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FORMULATION AND OPTIMIZATION OF ALOGLIPTIN ORALLY DISINTEGRATING TABLETS (ODTS) FOR IMPROVEMENT MANAGEMENT OF DIABETES

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ABSTRACT

Aim: The aim of this study is to develop and optimise an orally disintegrating tablet (ODT) formulation of Alogliptin using a systematic approach, focusing on rapid disintegration, high mechanical strength, and efficient drug release to enhance patient compliance and therapeutic efficacy.**Methods:** A direct compression method was employed to formulate Alogliptin ODTs. The optimization was carried out using the Design of Experiment (DoE) approach, specifically employing Central Composite Design (CCD) for evaluating critical formulation factors such as compression force, disintegrant concentration (sodium starch glycolate), and lubricant concentration (magnesium stearate). Preformulation studies were performed to assess solubility, melting point, and drug-excipient compatibility. Post-compression parameters such as tablet hardness, disintegration time, friability, and dissolution were evaluated to ensure the quality of the tablets. **Results:** The formulation optimization revealed that compression force and disintegrant percentage significantly impacted the hardness and disintegration time of the

tablets. The ANOVA results indicated that compression force had a major effect on both hardness and disintegration time ($p < 0.05$). Tablets showed satisfactory hardness (4.9–5.5 kg/cm²) and disintegration time (28–29 seconds), meeting the criteria for ODTs. Dissolution studies indicated that 90.14% of the drug was released within 15 minutes, with complete dissolution achieved by 45 minutes. The final optimised formulation successfully balanced rapid disintegration and mechanical strength, meeting the desired specifications.

KEYWORDS: Alogliptin, orally disintegrating tablets (ODTs), Design of Experiment (DoE), compression force, sodium starch glycolate, magnesium stearate, dissolution, tablet optimization.

1. INTRODUCTION

Type 2 diabetes is a complex and varied disorder that requires both genetic predisposition and environmental influences for its clinical manifestation. One hypothesis regarding its origin is that it stems from the development of a "thrifty genotype," which may have provided survival advantages in the past but is harmful in today's environment. Alternatively, another theory suggests that type 2 diabetes may be an adult metabolic response to malnutrition during fetal development. The hyperglycemia associated with type 2 diabetes arises from either an absolute or relative deficiency in insulin. Typically, relative insulin deficiency occurs due to an inadequate compensatory response to insulin resistance. This insulin resistance can result from various genetic or metabolic factors, with central obesity being the most prevalent cause. Insulin resistance is linked to a group of metabolic issues, including glucose intolerance, high blood pressure, a distinct type of dyslipidemia, a procoagulant state, and an increased risk of macrovascular disease. Clinical intervention studies have shown that reducing the long-term complications of type 2 diabetes, both microvascular and macrovascular, requires controlling hyperglycemia to achieve hemoglobin A1c levels below 7.0%, blood pressure under 130/80 mmHg, and plasma LDL-cholesterol levels below 2.6 mmol/L (100 mg/dL). Oral antihyperglycemic medications work by boosting endogenous insulin secretion, reducing insulin resistance, or lowering the postprandial plasma glucose rise by delaying the absorption of complex carbohydrates. Achieving long-term glycemic control in type 2 diabetes typically necessitates a progressive, stepwise approach involving combination treatment with oral agents, and eventually, the addition of insulin.[1]

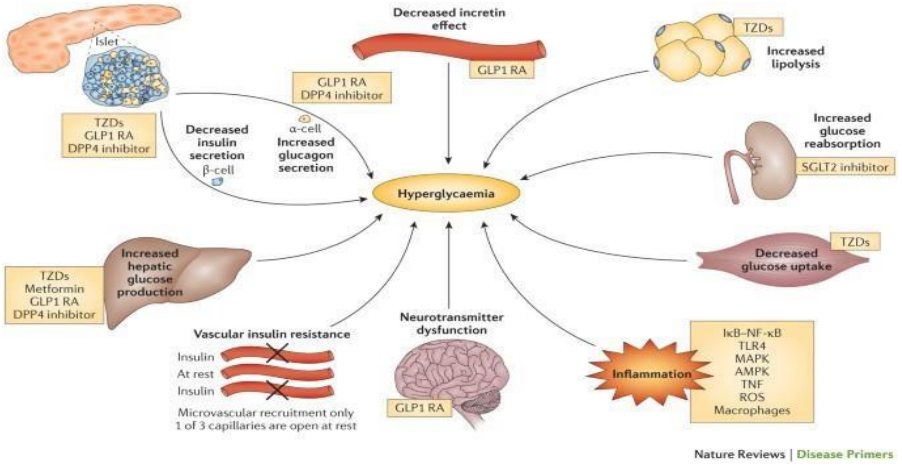


Figure: 1 Diabetics mellitus.

In 2011, it was estimated that 366 million people worldwide had diabetes mellitus (DM), and this number is projected to rise to 552 million by 2030. The prevalence of type 2 diabetes is increasing in every country, with 80% of those affected residing in low- and middle-income nations. In 2011, DM was responsible for 4.6 million deaths. By 2030, it is anticipated that 439 million people will have type 2 diabetes. The incidence of type 2 diabetes varies significantly across different geographical regions, largely due to differences in environmental and lifestyle risk factors.[2]

The development of type 2 diabetes mellitus is influenced by a complex interplay of genetic, environmental, and metabolic risk factors. Individuals with a strong family history of diabetes, advancing age, obesity, and physical inactivity are at the greatest risk. Additionally, minority populations face higher risks, not only due to genetic and familial factors but also because of exposure to American lifestyle factors, such as poor diet and lack of exercise. Women who have had gestational diabetes, along with their children, are also at an increased risk of developing type 2 diabetes. Insulin resistance further elevates the risk of progressing to impaired glucose tolerance and type 2 diabetes. People with insulin resistance often share many of the same risk factors as those with type 2 diabetes, including hyperinsulinemia, atherogenic dyslipidemia, glucose intolerance, hypertension, a prothrombotic state, hyperuricemia, and polycystic ovary syndrome. Current strategies for preventing and delaying the onset of type 2 diabetes focus on modifying environmental risk factors, such as reducing obesity and increasing physical activity. By increasing awareness of the risk factors for type 2 diabetes, there can be improved screening, early detection, and treatment in high-risk populations, ultimately aiming to reduce both microvascular and macrovascular complications.[3]

Diabetes is a far more varied condition than the current classification into type 1 and type 2 suggests; these categories likely represent the endpoints of a spectrum of diabetic disorders. Both type 1 and type 2 diabetes appear to emerge from an interaction between genetic susceptibility and environmental influences. While genetic factors set the foundation for vulnerability, rapid environmental changes—especially lifestyle factors—are the primary drivers of the rising incidence of both forms of diabetes. Many individuals carry genetic risks for both types, resulting in hybrid forms of diabetes, such as latent autoimmune diabetes in adults (LADA). Obesity is a powerful risk modifier for diabetes, contributing significantly not only to the prevalence of type 2 diabetes in Asia but also to the increasing number of adolescents affected by the disease. With advancements in patient profiling, the diversity of diabetic subgroups is expected to broaden even further.[4]

1.1 Pathophysiology

Glucose metabolism is typically controlled by a feedback loop involving islet β cells and insulin-responsive tissues, where tissue sensitivity to insulin influences the scale of the β-cell response. In cases of insulin resistance, β cells compensate to maintain normal glucose tolerance by increasing insulin production. However, when β cells are unable to secrete enough insulin to counteract insulin resistance, blood glucose levels begin to rise. While there is a strong genetic basis for β-cell dysfunction, environmental factors play a crucial role as well. Recent research has underscored the significant influence of hexoses, amino acids, fatty acids, and even alterations in the microbiome on both insulin resistance and β-cell dysfunction. Although various new treatment approaches have been introduced, there is a pressing need for more effective therapies to slow the progressive decline in β-cell function. Clinical trials have recently provided valuable insights into strategies for preventing and managing type 2 diabetes, along with the side effects of these treatments. Nevertheless, further long-term research on medications and bariatric surgery is essential to discover new prevention and treatment options for type 2 diabetes, ultimately aiming to mitigate the disease's harmful effects.[5]

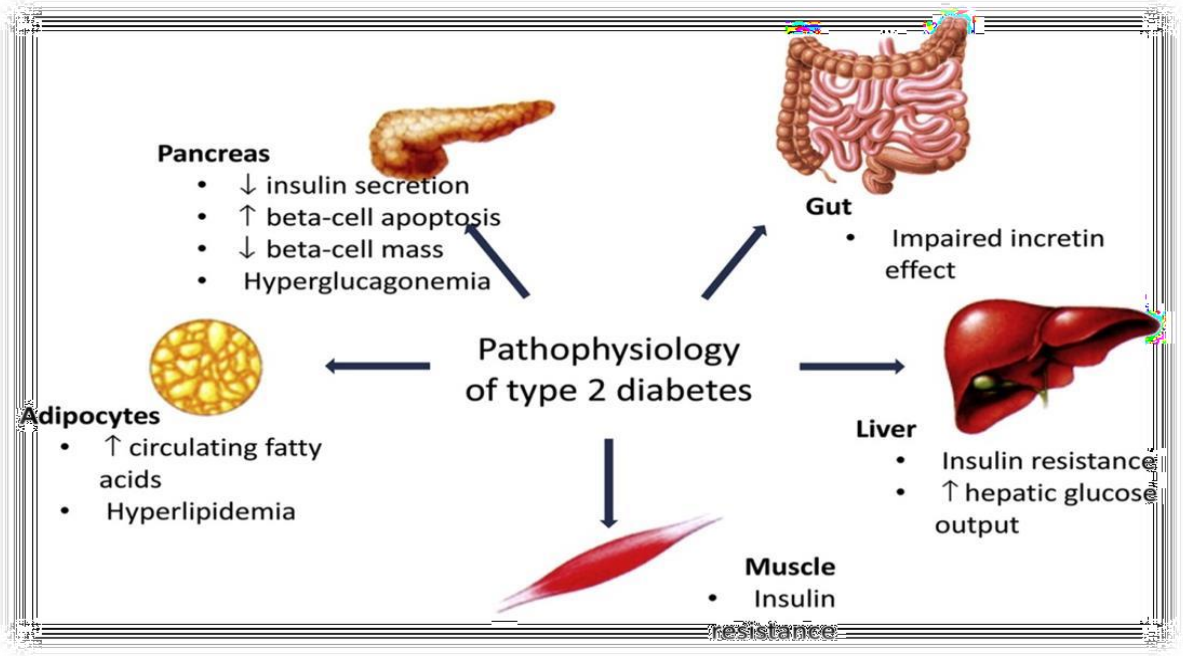


Figure: 2 Pathophysiology of type 2 diabetes.

Medication Adherence

Diabetes continues to impose a considerable clinical and economic strain on the U.S. healthcare system, with its incidence rising and projected to reach 15 per 1,000 people by 2050. Despite the development of new medications for type 2 diabetes, maintaining consistent glycemic control remains a significant challenge.[6]

Glycemic control, as indicated by hemoglobin A1c (HbA1c) levels, is vital for minimizing the severe clinical complications and associated economic costs of this chronic condition. However, real-world data from the 2007–2010 National Health and Nutrition Examination Survey reveals that only slightly more than 50% of patients achieve an HbA1c target of less than 7.0%.[7]

Using real-world claims data from 2012 to 2014, Kathryn Fitch, RN, MEd, Principal and Healthcare Management Consultant at Milliman, along with her colleagues, compared HbA1c laboratory results for commercially insured patients with type 2 diabetes to findings in the medical literature.[8]

Numerous studies have demonstrated that adherence to antidiabetic therapies is often inadequate. For instance, one meta-analysis found that only 67.9% of patients adhered to their diabetes treatment, meaning over 30% did not. Another meta-analysis of 27 studies conducted between 2004 and 2013 reported adherence rates ranging from 38.5% to 93.1%.

Unsurprisingly, poor adherence to diabetes therapy is linked to increased healthcare utilization and costs, partly due to higher hospitalization rates.[9]

In their research, Fitch and colleagues categorized patients into three cohorts to examine trends in medication adherence and HbA1c levels.

Cohort 1 consisted of 4,600 patients who had continuous coverage eligibility over the 3-year period and at least one HbA1c test each year. In this cohort, glycemic control was suboptimal and challenging to maintain over time. The proportion of patients achieving HbA1c levels below 7% dropped from 44% in 2012 to 38% in 2014. Among those with HbA1c levels below 7% in 2012, only 70% retained that level by 2013, and just 64% sustained it by 2014. Overall, in Cohort 1, only 24% of patients maintained consistent glycemic control throughout the 3 years of the study.[10]

Current treatment options for type2 diabetes mellitus

1.1.1 Biguanides

Biguanides, with metformin being the most commonly used, particularly in overweight and obese individuals, work by suppressing hepatic glucose production, increasing insulin sensitivity, enhancing glucose uptake through phosphorylation of GLUT-enhancer factors, increasing fatty acid oxidation, and reducing glucose absorption from the gastrointestinal tract. In addition, research published in 2008 revealed that metformin activates AMP-activated protein kinase, an enzyme that regulates the expression of hepatic gluconeogenic genes. Due to concerns regarding lactic acidosis, metformin should be used cautiously in elderly diabetic patients with renal impairment. Compared to sulfonylureas, metform in carries a lower risk of causing hypoglycemia.[11]

1.3.1 Sulfonylureas

Although generally well-tolerated, sulfonylureas carry a risk of hypoglycemia due to their stimulation of endogenous insulin secretion. Elderly patients with diabetes treated with sulfonylureas are at a 36% higher risk of hypoglycemia compared to younger patients. Glyburide is associated with a higher incidence of hypoglycemia than glipizide. Risk factors for hypoglycemia include impaired renal function, concurrent use of insulin or insulin sensitizers, age over 60, recent hospital discharge, alcohol abuse, caloric restriction, and the use of multiple medications that may potentiate sulfonylurea effects. Long-acting sulfonylureas like glyburide should be avoided in elderly patients, with short-acting

alternatives like glipizide being preferred.[12]

1.3.2 Meglitinides

Repaglinide and nateglinide are non-sulfonylurea secretagogues that stimulate insulin release from pancreatic beta cells by acting on ATP-dependent potassium channels, though they bind at a different site than sulfonylureas. These drugs have a rapid onset and short duration of action (4-6 hours), which reduces the risk of hypoglycemia. Administered before meals, meglitinides offer flexibility in case a meal is skipped, minimizing hypoglycemia risk. Repaglinide is primarily metabolized by the liver, with minimal renal excretion, so dose adjustments are generally not needed in patients with renal insufficiency, except those with end-stage renal disease.[13]

1.3.3 Thiazolidinediones

Thiazolidinediones, which include pioglitazone (following the restricted use of rosiglitazone due to cardiovascular concerns), improve insulin sensitivity by activating peroxisome proliferator-activated receptor gamma (PPARγ), addressing the underlying issue of insulin resistance in type 2 diabetes. Pioglitazone does not cause hypoglycemia and is safe for use in patients with renal impairment, making it a suitable option for older adults. However, due to risks like peripheral edema, fluid retention, and fractures in women, its use may be limited. Pioglitazone should be avoided in elderly patients with congestive heart failure and is contraindicated in those with class III-IV heart failure.[14]

1.3.4 Alpha-Glucosidase Inhibitors:

Acarbose, voglibose, and miglitol are α-glucosidase inhibitors that, while not widely used, are considered safe and effective for treating postprandial hyperglycemia in type 2 diabetes. These drugs should be avoided in patients with significant renal impairment and are often limited in use due to side effects like diarrhea and flatulence. Voglibose, the newest of the group, has shown promise in studies by improving glucose tolerance, delaying disease progression, and helping more patients achieve normoglycemia.[15]

1.3.5 Incretin-Based Therapies

Glucagon-like peptide-1 (GLP-1) analogues form the basis of incretin-based therapies, addressing previously unrecognized aspects of diabetes pathophysiology and leading to sustained improvements in glycemic control and body weight. These drugs, such as exenatide and liraglutide, can be used as monotherapy, alongside diet and exercise, or in combination

with other oral hypoglycemic agents for adults with type 2 diabetes. GLP-1 therapies carry no risk of hypoglycemia unless combined with insulin secretagogues. Emerging evidence also suggests that these therapies may positively impact inflammation, cardiovascular health, liver function, sleep, and the central nervous system.[16]

1.3.6 Insulin

Insulin therapy is used either alone or alongside oral hypoglycemic agents. Basal insulin therapy is helpful for patients with remaining beta-cell function, while basal-bolus therapy is necessary when beta-cell exhaustion occurs. In cases of glucose toxicity, insulin replacement therapy is needed to mimic normal pancreatic beta-cell insulin release. Insulin comes in various forms, including rapid-acting, short-acting, intermediate-acting, and long-acting ptions, with the latter being less likely to cause hypoglycemia.[17]

1.3.7 Insulin Analogues

Traditional intermediate- and long-acting insulins (e.g., NPH, lente, and ultralente) were limited by inconsistent absorption and peaks of action that could lead to hypoglycemia. Newer insulin analogues have more predictable pharmacokinetics and include rapid-acting options like insulin lispro and insulin aspart, and long-acting options such as insulin glargine.[18]

1.4.5 Future in Drug Therapy

Inhaled Insulin: Inhaled rapid-acting insulin was introduced in 2006 for treating both type 1 and type 2 diabetes, offering the advantage of delivery directly into the lungs. However, it was withdrawn from the market in 2007 due to poor sales.Quick-release bromocriptine is a recently developed treatment for type 2 diabetes, though its mechanism remains unclear. It has been shown to reduce HbA1c levels by 0.0% to 0.2% after 24 weeks of therapy.Ongoing research is exploring inhibitors of the sodium-glucose cotransporter 2 (which increase renal glucose elimination), inhibitors of 11ß-hydroxysteroid dehydrogenase 1 (which reduce glucocorticoid effects in the liver and fat), glucokinase activators, fatty-acid-receptor agonists, glucagon-receptor antagonists, and metabolic inhibitors of hepatic glucose output. These approaches are being investigated as potential new treatments for type 2 diabetes.[19]

1.4.6 Dipeptidyl-Peptidase IV Inhibitors

Dipeptidyl-peptidase IV (DPP-4) inhibitors prevent the breakdown of GLP-1 and GIP, thereby increasing the active levels of these hormones. This leads to improved islet function

and better glycemic control in type 2 diabetes. DPP-4 inhibitors, a relatively new class of anti-diabetic drugs, offer efficacy comparable to existing treatments. They can be used as monotherapy in patients not adequately controlled with diet and exercise or as add-on therapy in combination with metformin, thiazolidinediones, or insulin. These drugs are generally well tolerated, with a low risk of hypoglycemia, and are weight neutral, though they tend to be expensive. The long-term impact on glycemic control and beta-cell function remains to be fully established. DPP-4 inhibitors that have received FDA approval include sitagliptin, saxagliptin, linagliptin, andalogliptin. Meanwhile, vildagliptin has been approved by the European Medicines Agency (EMA), but not by the FDA.[20]

Type 2 diabetes mellitus (DM) is a chronic metabolic disorder marked by persistent hyperglycemia, which progressively contributes to vascular complications. As a globally prevalent disease, it imposes significant health risks and drives up healthcare costs. This review explores the historical development and current understanding of DM within pathophysiology, along with advancements in pharmacotherapy beyond insulin. The complex relationship between insulin secretion and resistance, once summarized as the "ominous triumvirate," has now expanded to the "ominous octet," underscoring the role of multiple organs in glucose regulation. Pharmacological treatments have evolved from early biguanides to a broad range of medications that may offer cardiovascular benefits. Despite these advances, treatment targets are often unmet, highlighting the need for future therapies that can address multiple metabolic pathways simultaneously. Ultimately, given the growing prevalence of type 2 DM, the most effective approach to reducing morbidity and mortality is likely to be a stronger focus on primary prevention.[21]

1.3.8 Alogliptin

The FDA granted approval to alogliptin in January 2013 for the treatment of type 2 diabetes mellitus (T2DM) in adults, with the goal of improving glycemic control. Alogliptin is a DPP-4 inhibitor (part of the "gliptin" class) and is intended to be used in combination with diet and exercise to manage blood sugar levels. The 2013 approval included three different formulations: one as a standalone treatment, one in combination with metformin, and another combined with pioglitazone.[22]

Alogliptin is a dipeptidyl peptidase-4 inhibitor approved globally for managing type 2 diabetes mellitus. Fixed-dose combinations, such as alogliptin/metformin and alogliptin/pioglitazone are also available. This review examines the effectiveness and

tolerability of oral alogliptin in type 2 diabetes treatment. Findings from randomized controlled trials indicate that alogliptin enhances glycemic control when used as a standalone therapy, in dual therapy with agents like metformin, pioglitazone, sulfonylurea, voglibose, or insulin, and in triple therapy with metformin and pioglitazone. Generally, alogliptin was well-tolerated by patients, did not cause weight gain, and posed a low risk of hypoglycemia. Results from the comprehensive EXAMINE trial demonstrated that alogliptin did not increase the risk of major cardiovascular events in patients with type 2 diabetes and recent acute coronary syndrome. In summary, alogliptin provides a valuable option for treating type 2 diabetes.[23]

Alogliptin benzoate (previously known as SYR-322) is a novel, orally administered, quinazolinone-based DPP-4 inhibitor designed to enhance glycemic control in type 2 diabetes. Studies indicate that alogliptin is highly selective for DPP-4, showing over 10,000-fold specificity compared to the similar enzymes DPP-8 and DPP-9, which is considered advantageous, as DPP-8/DPP-9 inhibition has been linked to toxicity in animals. Preliminary studies show alogliptin's favorable pharmacokinetics and safety, as well as significant improvements in early insulin release and glucose tolerance in Wistar fatty rats after a single dose.[24]

In this study, alogliptin's selectivity was assessed in vitro, alongside detailed pharmacokinetic and pharmacodynamic profiling across rats, dogs, and monkeys. The dose-dependent impact of alogliptin on DPP-4 activity, GLP-1 levels, insulin secretion, and glucose tolerance was further examined in Zucker fa/fa rats, a model of insulin resistance. Lastly, the potential of alogliptin to induce hypoglycemia was evaluated by analyzing fasting plasma glucose and insulin levels after a single dose in normoglycemic rats.[25]

1.3.9 Mechanism of action

Alogliptin is a highly selective and potent noncovalent inhibitor of DPP-4, developed through the use of Structure-based Drug Design System technology. It is over 10,000 times more selective for DPP-4 compared to DPP-2, -8, and -9 which is crucial because DPP-8 and -9 have been linked to the activation of pro-inflammatory caspase-1, a key player in pyroptosis. By inhibiting DPP-4, alogliptin reduces the breakdown of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones stimulate insulin secretion and suppress glucagon release in response to elevated glucose levels. Consequently, alogliptin aids in improving glycemic control via a

mechanism that is dependent on glucose.[26]

Alogliptin is quickly absorbed and distributes uniformly across tissues. Effective DPP-4 inhibition requires approximately 80% trough inhibition at steady state and alogliptin has been shown to inhibit DPP-4 activity by up to 99% after 14 days of once-daily dosing at Ther apeutic levels. Its bioavailability is complete (100%)and unaffected by food intake. Additionally, no clinically significant interactions have been noted with commonly used antidiabetic agents such as metformin, pioglitazone (a thiazolidinedione [TZD]), and glyburide (a sulfonylurea [SU]). Alogliptin undergoes minimal metabolism, with negligible involvement of cytochrome P450 (CYP) enzymes, allowing for its use without dose adjustments alongside CYP substrates or inhibitors. Furthermore, no significant interactions have been observed between alogliptin and either p-glycoprotein inhibitors or substrates. For further comparison of alogliptin's pharmacokinetic and pharmacodynamic characteristics relative to other DPP-4 inhibitors, readers are referred to the comprehensive review by Chen et al. (2015).[27]

1.3.10 Clinical benefits of alogliptin

Alogliptin has been shown to improve glycemic control, as measured by reductions in HbA1c, in both treatment-naïve and previously treated patients during global and Asian phase II/III studies. These studies were placebo-controlled or actively controlled and examined alogliptin's effectiveness in the following settings as a monotherapy as part of dual therapy (in combination with agents like metformin, sulfonylureas (SUs), TZDs, α-glucosidase inhibitors (α-GIs), or insulin) and in triple therapy (added to insulin with or without metformin, or to metformin combined with a TZD) . Here, we focus on phase III studies that primarily assessed changes in HbA1c from baseline to a minimum of 12 weeks, with most studies extending through 26 weeks.[28]

In treatment-naïve patients with poorly controlled type 2 diabetes mellitus (T2DM) on diet and exercise alone, alogliptin monotherapy at doses of 12.5 mg and 25 mg significantly improved glycemic control compared to placebo at week 26 (both doses, $p < 0.001$). In this trial, 44% of patients reached the target HbA1c of ≤7.0% (as recommended by guidelines) and a significant decrease in fasting plasma glucose was observed at 26 weeks in the alogliptin group compared to placebo ($p < 0.001$ for both doses). Five additional phase III trials, each lasting 26 weeks, investigated the efficacy of alogliptin as an add-on therapy (dual therapy with metformin or an SU) or as triple therapy (with pioglitazone ± metformin or an

SU, or with insulin ± metformin). Across all five studies, the 12.5 mg and 25 mg doses of alogliptin significantly reduced HbA1c compared to placebo ($p < 0.001$ for all).[29]

A meta-analysis of phase II/III and III trials highlighted that Asian patients experienced significantly greater reductions in HbA1c compared to non-Asian patients treated with alogliptin ($p = 0.02$), with similar safety profiles across both groups ($p = 0.71$). These findings are supported by additional studies in Asia that explored alogliptin's efficacy as monotherapy dual therapy (with metformin, pioglitazone, α-GI, or insulin) and triple therapy (with pioglitazone ± metformin).[30]

1.3.11 Benefit

Alogliptin has shown efficacy in improving glycemic control, as measured by reductions in HbA1c, across both treatment-naïve and previously treated patients. Studies have assessed alogliptin's effectiveness as (1) monotherapy, (2) dual therapy (in combination with metformin, sulfonylureas (SUs), thiazolidinediones (TZDs), α-glucosidase inhibitors (α-GIs), and insulin), and (3) triple therapy (added to insulin with or without metformin, or to metformin with a TZD) (see Online Resource, Table S1). Phase III studies focusing on HbA1c changes at 12 to 26 weeks consistently show significant HbA1c reductions with alogliptin versus placebo.[31]

In a 26-week study, treatment-naïve patients with uncontrolled type 2 diabetes on diet and exercise therapy alone who received alogliptin (12.5 mg or 25 mg) as monotherapy showed significant HbA1c improvement compared to placebo ($p < 0.001$ for both doses). Additionally, 44% of patients achieved the guideline-recommended HbA1c target of ≤7.0%, with marked reductions in fasting plasma glucose compared to placebo ($p < 0.001$). Five other phase III, placebo-controlled studies also demonstrated that alogliptin as dual or triple therapy significantly lowered HbA1c in patients with type 2 diabetes compared to placebo ($p < 0.001$).

A meta-analysis of phase II/III studies highlighted that Asian patients had greater HbA1c reductions than non-Asian patients treated with alogliptin ($p = 0.02$), with similar safety outcomes ($p = 0.71$). Studies conducted in Asia further supported the efficacy of alogliptin monotherapy, dual, and triple therapies in significantly reducing HbA1c versus placebo ($p < 0.001$).

1.3.12 Real-World Evidence

Alogliptin's effectiveness has also been validated in real-world studies, particularly in Japan. The ATTAK-J study in Japanese patients with type 2 diabetes showed a 0.54% ± 1.22% HbA1c reduction over one year. A higher proportion of patients reached HbA1c levels below 7.0% within three months of treatment ($p < 0.001$). Additional analysis showed that continued adherence to diet therapy further lowered HbA1c after 12 months, even without SU treatment. A long-term study over 3.5 years found similar HbA1c reductions in patients who maintained stable alogliptin and SU regimens, indicating durable glycemic control. Prescription trends indicate a growing preference for second-line treatments like DPP-4 inhibitors, sodium-glucose cotransporter 2 inhibitors (SGLT2is), and α-GIs. A prospective, large-scale observational study (J-BRAND Registry) involving 20,000 Japanese patients aims to compare the long-term safety and efficacy of alogliptin to other non-DPP-4i oral hypoglycemics, further clarifying its role in combination therapies.

1.3.13 Tolerability

Long-term studies (≥52 weeks) have demonstrated alogliptin's tolerability in both clinical and real-world settings. Compared to glipizide (an SU) and standard care (SoC), alogliptin showed similar incidence rates of adverse events (AEs), most of which were mild. In the ATTAK-J retrospective study, only 2.5% of patients reported AEs. A meta-analysis also confirmed that alogliptin is well-tolerated, with comparable rates of discontinuation due to AEs versus placebo or other antidiabetic agents. However, additional studies are recommended to investigate DPP-4 inhibitor effects on heart failure and pancreatitis.

1.3.14 Convenience and Preference

Treatment adherence in chronic conditions like type 2 diabetes is challenging, with an estimated 50% adherence rate in developed countries. To enhance adherence, patient preferences in treatment regimen, administration mode, frequency, risk of side effects, and efficacy are increasingly prioritized. A survey among U.S. and European diabetes patients indicated a preference for DPP-4 inhibitors due to their favorable regimen and risk profile over alternatives such as GLP-1 receptor agonists, SGLT2is, SUs, and TZDs. Patients favored DPP-4i oral tablets over injectable GLP-1 receptor agonists ($p < 0.001$). Additionally, fixed-dose combinations (FDCs), such as alogliptin/metformin or alogliptin/pioglitazone, may enhance adherence, simplify treatment, and reduce healthcare costs.

1.3.15 Health Economic Impact

Type 2 diabetes presents a substantial economic burden. According to the International Diabetes Federation, global healthcare costs related to diabetes were approximately $850 billion in 2017, with projections reaching $958 billion by 2045. Preventive and control interventions, such as intensive glycemic management, have demonstrated cost-effectiveness.

In a European analysis of randomized controlled trials, alogliptin as monotherapy or combination therapy with metformin showed greater cost-effectiveness than other DPP-4 inhibitors. In the UK, alogliptin plus metformin was projected to improve quality-adjusted life years (QALYs) with incremental cost-effectiveness ratios (ICERs) of £10,959/QALY (12.5 mg) and £7217/QALY (25 mg) compared to SU plus metformin. Further pharmacoeconomic analyses are needed to compare alogliptin's cost-effectiveness in combination with other diabetes treatments, especially in Asian populations.

1.3.16 Alternative Therapies

Alogliptin has been compared directly with other diabetes treatments in both international and Asian patient studies, focusing on dual and triple therapies. Across these studies, alogliptin with metformin, pioglitazone, or SUs significantly reduced HbA1c levels more effectively than monotherapies or placebo ($p < 0.05$ to $p < 0.0001$). As monotherapies, alogliptin and metformin provided similar HbA1c reductions after 26 weeks. Furthermore, a 2-year international study showed that alogliptin plus metformin outperformed glipizide in maintaining HbA1c levels below 7.0% without causing hypoglycemia or weight gain, supporting alogliptin as a long-term treatment choice for type 2 diabetes.

1.3.17 Innovative drug delivery system

Oral drug delivery is widely recognized as the gold standard in the pharmaceutical industry, being considered the safest, most convenient, and most cost-effective method of drug delivery, offering the highest level of patient compliance. The oral route remains the preferred mode of administration, with tablets and capsules being the most commonly chosen dosage forms. However, these conventional forms have certain drawbacks, particularly for geriatric and pediatric patients, who may experience choking or discomfort when swallowing.

To address these challenges, orally disintegrating tablets (ODTs) have been developed, providing solutions to both pharmaceutical and patient needs. These range from improved life-cycle management to easier dosing for pediatric, geriatric, and psychiatric patients,

especially those suffering from dysphagia. Over the past 30 years, ODTs have garnered significant attention as a favorable alternative to traditional tablets and capsules, largely due to their enhanced patient compliance.

ODTs are known by various names, including orodispersible, rapid-dissolving, mouth-dissolving, and rapid-disintegrating tablets. Pharmacopeias and regulatory agencies have provided definitions for these tablets: orodispersible tablets are uncoated and are designed to disperse quickly in the mouth before being swallowed, typically disintegrating within 180 seconds during disintegration testing. ODTs are formulated to break down rapidly in the mouth, aiding in the dispersion of the active ingredient before it is swallowed, with the goal of gastrointestinal delivery and/or absorption. According to the FDA, ODTs should be classified as solid oral preparations that disintegrate swiftly in the mouth, with an in-vitro disintegration time of around 30 seconds or less, as measured by the United States Pharmacopeia (USP) disintegration test or an alternative method.

Since their introduction in the 1980s, products based on ODT technology have seen a steady rise in demand, with their product pipelines rapidly expanding. In the past decade, the need for more patient-friendly and compliant dosage forms has significantly increased, driving the annual growth in the development of new ODT technologies. Companies such as Catalent Pharma Solutions (formerly Scherer DDS) in the UK, Cima Labs in the US, and Takeda Pharmaceutical Company in Japan have been pioneers in the development of ODTs.

The first ODT to receive approval from the US Food and Drug Administration (FDA) was the Zydis formulation of Claritin (loratadine) in December 1996. This was followed by the Zydis ODT formulations of Klonopin (clonazepam) in December 1997 and Maxalt (rizatriptan) in June 1998 Orally disintegrating tablets (ODTs) significantly enhance patient compliance in diabetic populations with swallowing difficulties (dysphagia) through several mechanisms.

Advancements in drug delivery systems are progressing as pharmaceutical researchers deepen their knowledge of the key physicochemical and biochemical factors influencing drug efficacy. Over the last 30 years, orally disintegrating tablets (ODTs) have emerged as a favored alternative to traditional tablets and capsules, largely due to improved patient compliance. ODTs are solid dose forms that dissolve swiftly, often within seconds, when placed on the tongue. First introduced to the market in the 1980s, ODT products have seen a

steady increase in demand and are experiencing rapid growth in development pipelines.

These evolving ODT technologies meet various pharmaceutical and patient needs, supporting areas like life-cycle management and easy administration for pediatric, geriatric, and psychiatric patients with swallowing difficulties. Consequently, both academic and industrial sectors are actively developing new formulations and innovative approaches for ODTs. This article aims to examine the evolution of ODTs, challenges in their formulation, advancements in technology and assessment methods, the suitability of different drug candidates, and future directions in this field.

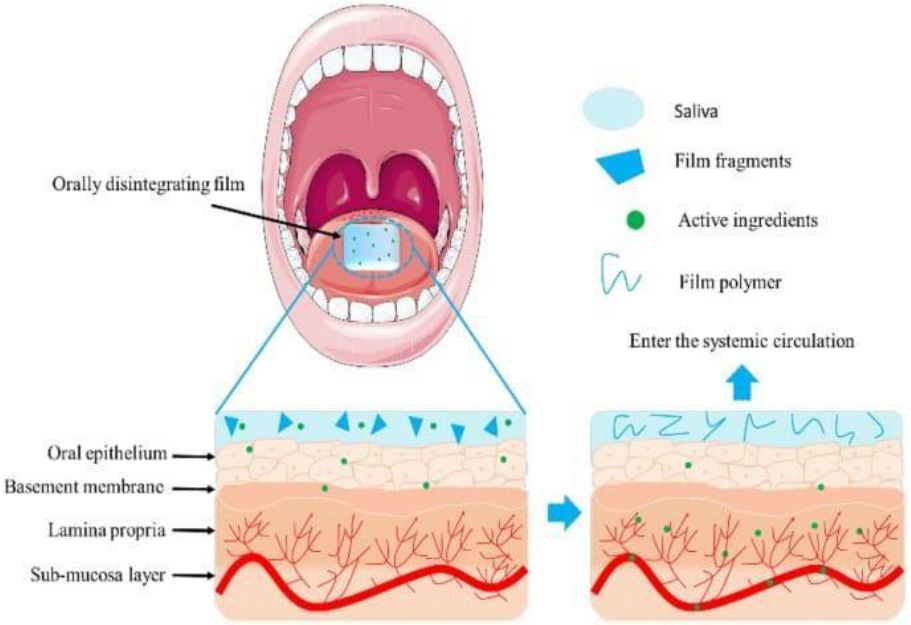


Figure: 3 Oral disintegrating film.

Orally disintegrating tablets (ODTs) are solid dosage forms specifically designed to enhance disintegration and dissolution rates of pharmaceuticals. Achieving rapid disintegration in these tablets relies on formulating them with high porosity, low density, and low hardness. This type of dosage form is often selected for patients who face challenges with swallowing, including geriatric and pediatric populations or individuals with dysphagia. Occasionally,

medications initially available in other dosage forms are reformulated as ODTs due to the unique benefits they offer. ODTs are also referred to by names such as orodispersible tablets, fast disintegrating tablets, mouth dissolving tablets, and rapimelts, though the United States Pharmacopeia (USP) formally recognizes these as "orally disintegrating tablets". The European Pharmacopoeia uses the term "orodispersible tablet" for tablets designed to disperse within three minutes in the mouth (European Pharmacopoeia, 2011a). The U.S. FDA defines

ODTs as tablets containing active ingredients that disintegrate on the tongue within seconds.

As a solid unit dosage form, ODTs offer good stability, precise dosing, efficient manufacturing, compact packaging, and are easy for patients to handle.They reduce the risk of gastrointestinal obstruction, particularly advantageous for patients without immediate access to water, such as those traveling.ODTs allow for convenient administration, particularly suited for pediatric, geriatric, mentally impaired, or psychiatric patients. The rapid disintegration of ODTs leads to swift drug dissolution and absorption, resulting in a quick onset of therapeutic action .They enhance the bioavailability of drugs absorbed in the mouth, pharynx, and esophagus.Drugs absorbed pregastrically bypass hepatic metabolism, increasing bioavailability and potentially reducing the required dose .

1.3.18 Swallowing pills

Patients with diabetes who have difficulty swallowing (a common issue among the elderly or those with diabetic complications like neuropathy) often struggle with traditional tablets or capsules. ODTs dissolve rapidly in the mouth without the need for water, making medication intake less daunting and more comfortable.

1.3.19 Convenience and Comfort

ODTs melt on the tongue, which removes the discomfort or fear associated with trying to swallow whole pills. This is especially important for diabetic patients who may also have other conditions, like diabetic neuropathy, which can exacerbate swallowing difficulties.

1.3.20 Overcoming Physical Barriers

Many diabetic patients with advanced complications like gastroparesis or nerve damage may experience impaired esophageal motility. ODTs bypass the need to pass through the esophagus, ensuring that patients get their medication without the risk of choking or delayed dissolution.

1.15.13 Increased Adherence

When medication becomes easier to take, adherence improves. Diabetic patients with swallowing issues are more likely to maintain consistent medication schedules if they find the method of administration manageable and less distressing. This consistency is crucial for maintaining stable blood glucose levels and avoiding complications from diabetes.

By offering a simpler, more comfortable method of drug administration, ODTs reduce the

challenges associated with pill swallowing and help diabetic patients adhere to their treatment plans more reliably.

1.15.14 Advantages of alogliptin ODTs

Alogliptin oral disintegrating tablets (ODTs) offer several advantages, particularly for populations that may struggle with conventional tablet forms, such as older adults or patients with dysphagia (difficulty swallowing). Here are some of the benefits highlighted in clinical and pharmaceutical research:

1.15.16 Improved Compliance

ODTs are particularly advantageous for patients with dysphagia, a common issue in elderly populations and those with certain comorbidities like diabetes. The quick dissolution of the tablet in the mouth eliminates the need for swallowing, making medication intake easier. Studies have shown that patients are more likely to adhere to their medication regimen when the formulation is easier to take, especially in populations that find it challenging to swallow traditional tablets.

ODTs can be taken without water, which adds convenience for patients who are on the go, bedridden, or have limited access to water at the time of dosing. The ability to take the medication without water is especially helpful during travel or in emergency situations where water is unavailable.

Many ODTs are formulated with pleasant flavors, which can enhance the patient experience, particularly in populations that may be more sensitive to the taste of medications. The ease of taking ODTs can reduce psychological resistance to medication intake, especially for patients with anxiety or fear related to swallowing pills.

Since ODTs dissolve quickly in the mouth, there is less risk of improper dosing or skipped doses due to difficulty swallowing. Consistent dosing is critical in maintaining optimal blood sugar control in diabetic patients. ODTs bypass the esophagus and are less likely to cause irritation compared to traditional tablets, potentially reducing gastrointestinal discomfort, which can sometimes affect diabetic patients. ODTs are particularly beneficial for older adults, who are more likely to have swallowing difficulties and may require more convenient forms of medication. Although diabetes is less common in children, ODT formulations can be beneficial in pediatric patients or younger adults who might have difficulty with

conventional tablet forms.

For healthcare providers administering alogliptin in clinical settings, ODTs can reduce the risk of dosing errors by eliminating the need for crushing tablets or preparing liquid formulations. Alogliptin oral disintegrating tablets (ODTs) offer improvements in both bioavailability and patient adherence when compared to conventional tablets due to their unique formulation and ease of administration.

Alogliptin ODTs are designed to disintegrate quickly in the mouth, often within seconds, upon contact with saliva. This allows for more rapid absorption of the active drug, potentially leading to quicker onset of action. In conventional tablets, the drug must pass through the gastrointestinal tract, where variability in gastric emptying, dissolution, and absorption can affect bioavailability.

While alogliptin is typically absorbed in the small intestine, the quick dissolution of ODTs in the mouth allows some absorption to begin through the oral mucosa. This partial absorption through the mucosal lining may reduce the extent of first-pass metabolism in the liver, thereby improving the overall bioavailability of the drug.

In some patients, the absorption of conventional tablets can be affected by factors such as stomach pH, food intake, and gastrointestinal motility. ODTs dissolve in the mouth, where these factors have less impact, reducing the variability in absorption and leading to more consistent drug plasma levels. One of the most significant benefits of ODTs is their suitability for patients who struggle with swallowing traditional tablets, such as the elderly, those with dysphagia, or individuals with neurological conditions. By eliminating the need for water and the mechanical act of swallowing, ODTs make it easier for these patients to consistently take their medication.

ODTs can be taken anywhere without the need for water, making them convenient for patients with active lifestyles or those who may not always have access to water. This convenience can encourage regular dosing, leading to better long-term adherence to therapy.

Alogliptin ODTs are often formulated with flavoring agents to mask any unpleasant taste, making them more palatable. This can be especially beneficial for patients who are sensitive to taste or have aversions to bitter medications, further promoting adherence. For patients who experience anxiety related to swallowing tablets, ODTs offer a more comfortable

alternative, reducing the mental burden of taking medication. This improved psychological experience can enhance willingness to adhere to prescribed treatments. The convenience of ODTs improves adherence in populations known for lower compliance rates, such as the elderly, pediatric patients, and individuals with cognitive impairments. With ODTs, these patients are less likely to miss doses due to difficulties swallowing or reluctance to take conventional tablets. Reduced Risk of Chewing or Crushing Errors**,** Some patients may resort to chewing or crushing conventional tablets if they struggle to swallow them, which can alter the drug's pharmacokinetics and decrease its efficacy. ODTs eliminate this risk by providing a pre- dissolved form of the drug that delivers consistent dosing without the need for modifications.

Alogliptin ODTs improve bioavailability by facilitating rapid disintegration and absorption, reducing the influence of gastrointestinal factors, and possibly bypassing part of the first-pass metabolism. This leads to more reliable drug absorption and plasma levels. Additionally, their patient-friendly design improves adherence, particularly in populations with swallowing difficulties, enhancing the overall effectiveness of diabetes management.

1.2 Allogliptin mouth disintegrating tablet

Allogliptin is a potent, selective dipeptidyl peptidase-4 (DPP-4) inhibitor used primarily in the management of type 2 diabetes mellitus. It functions by increasing the levels of incretin hormones, which in turn stimulate insulin secretion and decrease glucagon production in a glucose-dependent manner, aiding in glycemic control. With the increasing demand for more convenient and patient-friendly drug delivery systems, the development of allogliptin mouth disintegrating tablets (MDTs) has emerged as a promising approach to enhance patient compliance, especially among individuals who experience difficulty swallowing conventional tablets. Mouth disintegrating tablets (MDTs) are solid dosage forms that rapidly disintegrate in the oral cavity, releasing the drug without the need for water, making them particularly suitable for geriatric and pediatric patients as well as those with dysphagia.

The formulation of allogliptin MDTs involves meticulous design to ensure rapid disintegration, optimal drug release, and adequate taste masking, as the tablet dissolves directly in the mouth. Achieving these properties requires a careful selection of excipients, which play a crucial role in determining the mechanical strength, disintegration time, and overall stability of the tablet. Superdisintegrants, such as croscarmellose sodium, sodium starch glycolate, and crospovidone, are commonly incorporated to facilitate the swift

breakdown of the tablet upon contact with saliva. These agents function by promoting water uptake and creating an expansion force that rapidly disintegrates the tablet matrix. Additionally, flavoring agents and sweeteners, such as aspartame, sucralose, or natural flavors, are often included to mask the potentially bitter taste of allogliptin, enhancing the palatability of the dosage form and ensuring a pleasant experience for the patient.

The technological advancements in the production of mouth disintegrating tablets have enabled the use of innovative manufacturing techniques, such as direct compression, freeze-drying, and spray drying. Direct compression is the most commonly employed method due to its simplicity, cost-effectiveness, and suitability for heat-sensitive drugs like allogliptin. However, this method requires a thorough understanding of the powder characteristics, including flowability, compressibility, and particle size distribution, to achieve a robust and uniform tablet formulation. Freeze-drying, or lyophilization, produces tablets with extremely fast disintegration times but is generally more expensive and less scalable for commercial production. Spray drying, on the other hand, allows for the creation of fine particles with improved dissolution properties but may require specialized equipment and processing conditions. The choice of manufacturing method depends on various factors, including the physicochemical properties of allogliptin, the desired disintegration profile, and the intended shelf life of the product.

Pharmaceutical development of allogliptin MDTs also necessitates rigorous evaluation to ensure that the final product meets the required quality standards. Key parameters to assess include tablet hardness, friability, disintegration time, dissolution profile, and drug content uniformity. Tablet hardness is critical for ensuring that the product can withstand handling and packaging processes without compromising its integrity. However, an optimal balance must be maintained, as excessive hardness can delay disintegration. Friability testing evaluates the tablet's resistance to crumbling, ensuring that it remains intact during transportation and storage. Disintegration time is a crucial performance metric, with most pharmacopeias requiring MDTs to disintegrate within 30 seconds. The dissolution profile of allogliptin MDTs should be comparable to that of conventional tablets, providing consistent and reliable drug absorption for effective glycemic control. Furthermore, uniformity in drug content is essential to guarantee that each tablet delivers the intended therapeutic dose.

The stability of allogliptin MDTs is another critical consideration, as the formulation must

remain effective throughout its shelf life. Stability testing under different environmental conditions, such as varying temperature and humidity levels, helps to identify potential degradation pathways and optimize the formulation to prevent them. The hygroscopic nature of certain excipients, as well as the susceptibility of allogliptin to hydrolysis, necessitates the use of moisture-resistant packaging materials, such as blister packs with desiccants. Additionally, the use of appropriate antioxidants or stabilizers can further enhance the shelf life of the product. Regulatory guidelines, such as those outlined by the International Council for Harmonisation (ICH), provide a framework for conducting stability studies and ensuring that the product maintains its safety, efficacy, and quality over time.

Patient-centric design is at the core of developing allogliptin MDTs, with a focus on improving adherence to diabetes management regimens. The convenience of a tablet that disintegrates in the mouth without the need for water can be particularly beneficial for individuals with an active lifestyle or those who require medication on the go. Moreover, the rapid onset of action associated with MDTs may offer an added advantage in terms of postprandial glucose control, as the drug is quickly absorbed through the oral mucosa and gastrointestinal tract. The potential for enhanced bioavailability of allogliptin MDTs compared to conventional tablets has also been explored, although further clinical studies are needed to substantiate these claims. The use of patient feedback and acceptability studies can provide valuable insights into the overall effectiveness and user satisfaction of the product, guiding future improvements and innovations in drug delivery systems.

In conclusion, the development of allogliptin mouth disintegrating tablets represents a significant advancement in oral drug delivery, addressing the needs of patients who have difficulty swallowing and enhancing medication adherence in diabetes management. The formulation process involves a strategic selection of excipients and manufacturing techniques to achieve rapid disintegration, palatability, and stability. Ongoing research and development efforts continue to optimize these formulations, with the potential to improve patient outcomes and quality of life. As the pharmaceutical industry moves toward more patient-centric solutions, allogliptin MDTs exemplify how innovative drug delivery systems can be tailored to meet the unique challenges of managing chronic conditions like type 2 diabetes.

2. LITERATURE REVIEW

Nichols GA et al., (2018) found that Alogliptin may increase the risk of heart failure (HF) exacerbation, particularly in patients with established HF. Alogliptin was associated with a

low incidence of new-onset HF.A small number of patients discontinued alogliptin due to HF. There was no significant difference in HF exacerbations between patients on alogliptin who previously received saxagliptin. Healthcare providers should exercise caution when prescribing alogliptin to patients with established HF. The risk of HF exacerbation should be weighed against the potential benefits of alogliptin in individual patients. Patients receiving alogliptin, especially those with risk factors for HF, should be monitored for signs and symptoms of heart failure. The study was retrospective, which may introduce limitations due to data collection and selection biases. While the sample size was relatively large, further studies with larger cohorts may be needed to confirm the findings. The study did not fully explore the impact of concomitant cardiotoxic medications on HF risk. This provides evidence suggesting that alogliptin may increase the risk of HF exacerbation in patients with established HF. Healthcare providers should consider this risk when prescribing alogliptin and monitor patients for signs and symptoms of heart failure.

Harris MI et al., (2014) found that Oral Antidiabetic Agents for Type 2 Diabetes is the most oral antidiabetic agents effectively lower hemoglobin A1c levels compared to placebo. Different agents within the same class generally demonstrate similar efficacy. Combining agents often results in additional glycemic benefits. Despite similar efficacy, oral antidiabetic agents have different mechanisms of action, leading to distinct metabolic effects and adverse effect profiles. Long-term vascular risk reduction has been demonstrated only with sulfonylureas and metformin. The choice of oral antidiabetic agent should be tailored to the individual patient's needs, considering factors such as glycemic control goals, risk factors, and preferences. Combining agents may be beneficial for achieving optimal glycemic control in some patients. For patients with a high risk of cardiovascular disease, sulfonylureas or metformin may be preferred. The study focused on data available up to the time of publication, and newer agents or studies may have emerged since then. The study primarily evaluated the effects of oral antidiabetic agents on glycemic control and may not have fully addressed other important clinical outcomes. The study provides valuable insights into the comparative effectiveness of oral antidiabetic agents for type 2 diabetes. It highlights the importance of individualizing treatment based on patient factors and considering the potential benefits and risks of different drug classes.

Egede LE et al., (2014) Researched on Patient Perceptions of Oral Diabetes Medications. Patients generally recognize the importance of medications for managing type 2 diabetes,

even with associated risks. Despite passive acceptance of medication prescriptions, patients actively experiment with dosages and timing to optimize their treatment. The experience of taking oral medications for type 2 diabetes is distinct, influenced by factors like the lack of symptoms and the perceived relationship between medication and diet. Healthcare providers should acknowledge and address patients' concerns and preferences regarding medication use. Engaging patients in decision-making can improve medication adherence and overall outcomes. Developing interventions that address the specific challenges and motivations of patients with type 2 diabetes can enhance medication-taking behaviors. The study was conducted in 2014, and newer medications or treatment approaches may have emerged since then. The study focused on qualitative research and may not fully represent the experiences of all patients with type 2 diabetes. This provides valuable insights into patient perceptions and experiences of taking oral medications for type 2 diabetes. The findings highlight the importance of a patient-centered approach and the need for tailored interventions to improve medication adherence and outcomes.

Bennett WL et al., (2012) founded a DPP-4 Inhibitor for Type 2 Diabetes. Alogliptin is an oral medication used to treat type 2 diabetes mellitus (T2DM). It belongs to a class of drugs called dipeptidyl peptidase-4 (DPP-4) inhibitors. Alogliptin works by inhibiting DPP-4, an enzyme that breaks down incretin hormones. This leads to increased insulin secretion and decreased glucagon levels, helping to lower blood sugar. Alogliptin is effective both as a monotherapy and when combined with other diabetes medications. It has a low risk of hypoglycemia, weight gain, acute pancreatitis, and gastrointestinal side effects. Studies have shown a favorable safety profile compared to other diabetes drugs. Alogliptin may be more efficacious in Asian populations compared to non-Asian populations. While alogliptin generally has a favorable cardiovascular safety profile, more research is needed to fully understand its potential effects on heart failure. There have been rare reports of bullous pemphigoid and inflammatory bowel disease associated with alogliptin. Alogliptin is a valuable treatment option for patients with T2DM, especially in Asian populations. Its effectiveness, safety profile, and low risk of hypoglycemia make it a suitable choice for many individuals. However, as with any medication.

Inzucchi S.et al., (2015) Researched the Injectable Alogliptin ISGI for Type 2 Diabetes. They developed injectable, long-acting poly (lactide-co-glycolide) (PLGA)-based in situ gel implants (ISGI) loaded with alogliptin. The aim was to achieve sustained therapeutic

exposures and reduce dosing frequency. N-methyl-2-pyrrolidone (NMP) and dimethyl sulfoxide (DMSO) were found to be suitable solvents for ISGI preparation. The composition of PLGA (65:35) and the amount used affected the release rate of alogliptin. The optimized ISGI formulation significantly decreased blood glucose levels in diabetic rats compared to oral alogliptin solution. Reduced dosing frequency of injectable ISGI could potentially reduce the need for frequent dosing of alogliptin, improving patient convenience and compliance. Enhanced therapeutic efficacy sustained to release of alogliptin from ISGI could potentially lead to improved therapeutic outcomes. The ability to optimize the formulation based on individual patient needs could allow for more personalized treatment. Further clinical trials are needed to evaluate the safety and efficacy of injectable alogliptin ISGI in human patients with type 2 diabetes. Investigating the long-term effects of injectable ISGI on glycemic control, quality of life, and cardiovascular outcomes is essential. Exploring the potential benefits of combining injectable ISGI with other diabetes medications could provide additional therapeutic options. The research demonstrates the potential of injectable alogliptin ISGI as a promising approach for the treatment of type 2 diabetes. The ability to provide sustained release and improve glycemic control could offer significant advantages for patients.

Khan MAB et al., (2020) recsearched on Fotagliptin for Type 2 Diabete. Fotagliptin demonstrated superior efficacy in reducing HbA1c levels compared to placebo. Fotagliptin was non-inferior to alogliptin, another DPP-4 inhibitor. A significantly higher proportion of patients treated with fotagliptin or alogliptin achieved HbA1c levels below 7.0% compared to placebo. Both fotagliptin and alogliptin were well-tolerated, with a low incidence of hypoglycemia and no drug-related serious adverse events. Fotagliptin offers a new treatment option for patients with type 2 diabetes. Fotagliptin can effectively improve glycemic control, potentially reducing the risk of diabetes-related complications. The low incidence of adverse events makes fotagliptin a safe option for many patients. While the study lasted 52 weeks, longer-term studies are needed to evaluate the long-term effects of fotagliptin. The study focused on comparing fotagliptin to alogliptin and placebo. Further research is needed to compare fotagliptin to other DPP-4 inhibitors and different classes of diabetes medications. The study provides strong evidence for the efficacy and safety of fotagliptin in treating type 2 diabetes. Fotagliptin offers a promising new treatment option for patients seeking to improve glycemic control.

Buse, J.Bet al., (2015) Researched the Thermal Stability of Alogliptin. The exhibited thermal degradation when subjected to high temperatures. The degradation of alogliptin followed zero-order kinetics, indicating that the degradation rate was independent of drug concentration. The activation energy for alogliptin degradation was calculated to be between 31.0 and 35.9 kcal/mol. The degraded form of alogliptin was less toxic to CRIB cells compared to the undegraded form. The TGA method was found to be faster and more practical than the oven followed by LC-PDA for assessing alogliptin degradation. Understanding the thermal stability of alogliptin is crucial for developing stable formulations and appropriate storage conditions. The activation energy can be used to estimate the shelf life of alogliptin-containing products. The reduced cytotoxicity of degraded alogliptin suggests that the degradation products may be less harmful. The data obtained from this study can be used to optimize the formulation of alogliptin-containing products to enhance stability and reduce degradation. The study focused on a specific temperature range. Additional studies may be needed to evaluate alogliptin's stability at different temperatures. The study did not investigate the effects of different excipients or formulations on alogliptin's thermal stability. This research provides valuable insights into the thermal stability of alogliptin. The data obtained can be used to inform the development of stable formulations and appropriate storage conditions for alogliptin-containing products

Engelgau MM et al., (2014) Research on comparative Effectiveness of Oral Diabetes Agents. Similar glycemic control is most oral diabetes agents (thiazolidinediones, metformin, repaglinide) improved glycemic control to a similar extent as sulfonylureas. Thiazolidinediones increased HDL cholesterol but also increased LDL cholesterol, while metformin decreased LDL cholesterol. Sulfonylureas and repaglinide were associated with a higher risk of hypoglycemia, thiazolidinediones with a higher risk of heart failure, and metformin with a higher risk of gastrointestinal problems. Lactic acidosis was not more common in metformin recipients without comorbid conditions compared to those receiving other oral diabetes agents. Implications for Clinical Practice in older agents like sulfonylureas and metformin may be more cost-effective than newer agents. The choice of oral diabetes agent should be based on individual patient factors, including glycemic control goals, risk factors, and preferences. Larger, long-term studies are needed to compare the effects of oral diabetes agents on hard clinical end points, such as cardiovascular mortality. The review was limited by the availability of data on major clinical end points and the variability in reporting of adverse events across studies. The review did not include newer oral diabetes agents that

have become available since 2006. Overall, the study provides valuable insights into the comparative effectiveness of oral diabetes agents. While older agents like sulfonylureas and metformin may be equally effective and more cost-effective than newer agents, individualized treatment based on patient factors remains crucial. Future research is needed to evaluate the long-term effects of oral diabetes agents on hard clinical end points.

Deacon CF et al., (2012) Made the Research on Alogliptin and Adipose Tissue Insulin Resistance. Among the tested DPP-4 inhibitors, only alogliptin significantly reduced adipose tissue insulin resistance (adipo-IR). Alogliptin also improved certain lipid parameters, including LDL-C, T-C/HDL-C, and non-HDL-C/HDL-C. Patients in the alogliptin group exhibited a heterogeneous response to treatment, with some showing a significant decrease in adipo-IR and others showing an increase. Adipo-IR was associated with non-LDL-C lipid parameters rather than glycemic control in alogliptin-treated patients. The heterogeneous response to alogliptin suggests that a personalized approach may be necessary to optimize treatment outcomes. Alogliptin's ability to improve lipid parameters may have additional cardiovascular benefits. Targeting adipo-IR with alogliptin or other agents may be a promising strategy for improving metabolic health. The study was observational, limiting the ability to establish causality. Sample size was relatively small, and the findings may not generalize to the entire population. The study had a short-term follow-up period, and longer-term studies are needed to evaluate the long-term effects of alogliptin on adipo-IR and other metabolic parameters. This provides evidence that alogliptin may have a beneficial effect on adipose tissue insulin resistance and lipid parameters. However, further research is needed to confirm these findings and to explore the potential clinical implications.

AthaudaNeurobiol et al., (2016) researched on Alogliptin for Parkinson's Disease. Alogliptin, a DPP-IV inhibitor, exhibited neuroprotective effects in a LPS-induced experimental model of Parkinson's disease (PD). Alogliptin attenuated LPS-induced oxidative stress and elevation of neuroinflammatory cytokines. Alogliptin treatment improved motor function deficits in PD rats. Alogliptin helped preserve neuronal morphology in the striatal brain region. The findings suggest that alogliptin may have therapeutic potential for PD patients. Alogliptin's neuroprotective effects may be attributed to its antioxidant and anti-inflammatory properties, as well as its ability to modulate monoaminergic signals. Additional studies are needed to confirm the efficacy and safety of alogliptin in human patients with PD. The study used an experimental model of PD induced by LPS. While this

model provides valuable insights, it may not fully capture the complexity of human PD. The study's sample size may be relatively small, requiring further validation with larger cohorts. Study provides promising evidence for the neuroprotective potential of alogliptin in Parkinson's disease. Further research is warranted to explore its potential therapeutic applications in human patients.

Boyle JP et al., (2014) founded that the oral and Injectable Treatments for Type 2 Diabetes. In the past decade, there have been significant advancements in the treatment of type 2 diabetes, with the introduction of 4 new oral medication classes and 9 new injectable agents/insulin products. Metformin remains the preferred first-line treatment option for most patients with type 2 diabetes. The choice of treatment should be tailored to individual patient characteristics, considering factors such as glycemic control, risk factors, and preferences. The availability of a wider range of oral and injectable medications provides clinicians with more options to address the diverse needs of patients with type 2 diabetes. Tailoring treatment to individual patients can improve glycemic control and reduce adverse events. Continuous evaluation has given the evolving landscape of diabetes treatments, clinicians should stay updated on the latest research and guidelines to ensure optimal patient care. The study focused on information from 1993 to 2014, and newer developments may have occurred since then. Some studies may have limitations in terms of sample size, study design, or duration of follow-up. The study provides a valuable overview of the available oral and injectable treatments for type 2 diabetes. It highlights the importance of individualized treatment and the need for clinicians to stay informed about the latest developments in this field.

DeFronzo RA et al., (2018). Researched the Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control. DPP-4 Inhibitor for Type 2 Diabetesof Alogliptin is an oral antidiabetic medication approved in many countries to treat type 2 diabetes mellitus (T2DM). It works by inhibiting dipeptidyl peptidase-4 (DPP-4), an enzyme that breaks down incretin hormones. This leads to increased insulin secretion and decreased glucagon levels, helping to lower blood sugar. Efficacy and Safety is effective both as a monotherapy and when combined with other antidiabetic medications like metformin and pioglitazone. It is generally well-tolerated, with a low risk of hypoglycemia, weight gain, acute pancreatitis, and gastrointestinal side effects. Studies have shown a favorable safety profile compared to other diabetes drugs. Specific considerations of

Ethnic Differences in Alogliptin has been shown to be more efficacious in Asian patients than in non-Asian patients with T2DM. Cardiovascular Risk while alogliptin has a generally favorable cardiovascular safety profile, further research is needed to fully understand its potential effects on heart failure. There have been reports of bullous pemphigoid and inflammatory bowel disease associated with alogliptin. Alogliptin is a valuable treatment option for patients with T2DM, especially in Asian populations. Its effectiveness, safety profile, and low risk of hypoglycemia make it a suitable choice for many individuals. However, as with any medication, it's important to discuss the potential benefits and risks with your healthcare provider to determine the best treatment plan for you.

C.I. Jarvis et al., (2013) preferred Spectrophotometric Methods for Alogliptin Determination with Two novel methods. The researchers developed two visible spectrophotometric methods (A and B) for the determination of alogliptin. Both methods are based on the bromination of alogliptin using bromine produced from a bromate-bromide mixture. The residual bromine is determined by measuring the absorbance of either methyl orange (method A) or methylene blue (method B) at specific wavelengths. The methods were validated for linearity, accuracy, precision, and detection limit. The methods were successfully applied to the determination of alogliptin in tablet formulations. Implications for Quality Control by simple and sensitive methods offer a simple and sensitive approach for the quality control of alogliptin in pharmaceutical formulations. The validated methods demonstrate high accuracy and precision, making them suitable for routine analysis. The methods can be adapted for use in different laboratories and settings. Comparing these methods to other established methods for alogliptin determination can provide insights into their relative advantages and disadvantages. Investigating the potential effects of excipients and other components in tablet formulations on the accuracy of the methods could be beneficial. Exploring the possibility of automating these methods could improve efficiency and reduce the risk of human error. The research provides a valuable contribution to the field of analytical chemistry by introducing two new and reliable spectrophotometric methods for the determination of alogliptin. These methods can be used for quality control purposes in the pharmaceutical industry.

A.B. Marino et al.,(2015) A Promising Treatment for Type 2 Diabetes via Alogliptin a medication that belongs to the class of drugs called dipeptidyl peptidase-4 (DPP-4) inhibitors. It is used to treat type 2 diabetes.Alogliptin works by increasing the levels of a hormone called glucagon-like peptide-1 (GLP-1) in the body. GLP-1 helps the body produce more

insulin and use it more effectively, leading to lower blood sugar levels. Effective glycemic control have shown that alogliptin can effectively lower blood sugar levels in patients with type 2 diabetes, both as monotherapy and in combination with other diabetes medications. Alogliptin has a generally good safety profile, with a low risk of hypoglycemia and weight gain. Alogliptin is generally well-tolerated by patients, with few serious side effects.

Clinical trials: Alogliptin has undergone extensive clinical testing, including Phase II and III studies, which have demonstrated its efficacy and safety in treating type 2 diabetes. Overall, alogliptin is a promising treatment option for type 2 diabetes. Its ability to improve glycemic control while maintaining a favorable safety profile makes it a valuable addition to the therapeutic arsenal for this condition.

Aroda VR et al., (2011) The safety and tolerability of GLP-1 receptor agonists in the treatment of type 2 diabetes DPP-4 Inhibitor for Type 2 Diabetes. Alogliptin is a medication used to treat type 2 diabetes. It belongs to a class of drugs called dipeptidyl peptidase-4 (DPP-4) inhibitors. How it works: Alogliptin increases the levels of a hormone called glucagon-like peptide-1 (GLP-1) in the body. GLP-1 helps the body produce more insulin and use it more effectively, leading to lower blood sugar levels. Effective glycemic control has been shown to improve blood sugar control when used as monotherapy or in combination with other diabetes medications. Alogliptin is generally well-tolerated, with a low risk of hypoglycemia and weight gain. Studies have shown that alogliptin is not associated with an increased risk of major cardiovascular events. Alogliptin is available as a single agent. Fixed-dose combinations is also available in combination with metformin (Kazano®, Vipdomet®) and pioglitazone (Oseni®, Incresync®). Overall, alogliptin is a versatile and effective treatment option for type 2 diabetes. It offers good glycemic control, a favorable safety profile, and can be used as monotherapy or in combination with other diabetes medications.

Shaw JE et al., (2010) Alogliptin is a Versatile Treatment for Type 2 Diabetes. Alogliptin is a medication used to treat type 2 diabetes. It belongs to a class of drugs called dipeptidyl peptidase-4 (DPP-4) inhibitors. Effective glycemic control has been shown to improve blood sugar control when used as monotherapy or in combination with other diabetes medications. Alogliptin is generally well-tolerated, with a low risk of hypoglycemia and weight neutrality. The EXAMINE trial demonstrated that alogliptin is not associated with an increased risk of major cardiovascular events. Alogliptin is available as a single agent.Fixed- dose

combinations is also available in combination with metformin (Kazano®, Vipdomet®) and pioglitazone (Oseni®, Incresync®).Overall, alogliptin is a versatile and effective treatment option for type 2 diabetes. It offers good glycemic control, a favorable safety profile, and can be used as monotherapy or in combination with other diabetes medications.

J. Biol. Chem et al., (2016) Research that the Alogliptin effectively inhibited DPP-4 enzyme activity, leading to a significant increase in active GLP-1 levels. Chronic alogliptin treatment resulted in reduced glycosylated hemoglobin, plasma glucose, and triglycerides. The study demonstrated that alogliptin improved early-phase insulin secretion, increased pancreatic insulin content, and induced intense insulin staining in islets.Neutral Effects on Body Weight and Food Consumption of Alogliptin did not significantly alter body weight or food intake. Implications for Type 2 Diabetesare based on these findings, alogliptin and other DPP-4 inhibitors may be promising therapeutic options for patients with type 2 diabetes. By increasing GLP-1 levels, these drugs can enhance insulin secretion and reduce blood sugar levels.Reduce cardiovascular risk lowering triglyceride levels may contribute to a decreased risk of heart disease. By promoting insulin production and secretion, DPP-4 inhibitors could potentially slow the progression of beta-cell dysfunction, a hallmark of type 2 diabetes. To fully understand the long-term effects of alogliptin and other DPP-4 inhibitors, larger, randomized controlled trials are needed. Investigating the potential benefits of combining DPP-4 inhibitors with other diabetes medications, such as metformin or insulin, could provide additional insights into their efficacy. Further research is required to elucidate the precise mechanisms by which alogliptin improves beta-cell function and reduces cardiovascular risk. The study provides compelling evidence that alogliptin and other DPP-4 inhibitors offer a promising approach to managing type 2 diabetes. Their ability to improve glycemic control, enhance beta-cell function, and potentially reduce cardiovascular risk makes them valuable additions to the therapeutic arsenal for this condition.

Slavkova M, et al.,(2015) developed the ODTs did not improve medication adherence compared to non-ODT formulations in patients with post-stroke dysphagia. There were no notable differences in cardiovascular events or aspiration pneumonia between patients taking ODTs and those taking non-ODT medications. Both groups achieved a high proportion of days covered, exceeding 80%.Implications for Clinical Practice. Clinicians may choose to prescribe ODTs or non-ODT formulations based on patient preferences rather than relying solely on the presence of dysphagia. Other factors, such as patient's overall condition,

caregiver support, and medication regimen complexity, may influence medication adherence and clinical outcomes more significantly than the choice of formulation. Examining specific subgroups of patients with post-stroke dysphagia, such as those with severe swallowing difficulties or those taking multiple medications, could provide more insights into the potential benefits of ODTs. Evaluating the long-term effects of ODTs on medication adherence, clinical outcomes, and quality of life in patients with post-stroke dysphagia could provide valuable information for clinical decision-making. Investigating the efficacy of other formulations, such as liquid or enteral medications, in patients with post-stroke dysphagia could help identify alternative options for those who struggle with swallowing. Overall, the study suggests that ODTs do not offer a significant advantage over non-ODT formulations in improving medication adherence or clinical outcomes in patients with post-stroke dysphagia. While ODTs may be a convenient option for some patients, clinicians should consider a variety of factors when making prescribing decisions.

HeafJG, et al.,(2017) developed the oral pharmacotherapy for patients with type 2 diabetes who fail to achieve adequate glycemic control through lifestyle modifications, oral pharmacotherapy should be added. Metformin is recommended as the initial pharmacologic treatment for most patients with type 2 diabetes. If monotherapy with metformin fails to control hyperglycemia, a second agent should be added. The guideline is based on a systematic review of the literature published from 1966 to 2010. The review evaluated a range of clinical outcomes, including mortality, morbidity, and complications associated with type 2 diabetes. The recommendations are supported by high-quality evidence. Implications for Clinical Practice for metformin should be considered the first-line treatment option for most patients with type 2 diabetes. If metformin alone is insufficient, combining it with a second agent can help achieve better glycemic control. The choice of medication should be tailored to the individual patient's needs and preferences, considering factors such as risk factors, comorbidities, and tolerability. The guideline is based on literature published up to 2010, and newer studies may have emerged since then. The guideline primarily focuses on oral pharmacotherapy and may not address all available treatment options, such as injectable medications or newer drug classes. The ACP guideline provides valuable recommendations for the management of type 2 diabetes. It emphasizes the importance of metformin as a first-line treatment and highlights the need for a personalized approach to therapy.

Milano S et al., (2013) developedsuccessful treatment fororal disintegrating DDAVP was

effective in reducing polyuria and polydipsia in a patient with partial congenital NDI. The patient experienced a decrease in urine output and water intake, leading to an increase in body weight. The treatment was well-tolerated, with no reported side effects. Implications for Clinical Practice are potential treatment option for oral disintegrating DDAVP may be a promising treatment option for patients with partial congenital NDI, especially those who are unable or unwilling to receive subcutaneous injections. The optimal dosage of DDAVP will likely vary depending on the severity of NDI and individual patient factors. Further studies with a larger number of patients are needed to confirm the efficacy and safety of oral disintegrating DDAVP in treating congenital NDI. Research should investigate whether DDAVP therapy is effective in patients with more severe forms of congenital NDI. Exploring the potential benefits of combining DDAVP with other treatments, such as thiazide diuretics or amiloride, may be warranted in some cases. The case report provides encouraging evidence for the use of oral disintegrating DDAVP in patients with partial congenital NDI. While more research is needed to fully understand its efficacy and safety, this treatment option may offer hope for individuals with this rare condition.

Urol Ann. 2023 formulatedan oral formulation: CDI patients generally prefer the oral desmopressin ODT to the intranasal formulation. Both formulations maintained similar serum sodium levels. The incidence of hyponatremia, particularly severe hyponatremia, was significantly lower with desmopressin ODT compared to intranasal desmopressin. Given the patient preference for oral formulations and the reduced risk of hyponatremia, desmopressin ODT may be considered a more suitable treatment option for CDI patients. The optimal dosage of desmopressin ODT may vary depending on the severity of CDI and individual patient factors. Monitoring for hyponatremia for Close monitoring of serum sodium levels is important, especially during the initial adjustment to desmopressin ODT therapy. Further studies with a larger number of patients are needed to confirm the long-term efficacy and safety of desmopressin ODT in treating CDI. Comparing desmopressin ODT to other potential treatments for CDI, such as non-drug therapies or experimental approaches, could provide valuable insights. Evaluating the cost-effectiveness of desmopressin ODT compared to intranasal desmopressin can help inform clinical decision-making. The study suggests that desmopressin ODT is a promising alternative to intranasal desmopressin for the treatment of CDI. Its efficacy in controlling water balance and reducing the risk of hyponatremia make it a valuable option for patients with this condition.

N. Englet al.,(2013). Desmopressin ODT was as effective as intranasal desmopressin in maintaining antidiuresis. The proportion of patients with endpoint measurements within normal range was comparable between the two formulations. The optimal dose ratio of intranasal desmopressin to desmopressin ODT varied widely among patients, emphasizing the need for individual titration. Hyponatremia was generally mild and manageable through dose titration. Desmopressin ODT can be considered a suitable alternative to intranasal desmopressin for the treatment of CDI, offering patients the convenience of oral administration. Clinicians should be prepared to adjust the dosage of desmopressin ODT based on individual patient responses and the severity of CDI. Close monitoring of serum sodium levels is essential, particularly during the initial adjustment to desmopressin ODT therapy.

Future Research Directions. Further studies are needed to evaluate the long-term efficacy and safety of desmopressin ODT in treating CDI. Comparing desmopressin ODT to other potential treatments for CDI, such as non-drug therapies or experimental approaches, could provide valuable. Evaluating the cost-effectiveness of desmopressin ODT compared to intranasal desmopressin can help inform clinical decision-making. Overall, the study provides strong evidence for the efficacy and safety of desmopressin ODT in the treatment of CDI. Its ability to maintain antidiuresis and the convenience of oral administration make it a promising option for patients with this condition.

White, W. B. et al (2013) found that no significant difference in primary outcome: Early initiation of alogliptin did not reduce the risk of major cardiovascular events in subjects with type 2 diabetes. A post hoc analysis suggested that subjects who received DPP-4 inhibitors before a cardiovascular event had a lower risk of recurrent events compared to those who did not. While early alogliptin initiation did not show a significant benefit in reducing cardiovascular risk in this study, it may still be considered a reasonable strategy based on its potential to improve glycemic control and other metabolic factors. The post hoc analysis suggests that DPP-4 inhibitors may be beneficial in reducing the risk of recurrent cardiovascular events in patients who have already experienced a cardiovascular event.

Larger studies with longer follow-up periods are needed to confirm or refute the findings of this study. Examining specific subgroups of patients, such as those with different levels of cardiovascular risk or baseline glycemic control, could provide additional insights. Investigating the potential benefits of combining alogliptin with other diabetes medications or

cardiovascular therapies could help optimize patient outcomes. While the study did not demonstrate a clear benefit of early alogliptin initiation in reducing cardiovascular risk in subjects with type 2 diabetes, it does suggest that DPP-4 inhibitors may play a role in secondary prevention. Further research is needed to fully understand the potential benefits and risks of these agents.

Meece J et al., (2017)- Pancreatic islet dysfunction in type 2 diabetes: a rational target for incretin-based therapies. A DPP-4 Inhibitor for Type 2 Diabetes alogliptin is a medication used to treat type 2 diabetes. It belongs to a class of drugs called dipeptidyl peptidase-4 (DPP-4) inhibitors. Alogliptin helps increase the levels of a hormone called glucagon-like peptide-1 (GLP-1) in the body. GLP-1 helps the body produce more insulin and use it more effectively, leading to lower bloodsugar levels. Alogliptin has been shown to lower blood sugar levels, as measured by fasting plasma glucose and glycosylated hemoglobin (HbA1c). In general, alogliptin is well-tolerated, with a similar incidence of hypoglycemia compared to placebo. Alogliptin does not appear to significantly affect body weight or lipid parameters. Alogliptin is approved in Japan for the treatment of type 2 diabetes, either alone or in combination with other diabetes medications. Further studies are needed to establish the long-term safety and efficacy of alogliptin therapy, as well as its potential role in preventing cardiovascular complications. Alogliptin is a promising treatment option for type 2 diabetes. It offers effective blood sugar control with a favourable safety profile. However, more research is needed to fully understand its long-term benefits and risk.

3. AIM AND OBJECTIVES

AIM

The aim of this thesis is to develop and optimize a formulation for orally disintegrating tablets (ODTs) of Alogliptin using a systematic approach that ensures rapid disintegration, high mechanical strength, and efficient drug release, thus enhancing patient compliance and therapeutic efficacy.

OBJECTIVES

- To develop and optimize Alogliptin ODTs using direct compression.
- To apply Design of Experiment (DoE) for optimizing formulation parameters.
- To assess the optimized tablets for disintegration, hardness, and dissolution.

Plan of work Review of literature

- Selection of drug and excipients

Preformulation studies

- Melting point
- Solubility analysis
- Calibration curve
- Compatibility study using FTIR

Formulation of oral disintegrating tablets

- pre-screening of critical formulation factors
- Central Composite Design (CCD)

Evaluation of Powder Blend

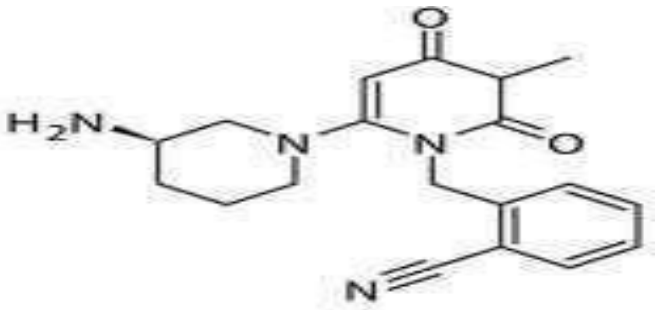
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio
- Angle of repose

Evaluation of post-compression parameters

- Tablet thickness
- Weight variation
- Hardness
- Friability
- Disintegration time
- *In vitro* dissolution study

4. DRUGPROFILE

5. ALOGLIPTIN: STRUCTURE



Alogliptin

Chemical Name: (2- ({6- [(3R) -3- aminopiperidin- 1- yl] -3 –methyl -2, 4-dioxo-1,2,3,4-tetrahy dropyrimidin-1-yl} methyl) benzonitrile)

Molecular Formula: C18H21N5O2

Molecular Weight : 339.39 g/mol

Chemical Structure : Alogliptinisapyrimidinedione-basedDPP-4inhibitor.

Physical Properties

Appearance : White to off -white powder.

Melting Point : Approximately 214-216 °C.

Solubility : Alogliptiniss lightly solublein water, and its solubility improves inorganic solve nts suchas methanol, ethanol, and DMSO.

LogP :1. 3, indicatingmoderatelipophilicity.

pKa: 8. 7, meaningitisweakly basic.

TherapeuticCategory

Class : Dipeptidyl Peptidase-4 (DPP-4) inhibitor.

Use : Alogliptinis primarily used to manage type 2 diabetes mellitus by regulating blood glucose levels.

Mechanism of Action

Alogliptin works by inhibiting theen zyme DPP-4, which is responsible for the degradation of incretin hormones like GLP-1 and GIP. These hormones help to regulate insulin secretion in response to meals, and their inhibition leads to increased insulin release, reduced glucagon secretion, and improved glycemic control.

Pharmacokinetics

Absorption: Alogliptin is well absorbed orally, with a bioavailability of approximately 100%. Time to peak concentration (Tmax): 1 to 2 hours.

Distribution: It has a moderate volume of distribution (about 417 L). Protein Binding: Approximately 20%.

Metabolism: Alogliptin is minimally metabolized, with most of the drug excreted unchanged.

Half-Life : The half-life of alogliptin is around 21 hours.

Excretion : Primarily eliminated via the urine, with about 60-70% of the dose excreted unchanged.

Indications

Type 2 Diabetes Mellitus: Alogliptin is prescribed as monotherapy or in combination with other antidiabetic agents like metformin, sulfonylureas, or insulin to improve glycemic control.

Dosage

Standard Dosage: 25 mg once daily.

Renal Impairment: Dosage adjustments are necessary for patients with moderate to severe renal impairment.

Side Effects

Common: Nasopharyngitis, headache, upper respiratory tract infection.

Serious: Hypersensitivity reactions, pancreatitis, hepatic impairment, and heart failure (risk in specific populations).

Drug Interactions

CYP Enzyme Interactions: Alogliptin is not a major substrate or inhibitor of CYP enzymes, so significant drug-drug interactions are rare.

Concomitant use with Insulin: May increase the risk of hypoglycemia, especially in combination with insulin or insulin secretagogues (e.g., sulfonylureas).

Warnings and Precautions

Cardiovascular Risk: There is a potential increased risk of heart failure in some patients.

Hepatic Dysfunction: Alogliptin has been associated with rare cases of liver injury.

Pancreatitis: Patients should be monitored for signs of pancreatitis, as DPP-4 inhibitors may increase the risk.

Contraindications

Type 1 Diabetes: Not indicated for type 1 diabetes.

Diabetic Ketoacidosis: Alogliptin should not be used in patients with diabetic ketoacidosis.

Marketed Formulations

Brand Name: Nesina.

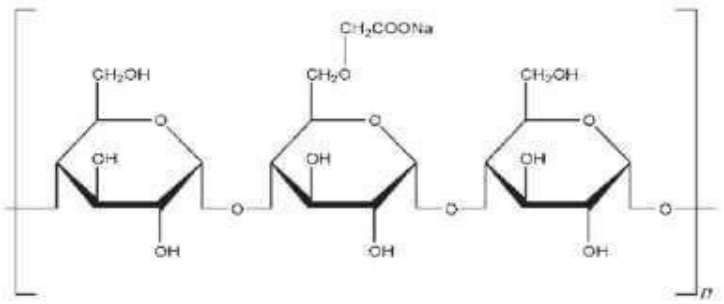
Combination Products: Often co-formulated with metformin (Kazano) or with pioglitazone (Oseni).

6. POLYMER PROFILE

6.1 SODIUM STARCH GLYCOLATE

Sodium Starch Glycolate (SSG (SSG) is a commonly used pharmaceutical excipient, especially as a disintegrant in tablet formulations. It is derived from starch, usually potato starch, and is chemically modified to enhance its properties. Sodium starch glycolate is a cross- linked polymer of potato starch. It consists of repeating units of glucose molecules, connected by glycosidic bonds, and modified by carboxymethyl groups. The sodium salt of the carboxymethyl groups is responsible for its improved solubility and water-absorbing properties.

1. Molecular Structure



Molecular Formula: (C6H10O5)n

2. Physical Properties

Appearance : White to off-white, odorless, fine, free-flowing powder.

Solubility : Insoluble in water but rapidly swells and absorbs water.

Swelling is essential for its disintegration action.

Particle Size : Typically ranges from 30 to 100 microns.

Density : Bulk density is approximately 0.75 g/cm³.

PhWhen dispersed in water, the pH of a 1% solution is usuallyaround 5.5-7.5.

Moisture Content : Generally contains around 10% moisture, though this can vary slightly.

3. Chemical Properties

Functional Groups: Hydroxyl groups (-OH) from glucose units. Carboxymethyl groups (-CH2COONa), which provide the disintegrant properties.

Cross-linking: Cross-linking between starch molecules prevents the compound from being too soluble while allowing it to swell and absorb water.

Hydrophilic Nature: Its water-absorbing capacity increases due to the sodium carboxymethyl groups, making it effective as a tablet disintegrant.

Pharmaceutical Use

Role: It is primarily used as a disintegrant in tablet formulations, ensuring that the tablet breaks apart in the digestive tract for rapid drug release.

Mechanism of Action: Sodium starch glycolate works by swelling upon contact with water, whichcauses the tablet to break apart (disintegrate). This allows the active drug to dissolve and becomeavailable for absorption.

Concentration Used: Typically used at a concentration of 2-8% w/w in tablet formulations.

Applications

Direct compression formulations. Wet granulation formulations.

Compatibility: Compatible with most active pharmaceutical ingredients (APIs) and excipients.

Pharmacokinetics

Absorption: Sodium starch glycolate itself is not absorbed in the gastrointestinal tract since it is anexcipient, not an active drug.

Metabolism: It remains unchanged in the gastrointestinal tract. Excretion: It is excreted unchanged in feces.

Safety and Toxicity

Non-toxic: Generally regarded as safe (GRAS) by regulatory agencies like the FDA.

Allergenicity: It is derived from starch, but modifications generally reduce allergenic potential. Irritation: Rare cases of hypersensitivity are reported, but it is generally well-tolerated.

Incompatibility: Avoid use with strong acids and bases, as they can affect its disintegration properties.

5. Advantages in Formulations:

Rapid Disintegration: Provides quick disintegration and thus fast dissolution of the drug. Wide Compatibility: Works with a wide range of APIs.

Cost-Effective: Relatively inexpensive and easy to produce.

6. Limitations

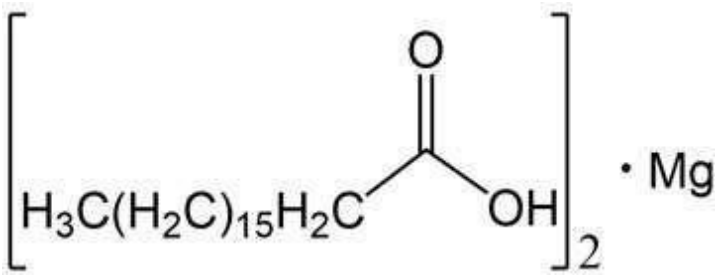
Moisture Sensitivity: Can absorb moisture, which may affect the stability of some formulations. Swelling Limitations: Swelling can lead to tablet expansion or deformation if used in large quantities.

7. Alternatives

Croscarmellose sodium and crospovidone are other commonly used disintegrants in tablet formulations that work similarly to sodium starch glycolate.

6.2 MAGNESIUM STEARATE

Molecular Structure



Chemical Formula : C36H70MgO4

Molecular Weight : 591.24 g/mol

Structure Description : Magnesium stearate is a salt formed from the reaction of stearic acid (C18H36O2) with magnesium oxide. It has a magnesium ion (Mg^{2+}) bonded to two stearate anions ($C18H35O2^{-}$). The long hydrocarbon chains of the stearate provide its hydrophobic

properties.

Physical Properties

Appearance : White, fine powder.

Melting Point : 88-92 °C.

Solubility : Insoluble in water and ethanol; soluble in hot ethanol.

Density : 1.09 g/cm^3.

Odor : Slight fatty odor.

Chemical Properties

Stability: Magnesium stearate is stable under normal conditions but can decompose at higher temperatures.

Incompatibility: Incompatible with strong oxidizing agents, acids, and water (forms stearic acid andmagnesium salts).

Decomposition: On heating, it decomposes, producing toxic fumes of magnesium oxide and organicvapors.

Classification : Lubricant and anti-adherent.

Uses in Pharmaceuticals

Magnesium stearate is widely used as a flow agent in the production of tablets, capsules, and powders. It helps prevent ingredients from sticking to manufacturing equipment and ensures consistent tablet formulation. It acts as a lubricant, improving the flow of powder blends in the tablet-making process.

Pharmacokinetics

Absorption: Magnesium stearate is not significantly absorbed through the gastrointestinal tract. Metabolism: The stearate part can undergo normal fatty acid metabolism.

Excretion: Any unabsorbed magnesium stearate is excreted through feces.

Toxicity and Safety

General Safety: Magnesium stearate is considered safe for use in pharmaceuticals at low concentrations. It is included in the FDA's list of substances generally recognized as safe (GRAS).

Toxicity: Excessive use or exposure to very high doses may lead to gastrointestinal discomfort orrespiratory irritation.

Allergy Risks: Rare reports of hypersensitivity reactions have been noted, but generally, it has a lowrisk of causing allergic reactions.

Applications

Pharmaceutical Industry: As a lubricant and anti-adherent, it is found in tablets, capsules, and vitamin supplements.

Cosmetics: Used in powders to improve consistency.

Food Industry: Functions as an anti-caking agent in powdered food products. Common Drug Formulations Containing Magnesium Stearate:

Tablets (oral medications): Acts as a lubricant to facilitate the tablet-making process. Capsules: Helps in the smooth encapsulation of the powder or active ingredients.

Supplements: Used in vitamins to ensure that tablets or capsules can be pressed consistently.

Side Effects

Magnesium stearate is generally well-tolerated at low concentrations. Potential Side Effects: Gastrointestinal issues if consumed in large quantities.

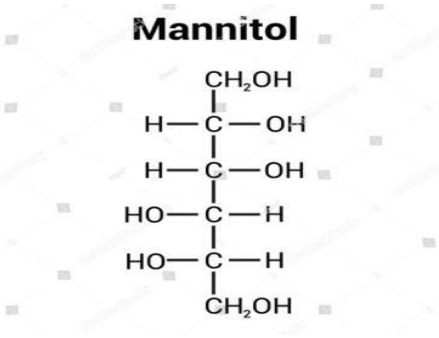
Respiratory problems (rare) if inhaled as a fine powder during manufacturing.

CONCLUSION

Magnesium stearate plays a crucial role as an excipient in pharmaceutical formulations, ensuring smooth manufacturing processes without altering the therapeutic properties of active ingredients. It is considered safe when used appropriately and contributes to the stability and uniformity of pharmaceutical products.

6.3 MANNITOL

1. Molecular Structure



Chemical Formula : $C_6 H_{14} O_6$

Molecular Weight : 182.17 g/mol

Structure : Mannitol is a hexahydroxy alcohol (sugar alcohol) with six carbon atoms, each bearing a hydroxyl (-OH) group. It has a linear structure in which the hydroxyl groups are arranged symmetrically around the carbon backbone.

2. Physical Properties

Appearance : White, odorless, crystalline powder

Melting Point : 165-168°C

Solubility : Soluble in water (18% at 25°C); practically insoluble in ether and chloroform

Taste : Mildly sweet

Stability : Stable under normal conditions; non-hygroscopic, meaning it does not absorb moisture from the air easily.

3. Chemical Properties

Polarity : Mannitol is polar due to the presence of multiple hydroxyl groups, making it highly soluble in water.

Ph : Neutral in aqueous solution

Chemical Reactivity : Mannitol is relatively inert, but it can participate in oxidation reactions under certain conditions.

Compatibility It is generally compatible with various drugs and excipients, making it suitable for use as a diluent in pharmaceuticals.

4. Pharmacology and Mechanism of Action

Drug Class : Osmotic diuretic Mechanism: Mannitol works by increasing the osmotic pressure in the renal tubules, which inhibits water reabsorption, causing diuresis (increased

urine output). This process reduces fluid volume, which is particularly beneficial for reducing intracranial or intraocular pressure.

5. Drug Profile

Indications

- Cerebral edema (to reduce intracranial pressure)
- Acute kidney failure (to improve urine output)
- Reduction of intraocular pressure in glaucoma
- Prevention of renal failure during surgery or traumatic injury

Administration: Commonly administered intravenously as a solution in clinical settings. Dosage: Dosage varies depending on the indication, but it is typically based on body weight and adjusted according to patient response. Onset of Action: Rapid, within 15–30 minutes of intravenous administration.

Duration of Action: Effects can last up to 6 hours.

Side Effects

- Electrolyte imbalance
- Dehydration
- Hypotension
- Kidney dysfunction at high doses

Contraindications

- Severe dehydration
- Congestive heart failure
- Pulmonary edema

Drug Interactions: Mannitol should be used cautiously with other diuretics and medications that affect renal function.

6. Clinical Pharmacokinetics

Absorption: Not absorbed from the gastrointestinal tract when administered orally, which limits its use to IV administration.

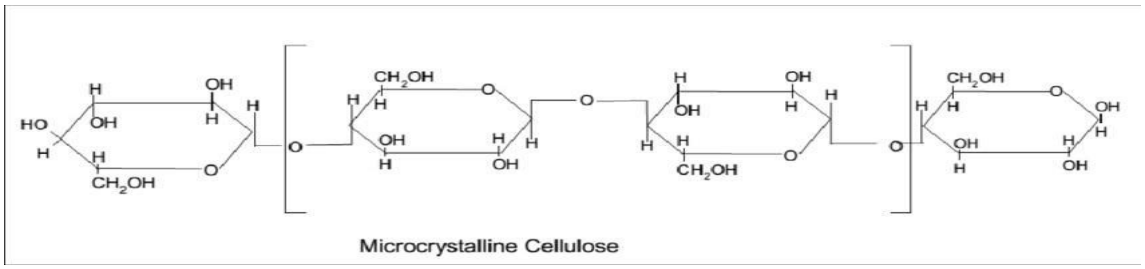
Distribution: Distributes mainly in the extracellular fluid compartment. Metabolism:Mannitol

is not significantly metabolized in the body.

Excretion: Primarily excreted unchanged by the kidneys.

Mannitol is widely used in clinical settings due to its effectiveness as an osmotic diuretic, especially in acute conditions requiring rapid reduction of fluid pressures.

4. MICROCRYSTALLINE CELLULOSE



Chemical Formula: $(C_6 H_{10} O_5)_n$ **Molecular Structure**

Physical Properties

MCC is a polysaccharide composed of glucose units linked through β-1,4-glycosidic bonds, forming a crystalline structure. The degree of polymerization (DP) in MCC is lower than in natural cellulose, ranging from 125 to 375, making it a fine powder.

Appearance : White, odorless, tasteless powder.

Particle Size : 20-250 microns, depending on the grade.

Bulk Density : 0.28 to 0.45 g/mL.

Specific Surface

Area : High surface area due to its fine particle size, aiding in compressibility.

Insolubility : Insoluble in water, organic solvents, and diluted acids but swells slightly in water.

Melting Point : Decomposes around 260-270°C without melting.

Chemical Properties

Stabilit : Chemically inert and stable under various conditions. pH : Neutral to slightly acidic, ranging from 5.0 to 7.5.

Incompatibility : Generally compatible with most drugs, but may have interactions with strong acids or oxidizing agents.

Degradation: Non-toxic and biodegradable, degraded by cellulase enzymes.

Pharmaceutical Uses

Excipient: Primarily used as a binder, filler, and disintegrant in tablet formulations due to its compressibility and binding properties.

Suspending Agent : Used in suspensions and emulsions to prevent settling.

Drug Delivery : Enhances the stability and bioavailability of drugs by providing a solid matrix that can control the release rate.

Applications in Controlled Release: Used to modify drug release profiles, especially in sustained- release formulations.

Advantages in Drug Formulation

- High Binding Capacity:MCC binds well with other excipients, resulting in strong tablets with minimal friability.
- Improved Flow Properties: It enhances powder flowability, essential for consistent tablet production.
- Inert and Non-reactive: Compatible with most drugs and other excipients, minimizing drug-excipient interaction risks.
- Enhanced Bioavailability:MCC's high surface area can improve the dissolution rate of poorly soluble drugs.

Common Drugs with MCC as an Excipient

Microcrystalline cellulose is used in formulations of various drugs, including:

- Analgesics: Acetaminophen, Ibuprofen.
- Antibiotics: Amoxicillin, Ciprofloxacin.
- Antidepressants: Sertraline, Fluoxetine.
- Antihypertensives: Lisinopril, Atenolol

Summary

Microcrystalline cellulose is a versatile, chemically stable, and biocompatible excipient, widely used in the pharmaceutical industry for its mechanical properties, which aid in creating robust, consistent drug delivery systems.

7. METHODOLOGY

1. Preformulation

Preformulation studies can be described as laboratory investigations aimed at identifying the properties of active pharmaceutical ingredients (APIs) and excipients that may affect the

design, development, and performance of a formulation and its manufacturing process. (Patel BP, Patel JK, Rajput GC, Thakor RS. Formulation and evaluation of mouth dissolving tablets of cinnarizine. Indian J Pharm Sci. 2010 Jul;72(4):522-5. doi: 10.4103/0250-474X.73930. PMID: 21218071; PMCID: PMC3013568.**)**

7.1 Melting point

To determine the melting point of alogliptin, a capillary tube was filled with approximately 3 mm of the substance. The open end of the capillary tube was inserted into the alogliptin, and it was gently tapped. The prepared capillary tube was then placed into the melting point apparatus, which was set to a high enough level for a rapid preliminary determination of the melting point. The melting process was observed through the magnifying lens(Yi D, Ma J, Wu H, Zhu K, Wang K, Cao R, Zhang P, Li T, Ren B. Solubility and thermodynamic properties of Alogliptin Benzoate form A in different mono-solvents. The Journal of Chemical Thermodynamics. 2021 Aug 1;159:106474.)

7.2 Solubility

The solubility of alogliptin was determined using the shake flask method with methanol, water, DMSO, and 0.01N HCl as solvents. Excess alogliptin (approximately 10-50 mg) was accurately weighed and added to separate test tubes, each containing 10 ml of one of the solvents. The test tubes were sealed and placed in a shaking incubator set at 25°C, shaking at a consistent speed of 150-200 rpm for 24 hours to ensure equilibrium. After the incubation period, the solutions were filtered through a 0.45 µm membrane filter to remove any undissolved particles. The filtered solutions were then analyzed using UV spectrophotometry to measure the concentration of dissolved alogliptin. The solubility of alogliptin in each solvent was calculated based on the concentration of the dissolved drug in the filtered solutions (Yadav PJ, Kadam VN, Mohite SK. Development and validation of UV spectrophotometric method for alogliptin benzoate in bulk drug and tablet formulation. Journal of Current Pharma Research. 2014 Jul 1; 4(4): 1286. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022271Orig1s000ClinPharmR.pdf).

7.3 Calibration curve

To prepare and analyze alogliptin using UV spectrophotometry, 50 mg of alogliptin was accurately weighed and transferred into a 50 ml volumetric flask. Methanol was added to the flask, and the solution was sonicated for five minutes to ensure complete dissolution of the drug. The volume was then made up to 50 ml with methanol, resulting in a standard stock

solution containing 1 mg/ml of alogliptin. An appropriate volume of this stock solution was pipetted out and diluted with water to achieve a final concentration of 20 µg/ml. The diluted solution was then scanned using a UV spectrophotometer over the range of 400 to 200 nm, and the absorption spectrum was recorded to determine the λ_{max}(wavelength of maximum absorbance) for alogliptin.The stock solution was then diluted to a concentration from 5 to 30µg/ml. The absorbance of the solution was then measured at λ_{max}. (Monteiro PF, Silva-Barcellos NM, Caldeira TG, Reis AC, Ribeiro AS, Souza JD. Effects of experimental conditions on solubility measurements for BCS classification in order to improve the biowaiver guidelines. Brazilian Journal of Pharmaceutical Sciences. 2021 Nov 26;57:e181083.).

7.4 Compatibility studies

FT-IR spectra were recorded using a Shimadzu FT-IR 8400S spectrometer, operating within the frequency range of 400-4000 cm^{-1} with a resolution of 4 cm^{-1}. The analysis employed the potassium bromide (KBr) disc technique. The samples, which included both individual components and a blend of the drug with the specified excipients, were finely pulverized and mixed with KBr for approximately 3-5 minutes using a mortar and pestle. The resulting mixture was then compressed into discs under a pressure of 5 tons for 5 minutes using a hydraulic press. The concentration of the sample in the KBr matrix ranged between 0.2% and 1%. These prepared pellets were positioned in the instrument's light path, and the spectra obtained were carefully examined to identify any potential interactions. Stulzer, H.K.; Tagliari, M.P.; Cruz, A.P.; Silva, M.A.S.; Laranjeira, M.C.M. Compatibility studies between piroxicam and pharmaceutical excipients used in solid dosage forms. *Pharm. Chem. J.* **2008**, *42*, 215– 219.

Kozakiewicz-Latała M, Junak A, Złocińska A, Pudło W, Prusik K, Szymczyk-Ziółkowska P, Karolewicz B, Nartowski KP. Adjusting the melting point of an Active Pharmaceutical Ingredient (API) via cocrystal formation enables processing of high melting drugs via combined hot melt and materials extrusion (HME and ME). Additive Manufacturing. 2022 Dec 1;60:103196.

7.5 Formulation

The preparation of alogliptin oral dispersible tablets was carried out using the direct compression method. The required quantities of alogliptin, sodium starch glycolate,

microcrystalline cellulose, mannitol, and magnesium stearate were accurately weighed. All ingredients were then sieved through a #40 mesh to achieve a uniform particle size and to eliminate any lumps. The weighed ingredients, excluding magnesium stearate, were blended thoroughly in a mixer for approximately 15 minutes to ensure homogeneity. Following this, magnesium stearate was incorporated into the mixture and blending continued for an additional 3-5 minutes to evenly distribute the lubricant, taking care to avoid over-mixing to prevent segregation. The final blend was then subjected to compression using a tablet compression machine (Proton Minipress). Kothiya, Olvishkumar M., et al. "Formulation and characterization of sustained release matrix tablets of ivabradine using 32 full factorial design." Int J Appl Pharm 10 (2018): 59-66.

7.6 Design of experiment

A 2-level full factorial design was employed to pre-screen and determine the critical factors influencing the hardness and disintegration time of alogliptin oral disintegrating tablets. The independent variables included compression force (5 kN, 7.5 kN, and 10 kN), disintegrant concentration (2%, 5%, and 8% of sodium starch glycolate), and lubricant concentration (0.5%, 1.25%, and 2% of magnesium stearate). The formulation blends were prepared using the direct compression technique, with each batch compressed at the specified forces. The compressed tablets were evaluated for hardness and disintegration time using standard methods. The data obtained were analyzed using ANOVA to assess the significance of the main effects and interactions among the factors. Residual plots were generated to check model adequacy, while interaction plots provided insights into the influence of factor combinations on the responses.

Independent variables			
Ingredients	**Lowest**	**Medium**	**Highest**
Compression force (KN)	5	7.5	10
Sodium starch glycolate (mg)	2	5	8
Magnesium stearate (mg)	0.5	1.25	2

Independent variables			
Disintegration time	__	__	__
Hardness	__	__	__

Input data requirements

Compression Force	**Disintegrant (%)**	**Lubricant (%)**
Low (5 kN)	Low (2%)	Low (0.5%)
Low (5 kN)	High (8%)	High (2%)
Medium (7.5 kN)	Medium (5%)	Medium (1.25%)

Medium (7.5 kN)	Low (2%)	High (2%)
Medium (7.5 kN)	High (8%)	Low (0.5%)
High (10 kN)	Low (2%)	Low (0.5%)
High (10 kN)	Medium (5%)	Medium (1.25%)
High (10 kN)	High (8%)	High (2%)
Low (5 kN)	Medium (5%)	Medium (1.25%)

The study was conducted using a Central Composite Design (CCD) within the framework of Design of Experiments (DoE) to optimize the formulation of oral disintegrating tablets. The independent variables considered were compression force (kN), disintegrant concentration (%), and lubricant concentration (%). The dependent variables measured were tablet hardness (kg/cm²) and disintegration time (s), as these factors critically determine the quality and effectiveness of the formulation.Mohammadi, Hafsa, and V. Hemanath Kumar. "Formulation and evaluation of solid dispersion incorporated fast disintegrating tablets of tenoxicam using design of experiment." International Journal of Pharmaceutical Sciences and Drug Research (2019): 35-44.

Evaluation of powder flow properties

6.7 Bulk density

The bulk and tapped density evaluations are critical for characterizing the physical properties of prepared powders. In this test, a specific quantity of powder (10g) is accurately weighed and placed into a 100ml measuring cylinder. The initial volume is recorded as V1, representing the bulk volume. The cylinder is then tapped 100 times, and the volume after tapping is noted as the tapped volume. USP. <616> Bulk density and tapped density. USP30 NF 25 (2007).

$$\text{Bulk density} = \frac{\text{Weight}}{\text{V1}}$$

$$\text{Tapped density} = \frac{\text{Weight}}{\text{tapped volume}}$$

6.8 Carr's Index

Carr's Index is calculated using the values for bulk density (ρb) and tapped density (ρt) to assess the compressibility of the powder, indicating its flow properties. Carr R. L. Evaluating flow properties of solids. Chem. Eng. 1965;72:69–72. [Google Scholar]

The formula used is

$$\text{Carr}'\text{s index} = \frac{\text{tappeddensity} - \text{bulkdensity}}{\text{tappeddensity}} \times 100$$

6.9 Hausner's ratio

Hausner's Ratio is another indicator of powder flow properties, derived from the ratio of tapped density to bulk density:Hausner H. H. Friction conditions in a mass of metal powder. Int. J. Powder Metall. 1967; 3: 7–13.

$$\text{Hausner}'\text{s ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

6.10 Angle of Repose

The angle of repose is measured to evaluate the flowability and cohesiveness of the powder. For this test, a funnel is positioned 1.5 cm above a flat surface. The powder is allowed to flow through the funnel, forming a heap. The angle of repose is determined using the following formula:

$$\text{Angle of repose}(\theta) = \tan^{-1}\frac{h}{r}$$

Here,

h = heap's average height r = heap's average radius.

The angle of repose was quantified by measuring the height (h) and radius (r) of the sample spread. This method allowed for the assessment of the flowability and cohesiveness of the formulated powder, providing insights into its potential for manufacturing low-dose.

Evaluation of post compression parameters of the tablets

6.11 Thickness

The thickness of the tablets was determined using a digital vernier caliper. Five tablets were selected, and the average thickness was calculated to ensure accuracy and uniformity. The caliper was positioned perpendicular to the tablet surface, and the jaws were gently closed to capture the thickness. The process was repeated for each tablet, and the recorded values were averaged to determine the overall tablet thickness.M. Rackl, F.E. Grötsch, M. Rusch, J. Fottner, Qualitative and quantitative assessmentof 3D-scanned bulk solid heap data, Powder Technol. 321 (201 7) 105–118,https://doi.org/10.1016/j.powtec.2017.08.009.

6.12 Weight Variation Test

A weight variation test was performed using a Wensar electronic balance to assess the

consistency of tablet weights. Twenty tablets were randomly chosen from each batch and individually weighed in accordance with the standard testing method. This test ensures that the tablets conform to the specified weight range and are uniformly distributed across the batch. Government of India, Ministry of health andfamily welfare, Indian Pharmacopoeia. Thecontroller of Publications Ghaziabad, 2007; Vol-II, 423-424

6.13 Hardness

The hardness of the tablets, an indicator of their resistance to mechanical shock, was assessed using a Monsanto hardness tester, which measures in kg/cm². Three tablets were randomly selected, and their hardness was measured to ensure accurate results. This evaluation is crucial for determining the mechanical strength of the tablets and their ability to resist breakage during handling. IndianPharmacopoeia 1996, the ControllerPublication. Vol. II. Delhi; 256-257

6.14 Friability Test

The Roche friability test was conducted to measure the friability of the tablets, expressed as a percentage (%). Ten tablets were weighed (W_0) and placed in the friability tester, which was set to rotate at 25 rpm for four minutes, equivalent to 100 revolutions. After the test, the tablets were reweighed (W), and the friability percentage was calculated. Tablets with friability values of less than 1% are considered acceptable, indicating that they have sufficient durability during handling and transportation. Shahi S.R., Agrawal G.R., Shinde N.V., ShaikhS.A., Shaikh S.S., Somani V.G., ShamkuvarP.B. and Kale M.A., Formulation and in vitroEvaluation of Or o-dispersible tablets ofEtoricoxib with emphasis on comparativefunctionality evaluation of three classes ofsuperdisintegrants ,Rasayan J. Chem Vol.1,No.2, 2008, 292-300

6.15 Disintegration Test

The disintegration test was performed according to Indian Pharmacopoeia (IP) guidelines using a USP-Electro lab USP-ED-2AL disintegration tester. Six tablets were placed in the apparatus, which was filled with distilled water at 37±0.2°C. The time required for the complete disintegration of the tablets was recorded when all particles passed through the wire mesh. The mean disintegration time was determined based on two measurements, ensuring that the tablets met the IP requirements. Radke R.S., Jadhav J.K., Chajeed M.R., Formulation and Evaluation of Orodispersibletablets Of Baclofen, International Journal of ChemTech

Research Vol.1, No.3, 517-521, July-Sept 2009

6.16 *In Vitro* Dissolution Studies

The dissolution rate of alogliptin tablets was determined using the paddle method with a USP dissolution apparatus II. The experiment was carried out in 900 ml of 0.1N HCl at 37±0.5ºC, with the paddle rotating at 50 rpm. At predetermined intervals, 10 ml samples were taken and replenished with fresh dissolution medium. The samples were diluted with 0.1N HCl, and their concentrations were analyzed using a Labindia UV-Visible double-beam spectrophotometer set to 277 nm. The cumulative drug release percentage was calculated based on an equation from a standard curve, allowing for evaluation of the tablets' dissolution and release profile. Klancke, James. "Dissolution testing of orally disintegrating tablets." *Dissolution technologies* 10.2 (2003): 6-9.

Ghourichay MP, Kiaie SH, Nokhodchi A, Javadzadeh Y. Formulation and Quality Control of Orally Disintegrating Tablets (ODTs): Recent Advances and Perspectives. Biomed Res Int. 2021 Dec 24;2021:6618934. doi: 10.1155/2021/6618934. PMID: 34977245; PMCID: PMC8719989.

RESULTS AND DISCUSSION

7 Preformulation studies

Preformulation studies are the foundation of any successful pharmaceutical formulation development. These studies provide critical insights into the physical and chemical properties of the drug substance, guiding formulation strategies and ensuring the stability, efficacy, and quality of the final product. Key parameters assessed during preformulation include solubility, melting point, stability, and compatibility with excipients.Lau, Edward. "Preformulation studies." Separation science and technology. Vol. 3. Academic Press, 2001. 173-233.

7.7 Melting point

In summary, the melting point of 226°C not only ensures the compound's purity and stability but also acts as a reliable identification marker for Alogliptin in various stages of pharmaceutical development. The melting point is a crucial physicochemical parameter, as it not only indicates the purity of the compound but also provides insight into its thermal stability. A sharp and consistent melting point, as observed with Alogliptin, typically suggests that the substance is pure with minimal impurities. Mohanty, Dibyalochan, et al. "Formulation

and optimization of alogliptin-loaded polymeric nanoparticles: In vitro to in vivo assessment." Molecules
27.14 (2022): 4470.

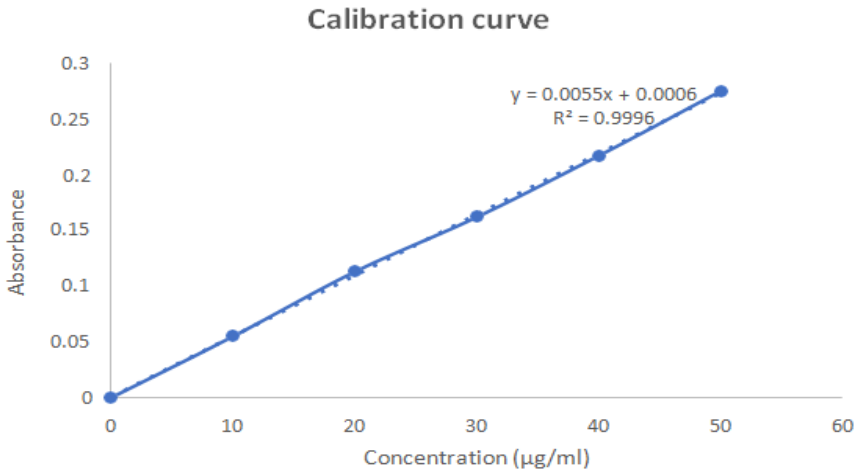
1.1. Solubility

Solvent	Solubility
Water	Sparingly soluble
Methanol	Sparingly soluble
Ethanol	Sparingly soluble
DMSO	Soluble
0.1N HCl	Soluble

The solubility profile of the drug was evaluated across different solvents, including water, methanol, ethanol, DMSO, and phosphate buffer (pH 6.8). The findings revealed varying degrees of solubility depending on the solvent used. In water, methanol, and ethanol, the drug was classified as sparingly soluble, indicating limited solubility in these solvents. This limited solubility could potentially pose challenges in formulations that require these solvents as the medium.Yi, Dongxu, et al. "Solubility and thermodynamic properties of Alogliptin Benzoate form A in different mono-solvents." The Journal of Chemical Thermodynamics 159 (2021): 106474.

7.8 Calibration curve

Concentration	Absorbance
10	0.055
20	0.113
30	0.162
40	0.217
50	0.275



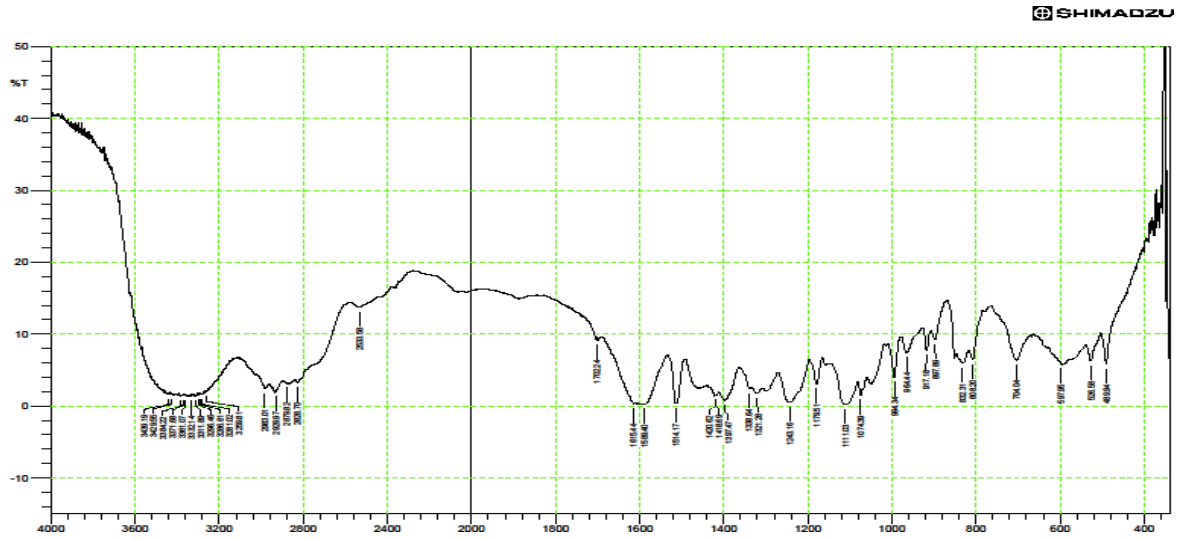
The calibration curve was plotted by measuring the absorbance of different concentrations (10, 20, 30, 40, and 50 µg/ml) of the drug at 277 nm using a UV spectrophotometer. The curve demonstrated a linear relationship between concentration and absorbance, as indicated by the equation y=0.0055x+0.0006 with an R^2 value of 0.9996. This high R^2 value signifies excellent linearity, suggesting that the method is reliable for determining drug concentration within the tested range. Naseef, Hani, Ramzi Moqadi, and Moammal Qurt. "Development and validation of an HPLC method for determination of antidiabetic drug alogliptin benzoate in bulk and tablets." Journal of Analytical Methods in Chemistry 2018.1 (2018): 1902510.

7.9 Compatibility

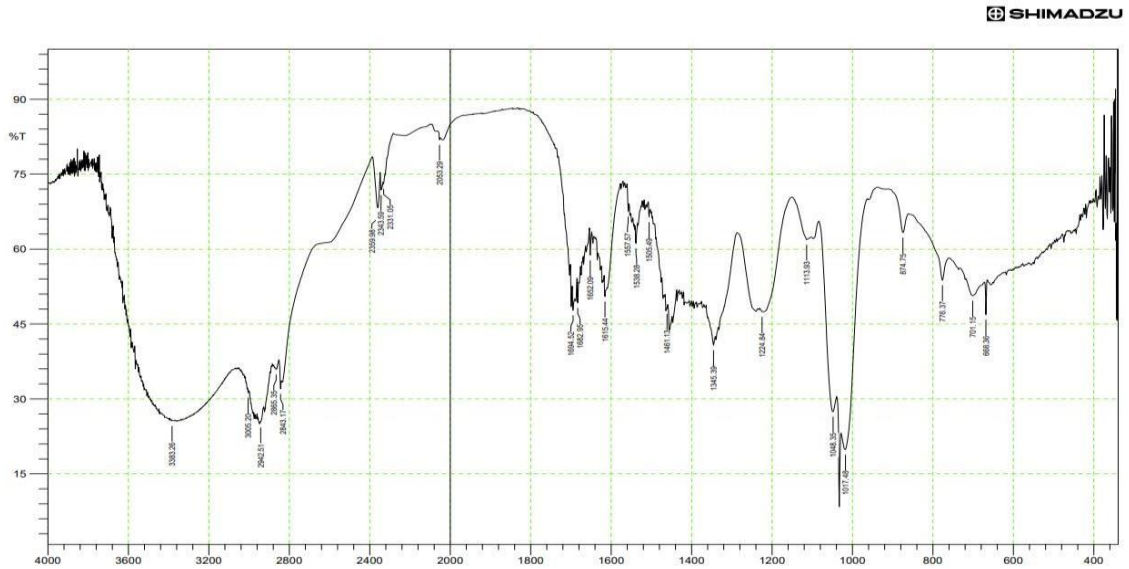
The FTIR spectral analysis was conducted to assess the presence and stability of functional groups in Alogliptin, its excipients (MCC, SSG, mannitol, magnesium stearate), and their physical mixture. The O-H stretching vibrations observed at 3429.56 cm^{-1} for Alogliptin were similarly retained in the physical mixture at 3421.30 cm^{-1}, indicating no significant interaction. The C-H stretching peaks for Alogliptin appeared at 2898.97 cm^{-1}, and the physical mixture showed a peak at 2901.04 cm^{-1}, again showing stability. The C=O stretching peak at 1689.40 cm^{-1} in Alogliptin was observed in the physical mixture at 1634.25 cm^{-1}, suggesting minimal interaction. Similarly, the -CH3 bending and aromatic C-H bending vibrations were preserved across the samples, confirming that no substantial interactions occurred. Minor shifts, such as the C-H bending vibration at 1818.69 cm^{-1} for Alogliptin appearing at 1672.09 cm^{-1} in the physical mixture, indicate only slight interactions. The NH2 stretching and C-N aliphatic amine peaks remained stable, reflecting consistent functional group integrity. Overall, the FTIR analysis confirms that Alogliptin's functional groups remain largely unaffected in the presence of excipients, suggesting minimal drug-excipient interactions and maintaining the drug's chemical integrity in formulation development. Nandi, U., et al. "COMPATIBILITY STUDY OF ALOGLIPTIN BENZOATE WITH WIDELY USED PHARMACEUTICAL EXCIPIENTS FOR SOLID DOSAGE FORM." Indian Drugs 55.2 (2018).

Functional groups	Alogliptin	MCC	SSG	Mannitol	Magnesium stearate	Physical mixture
O-H stretching		3429.56	3383.26	3472.26	3154.62	3421.30
C-H stretching	2898.97	2981.08		2943.47	2920.32	2901.04
C=O stretching	1689.40	1945.28			1636.85	1634.25
-CH3 bending			1461.13	1410.96	1472.60	1420.20
C-H bending	1818.69		1505.49	1647.26	1578.25	1672.09

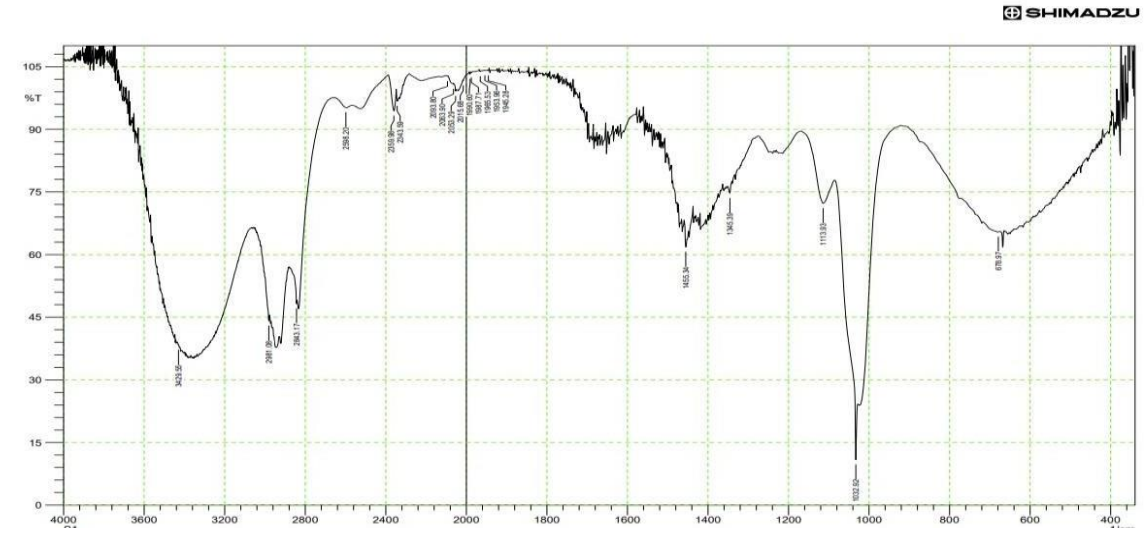
Aromatic C-H bending		1455.34				1459.20
NH2	1615.44					1622.22
C=N Nitrile conjugated stretching	2221					2302.73
C-N aliphatic amine	1201.16					1201.69
C-O carboxylic	1702.24		1649.52			1628.05



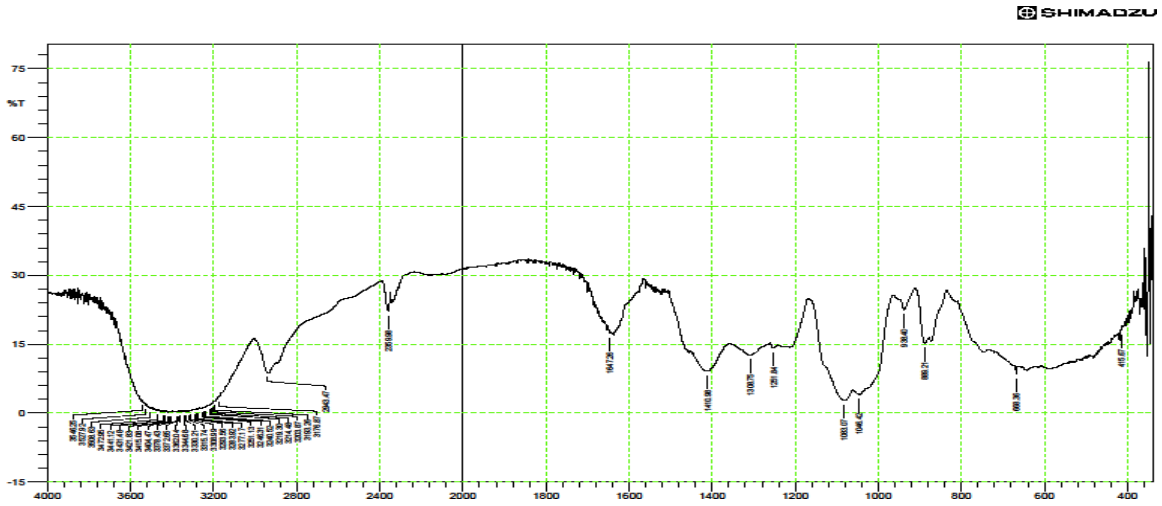
FTIR spectra of alogliptin.



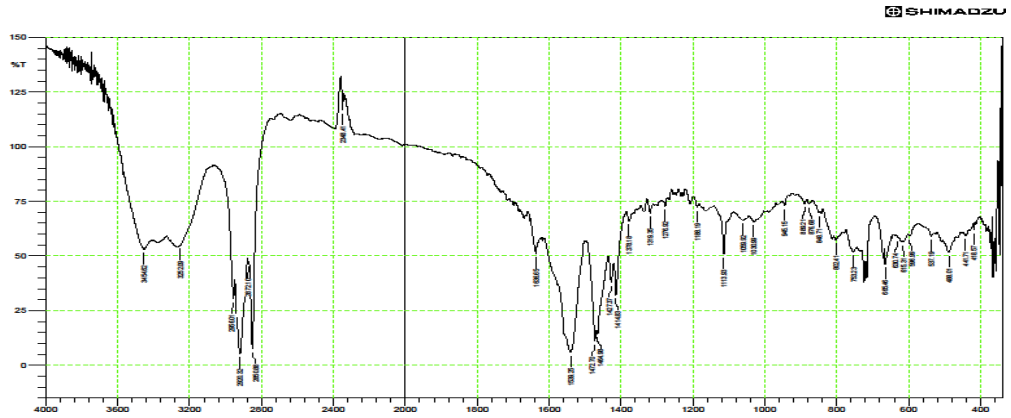
FTIR spectra of sodium starch glycolate.



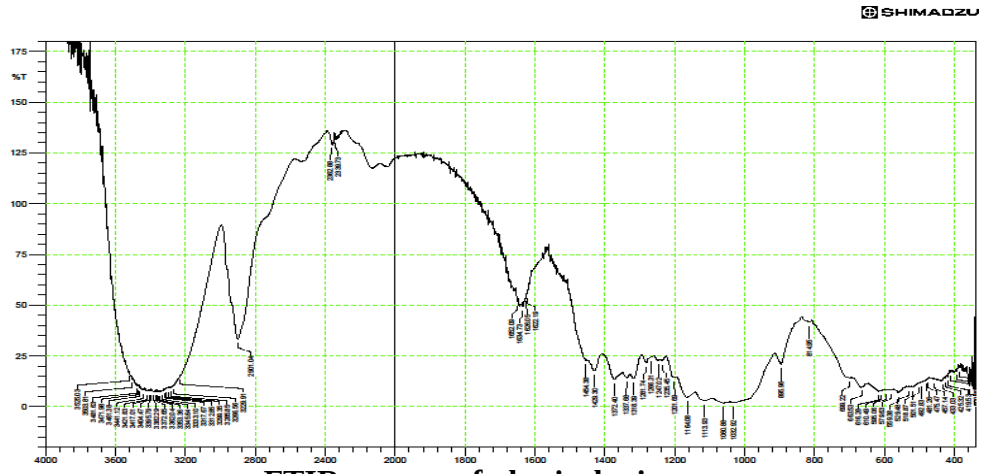
FTIR spectra of MCC.



FTIR spectra of mannitol.



FTIR Spectra of magnesium stearate.



FTIR spectra of physical mixture.

8 Formulation

The preparation of alogliptin oral dispersible tablets was carried out using the direct compression method. The process involved accurate weighing, sieving, blending, and compressing of ingredients to ensure uniformity and consistency. The tablets were formulated with a focus on achieving both adequate mechanical strength and rapid disintegration. Further the optimization was conducted using DOE. Ibrahim, Tarek M., et al. "Investigation of alogliptin- loaded in situ gel implants by 23 factorial design with glycemic assessment in rats." Pharmaceutics
14.9 (2022): 1867.

8.1 Design of experiment

8.1.1 Input data and prescreening

8.1.1.1 Overview of Pre-screening Analysis

The pre-screening study was conducted to identify the significant factors influencing the hardness and disintegration time of alogliptin oral disintegrating tablets (ODTs). The independent variables evaluated were compression force, disintegrant percentage (sodium starch glycolate), and lubricant percentage (magnesium stearate). A 2-level factorial design was employed, and the responses measured were tablet hardness (in kg/cm²) and disintegration time (in seconds).Kumar, Ganesh, and Meenakshi Bhatt. "Formulation and Optimization of Trandolapril Oro-dispersible Tablets using the Quality by Design (QbD) Approach." Letters in Drug Design & Discovery 20.9 (2023): 1194-1203.

Table: Input data and prescreening.

Compression Force	Disintegrant (%)	Lubricant (%)	Hardness (kg/cm²)	Disintegration Time (s)

Low (5 kN)	Low (2%)	Low (0.5%)	**3.5**	**20**
Low (5 kN)	High (8%)	High (2%)	**2.8**	**18**
Medium (7.5 kN)	Medium (5%)	Medium (1.25%)	**6**	**24**
Medium (7.5 kN)	Low (2%)	High (2%)	**6.8**	**27**
Medium (7.5 kN)	High (8%)	Low (0.5%)	**5.7**	**23**
High (10 kN)	Low (2%)	Low (0.5%)	**9.5**	**31**
High (10 kN)	Medium (5%)	Medium (1.25%)	**8.2**	**28**
High (10 kN)	High (8%)	High (2%)	**6.5**	**26**
Low (5 kN)	Medium (5%)	Medium (1.25%)	**4**	**22**

7.1.1.2 ANOVA Results

The ANOVA tables for both responses provided valuable insights into the significance of the factors. Hardness (kg/cm²)

Table. ANOVA results for hardness.

Factor	Df	Sum of Squares (SS)	Mean Square (MS)	F-Value	p-Value
Compression Force	2	32.55	16.27	28.22	0.0113
Disintegrant Percentage	2	2.94	1.47	2.55	0.2253
Lubricant Percentage	2	0.61	0.31	0.53	0.634
Residual	3	1.73	0.58	-	-

Disintegration Time (seconds):

Table . ANOVA results for time.

Factor	Df	Sum of Squares (SS)	Mean Square (MS)	F- Value	p- Value
Compression Force	2	104.67	52.33	18.29	0.0209
Disintegrant Percentage	2	18.75	9.38	3.28	0.176
Lubricant Percentage	2	2.75	1.38	0.48	0.6591
Residual	3	8.58	2.86	-	-

Significance of Compression Force

- The compression force showed a significant effect on both hardness (p = 0.0113) and disintegration time (p = 0.0209). This indicates that altering the compression force will have a direct impact on these responses. A higher compression force generally led to an increase in hardness and a slight increase in disintegration time.

Impact of Disintegrant Percentage

- The disintegrant percentage did not show a statistically significant effect in this pre-screening study (p > 0.05 for both responses). However, there was a noticeable trend:

increasing the disintegrant percentage slightly decreased both hardness and disintegration time. This trend suggests that, while not statistically significant in this limited pre-screening, the disintegrant percentage still plays a role and should be carefully considered in the full optimization study.

Minimal Effect of Lubricant Percentage

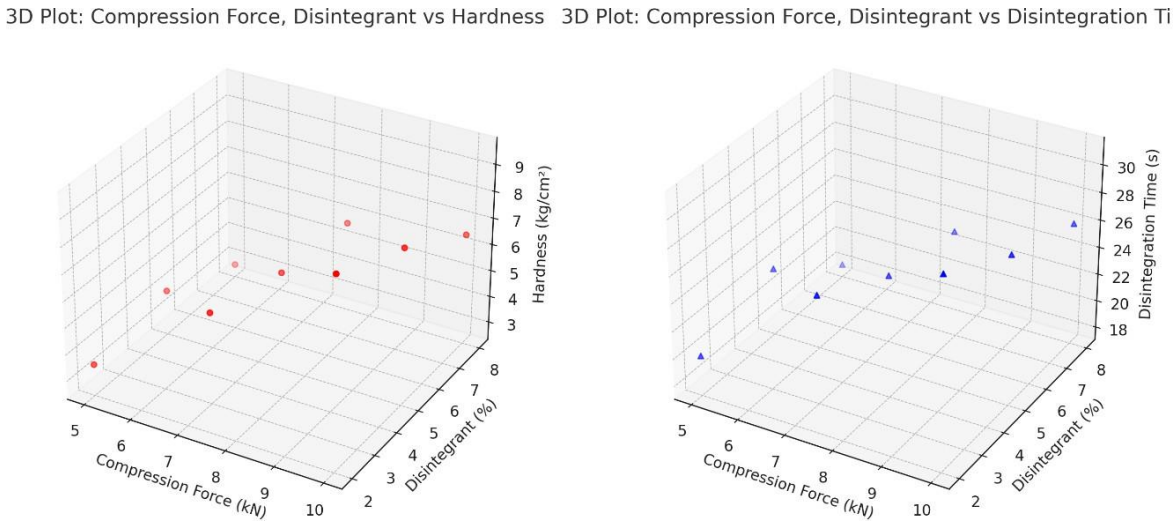
- The lubricant percentage had the least impact on both responses ($p > 0.6$). Given this result, it might be feasible to narrow its range or reduce its influence in the next phase of the study. Schiermeier, Simone, and Peter Christian Schmidt. "Fast dispersible ibuprofen tablets." European journal of pharmaceutical sciences 15.3 (2002): 295- 305.

Irshad, Asma, et al. "Effect of starch, cellulose and povidone based superdisintegrants in a QbD-based approach for the development and optimization of Nitazoxanide orodispersible tablets: Physicochemical characterization, compaction behavior and in-silico PBPK modeling of its active metabolite Tizoxanide." Journal of Drug Delivery Science and Technology 79 (2023): 104079.

7.1.1.3 Interaction and Residual Analysis

The interaction plots showed that the relationship between disintegrant percentage and responses (hardness and disintegration time) is more pronounced at higher compression forces. Residual analysis indicated slight non-linearities, suggesting that a more complex model, such as a quadratic model, might be appropriate for the full DOE study. Fukuda, Isa Martins, et al. "Design of experiments (DoE) applied to pharmaceutical and analytical quality by design (QbD)." Brazilian journal of pharmaceutical sciences 54 (2018): e01006.

The pre-screening analysis has identified compression force as the most critical factor influencing both hardness and disintegration time. While disintegrant percentage and lubricant percentage were less significant, their influence should still be explored in the Central Composite Design (CCD) study, particularly for optimizing the balance between rapid disintegration and appropriate tablet hardness.Brniak, Witold, Ewelina Maślak, and Renata Jachowicz. "Orodispersible films and tablets with prednisolone microparticles." European Journal of Pharmaceutical Sciences 75 (2015): 81-90.



Plot: Illustrates the relationship between Compression Force, Disintegrant Concentration, and Hardness (kg/cm²)

Right Plot: Displays the relationship between Compression Force, Disintegrant Concentration, and Disintegration Time (s).

7.1.2 Central composite design

Central Composite Design (CCD) is a popular response surface methodology used for optimizing processes with multiple factors. It includes factorial points, axial points, and center points to explore linear and quadratic relationships, capturing curvature in the response surface. CCD is effective in modeling complex interactions and determining optimal conditions with a relatively small number of experiments. The Central Composite Design (CCD) was selected for this study due to its ability to efficiently explore both linear and quadratic relationships among the key formulation factors—compression force, disintegrant concentration, and lubricant concentration. CCD is particularly suitable for optimizing processes where non-linear interactions and curvatures are expected, making it ideal for fine-tuning the balance between tablet hardness and disintegration time. This design provides a robust framework by including factorial points, axial points, and center points, allowing for a comprehensive analysis of factor interactions while capturing potential response surface curvature. Additionally, CCD offers flexibility in scaling the experiment, allowing precise control over the experimental runs while maximizing information gain. This makes it a powerful tool for identifying optimal formulation conditions with a minimal number of experimental runs, ensuring efficient use of resources. Pabari, Ritesh M., and ZebunnissaRamtoola. "Application of face centred central composite design to optimise

compression force and tablet diameter for the formulation of mechanically strong and fast disintegrating orodispersible tablets." International journal of pharmaceutics 430.1-2 (2012): 18-25.

7.1.2.2 Independent Variables and Levels

The independent variables and their levels are

Factor	Lowest Level (-1)	Medium Level (0)	Highest Level (+1)
Compression force (KN)	5	7.5	10
Sodium starch glycolate (mg)	2	5	8
Magnesium stearate (mg)	0.5	1.25	2

The CCD typically includes factorial points, axial points (to explore quadratic effects), and center points (to check for repeatability and model curvature).

- Factorial Points: Combinations of the lowest (-1) and highest (+1) levels for each factor.
- Axial Points: Points beyond the factorial levels, often at ±α, where α can be 1.68 (for rotatability).
- Center Points: Replicated runs at the medium level (0) for each factor.

7.1.2.3 Runs

Run	Compression Force (KN)	Sodium Starch Glycolate (mg)	Magnesium Stearate (mg)	Predicted Disintegration Time (s)	Predicted Hardness (N)
1	5	2	0.5	32	2.1
2	10	2	0.5	30	3.8
3	5	8	0.5	28	4.2
4	10	8	0.5	29	4.4
5	5	2	2	31	3.9
6	10	2	2	27	4.1
7	5	8	2	29	5.2
8	10	8	2	28	4.8
9	2.5	5	1.25	30	3.5
10	12.5	5	1.25	28	4
11	7.5	0.64	1.25	31	4.1
12	7.5	9.36	1.25	29	4.3
13	7.5	5	0.19	30	4
14	7.5	5	2.31	29	4.5
15	7.5	5	1.25	29	4.2
16	7.5	5	1.25	29	4.2
17	7.5	5	1.25	29	4.2
18	7.5	5	1.25	29	4.2
19	7.5	5	1.25	29	4.2

The ANOVA results reveal that the independent variables-compression force, sodium starch glycolate, and magnesium stearate play significant roles in determining both hardness and disintegration time. Pabari, Ritesh M., and Zebunnissa Ramtoola. "Application of face centred central composite design to optimise compression force and tablet diameter for the formulation of mechanically strong and fast disintegrating orodispersible tablets." International journal of pharmaceutics 430.1-2 (2012): 18-25.

Source of Variation	Sum of Squares (SS)	Degrees of Freedom (DF)	Mean Square (MS)	F-Value	P-Value
Model	24.74632	9	24.0136	32.77338	0.050129
Compression Force (A)	7.980625	1	7.980625	98.02648	3.89E-06
Sodium Starch Glycolate (B)	4.400832	1	4.400832	54.05568	4.32E-05
Magnesium Stearate (C)	2.052087	1	2.052087	25.2059	0.000719
Interaction: A * B	5.28125	1	5.28125	64.8699	2.10E-05
Interaction: A * C	1.36125	1	1.36125	16.72031	0.002721
Interaction: B * C	1.71125	1	1.71125	21.01938	0.001319
Quadratic: AA^2	0.806852	1	0.806852	9.910604	0.011773
Quadratic: BA^2	0.345373	1	0.345373	4.242231	0.069518
Quadratic: CA^2	0.074081	1	0.074081	0.909944	0.365046
Residual	0.732717	9	0.081413		
Lack of Fit	0.732717	9	0.081413		
Pure Error	0	0	0		
Total	25.47903	18	24.09501		

Effect on Hardness

The compression force (F-value: 98.03, p-value: 3.89E-06) is the most influential factor on hardness. As compression force increases, tablet hardness also increases due to higher density and compactness, leading to a stronger tablet structure. Sodium starch glycolate (F-value: 54.06, p-value: 4.32E-05) is also significant, though its primary role is in disintegration; it contributes to hardness by influencing the tablet's internal structure. Magnesium stearate (F-value: 25.21, p-value: 0.0007), a lubricant, has a notable but smaller impact on hardness by reducing friction during compression, which in turn can affect tablet density. Shikifumi Kitazawa, Ikuo Johno, Yoko Ito, Shigeo Teramura, Jutaro Okada, Effects of hardness on the disintegration time and the dissolution rate of uncoated caffeine tablets, Journal of Pharmacy and Pharmacology, Volume 27, Issue 10, October 1975, Pages 765–770, https://doi.org/10.1111/j.2042- 7158.1975.tb09397.x

Effect on Disintegration Time

For disintegration time, sodium starch glycolate (F-value: 54.06, p-value: 4.32E-05) has the most significant effect. Higher concentrations of this disintegrant lead to faster disintegration due to its ability to absorb water and swell. Compression force (F-value: 98.03, p-value: 3.89E-06) also impacts disintegration time but in a more complex manner-excessive compression reduces porosity and can delay disintegration. Magnesium stearate (F-value: 25.21, p-value: 0.0007) has a moderate influence, slightly delaying disintegration due to its hydrophobic nature. Pabari, R. M., and Z. Ramtoola. "Effect of a disintegration mechanism on wetting, water absorption, and disintegration time of orodispersible tablets." Journal of young pharmacists 4.3 (2012): 157-163.

Interaction Effects

The interactions between these factors are significant. For instance, the interaction between compression force and sodium starch glycolate (F-value: 64.87, p-value: 2.10E-05) is highly impactful. This interaction suggests that the combined effect of these factors is not simply additive; they work together to either enhance or mitigate the tablet's properties. The interactions between compression force and magnesium stearate (F-value: 16.72, p-value: 0.0027) and between sodium starch glycolate and magnesium stearate (F-value: 21.02, p-value: 0.0013) are also significant, indicating a complex relationship between these variables. Principles of research designs, settings and procedures 3(13):188-189.

Quadratic Effects

The quadratic terms for compression force (F-value: 9.91, p-value: 0.0118) and sodium starch glycolate (F-value: 4.24, p-value: 0.0695) are significant, suggesting that these factors have a nonlinear effect on the responses, where increasing them beyond certain levels can lead to diminishing or even adverse effects.

The numerical ANOVA values highlight the importance of carefully balancing these independent variables to achieve the desired tablet properties. Compression force is critical for both hardness and disintegration time, while sodium starch glycolate plays a crucial role in optimizing disintegration. Magnesium stearate, although less impactful, must be controlled to fine-tune the balance between hardness and disintegration.Almotairi, Nawaf, et al. "Design and optimization of lornoxicam dispersible tablets using Quality by Design (QbD) Approach." Pharmaceuticals 15.12 (2022): 1463.

Residual Analysis

The residual plots are crucial to check the randomness of residuals, which ensures the model assumptions are met.

- **Residual Plot for Disintegration Time:** The scatter plot of fitted values versus residuals should show no clear pattern. If residuals are randomly scattered around zero, it indicates a good model fit.
- **Residual Plot for Hardness:** Similarly, for hardness, a random distribution of residuals suggests that the model is appropriate for predicting the response.

The analysis shows that the model fits well if the residuals are random and the R^2 values are strong. If you noticed specific numerical values, we can interpret further to determine model accuracy.Almotairi, Nawaf, et al. "Design and optimization of lornoxicam dispersible tablets using Quality by Design (QbD) Approach." Pharmaceuticals 15.12 (2022): 1463.

Here is the summary of the R^2 and adjusted R^2 values

Response	R^2	Adjusted R^2
Disintegration Time (S)	0.97	0.946
Hardness (KG/cm2)	0.955	0.922

The R^2 and adjusted R^2 values provide insights into how well the model explains the variability in the response variables (disintegration time and hardness). For both responses, the high R^2 values indicate that a significant portion of the variability is captured by the independent variables in the model.

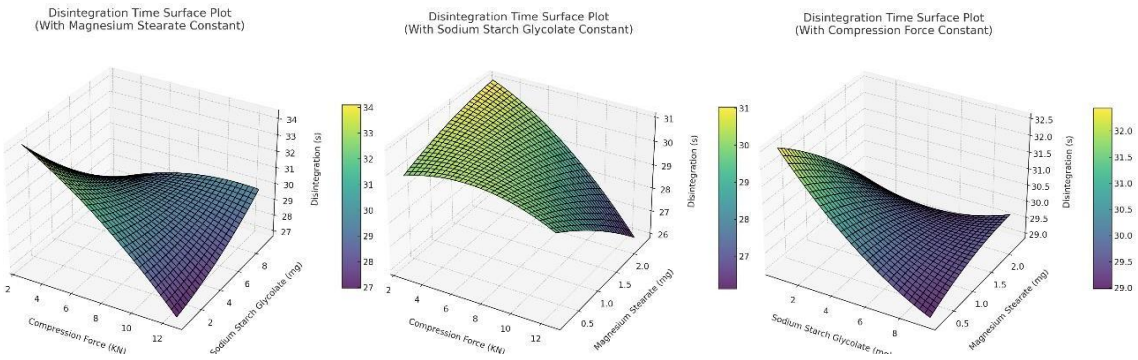
- **Disintegration Time:** The R^2 value of 0.9700 indicates that 97% of the variability in disintegration time is explained by the model. The adjusted R^2 of 0.9460 accounts for the number of predictors in the model, confirming that the model is robust and effective even with multiple factors.
- **Hardness:** The R^2 value of 0.9550 signifies that 95.5% of the variability in hardness is explained by the model. The adjusted R^2 of 0.9220 suggests that the model remains highly accurate when considering the number of predictors.

The residual plots show that the residuals are randomly distributed around zero for both responses. This randomness suggests that the model does not suffer from systematic errors, indicating a good fit. No clear patterns or trends were observed, reinforcing the validity of the model.

In conclusion, the high R^2 values combined with random residuals demonstrate that the

model is suitable for predicting both disintegration time and hardness with a high degree of accuracy. The next step could involve optimizing the independent variables to achieve desired outcomes for these responses.

3D surface plots



Plot 1: Compression Force vs. Sodium Starch Glycolate (Disintegration Time).

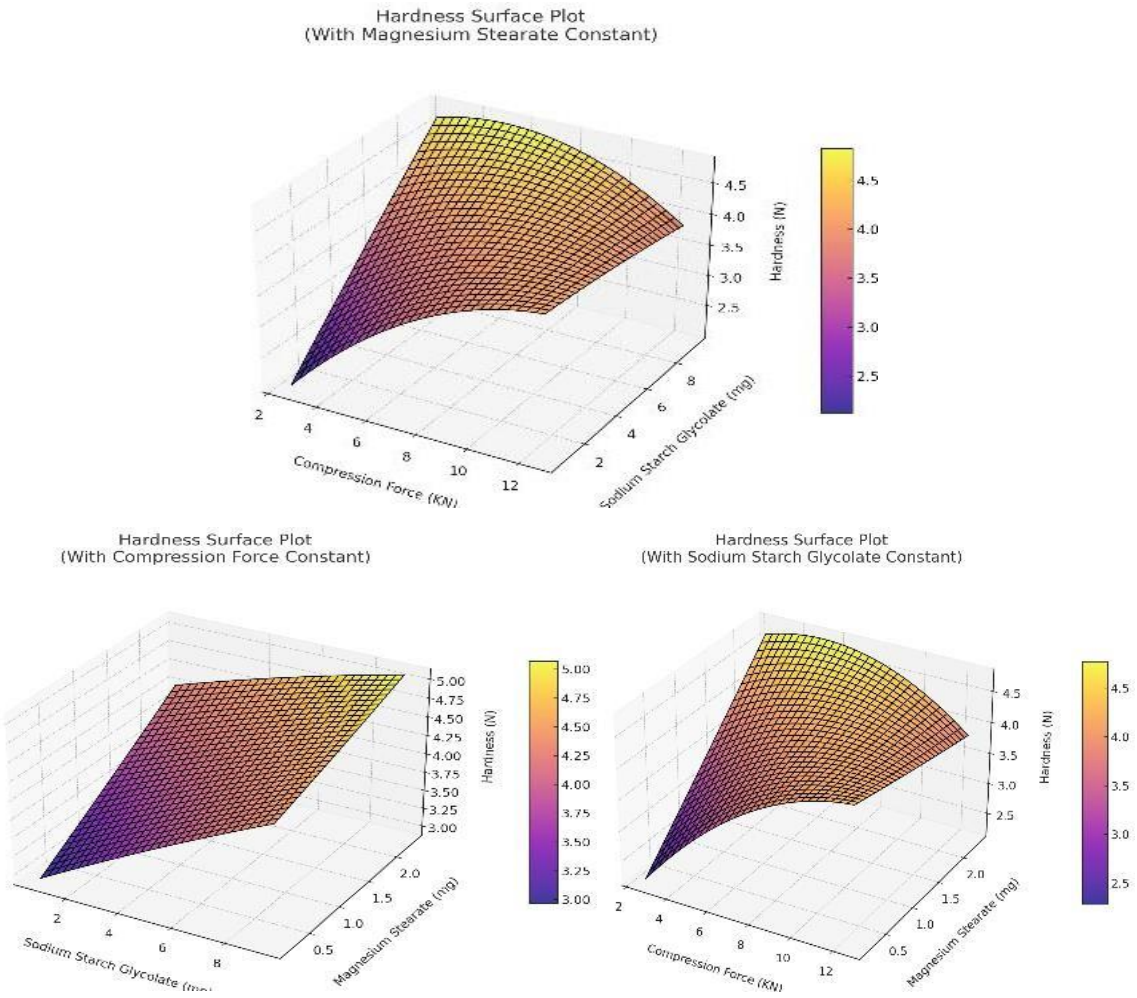
This plot shows how disintegration time is influenced by the interaction between compression force and sodium starch glycolate while keeping magnesium stearate constant. As compression force increases, disintegration time generally decreases due to reduced porosity, which makes the tablet more compact. On the other hand, higher levels of sodium starch glycolate, a disintegrant, reduce disintegration time by promoting faster breakdown. The plot highlights a balance point where these factors work together optimally.

Plot 2: Compression Force vs. Magnesium Stearate (Disintegration Time)

In this plot, the impact of compression force and magnesium stearate on disintegration time is explored while maintaining sodium starch glycolate at a constant level. Increasing compression force reduces disintegration time, but adding more magnesium stearate slightly delays it due to its hydrophobic properties. This plot emphasizes the need to control lubricant concentration, as excess magnesium stearate can slow down the disintegration process.

Plot 3: Sodium Starch Glycolate vs. Magnesium Stearate (Disintegration Time)

This plot shows the interaction between sodium starch glycolate and magnesium stearate while keeping compression force constant. Sodium starch glycolate significantly reduces disintegration time, especially at higher levels, due to its water absorption capacity. Magnesium stearate, however, introduces some delay in disintegration. The plot illustrates that sodium starch glycolate's disintegrating power can outweigh the slowing effects of magnesium stearate if used in sufficient amounts.



Plot 4: Compression Force vs. Sodium Starch Glycolate (Hardness)

This plot highlights how compression force and sodium starch glycolate affect tablet hardness, with magnesium stearate held constant. As expected, higher compression forces result in harder tablets due to increased density. Sodium starch glycolate, while primarily a disintegrant, also contributes to hardness by forming a more rigid internal structure at higher levels. The plot underscores the importance of balancing these factors for optimal tablet strength.

Plot 5: Compression Force vs. Magnesium Stearate (Hardness)

In this plot, the relationship between compression force and magnesium stearate with respect to hardness is examined while sodium starch glycolate remains constant. Higher compression forces naturally lead to greater hardness, but increasing magnesium stearate levels has a mixed effect. Although it helps reduce friction during compression, excessive amounts can

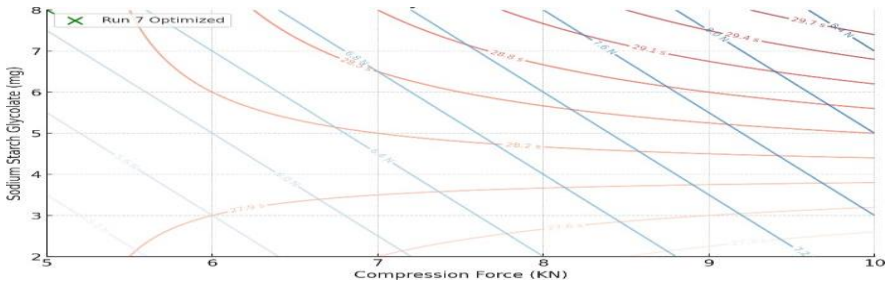
reduce tablet compactness. This plot demonstrates that magnesium stearate should be carefully adjusted to maintain the desired hardness.

Plot 6: Sodium Starch Glycolate vs. Magnesium Stearate (Hardness)

This plot shows how sodium starch glycolate and magnesium stearate interact to influence hardness while compression force is kept constant. Sodium starch glycolate has a less pronounced effect on hardness compared to compression force, but it still contributes at higher levels. Magnesium stearate slightly reduces hardness when increased, likely due to its role in reducing tablet compactness. The plot reveals that finding the right balance between these factors is key to achieving consistent hardness in tablet formulation.Yasmin, Riffat & Shoaib, Muhammad & Ahmed, Farrukh & Qazi, Faaiza & Ali, Huma & Zafar, Farya. (2020). Aceclofenac fast dispersible tablet formulations: Effect of different concentration levels of Avicel PH102 on the compactional, mechanical and drug release characteristics. PLOS ONE. 15. e0223201. 10.1371/journal.pone.0223201.

7.1.2.4 Desirability function

The desirability function was refined to prioritize achieving a disintegration time of less than 30 seconds while ensuring the hardness falls within the specified range of 4 to 6 N. The desirability for disintegration was maximized when the time was 30 seconds or less, with hardness optimized within the desired range. By applying response surface methodology (RSM) and desirability functions, the optimal levels for compression force, sodium starch glycolate, and magnesium stearate were adjusted to favor rapid disintegration while maintaining sufficient tablet strength. The resulting optimal formulation met the criteria of disintegration time below 30 seconds and hardness within the range of 4 to 6 N. This outcome was visually confirmed through an overlay plot, which highlighted the region where both responses simultaneously meet these requirements.Ugandar, R. E., et al. "A Study On Feasibility Of Optimization Technique In Formulation Of Dispersible Tablets By Factorial Design." International Journal of Pharmaceutical Sciences and Research 5.4 (2014): 1208.



Here is the original overlay plot with the green marker clearly highlighting the optimized settings for Run 7 (5 KN compression force and 8 mg sodium starch glycolate). The detailed contour lines for both disintegration time and hardness are maintained, while the optimized point is prominently marked in green for easy identification.

Optimized formula

Run	Compression Force (KN)	Sodium Starch Glycolate (mg)	Magnesium Stearate (mg)	Predicted Disintegration Time (s)	Predicted Hardness (N)
4	10	8	0.5	29	4.4

8 Evaluation of powder flow properties

8.1 Bulk density

Bulk density was found in 0.2g/cm^3 and tapped density between 0.25g/cm^3 as shown in Table No. The evaluation of bulk and tapped densities is essential in understanding the physical characteristics and flow properties of the prepared powders. In this study, the bulk density of the powder was found to be 0.2 g/cm³, while the tapped density was measured at 0.25 g/cm³. The difference between the two values indicates that the powder has a certain degree of compressibility, as shown by the reduction in volume after tapping. This reduction is a result of particles rearranging and filling void spaces, leading to a denser packing.

USP. <616> Bulk density and tapped density. *USP30 NF 25* (2007).

Bulk density (g/cm3)	Tapped density (g/cm3)
0.2	0.25

8.2 Carr’s Index

The compressibility index (Carr's index) is a key indicator of the flowability of powder blends, with lower values suggesting better flow properties. In this study, the powder blends across all formulations exhibited a Carr’s index of 20%, which indicates satisfactory flowability. A compressibility index between 15-20% is generally considered to reflect good flow characteristics, which is crucial for efficient processing, especially in tablet compression and capsule filling. The 20% Carr's index shows that the powder blends possess adequate flowability, minimizing the risk of issues such as segregation, inconsistent dosing, or poor compaction during manufacturing.Carr R. L. Evaluating flow properties of solids. *Chem. Eng.* 1965; 72: 69–72. [Google Scholar]

8.3 Hausner's ratio

The Hausner's ratio is an important metric for assessing the flow characteristics and compressibility of powder blends. In this study, the powder blend demonstrated a Hausner's ratio of 1.15, which reflects a good level of compressibility. Hausner's ratios below 1.2 are generally associated with good flowability, while ratios exceeding 1.5 often suggest poor flow behavior.Hausner H. H. Friction conditions in a mass of metal powder. *Int. J. Powder Metall.* 1967; 3: 7–13. [Google Scholar]

With a ratio of 1.15, the powder blend is expected to flow smoothly, reducing the likelihood of issues during manufacturing processes such as inconsistent dosing or difficulty in compaction. The favorable flow properties indicated by this Hausner's ratio enhance the ease of handling and processing the powder during pharmaceutical formulation, making it suitable for efficient production.USP. <1174> Powder flow. *USP30 NF 25* (2007).

8.4 Angle of Repose

The angle of repose is a widely used parameter to assess the flowability of powders. In this study, the powder blends exhibited an angle of repose of $\theta = 30°$, which is generally indicative of good flow characteristics. Typically, an angle of repose below 35° suggests that the powder has free-flowing properties, which is essential for ensuring smooth handling during the manufacturing process.

This favorable angle of repose reinforces the compressibility and flowability data, supporting the conclusion that the powder blend is well-suited for pharmaceutical applications. The good flow properties reduce the likelihood of issues like clogging or uneven filling, ensuring consistent performance in processes like tablet compression

9 Evaluation of post compression parameters of the tablets

9.1 Thickness

The thickness of all the tablets was measured, and the values were consistent across all samples, with each tablet showing a thickness of 0.7 mm. The limit for thickness variation is set at 5%, and the results show no variation in thickness among the tested tablets, indicating excellent uniformity. The lack of variation in thickness across the samples suggests that the manufacturing process is well-controlled and efficient. Maintaining consistent thickness is essential for ensuring product quality, as deviations can affect the drug's release rate and

bioavailability. Nandhini, J., and A. N. Rajalakshmi. "Formulation development and evaluation of methylprednisolone dispersible tablets." Asian J Pharm Pharmacol 4 (2018): 514-21.

S. No.	Thickness (mm)
1	0.7
2	0.7
3	0.7
4	0.7
5	0.7

9.2 Weight Variation Test

All the tablets passed the weight variation test, with the percentage weight variation falling well within the ±7.5% limit specified by the Pharmacopoeia. The uniformity in tablet weights, with low standard deviation values, highlights the precision in the formulation process, indicating effective mixing of the drug, disintegrants, and excipients.

The highest percentage weight variation observed was 0.536%, while the lowest was 0.861%. Both values are significantly lower than the acceptance criteria of 7.5%, demonstrating excellent control over the tablet production process.4th ed. New Delhi: The controller of publications; 1996. Indian Pharmacopoeia, Ministry of Health and Family Welfare, Govt. of India; p. A-54. [Google Scholar]

S.No.	Tablet weight
1	199.18
2	198.27
3	199.97
4	198.11
5	197.46
6	198.93
7	199.34
8	199.72
9	198.69
10	198.12
11	198.85
12	199.94
13	198.83
14	198.99
15	198.99
16	199.91
17	198.01
18	197.19
19	199.72
20	199.84

9.3 Hardness

The hardness of the tablets was evaluated, and the values ranged from 4.9 kg/cm² to 5.5 kg/cm², with an average hardness of 5.2 kg/cm². This falls within the acceptable range of 4-6 kg/cm², which is considered ideal for maintaining the mechanical strength and integrity of the tablets. The individual hardness values for the tablets are as follows:

S. No.	Hardness (kg/cm^2)
1	5.3
2	5
3	5.5
4	4.9
5	5.3

The results indicate that the tablets exhibit satisfactory hardness, with an average value of 5.2 kg/cm², which is within the ideal range of 4-6 kg/cm². This level of hardness ensures that the tablets possess adequate mechanical strength, preventing breakage during handling, packaging, and transportation, while still allowing for efficient disintegration upon administration.

The minimal variation in hardness values (ranging from 4.9 to 5.5 kg/cm²) indicates consistent formulation and compression processes. The hardness values are well within the acceptable limits, ensuring that the tablets maintain both their structural integrity and appropriate dissolution profiles . Nikam, V.K., Shete, S.K. &Khapare, J.P. Most promising solid dispersion technique of oral dispersible tablet. Beni-SuefUniv J Basic Appl Sci 9, 62 (2020). https://doi.org/10.1186/s43088-020-00086-4

9.4 Friability test

The friability of the tablets was evaluated, and all formulations exhibited values well below the 1% limit as per IP (Indian Pharmacopoeia) standards, indicating good mechanical resistance. The friability values ranged from 0.24% to 0.34%, demonstrating the robustness of the tablets against mechanical stress during handling and transportation. Lachman L, Lieberman A, Kinig JL. 4th ed. Bombay: Varghese Publishing House; 1991. The Theory and Practice of Industrial Pharmacy; pp. 67–8. [Google Scholar]

The detailed friability values for each tablet are as follows

S. No.	Friability (%)

1	0.34
2	0.25
3	0.24
4	0.26
5	0.24
6	0.24
7	0.32
8	0.27
9	0.24
10	0.24

The friability test results confirm that all formulations exhibit strong mechanical resistance, with friability values ranging from 0.24% to 0.34%. These values are well below the 1% threshold required by IP standards, indicating that the tablets have excellent durability and are unlikely to break or crumble during handling, packaging, or transportation.

The low friability values demonstrate the formulation's ability to maintain its integrity while withstanding mechanical stresses. Tablets with friability values below 1% are considered to have good physical strength, ensuring that they will remain intact throughout the distribution process and during patient use.

9.5 Disintegration Test

The disintegration time for all the tablets was tested, and the results were within the acceptable range for dispersible tablets, which require a disintegration time of less than 30 seconds. The disintegration times across the samples ranged from 28 to 29 seconds, all well below the prescribed limit.

S.No.	Disintegration time (S)
1	29
2	28
3	29
4	29
5	29
6	29

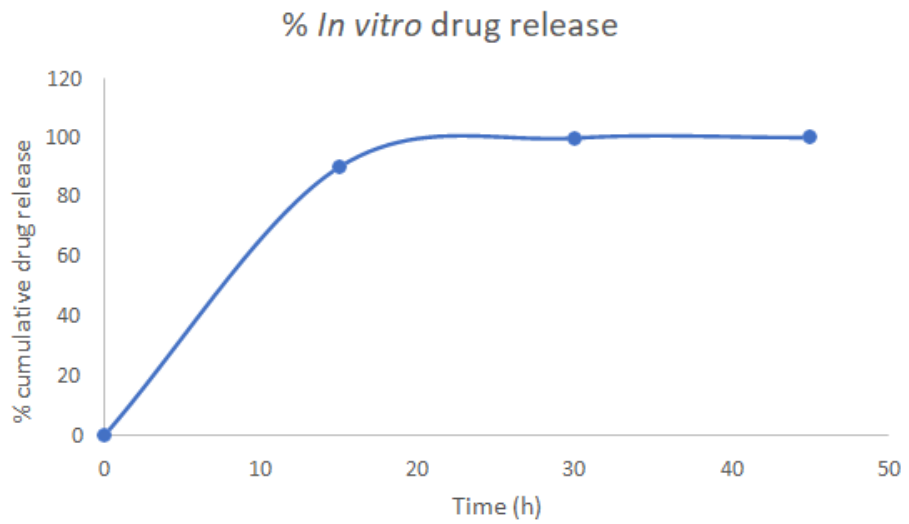
The results demonstrate that all the tablets disintegrated within the required limit of less than 30 seconds, with disintegration times ranging between 28 and 29 seconds. This consistency in performance ensures that the tablets disintegrate rapidly, meeting the regulatory criteria for dispersible tablets.

The uniformity in disintegration times reflects a well-controlled formulation process, ensuring reliable and fast disintegration for all tablets. This is particularly important for dispersible tablets, which must dissolve quickly to facilitate rapid absorption and therapeutic action.Paul, Yash, Sarvan Tyagi, and Bhupinder Singh. "Formulation and evaluation of oral dispersible tablets of zidovudine with different superdisintegrants." International journal of current pharmaceutical review and research 2.2 (2011): 80-85.

9.6 Dissolution studies

The data indicates that 90.14% of the drug was released within the first 15 minutes, with near-complete dissolution (99.83%) achieved by 30 minutes. By 45 minutes, the tablets had fully dissolved, with 100% drug release.

Time (min)	% Drug Released
0	0
15	90.14
30	99.83
45	100



8 CONCLUSION

The study aimed to develop and optimise orally disintegrating tablets (ODTs) of Alogliptin using direct compression and a systematic approach to ensure rapid disintegration, high mechanical strength, and efficient drug release. Through preformulation studies, including solubility and compatibility tests, crucial insights into the drug's physical and chemical properties were obtained, ensuring the formulation's stability and efficacy. The formulation process incorporated Design of Experiment (DoE), which revealed the significant effects of

compression force, disintegrant percentage, and lubricant percentage on tablet hardness and disintegration time. Central Composite Design (CCD) allowed for a comprehensive analysis of these factors and optimization of formulation parameters. The results of the study demonstrated that compression force is a critical factor influencing both tablet hardness and disintegration time. Sodium starch glycolate significantly impacted disintegration time, while magnesium stearate played a role in balancing tablet hardness and disintegration. The optimised formulation achieved a disintegration time of less than 30 seconds and hardness within the ideal range of 4 to 6 N. These properties were validated through post-compression evaluations, which showed consistent tablet quality with excellent uniformity in weight, hardness, friability, and disintegration time. Furthermore, the dissolution studies confirmed near-complete drug release, highlighting the formulation's potential for enhanced patient compliance and therapeutic efficacy. Overall, this study successfully developed Alogliptin ODTs with optimised properties that meet the required standards for fast disintegration, robust mechanical strength, and efficient drug release, offering a promising solution to improve patient adherence and treatment outcomes. Further studies may focus on long-term stability testing and clinical evaluations to fully validate the formulation's therapeutic potential.

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