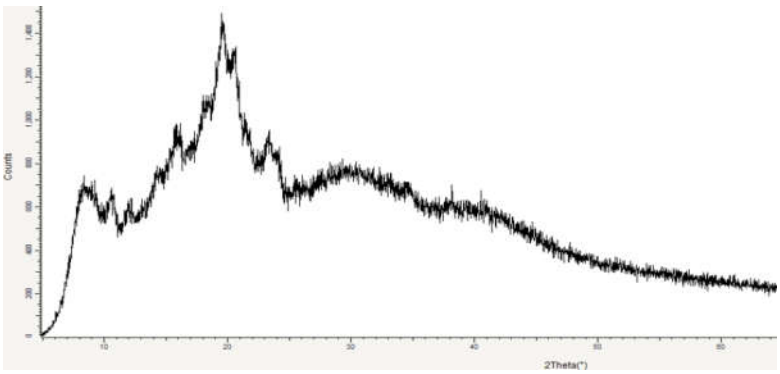

Figure IV.6 : X-ray diffractogram of (a) MT, (b) HPC, (c) Physical mixture, and (d) MTMPs

IV.1.5 Morphology study of metoprolol tartrate (MT):

The size, extent dispersion and morphology of microparticles were performed using scanning electron microscopy (SEM).

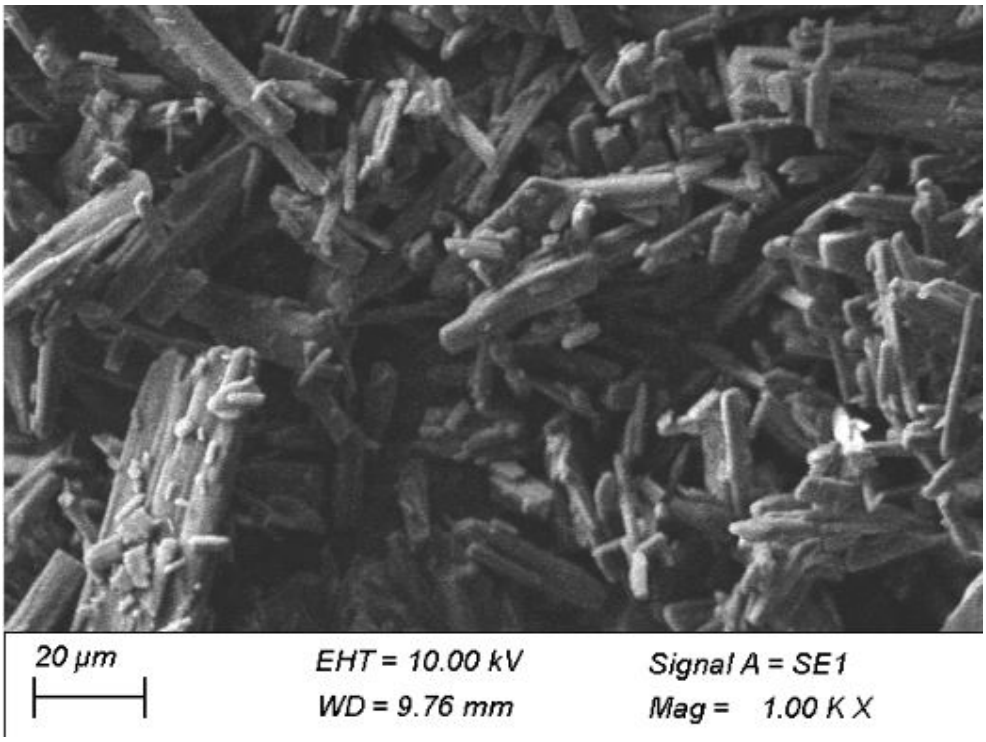

Figure IV. 7: Scanning electron microscopy of MTMPs

The SEM micrograph of Metoprolol tartrate hydroxypropyl cellulose microparticles illustrates a relatively continuous structure. Generally, the particle size ranged from 5 μm to 50μm. Aggregates, round shape, and elongated particles constituted the sheer bulk of materials.

After the microencapsulation reaction, rough morphology of the surface of functionalized microparticles is clearly observed. It may arise because of the polar difference of hydroxyl groups in cellulose and the interruption of intermolecular hydrogen bonds and crystalline regions in cellulose.

The MTMPs tend to aggregate and form dense masses that can affect their performances and therapeutics properties.

The various techniques used to disaggregate microparticles may not be productive and useful to prepare consistent forms. Therefore, the disaggregation of microparticles can be performed by the sonication process at a high energy level to produce usable formulations. Sonication at an energy level high enough to disaggregate the particles or the inclusion of HPC and MT as stabilizers may be better alternatives for producing usable microparticles.

IV.2 Drug loading and encapsulation efficiency

The release of MT from MTMPs was performed using a phosphate buffer solution at pH 7.4 and pH 4.8. The drug loading and encapsulation efficiency of MT in MTMPs were 42.95%and 99.84 %, respectively. The percentage yield of the prepared microparticles was 77.48%.

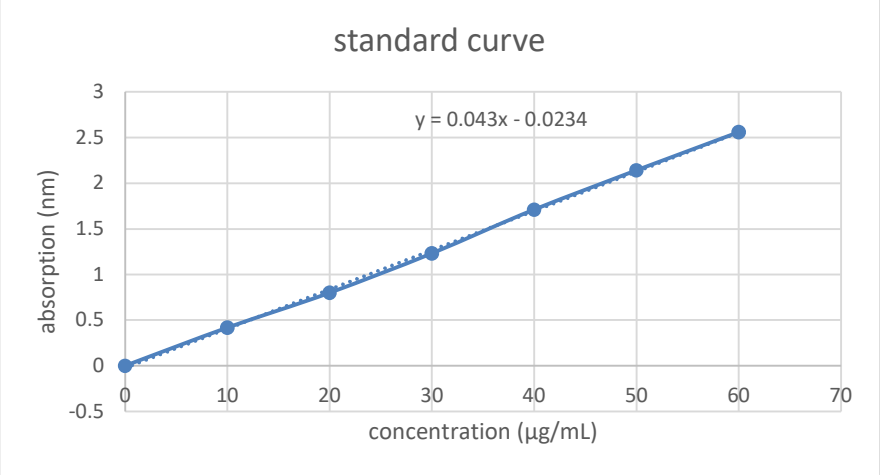

Figure IV.8: Calibration curves of various concentrations of MT and vs absorbance

IV.3 Controlled release study of MTMPs

An initial release burst was recorded for the first 1680 min in Figure IV.9. MT was released fastly from MTMPs up to 95%, 96% at pH 7, and 78%, 88% at pH 4, respectively. The rapid initial release of MT at pH 7 and pH 4, respectively, was attributed to the weak absorption or bonding of the surface of MTPs. A much slower sustained release of MT from MTMPs at pH 4 over a prolonged period of 4140 min than pH 7 was recorded.

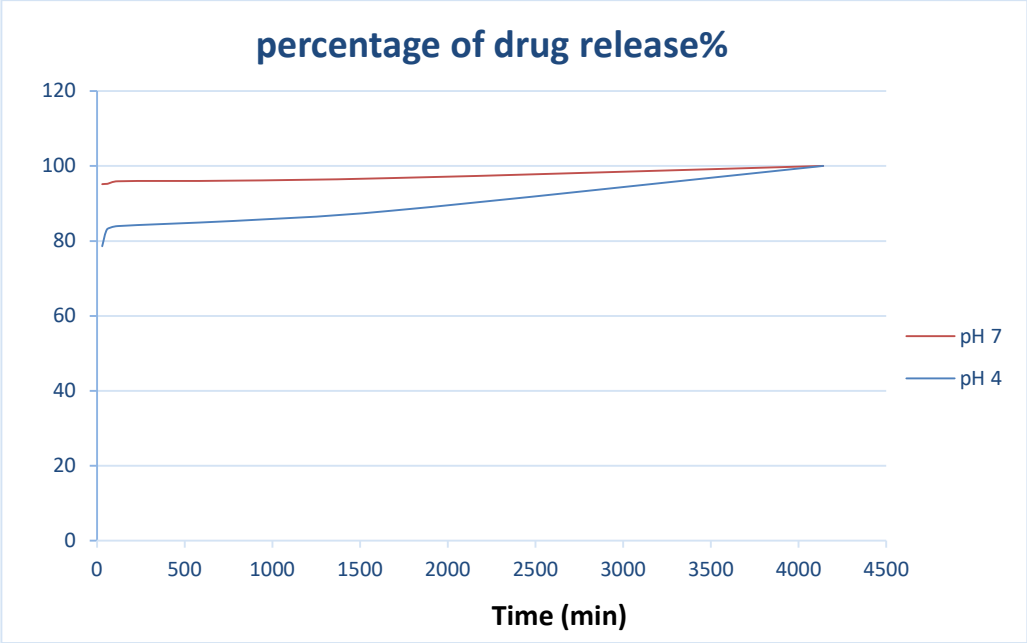

Figure IV.9: Release profiles of MT from MT

CONCLUSION

CONCLUSION

The aim of any drug delivery system is to administer the drug to a specific site in the body and to achieve and maintain the desired drug concentration in the blood.

Metoprolol tartrate is the prototype of a cardio selective (β1) blocker used in the treatment of several diseases of the cardiovascular system, especially hypertension. Metoprolol tartrate has a half-life of 3 to 4 hours in most people when taken as non-extended-release tabs.

The main goal of this study was the preparation of metoprolol tartrate loaded with hydroxypropyl cellulose microparticles by freeze drying technique ratio 2:1 and its characterization and evaluation.

According to the results, the preparation of microparticles was successful. The particle size ranged from 5 μm to 50μm.

The identification of metoprolol tartrate was carried out by FTIR spectroscopy. The examination of the physical state and decomposition of the compounds were performed using DSC analysis. The XRD analysis confirms that there is an interaction between MT and HPC in MTPMs.

The drug loading and encapsulation efficiency of MT in MTMPs were 42.95% and 99.84%, respectively. The percentage yield of the prepared microparticles was 77.48%.

In this study, metoprolol tartrate was coated with hydroxypropyl cellulose in a 2:1 ratio using freeze-drying technique, so in the future studies should investigate alternative excipients or ratios or techniques might further optimize drug loading and release characteristics.

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