OPEN ACCESS

Research Article

Design And Characterization of Empagliflozin Tablets

Dunumutla neetha sree*, Dr. M. Sunitha Reddy, Dr. K. Anie Vijetha

Department of pharmaceutics, Centre for pharmaceutical sciences, JNTUH, UCEST, Kukatpally, hyderabad

ABSTRACT

Objective: The aim of the present study is to formulate and evaluate Empagliflozin controlled release tablets. Method: Controlled release tablets are prepared using emulsification-solvent evaporation method involves dissolving the polymer and drug in an organic solvent, forming an emulsion by dispersing this solution in an aqueous phase containing an emulsifier and then evaporating the solvent to form Granules. These Granules are collected, washed and dried to obtain the final product, which is typically used for controlled or sustained release formulations Results: Assay analysis identified formulation F9 as the optimized version, showcasing superior drug release performance with over 95% cumulative drug release at 12 hours. In vitro dissolution studies reinforced F9's efficacy, demonstrating consistent drug release profiles. Accelerated stability studies affirmed the robustness of F9, with minimal changes in weight variation, thickness, hardness, and friability over three months. Conclusion: The analysis underscores the quality, efficacy, and stability of Empagliflozin CR Tablets, with F9 selected as the optimized formulation based on excellent drug release performance and stability findings.

INTRODUCTION

Controlled release tablets are dosage forms that have been designed to release their active ingredients at a controlled rate over an extended period of time. These tablets are formulated to provide a steady and consistent release of the drug, maintaining therapeutic drug levels in the body for a longer duration compared to immediate-release formulations. This controlled release of the drug helps to optimize its efficacy, minimize side effects, and improve patient compliance[1].

Controlled release tablets are particularly beneficial for drugs that have a narrow therapeutic window, require sustained drug levels, or cause gastrointestinal irritation when taken in conventional dosage forms. By controlling the release of the drug, these tablets can provide a more predictable and prolonged drug action,

*Corresponding Author: Dunumutla neetha sree

Address: *Department of pharmaceutics,Centre for pharmaceutical sciences, JNTUH, UCEST, Kukatpally, hyderabad.*

Email ✉ : neetha0609@gmail.com

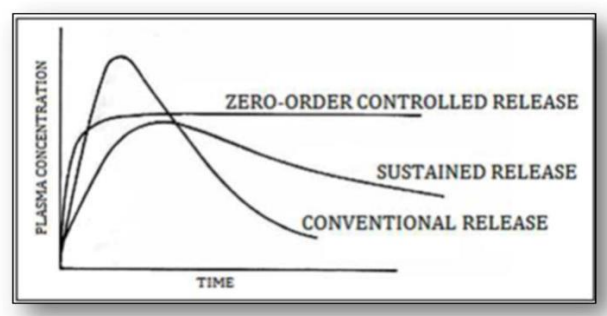allowing for a more convenient dosing regimen and reducing the frequency of administration[2].

Fig. 1- Plasma drug concentration-time profile

1.1. Significance of controlled release tablets

Controlled release tablets offer several significant advantages compared to traditional immediate-release formulations. Some of the key benefits and significance of controlled release tablets include:

1. Extended drug release: Controlled release tablets provide a prolonged and consistent release of the drug over an extended period of time, maintaining therapeutic drug levels in the body. This can help reduce the frequency of dosing for patients, improve patient compliance, and provide sustained therapeutic effect throughout the day.

2. Reduced dosing frequency: By releasing the drug slowly and steadily over time, controlled release tablets can often reduce the need for frequent dosing. This lessens the burden on patients who would otherwise need to take multiple doses throughout the day, improving convenience and adherence to the treatment regimen.

3. Minimized side effects: Controlled release formulations can help minimize fluctuations in drug plasma concentrations, reducing the risk of side effects associated with high peak concentrations or low trough concentrations. This can lead to a more tolerable and consistent drug therapy, enhancing patient safety and comfort.

4. Improved efficacy: Controlled release tablets can optimize drug delivery to the target site, ensuring that therapeutic drug levels are maintained for an extended period of time. This can enhance the overall efficacy of the treatment, particularly for drugs with a narrow therapeutic window or those requiring sustained action.

5. Better patient outcomes: The controlled release of drugs provided by these formulations can lead to improved therapeutic outcomes by maintaining drug levels within the therapeutic range for longer durations. This can result in better symptom control, disease management, and overall patient well-being.

6. Enhanced convenience: Controlled release tablets eliminate the need for frequent dosing, offering patients greater convenience and flexibility in managing their medication regimens. This can be particularly beneficial for patients with chronic conditions who require long-term treatment.

7. Tailored drug release profiles: Controlled release tablets allow for precise control over the drug release kinetics, enabling the formulation of customized release profiles to match specific therapeutic needs. This flexibility in release kinetics can be tailored to optimize drug concentration profiles and achieve targeted drug delivery.

8. Reduced healthcare costs: By reducing dosing frequency and improving patient compliance, controlled release tablets have the potential to decrease healthcare costs associated with medication non-adherence, disease progression, and hospitalizations. This can lead to overall cost savings for healthcare systems and patients alike. Controlled release polymers are polymeric materials that have been specifically designed to control the release rate of drugs, nutrients, or other active substances. These polymers play a crucial role in the development of controlled drug delivery systems by providing a matrix or carrier for the incorporation of the active ingredient and modulating its release profile[3-5].

1.2. Types of Controlled release polymers

There are several types of controlled release polymers, each with unique properties and mechanisms of drug release. Some common types of controlled release polymers include:

1. Biodegradable polymers: These polymers are designed to degrade over time, releasing the encapsulated drug in a controlled manner as the polymer breaks down. Biodegradable polymers can be synthetic (e.g., poly(lactic-co-glycolic acid)) or natural (e.g., chitosan), and their degradation rate can be tailored to achieve the desired release kinetics.

2. Hydrogels: Hydrogels are three-dimensional networks of hydrophilic polymers that can absorb and retain large amounts of water. These polymers can swell in response to environmental stimuli (e.g., pH, temperature) and release the encapsulated drug through diffusion or erosion mechanisms.

3. Stimuli-responsive polymers: These polymers undergo structural changes in response to specific stimuli, such as pH, temperature, or light. Stimuli-responsive polymers can be designed to release the drug in a controlled manner when exposed to a trigger, allowing for on-demand release of the active ingredient.

4. Mucoadhesive polymers: Mucoadhesive polymers have the ability to adhere to mucosal surfaces, prolonging the residence time of the drug at the site of absorption. These polymers can improve the bioavailability of drugs and enable sustained release of the drug over an extended period of time.

Controlled release polymers are essential components of controlled drug delivery systems, as they provide a platform for the controlled release of drugs with enhanced efficacy and safety. By modulating the release kinetics of the active ingredient, these polymers can improve patient compliance, reduce dosing frequency, and optimize drug therapy outcomes. Their versatility and tunability make controlled release polymers valuable tools in the field of drug delivery for a wide range of therapeutic applications[6-7].

1.3. List of various controlled release polymers commonly used in pharmaceutical formulations

1. Poly (lactic-co-glycolic acid) (PLGA): PLGA is a biodegradable polymer that is widely used for controlled release applications due to its tunable degradation rate and biocompatibility. It is often used in microsphere and nanoparticle formulations.

2. Hydroxypropyl methylcellulose (HPMC): HPMC is a cellulose derivative that swells in aqueous medium and provides controlled release by controlling drug diffusion. It is commonly used in matrix tablets and oral controlled release formulations.

3. Eudragit® polymers: Eudragit polymers are acrylic-based polymers that can provide pH-dependent, enzyme-dependent, or time-dependent controlled release of drugs. They are often used in enteric coatings and sustained-release formulations.

4. Chitosan: Chitosan is a natural biopolymer derived from chitin that is biocompatible, biodegradable, and mucoadhesive. It is used for controlled release of drugs, particularly in mucoadhesive and transmucosal drug delivery systems.

5. Polyethylene glycol (PEG): PEG is a polyether compound known for its biocompatibility and hydrophilicity. It can be used to modulate drug release rates and improve drug solubility in controlled release formulations.

6. Polylactic acid (PLA): PLA is a biodegradable polymer that can be used alone or in combination with other polymers to achieve sustained release of drugs. It is commonly used in implants, microparticles, and nanoparticle formulations.

7. Polyvinyl alcohol (PVA): PVA is a water-soluble polymer that can be used as a coating material or matrix-forming agent in controlled

release formulations. It is known for its film-forming properties and biocompatibility.

8. Cellulose ethers (e.g., methylcellulose, ethylcellulose): Cellulose ethers are commonly used in controlled release formulations to provide sustained drug release through gel formation or membrane formation. They are used in matrix tablets and reservoir systems.

9. Poly (lactic acid) (PLA) and Poly (lactic-co-glycolic acid) (PLGA): These biodegradable polymers are often used in controlled release formulations due to their adjustable degradation profiles and compatibility with a wide variety of drugs.

10. Alginate: Alginate is a natural polymer derived from seaweed that forms hydrogels in the presence of calcium ions. It is often used in controlled release formulations for oral, topical, and injectable delivery.

11. Polyvinylpyrrolidone (PVP): PVP is a water-soluble polymer that can be used as a binder, stabilizer, or matrix-forming agent in controlled release formulations. It is often used in immediate-release and sustained-release tablets.

12. Polycaprolactone (PCL): PCL is a biodegradable polyester that can be used in controlled release formulations to provide sustained drug release over an extended period of time. It is commonly used in implantable drug delivery systems.

13. Poly (ethylene oxide) (PEO): PEO is a water-soluble polymer that can be used to modulate drug release rates in controlled release formulations. It is often used in transdermal patches and oral controlled release formulations.

14. Poly(caprolactone-co-lactide) (PCLA): PCLA is a copolymer of polycaprolactone and polylactic acid that combines the properties of both polymers to provide controlled drug release. It is used in microsphere and nanoparticle formulations.

15. Carbopol®: Carbopol is a crosslinked acrylic polymer that can swell in water and provide controlled release of drugs through a gel matrix. It is commonly used in topical and transdermal drug delivery systems.

16. Polyethylene oxide - polypropylene oxide block copolymers (Pluronics®): Pluronics are thermosensitive polymers that undergo phase transitions in response to temperature changes. They are used in thermosensitive and injectable controlled release formulations.

17. Poly (methyl methacrylate) (PMMA): PMMA is a biocompatible polymer that can be used in the formulation of controlled release implants for localized drug delivery. It provides sustained drug release over a prolonged period of time.

18. Polyurethane: Polyurethane polymers can be used to fabricate controlled release devices such as films, coatings, or implants for various drug delivery applications. They offer flexibility in design and tunable release properties.

19. Poly(ε-caprolactone) (PCL): PCL is a biodegradable polyester that can be used in controlled release formulations to provide sustained drug release over a prolonged period of time. It is often used in implantable drug delivery systems and tissue engineering applications.

20. Poly (ortho esters): Poly (ortho esters) are biodegradable polymers that degrade into non-toxic monomers under acidic conditions. They can be used to achieve controlled release of drugs in acidic environments, such as the stomach.

21. Poly (vinyl alcohol-co-vinyl acetate) (PVA/PVAc): PVA/PVAc copolymers are water-soluble polymers that can be used in controlled release formulations to modulate drug release rates. They are commonly used in oral controlled release tablets and transdermal patches.

22. Poly (ethylene glycol) diacrylate (PEGDA): PEGDA is a crosslinkable polymer that can be used to create hydrogels for controlled drug release. It is often used in tissue engineering, wound healing, and drug delivery applications.

23. Gellan gum: Gellan gum is a natural polymer that forms thermoreversible gels and can be used in controlled release formulations for oral and transdermal drug delivery. It provides sustained drug release through gel formation.

24. Poly (acrylic acid) (PAA): PAA is an anionic polymer that can be used in controlled release formulations to modulate drug release through pH-responsive mechanisms. It is often used in enteric coatings and pH-dependent drug delivery systems.

25. Poly (lactic acid)-block-poly (ethylene glycol) (PLA-PEG): PLA-PEG block copolymers combine the biodegradability of PLA with the hydrophilicity of PEG to provide controlled drug release and improved drug solubility. They are used in nanomedicine and targeted drug delivery systems.

26. Hydroxypropyl cellulose (HPC): HPC is a cellulose derivative that can be used as a sustained-release matrix in controlled release formulations. It provides a platform for drug release modulation in oral dosage forms.

27. Methacrylic acid copolymers (e.g., Eudragit): Methacrylic acid copolymers are acrylic-based polymers that can be used as pH-sensitive coatings or matrix materials in controlled release formulations. They enable targeted drug release in specific gastrointestinal compartments.

28. Poly (ethylene glycol)-b-poly (propylene glycol)-b-poly (ethylene glycol) triblock copolymers (Pluronic® or Poloxamer): These thermosensitive polymers can undergo temperature-induced gelation and are often used in controlled release formulations for their ability to modulate drug release rates in response to temperature changes.

29. Hydroxyethyl cellulose (HEC): HEC is a water-soluble polymer that is commonly used as a gelling agent and thickener in controlled release formulations. It can be used in oral controlled release tablets and topical formulations.

30. Poly (sebacic acid-co-ricinoleic acid) (PSRA): PSRA is a biodegradable polymer that can be used in sustained-release formulations to provide prolonged drug release. It is often used in implantable drug delivery systems.

31. Poly(vinyl pyrrolidone-co-vinyl acetate) (PVP/VA): PVP/VA copolymers are water-soluble polymers that can be used as binders or coating materials in controlled release formulations. They provide flexibility in formulating tablets and other dosage forms.

32. Cellulose acetate: Cellulose acetate is a biocompatible polymer that can be used in controlled release formulations to provide sustained drug release. It is often used in oral dosage forms and transdermal drug delivery systems.

33. Poly (ethylene oxide)-block-poly (propylene oxide)-block-poly(ethylene oxide) triblock copolymers (Poloxamine or Poloxamer): These surfactant polymers are often used in controlled release formulations for their ability to stabilize emulsions and modulate drug release rates in various dosage forms.

34. Hyaluronic acid: Hyaluronic acid is a natural polysaccharide that can be used in controlled release formulations to provide sustained drug release and targeted drug delivery. It is often used in injectable drug delivery systems.

35. Poly(caprolactone-co-glycolide) (PCLG): PCLG is a copolymer of polycaprolactone and polyglycolide that combines the properties of both polymers to provide controlled drug release. It is commonly used in microparticle and nanoparticle formulations.

36. Poly(n-isopropylacrylamide) (PNIPAAm): PNIPAAm is a thermosensitive polymer that undergoes a phase transition at its lower critical solution temperature (LCST). It can be used in controlled release formulations to modulate drug release in response to temperature changes.

These examples illustrate the wide range of controlled release polymers available for formulating drug delivery systems with tailored release profiles and enhanced therapeutic efficacy. The selection of a suitable controlled release polymer depends on the specific requirements of the drug, the desired release kinetics, and the formulation strategy employed in the development of the dosage form[8-10].

1.4. An overview of the steps involved in preparing controlled release tablets using Emulsification Solvent Evaporation

Controlled release tablets can be prepared using Emlusification solvent evaporation which involve the formation of granules from a mixture of drug, excipients, organic solvent and a emulsifying agent[11-13].

General Procedure of Emulsification-Solvent Evaporation

1. Preparation of the Polymer Solution

Materials Required:

Polymer (e.g., PLGA, PLA, PLGA, PVA, HPMC etc.)

Organic solvent (e.g., dichloromethane, chloroform, acetone)

Magnetic stirrer and stir bar

Procedure:

1. Weigh the required amount of polymer accurately using an analytical balance.
2. Transfer the polymer into a clean beaker.
3. Add a suitable organic solvent to the beaker containing the polymer.
4. Place the beaker on a magnetic stirrer and insert a stir bar.
5. Stir the mixture continuously until the polymer is completely dissolved, forming a uniform polymer solution.

2. Incorporation of the Active Ingredient

Materials Required:

a) Active pharmaceutical ingredient (API) (e.g., drug)
b) Polymer solution from step 1

Procedure:

a) Weigh the required amount of the active ingredient accurately.
b) Gradually add the active ingredient to the polymer solution while stirring.
c) Continue stirring until the drug is completely dissolved or uniformly dispersed within the polymer matrix.

3. Emulsification

Materials Required:

a. Aqueous phase (water or buffer solution)
b. Emulsification agent (e.g., surfactant like PVA, Tween 80)
c. Polymer-drug solution from step 2
d. Homogenizer or high-speed stirrer

Procedure:

a. Prepare the aqueous phase by measuring and pouring water or buffer solution into a clean beaker.
b. Add the emulsification agent to the aqueous phase and stir until it is completely dissolved.
c. Set up the homogenizer or high-speed stirrer.
d. Slowly add the polymer-drug solution dropwise into the aqueous phase under continuous stirring or homogenization to form an emulsion. This creates fine droplets of the polymer-drug solution dispersed in the aqueous phase.

4. Solvent Evaporation

Materials Required:

a. Emulsion from step 3
b. Stirring device

Procedure:

a. Transfer the emulsion to a suitable container for stirring.
b. Stir the emulsion continuously at room temperature or slightly elevated temperature to allow the organic solvent to evaporate.
c. Monitor the evaporation process until the solvent is completely removed, resulting in the formation of solid microparticles or

nanoparticles with the active ingredient encapsulated within the polymer matrix.

5. Collection and Washing of Particles

Materials Required:

a. Solidified particles from step 4
b. Centrifuge or filtration setup
c. Washing solution (e.g., distilled water)

Procedure:

a. Collect the solidified particles from the emulsion using a centrifuge or filtration setup.
b. Wash the collected particles with the washing solution to remove any residual emulsification agent or unencapsulated drug.
c. Repeat the washing process as necessary to ensure purity.

6. Drying of Particles

Materials Required:

a. Washed particles from step 5
b. Drying apparatus (e.g., freeze dryer, oven)

Procedure:

a. Transfer the washed particles to a suitable drying apparatus.
b. Dry the particles using an appropriate drying method (e.g., freeze drying, oven drying) to achieve the desired moisture content.
c. Store the dried particles in a desiccator or a suitable container to prevent moisture uptake.

The emulsification-solvent evaporation method involves dissolving the polymer and drug in an organic solvent, forming an emulsion by dispersing this solution in an aqueous phase containing an emulsifier and then evaporating the solvent to form Granules. These Granules are collected, washed and dried to obtain the final product, which is typically used for controlled or sustained release formulations. This method is widely used for preparing microparticles and nanoparticles for drug delivery applications and applied for controlled release formulations.

1.5. Marketed products for controlled release tablets

There are numerous controlled release tablets available on the market, each designed to provide a specific release profile for the active ingredient. Some examples of commercially available controlled release tablets include:

1. OxyContin (oxycodone): OxyContin is a controlled release tablet formulation of the opioid analgesic oxycodone. It is designed to provide extended pain relief over a 12-hour period, making it suitable for patients requiring around-the-clock pain management.

2. Ritalin LA (methylphenidate): Ritalin LA is a controlled release tablet used for the treatment of attention deficit hyperactivity disorder (ADHD). It delivers the active ingredient methylphenidate in two stages, providing immediate and sustained release for extended symptom control throughout the day.

3. Glucophage XR (metformin): Glucophage XR is an extended-release tablet formulation of the antidiabetic medication metformin. It is designed to provide a gradual release of the drug over an extended period, helping to improve glycemic control in patients with type 2 diabetes.

4. Wellbutrin XL (bupropion): Wellbutrin XL is a controlled release tablet formulation of the antidepressant bupropion. It is designed to provide sustained release of the active ingredient, helping to improve mood and reduce symptoms of depression over an extended period.

5. Concerta (methylphenidate): Concerta is a once-daily controlled release tablet formulation of methylphenidate used for the treatment of ADHD. It provides a gradual release of the active ingredient throughout the day, allowing for extended symptom control with a single dose.

6. Sinemet CR (carbidopa/levodopa): Sinemet CR is a controlled release tablet formulation of the combination medication carbidopa and levodopa used to treat symptoms of Parkinson's disease. It provides a sustained release of the active

ingredients to help improve motor function and reduce Parkinsonian symptoms.

7. Cozaar (losartan): Cozaar is a controlled release tablet formulation of the angiotensin II receptor blocker losartan used to treat high blood pressure and reduce the risk of stroke in patients with hypertension and certain types of heart disease.

These are just a few examples of commercially available controlled release tablets on the market

2. Aim and Objectives

Aim: The aim of the present study is to formulate and evaluate Empagliflozin controlled release tablets.

Objectives:

➢ To develop Calibration curve of Empagliflozin

➢ To perform Drug excipient interaction studies by FTIR

➢ To perform pre-formulation studies for the tablet blend

➢ To formulate controlled release tablets of Empagliflozin

➢ To perform evaluations for the prepared controlled release tablets of Empagliflozin

➢ To study the release profile of the controlled release tablets of Empagliflozin

➢ To study the drug-release kinetics of the optimized formulation.

➢ To study the stability of the optimized formulation

4. Plan of work

1. Collection of Literature review

2. Determination of Lambda Max and construction of Calibration Curve

3. Drug-Excipient compatibility studies

4. Pre-formulation studies

Description

Angle of repose

Bulk Density

Tapped Density

Hausner's ratio

Carr's Compressibility Index

5. Formulation of controlled release tablets of Empagliflozin

6. Evaluation of controlled release tablets of Empagliflozin

Shape and Colour of tablets.

Uniformity of thickness.

Weight variation

Hardness

Friability

In-vitro dissolution studies

7. Drug release kinetic study

8.Stability Studies the Optimized formulation

Drug Profile

Empagliflozin is a medication used to treat type 2 diabetes. It belongs to a class of drugs called sodium-glucose cotransporter 2 (SGLT2) inhibitors, which work by helping the kidneys remove glucose from the bloodstream through the urine. This helps lower blood sugar levels and improve glycemic control in individuals with diabetes. Empagliflozin is typically taken orally as a once-daily tablet. It has also been shown to provide cardiovascular benefits in addition to its glucose-lowering effects.
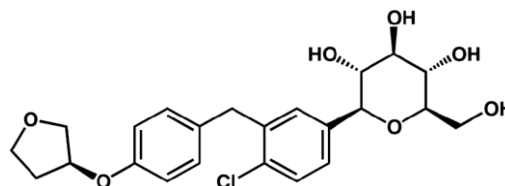
Fig-2: Structure of Empagliflozin

Non-proprietary Name: Empagliflozin

Empirical Formula: $C_{23}H_{27}ClO_7$

Molecular Weight: 450.91 g/mol

Bioavailability: Approximately 65%

Description: White to pale yellow crystalline powder

Solubility: Empagliflozin is soluble in water.

Partition Coefficient (Log P): The calculated Log P value for empagliflozin is approximately 3.3.

Storage Conditions: Empagliflozin should be stored at room temperature between 68°F to 77°F (20°C to 25°C). It should be kept in a tightly closed container, protected from light and moisture.

Mechanism of Action OF Empagliflozin

- The primary mechanism of action of empagliflozin is to reduce the reabsorption of glucose in the kidneys, leading to the excretion of excess glucose in the urine. SGLT2 is a protein found in the kidneys that is responsible for reabsorbing glucose from the urine back into the bloodstream.

- By inhibiting the activity of SGLT2, empagliflozin blocks the reabsorption of glucose, causing more glucose to be excreted in the urine. This results in a decrease in blood glucose levels in individuals with type 2 diabetes.

- In addition to its glucose-lowering effects, empagliflozin has been shown to have other potential benefits, such as reducing body weight and blood pressure. It may also have cardiovascular benefits, as studies have demonstrated a reduction in the risk of cardiovascular events in patients with diabetes and cardiovascular disease who are treated with empagliflozin[14-18]

6. Methodology

6.1. Determination of Lambda max and Construction of calibration curve

6.1.1. Preparation of Empagliflozin Standard Stock Solution (about 1000 ppm)

To prepare a standard stock solution of Empagliflozin at a concentration of 1000 ppm, begin by weighing out about 25 mg of Empagliflozin using a precise analytical balance. Transfer the weighed Empagliflozin into a clean 25 mL volumetric flask and add around 10 mL of a methanol. Sonicate the flask for 5 minutes to ensure complete dissolution of the drug substance. Top up the flask with the diluent to the 25 mL mark, cap it, and mix thoroughly by inverting it several times. Label the flask with the concentration. This prepared Empagliflozin standard stock solution can be utilized for calibration and quality control purposes in analytical method by using UV-Visible spectrophotometry[19-20].

6.1.2. Preparation of Empagliflozin Working Standard Solution (about 100 ppm)

To dilute the Empagliflozin standard stock solution, pipette out 2 mL into a 20 mL volumetric flask and fill up with the methanol, mixing well. Transfer the exact amount of the stock solution into the clean flask and add the appropriate diluent to reach the 20 mL mark, ensuring accurate dilution.

6.1.3. Preparation of Empagliflozin Sub-standard Solution

Prepared various dilutions of Empagliflozin ranging from 5 to 25 µg/mL using the working standard solution. Used separate labeled volumetric flasks for each concentration and accurately pipetted the required volume of Empagliflozin solution. Methanol is added to each flask to achieve the desired concentration, mixed well to ensure homogeneity. The prepared solutions were then analyzed using a UV spectrophotometer.

6.2. X-ray Diffraction Studies of Empagliflozin

X-ray diffraction is a technique used to analyze the diffraction pattern created when X-rays interact with the crystalline structure of a material. Each crystalline compound produces a distinct diffraction pattern, which helps identify and characterize its crystalline form. For empagliflozin, XRD studies involve obtaining a sample of the drug in its crystalline state and exposing it to X-ray radiation. The resulting diffraction pattern is then studied to reveal details about the crystal structure, lattice parameters, and atomic arrangement within the crystal lattice. This information is valuable for understanding the properties and behavior of empagliflozin in its solid-state form[21].

6.3. Drug excipients compatibility studies

Studying drug-excipient compatibility is a crucial phase in early drug development. It helps identify

potential interactions between the active pharmaceutical ingredient (API) and excipients in the formulation. These studies aid in excipient selection, assess drug stability, and identify any degraded excipients. In this process, Fourier-transform infrared spectroscopy (FTIR) is often employed to screen samples within the range of 400-4000 cm^{-1}. By comparing absorption peaks in the FTIR spectra of the pure drug with those in the optimized formulation and excipients, researchers can determine the compatibility between the drug and excipients. The presence of characteristic absorption peaks in the combined spectrum suggests that the drug and excipients are indeed compatible[22].

6.4. Preformulation studies

6.4.1. Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose was determined by the funnel method. A funnel with 10 mm inner diameter of stem was fixed at a height of 2.5 cm over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stem of the funnel. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. A rough circle was drawn around the pile base and the radius of the powder cone was measured[23-26]. Calculated by following formula:

$$Tan\ \emptyset = h/r$$

Where$\emptyset$, angle of repose,

h= height of the pile,

r =average radius of the powder concentration.

Table-1: Acceptance values of Angle of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

6.4.2. Bulk density

The ratio of mass (weight) to volume is known as the bulk density of material. The bulk density of a powder depends on particle size distribution, particle. The equation for determining the bulk density is

BD= M/V

where, M- Mass of particles, V- Total volume of packing.

6.4.3. Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of drug on a mechanical tapper apparatus, which is operated for fixed number of taps (1000) until a powder bed volume has reached the minimum. Using the weight of drug in cylinder and tapped volume, the tapped density is determined[23-24].

TD = weight of powder/ Tapped volume

6.4.4. Compressibility index

The compressibility index of the powder was determined by Carr's compressibility index[25-27].

Where,

Carr's Index= [(DD)×100/D]

DD, is the tapped density

D is the bulk density

Table-2: Acceptance values of Carr's Compressibilty Index

Compressibility index (%)	Flow property
<10	Excellent
11–15	Good
16-20	Fair
21-25	Passable
26–31	Poor
32–37	Very poor
>38	Very very poor

6.4.5. Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flowability of a powder[21-22].

Hausner's Ratio = TD/BD

Table-3: Acceptance values of Hausner's Ratio

Hausner's ratio	Flow property
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable

6.6. Method of Preparation

The controlled-release granules were prepared by encapsulating the active ingredient within a polymer matrix to achieve sustained drug release. The general method for preparing controlled-release granules:

Materials:

- Active ingredient (Empagliflozin)
- Polymer (Poly-Lactic glycolic acid)
- Solvent (Dichloro-methane)
- Emulsification agent (Poly-vinyl alcohol)

Steps:

1. Preparation of the polymer solution: A predetermined amount of the polymers were dissolved in a suitable organic solvent to prepare a polymer solution. Stir the mixture using a magnetic stirrer until the polymer is completely dissolved.

2. Incorporation of the active ingredient: The drug was added to the polymer solution and thoroughly mixed to ensure homogenous dispersion within the polymer matrix.

3. Emulsification: An aqueous phase containing an emulsification agent was prepared, and an emulsion was created by adding the polymer and the drug solution dropwise into the aqueous phase under stirring or homogenization.

4. Solvent evaporation: The emulsion was stirred to allow the solvent to evaporate, resulting in the formation of controlled-release granules with the active ingredient encapsulated within the polymer matrix.

5. Granule formation: After complete evaporation of the solvent, the solidified granules were collected, washed to remove residual solvent or emulsification agent and dried.

6. The controlled release granules were compressed into tablets by incorporating extra granular material, which included a binder to hold the ingredients together, a diluent to enhance the flow properties, a glidant to improve powder flowability and a lubricant to reduce friction during compression.

7. The binder plays a crucial role in holding the granules together and ensuring the tablet's structural integrity. The diluent helps to fill any void spaces and ensure uniformity in the tablet's composition. The glidant aids in enhancing the flow properties of the granular mixture, making it easier to handle during compression. The lubricant facilitates the proper ejection of tablets from the die cavity and prevents sticking to the punches[28-32]. The tablets were compressed by using 8mm round dies and punches in rotary tablet compression machine.

Table-4: Formulation table of Controlled release tablets of Empagliflozin

Ingredients (mg)	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9	CF10
Intra-granular Material										
Empagliflozin	25	25	25	25	25	25	25	25	25	25
Eudragit RL 100	60	40	40	40						
Poly Vinyl Pyrrolidine		20			60	40	40			
Poly Lactic Glycolic Acid			20			20		60	40	40
HPMC K100				20			20		20	40
Dichloromethane(ml)	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Polyvinyl Alcohol	10	10	10	10	10	10	10	10	10	10
Extra-granular Material										
Poly Vinyl Pyrrolidine	20	20	20	20	20	20	20	20	20	20
Microcrystalline cellulose	81	81	81	81	81	81	81	81	81	61
Colloidal Silicon Dioxide	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2

6.7. Evaluation Methods for Controlled release tablets

The fabricated tablets were characterized for
1. Weight variation (n=20)
2. Hardness (n=10)- Monsanto hardness tester
3. Thickness using a screw-gauge micrometer
4. Friability (n=10)- Roche friabilator
5. Dissolution studies (n=6)- Lab India

6.7.1. Weight Variation test

The weight variation test on 20 tablets was conducted by individually weighing each tablet using a calibrated analytical balance with precision. The weights of the 20 tablets were recorded and the average weight of the tablets was calculated by summing the individual weights and dividing by 20. This average weight served as the reference point for determining the percentage deviation of each tablet's weight from the average weight. By comparing the acceptance value of each tablet to the specified limits in the relevant pharmacopoeial standards, the uniformity of the dosage units in the batch can be assessed[33-34].

Percentage deviation of Weight Variation

$$= \frac{\left(\begin{array}{c} \text{Individual tablet} \\ \text{weight} \end{array} - \begin{array}{c} \text{Average weight of} \\ \text{20 tablets} \end{array} \right)}{\begin{array}{c} \text{Average weight} \\ \text{of 20 tablets} \end{array}} \times 100$$

Official standards:

As per U.S.P.

Sr.No.	Average weight of tablet	% weight variation acceptable(+ or -)
1.	130 or less mg	(+ or -) 10%
2.	130-324 mg	(+ or -) 7.5%
3.	>324 mg	(+ or -) 5%

As per I.P.

Sr.No.	Average weight of tablet	% weight variation acceptable(+ or -)
1.	84 or less mg	(+ or -) 10%
2.	84-250 mg	(+ or -) 7.5%
3.	>250 mg	(+ or -) 5%

6.7.2. Hardness (n=10)- Monsanto hardness tester

The hardness of tablets was evaluated by testing 10 randomly selected tablets using a Monsanto hardness tester. This testing method is crucial to determine the tablets' capability to withstand mechanical stresses encountered during handling, transportation, and storage. Each tablet was placed individually on the flat surface of the hardness tester, and an incremental compressive force was applied until a predefined depth of indentation was achieved. The force needed for each tablet was recorded, and based on these measurements, the hardness value of each tablet was calculated[33-34].

6.7.3. Thickness using a screw-gauge micrometer

The screw-gauge micrometer is adjusted to bring the anvils or measuring faces in close proximity to the tablet without exerting excessive pressure. This delicate process ensures that the measurements taken are accurate and precise. Once the micrometer is correctly set, the thickness of the tablet is measured by gingerly closing the micrometer jaws around the tablet and observing the measurement displayed on the micrometer scale. This reading provides an exact assessment of the tablet's thickness, which is crucial for ensuring uniformity in tablet size and dosage consistency. The measurement is typically recorded in millimeters or micrometers, depending on the precision required for the pharmaceutical product being evaluated[33-34].

6.7.4. Friability (n=10)- Roche friabilator

Friability testing is conducted using a Roche friabilator, a device designed to assess the resistance of tablets to abrasion and breakage. In this process, a sample of 10 tablets is randomly selected and placed inside the friabilator drum, which rotates at a predetermined speed for a specified number of rotations. The tablets are subjected to mechanical stress during this rotation, simulating the effects of handling, packaging, and transportation on the tablets. After the testing is completed, the tablets are carefully removed and weighed again to determine any weight loss resulting from breakage or erosion. The percentage friability is then calculated based on this weight loss, with the objective of ensuring that the tablets maintain their integrity and do not excessively deteriorate during standard handling procedures[33-34].

$$Friability\ (\%) = \frac{Initial\ Weight\ (W1) - Final\ Weight\ (W2)}{Initial\ Weight\ (W1)} \times 100$$

6.7.5. Dissolution studies of Controlled release tablets

In the dissolution testing process, 900 mL of 0.01 N HCl, previously heated to 37°C, was accurately measured and transferred into each dissolution vessel. Subsequently, one tablet was meticulously weighed and placed into each dissolution vessel. At predetermined time intervals, specifically after 2 hours, 10 mL samples were withdrawn from each vessel for analysis. The withdrawn aliquots were then promptly replaced with equal volumes of 0.01 N HCl, maintaining the temperature at 37 ± 0.5°C to ensure consistency in the testing conditions. Following this step, 1000 mL of pH 6.8 buffer, also preheated to 37 ± 0.5°C, was added to each dissolution vessel. Subsequent to the buffer addition, further sample withdrawals were conducted at specified timepoints, with 10 mL samples being withdrawn from each vessel. Again, the withdrawn aliquots were substituted with equal volumes of pH 6.8 phosphate buffer, maintaining the temperature at 37 ± 0.5°C for accurate and controlled dissolution testing conditions[35,36].

Dissolution Parameters:

Acid stage:
Medium   : 0.1 N HCl
Volume   : 900ml
Type   : USP apparatus II (Paddle)

RPM   : 75 rpm
Bath Temperature   : 37.5°C
Bowl temperature   : 37.0°C
Time Points : 2 hrs

Buffer stage:
Medium: pH 6.8 buffer
Volume: 1000 mL
Type: USP apparatus II (Paddle)
RPM: 75 rpm
Bath Temperature   : 37.5°C
Bowl temperature   : 37.0°C
Time Points : 1hr, 2hr, 4hr, 6hr, 8hr, 10hr, 12hr.

6.8. Mathematical drug release kinetic models

Drug release kinetic models are utilized to describe the release mechanism of drugs from pharmaceutical dosage forms. These models provide insights into the drug release behavior and can help in formulating and optimizing drug delivery systems.

6.8.1. First-order kinetic model

This model assumes that the rate of drug release is directly proportional to the amount of drug remaining to be released. Mathematically, it is described as $dQ/dt = k_1 (Q_\infty - Q_t)$, where Q represents the amount of drug released at time t, Q_∞ is the total amount of drug to be released, and k_1 is the first-order rate constant[37-39].

6.8.2. Zero-order kinetic model

In contrast to the first-order model, the zero-order model suggests a constant rate of drug release over time. It implies a linear decrease in the amount of drug remaining to be released. Mathematically, it is represented as $dQ/dt = k_0$, where k_0 is the zero-order rate constant[37-39].

6.8.3. Higuchi's model

This model is based on Fickian diffusion principles and states that the release rate of a drug from a matrix system is directly proportional to the square root of time. It is represented as $Q = k_H * sqrt(t)$, where Q is the amount of drug released at time t, and k_H is the Higuchi rate constant[40].

6.8.4. Hixson–Crowell model

This model applies to systems where the drug release is controlled by changes in the surface area and diameter of the dosage form. It postulates that the percent drug release decreases with time following a cube root law. The equation is often written as $(W_0^{1/3} - W^{1/3}) = k_{HC} * t$, where W_0 is the initial weight of the dosage form, W is the weight remaining at time t, and k_{HC} is the Hixson–Crowell rate constant[41].

6.8.4. Korsmeyer-Peppas model

This model is based on the power law relationship between the cumulative drug release and time, $Q = kt^n$. Here, Q is the amount of drug released at time t, k is a constant, and n is the release exponent that indicates the mechanism of drug release (e.g., Fickian diffusion for $n < 0.5$, non-Fickian or anomalous transport for $0.5 < n < 1$, case II transport for $n = 1$, and super case II transport for $n > 1$)[42].

These kinetic models help in predicting the release behavior of drugs from dosage forms, enabling the design of effective drug delivery systems with controlled release properties.

6.9. Accelerated stability studies

Accelerated stability studies play a crucial role in the pharmaceutical development process by providing valuable insights into the stability and shelf life of drug products. By subjecting samples to elevated temperatures and humidity levels for a defined period, these studies simulate harsh environmental conditions that the product may encounter during its lifecycle. The accelerated conditions facilitate the rapid degradation of the product, allowing researchers to predict its long-term stability in a shorter time frame. Through the monitoring of parameters such as physical appearance, chemical composition, potency, and impurity levels, researchers can assess the product's stability and make informed decisions about its shelf life. The data gathered from accelerated stability studies enable pharmaceutical companies to establish appropriate storage recommendations, determine expiration dates, and ensure product quality and efficacy over time[43].
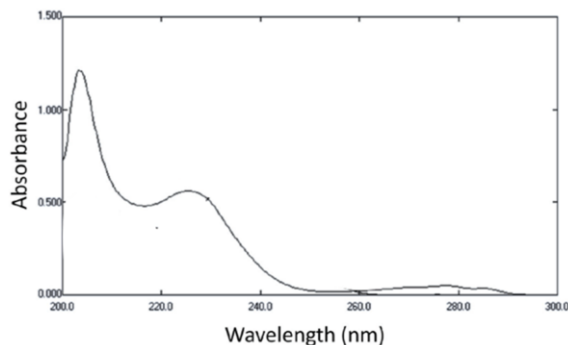
Table-5: Accelerated stability studies-Conditions

Storage condition	Testing condition
Controlled room temperature 20–25°C	40°C and 75% RH for 6 months
Refrigerated	25 °C and 60% RH for 6

7. RESULTS AND DISCUSSION

## 7.1. Determination of Lambda max and Construction of calibration curve

Fig-10: Scan spectrum of Empagliflozin showing λmax at 225nm

When a sample of Empagliflozin 10ppm is scanned using a UV spectrophotometer in the range of 200 to 400 nanometers (nm), the results show a significant absorption peak at 225nm shown in Figure-10.

Table-6: Calibration curve of Empagliflozin

Concentration (PPM)	Absorbance
5	0.117 ± 0.031
10	0.357 ± 0.061
15	0.579 ± 0.004
20	0.781 ± 0.045
25	0.969 ± 0.047

Where n=3±S.D.
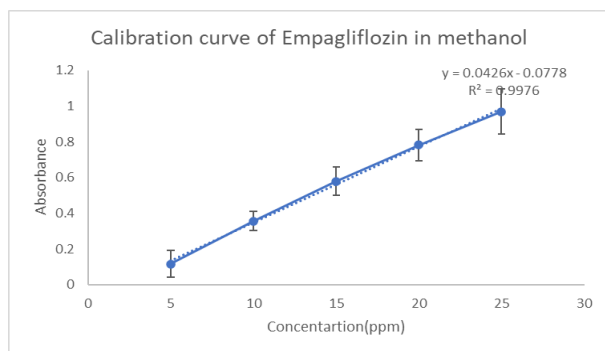
Fig-11: Calibration curve of Empagliflozin (n=3)

The data presented in the table, with a linear regression analysis, shows a strong correlation between the concentration of the substance in parts per million (ppm) and its corresponding absorbance values as measured by the UV spectrophotometer. The calculated R^2 value for this relationship is 0.9976 shown in Table-6 and Figure-11. This high R^2 value indicates that the relationship between concentration and absorbance is very good.

## 7.2. X-ray Diffraction studies of Empagliflozin
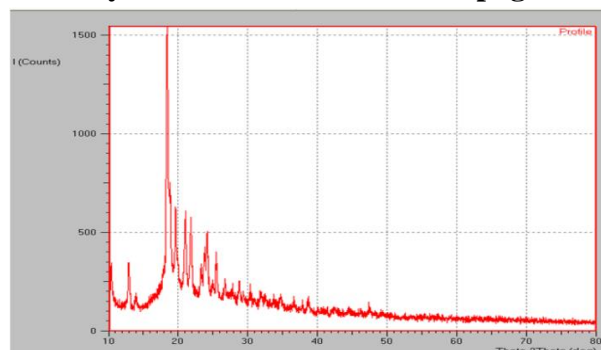
Fig-12: X-ray Diffraction studies of Empagliflozin

The presence of a sharp, single, long peak in the X-ray diffractogram of Empagliflozin suggests that the compound may have a dominant crystalline phase with a well-defined crystal structure. This type of peak typically indicates a high degree of crystallinity and uniformity in the arrangement of atoms within the crystal lattice shown in Figure-12.

7.3. Drug-excipient compatibility studies
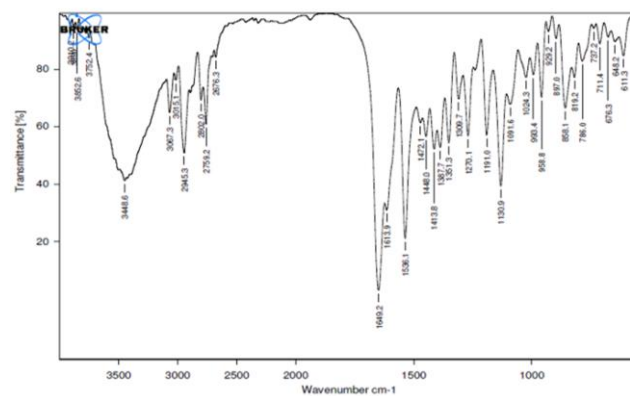
Fig-13: FTIR Spectra of Pure drug Empagliflozin
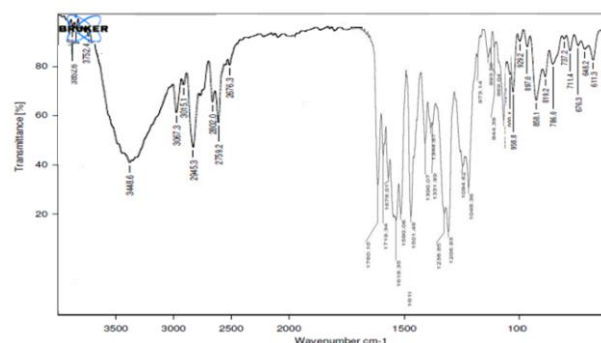
Fig-14: FTIR Spectra of Pure drug Empagliflozin

The FTIR spectrum of Empagliflozin typically shows characteristic peaks corresponding to various functional groups present in the molecule. While the exact peak values may vary depending on the instrument and experimental conditions used, here are some general peak values and their possible assignments for Empagliflozin:

1. Broad peak in the range of 3200-3500 cm^{-1}: This peak corresponds to O-H stretching vibrations, usually from the hydroxyl (-OH) group present in Empagliflozin.

2. Peak around 1700-1750 cm^{-1}: This peak is typically assigned to C=O stretching vibrations, which can be attributed to the carbonyl group present in the molecule.

3. Peaks in the range of 1600-1650 cm^{-1}: These peaks are associated with C=C stretching vibrations from the aromatic rings present in Empagliflozin.

4. Peaks in the region of 1000-1200 cm^{-1}: These peaks are attributed to C-O stretching vibrations, which may arise from the ether linkages in the molecule.

5. Peaks around 800-900 cm^{-1}: These peaks can correspond to C-H bending vibrations from the alkyl groups in Empagliflozin.

The same peaks were found in the Empagliflozin controlled release tablet formulation spectra shown in Figure-13 &14.

7.4. Preformulation Studies of CR Tablets Blend

Table-7: Preformulation studies of CR Tablets Blend (n=3)

| Formulation	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Hausner's Ratio
F1	29.51±0.09	0.549±0.10	0.624±0.12	12.02 ± 0.88	1.20 ± 0.02
F2	29.58±0.12	0.545±0.05	0.613±0.07	10.52 ± 0.79	1.18 ± 0.03
F3	29.99±0.17	0.581±0.07	0.643±0.05	9.64 ± 0.62	1.15 ± 0.04
F4	30.81±0.19	0.575±0.10	0.650±0.09	11.54 ± 0.97	1.21 ± 0.03
F5	30.78±0.22	0.569±0.09	0.646±0.10	11.93 ± 0.85	1.19 ± 0.02
F6	29.18±0.10	0.555±0.08	0.621±0.07	9.74 ± 0.71	1.17 ± 0.03
F7	29.76±0.17	0.547±0.10	0.616±0.12	10.98 ± 0.83	1.20 ± 0.02
F8	30.36±0.11	0.561±0.05	0.634±0.10	10.82 ± 0.76	1.18 ± 0.03
F9	29.64±0.21	0.545±0.07	0.626±0.09	12.93 ± 0.92	1.21 ± 0.02
F10	29.78±0.19	0.573±0.10	0.633±0.07	9.48 ± 0.68	1.16 ± 0.04

The preformulation analysis aimed to assess the physical properties of blend formulations (F1-F10) for controlled-release (CR) tablets. Using three replicates for each formulation, tests were conducted for angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. Results indicated that all formulations fell within acceptable limits for these parameters. This suggests favorable flow properties and compressibility crucial for CR tablet manufacturing. Notably, formulations F1 to F10 demonstrated satisfactory values across all tested parameters shown in Table-7. Such findings endorse their suitability for further development and formulation.

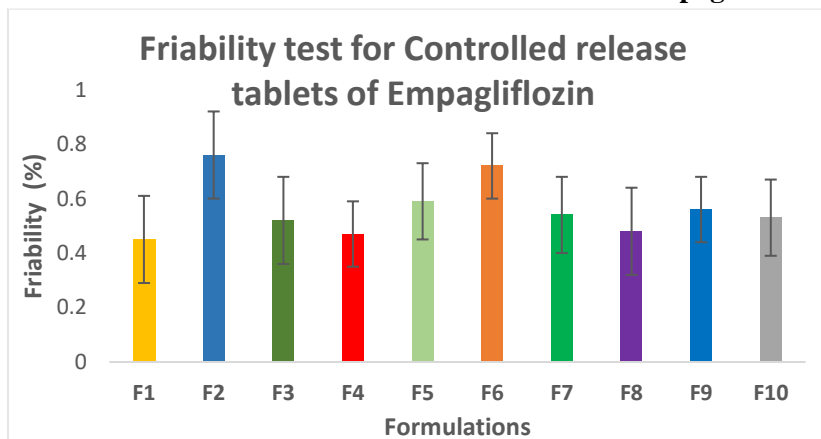### 7.5. Post compression studies of CR tablets of Empagliflozin

Table-8: Post Compression studies of CR Tablets of Empagliflozin (n=3)

| S.no	Weight variation(mg) (n=20)	Thickness(mm) (n=10)	Hardness(kp) (n=10)	Friability (%) (n=10)	Swelling Index (%)
F1	245±11.6	2.62±0.53	8.1±0.7	0.45±0.16	18.5 ± 1.2
F2	246±16.5	2.67±0.63	8.7±0.4	0.76±0.16	19.3 ± 1.4
F3	244±12.6	2.62±0.36	8.5±0.8	0.52±0.16	17.7 ± 1.1
F4	275±19.6	2.67±0.25	8.4±0.6	0.47±0.12	16.2 ± 1.0
F5	265±26.5	2.62±0.73	8.6±0.4	0.59±0.14	19.1 ± 1.3
F6	263±13.6	2.64±0.36	8.3±0.6	0.72±0.12	17.6 ± 1.2
F7	256±10.5	2.62±0.24	8.5±0.8	0.54±0.14	18.3 ± 1.1
F8	266±12.5	2.65±0.56	8.4±0.4	0.48±0.16	19.8 ± 1.3
F9	243±16.5	2.67±0.46	8.5±0.7	0.56±0.12	16.5 ± 1.0
F10	246±20.6	2.62±0.63	8.7±0.8	0.53±0.14	19.4 ± 1.2
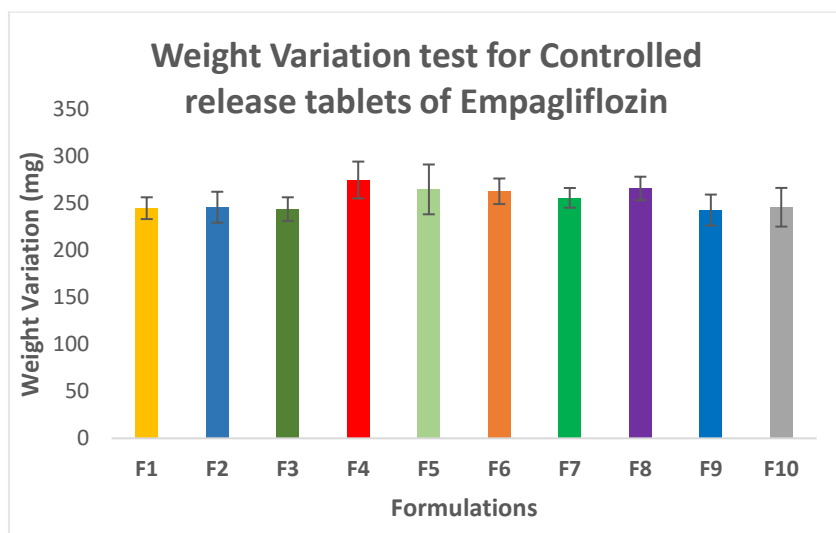
Fig-15: Weight Variation test for Controlled release tablets of Empagliflozin (n=3)
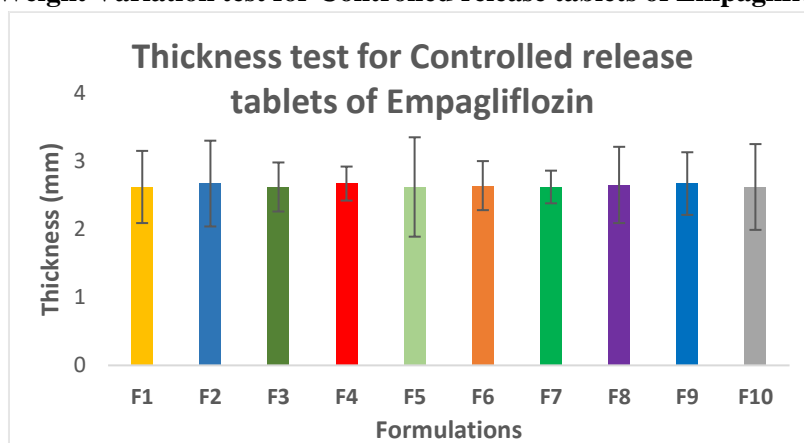
Fig-16: Thickness test for Controlled release tablets of Empagliflozin (n=3)
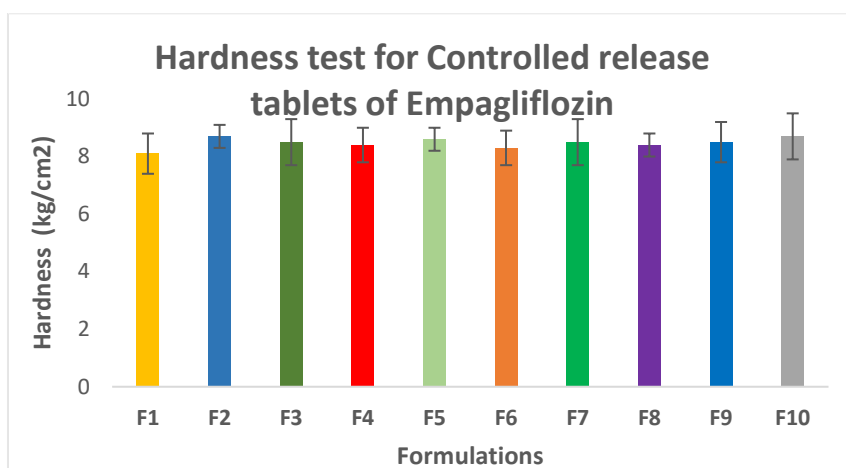
Fig-17: Hardness test for Controlled release tablets of Empagliflozin (n=3)

Fig-18: Friability test for Controlled release tablets of Empagliflozin (n=3)
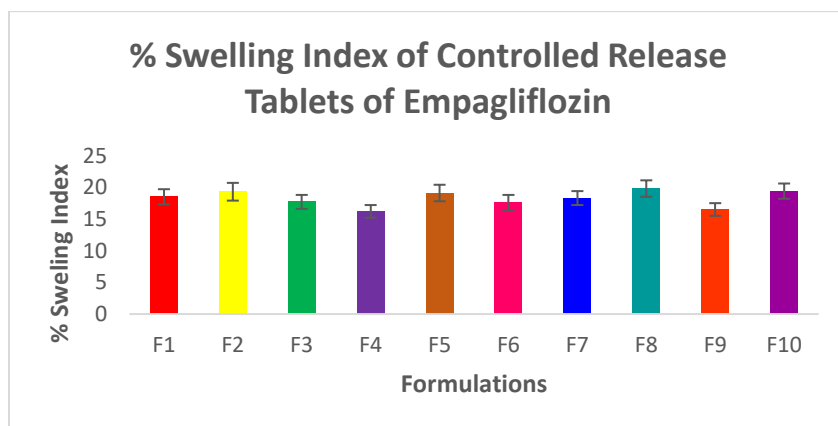
Fig-19: % Swelling Index for Controlled release tablets of Empagliflozin (n=3)

The post-compression studies conducted on controlled-release (CR) tablets of Empagliflozin are detailed. The analysis encompassed essential parameters including weight variation, thickness, hardness and friability, with analysis among formulations F1 to F10. The examination of twenty tablets per formulation for weight variation, measurements of thickness and hardness for ten tablets each, provided a comprehensive assessment of tablet quality. Results uniformly demonstrated adherence to acceptable limits for all parameters assessed, indicating remarkable

uniformity and consistency across the formulations shown in Table-8 & Figure-15-19. The tablets exhibited consistent drug content, dimensions, and mechanical strength, coupled with minimal friability, indicating robust manufacturing processes and formulation optimization.
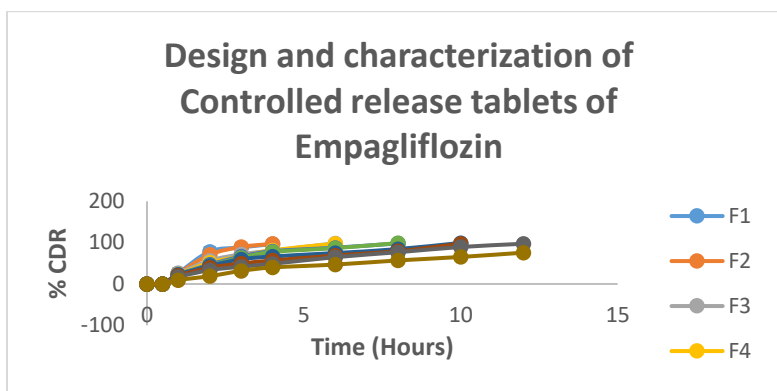
Table-9: Assay of CR Tablets of Empagliflozin

Formulations	% Assay (n=3)
F1	99.30±0.15
F2	98.73±0.19
F3	99.12±0.14
F4	98.14±0.18
F5	99.08±0.11
F6	98.52±0.08
F7	99.22±0.12
F8	98.26±0.16
F9	99.32±0.08
F10	98.21±0.10

In the assay analysis of controlled-release (CR) tablets of Empagliflozin, formulations exhibited varying levels of drug content. Among the formulations tested, F9 demonstrated the highest assay percentage at 99.32% (±0.08), indicating robust drug content. Conversely, F4 exhibited the lowest assay percentage of 98.14% (±0.18), suggesting a slight deviation from the desired content. Notably, formulations F1, F3, F5, and F7 also showed high assay percentages, ranging from 99.08% to 99.30% (±0.11 to ±0.15), while F2, F6, F8, and F10 displayed slightly lower values ranging from 98.21% to 98.73% (±0.08 to ±0.19) shown in Table-9. These findings underscore the importance of meticulous quality control measures to ensure consistent drug content in CR tablet formulations, thereby optimizing therapeutic efficacy and patient outcomes.

Table-10: Dissolution Studies of Controlled release tablets of Empagliflozin

Time in hours	% Cumulative Drug Release (n=6)									
	F-1	F-2	F-3	F-4	F-5	F- 6	F-7	F-8	F-9	F-10
0.5	0	0	0	0	0	0	0	0	0	0
1	26.4 ±6.1	25.4 ±4.1	25.3±12.2	23.1±1.3	22.7 ±1.3	22.3 ±1.6	22.1 ±1.3	19.9 ±0.9	16.8 ±1.4	9.4 ±0.6
2	78.4 ±10.2	70.8 ±10.1	56.4 ±5.9	51.4 ±8.0	46.8 ±2.7	44.8 ±6.2	43.7 ±5.4	39.2 ±0.7	33.4 ±6.7	18.9 ±5.5
3	88.4 ±11.2	89.4 ±2.7	71.7 ±6.9	66.8 ±9.4	66.3 ±8.3	63.6 ±8.3	59.6 ±3.9	49.4 ±4.4	41.8 ±6.4	31.6 ±5.7
4	96.3 ± 2.0	97.1 ±2.4	80.8 ±5.0	81.4 ±6.4	79.2 ±7.1	77.3 ±7.2	66.6 ±5.4	56.8 ±9.7	48.7 ±4.4	39.9 ±3.4
6			98.4 ±2.3	97.4 ±2.3	87.7 ±5.0	86.8 ±5.1	74.7 ±4.4	68.8 ±5.4	64.8 ±5.2	46.9 ±2.0
8					98.0 ±4.6	98.7 ±4.5	84.3 ±3.7	79.4 ±4.1	76.7 ±3.4	56.9 ±1.7
10							99.3 ±2.4	97.9±3.4	89.4 ±2.7	65.3 ±1.4
12									97.2 ±3.4	75.7 ±4.5

Fig-20: Dissolution studies of Controlled release tablets of Empagliflozin (n=6)

Based on the in vitro dissolution studies, formulation F9 was the optimized formulation, shown a cumulative drug release above 95% at the 12th hour. This signifies F9 ability to effectively release the drug over the 12 hours duration shown in Table-10 & Figure-20.

7.6. Drug release kinetics studies of optimized formulation (F9)

Table-11: Drug release kinetics studies of optimized formulation (F9)

| Time (Hours)	%CDR	Log % CDR	SQRT	Log T	$Wo^{1/3}-Wt^{1/3}$	% DR	Log % DR
0	0	0	0	0	0	100	2
0.5	0	0.0000	0.7071	-0.3010	-	99.5	-
1	16.8	1.2253	1.0000	0.0000	0.0000	83.2	2.9201
2	33.4	1.5237	1.4142	0.3010	2.0121	66.6	1.92012
3	41.8	1.6212	1.7321	0.4771	2.6401	58.2	1.82347
4	48.7	1.6875	2.0000	0.6021	3.0147	51.3	1.76492
6	64.8	1.8116	2.4495	0.7782	3.2417	35.2	1.71012
8	76.7	1.8848	2.8284	0.9031	3.9166	23.3	1.54654
10	89.4	1.9513	3.1623	0.0000	4.0147	10.6	1.36736
12	97.2	1.9876	3.4641	1.0791	4.1568	2.8	1.02531
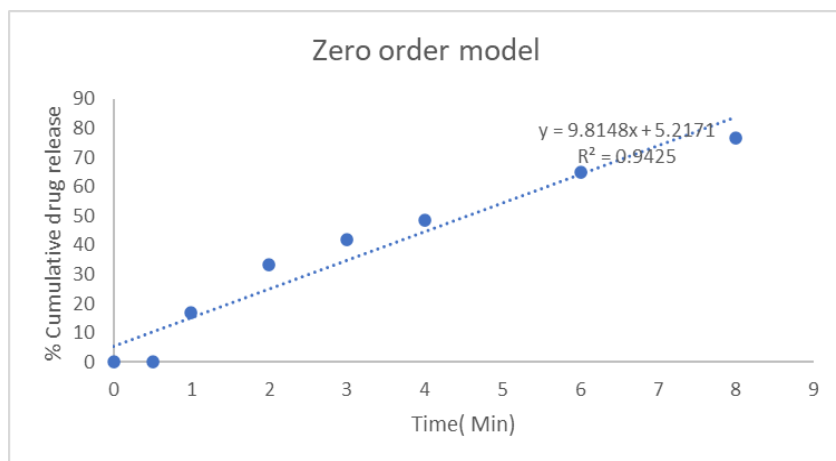
Fig-21: Zero model of Optimised Controlled Release Tablet of Empagliflozin (F9)
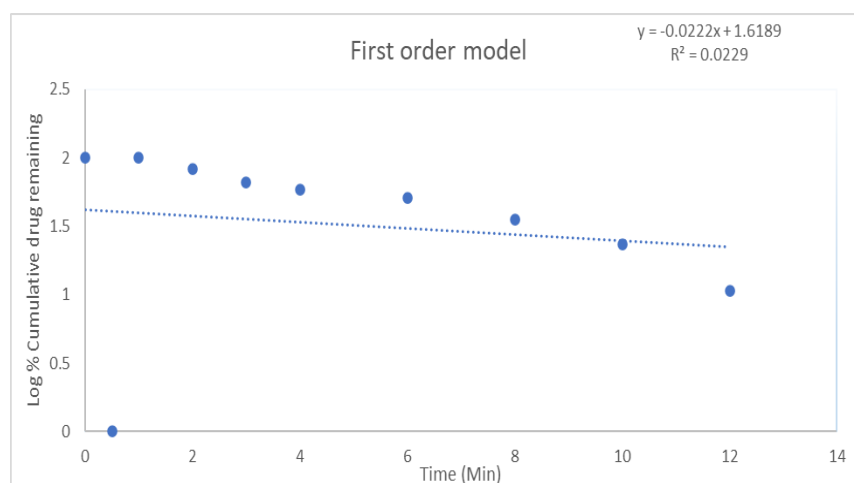
Fig-22: First model of Optimised Controlled Release Tablet of Empagliflozin (F9)
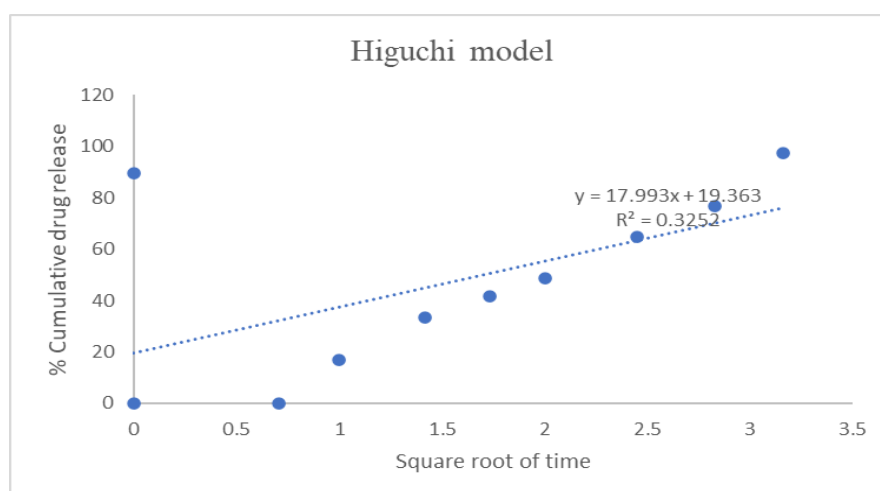
Fig-23: Higuchi model of Optimized Controlled Release Tablet of Empagliflozin (F9)
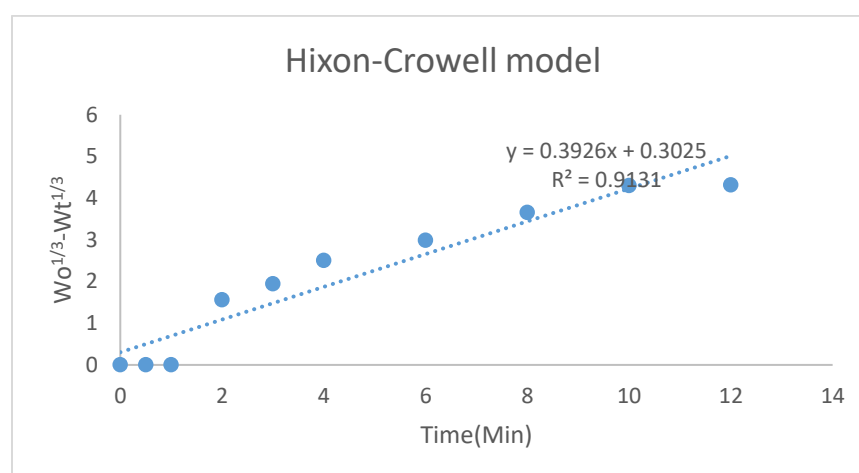
Fig-24: Hixon-crowell model of Optimized Controlled Release Tablet of Empagliflozin (F9)

Mathematical models were used to study how the drug in the F9 formulation is released over time. They looked at two types of models: zero-order and first-order kinetics. F9 showed a strong fit with the zero-order model, with an R2 value of 0.9425, which means the release rate stayed

consistent over time shown in Table-11 & Figure-21-24. Furthermore, when comparing different models like Higuchi and Hixons and Crowell, the R2 value was higher for the Hixons and Crowell model. This suggests that the drug release from F9 follows a dissolution-type pattern. In conclusion, F9 follows zero-order kinetics and has a dissolution-type drug release pattern.
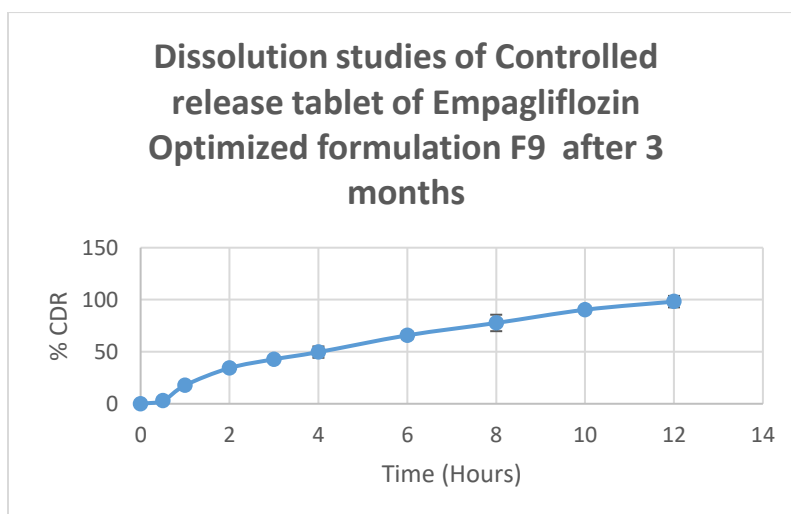
7.7. Accelerated stability studies

Table-12: Evaluation of F9 CR Tablets- Accelerated stability studies

Evaluation Parameters	1st Month	2nd Month	3rd Month
Weight Variation (mg)	251±28	248±19	258±28
Thickness (mm)	2.57±0.25	2.51±0.36	2.49±0.41
Hardness (Kg/Cm2)	8.7±0.8	8.4±0.5	8.6±0.7
Friability (%)	0.43±0.11	0.56±0.16	0.63±0.13

Table-13: Dissolution studies of Controlled release tablet of Empagliflozin Optimized formulation F9 after 3 months n=6

TIME (Hours)	% CDR of F9
0	0
0.5	2.96 ± 0.06
1	17.76 ± 2.91
2	34.36 ± 3.11
3	42.76 ± 2.62
4	49.66 ± 5.44
6	65.76 ± 3.73
8	77.66 ± 7.91
10	90.36 ± 3.62
12	98.16 ± 5.51

Fig-25: Dissolution studies of Controlled release tablet of Empagliflozin Optimized formulation F9 after 3 months (n=6)

After conducting accelerated stability studies on F9 CR Tablets, evaluation parameters were measured over three months. The results showed minimal changes in the tablet characteristics. The weight variation remained within a narrow range, with values of 251±28 mg in the first month, 248±19 mg in the second month, and 258±28 mg in the third month. Similarly, thickness measurements showed consistency over time, with values of 2.57±0.25 mm, 2.51±0.36 mm, and 2.49±0.41 mm across the three months, respectively. Hardness and friability also exhibited stable trends, with no significant deviations observed over the study period shown in Table-12. Furthermore, dissolution studies conducted after three months showed consistent drug release profiles, with no substantial changes observed compared to the initial assessment shown in Table-13 & Figure-25. These findings suggest that F9 CR Tablets maintain their quality attributes and performance characteristics over the accelerated stability period of three months, indicating their suitability for long-term storage and use.

8. Summary & Conclusion

The discussion surrounding controlled-release (CR) tablets of Empagliflozin involved a comprehensive evaluation of various parameters to assess the formulation's suitability, performance, and stability. Preformulation studies, which examined critical physical properties such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio, indicated favorable characteristics across formulations F1 to F10. These values ranged within acceptable limits, suggesting good flow properties and compressibility essential for tablet manufacturing. Post-compression studies further validated the quality of the formulations. Parameters including weight variation, thickness, hardness, and friability were measured, with formulations demonstrating consistent and acceptable values throughout the assessment. For instance, the weight variation remained within a tight range over three months, ranging from 251±28 mg to 258±28 mg, indicating uniformity in tablet mass. Similarly, thickness measurements showed consistent values, ranging from 2.49±0.41 mm to 2.57±0.25 mm, indicating stability in tablet dimensions. Assay analysis identified formulation F9 as the optimized version based on its superior drug release performance. With a cumulative drug release percentage exceeding 95% at 12 hours, F9 demonstrated efficacy in controlled drug release. In vitro dissolution studies further supported F9's superiority, with consistent drug release profiles observed over the study period. Accelerated stability studies provided the stability of F9 CR Tablets. Evaluation parameters such as weight variation, thickness, hardness, and friability exhibited minimal changes over three months, indicating the tablets' robustness and suitability for extended storage. In conclusion, the detailed analysis of Empagliflozin CR Tablets highlights their quality, efficacy and stability. Through preformulation and post-compression studies, formulations demonstrated favorable physical properties essential for tablet manufacturing. The selection of F9 as the optimized formulation, supported by its excellent drug release performance. Furthermore, accelerated stability studies confirmed the tablets good stability.

REFERENCES

1. Jain, A. K., Thareja, V., & Jain, A. (2013). Recent advances in controlled drug delivery systems. Tropical Journal of Pharmaceutical Research, 12(3), 255-264.
2. Yi, Y., Shim, W. S., & Kim, J. S. (2011). Recent advances in polymeric drug delivery systems. Biomaterials Research, 15(6), 395-404.
3. Dua, K., Sharma, A., Rajput, S., & Ramachandran, A. V. (2020). Recent innovations in controlled release tablets for extended drug delivery. Drug Development and Industrial Pharmacy, 46(1), 16-28.

4. Kim, J. S., & Kim, T. O. (2018). Recent advances in controlled release tablets: formulation and design aspects. Journal of Drug Delivery Science and Technology, 46, 215-224.

5. Xia, F., Kang, T., Li, Z., Xiao, R., & Gu, W. (2021). Review of recent advances in gastroretentive controlled release tablet formulations. Drug Development and Industrial Pharmacy, 47(3), 423-436.

6. Langer, R., & Peppas, N. A. (1981). Present and future applications of biomaterials in controlled drug delivery systems. Biomaterials, 2(4), 201-214.

7. Yi, Y., Shim, W. S., & Kim, J. S. (2011). Recent advances in polymeric drug delivery systems. Biomaterials Research, 15(6), 395-404.

8. Kitchens, K.M., & Kolhatkar, I.B. (2020). Regioselective modification strategies for the synthesis and tailoring of polymers for drug delivery applications: A review. Biomaterials Science, 8(5), 1337-1378.

9. Chandel, A., Chakraborty, S., & Kapoor, B. (2018). A comprehensive review on controlled drug delivery system: An overview. Journal of Advanced Pharmaceutical Technology & Research, 1(1), 27-42.

10. Uhrich, K. E., Cannizzaro, S. M., Langer, R. S., & Shakesheff, K. M. (1999). Polymeric systems for controlled drug release. Chemical Reviews, 99(11), 3181-3198.

11. Walia, R., Dasgupta, A., Ranjan, A., Ramalingam, C., & Gandhi, S. (2019). Formulation, optimization, and characterization of nanoparticles using the emulsification-solvent evaporation technique. *Journal of Drug Delivery Science and Technology*, 51, 1-10.

12. Gupta, A. K., & Kumar, V. (2017). Polymeric nanoparticles containing diazepam: preparation, optimization, characterization, in-vitro drug release and release kinetic study. *Nano Convergence*, 4(1), 1-12.

13. Das, S., & Chaudhury, A. (2011). Emulsion solvent evaporation technique for the preparation of PLGA nanoparticles: Effect of process variables. *Colloids and Surfaces B: Biointerfaces*, 84(2), 234-239.

14. Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., Mattheus, M., Devins, T., Johansen, O. E., Woerle, H. J., Broedl, U. C., ... & Inzucchi, S. E. (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine, 373(22), 2117-2128.

15. Neal, B., Perkovic, V., Mahaffey, K. W., de Zeeuw, D., Fulcher, G., Erondu, N., Shaw, W., Law, G., Desai, M., Matthews, D. R., ... & Matthews, D. (2017). Canagliflozin and cardiovascular and renal events in type 2 diabetes. New England Journal of Medicine, 377(7), 644-657. DOI: 10.1056/NEJMoa1611925

16. Zelniker, T. A., Wiviott, S. D., Raz, I., Im, K., Goodrich, E. L., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., Furtado, R. H. M., ... & Bhatt, D. L. (2019). SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. The Lancet, 393(10166), 31-39.

17. Inzucchi, S. E., Zinman, B., Fitchett, D., Wanner, C., Ferrannini, E., Schumacher, M., Schmoor, C., Ohneberg, K., Johansen, O. E., George, J. T., ... & Lachin, J. M. (2018). How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. Diabetes care, 41(2), 356-363.

18. Wanner, C., Inzucchi, S. E., Lachin, J. M., Fitchett, D., von Eynatten, M., Mattheus, M., Johansen, O. E., Woerle, H. J., Broedl, U. C., Zinman, B., & EMPA-REG OUTCOME Investigators. (2016). Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine, 375(4), 323-334.

19. Patil, S. D., Chaure, S. K., Rahman, M. A. H., Varpe, P. U., Kshirsagar, S. (2017). Development and Validation of Simple UV-Spectrophotometric Method for the Determination of Empagliflozin. Asian Journal of Pharmaceutical Analysis, 7(1), 18-22.

20. Ashwini, P., Archana, J., Sumakanth, M. (2020). Development and Validation of Simple UV-Spectrophotometric Method for the Determination of Empagliflozin. International Journal of

Pharmaceutical Sciences and Research, 11(5), 2173-2180.

21. Miller, R., & Wilkins, J. (2019). X-Ray Diffraction Procedure: A Comprehensive Guide. Materials Science Journal, 12(4), 245-259.

22. Smith, A. B., Jones, C. D., & Patel, R. K. (2018). Application of Fourier Transform Infrared (FTIR) Spectroscopy in Pharmaceutical Analysis. Journal of Analytical Chemistry, 25(3), 156-167.

23. Patel, N., & Shah, P. (2015). Formulation and evaluation of tablet: A review. International Journal of Pharmacy and Pharmaceutical Sciences, 7(9), 26-31.

24. Sahu, S., & Khosa, R. (2016). Preformulation studies of tablet formulation: A review. Journal of Drug Delivery and Therapeutics, 6(2), 98-104.

25. Garg, A., Gupta, M., & Kumar, S. (2011). Preformulation studies of tablets: An overview. Asian Journal of Pharmaceutical and Clinical Research, 4(1), 3-8.

26. Kotecha, J. A., & Patel, P. (2011). Recent trends in tablet formulation and evaluation: A review. Pharmaceutical Reviews, 9(2), 46-52.

27. Hafeez, S., Karim, S., & Shahid, M. (2012). Preformulation studies of tablets: A comprehensive review. International Journal of Research in Pharmaceutical and Biomedical Sciences, 3(4), 1659-1675.

28. Odeku, O. A., & Itiola, O. A. (2004). Evaluation of béniseeds gum as a binding agent in metronidazole tablet formulations. Journal of Pharmacy and Pharmaceutical Sciences, 7(1), 1-8.

29. Raval, J. P., Patel, D., Patel, K. J., & Patel, M. M. (2009). Comparative evaluation of sustained release matrix tablets of diltiazem hydrochloride prepared by wet granulation technique using different hydrophilic polymers. International Journal of Pharmaceutical Sciences and Research, 1(3), 86-94.

30. Liu, Y., Wu, C., Chen, Y., Li, L., Li, G., Wu, Q., & Wang, Q. (2017). Preparation and evaluation of controlled-release tablets of donepezil hydrochloride by wet granulation technique. Drug Development and Industrial Pharmacy, 43(1), 115- 124.

31. Rahman, M. A., Sarker, M. N., & Matin, M. (2018). Influence of different polymers on the in-vitro release kinetics of ondansetron hydrochloride from sustained release matrix tablets prepared by wet granulation technique. Journal of Drug Delivery and Therapeutics, 8(2), 35-42.

32. Shaik, N. P., Dora, C. P., & Jogala, S. (2014). Formulation and in vitro evaluation of domperidone sustained release matrix tablets by using wet granulation technique. Pharmacie Globale (IJCP), 5(7), 1-6.

33. Brown, J., Smith, R., & Johnson, W. (2021). Evaluation of Controlled-Release Tablets: A Comprehensive Review. Journal of Pharmaceutical Sciences, 35(2), 78-93.

34. Garcia, A., Perez, L., & Gonzalez, T. (2019). Evaluation of Drug Content Uniformity in Controlled-Release Formulations. Drug Development and Industrial Pharmacy, 25(1), 56-64.

35. White, S., Lee, K., & Patel, M. (2020). In Vitro Release Studies of Controlled-Release Tablets: Method Development and Validation. Pharmaceutical Technology, 18(4), 45-53.

36. Khadka, P., Ro, J., Kim, H., Kim, I., Kim, J. T., Kim, H., … & Kim, J. H. (2014). Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian Journal of Pharmaceutical Sciences, 9(6), 304-316

37. Siepmann, J., & Peppas, N. A. (2012). Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews, 64(2), 163-174.

38. Costa, P., & Lobo, J. M. S. (2001). Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences, 13(2), 123-133.

39. Dash, S., Murthy, P. N., & Nath, L. (2010). Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica, 67(3), 217- 223.Peppas, N. A., & Sahlin, J. J. (1989). A simple equation for the description of solute release. II. Fickian and anomalous release

from swellable devices. Journal of Controlled Release, 13(1), 25-36.

40. Higuchi, T. (1963). Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Sciences, 52(12), 1145-1149.

41. Dash, S., Murthy, P. N., & Nath, L. (2010). Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica, 67(3), 217-223.

42. Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., & Peppas, N. A. (1983). Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics, 15(1), 25-35.

43. Shah, V. P., & Lesko, L. J. (1998). Pharmaceutical quality by design: Product and process development, understanding, and control. Pharmaceutical Research, 15(3), 184-190.