

**DESIGN AND DEVELOPMENT OF DAPAGLIFLOZIN AND METFORMIN
XR TABLET BY DRUG LOADING TECHNIQUE**



SUPERIOR UNIVERSITY

Thesis Submitted to

The Superior University Lahore

In Partial Fulfillment of the

Requirement for the Degree of

M.Phil Chemistry

By

ALI HAIDER

Roll No. SU92-MSCHW-S23-016

Session: 2023-2025

Faculty of Sciences

2023-2025

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FOS

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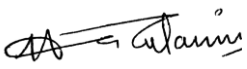
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Supervisor Name: Dr Noor Ul Ain

Designation: Senior Lecturer

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This is to certify that the research work presented in this thesis, titled “**Design and development of Dapagliflozin and Metformin XR tablet by drug loading technique**” was conducted by “**Ali Haider**” under the supervision of “**Dr Noor Ul Ain**”

No part of this thesis has been submitted anywhere else for any other degree. This thesis is submitted to the Faculty of Sciences, The Superior University, Lahore in partial fulfillment of the requirements for the degree of Master of Science/Master of Philosophy in the field of “**Chemistry**” in Faculty of Sciences at The Superior University, Lahore.

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Dedication

This is dedicated to Almighty Allah the Lord of Lords also my Parents, my Family, my friends, and for all those who love, support and encouraging me throughout my studies.

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All praises and thanks are for **Almighty ALLAH**, the source of all knowledge and wisdom endowed to mankind, to whom we should bow down for guidance in difficulties and darkness, who guides us and help us in all thick and thin of life. All respect is for our **Holy Prophet MUHAMMAD (PBUH)** who enabled us to recognize our creator and showed us the right path to humanity.

I dedicated my research to my **grandfather & grandmother (RIP)**, to my **father & mother**, who tirelessly encouraged me throughout my academic career. Whose feet are calloused by days of long hard work, whose tears have survived my family for years. To my Sweet **Brothers and Sisters (Akash Haider, Urooj Zahra, Abbas Haider, & Beloved Noor Zahra)** for their support and Love. This is for you my Family

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Table of Contents	Page
Author's Declaration	I
Plagiarism Undertaking.....	II
Research Completion Certificate.....	III
Certificate of Approval.....	IV
Dedication	V
Acknowledgements	VI
Table of contents	VII
List of tables.....	IX
List of figures	X
List of abbreviations.....	XI
Abstract	XII
Chapter 1: Introduction	1
1.1 Drug delivery system	1
1.2 The need for clinical practice oral drug delivery	2
1.5 Diabetes Type II.....	3
1.6 Metformin (C ₄ H ₁₁ N ₅).....	6
1.8 Dapagliflozin.....	9
1.9 Metformin and Dapagliflozin Combination.....	11
1.10 Drug Loading Techniques for XR Formulation.....	11
1.11 Formulation Development Process.....	12
1.15 AIM and Objectives	13
Chapter 2: Literature Review	20
Chapter 3: Methodology	34
3.1 Material Required.....	34
3.3 Formulations.....	38
3.7 Physico-Chemical Test Parameters.....	45

Chapter 4: Results	49
4.1 Preparation and Characterization	49
4.2 FTIR Analysis	55
4.3 Post Formulation Studies... ..	61
Chapter 5: Discussion.....	70
Chapter 6: Conclusion... ..	72
References	73

List of Tables

Description	Page
Table 3.1: Material required for the Tablet Formulation	34
Table 3.2: Chemicals Used.....	35
Table 3.3: Equipment	35
Table 3.4: Composition Of All Formulations.....	40
Table 3.5: Standard Reference Chart	44
Table 4.1: Concentration of standard solutions of Metformin HCl and its absorbance Values.....	49
Table 4.2: Concentration of standard solutions of Dapagliflozin and absorbance values.....	50
Table 4.3: Actual assessment of powder before Compression.....	53
Table 4.4 Post Compression Parameters	61
Table 4.5: Quantitative assay Results	62
Table 4.6: The dissolution results of Tablet.....	65
Table 4.7: Dissolution profile of Dapagliflozin	66
Table 4.8: Dissolution profile of Metformin HCl	67
Table 4.9: Pharmacokinetic results	68

List of Figures

Description	Page
Figure 1.1 Chemical structure of Dapagliflozin	01
Figure 1. Chemical structure of Metformin HCl.....	04
Figure 1.3 Calibration Curve of Metformin HCl at 220nm	04
Figure 1.4 Calibration Curve of Dapagliflozin at 220nm	05
Figure 1.5 FTIR Chromatogram of Glyceryl behenate	05
Figure 4.1 FTIR Chromatogram of Dapagliflozin.....	27
Figure 4.2 FTIR Chromatogram of Metformin HCL	27
Figure 4. 3 FTIR Chromatogram of PVP K-30.....	28
Figure 4.4 FTIR Chromatogram of Microcrystalline cellulose.....	29
Figure 4.5 FTIR Chromatogram of Lactose Anhydrous	30
Figure 4.6 FTIR Chromatogram of Kollidon CL.....	32
Figure 4.7 FTIR Chromatogram of HPMC K-100.....	32
Figure 4.8 FTIR Chromatogram of Mg-stearate	30
Figure 4.9 FTIR Chromatogram of Final Sunset Yellow Color.....	32
Figure 4.10 FTIR Chromatogram of Formulation F11	32
Figure 4.11 Assay Chromatogram of Quantitative Assay.....	30
Figure 4.12 Assay Chromatogram of mobile phase.....	32
Figure 4.13 Assay Chromatogram of standard solution.....	32
Figure 4.16 Assay Chromatogram of Final formulation F11	30
Figure 4.17 Dissolution Profile graphically represented for tablet	32
Figure 4.18 Dissolution profile graphically represented for Dapagliflozin.....	32
Figure 4.19 Dissolution profile graphically represented for Metformin HCL	30

LIST OF ABBREVIATIONS

AOT	Dioctyl Sulfosuccinate
API	Active Pharmaceutical Ingredient
B.P	Blood Pressure
CVD	Cardiovascular disease
CCB	Calcium Channel Blocker
CHD	Chronic Heart Disease
CVS	Cardiovascular System
C.I	Carrier's compressibility index
Cm ³	Cubic centimeter
D.T	Disintegration time
DCL	Co-ordinate Compressible Lactose
FTIR	Fourier transform infrared spectroscopy
GI	Gastrointestinal
GIT	Gastrointestinal Tract
GMP	Good Manufacturing Practices
G	Gram
HCl	Hydrochloric Acid
HMG-CoA	3-Hydroxy-3-methyl-3-glutryl-coenzyme A reductase
HCT	Hydrochlorothiazide
H.R	Hausner's ratio
HPMC	Hydroxy propyl methyl cellulose
hr.	Hour
JNC	Joint national committee
LH	Low substituted hydroxy propyl cellulose
LDL-C	Low density lipoprotein cholesterol
L.O.D	Loss on drying
ml	Milliliter
mg	Milligram
MLCK	Myosin light chain kinase
NF	National Formulary
NHANES III	National Health and Nutrition Examination Survey

ODS	Octadecyl silyl
Rpm	Revolutions per minute
S.D	Standard deviation
UV/VIS	Ultraviolet and visible
USP	United States Pharmacopoeia
Wt.	Weight
λ_{max}	Maximum wavelength

ABSTRACT

This study focuses on the formulation of an extended-release (XR) tablet containing Dapagliflozin and Metformin, aimed at improving diabetes mellitus type 2 treatment. A drug loading technique was employed to incorporate both active pharmaceutical ingredients into a single dosage form. The goal was to enhance patient compliance, reduce dosing frequency, and maintain stable blood glucose levels. Various polymers and excipients were tested to achieve optimal drug release and tablet integrity. Pre-compression and post-compression parameters were evaluated, ensuring proper flowability, hardness, and uniformity. In-vitro dissolution studies demonstrated regulated and prolonged release of both drugs for a long time. The formulation showed excellent stability under accelerated conditions. Drug content analysis confirmed uniform distribution across all batches. The XR tablet successfully met the desired quality standards. This dual-drug system simplifies therapy for diabetic patients. The study concludes that the drug loading technique is a promising method for developing fixed-dose combination tablets with extended-release profiles.

CHAPTER 1

INTRODUCTION

1.1 DRUG DELIVERY SYSTEM

The oral drug delivery system is the most talked-about method of administering pharmaceutical products with a range of dose formulations for systemic medication delivery. The many advantages of oral drug delivery, such as its ease of use, portability, and quick digestion, make it popular. Despite discussing the mode of release and dosage form design, this is the primary reason why the majority of newly developed medications are in oral form; instead, they should be created with consideration for the inherent features of gastrointestinal physiology. Basic understanding of GI physiology, pharmacokinetics, pharmacodynamics, and formulation design are therefore important [1].

Scientists' primary focus these days is creating long-term remedies for conditions like diabetes and high blood pressure [2]. This therapy is gaining popularity because it reduces dose-dependent side effects. By combining drugs, one can enhance the effectiveness of others, allowing for lower dosages to achieve the desired results. This approach minimizes toxic effects that can occur with high doses of a single drug, which is the traditional method [3]. Bilayer tablets fall under combination therapy, which involves taking two distinct medications. This innovative drug delivery method likely saves patients from the inconvenience of taking several medications at short intervals, improves patient adherence, speeds up the healing process for those who are ill, and produces longer-lasting effects with lower dosages while demonstrating improved plasma level management [4]. The Joint National Committee VI acknowledges the importance of combination therapy and proposes that combining medications with distinct mechanisms of action will reduce dosages for greater control and fewer dose-dependent negative consequences. Combination therapy is preferable for chronic physiology, pharmacokinetics, and pharmacodynamics, as well as formulation design, according to JNC VI guidelines [5].

1.2 THE NEED FOR CLINICAL PRACTICE ORAL DRUG DELIVERY

At present, nearly all oral dosage forms, including tablets, simple injection solutions, and syrups, are administered as conventional oral medications. Advanced drug delivery systems have not been implemented in practice. However, nano-formulations and combination therapies, such as bi-layer or tri-layer systems, can be effectively utilized for the management of multiple chronic diseases [6]. The advantages of modern drug delivery technologies are now better understood.

1.3 FROM CONVENTIONAL TO ADVANCED DRUG DELIVERY SYSTEM

The adoption of sophisticated medication delivery systems has increased in recent years as the significance of contemporary drug delivery systems has been acknowledged. The advantages of traditional dose forms may be the cause of this increase.

1.3.1 Tablets with layers

Bi-layer or tri-layer tablets are formed by compressing two or three distinct layers of granules or powders. This multi-layered structure gives the tablets a visual resemblance to a sandwich, with the exposed edges of each layer creating a clear distinction between them. The flattened corners of the tablets enhance this sandwich-like appearance, making them easily recognizable. To ensure the stability of the tablet and prevent any potential interactions between incompatible ingredients, an inert barrier is strategically placed between the different layers. This barrier serves as a protective layer, allowing for the effective delivery of each component while maintaining the integrity of the overall formulation [7].

1.4 PURPOSE OF DRUG LOADING TECHNIQUES

There are the following purposes of drug loading techniques

- Improve bioavailability and efficacy of drugs
- Enhance patient compliance
- Reduce side effects
- Increase drug stability
- Optimize drug release profiles

1.5 DIABETES TYPE II

Type 2 diabetes is a significant metabolic disorder that results in elevated blood sugar levels. The impact of diabetes can vary widely: some individuals effectively manage the disease, while others experience escalating health issues over time. Type 2 diabetes is distinguished by relative insulin deficiency due to pancreatic β -cell dysfunction and insulin resistance in target organs. It's crucial to understand the implications of this condition and take proactive steps to manage it effectively [8].

1.5.1 Prevalence and global impact

Youth-onset type 1 and type 2 diabetes are serious chronic health conditions. Individuals with youth-onset diabetes are at risk for early complications, comorbidities, and increased mortality, especially among those from racial and ethnic minority groups and those who get type 2 diabetes. A growing number of young people are being diagnosed with type 2 diabetes, which currently makes up 20% to 50% of new-onset diabetes cases and disproportionately affects people of color. Despite the paucity of longitudinal research, it has been proposed that rising rates of childhood obesity are the cause of the rise in type 2 diabetes in young people. Youth obesity has been rising since the 1960s, but new research points to a plateau [9].

The groundbreaking Diabetes in Youth Study has uncovered a concerning trend – a rise in both type 1 and type 2 diabetes among US youths aged 19 years or younger from 2001 to 2009. Shockingly, it was estimated that in 2009, 187,246 US youths were living with diabetes. In a recent 2020 article, data from the SEARCH study painted a grim picture, demonstrating an alarming increase in the incidence of type 1 and type 2 diabetes in the US from 2002 to 2015 [10].

The disparities are stark, with non-Hispanic *White* youths leading in type 1 diabetes incidence, while non-Hispanic Black, Hispanic, and Asian or Pacific Islander youths witnessed larger relative per cent increases in incidence. Furthermore, American Indian and Black youths aged 10 to 19 years had the highest type 2 diabetes incidence, with significant increases observed among various ethnic groups. These findings underscore the urgent need for action and intervention to address the concerning rise in diabetes among our youth [11].

1.5.2 Pathophysiology of type-ii diabetes

Insulin-sensitive tissues and islet β cells usually participate in a feedback loop that controls glucose metabolism. The β -cell response is influenced by tissue

sensitivity to insulin. By producing more insulin, β cells can preserve normal glucose tolerance in the case of insulin resistance. When insulin resistance is present and β cells are unable to produce enough insulin, glucose concentrations increase. Although there is a definite hereditary component to β -cell malfunction, environmental alterations are equally crucial. The important roles of hexoses, amino acids, and fatty acids in insulin resistance and β -cell dysfunction, as well as the possible effects of alterations in the microbiome, have been established by recent studies. Several new approaches for treatment have been developed, but more effective therapies to slow the progressive loss of β -cell function are needed. Recent findings from clinical trials provide important information about methods to prevent and treat type 2 diabetes, including some of the adverse effects of these interventions. To find innovative strategies to prevent and cure type 2 diabetes and lessen its negative effects, further long-term research on medications and bariatric surgery is necessary [12].

1.5.2.1 Insulin resistance

One risk factor for type 2 diabetes is muscle insulin resistance, as assessed by the euglycemic-hyper-insulinemic clamp. However, hepatic rather than muscular insulin resistance is linked to the pathogenesis of hyperglycemia in people with diabetes. Disulphide bonds bind the two α and two β subunits that make up the insulin receptor (IR), which is a heterotetramer. Insulin stimulates the tyrosine kinase in the β subunit of the insulin receptor by binding to the α subunit. The activation of the insulin receptor's tyrosine kinase causes the β subunit to autophosphorylate; phosphorylation of three tyrosine residues (Tyr-1158, Tyr-1162, and Tyr-1163) is necessary for the kinase activity to be amplified. The majority of insulin's effects on metabolism and apoptosis are mediated by a signalling pathway that includes phosphorylating the insulin receptor substrate (IRS) proteins and activating Akt (also called protein kinase B), p70 S6 kinase, the molecular target of rapamycin (mTOR), and phosphatidylinositol (PI) 3-kinase. The p85 regulatory component of PI3-kinase targets the phosphotyrosine residues on IRS proteins after the insulin receptor tyrosine kinase phosphorylates the IRS proteins. Phosphoinositide-dependent kinase 1 (PDK1) is bound by 3'-phosphoinositides produced by activated PI3-kinase, namely phosphatidyl-inositol-3,4-bisphosphate (PIP2) and phosphatidyl-inositol-3,4,5-trisphosphate (PIP3). Atypical versions of protein kinase C (PKC) and protein kinase B (PKB) are known substrates of PDKs [13].

Studies on calorie restriction in type 2 diabetes have shown the difference between insulin resistance in the liver and muscles. Without altering muscular insulin resistance, calorie restriction decreased liver fat and restored normal hepatic insulin sensitivity and plasma glucose levels. As intrapancreatic fat content dropped, severe calorie restriction also demonstrated a long-term recovery to normal insulin secretion [14].

1.5.2.2 Glucose homeostasis

Mitochondrial metabolism is essential for normal β -cell function. APPL1 proteins are reported to influence mitochondrial function and β -cells by maintaining the expression of several key genes involved in mitochondrial biogenesis. APPL1 also contributes to the regulation of both the first and second phases of glucose-stimulated insulin secretion and therefore has the potential as a therapeutic target for anti-T2DM drug discovery. Therapeutic intervention for type 2 diabetes may benefit from the use of additional medicines that enhance mitochondrial function, such as the regulators of NAD-dependent protein deacetylase sirtuin 1, peroxisome proliferator-activated protein kinase, and uncoupling protein 2 (UCP2). As the "glucose sensor" and a stimulator of glycolysis in β cells, glucokinase is an important therapeutic target [15].

Nevertheless, a number of glucokinase activators have not worked due to side effects or ineffectiveness. Though their utility may be limited by α cell hyperplasia and elevated hepatic aminotransferase levels, glucagon receptor antagonists have demonstrated considerable therapeutic efficacy. Although gluconeogenic inhibitors have demonstrated some effectiveness, there are safety concerns with hypoglycemia and lactic acidosis [16].

1.6 METFORMIN (C₄H₁₁N₅)

Patients with non-insulin-dependent diabetic mellitus (NIDDM) can use the oral medication metformin (dimethyl biguanide) to lower their blood glucose levels. It reduces the insulin resistance that is common in NIDDM by increasing insulin sensitivity. Despite having different mechanisms of action, metformin and sulfonylureas both effectively regulate blood sugar levels. When sulfonylurea therapy is insufficient on its own, metformin can be administered as a supplement or as the first line of treatment. A popular biguanide medication because of its affordability and safety is metformin. Because of its exceptional capacity to lower plasma glucose

levels, it has been used for more than 60 years to treat type 2 diabetes in its early stages. As time went on, new applications for metformin were found, and its advantages for several illnesses and even ageing were confirmed. malignancies (such as breast, endometrial, bone, colorectal, and melanoma malignancies), obesity, liver, cardiovascular, and renal disorders are among these illnesses. Metformin exerts different effects through different signaling pathways [17].

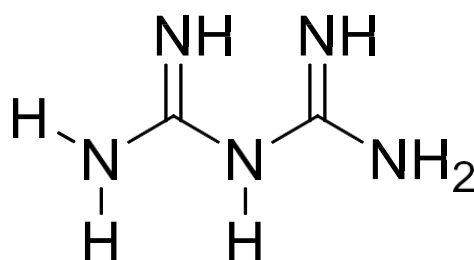


Figure 1: Metformin (C₄H₁₁N₅)

1.6.1 Mechanism of action of metformin:

By lowering fasting plasma glucose and insulin concentrations, metformin treatment increases insulin sensitivity; it is ineffective without insulin. The primary causes of the glucose-lowering impact in NIDDM patients are improved peripheral glucose absorption and decreased hepatic glucose production. Reduced fatty acid oxidation and enhanced intestinal glucose uptake are two other processes that might be involved. In patients with NIDDM, metformin reduces basal hepatic glucose production, which is a keyway that the medication lowers fasting plasma glucose levels. Therapeutic doses of metformin decrease glucagon-stimulated gluconeogenesis and increase insulin-induced inhibition of gluconeogenesis in isolated hepatocytes.

1.6.2 Insulin-stimulation:

In most investigations employing hyper-insulinemic-, euglycemic-, and hyperglycemic-clamp procedures in patients with NIDDM, metformin has improved glucose elimination, with muscle being suggested as its primary site of action. Metformin boosts the muscle's insulin-stimulated absorption of glucose in animals, which leads to enhanced glucose oxidation and glycogen synthesis but not to a rise in lactate generation. Additionally, metformin promotes lipogenesis and the absorption and oxidation of glucose by adipose tissue [18].

1.6.3 Oral glucose tolerance:

While the plasma insulin response to glucose remains similar or may even decrease in people with hyperinsulinemia, metformin enhances oral glucose tolerance. Frequently, the decrease in the gradual rise in plasma glucose levels following oral glucose delivery is comparable to the decrease in fasting plasma glucose levels. However, metformin therapy lowers postprandial plasma glucose concentrations throughout daytime glucose profiles, particularly after the noon meal. Although metformin does not decrease the total absorption of a glucose load, these alterations could be the result of delayed glucose absorption, or they could represent the time needed for metformin absorption and drug accumulation in tissue [19].

1.6.4 Decreases fatty-acid oxidation:

Using the glucose fatty acid cycle, metformin lowers plasma glucose concentrations by 10–20% by reducing fatty-acid oxidation. Glycogen synthesis is a key component of the increased glucose disposal, as indirect calorimetry shows that metformin has little overall effect on oxidative metabolism (it produces a slight decrease in fatty-acid oxidation and a slight increase in glucose oxidation). In tissues such as the brain, renal medulla, and skin that are acutely insulin insensitive, metformin seems to be ineffective [20].

1.7 ADVERSE EFFECTS

1.7.1 GI effects:

The most frequent GI adverse effects of metformin include nausea, diarrhoea, and/or discomfort in the abdomen. Although they are often moderate, temporary, and dose-related, they can happen to as many as 50% of patients who are taking the drug. Even at modest dosages, the medication is intolerable to about 5% of people. Gradual titration or dose reduction can help reduce symptoms. These adverse effects might be connected to drug buildup in the small intestine's enterocytes. Reduced gastrointestinal symptoms are linked to slow-release formulations, such as extended-release metformin [metformin XR] [21].

1.7.2 Lactic acidosis:

Lactic acidosis is a far less common but more worrisome side effect of biguanide treatment. Because of this link, phenformin, an earlier member of this class, was no longer used in the 1970s. Lactic acidosis is a potentially fatal side effect that has been linked to the stimulation of anaerobic metabolism by interfering with mitochondrial respiration, which raises the production of lactate. This is especially

true in cases of acute kidney injury or advanced chronic kidney disease, where reduced renal clearance causes medication levels to rise into the hazardous range (> 5.0 mg/l [therapeutic limits, 0.5–2.0 mg/l]). Recognition of this risk substantially delayed the approval of metformin in the USA in the early 1990s. Metformin-associated lactic acidosis (MALA) is rare, with an estimated incidence of 3–10 per 100,000 person-years. Of note, the risk of developing lactic acidosis from metformin has been calculated to be 20 times less frequent than with phenformin. Conditions including sepsis, cardiogenic shock, and alcoholism that cause elevated lactate production are additional risk factors for MALA [22].

1.7.3 B¹² Deficiency:

Another possible side effect of metformin is vitamin B12 malabsorption, which has been conclusively shown in numerous case reports as well as cross-sectional and longitudinal investigations. In a 52-month randomised trial with 256 participants, 19 (9.9%) of those randomly assigned to metformin therapy experienced vitamin B12 deficiency (<150 pmol/l), compared to five (2.7%) in the placebo group; an additional 35 (18.2%) of those assigned to metformin, as opposed to 13 (7.0%) in the placebo group, experienced low vitamin B12 concentrations (150–220 pmol/l). Long-term biguanide medication was also linked to an increased risk of low vitamin B12 levels, according to the Diabetes Prevention Program Outcomes Study (DPPOS). Furthermore, a relatively small percentage ($n = 13$) of metformin-treated DPPOS patients who experienced low vitamin B12 levels also had a higher prevalence of peripheral neuropathy (as determined by monofilament testing). Few additional studies have demonstrated that any clinical symptoms are brought on by drug-induced variations in vitamin B12 levels. However, considering the biochemical alterations and the possible irreversible neurological consequences of an undiagnosed vitamin B12 deficiency, it is recommended that patients receiving long-term metformin therapy have their vitamin B12 levels checked on a regular basis, particularly if they have peripheral neuropathy or anemia. Oral vitamin B12 supplements could be recommended as a preventative measure [23].

1.8 DAPAGLIFLOZIN

Dapagliflozin is used to treat type 2 diabetes and is the first in a new class of glucose-lowering medications called sodium-glucose co-transporter-2 (SGLT2) inhibitors. By blocking the kidney's SGLT2 transporter protein, dapagliflozin lowers renal glucose reabsorption, which lowers blood glucose levels and causes glucose to be excreted in urine. The effectiveness of dapagliflozin is not dependent on the secretion or action of insulin, in contrast to oral antidiabetic medications from a number of other classes. Consequently, dapagliflozin's distinct mode of action offers complimentary therapy when taken with other antidiabetic medications [24].

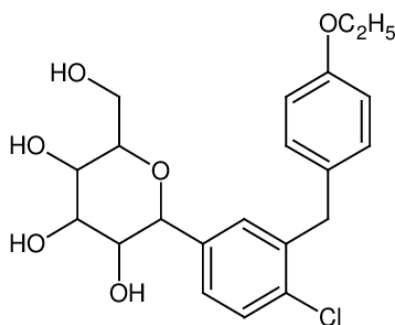


Figure 2: Dapagliflozin ($C_{21}H_{25}ClO_6$)

1.8.1 ACTION MECHANISM

One such SGLT2 inhibitor that is authorised for the treatment of type 2 diabetes in a number of nations, including the USA and the EU, is dapagliflozin. A thorough assessment of dapagliflozin's pharmacological characteristics and clinical application in people with type 2 diabetes has already been published in [Drugs](#).

1.8.1.1 Patients with hypertension:

In two phase 3 trials, dapagliflozin 10 mg once daily decreased blood pressure and enhanced glycaemic control in patients with poorly managed hypertension and type 2 diabetes who were receiving antihypertensive medication (angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) therapy either alone or in conjunction with another antihypertensive medication).

1.8.1.2 Patients with cardiovascular disease:

When added to standard background medication, dapagliflozin 10 mg once daily improved glycaemia control and decreased body weight and SBP in two phase 3 studies in patients with poorly managed type 2 diabetes (HbA1c 7–10.5% across the studies), pre-existing cardiovascular disease, and hypertension. [25].

1.8.2 ADVERSE EVENTS

1.8.2.1 Hypoglycemia:

This was observed in 14% of dapagliflozin users and 12% of placebo receivers in the pooled analysis of 13 studies. The dapagliflozin group experienced three significant hypoglycemic events, while the placebo group experienced two. Most of these events were in patients receiving insulin as background medication, but a single occurrence in a patient getting dapagliflozin plus insulin and metformin led to the therapy being stopped. Significantly fewer dapagliflozin receivers experienced serious bouts of hypoglycemia in DECLARE-TIMI 58 than placebo users (0.7 vs. 1.0%; $p = 0.02$) [26].

1.8.2.2 Genital infections:

In the 13-study pooled analysis, these infections were more common with dapagliflozin than with placebo (5.5% vs. 0.6%), and they happened at least twice as frequently in women as in men in both treatment groups. Just 0.2% of participants in the dapagliflozin group and none in the placebo group needed to stop their therapy since all genital infections were mild to moderate in severity [27]. In this investigation, UTIs occurred in 5% of dapagliflozin and 4% of placebo patients, with women experiencing UTIs nearly five times more commonly than males, irrespective of treatment group. The majority of UTIs were mild to moderate in severity, had symptoms like those of T2D patients, weren't kidney infections, and didn't need stopping treatment (UTI-related discontinuation rate $\leq 0.2\%$ in both groups). In both treatment groups, most of the genital infection or UTI patients responded well to early antimicrobial therapy and did not need further care [28].

1.8.2.3 Parathyroid hormone:

Small increases in parathyroid hormone were linked to dapagliflozin treatment; patients with greater baseline parathyroid levels experienced larger increases. During two years of treatment, dapagliflozin did not cause any bone loss in

patients with mild or normal renal impairment [29].

1.9 METFORMIN AND DAPAGLIFLOZIN COMBINATION

In the United States, diabetes has become a serious health concern. A third of Americans without diabetes go undetected, despite the fact that 14% of adults in the US have the disease. It is anticipated that 20% of the 86 million individuals with prediabetes would develop diabetes within five years, increasing the disease's prevalence. Type 2 diabetes mellitus (T2DM) is linked to older age, obesity, sedentary lifestyle, family history, gestational diabetes, and ethnicity. It makes up 90% to 95% of all adult cases. Individuals with type 2 diabetes are more likely to experience severe health issues such heart disease, stroke, nephropathy, hypertension, blindness, and neuropathy [30].

Dapagliflozin or metformin XR improves glycemic control, and both are generally well tolerated as initial pharmacotherapy for type 2 diabetes. Dapagliflozin-treated patients experienced a greater incidence of events suggestive of urinary tract and genital infections vs. metformin-treated patients; most of these events were clinically manageable [31]. Dapagliflozin 10 mg monotherapy was non-inferior to metformin in lowering HbA1c and superior to metformin in lowering fasting plasma glucose and body weight. In patients who were new to medication and had insufficient glycemic control, dapagliflozin and metformin together yielded even larger advantages in lowering body weight and hyperglycemia.

1.10 DRUG LOADING TECHNIQUES FOR XR FORMULATION

Several drug-loading techniques can be used in the formulation of XR tablets, each aimed at controlling the release rate of the drug.

1.10.1 Matrix-based systems:

1.10.1.1 Hydrophilic matrix system:

Although hydrophilic medicines are effective therapeutic agents, delivering them is a challenging issue. Therefore, creating an effective medicine delivery system might call for a multifaceted strategy. It is well established that colloidal drug delivery methods, including noisome, polymeric nanoparticles, emulsions, liposomes, and nano emulsions, improve the pharmacokinetic profiles of hydrophilic medicines and increase drug entrapment and bioavailability.

The drug is evenly distributed within a polymer matrix designed to enhance its delivery. Upon contact with gastrointestinal fluids, this matrix swells and transforms

into a gel, which plays a crucial role in controlling the rate of drug diffusion into the body. This mechanism allows for a more sustained release of the drug, improving its therapeutic efficacy. The polymers used in this formulation include hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), and Carbopol [32].

1.10.1.1.1 Methods:

1.10.1.1.1.1 Physical entrapment:

This method involves mixing the drug with hydrophilic polymers that attract water to form a gel-like matrix. As the matrix swells, it allows the drug to gradually diffuse out, maintaining consistent levels in the bloodstream over time. Common hydrophilic polymers used include polyethylene glycol (PEG) and polyvinyl alcohol (PVA).

1.10.1.1.1.2 Granulation:

This method uses a wet granulation procedure to combine the active pharmaceutical ingredient (API) with HPMC, also known as other hydrophilic polymers. This entails mixing the powder combination with a liquid binder, which encourages granule development. Utilizing HPMC, which is well-known for its high-water retention and gel-forming capabilities, guarantees that the medication is dispersed adequately throughout the granule matrix. Achieving regular release rates and enhancing the drug's total bioavailability depend on this even distribution. Before the mixture is made into dosage forms like tablets or capsules, it is typically dried after granulation and may be milled to reach the required particle size. These techniques are crucial for creating formulations with continuous release, which can improve patient adherence and reduce adverse effects. These methods are instrumental in developing sustained-release formulations, which can enhance patient compliance and minimize side effects by reducing the frequency of dosing [33].

This method offers a clear approach to product formulation, ensuring a consistent release profile. It involves selecting the right polymer grade and assessing its hydration properties, both of which are vital for the release characteristics of the final product. Misalignment in these parameters can lead to issues such as burst release, where the active ingredient is released too quickly, or incomplete release, where it is not fully delivered, affecting efficacy. Thus, understanding polymer characteristics and hydration behavior is crucial for achieving the desired release profile [34].

1.10.1.2 Hydrophobic matrix system

This system effectively incorporates the drug into a hydrophobic matrix that acts as a barrier to hydration. Consequently, the drug is released gradually over time, delivering a sustained therapeutic effect. The polymers selected for this system, Ethyl cellulose and Polyvinyl Acetate (PVA), are well-established for their hydrophobic properties and compatibility with a variety of drugs. This innovative approach not only enhances patient compliance but also minimizes the need for frequent dosing. By ensuring that the medication remains effective for an extended period, this system significantly improves treatment outcomes [35].

1.10.1.2.1 Methods:

1.10.1.2.1.1 Physical entrapment:

This method involves incorporating the drug into a hydrophobic polymer matrix, such as poly(lactic-co-glycolic acid) (PLGA) or polyethylene glycol (PEG). The matrix acts as a protective barrier, minimizing the interaction between the drug and aqueous environments. This limited water penetration slows down the drug's diffusion and release rate. As a result, the encapsulated drug can provide prolonged therapeutic effects, making this approach particularly useful for sustained-release formulations in various medical applications, including oncology and pain management.

1.10.1.2.1.2 Hot melt extrusion:

This advanced technique consists of heating the drug and a compatible polymer, often at temperatures exceeding the melting point of the polymer. Common polymers used include polyvinyl alcohol (PVA) and ethylcellulose. The heating process transforms the solid polymer into a viscous liquid, allowing for the homogeneous mixing of the drug. Once the drug is evenly distributed in the molten polymer, the mixture is extruded through a die, forming a solid dispersion upon cooling. This resulting matrix not only ensures uniform drug distribution but also enables a controlled release profile, which can be finely tuned by adjusting the formulation parameters. This method is widely used in the pharmaceutical industry due to its scalability and efficiency in creating robust drug delivery systems [36].

This drug delivery system provides a sustained release for water-soluble medications, helping to maintain steady therapeutic levels and improving patient compliance by reducing dosing frequency. However, if the matrix disintegrates too

quickly, it can lead to uncontrolled drug release, causing rapid spikes in concentration that may result in side effects or toxicity. Additionally, factors like gastrointestinal conditions, pH changes, and food intake can impact the disintegration rate, complicating the release profile.[37].

1.10.1.3 Coated matrix systems

Different oral, transdermal, or implantable medication formulations are handled by these systems. Depending on the therapeutic demands and the drug's pharmacokinetics, the matrix and coating designs can be altered. The basic idea behind coated matrix systems is to encapsulate the therapeutic ingredient in a core matrix that acts as a reservoir. A polymeric coating then governs the drug's release, controlling both its rate and its extent. Numerous elements, including the kind of polymer applied, the coating's thickness, and the characteristics of the medication itself, can affect this control [38].

1.10.1.3.1 Methods:

1.10.1.3.1.1 Coacervation:

Coacervation is a versatile microencapsulation technique used to coat drug-containing core matrices with polymers. This method is widely applied for preparing sustained or controlled-release formulations. The process involves creating a polymer-rich phase (coacervate) that forms a coating around the drug-loaded core, which can then control drug release based on the coating's properties.

1.10.1.3.1.2 Solvent diffusion method:

Solvent diffusion is another popular technique used for drug encapsulation. In this method, the drug is dispersed in a core matrix, and a polymer coating is applied using solvent-based techniques. The coating forms a diffusion barrier, which controls the release of the drug from the core matrix over time [39].

This process is advantageous due to its simplicity, scalability, and precise control over drug release by adjusting polymer film thickness. It is suitable for various drugs, particularly those sensitive to moisture or heat, since solvent evaporation occurs at room temperature. However, it has drawbacks, such as potential environmental and health concerns related to organic solvents. It may not be suitable for drugs that degrade in these solvents, and removing solvent residues completely can be challenging, potentially affecting product quality [40].

1.10.1.4 Osmotic systems

Drugs can be released gradually and under control thanks to the advanced technology described as the osmotic drug delivery system (ODDS). It controls the drug's release from the tablet or other dose form over time by using the osmotic pressure produced inside the system. By reducing variations in drug concentration, this approach is especially helpful for medications that need to be present in the body at steady levels for therapy. The medicinal product is released from the tablet through a laser-drilled hole under the influence of osmotic pressure. The polyethylene oxide (PEO) and cellulose acetate are common polymers for this [41].

1.10.1.4.1 Methods:

1.10.1.4.1.1 Osmotic core:

Once the core of an osmotic drug delivery system (ODDS) is prepared, it is subsequently coated with a semi-permeable membrane, generally composed of polymers such as cellulose acetate. This membrane serves to regulate water penetration and control the release of the drug. It permits the entry of water into the core while preventing the escape of the drug and osmogene until sufficient osmotic pressure is achieved. The application of the membrane can be executed through various techniques, including pan-coating, where the core is uniformly sprayed with a polymer solution while it rotates within a pan, or fluidized-bed coating, in which the cores are suspended in an air stream during the application of the coating solution. The thickness of the coating can be adjusted by altering the polymer concentration, the number of coats applied, and the duration of the coating process.

Moreover, plasticizers such as polyethylene glycol or glycerin are integrated to enhance the flexibility and permeability of the membrane. These modifications reduce brittleness and facilitate improved water penetration, thereby significantly influencing the overall rate of drug release.

1.10.1.4.1.2 Controlled release:

The rate of water influx and drug release is controlled by the membrane thickness and the size of the orifice [42]. The extremely precise and predictable drug release of ODDS helps maintain stable plasma drug levels throughout time by eliminating drug level peaks and troughs and reducing the need for frequent dosing. ODDS allows persistent drug release, which improves patient adherence for drugs that

need to be administered often or have a short half-life. Push-pull systems can be designed that enhance the administration of drugs that dissolve poorly by facilitating the medication's departure from the orifice. ODDS can lessen the occurrence of adverse effects linked to high drug concentrations, such as in medications with a limited therapeutic window, by preserving constant drug levels. Comparing ODDS to traditional dosage forms, the cost of manufacture is higher due to the need for advanced machinery and technology (such as laser-drilled orifices). The drug may be released suddenly and quickly if the semi-permeable membrane is weakened or broken, which could result in an overdose. Due to their inability to diffuse via the delivery orifice, biologics and big molecular-weight medications may not be appropriate candidates for ODDS, which is usually employed for tiny molecules [43].

1.11 FORMULATION DEVELOPMENT PROCESS

1.11.1 Pre-formulation studies

1.11.1.1 Solubility studies:

Solubility studies assess how well the active pharmaceutical ingredient (API) dissolves in various solvents, especially water, which is essential for osmotic drug delivery systems. Since these systems rely on osmotic pressure for drug release, the API must be sufficiently soluble in gastrointestinal fluids for gradual release. The studies involve testing the API in solvents like water, ethanol, and buffer solutions at different pH levels. If solubility is poor, solubilizing agents, surfactants, or salt forms can be used to improve dissolution and ensure effective release through the osmotic pump.

1.11.1.2 Compatibility studies:

Compatibility studies evaluate possible drug-excipient interactions that may affect the stability, release profile, or effectiveness of the medication. Two popular techniques are Fourier-Transform Infrared Spectroscopy (FTIR), which examines molecular vibrations to detect changes in chemical structure, and Differential Scanning Calorimetry (DSC), which measures heat flow during material transitions (such as melting or crystallization) to detect changes in the drug's thermal properties when mixed with excipients, suggesting potential interactions. After mixing, changes in the infrared spectrum could indicate chemical processes or interactions like hydrogen bonds [44].

1.12 GRANULATION TECHNIQUES

1.12.1 Wet granulation:

In wet granulation, the active pharmaceutical ingredient (API) is combined with liquid binder, excipients, and other ingredients to create granules. The binder solution facilitates the adhesion of the powder particles, creating a wet mass that is subsequently dried and ground into homogeneous granules before being compacted into tablets [45].

1.12.2 Dry granulation:

For medications that are heat or moisture-sensitive, dry granulation is utilized. It entails compacting the powder mixture straight away without using any liquid binders. Following the compacting process, the material is broken down into granules and compressed into tablets [46].

1.13 COMPRESSION OF TABLETS

1.13.1 Direct compression (Dc):

Direct compression is a simpler and faster method for tablet manufacturing that involves compressing powder directly into tablets without prior granulation. This technique is suitable for certain types of formulations where the powder mixture has sufficient flowability and compressibility.

1.14 DRUG LOAD IN COATING PROCESS

Drug Load in Coating is the amount of active pharmaceutical ingredient (API) incorporated into a coating formulation, expressed as a percentage of the total coating weight.

Mathematical Representation:

$$\text{Drug Load (\%)} = (\text{API Weight} / \text{Coating Weight}) \times 100$$

1.14.1 Coating processes:

1.14.1.1 Spray coating:

Spray Coating in Drug Loading is a process where a coating solution containing the active pharmaceutical ingredient (API) is sprayed onto a substrate, such as tablets, pellets, or capsules.

1.14.1.2 Dip coating:

Dip Coating in Drug Loading is a process where a substrate (e.g., tablets, pellets, capsules) is immersed in a coating solution containing the active pharmaceutical ingredient (API), and then withdrawn, leaving a thin layer of coating.

1.14.1.3 Pan coating:

Pan Coating in Drug Loading is a process where a rotating pan or drum is used to coat pharmaceutical substrates (e.g., tablets, pellets, capsules) with a coating slution containing the active pharmaceutical ingredient (API).

1.14.1.4 Electrostatic coating:

Electrostatic coating uses the principle of electrostatic attraction to deposit charged particles onto a substrate. The coating material is charged with an electrostatic charge, which attracts it to the substrate.

1.15 AIM & OBJECTIVES

- Formulation of tablet by drug loading technique
- Dapagliflozin will be immediately released approximately within 30 minutes
- Metformin HCL will be an Extended-release tablet.
- Determination of in-vitro drug release profiles

CHAPTER 2

LITERATURE REVIEW

Dapagliflozin, a highly specific sodium-glucose cotransporter-2 inhibitor (SGLT2) used to treat type 2 diabetes, was the subject of research by Al-Arjani et al. in 2021. In addition, pioglitazone, also known as Glitazone or Thiazolidinedione (TZD), is a significant class of insulin sensitizers used to treat type 2 diabetes. Pharmaceutical companies like to mix metformin with other classes of anti-hyperglycemic medications because it is the most often used medication for type 2 diabetes. Consequently, it would be more effective to combine these three classes into a single pharmaceutical dosage form rather than using either medication alone to manage hyperglycemia. Thus, the purpose of this study was to create a new, straightforward one. A precise, accurate, and specific reversed-phase High-Performance Liquid Chromatography (HPLC) method has been developed and validated for the simultaneous estimation of Dapagliflozin, Pioglitazone, and Metformin in pharmaceutical formulations in an effort to improve patient compatibility by creating a new combination of these three medications in a single tablet. The ACE C18 (250 x 4.5 mm), 5 μ m column with Acetonitrile was used to achieve the separation. Using potassium dihydrogen phosphate buffer (pH 3.4) adjusted with orthophosphoric acid at a flow rate of 1 mL/min, the detection was performed at 230 nm. The retention durations for metformin, dapagliflozin, and pioglitazone were 2.8, 6.9, and 4.4 minutes, respectively. According to ICH requirements, the analysis's results were deemed satisfactory after being validated for precision, linearity, accuracy, limit of quantification, limit of detection, dissolution, and stability. 2. These methods' excellent recovery and low relative standard deviation demonstrated their applicability and may be used for routine analysis of tablets containing metformin, pioglitazone, and dapagliflozin. Such medications can be quantified using the method described. Benefits include the ease of producing the sample and the low cost of the chemicals utilised. The recommended HPLC settings for the compounds ensure adequate resolution and precise quantitation [47].

Hinnen (2015) studied dapagliflozin, It is an authorised medication for type 2 diabetes mellitus (T2DM) in the US, EU, and other nations. It is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor. Dapagliflozin's mode of action complements those

of other antidiabetic drugs and promotes renal glucose excretion without the need for insulin. Dapagliflozin improves glycaemic parameters in people with type 2 diabetes when administered alone or in conjunction with insulin or other oral antidiabetic drugs. Treatment with dapagliflozin is also linked to decreased blood pressure and weight loss, both of which may help individuals with type 2 diabetes. Because of its mechanism of action, dapagliflozin has a low intrinsic propensity to cause hypoglycemia. Overall, dapagliflozin is well tolerated, with the frequency of most side events equivalent to that reported with placebo. Dapagliflozin-treated groups have seen a higher incidence of genital infections and, in certain trials, urinary tract infections than placebo groups. In the clinical development program, patients treated with dapagliflozin had a higher incidence of newly diagnosed bladder cancer (0.17%) than those treated with a placebo or comparator (0.03%). Dapagliflozin should not be used in individuals with bladder cancer and should be taken cautiously in patients with a history of bladder cancer, despite the fact that there were not enough cases to establish causation. In people who are old or have compromised renal function, dapagliflozin may lower glomerular filtration rate (GFR). Monitoring renal function is necessary prior to starting dapagliflozin. In individuals with an estimated GFR of less than 60 ml/min/1.73 m², dapagliflozin should not be administered. There are currently no cardiovascular safety signals for dapagliflozin, and a long-term cardiovascular outcomes research is being conducted. Dapagliflozin appears to be a viable new therapy option for type 2 diabetes, according to evidence from clinical trials [48].

Hassoun *et al.*, (2022) worked and provide Although there is evidence that sodium-glucose cotransporter type 2 inhibitors (SGLT2is) enhance glycaemic management, reduce weight, and lower blood pressure (BP), there is a dearth of empirical data about the possible advantages of SGLT2i for the Middle Eastern diabetic population. Our study aimed to describe glycemic control, changes in body weight, body mass index (BMI), lipid profile, and BPs in patients receiving dapagliflozin with other antidiabetic medication. The study was a multicenter, post-authorization, prospective, open-label, noninterventional, real-world, cohort study. 511 adults with type 2 diabetes mellitus who were taking antidiabetic drugs were included. After starting dapagliflozin, these individuals were monitored for a year to evaluate any changes in their lab and clinical results. With an absolute change of 0.9%, the mean HbA1c dropped from $8.5 \pm 1.6\%$ at baseline to $7.6 \pm 1.3\%$ after 12 months (p value <0.001).

41.6% of the individuals in the trial achieved a HbA1c level below 7% (53 mmol/mol). There was no change in the diastolic pressure, while the systolic pressure improved (mean change = -1.9 mm Hg, p value = 0.003). A substantial decrease of 0.7 kg and 0.2 kg/m² was seen in both body weight and BMI (p value <0.001). Approximately 57.4% of patients were using antihypertensives, while 84.5% were taking anti-dyslipidemic medications. Mild adverse events made up about 83.6% of all adverse events. Ninety occurrences of hypoglycemia were recorded, however none of them were severe. When dapagliflozin was used alongside other antidiabetic drugs, glycaemic control, weight, BMI, and systolic blood pressure all significantly improved in a real-world scenario. Furthermore, its safety profile was well-tolerated [49].

Elkind-Hirsch *et al.*, (2020) examined the history of gestational diabetes mellitus (GDM) in women, who are significantly more likely to develop type 2 diabetes (T2D) and GDM recurrence. The decline in pancreatic beta-cell compensation for insulin resistance is closely linked to weight gain, especially increased central adiposity following delivery. These women, who are at a high risk of acquiring type 2 diabetes, may benefit greatly from weight management following GDM. To assess how well dapagliflozin (DAPA) and metformin (MET), both separately and in combination (DAPA-MET), affect body weight, anthropometric, cardiovascular, and metabolic parameters in women who are overweight and have recently been diagnosed with GDM. Research Design. Three parallel treatment groups participated in this prospective, single-blind, randomised outpatient clinical study. Females ($n=66$; 54, 18–45 years old) who were overweight or obese (body mass index [BMI] >25) and had a GDM pregnancy during the previous 12 months were randomised, single-blindly, to DAPA, MET, or DAPA-MET for 24 weeks. At baseline and at the end of the experiment, measurements were made of blood pressure, height, BMI, waist circumference (WC), waist-to-height (WHtR) ratio, and body weight. In order to quantify glycemia, mean blood glucose (MBG), and calculate insulin sensitivity (IS) and secretion (SI) parameters, oral glucose tolerance tests (OGTTs) were conducted at baseline and 24 weeks. Plasma lipid fractions, TSH, and liver enzymes were also assessed in the fasting sample at the start and completion of the study trial. The study was completed by forty-nine (74%) participants. Significant reduction of weight, WC, WHtR, improved glycemia and ISOGTT index was found with DAPA-MET versus MET monotherapy. Both DAPA and DAPA-MET therapy outperformed MET in

terms of raising HDL 4 levels, decreasing TRG concentrations, lowering the ratio of TRG to HDL cholesterol, and enhancing glucose excursion following an OGTT. When comparing DAPA-MET alone to single-drug therapies, the early insulin response to a glucose challenge improved dramatically. For the first time, the effectiveness of an SGLT2 inhibitor by itself and in conjunction with metformin in this patient population is being compared. In women who were overweight or obese and had a recent history of GDM, we discovered that a 24-week course of dapagliflozin and metformin medication improved 70 body weight, WC, glycaemic, cardiovascular, and metabolic markers more than metformin monotherapy did [50].

Elbordiny *et al.*, (2022) discovered that rosuvastatin-metformin is a new fixed-dose combination (FDC) for the management of dyslipidaemia linked to diabetes mellitus. In general, FDC's positive effects on lowering the burden of pills, costs, and complexity of medication protocols inspired analysts and us to create quick, sustainable analytical techniques for the simultaneous assessment of such significant drug combinations. In this context, two approved analytical techniques have been used to separate and quantify metformin (MET) and rosuvastatin (RSV) in the presence of the pharmacopeial impurities rosuvastatin-related substance B (RSV-impurity B) and cyanoguanidine (CYG), which is impurity A of MET. The latter was made from scratch and verified using LC-MS, or liquid chromatography-mass spectrometry. Method I, which used Micellar Electrokinetic Chromatography (MEKC) for the assay of this FDC, was the first electro-driven separation technique. A deactivated fused silica capillary (50 cm effective length $\times$ 50 μ m id) was employed under ideal circumstances, which included 50 mM borate buffer with 100 mM sodium dodecyl sulphate (SDS) at pH 9.2. Method II involved the use of a Microsorb MV-C18 (4.6 $\times$ 250 mm, 5 μ m particle size) column with 20 mM sodium dihydrogen phosphate buffer (pH 3.5), acetonitrile, and methanol as components of the mobile phase for High Performance Liquid Chromatography (HPLC). Using a linear gradient program and a flow rate of 1.5 mL/min throughout the run, the separation was accomplished. In both techniques, the Diode Array Detector (DAD) detector was tuned to 243 nm for RSV and 235 nm for MET. For procedures I and II, the four peaks were separated in roughly 8 and 5 minutes, respectively. Linear relationships were obtained between peak areas and concentrations of metformin and rosuvastatin in the ranges 10–100 μ g/mL for MEKC and 1–150 μ g/mL for HPLC. The 2 techniques fulfilled the International Council for Harmonization (ICH) validation

criteria, Additionally, the most popular AGREE, hexagon, and RGB12 tools were used to assess the green and white analytical chemistry concepts. According to the score interpretation, the recommended approaches fared better in terms of sustainability and environmental friendliness than the ways that were reported. They provided quick, practical, stability-indicating, and precise drug analysis for both pills and bulk [51].

Yu *et al.*, (2023) intended to create and synthesise multicomponent molecular salts including metformin (MET) and rhein (RHE) in order to create an efficient treatment for diabetes and its consequences, based on the benefit of the complementary drug-drug salt strategy. The polymorphism of salts generated by MET and RHE was finally demonstrated by the salts of MET–RHE (1:1), MET–RHE–H₂O (1:1:1), MET–RHE–ethanol–H₂O (1:1:1:1), and MET–RHE–acetonitrile (2:2:1). A mix of theoretical computation and characterisation experiments were used to analyse the structures, and the formation mechanism of polymorphism was examined. A basis for increasing the bioavailability of MET and RHE in vivo was established by the in vitro assessment results, which demonstrated that MET–RHE had a similar hygroscopicity with metformin hydrochloride (MET·HCl) and that the solubility of the RHE component increased by almost 93 times. MET–RHE demonstrated superior hypoglycemic activity compared to the parent medications and the physical mixes of MET and RHE, according to the examination of hypoglycemic activity in mice (C57BL/6N). The aforementioned results show that this study used the multicomponent pharmaceutical salification technique to obtain the complementing benefits of MET and RHE and offer new avenues for the treatment of problems associated with diabetes [52].

Davis *et al.*, (2016) discovered that dapagliflozin works well to treat type 2 diabetes. to examine clinical data supporting the sodium-glucose cotransporter 2 inhibitor dapagliflozin (Farxiga-AstraZeneca)'s effectiveness, safety, and tolerability when used alone or in conjunction with other hypoglycemic medications to treat type 2 diabetes. A comprehensive MEDLINE search of dapagliflozin clinical trial findings was used to find relevant literature. Dapagliflozin's effectiveness, safety, and tolerability as a monotherapy or in conjunction with other treatments for type 2 diabetes have been demonstrated by numerous controlled clinical trials. To treat type 2 diabetes, the Food and Drug Administration has approved dapagliflozin as a monotherapy or as a supplement to existing glucose-lowering medications, such as insulin [53].

Ritesh *et al.*, (2022) worked on dapagliflozin and used to improve glycemic control, along with diet and exercise, in adults with type 2 diabetes is the model drug selected in the design, optimization, and characterization of dapagliflozin-loaded NLC using box-behnken design as the title of the current study. Anti-diabetic compounds can be delivered site-specifically by nanoformulations to their precise site of action, increasing the drug's loco-regional concentration and lowering systemic side effects. utilizing stearic acid as the lipid and tweens and spans as the surfactant, dapagliflozin-loaded NLCs were made utilizing the emulsion-evaporation process. NLCs were evaluated in terms of drug release percentage, entrapment efficiency, zeta potential, and particle size. Drug entrapment efficiency, zeta potential, particle size, and in vitro drug release behavior were all optimized in relation to the composition of lipid materials, the surfactant combination, and the speed of homogenization. At 69.99 nm, 81.94%, and -28.99 nm, respectively, the optimized formulation OPT-DP-NLC has demonstrated particle size, entrapment efficiency, and Zeta potential within predicted bounds [54].

Zafar *et al.*, (2020) Of all the drug administration routes, the oral route is the most widely used. An oral hypoglycemic medication called dapagliflozin is used to reduce blood glucose levels. In order to improve oral administration, dapagliflozin-loaded nanostructured lipid carriers (DG-NLCs) are being created and optimised. Lipid, surfactant, and homogenisation cycle were used as independent variables in the Box-Behnken design software to optimise the DG-NLCs, which were made utilising a high-pressure homogenisation process (hotDG-NLCs were assessed for drug release (Y3), entrapment efficiency (Y2), and particle size (Y1). In addition, the DG-NLCs were assessed for stability, ex-vivo intestinal penetration, thermal and X-ray diffraction studies, and shape. All seventeen formulations' particle sizes (nm), entrapment efficiency (%), and drug release (%) fell within 113.71-356.22 nm, 60.43-96.54%, and 63.44-83.62%, respectively. Morphology of optimized formulation exhibited spherical in shape confirmed by transmission electron microscopy. Thermal and X-ray diffraction analysis of NLCs showed the drug was solubilized and lost the crystallinity. DG-NLCs-opt exhibited dual release pattern initial fast and later sustained-release ($90.01 \pm 2.01\%$ in 24 h) whereas DG-dispersion showed $31.54 \pm 1.87\%$ release in 24 h. The best fit model was determined to be the Korsmeyer-Peppas model ($R^2=0.999$). Compared to DG-dispersion ($0.2683 \mu\text{g}/\text{cm}^2/\text{h}$), the DG-NLCs-opt showed a significantly higher flow ($p < 0.05$, $1.293 \mu\text{g}/\text{cm}^2/\text{h}$). In

comparison to DG-dispersion (8.61×10^{-6} cm/min), the apparent permeation coefficient of DG-NLCs-opt was found to be significantly greater ($p < 0.05$, 4.14×10^{-5} cm/min). After six months of storage at $25 \pm 2^\circ\text{C}$ and $60 \pm 5\%$ relative humidity, the formulation did not exhibit any significant alterations ($p < 0.05$). The results showed that a lipid nanocarrier based on quality by design (QbD) for oral administration may be a viable method of administering dapagliflozin for the treatment of diabetes [55].

Shah *et al.*, (2019) have created and approved a single LC-MS/MS test that uses ion-pair solid-phase extraction to detect metformin and dapagliflozin in human plasma simultaneously. Using acetonitrile–15 mm ammonium acetate, pH 4.5 (70:30, v/v) as the mobile phase, the analytes and their internal standards were separated chromatographically on a reversed-phase ACE 5CN (150×4.6 mm, $5 \mu\text{m}$) column. A polarity switching technique was used in mass spectrometric analysis to increase the analytes' sensitivity and selectivity. In the positive and negative modes, the ion transitions that were examined utilising various reaction monitoring modes were m/z 130.1 $[\text{M} + \text{H}]^+ / 60.1$ for metformin and m/z 467.1 $[\text{M} + \text{CH}_3\text{COO}]^- / 329.1$ for dapagliflozin, respectively. To improve the evaluation of the pharmacokinetics of the medications, the assay's linear calibration range was set from 1.00 to 2000 ng/mL for metformin and from 0.10 to 200 ng/mL for dapagliflozin. The analytes' respective limits of detection and quantification were 0.39 and 1.0 ng/mL for metformin and 0.03 and 0.1 ng/mL for dapagliflozin. The plasma matrix from various sources, such as hemolyzed and lipemic plasma, did not interfere. The approach was effectively used to investigate how diet affects the pharmacokinetics of dapagliflozin and metformin in healthy individuals [56].

Khalifa *et al.*, (2023) Using a solvent casting approach, a pullulan-based sublingual film carrying an Alogliptin/Dapagliflozin (ALO/DAPA) combo was created and statistically optimised to offer a potential treatment for type 2 diabetes. Using a central composite design produced by the Design Expert® program, sublingual films were optimised. A new environmentally friendly micellar HPLC technique was used to further determine the optimised recipe. On a Kinetex C18 column ($100 \text{ mm} \times 4.6 \text{ mm i.d.}$, $2.6\text{-}\mu\text{m}$ particle size), the separation was performed using isocratic elution at a flow rate of 1 mL/min and UV detection at 230 nm. The separation was carried out using a micellar aqueous mobile phase consisting of 50 mM sodium dihydrogen phosphate (pH 3.5), 15% pentanol, and 50 mM sodium dodecyl sulphate. ALO/DAPA sublingual films' antidiabetic effects on diabetic rats' blood glucose levels as well as

their impact on kidney and pancreatic histology were investigated. The devised method was exact and accurate, and it may be used to estimate both medications at the same time without interfering with their sublingual films. Additionally, the Green Analytical Procedure Index and analytical Eco-scale have been used to assess the suggested method's greenness, and the results indicate that it has the least negative environmental impact [57].

Alruwaili *et al.*, (2020) investigated and created a structural process to create ternary solid dispersions (SDs) loaded with dapagliflozin (DFG) using the carrier blend of poloxamer 188 (PLX 188) and polyethylene glycol 6000 (PEG 6000). The produced DFG-SDs were assessed for molecular simulation, physicochemical characterisation, and solubility. When compared to pure DFG and DFG physical combination, the produced DFG-SDs demonstrated noticeably greater solubility and dissolution. The composition with the maximum solubility (0.476 ± 0.016 mg/mL) was DFG:PEG:PLX (1:2.25:0.75 mM). The polymorphic transition of DFG from a crystalline state to a stable amorphous form is confirmed by the physicochemical characterisation. Compared to pure DFG ($15.70 \pm 3.54\%$), the produced DFG-SDs demonstrated a considerably higher dissolution ($64.78 \pm 2.34\%$ to $78.41 \pm 2.39\%$). Compared to pure DFG (14.97 ± 3.32 $\mu\text{g}/\text{cm}$), DFG-SD2 demonstrated a considerably improved drug permeability ($p < .05$) of 58.76 ± 4.65 $\mu\text{g}/\text{cm}$. Because of the lowest energy posture, the results of the molecular docking investigation showed that DFG had an excellent hydrophobic contact with the employed carrier. The core hydrophobic chain of the polymer's polyoxypropylene interacts with the methylene bridges. In order to improve the solubility and in vitro dissolving performance, DFG-SDs made by the microwave irradiation method utilising a hydrophilic carrier blend may be a viable approach [58].

Mohammad *et al.*, According to research, Type 2 diabetes mellitus is a common and progressing condition that requires novel treatment agents to keep improving disease management. The second medication in a novel class of oral antihyperglycemic medications known as sodium-glucose cotransporter 2 (SGLT2) inhibitors is dapagliflozin. Most renal glucose reuptake is caused by sodium-glucose cotransporter 2 inhibitors. Reduced plasma glucose levels result from enhanced renal glucose excretion made possible by cotransporter inhibition. Dapagliflozin rarely results in hypoglycemia because this method does not require the action of insulin. As a result, it is beneficial in patients at both early and late stages of their condition. Dapagliflozin

has been shown in studies to be effective when used alone as well as in conjunction with insulin and oral antihyperglycemic medications. In clinical trials, nasopharyngitis, urinary tract infections, and female genital mycotic infections were the most frequent side effects of dapagliflozin. Dapagliflozin is a novel oral medication for type 2 diabetes that was approved by the FDA in 2014. It works similarly to dipeptidyl peptidase 4 inhibitors in the short run. The Biguanides group's most recommended euglycemic monotherapy for type 2 diabetes is metformin. The 1-deoxy form of glucose, 1,5 anhydro glucitol (1,5-AG), is a verified indicator of short-term glycaemic management. A mathematical model called the Homeostasis Model Assessment (HOMA) can be used to estimate a person's level of beta cell function and insulin sensitivity. Objectives: This study looked at how metformin alone and metformin plus dapagliflozin affected glycated haemoglobin A1c (HbA1c), fasting plasma glucose (FPG), fasting serum 1,5AG, and HOMA of insulin resistance (HOMA-IR). Methods: The study comprised sixty-three T2DM patients, aged between 38 and 72 years, both male and female. The enrolled patients were split into two groups. Group 1 had 30 patients who received oral metformin exclusively for the duration of the research, which was 24 weeks. 33 individuals in Group 2 received oral metformin and dapagliflozin as treatment. Each patient was then asked to provide fasting serum insulin, FPG, HbA1c, and 1,5AG. Every parameter was first assessed prior to any interventions, and then again at two different points in time—the 12th and 24th weeks of the study period. To measure the biochemical profiles proposed in this investigation, standard kits were utilised. Tests were conducted and interpreted in accordance with the guidelines provided in each kit. Both 1,5AG (p 0.013, 0.030) and HbA1c (p 0.012, 0.020) significantly improved following 24 weeks of treatment with metformin alone and metformin plus dapagliflozin. The p values for HOMA-IR with metformin monotherapy and metformin plus dapagliflozin were, respectively, p 0.110 and 0.126; both findings indicated a statistically insignificant apparent improvement. HbA1c and 1,5AG blood levels are statistically significantly improved by metformin alone and metformin with dapagliflozin. There was just a slight apparent improvement in HOMA-IR in both therapy groups [59].

Tomar *et al.* (2019) investigated metformin hydrochloride. It is the preferred first-line medication for treating type II diabetes because it reduces peripheral insulin resistance and hepatic glucose production. One Patients who are overweight and have normal

kidney function can take it. Preformulation testing's main goals are to ascertain the drug's stability and kinetics, verify drug excipient compatibility, and produce information that will help the formulator create stable and bioavailable dosage forms. The medicine was found to be of the standard prescribed purity and quality after a preformulation study was conducted, with all results falling within the range specified in the Indian Pharmacopoeia. The drug's infrared spectra showed that the drug polymers did not significantly interact with one another. A 200–400 nm scan was performed on a solution containing 10µg/mL of metformin HCl. The medication has a good repeatability graph and showed the λ_{max} at 234 nm in pure water. Metformin HCl was estimated using the UV technique, and absorbance values were determined at λ_{max} 234 nm using an ultraviolet-visible (UV-VIS) spectrophotometer [60].

Faerch *et al.* (2021) sought to examine the safety and short-term effectiveness of three glucose-lowering treatments in overweight or obese people with prediabetes as determined by HbA1c. The Steno Diabetes Centre Copenhagen in Gentofte, Denmark, conducted the randomised, controlled, parallel, multi-arm, open-label, non-blinded PRE-D Trial. A total of 120 individuals with a BMI of ≥ 25 kg/m², aged between 30 and 70 years, and prediabetes (HbA1c 39–47 mmol/mol [5.7–6.4%]) were randomly assigned 1:1:1:1 to either dapagliflozin (10 mg once daily), metformin (1700 mg daily), interval-based exercise (5 days a week, 30 minutes per session), or control (habitual lifestyle). At baseline and six, thirteen, and twenty-six weeks after randomisation, the participants were analysed. A continuous glucose monitoring system was used to measure the 13-week change in glycaemic variability, which was defined as the mean amplitude of glycaemic excursions [MAGE] (pre-specified minimal clinically significant difference in MAGE ~30%). A total of 111 participants attended the follow-up visit at 26 weeks, while 121 participants attended the examination at 13 weeks. MAGE decreased slightly in the dapagliflozin group (17.1% [95% CI 0.7, 30.8], $p = 0.042$) and slightly, but not significantly, in the exercise group (15.3% [95% CI -1.2, 29.1], $p = 0.067$) when compared to the control group. In contrast, MAGE remained constant in the metformin group (0.1% [95% CI -16.1, 19.4], $p = 0.991$). With no difference between exercise and dapagliflozin (2.2% [95% CI -14.8, 22.5], $p = 0.815$), MAGE was 17.2% (95% CI 0.8, 30.9; $p = 0.041$) lower in the dapagliflozin group and 15.4% (95% CI -1.1, 29.1; $p = 0.065$) lower in the exercise group after 13 weeks compared to the metformin group. The control group

experienced one severe adverse event, which was lung cancer. Compared to control and metformin therapy, dapagliflozin and interval-based exercise treatment produced comparable but marginally greater reductions in glycaemic variability. It's unclear if these findings have any clinical significance in prediabetes [61].

Phadke *et al.* (2024) One of the recommended treatments for Type 2 diabetes mellitus (T2DM) is the combination of sodium-glucose cotransporter 2 inhibitors with metformin. Using dapagliflozin and metformin (Dapa-Met) as the first choice fixed-dose combination (FDC), we evaluated prescribing patterns in T2DM patients. We evaluated changes in cardiometabolic parameters and the indications for selecting Dapa-Met FDC. We included T2DM patients who started Dapa-Met FDC as their first medication and had a haemoglobin A1C (HbA1C) of greater than 7% in this retrospective analysis. After six months of Dapa-Met FDC, measurements of HbA1C, weight, systolic and diastolic blood pressure, fasting and postprandial plasma glucose were made. Overall, 485 T2DM patients (mean age: 59.7 ± 9.8 years) had their data incorporated. The average number of years with diabetes was 6.9 ± 4.7 . Strengths of 10 mg and 500 mg were the most favoured for Dapa-Met FDC. Almost 78% of patients needed more anti-diabetic medications. The most often co-prescribed medications were dipeptidyl peptidase 4 inhibitors (36.7%) and sulphonylureas (50.7%). Dapa-Met FDC was recommended for weight loss (77.1%) and lowering cardiovascular events and associated hospitalisations (46.8%) in addition to glycemia control. Changes in FPG (D - 21.4 mg/dL, $P < 0.0001$), PPG (D - 37.1 mg/dL, $P < 0.0001$), and HbA1C (D - 2.19%, $P < 0.0001$) were significant after six months. The most frequent adverse events were genitourinary infections (8.9%) and hypoglycemic episodes (16.7%). When used as the first line of treatment for type 2 diabetes in Indian individuals, Dapa-Met (10/500 mg) as FDC is both safe and efficacious. It can take more antidiabetic medications to reach glycaemic goals [62].

Yu *et al.*, (2017) sought to identify the safety and effectiveness information of saxagliptin, dapagliflozin, and their combination in the treatment of individuals with type 2 diabetes. There is also evidence to support the usage of the single-tablet combination formulation. A nonsystematic review of the literature was conducted using the Google Scholar, PubMed, and Ovid databases. When dapagliflozin/saxagliptin is added to metformin, the mean haemoglobin A1c can drop by up to 1.47%, and 0.5–2.0 kg of weight can be lost. Combination medication has a lower risk of genital infections than dapagliflozin alone, which may indicate a

preventive effect. At the 52-week follow-up, the risk of adverse events was not higher than it was with either monotherapy. The combination of dapagliflozin and saxagliptin is usually well tolerated and works effectively to help diabetic individuals achieve better glycaemic control [63].

Nauck *et al.* (2011) conducted studies and found that while sulfonylureas are initially beneficial, they are linked to weight gain, hypoglycemia, and poor glycaemic durability. By raising urine glucose excretion independently of insulin, dapagliflozin, a selective inhibitor of sodium-glucose cotransporter 2 (SGLT2), lowers hyperglycemia and may have fewer of these side effects. In patients with type 2 diabetes that metformin monotherapy was unable to adequately treat, we compared the safety, effectiveness, and tolerability of dapagliflozin with the sulfonylurea glipizide. Patients with type 2 diabetes (baseline mean HbA1c, 7.7%), receiving metformin monotherapy, were randomised to add-on dapagliflozin (n = 406) or glipizide (n = 408), up-titrated over 18 weeks based on glycaemic response and tolerability, to ≤ 10 or ≤ 20 mg/day, respectively, in this 52-week, double-blind, multicenter, active-controlled, noninferiority trial. When compared to glipizide (−0.52%), the primary outcome, adjusted mean HbA1c reduction with dapagliflozin (−0.52%), was statistically non-inferior after 52 weeks. Important secondary endpoints: dapagliflozin significantly reduced the proportion of patients experiencing hypoglycemia (3.5%) versus glipizide (40.8%; $P < 0.0001$), significantly increased the proportion of patients achieving $\geq 5\%$ body weight reduction (33.3%) versus glipizide (2.5%; $P < 0.0001$), and significantly produced adjusted mean weight loss (−3.2 kg) versus weight gain (1.2 kg; $P < 0.0001$) with glipizide. Dapagliflozin was associated with a higher frequency of events suggestive of lower urinary tract infections and vaginal infections than glipizide; nevertheless, these events were responsive to routine therapy and infrequently resulted in the termination of the study. Dapagliflozin decreased weight and caused less hypoglycemia than glipizide in type 2 diabetes that was not properly managed with metformin, even though their 52-week glycaemic efficacy was comparable. To further assess vaginal and urinary tract infections with SGLT2 inhibitors, longer-term research is needed [64].

Paul *et al.* (2024) investigated and investigated diabetic mellitus treatment approaches, with an emphasis on enhancing treatment results and patient adherence by creating and characterising an immediate-release dapagliflozin formulation. Pre-compression parameters like angle of repose (40.2 to 61.02), Hausner ratio (1.30 to

1.5), Carr's index (23.5 to 33.3), physical attributes (weight (145–155 mg), thickness (4.42 ± 0.04 to 4.46 ± 0.05 mm), hardness (3.7–5.6 kg/cm²), friability (<1%), and disintegration time were used to develop eight formulations using a wet granulation process with multiple super-disintegrating agents. Additionally, tests using FT-IR, SEM, and TGA showed no evidence of a drug-excipient interaction. After conducting in-vitro dissolution studies, the release profile was found to be F1 (80.50 ± 5.2) > F3 (75.97 ± 1.4) > F2 (75.30 ± 3.3) > F5 (74.14 ± 2.3) > F8 (70.13 ± 3.7) > F7 (68.12 ± 4.1) > F6 (66.45 ± 3.1) > F4 (54.74 ± 1.3) > pure drug (38.14 ± 2.1) within 30 minutes. Meanwhile, the F1 formulation met the USP requirements for formulas with immediate release. Furthermore, the results showed that the F1 formulation's medication release profile worked noticeably better than that of commercially available alternatives, suggesting that it may improve glycaemic control and patient adherence in the treatment of type 2 diabetes [65].

Parikh *et al.* (2015) Numerous treatments have been studied, and people with type 2 diabetes mellitus (T2DM) often report that they are unable to attain or sustain glycaemic control. Additionally, adverse effects including weight gain and hypoglycemia may restrict the options for treatment. A novel treatment for type 2 diabetes, dapagliflozin is a selective sodium-glucose cotransporter-2 inhibitor that lowers hyperglycemia by raising glucosuria without the need for insulin. The effectiveness, safety, and tolerability of dapagliflozin were assessed in numerous clinical trials. We assessed dapagliflozin 10-mg safety data from 12 placebo-controlled trials, cardiovascular safety and malignancy data from 19 dapagliflozin studies, and dapagliflozin 10-mg efficacy data from (i) two short-term, active-comparator studies (versus metformin-XR over 24 weeks and versus glipizide over 52 weeks), (ii) pooled 24-week analyses of five placebo-controlled trials (as monotherapy or add-on therapy), and (ii) long-term studies spanning 2 years. Similarly to metformin-XR (–1.44%), dapagliflozin (–1.45%) decreased HbA1c in treatment-naïve patients (baseline HbA1c 9%). Dapagliflozin and glipizide both produced a clinically significant decrease (–0.52%) in patients treated with metformin (baseline HbA1c 7.7%). The differences between dapagliflozin and placebo in weight, systolic blood pressure (SBP), and HbA1c were –0.60%, –1.61 kg, and –3.6 mmHg, respectively, in pooled 24-week analyses. Differences in HbA1c, weight, and SBP at 2 years were –0.44 to –0.80% and –2.41 to –3.19 kg, respectively, for dapagliflozin and glipizide, and –0.18%, –5.06 kg, and –3.89 mmHg, respectively, for glipizide.

Dapagliflozin seldom caused significant hypoglycemia (<0.1%). Dapagliflozin was more likely to cause vaginal and urinary tract infections, however these infections were usually treated with conventional care and infrequently resulted in trial termination. Malignancies and renal failure/impairment events were few and evenly distributed among therapy groups. Dapagliflozin did not raise the risk of cardiovascular events, according to pooled analyses. Across the spectrum of type 2 diabetes, dapagliflozin reduced blood pressure, body weight, and glycaemic control; these improvements were maintained over time [66].

CHAPTER 3

METHODOLOGY

3.1 MATERIALS REQUIRED

To design and develop Dapagliflozin and Metformin XR tablets by drug loading technique, the following materials are required:

Table 3.1: Material required for the Tablet Formulation.

PROCESS	MATERIALS	SOURCE
Active Pharmaceutical Ingredients	Dapagliflozin	Fuxin long rui Pharmaceuticals China
	Metformin Hydrochloride	Wanburry India
Polymeric Matrix	HPMC K-100	Colorcon Limited china.
Binders	Microcrystalline Cellulose(Avicel 101) Povidone k30	JRS Pharma GMBH 7 Co K.G
Coating Material	Titanium dioxide	LB Group
Lubricants	Magnesium stearate Talcum	Peter Greven Asia
Plasticizer	Polyethylene Glycol	<u>Saibaba Surfactants Pvt Ltd</u>
Pigmented	Titanium dioxide Opadry Pink	Colorcon Limited
Extended release polymer	Glyceryl behenate	Colorcon Limited
Solubilizer	Povidone k30	zuo Meida Fine chemicals Co.Ltd China

Table 3.2: Chemicals Used for HPLC

S. NO.	CHEMICALS NAME	SOURCE
1.	Acetonitrile (HPLC grade)	Merck, Germany
2.	Phosphate buffer 6.8	Fischer Chemicals
3.	Methanol HPLC grade	Merck, Germany
4.	HPLC water	Milli Q water purification system, Merck

Table 3.3: Equipment used in the formation of Tablet

S. NO.	Equipment	Source / Model
1	Analytical balance	Sartorius
2	Double Cone Blender	<u>Sama Engineering</u>
3	High-Shear Mixer	Silverson industrial
4	Fluid Bed Granulator	Canaan, china
6	Fluid Bed Dryer	Canaan, China
10	Pan Coater or Fluidized Bed Coater	Yichun Wonsen, China
11	Dissolution Tester	Ereweka, Germany
12	Column, C18 (250 x 4.6)mm, 5µm	Agilent
13	Ultrasonic bath	Branson
14	Filter paper having diameter of 47mm and pore size of 0.45µm	Sartorius AG, Germany
15	Hardness and Friability Testers	Erweka, Germany
16	High performance liquid chromatography (HPLC) system	Agilent, 1260 series

17	UV-Visible Spectrophotometer	Shimadzu
18	Vacume filtration assembly	Pyrex, Germany
19	Sieve analyzer	Restch GMBH Germany
20	Glass apparatus	Pyrex
21	FTIR	Bruker
22	pH meter	Mettler Toledo

3.2 EXCIPIENTS:

3.2.1 Hydroxypropyl methyl cellulose k-100 (HPMC K-100)

It is utilized as enteric coated pellets, powder, and suspensions as hydroxypropyl methylcellulose K-100. The formulation of sustain-release tablets also makes use of it. HPMC K-100 creates a lipid matrix with sustained release effects for oral preparation. Additionally, it serves as a lubricant in oral tablets and capsules. Additionally, it serves as a binder for tablets and capsules (Sun et al., 2024) [67].

3.2.2 Microcrystalline cellulose(Avicel 101)

Microcrystalline cellulose is a white, tasteless, crystalline powder with porous particles that is a refined, partially depolymerised version of cellulose. In oral dose formulations, microcrystalline cellulose is frequently used as a binder or diluent. It is used in both direct-compression and wet-granulation techniques. Because it acts as a binder and diluent and has lubricating and disintegrant properties, microcrystalline cellulose is useful in tableting (THOORENS ET AL., 2014) [68].

3.2.3 Titanium Dioxide

The most significant white pigment utilized in the coatings business is titanium dioxide (TiO₂). It is frequently employed because, when added to a coating, it effectively scatters visible light, adding whiteness, brightness, and opacity. There are two crystal forms of titanium dioxide that are sold commercially: rutile and anatase. Rutile TiO₂ pigments are favoured over anatase pigments due to their superior light-scattering efficiency, stability, and durability. From a small number of primary resin/crosslinking systems, thousands of distinct formulas have been developed as a result of powder coatings' ongoing rise as a substantial and rapidly expanding market segment. The main foundation for technological advancements has been the growth and better understanding of resin chemistry. Formulators can now choose pigments with different chemical and physical characteristics according to recent research on the impact of TiO₂ in powder coating systems. To maximise the processing and end-use performance of certain powder formulations, a variety of Ti-Pure grades are available (Matsushima et al., 2024) [69].

3.2.4 Glyceryl Behenate

It is granular powder white in color. Glyceryl behenate is used in the enteric coated pellets, powder and suspension. It is also used in the sustain release tablet formulation. For oral preparation glyceryl behenate form lipid matrix in sustain release effects. It is also used as lubricant in the oral tablet and capsule. It is also used as tablet and capsule binder (Kang, Lee et al. 2018).

3.2.5 Magnesium Stearate

Magnesium stearate is a bright white, incredibly fine powder that can be ground or ground. The powder has a characteristic flavour, a low bulk density, and a faint stearic acid odour. It is also impalpable. The powder adheres to the skin readily and feels oily. With concentrations ranging from 0.25 percent to 5.0 percent w/w, it is mostly used as a lubricant in the manufacturing of capsules and tablets (Ertel and Carstensen 1988).

3.2.6 Yellow Color

Yellow is a colour used in food and medical products, cosmetics, and tablet formulation. Opadry yellow is a yellow powder that is used in the pharmaceutical sector as a colour coating ingredient.

3.2.7 Povidon K-30

A particular grade of polyvinylpyrrolidone (PVP) called povidone K30 is used in tablet formulation as a solubilizer (which improves the dissolution of poorly soluble APIs) and binder (which increases the hardness and durability of tablets).

3.3 FORMULATIONS

The table of metformin HCl with dapagliflozin below includes twelve distinct formulations. The metformin HCl extended-release layer in the twelve formulations below has the same quantity of active ingredient, but the types of polymers and binders and their concentrations are variable. All twelve variants of dapagliflozin immediate layer had the same composition.

3.3.1 Formulation 1

Glyceryl behenate (4.82%) and HPMC K-100 (11.03%) are the prolonged release polymers, hydroxy propyl cellulose (4.96%) is the binder, and Avicel 101 (9.51%) is a diluent in the first formulation.

3.2.2 Formulation 2

The second formulation includes 5.51% hydroxy propyl cellulose as a binder, 9.51% Avicel 101 as a diluent, 7.93% glyceryl behenate as an extended-release polymer, and 7.93% HPMC K-100 as an extended-release polymer.

3.2.3 Formulation 3

The third formulation includes 9.51% Avicel 101 as a diluent, 4.82% HPMC K-100 as an extended-release polymer, 4.96% Hydroxypropyl Cellulose as a binder, and 11.03% Glyceryl Behenate as an extended-release polymer.

3.2.4 Formulation 4

Glyceryl behenate (4.82%) as an extended-release polymer, HPMC K-100 (11.03%), Povidone K-30 (3.58%) as a binder, and Avicel 101 (10.89%) as a diluent are all present in the fourth formulation.

3.2.5 Formulation 5

The fifth formulation includes 10.89% Avicel 101 as a diluent, 3.58% Povidone K-30 as a binder, 7.93% Glyceryl Behenate as an extended-release polymer, and 7.93% HPMC K-100 as an extended-release polymer.

3.2.6 Formulation 6

The sixth formulation includes 10.89% Avicel 101 as a diluent, 3.82% HPMC K-100 as an extended-release polymer, 3.58% Povidone K-30 as a binder, and 11.03% glyceryl behenate as an extended-release polymer.

3.2.7 Formulation 7

The seventh formulation has a diluent of 13.65% Avicel 101, a binder of 4.96% Hydroxy propyl cellulose, and an extended-release polymer of 11.72% HPMC K-100.

3.2.8 Formulation 8

The eighth formulation has 4.96 percent hydroxy propyl cellulose as a binder, 10.89 percent Avicel 101 as a diluent, and 14.48% HPMC K-100 as an extended-release polymer.

3.2.9 Formulation 9

9.44% of Avicel 101 is used as a diluent, 17.93% of HPMC K-100 is used as an extended release polymer, and 4.96% of hydroxy propyl cellulose is used as a binder in the ninth formulation.

3.2.10 Formulation 10

The 10th formulation has a diluent of 14.34% Avicel 101, a binder of 4.96% Hydroxypropyl Cellulose, and an extended release polymer of 11.72% Glyceryl Behenate.

3.2.11 Formulation 11

The eleventh formulation has a diluent of 10.89% Avicel 101, a binder of 4.96% Hydroxypropyl Cellulose, and an extended release polymer of 14.48% Glyceryl Behenate.

3.2.12 Formulation 12

In the 12th formulation, there are three distinct tablet formulations: 17.93% Glyceryl Behenate as an extended-release polymer, 7.44 percent Avicel 101 as a diluent, and 4.96 percent Hydroxy propyl cellulose.

Table 3.4: Composition of all formulations of tablet

S. No.	Composition	Formulations											
Metformin HCl Layer		F1 (mg)	F2 (mg)	F3 (mg)	F (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
1	Metformin Hcl	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
2	Glyceryl Behenate	70	115	160	70	115	160	-	-	-	170	210	260
3	HPMC K-100	160	115	70	160	115	70	170	210	260	-	-	-
4	Hydroxy Propyl Cellulose	72	72	72	-	-	-	72	72	72	72	72	72
5	Povidone K30	-	-	-	52	52	52	-	-	-	-	-	-
6	Avicel 101	138	138	138	158	158	158	198	158	108	208	158	108
7	Magnesium Stearate	10	10	10	10	10	10	10	10	10	10	10	10
Weight of 1 st Layer		1450	1450	1450	1450	1450	1450	1450	1450	1450	1450	1450	1450
Dapagliflozin Layer by Drug loading Solution													
1	Dapagliflozin Propanediol MH	12.30	12.30	12.30	12.30	12.30	12.30	12.30	12.30	12.30	12.30	12.30	12.30
2	Opadry Pink	145	145	145	145	145	145	145	145	145	145	145	145
3	PEG-6000	3	6	9	12	15	18	21	24	27	30	33	36
3	Talc	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
4	Titanium dioxide	9.7	9.7	9.7	9.7	9.7	9.7	9.7	9.7	9.7	9.7	9.7	9.7
5	Purified water	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml
Weight of 2 nd Layer		180	183	186	189	192	195	198	201	204	207	210	213
Film Coating													
Opadry Pink		50	50	50	50	50	50	50	50	50	50	50	50
Purified water		80ml	80ml	80ml	80ml	80ml	80ml	80ml	80ml	80ml	80ml	80ml	80ml
Total Target weight of coated Tablet						1700±5%							

3.3 MANUFACTURING

3.1 PROCEDURE

3.1.1 METFORMIN HCL LAYER:

First, sieve all the materials according to their formulation sieve and put all sieved material in a double cone mixer and mix for approximately 10 minutes. After that, sieved magnesium stearate into the double cone mixer and mix approximately for 3 minutes.

3.1.2 DRUG LOADING MATERIAL

First, sieve all the materials according to their formulation sieve and put all sieved material in a double cone mixer and mix for approximately 10 minutes. After that, sieved magnesium stearate into the double cone mixer and mix approximately for 3 minutes.

3.2 Compression Of Metformin Layer

Following the last powder mixing, each metformin layer composition was tested under various conditions, and the best formulations were compressed using a compression machine. The final pill weighed 1450 mg and was compacted using an oblong biconvex punch.

3.3 Drug Loading Technique

A liquid formulation comprising the medication and additional excipients was loaded onto compressed tablets in a coater.

3.4 Film Coating

Opadry yellow is added to purified water while being constantly stirred to create a film coating solution. A tiny coating pan is used to apply a coating to compressed tablets.

3.5 Storage of manufactured tablet

Tablets were stored in airtight package till the further testing.

3.6 Physico chemical evaluation

3.6.1 Testing parameters of powder granules

3.6.1.1 Angle of repose

The angle formed by the pile surface and the material's horizontal surface is known as the angle of repose. The angle of repose is affected by the material's nature. Materials with rough particles can be piled vertically, but powder granules with a round, smooth surface cannot. The value of the angle of repose ranges from 0 to 90 degrees (Geldart, Abdullah et al. 2006).

When powdered granules are dumped onto the ground, a conical pile will form. Materials with a low angle of repose will produce a flatter pile, while materials with a high angle of repose would form a steeper pile (USP NF, 2008). The substance is passed through a funnel on a petri plate to determine the angle of repose. The height of the pile is measured with a ruler. Additionally measured and multiplied by 0.5 was the horizontal distance.

The angle of repose can be calculated using the method

$$\theta = \arctan(h/r)$$

Where,

h = Cone height

r = Radius of half of the diameter of the cone which is formed by falling of the powder on a smooth surface from funnel.

AR of the powdered granules were measured (Geldart, Abdullah *et al.* 2006).

3.6.1.2 Compressibility Index

By evaluating the compressibility index, we may determine a powder's ability to flow freely. The bulk and tapped density values of powder with free-flowing properties varied very little. Free-flowing powder has a lower compressibility index value. The bulk and tapped density values of powder with poor flowing properties varies significantly (Kaleem, Alam et al. 2020). Powder has good flow when the compressibility index value is less than 15, and bad flow when the value is greater than 25. Each formulation's 100 g of powder was placed in a measuring cylinder (Lachman 1986) (Bowker and Stahl 2008).

V_o is the initial volume, powder was allow to fall by its own weight from height of 3cm at regular interval.

- Continue the tapping procedure until not observe any change in its volume.
- Measure the volume when tapping was stopped as final volume V_f .
- USP method was used to measure the value of compressibility index and Haunser ratio by following equation:

$$CI = \frac{V_f - V_o}{V_f} \times 100$$

Where,

V_o indicate bulk density as initial volume

V_f indicate tapped density as final volume

3.6.1.3 Bulk Density

It is the bulk density of powder without the tapping process. Bulk density is measured using a graduated cylinder. Note the original volume after weighing the powder and placing it in a graduated cylinder. It is computed by dividing the volume by the mass. It is measured in g/cm³. Brady and Buckman (1960).

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Volume}}$$

3.6.1.4 Tapped Density

Tapped density is the result of mechanically tapping a powder inside a graded cylinder. The process of tapping involves raising the cylinder and letting it drop from a predetermined distance on its own. g/cm³ is its unit (Carr 1965). It is represented by 'p'.

Formula used to calculate the Tapped density:

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Volume after tapping.}}$$

3.6.1.5 Hausner's Ratio

Calculating the flow characteristics of powder grains is another use for it. The first person to determine its worth was Henry H. (Beddow 1995).

Formula to calculate its value is:

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk density}}$$

A Hausner's ratio value greater than 1.25 indicates inadequate flow in powdered material. HI is a measure used in the pharmaceutical industry to determine the powder flow characteristics (Grey and Beddow 1969).

3.6.1.6 Flow Rate

The weighted amount of powder is also passed from a metallic funnel with a tiny orifice at the bottom to measure the flow rate. The time is calculated using a stopwatch (USP-NF, 2008).

Flow rate is calculated by formula:

$$\text{Flow rate} = \frac{\text{Mass}}{\text{Time}}$$

Table 3.5: Standard Reference Chart.

FLOW RATE TYPE	HAUNSER RATIO	ANGLE OF REPOSE	COMPRESSIBILITY INDEX	REMARKS
Excellent	1-1.11	25-30°	≤10	Excellent
Good	1.12-1.18	31-35°	11-15	Good
Fair	1.19-1.25	36-40°	16-20	Fair aid
Passable	1.26-1.34	41-45°	21-25	Passable
Poor	1.35-1.45	46-55°	26-31	Poor

Very poor	1.46-1.59	56-65°	32-37	Very poor
Very poor	>1.60	>66°	>38	Very poor

3.7 Physico-Chemical Test Parameters.

3.7.1 Average weight

Each formulation's twenty tablets are precisely weighed in milligrammes (mg) using an analytical balance (Sartorius).

3.7.2 Tablet Hardness and Thickness

A hardness and thickness tester is used to determine the hardness and thickness parameter after 10 tablets have been compressed. (Erweka).

3.7.3 Friability

Ten tablets from each formulation were precisely weighed (W₁) after compression and placed in a friabilator to determine their friability. For four minutes, the friabilator was rotated at 25 rpm.

Dedust the tablet using a blower when the friabilator finishes rotating, then weigh the tablets (W₂) once again to determine the weight decrease.

Following formula is used to calculate the friability:

$$F(\%) = \frac{W_1 - W_2}{W_1} \times 100$$

3.7.4 FT-IR Analysis

For compatibility of formulation FTIR test will be performed.

3.7.5 QUANTITATIVE ASSAY

Diluent

Mobile phase

Preparation of phosphate buffer (pH 6.8) for mobile phase:

In a 1000 mL beaker, weigh 6.8 g of potassium dihydrogen phosphate, then dissolve it in 1000 mL of water of HPLC quality. Use NaOH to bring the solution's pH down to 6.8.

Standard Solution.

Solution A

Accurately weigh 40 mg of dapagliflozin propanediol monohydrate in a 200 ml volumetric flask using an analytical balance working standard. Add mobile phase

to the flask and sonicate for five minutes.

Solution B

Accurately weigh 40 mg of metformin HCl using an analytical balance according to standard operating procedures in a 200 ml volumetric flask with mobile phase, then sonicate for five minutes.

Standard solution:

Transfer 2 millilitres from solution A to solution B, then use the mobile phase to increase the volume to the desired level. Run the fluid through a 0.45 µm-pore membrane filter.

Note: 119mg of Dapagliflozin Propanediol is equal to 100mg of Dapagliflozin.

Sample Preparation:

Put the ground powder of the Metformin HCl layer (equal to 1000 mg of Metformin HCl) and the powdered powder of the Dapagliflozin layer (corresponding to 10 mg of Dapagliflozin) into a 500 ml volumetric flask, weigh them precisely on an analytical balance, add 50% diluent, and mix for 30 minutes. Sonicate it for 20 minutes after mixing, then add diluent to adjust the volume.

Transfer 5 millilitres of this solution into a 50 millilitre volumetric flask, dilute with mobile phase to the appropriate level, and shake thoroughly. Run the fluid through a 0.45 µm-pore membrane filter.

Chromatographic conditions:

Flow rate: 1.0 ml/min

Detection: UV, 220 nm

Column: C-18 (250mm x 4.6mm; 5µm)

Injection Volume: 20µl

Temperature: 25°C

Run Time: 10 min

Mobile phase:

Acetonitrile : Buffer (pH 6.8)

55 : 45

Diluent : Mobile phase

3.7.6 DRUG DISSOLUTION

Preparation of dissolution media:

40.8 grammes of potassium dihydrogen phosphate should be weighed into six litres of distilled water. Use NaOH to bring the solution's pH down to 6.8.

Preparation of phosphate buffer (pH 6.8) for mobile phase

In a 1000 mL beaker, weigh 6.8 g of potassium dihydrogen phosphate, then dissolve it in 1000 mL of water of HPLC quality. Use NaOH to bring the solution's pH down to 6.8.

Standard Preparation

Solution A: Weigh precisely using the Dapagliflozin analytical balance operating standard. Fill a 200 ml volumetric flask with propanediol monohydrate (equal to 40 milligrammes of dapagliflozin), add the mobile phase, and sonicate for five minutes.

Solution B: Using an analytical balance, precisely weigh 40 mg of metformin HCl in a 200 ml volumetric flask with mobile phase, then sonicate for five minutes.

Note: 123mg of Dapagliflozin Propanediol monohydrate is equal to 100mg of Dapagliflozin.

Transfer 2 millilitres from solution A to solution B, then use the mobile phase to adjust the volume to the desired level.

Sample Preparation:

Fill each vessel with 1000 millilitres of the medium after assembling the dissolution device. Rotation speed should be set to 100 rpm. Let the temperature in each vessel reach 37°C. Place one Dapagliflozin tablet and ten or a thousand metformin tablets in each vessel, then start the dissolution process. After 30 minutes, 1 hour, 3 hours, and 10 hours, remove the sample and filter the mixture. Fill a 50 ml volumetric flask with 10 ml of the filtered sample, then add enough mobile phase to reach the desired volume.

Dissolution Parameters:

Apparatus: Basket

Medium: Buffer pH 6.8

Volume of medium: 1000ml/vessel

RPM: 100

Temperature: 37°C

Chromatographic condition:

Flow rate: 1.0 ml/min

Detection: UV, 220 nm

Column: C-18 (250mm x 4.6mm; 5µm)

Injection Volume: 20µl

Temperature: 25°C

Run Time: 10 min

CHAPTER 4

RESULTS

4.1 PRE FORMULATION CHARACTERIZATION

4.1.1 CALIBRATION CURVE

Dapagliflozin and metformin HCl concentrations were measured using the HPLC technique. To identify the calibration curve, a standard curve with varying concentrations was produced. Both dapagliflozin and metformin HCl showed their best results at 220 nm. All solutions' absorbance was then measured at 220 nm. Tables 4.1 and 4.2 present the findings. As seen in figures 4.1 and 4.2, the calibration curve.

Table 4.1: Concentration of standard solutions of Metformin HCl and its absorbance values

(Metformin HCl)				
Linearity & Range				
S. No.	Conc. (ppm)	Peak Area	MEAN	RSD (%)
1	80.0	4686.9	4683.7	0.060%
2	80.0	4681.5		
3	80.0	4682.8		
4	120.0	6789.1	6789.7	0.008%
5	120.0	6790.0		
6	120.0	6790.0		
7	140.0	8154.9	8162.1	0.079%
8	140.0	8163.9		
9	140.0	8167.5		
10	160.0	9152.9	9147.8	0.054%
11	160.0	9142.9		
12	160.0	9147.6		
13	180.0	10233.8	10243.8	0.104%
14	180.0	10254.9		
15	180.0	10242.7		
16	200.0	11156.7	11166.6	0.077%
17	200.0	11171.9		
18	200.0	11171.3		
19	220.0	11786.6	11799.4	0.094%

20	220.0	11805.8		
21	220.0	11805.8		
22	240.0	12674.2		
23	240.0	12682.5	12677.6	0.034%
24	240.0	12676.2		
25	260.0	13412.4		
26	260.0	13417.7	13419.2	0.057%
27	260.0	13427.5		
28	280.0	13929.8		
29	280.0	13998.7	13968.5	0.252%
30	280.0	13976.9		
31	400.0	19775.9		
32	400.0	19745.3	19751.6	0.111%
33	400.0	19733.6		

Table 4.2: Concentration of standard solutions of Dapagliflozin and absorbance values

(Dapagliflozin)				
Linearity & Range				
S. No.	Conc. (ppm)	Peak Area	MEAN	RSD (%)
1	0.8	44.5		
2	0.8	44.3	44.5	0.267%
3	0.8	44.5		
4	1.2	67.3		
5	1.2	67.2	67.3	0.099%
6	1.2	67.2		
7	1.4	77.5		
8	1.4	77.5	77.6	0.172%
9	1.4	77.7		
10	1.6	88.3		
11	1.6	88.4	88.4	0.104%
12	1.6	88.5		
13	1.8	100.2		
14	1.8	100.3	100.3	0.057%
15	1.8	100.2		
16	2.0	111.9		
17	2.0	111.9	111.9	0.021%
18	2.0	111.9		

19	2.2	119.6	119.6	0.035%
20	2.2	119.6		
21	2.2	119.6		
22	2.4	132.3	132.4	0.089%
23	2.4	132.3		
24	2.4	132.5		
25	2.6	144.3	144.3	0.060%
26	2.6	144.2		
27	2.6	144.4		
28	2.8	155.1	155.2	0.082%
29	2.8	155.4		
30	2.8	155.2		
31	4.0	222.9	222.9	0.070%
32	4.0	222.8		
33	4.0	223.1		

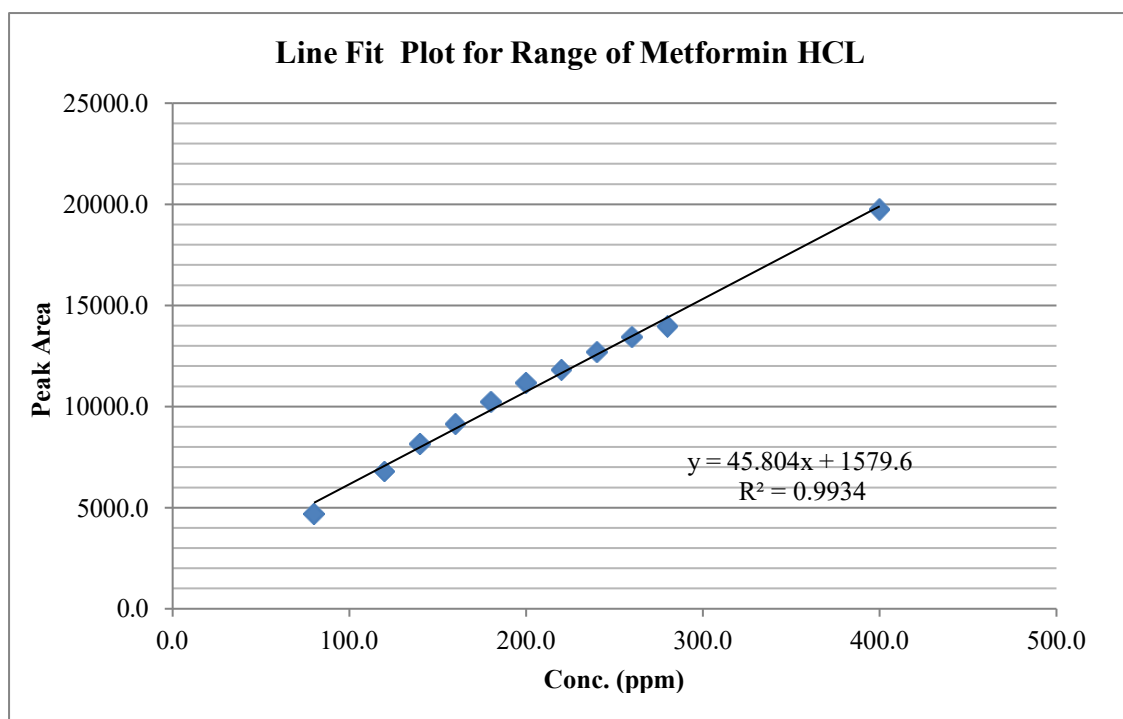


Fig. 4.1: Calibration Curve of Metformin HCl at 220nm

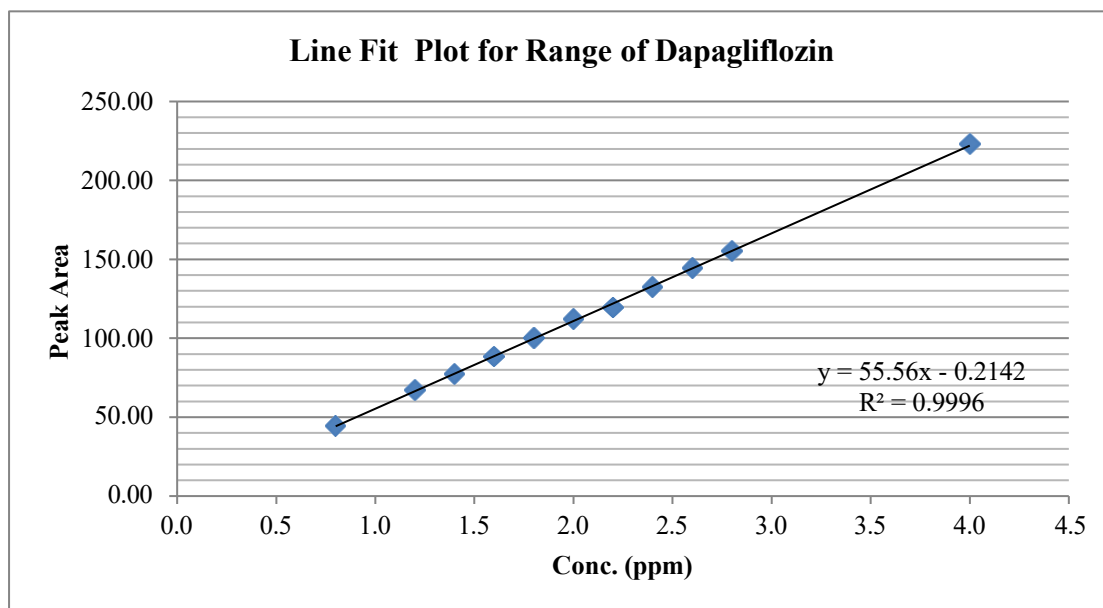


Fig. 4.2: Calibration Curve of Dapagliflozin at 220nm

4.1.2 Angle Of Repose

The angles of repose for the twelve formulations of the Metformin HCl layer are 41°, 40°, 37°, 40°, 39°, 35°, 36°, 40°, 43°, 32°, 30°, and 29°, while for the Dapagliflozin layer, they are 30°, 29°, 31°, 28°, 30°, 30°, 29°, 31°, 30°, 31°, 29°. According to the data, there are notable differences between the twelve formulations in the Metformin HCl layer because of variations in the concentration of the polymers used for the extended-release effect. However, all the formulations in the Dapagliflozin layer exhibit superior outcomes because of the same concentration. Because of the high concentration of HPMC K-100 in formulations F1, F2, F4, F5, F8, and F9, the metformin HCl layer has a high value of angle of repose, indicating poor SR layer flow.

4.1.3 Compressibility Index

The confidence intervals (CI) for the twelve formulations of the Metformin HCl layer are 31.2, 22.9, 16.6, 36, 31.9, 28.2, 41.3, 31.2, 28.5, 15.2, 14.8, and 13. For the Dapagliflozin layer, the CI findings are 15.7, 16.3, 18.7, 18.3, 19.1, 15.7, 12.5, 18.7, 14.2, 21.2, 18.7, 14.2.

According to the results, the compressibility index in the Metformin Layer changes depending on the concentration of the extended-release polymer, such as Glyceryl Behenate and HPMC K-100. Formulations with high concentrations of Glyceryl Behenate F3, F10, F11, and F12 exhibit good compressibility indices between 13 and

16, indicating excellent compressibility, followed by formulations with high concentrations of HPMC K-100. However, in the Dapagliflozin layer, all formulations exhibit good compressibility indices.

4.1.4 Bulk Density

The bulk density of all the formulations of the metformin layer is nearly the same, ranging from 0.46 to 0.49, same as the formulations of the dapagliflozin layer. It was found that altering the polymer kinds and concentrations on the Metformin layer had no discernible impact on the bulk density. Table 14 displays the findings.

4.1.5 Tapped Density

It was discovered that formulations with high concentrations of Glyceryl behenate polymers F3, F6, F10, F11, and F12 had low tapped density values in the Metformin HCL layer, while formulations with high concentrations of HPMC K-100 had high tapped density values. Thus, it shows that the kind and concentration of polymers affect the tapping density findings.(Hossen, Hasan, and others, 2014).

4.1.6 Hausner Ratio

It was discovered that formulations with high concentrations of Glyceryl behenate polymers in the Metformin HCL layer had Hausner ratio values between 1.16 and 1.25, indicating good powder flow (Hasan, Hossen et al. 2014). Formulations with high concentrations of HPMC K-100 had Hausner ratio values between 1.25 and 1.36, indicating poor material flow, indicating good flow properties for Glyceryl behenate.

Table 4.3: Actual assessment of powder before Compression.

Formulation code		Bulk density (g/cm ³)	Tapped density (g/cm ³)	Hausner's ratio	Angle of repose (°)	Cars compressibility index (%)
F1	Metformin Layer	0.48	0.63	1.31	41°	31.2
F2	Metformin Layer	0.48	0.59	1.22	40°	22.9
F3	Metformin Layer	0.48	0.56	1.16	37°	16.6
F4	Metformin Layer	0.47	0.64	1.36	40°	36

F5	Metformin Layer	0.48	0.62	1.31	39 ^o	31.9
F6	Metformin Layer	0.46	0.59	1.28	35 ^o	28.2
F7	Metformin Layer	0.46	0.65	1.41	36 ^o	41.3
F8	Metformin Layer	0.48	0.63	1.31	40 ^o	31.2
F9	Metformin Layer	0.49	0.63	1.28	43 ^o	28.5
F10	Metformin Layer	0.45	0.53	1.15	32 ^o	15.2
F11	Metformin Layer	0.46	0.54	1.17	30 ^o	14.8
F12	Metformin Layer	0.45	0.52	1.13	29 ^o	13.0

4.2 FT-IR Analysis

FTIR stands for Fourier Transform Infrared Spectroscopy. To ascertain functional groups and product compatibility, FTIR is frequently utilized. The chromatograms for each API and excipient are provided below, along with the chromatogram for the tablet's final formulation F11.

4.2.1 Glycerol Behenate

An FTIR analysis of glycerol behenate showed a broad band between 3650 and 3100 cm^{-1} , with the C—O stretching at 1740 cm^{-1} , as a result of the —OH stretching. Several vibrational bands observed in FTIR spectra between 700 and 1500 cm^{-1} were associated with the methylene groups. Aburahma (2014).

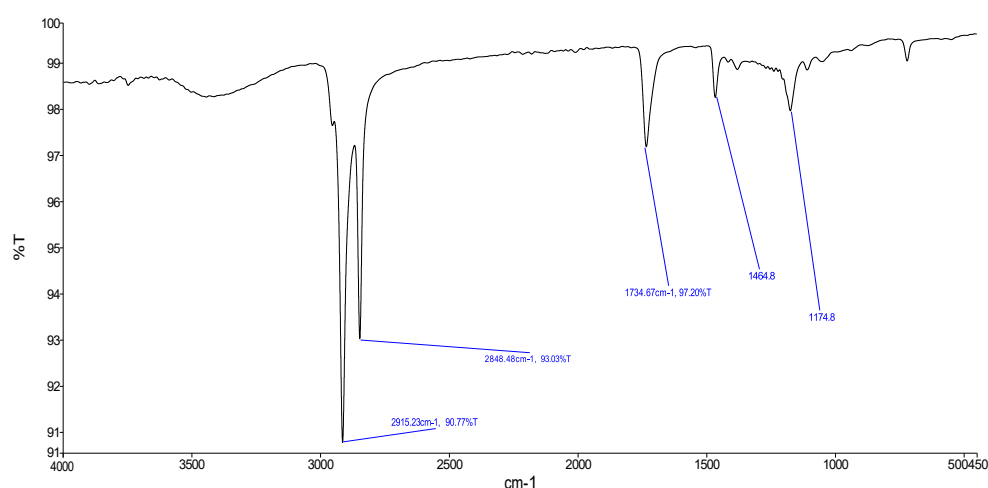


Fig. 4.3. Chromatogram of Glycerol behenate

4.2.2 Dapagliflozin

The FTIR spectra of DAP revealed characteristic absorption peaks at 3350.14 cm^{-1} , 2860.11 cm^{-1} , 1611.08 cm^{-1} , and 1243.30 cm^{-1} , respectively, as a result of hydroxyl OH bond stretching, C—H bond stretching, aromatic C=C bond stretching, and ester C—O bond stretching (Algahtani, Mohammed et al. 2021).

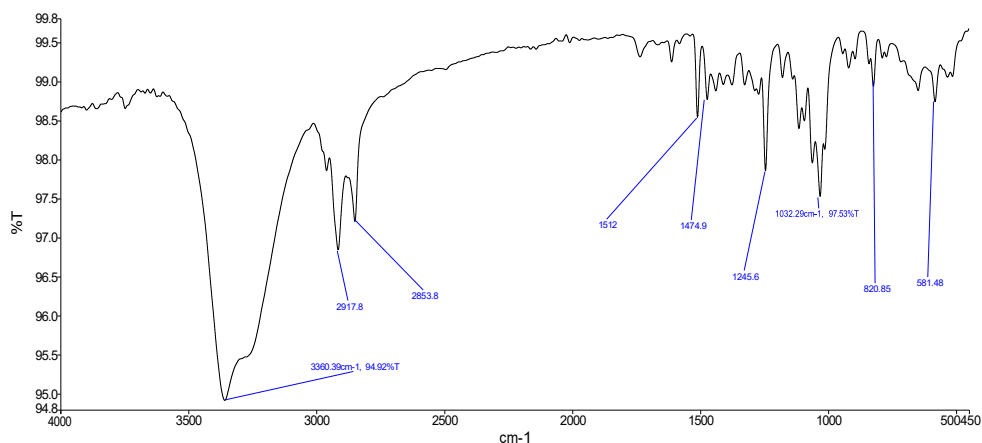


Fig. 4.4 : Chromatogram of Dapagliflozin

4.2.3 Metformin HCl

According to Jagdale, Patil et al. (2011), the infrared spectra show two characteristic bands at 3369 cm⁻¹ and 3294 cm⁻¹ that are related to the N-H main stretching vibration, a band at 3155 cm⁻¹ that is due to the N-H secondary stretching vibration, and two distinctive bands at 1626 cm⁻¹ and 1567 cm⁻¹ that are related to C-N stretching.

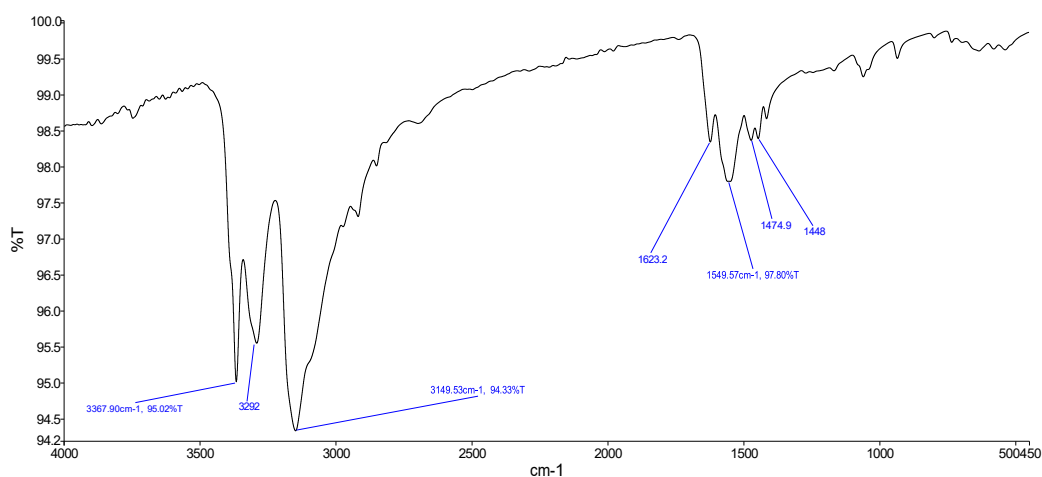


Fig 4.5. Chromatogram of Metformin HCl

4.2.4 PVP K-30

An FTIR spectrogram of PVP K30 obtained under the same conditions was placed on the FT-IR image. At 1278 cm⁻¹, PVP K30 displayed a noticeable absorption peak that is indicative of O-H in-plane bending vibrations. According to Zhu et al. (2021), PVP K-30 shows a peak at 1654 cm⁻¹, which represents the hydroxyl groups'

bending vibration and the alkene bonds' C = C stretching vibration.

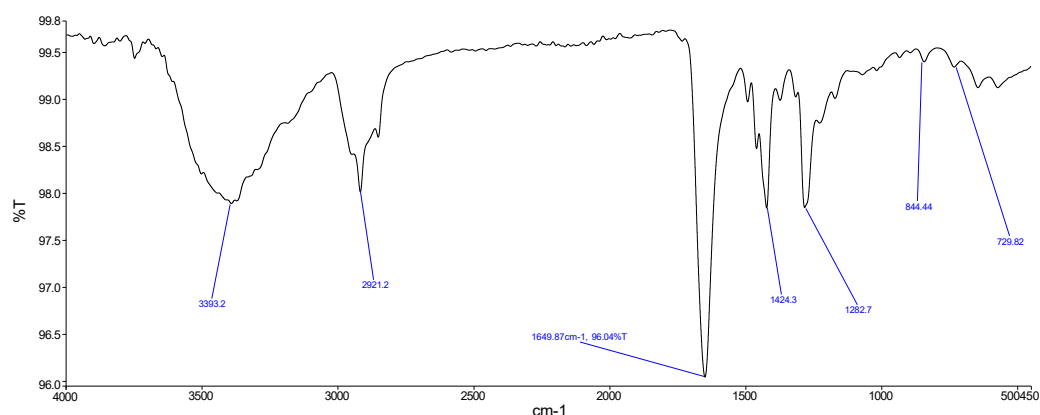


Fig. 4.6. Chromatogram of PVP K-30

4.2.5 Microcrystalline Cellulose

The next step is to identify the absorption bands. The observed peaks in the 3660–2900 cm⁻¹ wave number range are characteristic of stretching vibrations of O–H and C–H bonds. The hydroxyl group's stretching vibration is seen by the large peak at 3331 cm⁻¹. The intramolecular and intermolecular hydrogen bond vibrations in cellulose are also included in this peak. The band at 2894 cm⁻¹ is caused by the CH stretching vibration of all hydrocarbon components in polysaccharides. The typical range of cellulose bands was 1630–900 cm⁻¹. The stretching and bending vibrations of the -CH₂ and -CH, -OH, and C-O bonds in cellulose are indicated by the absorption bands at 1428, 1367, 1334, 1027 cm⁻¹, and 896 cm⁻¹ (Hospodarova, Singovszka et al. 2018).

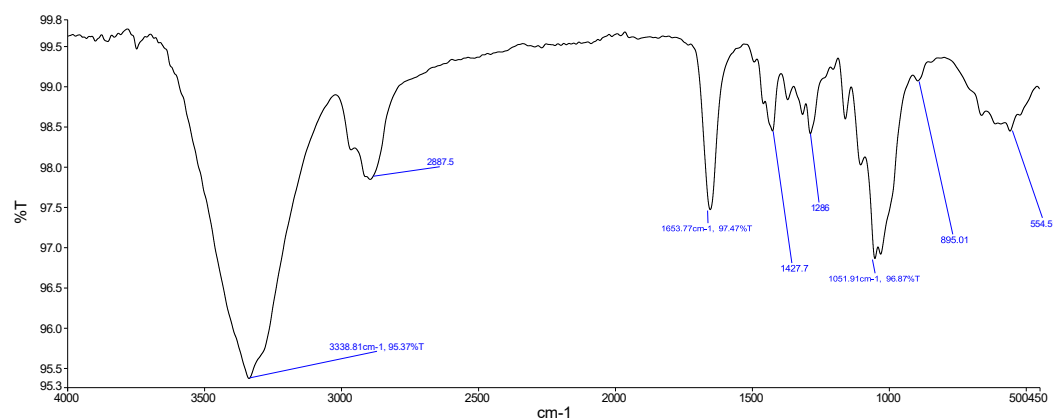


Fig. 4.7. Chromatogram Of Microcrystalline cellulose

4.2.6 Lactose Anhydrous

The stretching vibrations of free or bound lactose alcohol groups were represented by the absorption bands that lactose monohydrate showed between 3600 and 3200 cm^{-1} . The stretching vibrations of two different types of C-H bonds have been linked to two distinct bands at 3000–2800 cm^{-1} . The bending vibrations of C-H bonds are described by the bands observed at 1500–1200 cm^{-1} . The asymmetrical stretching vibrations of C–O–C ether unit bonds are responsible for all bands between 1040 and 1160 cm^{-1} (Hospodarova, Singovszka et al. 2018).

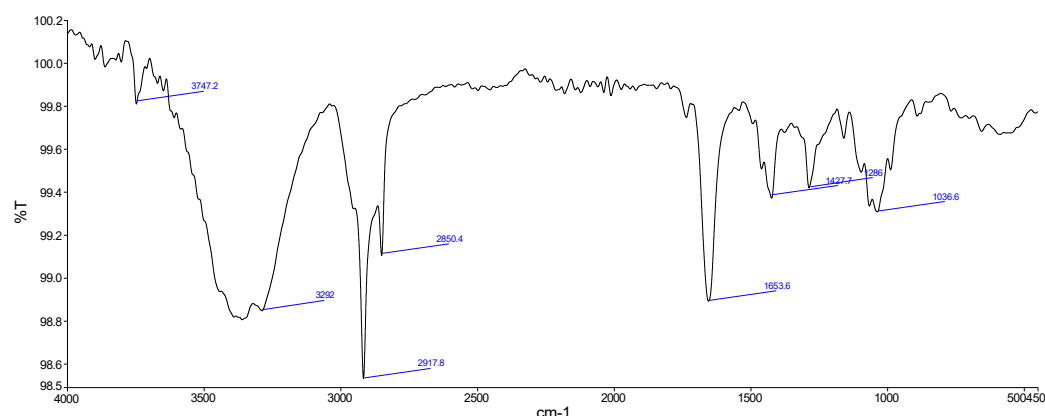


Fig. 4.8. Chromatogram of Lactose Anhydrous

4.2.7 Kollidon CL

An FTIR spectrogram of Kollidon CL obtained under the same conditions was placed on the FT-IR image. The bending vibration of the hydroxyl groups and the C = C stretching vibration in alkene bonds are reflected in Kollidon CL's significant absorption peak at 1654 cm^{-1} , while the O-H in-plane bending vibration is represented by the peak at 1278 cm^{-1} (Szakonyi, 2012).

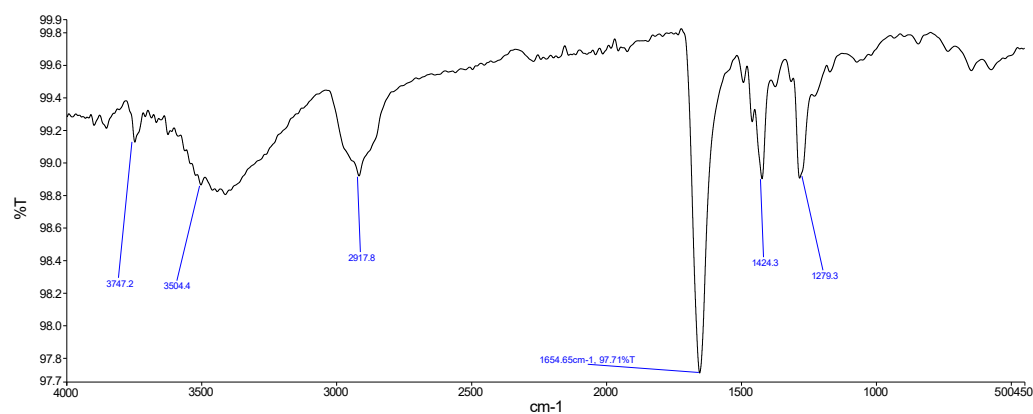


Fig. 4.9. Chromatogram of Kollidon CL

4.2.8 HPMC K-100

The stretching of the hydroxyl (OH) group is 3421.48 cm^{-1} , that of the C-H bond is 2891.10 cm^{-1} , and that of the CH_2 group is 1456.16 cm^{-1} . The band at 1377 cm^{-1} is caused by the vibration of the OH group, and the band at 1066.08 cm^{-1} is caused by the vibration of the C-O groups (van der Weerd, 2005).

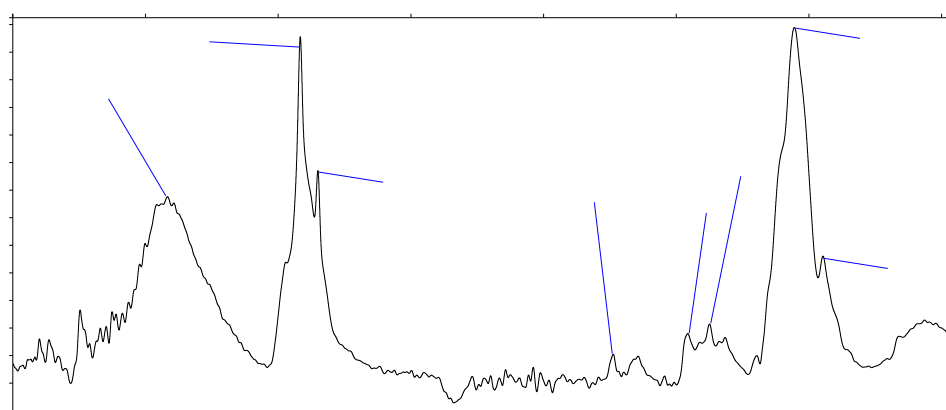


Fig. 4.10. Chromatogram Of HPMC K-100

4.2.9 MG- STEARATE

Magnesium stearate's FTIR spectra show twin peaks at 1577 and 1466 cm^{-1} , which are ascribed to the symmetric and asymmetric carboxylate (COO^-) stretching vibrations, respectively. The peaks at 2917 and 2850 cm^{-1} are caused by the C-H stretching vibration. The broad band at roughly 3452 cm^{-1} is caused by the corresponding water molecule's OH stretching vibration. (Conway and Nep, 2012).

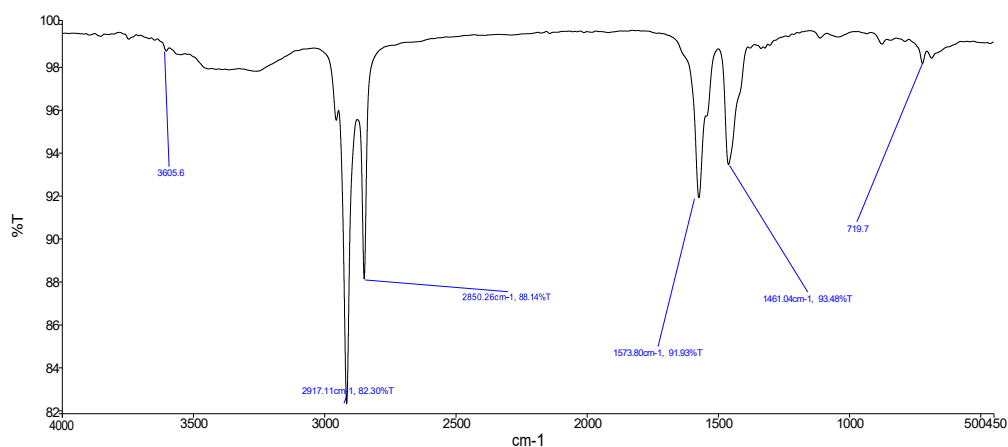


Fig. 4.11. Chromatogram Of Magnesium Stearate

4.2.10 Sunset Yellow Color

Asymmetric carboxylate (COO-) stretching vibration and symmetric carboxylate stretching vibration are responsible for the twin peaks at 1577 and 1466 cm⁻¹ in the Sunset yellow FTIR spectra, respectively. The peaks at 2917 and 2850 cm⁻¹ are caused by the C–H stretching vibration. The broad band at roughly 3452 cm⁻¹ is caused by the corresponding water molecule's OH stretching vibration. Yin (2018).

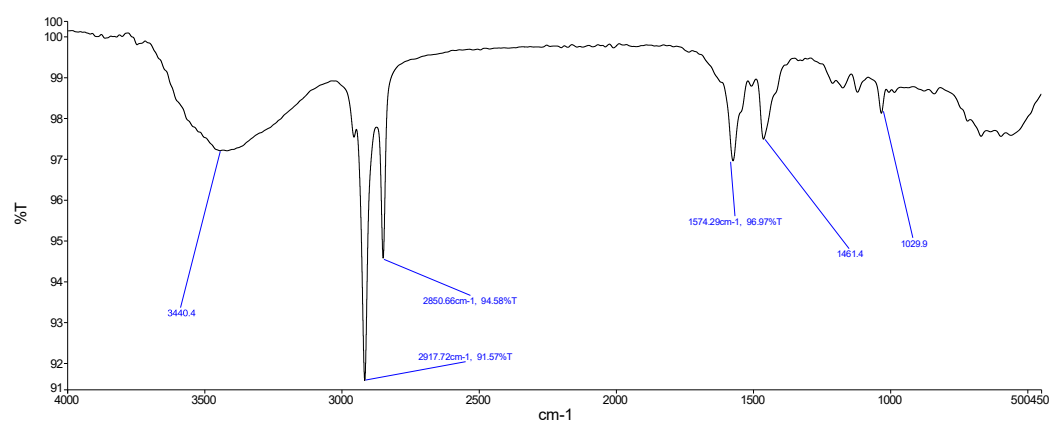


Fig. 4.12. Chromatogram Of Sunset yellow lake color

4.2.11 Final Formulation Of Tablet F 11

The final formulation's FTIR spectrum F11 indicates that there is no drug-excipient interaction because the peaks are close to those of dapagliflozin and metformin tablets. The product is stable and doesn't interfere in any way.

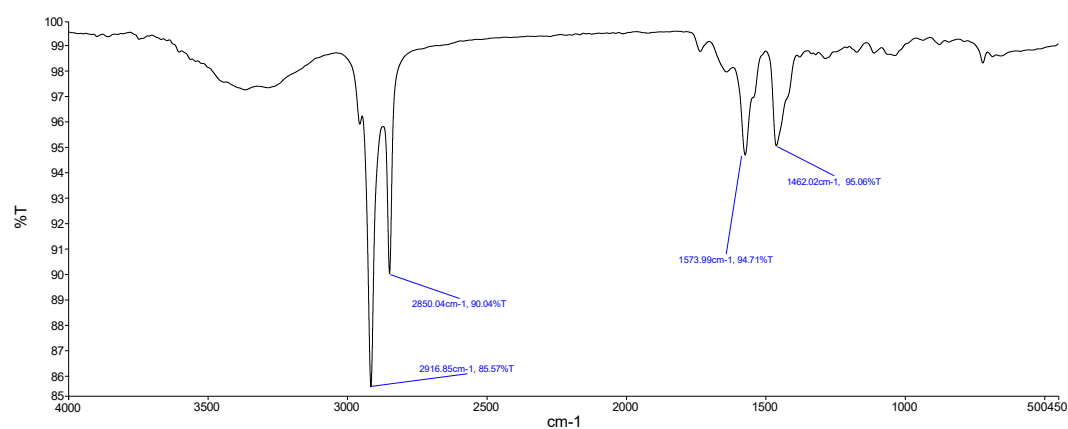


Fig. 4.13. Final Formulation of tablet

4.3 POST FORMULATION STUDIES

Following the compression of the lubricating powder into tablets, physical and chemical tests were conducted and the results were compiled in a table.

4.3.1 Hardness Of Compressed Tablets

The tablets' hardness was listed in the table. Due to its high compressibility index, it was discovered that tablets containing a high concentration of glyceryl behenate had a hardness in the high range of 15-20 Kp, while tablets with a high concentration of HPMC K-100 had a hardness of 8-12 Kp. Thus, it suggests that microcrystalline cellulose and the polymer glyceryl behenate directly affect the hardness value (Hasan, Hossen et al. 2014).

4.3.2 Friability

All twelve formulations had the following findings when we examined their friability: 1.21%, 0.92%, 0.76%, 1.18%, 0.91%, 0.70%, 1.42%, 1.51%, 1.53%, 0.46%, 0.39%, and 0.21%. It was discovered that tablets made with a high concentration of glyceryl behenate had a friability value of less than 1%, indicating that they were durable when prepared using the direct compression method. In contrast, tablets made with a high concentration of HPMC K-100 had a friability value of more than 1%, indicating that they were not durable (Hasan, Hossen et al. 2014).

4.3.3 Weight Variation & Hardness

Use an analytical weighing scale to weigh each tablet separately, then use a hardness tester to verify the thickness and hardness specifications. According to USP criteria, formulation weight variations are kept to a minimum. High compaction formulations using glyceryl behenate have a hardness of greater than 10 Kp, while formulations including a high concentration of HPMC have a hardness of less than 10 Kp. (Hossen, Hasan, and others, 2014).

Table 4.4: Post Compression Parameters.

Formulations	Weight/ Tablet (1450mg)	Hardness (Kp)	Thickness (mm)	Length (mm)	Friability NMT 1%
F1	1454	25	7.56	16.95	1.21
F2	1455	26	7.58	16.97	0.92
F3	1456	27	8.09	16.96	0.76
F4	1453	25	7.51	16.95	1.18
F5	1455	32	7.50	16.95	0.91
F6	1449	33	7.97	16.96	0.70
F7	1450	31	7.48	16.95	1.42
F8	1451	29	7.49	16.95	1.51
F9	1452	28	7.52	16.97	1.53
F10	1451	27	8.10	16.95	0.46
F11	1450	30	7.90	16.97	0.39
F12	1452	33	8.21	16.95	0.21

4.3.4 Quantitative Assay:

We carried out the formulation's assay examination that conforms with the physical characteristics. Analytical results cannot be obtained from formulations that fail physical testing. Formulations F3, F6, F10, F11, and F12 meet the physical testing requirements. Metformin HCl assay findings are 98.6%, 97.2%, 98.6%, 100.5%, and 98.5%, while Dapagliflozin assay results are 99.5%, 98.9%, 97.9%, 99.5%, and 97.8%.

Assay Results are given in Table 4.5

Table 4.5: Quantitative assay Results

Physical Test	Acceptance Criteria	Name of layer	F3 %	F6 %	F10 %	F11 %	F12 %	Name of layer
Quantitative Assay	90-110%	Metformin HCl	98.6	97.2	98.6	100.5	98.5	Metformin HCl
		Dapagliflozin	99.5	98.9	97.9	99.5	97.8	Dapagliflozin

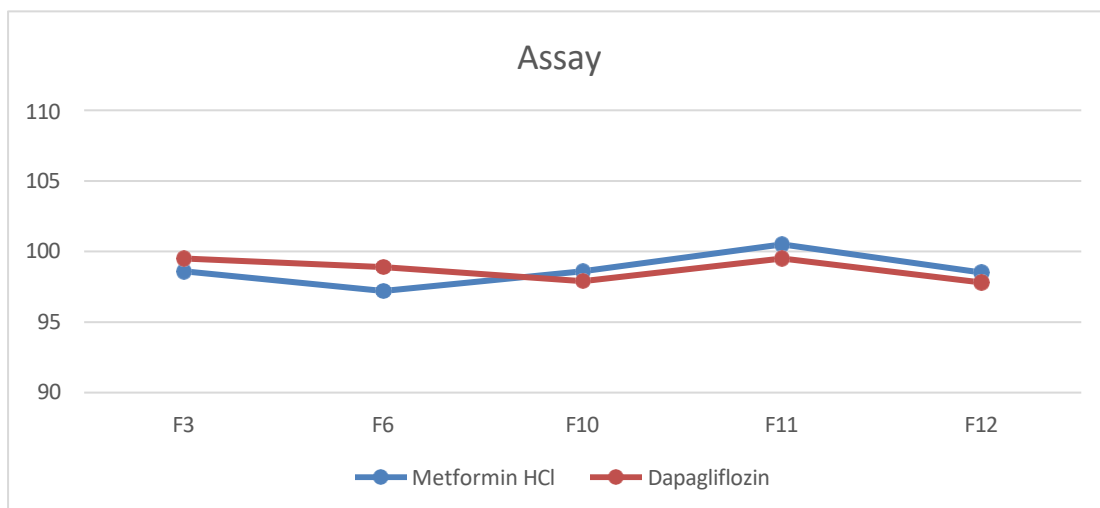


Fig. 4.14: Quantitative Assay graphically represented for all tablet formulations

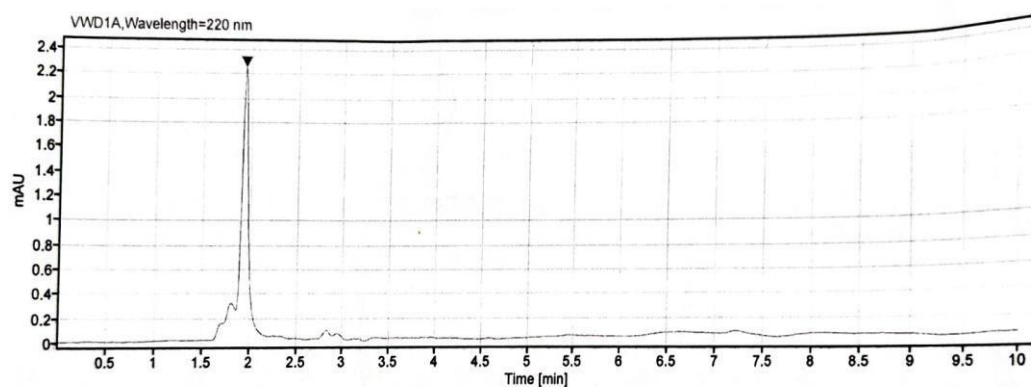
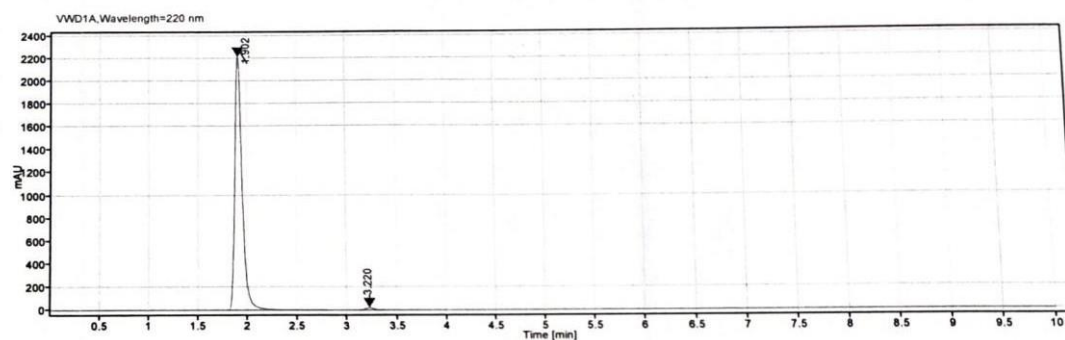


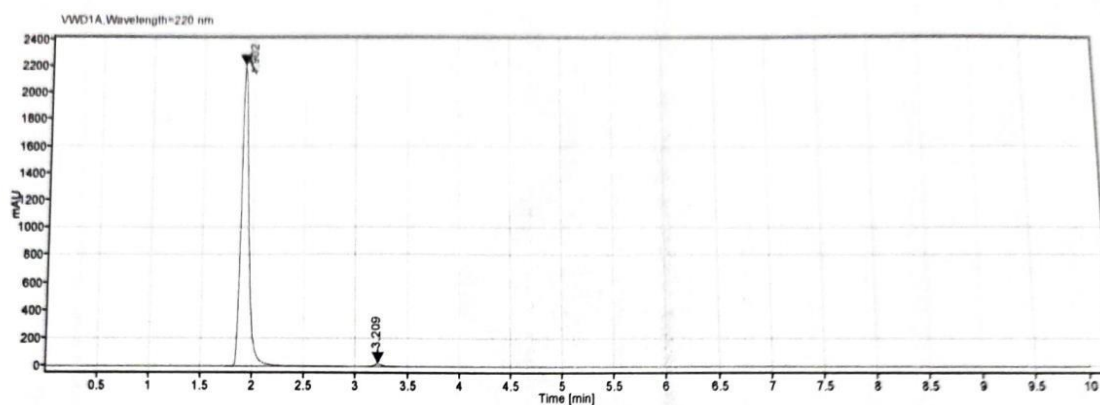
Fig. 4.15: Chromatogram of Mobile Phase of tablet.



Signal: VWD1A,Wavelength=220 nm

Name	RT [min]	Area	Height	Peak Theoretical Plates USP	Peak Resolution USP	Peak Symmetry (classic)
Metformin HCl	1.902	11423.26	2212.68	3461.52034		0.63991
Dapagliflozin	3.220	121.45	19.84	7270.90072	9.41816	0.72551
Sum		11544.71				

Fig. 4.16: Chromatogram of Standard solution of layered tablet.



Signal: VWD1A, Wavelength=220 nm

Name	RT [min]	Area	Height	Peak Theoretical Plates USP	Peak Resolution USP	Peak Symmetry (classic)
Metformin HCl	1.902	11368.93	2206.26	3480.26999		0.64195
Dapagliflozin	3.209	121.36	19.80	7229.78367	9.34045	0.72696
Sum		11490.29				

Fig. 4.17: Chromatogram of Sample solution of final optimized formulation (F11)

4.3.5 Dissolution Studies

The formulation's dissolving test, which conforms with the physical parameters, was executed well. Analytical results cannot be obtained from formulations that fail physical testing. Formulations F3, F6, F10, F11, and F12 meet the physical testing requirements. Table 18 shows the findings of the dissolution of dapagliflozin and metformin HCl.

Tableted tablets with an optimised IR layer and different SR layer compositions were subjected to in vitro dissolving tests in 6.8pH buffer using the USP apparatus II (Hasan, Hossen et al. 2014) method at different sampling points of 30 minutes for the dapagliflozin IR layer and 1 hour, 3 hours, and 10 hours for the metformin HCl sustain release layer. The cumulative percent drug dissolved values of dapagliflozin at 30 minutes are similar across all formulations due to its same composition (Rajani, Prasad et al. 2018). The content of glyceryl behenate and HPMC K-100 determines the release profile of the metformin hydrochloride layer (Lee, Kim et al. 2012). The concentration of metformin HCL decreases as the concentration of polymers increases.(Hossen, Hasan, and others, 2014). The medication release profile decreases as the glyceryl behenate content rises. With a glyceryl behenate concentration of

14.48% of the total metformin layer composition, the optimised formulation F11 exhibits a superior dissolving profile at every time point. The dissolving profile decreases as the glyceryl behenate content in F12 is raised to 17.93%. The type of binder used in formulations containing polymers, such as Klucel EXF and PVP k-30, also affects the drug release profile. (Lee, Kim, and others, 2012) .

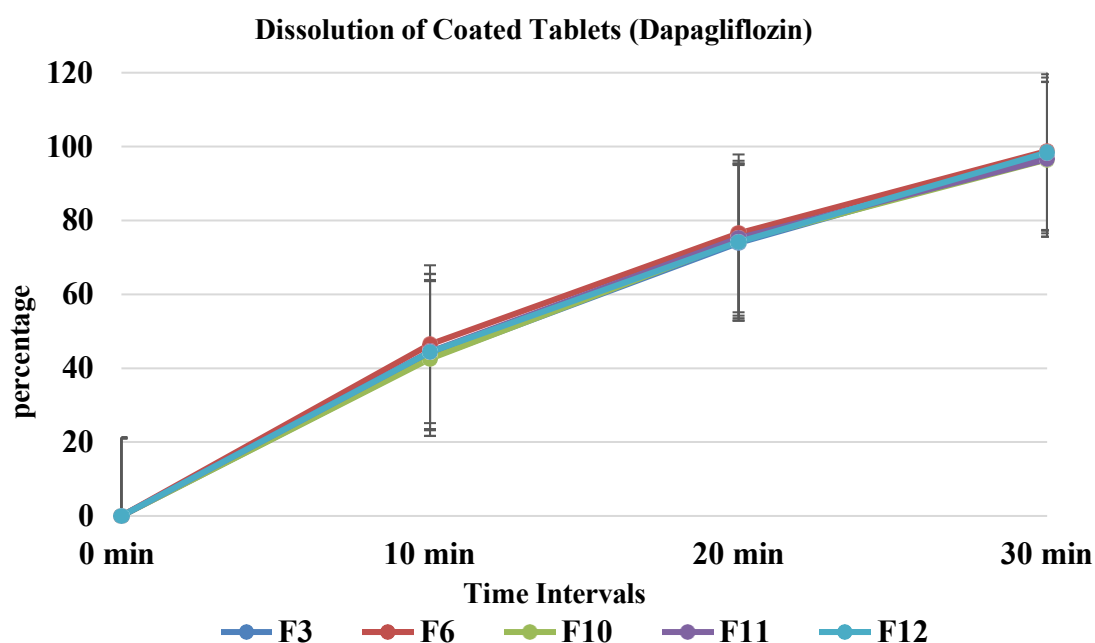


Fig. 4.18: Graphically representation of Dissolution of Dapagliflozin in tablet

Table 4.6: The dissolution results of Tablet

Physical Test	Name of layer	Acceptance Criteria	F3 %	F6 %	F10 %	F11 %	F12 %
Dissolution	Metformin HCl	After 1 Hour 20%-40%	55.6	51.8	48.6	32.22	24.5
		After 3 Hour 45%-65%	84.7	79.6	74.8	61.26	45.9
		After 10 Hour NLT 85%	99.8	98.7	95.6	101.67	90.2
	Dapagliflozin	NLT 80% after 30 min	97.5	96.8	94.6	97.29	96.5

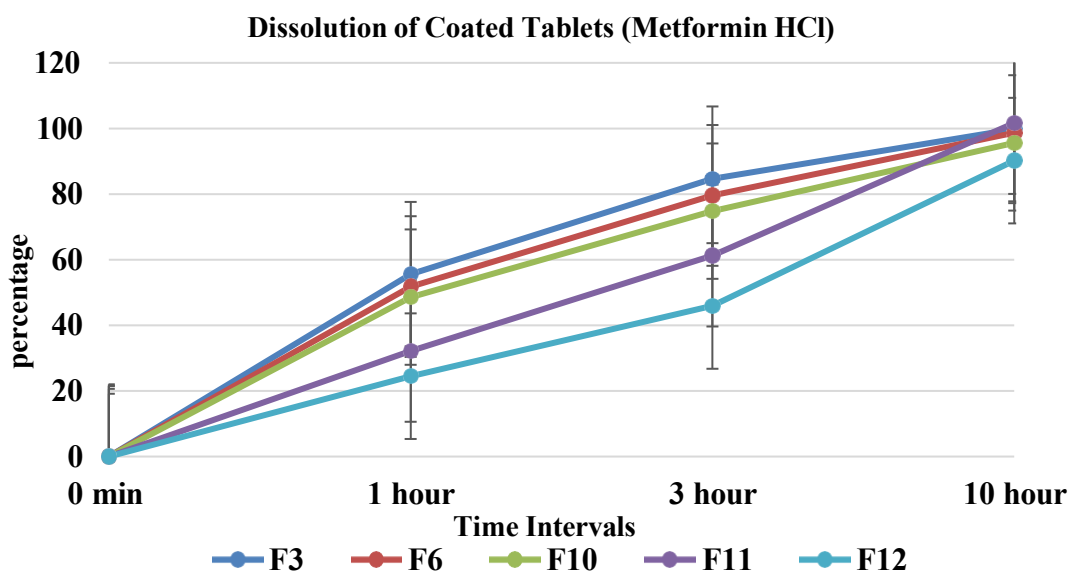


Fig. 4.19: Graphically representation of Dissolution of Metformin Hcl in tablet

4.3.6 Dissolution Release Profile Of Dapagliflozin

Verification of the percentage of dapagliflozin released revealed that all formulations F3, F6, F10, F11, and F12 had dissolved. The sample was collected at different times. A graph connecting the time and percentage medication release values was created, as shown in Figure 22. Fifty percent of the medication was released within 15 minutes, according to the results. Dapagliflozin outcomes gradually improve for up to half an hour. A straight curve was generated, showing that the product responded similarly to medications that were delivered right away and that around 100% of the medication was released in about 30 minutes.

Table 4.7: Dissolution profile of Dapagliflozin

	Time	F3 %	F6 %	F10 %	F11 %	F12 %
Dapagliflozin	0 min	00	00	00	00	00
	05 min	30.9	32.5	35.9	35.9	36.51
	10 min	42.8	46.5	42.6	44.5	44.38
	15 min	65.8	62.4	64.9	64.5	63.15
	20 min	73.9	76.5	74.5	75.2	74.16
	30 min	97.6	98.8	96.5	96.62	98.39
	45 min	99.9	100.2	99.8	100.7	100.5

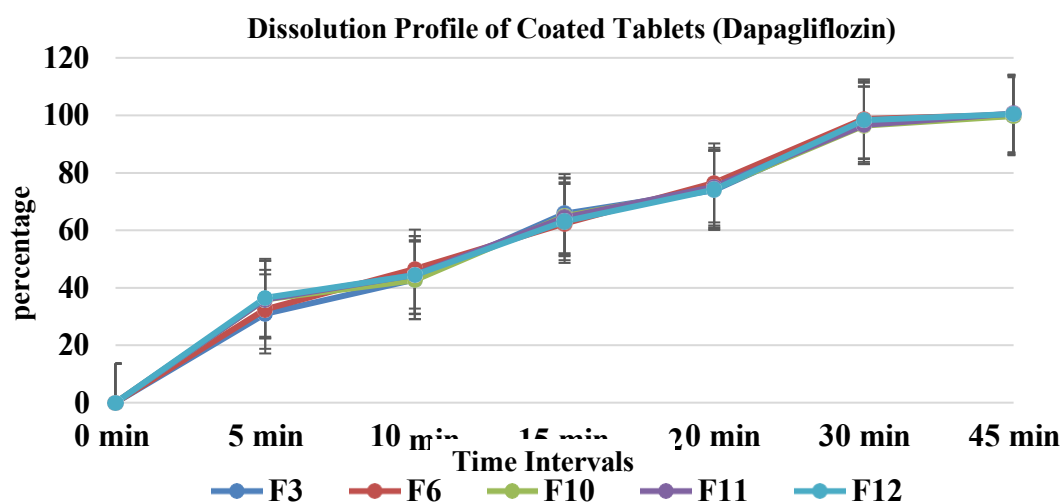


Fig. 4.20: Dissolution Profile of dapagliflozin

4.3.7 Dissolution Profile of Metformin HCl

All formulations F3, F6, F10, F11, and F12 were dissolved, despite the fact that the percentage of metformin HCl released was verified. The sample was collected at different times. A graph connecting the time and percentage medication release values was created, as shown in Figure 26. The findings indicate a steady improvement in the Metformin HCl results up to the tenth hour of Formulation F11. For formulation F11, a straight line was created, showing that about 100% of the drug was released in about ten hours, indicating that the product exhibits extended release behaviour.

Table 4.8: Dissolution profile of Metformin HCl

	Time	F3 %	F6 %	F10 %	F11 %	F12 %
Metformin HCl	0 min	00	00	00	00	00
	30 min	40.2	39.9	30.5	18.4	14.2
	1 hr.	56.4	53.2	47.5	30.5	23.4
	3 hr.	86.8	80.4	76.5	58.4	47.6
	10 hr.	98.4	97.4	96.5	99.8	89.5

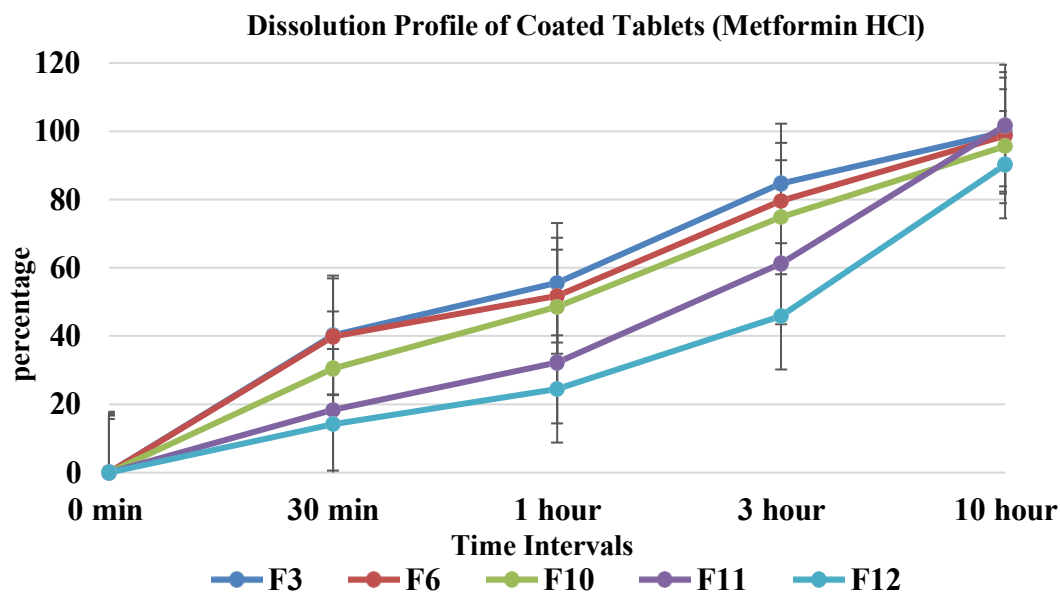


Fig. 4.21: Dissolution Profile of Metformin HCl

4.3.8 Release kinetics.

Numerous kinetic models, such as the Zero order, First Order, and Higuchi models, were used to fit the in vitro release data from various formulations of metformin hydrochloride. In zero order ($Q_t = Q_0 + K_0t$), the graph showed the cumulative percent of drug release versus time; in first order ($\ln Q = \ln Q_0 - K_1t$), the graph showed the log cumulative percent of medication remaining vs time. The Higuchi model Kinetics was used to display the line in cumulative percent of drug released vs square root of time ($Q_t = K_2 t^{1/2}$) (Hasan, Hossen et al. 2014). The findings are displayed in table 4.9.

Table 4.9: Pharmacokinetic results.

Metformin	Zero order		Ist order		Higuchi	
	R ²	K ₀	R ²	K ₁	R ²	K _H
F3	-0.0092	11.981	0.9897	0.856	0.7670	37.678
F6	0.0664	11.686	0.9714	0.758	0.8073	36.460
F10	0.3020	11.404	0.9852	0.591	0.8883	34.947
F11	0.7862	11.001	0.9921	0.327	0.9951	34.742
F12	0.8631	9.690	0.9919	0.230	0.9897	27.511

The ideal matrix formulation would release its drug content in a sustained release

profile over a manageable amount of time, using polymers and diluents as much as is practical (Nanjwade, 2011). Kinetic parameters like Zero order, First order, and Higuchi for metformin prolonged release from the controlled release matrix tablet are given in order to investigate the drug release-rate kinetics process. According to the results of the optimised formulation F11 in Table 21, the metformin extended release layer follows a first order kinetic process ($R^2 = 0.9921$), meaning that drug concentration affects drug release (ALETI, 2021). The formulation's (F11) diffusion-regulated release of metformin hydrochloride is demonstrated by the Higuchi value of 0.9951 (Lee, 2012).

CHAPTER 5

DISCUSSIONS

Using a variety of excipients, a new combination of APIs, such as dapagliflozin and metformin HCl, creates a tablet that can be made by the drug loading approach. Formulations F1–F12 were created using excipients at varying concentrations. After determining the final combined powder's angle of repose, bulk density, compressibility index, tapped density, and hausner ratio, formulation characteristics were compared. After that, the compressed tablets were assessed and subjected to physicochemical investigations to determine their hardness, friability, dissolution release profile, and FTIR analysis quantitative test. The same ingredients are used in all Dapagliflozin immediate release tablet formulations from F1 to F12, including titanium dioxide to enhance the tablets' look and flowability and Opadry Pink Talc as a lubricant and glidant. The Dapagliflozin layer's PEG-6000 concentration changed from F1 to F12 by 1.66%, 3.27%, 4.83%, 6.34%, 7.81%, 9.23%, 10.60%, 11.94%, 13.23%, 14.49%, 15.94%, and 16.90%. The extended-release polymers Glyceryl behenate (4.82%, 7.93%, and 11.03%) and HPMC K-100 (11.03%, 7.93%, and 4.82%) are both present in the metformin HCl extended-release layer in varying concentrations. The binder is hydroxy propyl cellulose (4.96%), and the diluent is Microcrystalline cellulose 101 (9.51%). Both HPMC K-100 (11.03%, 7.93%, and 4.82%) and the prolonged release polymer Glyceryl behenate (4.82%, 7.93%, and 11.03%) are present in formulations F4, F5, and F6 along with the binder Povidone K-30 (3.58%) and the diluent Microcrystalline cellulose 101 (10.89%). The formulations from F7, F8, and F9 exclusively include the extended-release polymer HPMC K-100 (11.72%, 14.48%, and 17.93%), together with the diluent Microcrystalline cellulose 101 (13.65%, 10.89%, and 7.44%) and the binder hydroxy propyl cellulose (4.96%). The only prolonged release polymer in formulations F10, F11, and F12 is glyceryl behenate (11.72%, 14.48%, and 17.93%), together with the binder Hydroxy propyl cellulose (4.96%) and the diluent Microcrystalline cellulose 101 (14.34%, 10.89%, and 7.44%).

All of the physical and chemical results indicate that formulation F11 performs adequately in the powder flow, hardness, and friability tests. In addition, formulation no. 11's invitro drug release results demonstrate extended release of metformin HCl and faster drug release of dapagliflozin when compared to other formulations that

contain HPMC K-100. Details of the dissolving profiles were also assessed, and the results demonstrated that all Metformin HCL formulations adhere to first-order drug release.

CHAPTER 6

CONCLUSIONS/ RECOMMENDATIONS

CONCLUSION

It is determined that glyceryl behenate, an extended-release medication, can be used to make Dapagliflozin and metformin HCl tablets utilizing the drug loading technique. When compared to formulations including HPMC K-100, polymer and glyceryl behenate provide superior outcomes in terms of physical and chemical parameters.

Further research on formulation optimization and scale up, stability testing, and bioequivalence testing is necessary to determine the suitability of these developed prolonged release tablets.

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