“Formulation and Development of Oral Dispersible Tablet of Tramadol”

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Abstract:

The present study aimed to formulate, develop, and evaluate oral dispersible tablets (ODTs) of Tramadol hydrochloride using the direct compression method. These tablets are designed to dissolve quickly in the mouth, making them easier to take, especially for patients who have difficulty swallowing conventional tablets. The main objective was to develop tablets with good physical properties, rapid disintegration, effective drug release, and satisfactory stability.Preformulation studies were carried out to examine the physical and chemical properties of Tramadol hydrochloride, including its melting point, solubility, partition coefficient, moisture content, and powder flow properties. Fourier-transform infrared spectroscopy (FTIR) was used to check the compatibility between the drug and the excipients. Ten formulations (F1–F10) were prepared using the direct compression technique with suitable excipients and superdisintegrants. The tablets were evaluated for weight variation, thickness, hardness, friability, wetting time, disintegration time, drug content uniformity, and in vitro drug release. The optimised formulation was also subjected to accelerated stability testing for three months at 40 ± 2°C and 75 ± 5% relative humidity.The results showed that all the formulations had acceptable physical properties. Among the ten formulations, F2 was selected as the optimised formulation because of its overall performance. It showed a wetting time of 25 ± 2 seconds, a disintegration time of 20 ± 2 seconds, and a drug content of 99.2 ± 1.0%. The in vitro dissolution study showed that approximately 99% of the drug was released within 20 minutes, which was comparable to the marketed formulation. During the three-month stability study, F2 maintained satisfactory physical properties and drug-release performance. Its drug content decreased slightly from 99.2% to 98.1%, while drug release at 20 minutes decreased from 99% to 96%.In conclusion, the study showed that Tramadol hydrochloride oral dispersible tablets can be successfully prepared using the direct compression method. Formulation F2 showed rapid wetting and disintegration, high drug content, good drug release, and satisfactory stability under accelerated conditions. These results indicate that F2 may be a promising formulation for oral administration. However, further stability studies and in vivo investigations are needed to confirm its performance in the body and determine its potential therapeutic benefits.

Keywords: Tramadol hydrochloride, oral dispersible tablets, direct compression, formulation development, superdisintegrants, in vitro drug release, stability studies.

INTRODUCTION

1.1 Background of Oral Drug Delivery Systems

Oral drug delivery systems are commonly used for therapeutic agents due to convenience. They include range of dosage designed to deliver through the gastrointestinal tract for systemic or local effects (Aulton & Taylor, 2018).

1.1.1 Importance of Oral Route

High level of patient acceptability (Allen et al., 2014). It is seen to be the most natural and non-invasive approach, enabling patients to self-administer drugs without the assistance of qualified professionals. This is especially beneficial for chronic medicines that call for ongoing care (Shargel et al., 2015). Patient compliance and adherence to recommended treatment regimens are greatly enhanced by this simplicity of delivery.

The potential of the oral route to promote systemic medication administration through absorption through the gastrointestinal (GI) tract is one of its main benefits. The intestine is main location medication due to abundant blood supply, and advantageous permeability properties (Aulton & Taylor, 2018). This makes it possible for medication molecules to enter the systemic circulation efficiently. Furthermore, different release profiles, such as immediate release for quick therapeutic action and sustained or controlled release for long-term drug effect, can be achieved by oral drug delivery systems, improving therapeutic efficacy and lowering dosing frequency (Kumar et al., 2012).

When compared to alternative delivery methods, the oral route is also quite cost-effective. It is appropriate for large-scale production and extensive distribution because to its cheaper manufacturing costs, easier packing requirements, and simplicity of storage and transportation (Deshmukh, 2012). Additionally, parenteral administration is widely accepted by patients of all ages due to the lack of discomfort, infection risk, and consequences.

The oral route has many drawbacks despite these benefits. Variability in bioavailability may result from a number of physiological variables that affect drug absorption, such as stomach pH, gastrointestinal motility, the presence of food, and enzymatic activity (Shargel et al., 2015). Furthermore, certain medications undergo significant hepatic first-pass metabolism, which lowers the quantity of active medication that enters the bloodstream. Additionally, certain medications may induce gastrointestinal distress or become unstable in the stomach's acidic environment.

However, popular favoured method medication because of its many benefits and versatility. Innovative dosage forms like oral dispersible tablets are the result of pharmaceutical technology's constant efforts to overcome its constraints and increase its effectiveness.

1.1.2 Advantages of Oral Drug Delivery

The simplicity, ease of use, and high level of patient acceptance of oral medication delivery systems make them popular. They greatly improve patient compliance, especially in chronic therapy, by enabling simple self-administration without the need for qualified healthcare personnel. Because oral delivery is non-invasive, it is more acceptable to a variety of patient populations because it removes the dangers and pain associated with parenteral approaches.

The cost viability of oral medication distribution is one of its main advantages. The capsules involves well-established manufacturing techniques that scalable. Furthermore, lack strict sterility requirements for these formulations lowers the total cost of manufacture and storage (Kaushik et al., 2004). Because of this, oral medication administration is ideal for large-scale manufacturing and international distribution.

Additionally, oral dose forms provide a great deal of formulation design freedom. To get the intended therapeutic results, medications can be designed into immediate-release, delayed-release, or controlled-release systems. This flexibility makes it possible to minimise adverse effects, optimise medication plasma concentration profiles, and decrease dose frequency (Valleri et al., 2004). Excipients that improve a drug's stability, solubility, and bioavailability can also be added to oral preparations.

The lower incidence of complications and systemic infections as compared to invasive methods is another significant benefit. The safety profile of oral administration is enhanced by the avoidance of problems such needle-related injuries and infection transmission (Chein, 1992). Furthermore, depending on the medication and formulation, oral drug administration permits both systemic effects upon absorption and local activity within the gastrointestinal tract.

Overall, oral drug popular method in pharmaceutical therapy, affordability, safety, formulation flexibility, which propels ongoing developments in drug delivery technology.

1.1.3 Limitations of Conventional Dosage Forms

Despite being extensively utilised, conventional dose forms like tablets and capsules have a number of drawbacks that may have an impact on patient compliance and therapeutic efficacy. One of the main disadvantages is dysphagia, or difficulty swallowing, which is frequent in bedridden, elderly, and paediatric patients (Ghosh & Ghosh, 2011). This frequently results in poor drug adherence, which might jeopardise the effectiveness of treatment.

The delayed commencement of effect is another major drawback. Conventional pills may cause a delayed therapeutic response since they must dissolve and disintegrate in the gastrointestinal system before medication absorption can take place. When circumstances like acute pain or allergic responses call for a quick initiation of action, this delay can be very troublesome (Hirani et al., 2009). Additionally, physiological variables including stomach can cause variations in medication absorption when using typical oral dose forms. Inconsistent bioavailability may result from these variables' effects on drug permeability and dissolution (Ratnaparkhi et al., 2009). Additionally, medications taken orally frequently experience considerable drastically lower quantity active medication that enters the systemic circulation. Another drawback is the possibility of gastrointestinal irritation brought on by some medications, which might result in negative side effects such nausea, vomiting, or stomach pain (Fu et al., 2004). Additionally, certain medications lose their therapeutic value because stomach's are broken down digestive enzymes. These limitations highlight the need for systems, oral dispersible, which can overcome issues related to swallowing difficulties, delayed onset of action, and variable bioavailability, thereby improving overall therapeutic performance.

1.2 Patient Compliance and Need for Novel Dosage Forms

The effectiveness of medication therapy is largely dependent on patient compliance. However, conventional dosage forms often fail to ensure adequate adherence due to factors frequent dosing, (Jin et al., 2008; Brown & Bussell, 2011). Due to these restrictions, several medication delivery methods have been developed with the goal of increasing patient acceptability, convenience, and therapeutic results (Dixit & Puthli, 2009).

1.2.1 Concept of Patient Compliance

The degree complies instructions about dose, timing, and duration of therapy is known as patient compliance, also known as medication adherence (Osterberg & Blaschke, 2005). It is essential to get the best possible treatment results, especially when long-term medicine is needed for chronic conditions including diabetes, hypertension, and pain management. Treatment failure, illness progression, and higher healthcare expenses are all linked to poor compliance, which is a significant worldwide health concern (Sabaté, 2003).Patient-related, therapy-related, and formulation-related variables are the three main categories of factors that affect patient compliance. Lack of knowledge, misinterpretation of medical problems, amnesia, and psychological resistance to medicine are examples of patient-related variables (Jin et al., 2008). Adherence is further hampered by therapy-related issues such complicated dosage schedules, protracted treatment, and negative medication responses (Brown & Bussell, 2011). All of these elements work together to provide less than ideal treatment results.

Patient compliance is also significantly influenced by formulation-related variables. Patient acceptance is strongly impacted by the physical attributes of dose forms, including size, shape, taste, and convenience of administration. Particularly for paediatric and elderly populations, large or poorly constructed, which might result in partial dose or medication withdrawal (Mittal et al., 2011). Furthermore, a patient's willingness to continue taking medication may be adversely affected by an unpleasant taste and a delayed beginning of effect.

The creation of patient-centric medication delivery systems has received a lot of interest as a solution to these problems. By quickly dissolving, novel dosage forms like oral dispersible pills are intended to make administration easier. These formulations lessen the burden of swallowing issues, improve palatability, and increase patient convenience (Dixit & Puthli, 2009). Therefore, these cutting-edge delivery methods are essential for enhancing patient compliance and overall treatment efficacy.

1.2.2 Dysphagia and Swallowing Difficulties

The traditional dose is greatly impacted by dysphagia, a common problem that is described as difficulty swallowing. In addition to people with neurological problems, stroke, Parkinson's disease, and other illnesses affecting the muscular and neural regulation of swallowing, it is especially common in paediatric and elderly populations (Logemann, 1998). Because patients may be unable or reluctant to take pharmaceuticals in solid dose forms, this disease presents a significant obstacle to attaining successful pharmacological therapy.

The mouth cavity, throat, and oesophagus all work in unison during the intricate physiological process of swallowing. Any disruption in this process may make it harder to swallow solid oral dose forms, which might cause pain, increase the risk of choking, or cause aspiration (Matsuo & Palmer, 2008). As a result, dysphagic patients frequently break, crush, or chew pills, which might change the medication release profile and jeopardise the safety and effectiveness of treatment.
Patient compliance and adherence to prescription regimens are significantly impacted by dysphagia. According to studies, a significant percentage of patients have trouble swallowing pills, which can result in missed doses, incorrect administration, or total medication withdrawal (Liu et al., 2014). This is especially problematic for chronic illnesses, because taking medicine consistently is crucial to successful treatment. Additionally, dysphagic patients' demands are not met by traditional dose forms. The issue is made worse by the large pill size, poor palatability, and the need for water to swallow. In such cases, alternative dosage forms that do not require swallowing, such as oral dispersible tablets, offer a promising solution. Thus, presence dysphagia highlights the necessity for patient-friendly, enhance compliance, and ensure better therapeutic outcomes.

1.2.3 Need for Fast-Acting Drug Delivery Systems

Due to the necessity for quick therapeutic response in a variety of clinical diseases, including acute pain, allergic responses, migraines, and emergency circumstances, dramatically in recent years. Because they need to dissolve, disintegrate, before medication enters, conventional dosage forms frequently show a delayed beginning of action (Bhowmik et al., 2009). Treatment efficacy may be diminished by this delay, particularly in situations when prompt alleviation is crucial. By increasing the rate of medication release and absorption, fast-acting drug delivery devices are intended to get around these restrictions. These systems speed up the beginning of pharmacological activity by facilitating fast disintegration and breakdown. The time needed to reach therapeutic plasma concentrations is shortened by formulations like oral dispersible tablets, which make medication available absorption either through the buccal mucosa or after swallowing (Kuccherkar et al., 2003). Enhanced patient compliance is a key factor propelling the creation of fast-acting technologies. Quick symptom alleviation is typically preferred by patients, which increases their desire to follow treatment plans (Seager, 1998). Fast-acting formulations can help those who have trouble swallowing since they make it easier to administer medications and do away with the requirement for water. Additionally, by reducing pre-systemic metabolism and gastrointestinal tract degradation, fast drug delivery devices can increase bioavailability. These systems can improve therapeutic efficacy while perhaps lowering the necessary dosage and related adverse effects by speeding up absorption (Chang et al., 2000). With the goal of offering quick onset of action.

1.3 Oral Dispersible Tablets (ODTs): An Overview

A new family of solid dose forms called oral dispersible tablets (ODTs) was created to increase patient compliance and offer quick medication action. (Habib and others, 2000).

1.3.1 Definition and Concept of ODTs

By removing the requirement for water and promoting fast disintegration, the basic idea behind ODTs is to improve patient convenience and guarantee a prompt commencement of action. Superdisintegrants and other excipients that facilitate quick water absorption and tablet disintegration by processes including swelling, wicking, and deformation are used in the formulation of these tablets. Consequently, the medication is released rapidly, which enhances its solubility and absorption properties (Bi et al., 1996).

When it comes to patient-centric medication distribution, ODTs are a huge benefit, especially for young. Furthermore, by permitting partial absorption via the oral mucosa, these formulations can improve the beginning of therapeutic action and, in some situations, increase bioavailability (Fu et al., 2004). Due to developments in formulation technologies and the growing need for dosage forms that are easy to use, the idea of ODTs has been increasingly significant in recent years. ODTs with sufficient mechanical strength.

1.3.2 Mechanism of Disintegration in Oral Cavity

The interaction between the tablet matrix and saliva drives the quick and intricate breakdown of oral dispersible tablets (ODTs) in the oral cavity. Because of its porous nature, saliva immediately enters, causing breakdown without need for outside stimulation. The kind and concentration of superdisintegrants as well as the formulation's physicochemical characteristics this technique (Shangraw, 1980). Wicking, also known as capillary action, is one of the main processes at play. Saliva is sucked into the tablet through capillary pores, lowering the cohesive forces between particles and promoting tablet breakdown. Another important process is swelling, in which superdisintegrants expand after absorbing water, creating internal pressure that speeds up pill disintegration. Cross-linked polymers, for example, are very successful in this role because of their large swelling capacity (Zhao & Augsburger, 2005). Deformation recovery has a role in disintegration in addition to wicking and swelling. Particles are deformed during compression and tend to return shape, which disrupts the tablet matrix's structural integrity. Another process is particle repulsion, in which hydration increases the electrostatic interactions between particles, encouraging disintegration and separation. (Markl & Zeitler, 2017).

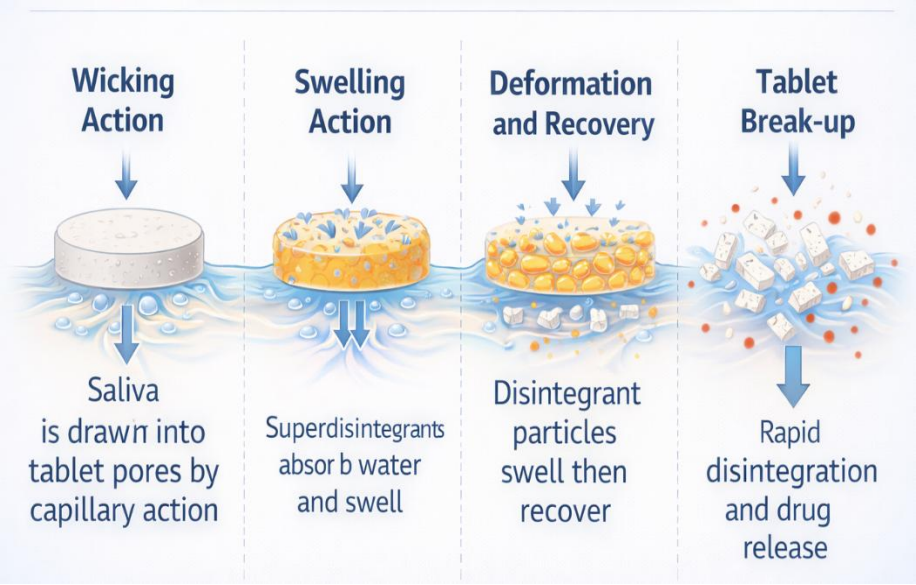

Fig 1.1: Mechanism of Disintegration of ODTs

1.3.3 Advantages of ODTs

Oral dispersible tablets (ODTs) their numerous benefits. Improved patient compliance is one of the most significant advantages, especially for younger, older, conventional pills. ODTs' capacity convenience and administration simplicity (Dobetti, 2001). ODTs have a speedy beginning of effect because they dissolve and disintegrate quickly in saliva, making drugs more readily available for absorption. This advantageous for medications that need to start working right away. Enhanced patient acceptance is another significant benefit. ODTs are made with flavourings, sweeteners, and pleasant tastes to improve patient satisfaction and palatability. This is especially significant for paediatric formulations, where adherence is greatly influenced by taste. ODTs also make vulnerable persons safer by lowering the danger of aspiration and choking. Because ODTs may be administered without water, they are also portable and convenient for usage while on the road. From a medicinal standpoint, they provide precise dosage and may be made for both systemic and local drug administration. All things considered, ODTs are a patient-centered strategy that enhances treatment effectiveness, convenience, and compliance.

1.3.4 Limitations and Challenges of ODTs

ODT research and formulation face a number of difficulties despite their many benefits. Low mechanical strength is one of the main drawbacks since the high porosity needed for quick disintegration frequently produces breaking, packing, transit (Habib et al., 2000). For formulators, striking a balance between adequate hardness and quick disintegration continues to be a crucial task.

Moisture sensitivity is another important problem. Because of their hydrophilic excipients and porous structure, ODTs surroundings. This may cause moisture-sensitive medications to degrade, disintegrate too soon, and become less stable. Therefore, specific packaging is needed, such as desiccant-containing containers or moisture-resistant blister packs (Seager, 1998). Since the medication is delivered in the oral cavity and comes into close touch with taste buds, flavour masking is a significant formulation problem. Patient acceptability may be adversely affected by the bitter or disagreeable taste of many active medicinal substances. To solve this problem, effective taste masking methods such coating, complexation, or flavouring compounds are crucial (Sohi et al., 2004). Additionally, because excessive dosages may jeopardise tablet integrity and disintegration qualities, ODTs have a restricted capacity for drug loading. This dosage form is frequently inappropriate for medications with high dosages, poor compressibility, or instability in saliva.Furthermore, differences in excipient characteristics and processing circumstances might make it difficult to maintain consistency and repeatability during large-scale manufacture. Therefore, careful formulation design, optimisation, and suitable packaging methods are necessary to overcome these limits and guarantee product quality and stability, even if ODTs provide substantial advantages in terms of patient compliance and quick drug action.

Table 1.1: Ideal Characteristics of Oral Dispersible Tablets

Property	Requirement
Disintegration Time	Less than 30 seconds
Mechanical Strength	Adequate for handling
Taste	Pleasant / masked
Mouthfeel	Smooth, non-gritty
Stability	Low moisture sensitivity
Drug Release	Rapid and complete
Dose Uniformity	High
Compatibility	With excipients

1.4 Key Components of ODT Formulation

A variety of specialised oral dispersible tablets guarantee quick disintegration, sufficient mechanical strength, and palatability. Superdisintegrants, fillers, lubricants, and taste-masking agents are some of these ingredients that are essential to the formulation's intended performance.(Rowe et al., 2009).

1.4.1 Superdisintegrants

In order to facilitate quick disintegration upon contact with saliva, superdisintegrants are an essential utilised oral dispersible. Although they are introduced in little amounts, they significantly affect the dosage form's overall performance and disintegration time. Superdisintegrants are primarily used to break up tablets into tiny pieces, which increases the surface area accessible for dissolving and improves medication release.

Deformation recovery, which contributes to structural disruption, happens when compressed particles resume their former shape after hydration (Mohanachandran et al., 2011). These materials are favoured because they are very effective, operate quickly, and work well with a variety of medications and excipients. Because of their biocompatibility, affordability, and environmental friendliness, natural superdisintegrants made from plant sources are also being investigated (Sharma et al., 2010). The kind and concentration of superdisintegrant have a big impact on how well ODTs work. An ideal concentration is crucial since too much can compromise tablet stability and hardness, while too little can cause incomplete disintegration.

Table 1.2: Commonly Used Superdisintegrants in ODT Formulation

Superdisintegrant	Mechanism of Action	Typical Concentration (%)	Key Advantages
Croscarmellose Sodium	Swelling & wicking	1–5%	Rapid disintegration, high efficiency
Sodium Starch Glycolate	Swelling	2–8%	High water uptake capacity
Crospovidone	Wicking & deformation	2–5%	Fast action, no gel formation
Low-substituted Hydroxypropyl Cellulose	Swelling	2–10%	Good compressibility

1.4.2 Fillers and Diluents

In (ODTs), fillers diluents are essential excipients that are mainly used to boost the formulation's bulk and guarantee precise dosage, especially when the active pharmaceutical component is present in tiny amounts. Fillers major physicochemical aspects tablets, such as compressibility, flow characteristics, porosity, and overall tablet integrity, in addition to their basic function as bulking agents.

The choice of fillers is crucial when it comes to ODTs since these formulations need to dissolve quickly and have a nice mouthfeel. Because they dissolve fast in saliva and help create a smooth, non-gritty feel, water-soluble and hydrophilic fillers are typically selected. Mannitol is one of the most popular fillers because of its exceptional solubility, non-hygroscopic nature, and natural sweet flavour, which improves patient acceptance and creates a cooling feeling in the tongue (Ohrem et al., 2014).

Another popular diluent is lactose, which is compatible with a variety of medications and has high compressibility. It offer distinct compaction and flow characteristics appropriate for direct compression. However, those who are lactose intolerant may not be able to utilise it. Because of their sweetness and quick solubility, dextrose and sorbitol are also used as fillers in ODT formulations, improving the organoleptic characteristics of the dosage form (Sheskey et al., 2017).

Because of its many uses, microcrystalline cellulose (MCC) is often utilised in ODT formulations. In addition to serving as a filler, it also improves compressibility and facilitates disintegration by encouraging water absorption. MCC is a popular excipient in directly compressed ODTs because it gives the tablet enough mechanical strength while retaining quick disintegration (Thoorens et al., 2014). Tablet performance is also significantly influenced by the fillers' morphology, moisture content, and particle size. While coarse particles increase flow but may decrease tablet strength, fine particles may increase compressibility. Guarantee constant tablet quality and homogeneous die filling, an ideal

equilibrium must be reached. Furthermore, the stability of ODTs may be affected by the hygroscopic nature of certain fillers, especially in situations with high humidity.

All things considered, fillers and diluents are essential to the effective formulation of ODTs and are not only inert ingredients. In order to attain the ideal balance between quick disintegration, sufficient mechanical strength, and palatability, their appropriate selection and optimisation are crucial, eventually guaranteeing the dosage form's efficacy and patient acceptance.

1.4.3 Lubricants and Glidants

In order to increase the manufacturability and processing efficiency of tablet formulations, lubricants and glidants are essential excipients in the formulation of oral dispersible tablets (ODTs). By lowering friction, improving powder flow, and guaranteeing regular die filling, these excipients are essential during tablet compression and help produce tablets with constant weight, hardness, and quality (Patel & Poddar, 2011).

Tablet material and punch surfaces, lubricants are added to tablet compositions. This lessens the likelihood of wear and strain on the equipment as well as sticking, picking, and damage to the tablet. Stearic acid, sodium stearyl fumarate, and magnesium stearate are common lubricants. Because of its superior lubricating qualities and efficacy at low concentrations (usually 0.25–2%), magnesium stearate is the most often utilised of these (Perrault et al., 2009).

However, excessive lubricant usage might negatively impact tablet characteristics, thus it must be properly regulated. In ODT formulations where quick disintegration is required, hydrophobic lubricants like magnesium stearate can create a film over particles, decreasing wettability and slowing down disintegration and dissolution. Therefore, to combine lubrication efficiency with tablet performance, lubricant concentration optimisation and appropriate mixing procedures are crucial. Conversely, by lowering interparticle friction, glidants are employed to enhance the flow characteristics of powder mixes. For consistent die filling and to avoid weight fluctuation in tablets, good flowability is essential. Colloidal silicon dioxide and talc are common glidants that improve bulk movement and powder flow by decreasing particle cohesion. (Carstensen & Rhodes, 2000).

1.4.4 Sweeteners and Flavoring Agents

In (ODTs), sweeteners, flavouring agents are essential excipients because they have a major impact on the dosage form's palatability and patient acceptance. Taste masking is a crucial part of formulation development since ODTs dissolve immediately, bringing into direct touch with taste receptors (Mennella & Beauchamp, 2008). Poor patient compliance can result from an unpleasant or bitter taste, especially in younger and older patients.

Sweeteners are added to medications to make them taste better and to cover up their harshness. They may be roughly divided into two categories: artificial and natural sweeteners. Because of their compatibility and palatable taste characteristics, natural sweeteners including sucrose, glucose, sorbitol, and mannitol are frequently utilised. Because of its non-hygroscopic nature, quick solubility, and chilling sensation—all of which improve mouthfeel and patient satisfaction—mannitol is frequently used in ODT formulations. In addition to its

sweetness, sorbitol has other advantages such better texture and moisture retention (Rowe et al., 2009).

Aspartame, saccharin sodium, and sucralose are examples of artificial sweeteners that are widely used because of their high sweetness intensity, which enables efficient taste masking at low doses without appreciably affecting tablet size or weight (Walsh et al., 2013). These sweeteners are very helpful in formulations that need to have as little sugar as possible, including those for people with diabetes. However, while developing a formulation, their stability and compatibility with other excipients need to be carefully considered.

Sweeteners and flavouring agents work together to improve ODTs' overall sensory profile. These substances offer a nice aftertaste and assist to cover any lingering bad tastes. Fruit flavours including orange, strawberry, and banana are frequently utilised, along with mint and vanilla. Because some flavours are better at concealing particular forms of bitterness, composition target audience (Ayenew et al., 2009).

Sweeteners and flavouring agents must be carefully chosen and optimised, taking into account things like compatibility, stability, and how they affect tablet qualities. Tablet hardness, disintegration time, and overall formulation stability may all be impacted by overuse of these excipients. Regulations pertaining to artificial sweeteners' safety and permissible daily use must also be taken into mind.

All things considered, essential creation ODTs because they improve mouthfeel, taste, and patient compliance. Their proper mix and selection greatly enhance the dose form's acceptability and efficacy.

1.5 Rationale for Developing ODTs

The aim to increase patient compliance, improve convenience, and get around the drawbacks of traditional oral dose forms oral dispersible tablets (ODTs). Because these formulations dissolve quickly, they especially well-suited trouble and for circumstances when prompt medication delivery is necessary (Scarpa et al., 2017).

1.5.1 Need for Rapid Onset of Action

In effectively manage a variety of acute and emergency clinical diseases, including severe pain, migraines, allergic reactions, and cardiovascular events, when prompt therapeutic intervention is required, rapid beginning of action is a critical prerequisite. Any delay in the medication's effects in these circumstances might increase the patient's suffering and even cause major problems. Due to the sequential processes of disintegration, dissolution, gastric emptying, and intestinal absorption, which together postpone the achievement of effective plasma drug concentrations, frequently show a slower onset of action (Dressman et al., 1998).

To get around these restrictions, oral dispersible tablets dissolve quickly—usually a matter of seconds.

ODTs rapidly break down into tiny saliva after being administered, thereby expanding the surface area accessible for dissolving. This quick disintegration facilitates quicker medication availability for systemic circulation by speeding up the dissolving process, which is frequently the rate-limiting stage for drug absorption (Klancke, 2003).

ODTs may facilitate pre-gastric absorption of certain medications through the buccal and sublingual mucosa in addition to improving dissolution. Because of the oral mucosa's high vascularization, medication molecules. For medications with appropriate physicochemical characteristics like low molecular weight and sufficient lipophilicity, this can lead to improved bioavailability and a faster pharmacological response (Senel &Hıncal, 2001).

The decrease in gastric transit time dependence is another significant aspect that contributes to quick onset. ODTs eliminate the lag time associated with tablet breakdown by dissolving or dispersing the medicine in the mouth before it enters the gastrointestinal tract. Faster absorption and more consistent pharmacokinetic profiles result from this. Additionally, better patient satisfaction and adherence are strongly associated with quick intervention. Patients are more inclined to accept and choose formulations that provide rapid therapeutic benefits when dealing with painful or uncomfortable situations. Compliance and overall treatment results are improved by this psychological advantage (Herdman, 2007).

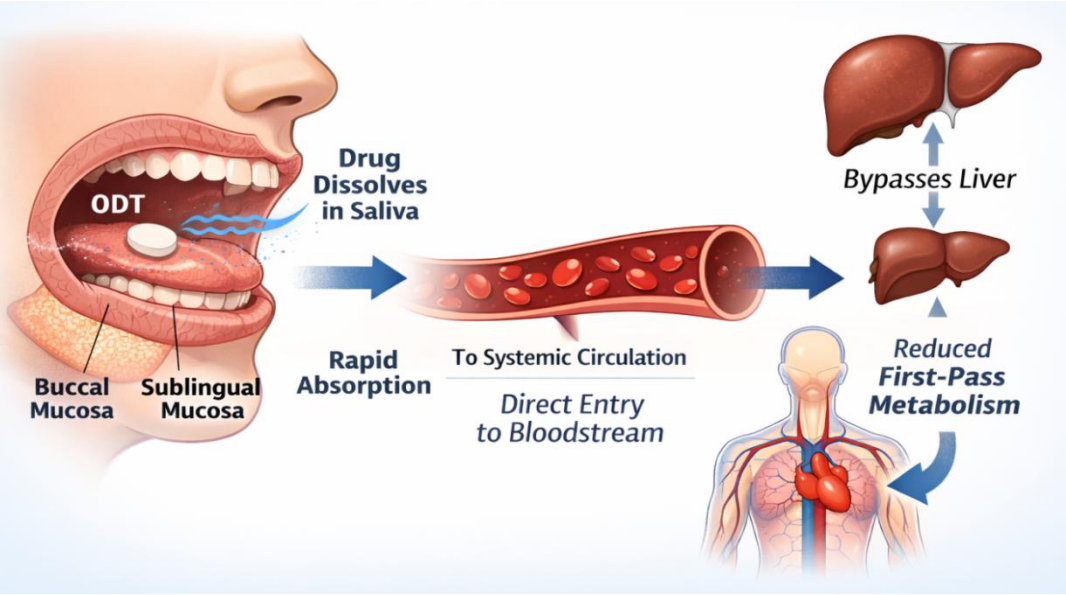

Fig 1.2: Oral Cavity Absorption Pathway

1.5.2 Improvement in Patient Compliance

Achieving the best possible treatment results depends on patient compliance, which is the degree to which patients adhere to recommended drug schedules. However, due to things like trouble swallowing, the requirement for water, an unpleasant taste, and a delayed beginning of action, standard dose forms frequently fail to guarantee appropriate adherence (Claxton et al., 2001).

By providing a patient-friendly dose dissolves oral dispersible tablets especially made to address these issues.

Because of this feature, ODTs are especially helpful for dysphagic. ODTs greatly lessen the difficulty of taking medications and increase therapeutic adherence by streamlining the administration procedure (Ibrahim & El-Setouhy, 2010).

The increased palatability of ODTs is another significant element that contributes to better compliance. Patients find the formulation more. This is particularly important for young

patients, whose desire to take medication is greatly influenced by taste (Venugopal, 2011). Because ODTs don't require water and may be taken anywhere at any time, they also offer ease and flexibility in administration. This is especially helpful when patients are travelling or there is restricted access to water. Furthermore, ODTs' speedy beginning of action results in faster symptom alleviation, which improves patient perception and therapy adherence (Sastry et al., 2000).

Psychologically speaking, immediate therapeutic response and simplicity of administration boost patient trust in the drug, which encourages compliance even more. Better adherence is also influenced by less dose mistakes, particularly in older patients, and increased safety because of a decreased danger of choking. All things considered, the creation of ODTs exemplifies a patient-centric approach to pharmaceutical design, overcoming significant obstacles to compliance and guaranteeing increased therapeutic efficacy through better palatability, convenience of administration, and quick action.

1.5.3 Advantages over Conventional Tablets

Oral dispersible tablets (ODTs) are a popular option in contemporary drug delivery systems because they have a number of clear benefits over traditional tablets. One of the biggest benefits is that they dissolve quickly, eliminates the issues that come traditional pills. Paediatric, elderly, and dysphagic patients—who frequently struggle with conventional solid dose forms—benefit most from this characteristic (Kuchekar& Arumugam, 2001; Fu et al., 2004).

The quick beginning of action of ODTs is another significant benefit. ODTs dissolve fast in saliva, making the medication easily accessible for absorption, in contrast to traditional tablets, which take time to dissolve and disintegrate in the digestive system.

This leads to quicker therapeutic effects, which is crucial for ailments including pain, nausea, and allergic responses that need to be relieved right away (Chang et al., 2000; Bhowmik et al., 2009). ODTs greatly increase patient convenience and compliance. They can be used while travelling or in places. Furthermore, using sweeteners and flavouring compounds to improve taste and mouthfeel increases patient acceptance, especially in paediatric populations (Hirani et al., 2009). ODTs may provide improved bioavailability for some medications from a pharmacokinetic standpoint. The medication can sometimes avoid hepatic partial through oral mucosa, quick disintegration and dissolution enhance the surface area accessible for absorption. (Ghosh & Pfister, 2005).

The lower danger of aspiration and choking, which is frequently linked to traditional pills, is another significant benefit, particularly for older and bedridden patients. Compared to liquid dosage forms, which may have problems with microbiological contamination and a shorter shelf life, ODTs also offer precise dosing and superior stability (Seager, 1998). Additionally, because ODTs methods, lyophilization, sublimation, they provide benefits in terms of production flexibility. Tablet characteristics including hardness, porosity, and disintegration time may be optimised using these methods (Hirani et al., 2009).

Despite these benefits, formulation issues including flavour masking, moisture sensitivity, and mechanical strength need to be carefully considered. Nevertheless, due to their numerous clinical and patient-centric benefits.

Table 1.3: Comparative Features of Oral Dispersible Tablets and Conventional Tablets

Parameter	**Oral Dispersible Tablets (ODTs)**	**Conventional Tablets**
Disintegration Time	Very rapid (within seconds)	Slow (minutes)
Water Requirement	Not required	Required
Patient Compliance	High	Moderate to low
Suitable Population	Pediatric, geriatric, dysphagic	General population
Onset of Action	Rapid	Delayed
Risk of Choking	Very low	Higher
Bioavailability	May be improved	Normal
Taste Masking	Essential	Less critical
Convenience	High (portable, easy use)	Moderate

1.6 Scope of the Study

In order to increase patient compliance, guarantee quick drug release, and boost therapeutic efficacy, development oral dispersible (ODTs). In order to improve patient-centric drug delivery systems, the study intends to optimise formulation parameters and assess ODT efficacy in relation to traditional dose forms (Preis et al., 2014).

1.6.1 Clinical Significance

Oral dispersible tablets (ODTs) are clinically significant because they potentially solve major issues with traditional oral drug delivery, especially those related to patient compliance, administration simplicity, and quick therapeutic response. These formulations are particularly helpful in clinical situations including acute pain, migraines, allergic reactions, and neurological crises where prompt pharmacological action is necessary (Kumar et al., 2012).

ODTs quite beneficial. ODTs increase medicine adherence and lower the risk of missed doses or incorrect administration by removing the requirement for water and facilitating quick breakdown in the oral cavity (Liu et al., 2014).

Because of their quick disintegration and dissolution, ODTs can improve medication effectiveness from a therapeutic standpoint by offering a quicker beginning of action. Drugs may occasionally increasing bioavailability (Boateng & Auffret, 2015). Better clinical results and more consistent pharmacokinetic profiles may result from this.

Additionally, ODTs are crucial in enhancing patient safety. The reduced risk of choking and aspiration makes them suitable for elderly neurological impairments. Their therapeutic efficacy is further enhanced by their simplicity of administration in emergency conditions, especially when water is scarce.

Additionally, by providing ease, palatability, and quick symptom alleviation, ODTs enhance patient happiness and quality of life. Together, these elements encourage greater commitment to treatment plans, which eventually improves therapeutic outcomes.

Therefore, the creation of ODTs has significant therapeutic significance as it addresses unmet requirements in contemporary healthcare and offers a practical and patient-friendly substitute for traditional dose forms.

1.6.2 Industrial Relevance

Due to their increasing demand in the global pharmaceutical industry and their potential to improve product differentiation and lifecycle management, the development of oral dispersible tablets (ODTs) has substantial industrial importance. Pharmaceutical companies are concentrating on novel dosage forms like ODTs to boost patient compliance and get a competitive edge in light of the growing emphasis on patient-centric (Arya., 2010).

Market potential economic feasibility of ODTs is one of their main industrial advantages. Convenient and simple-to-administer dose forms are becoming more and more popular, especially among younger and older populations. ODTs successfully meet this requirement, which boosts product adoption and broadens the market. Additionally, by creating new formulations, pharmaceutical companies may use ODT technology to prolong the lifespan of current medications, preserving market exclusivity and increasing revenue (Fu et al., 2004).

From a production standpoint, ODTs may be made with traditional tableting methods such direct compression, which are readily scalable and reasonably priced. Large-scale manufacturing is made easier and production complexity is decreased without needing major changes to current machinery. Despite being more complicated, advanced technologies like lyophilization and sublimation provide greater chances for product innovation and differentiation (Bhaskaran & Narmada, 2002).

Additionally, ODTs provide benefits for distribution and packaging. Many ODTs created by direct compression show enough stability for conventional packaging methods, even though other formulas call for specific moisture-resistant packaging. Compared to liquid formulations, its solid dosage form guarantees greater stability and a longer shelf life, minimising storage, transportation, and microbiological contamination issues.

Additionally, ODTs are in line with patient-centered and regulatory developments in the pharmaceutical sector. The creation of formulations that enhance patient adherence and therapeutic results is being promoted more and more by regulatory bodies. ODTs' acceptance is increased and regulatory clearance procedures are made easier when they can live up to these expectations.

Additionally, ODTs offer chances for brand innovation and differentiation, enabling pharmaceutical businesses to market their medications as more practical and user-friendly substitutes for traditional tablets. This can have a big impact on patient preferences and prescribing practices, which will eventually lead to a larger market share.

ODTs are therefore a key emphasis area in pharmaceutical research and development due to their significant market demand, simplicity of production, potential for product innovation, and alignment with contemporary healthcare demands.

1.6.3 Future Prospects of ODTs

Oral dispersible tablets (ODTs) have become a viable drug delivery strategy, and the rising emphasis on personalised treatment, patient desire for convenient dose forms, and continuous improvements in pharmaceutical technology all significantly support their future prospects. It is anticipated that the performance and suitability of ODTs in contemporary therapies will be further improved by the ongoing development of formulation techniques and excipient technologies.

Cutting-edge technologies, solid dispersions nanotechnology, to increase the solubility and bioavailability medications is future objectives ODT research. Spectrum of medications appropriate for this dosage form can be increased by including nanoparticles and amorphous solid dispersions into ODT formulations, which can greatly improve drug solubility and absorption. The utilisation of innovative and multipurpose excipients, such as co-processed excipients that combine several functions including increased stability, greater compressibility, and quick disintegration, is another crucial area of study. The biocompatibility, sustainability, and affordability of natural polymers and plant-derived superdisintegrants are also attracting interest (Thoorens et al., 2014).

Additionally, patient-centric and personalised care methods are intimately related to the future of ODTs. It is now feasible to create personalised ODTs with specific medication dosages, forms, and release profiles based on the requirements of each patient thanks to technological developments like 3D printing. In paediatric and geriatric treatment, when dosage flexibility is crucial, this strategy is very helpful (Scoutaris et al., 2018).

Furthermore, there is growing interest in creating ODTs for complex pharmacological compounds and biopharmaceuticals, which have historically had difficulties with oral administration. Peptides, proteins, and other delicate compounds may be successfully included into ODT systems thanks to advancements in formulation and stabilisation procedures.

From an industrial standpoint, simplicity enhanced ODTs are expected to lead to a substantial increase in their demand worldwide. In order to produce novel ODT formulations with improved performance and wider therapeutic uses, pharmaceutical companies are probably going to invest more in research and development.

CHAPTER-2

LITERATURE REVIEW

Introduction to Oral Drug Delivery Systems

Ye et al.,(2025) reported that "(IBS) widely occurring associated with psychological disturbances, abdominal pain, and changes in bowel habits, with prevalence rates exceeding 20% in certain regions. Experience greater variations in drug bioavailability following oral administration compared to healthy individuals. Despite this challenge, only limited studies have focused IBS management. Present combining tanshinone IIA-loaded liposomes with spirulina was developed to improve IBS therapy. The passive targeting ability toward intestinal villi along with the enhanced adhesive properties of spirulina and nanoparticles provided superior pharmacokinetic stability compared to conventional enteric-coated capsules. Moreover, SP@TIIAn showed significant effectiveness in alleviating several gut–brain-related symptoms of IBS."

Han et al.,(2024) reported that "Oral targeted delivery has emerged as a rapidly advancing domain within targeted therapeutic systems, gaining substantial scientific interest over recent years. Beyond its conventional application in achieving localized treatment within the gastrointestinal tract (GIT), current research is increasingly focused on enabling oral delivery systems to access and treat pathological conditions situated at sites distant from the GIT. This review summarizes the core principles and contemporary progress achieved in this area. Since numerous physiological barriers exist throughout the gastrointestinal environment, delivery carriers are required to successfully penetrate the intestinal epithelium to attain systemic distribution toward remote tissues. Recent pioneering studies have confirmed that both micro- and nanoscale carriers are capable of crossing gastrointestinal barriers in their intact form and subsequently reaching various peripheral organs and tissues. Among the proposed uptake mechanisms, transport mediated by microfold (M) cells is regarded as the dominant pathway for particulate absorption, although transcellular and paracellular routes are also recognized for their contributory roles. Furthermore, apart from established biological and physicochemical determinants, the adsorption of biomolecules leading to protein corona formation influencing in vivo destiny performance. This concept remains the phases of development, directed toward extraintestinal exhibited encouraging therapeutic prospects for conditions associated with inflammation, cancer, and disorders involving the lymphatic and mononuclear phagocyte systems."

Bahraminejad et al.,(2025) reported that "This review aimed to highlight the historical evolution systems. An analysis of publications related to sublingual and buccal administration revealed four distinct periods of progressive research growth between 1950 and 2025. During the initial stage (1950–1982), only limited potential these delivery routes. Subsequent exploratory expansion phase (1983–1993) witnessed increased attention toward the therapeutic application of nitroglycerin for cardiovascular disorders, opioid-based pain therapies, and peptide as well as hormonal treatments. Advancement characterized molecule therapeutics dependence analgesic therapy, extensive utilization of animal models to better understand pharmacokinetic behavior through buccal and sublingual pathways, incorporation

of permeation enhancers, continued peptide and hormone-based therapies, and several notable approvals by the FDA. The most recent phase, termed the innovation and integration era (2010–2025), involved substantial technological progress."

Yoshida et al.,(2023) stated that "(DDS regulate dosage, rate, target site drug administration. Among the different DDS approaches, quantity-controlled systems primarily enhance drug solubility and absorption, thereby improving bioavailability. Controlled-release formulations that regulate both the timing and quantity of drug release are generally categorized into membrane-based, matrix-based, osmotic, and ion-exchange systems. Timed-release formulations similarly modulate drug release behavior and absorption patterns. Site-specific and quantity-regulated DDS mainly include colonic targeting and intestinal lymphatic delivery systems aimed at optimizing drug release and pharmacokinetic performance. In addition, systems capable of simultaneously controlling site, time, and quantity of drug release include gastroretentive formulations and localized oral cavity delivery platforms, which improve retention time, release characteristics, and ADME properties. Overall, DDS technologies contribute to enhanced therapeutic efficacy, minimization of adverse reactions, and optimization of dosing schedules, ultimately improving patient outcomes and treatment value. This review emphasizes the clinical significance and industrial relevance of commercially available oral DDS technologies. It discusses the technological aspects of both investigational and marketed systems while outlining the advantages and limitations associated with their industrial-scale development, considering factors such as excipient selection, manufacturing processes, and storage stability. Furthermore, the review highlights patient-centered benefits demonstrated through clinical studies, including expanded therapeutic options, improved efficacy, reduced side effects, lower dosing frequency and hospital visits, simplified administration."

Yang et al.,(2023) stated that "Protein and peptide therapeutics are commonly administered through injectable routes to ensure high bioavailability; however, this mode of administration often reduces patient compliance. Consequently, oral and transdermal delivery systems, which are minimally invasive and associated with better patient adherence, have emerged as promising alternatives to injections. Despite their advantages, the successful oral and transdermal delivery of biologically active proteins requires overcoming significant physiological barriers, specifically the gastrointestinal barrier in oral delivery and the skin barrier in transdermal administration. Recent advancements in material science and emerging technologies have shown considerable potential in addressing these challenges. This review summarizes recent progress approaches, modification techniques, nanoparticle-based carriers, platforms, along with permeation delivery microneedle technologies for transdermal systems. Additionally, the review discusses current limitations, future opportunities, and translational aspects of these innovative delivery strategies with particular emphasis on technological advancement and clinical applicability."

Zhang et al.,(2022) reported that "Topical drug administration within the oral cavity is associated with several limitations due to the unique and highly complex nature of the oral environment. Multiple factors can influence the effectiveness of locally applied medications, as conditions such as saliva secretion, food intake, and continuous mechanical activity may interfere with the performance and retention of free drug molecules. These delivery systems have found important applications in the prevention and management of dental caries, periodontal disorders, periapical infections, and localized anesthetic administration. Various

carrier platforms have been designed for clinical use, including nanoparticles, hydrogels, nanofibers, films, and scaffold-based systems. This review focuses on the comparative advantages and limitations of these carrier materials while also discussing their preparation techniques and therapeutic applications, with the aim of providing updated insights into the design."

Overview of Oral Dispersible Tablets (ODTs)

Hannan et al.,(2016) stated that "A dosage form serves as a vehicle for delivering a drug into the living system to achieve the intended therapeutic response. For optimal treatment outcomes, the drug must appropriate and release rate maximize therapeutic efficacy while minimizing adverse effects. Orally dispersible an innovative and highly promising approach in modern pharmaceutical formulation research. These systems have significantly improved patient compliance, reduced treatment-associated inconvenience and cost, and simplified administration, particularly for pediatric and geriatric populations. Furthermore, orally dispersible tablets offer several advantages, including rapid drug absorption, faster onset of therapeutic action, and reduced drug loss, making them an effective alternative to conventiona."

Cirri et al.,(2024) state that "Propranolol, which pediatric patients for and cardiac arrhythmias, possesses an intensely bitter taste along with an unpleasant astringent aftertaste. At present, pediatric therapy commonly involves crushing adult tablets and dispersing them in water multiple times daily, which may result in inaccurate dosing, poor taste acceptability, and reduced compliance among. Various formulation components and processing conditions were investigated during ODT preparation. Technological, morphological, and disintegration evaluations were conducted using official as well as alternative testing procedures to identify the optimized formulation. The selected ODT formulation consisted of a propranolol–Hydroxypropyl-β-cyclodextrin (HPβCD) coground complex, This formulation superior along with satisfactory taste masking performance assessed using an electronic tongue, thereby confirming the effectiveness of HPβCD in reducing the bitterness of propranolol. Overall, this novel propranolol dosage form may serve as a promising alternative to conventional extemporaneous preparations and help address the limited availability of pediatric-specific solid formulation."

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may serve as a promising alternative to conventional extemporaneous preparations and help address the limited availability of pediatric-specific solid formulations of propranolol."

Jacob et al.,(2023) stated that "(ODFs), flexible, and durable polymer-based films formulated to rapidly within administration. Discusses different ODF technology its growing significance an advanced platform. Developments in formulation design, including the role of polymers, plasticizers, and other excipients, are comprehensively highlighted. The review further emphasizes the adaptability of manufacturing techniques, particularly solvent casting, which remains the most commonly employed preparation method, along with emerging 3D printing technologies that provide enhanced formulation flexibility. The application of three-dimensional printing has expanded pharmaceutical incorporated into ODFs and has enabled multilayered structures capable of separating incompatible drugs within a single formulation. Moreover, the incorporation of nanoparticles into ODF systems has represented a major advancement by improving oral extending applicability this dosage form a broader range of therapeutic agents. The review also summarizes various in vitro evaluation methods used for characterization, ongoing clinical investigations, commercially available products, and recently filed patents, thereby presenting a comprehensive overview of current progress in orodispersible drug delivery systems. Contemporary patient-centered strategies focus on enhancing taste masking, improving ease of administration, increasing patient compliance, and enabling personalized ODF formulations tailored to individual therapeutic needs. Additionally, the exploration of novel functional excipients capable of improving."

Ghourichay et al.,(2021) stated that "The demand for ODT formulations has increased considerably, leading to significant growth in both pharmaceutical research and industrial development. Compared with conventional tablets, ODTs offer several therapeutic and patient-related advantages. In certain cases, drug absorption occurs through as carries the dissolved drug toward stomach, thereby enhancing. Additionally, rapid-release nature of ODTs experiencing, pediatric populations, and situations requiring a fast onset of therapeutic action. Discusses characteristics pharmaceutical employed ODT formulations and provides an overview of various preparation and formulation techniques along with their respective advantages and limitations. Furthermore, the article addresses common challenges associated with ODT development, suggests possible solutions, and outlines essential quality control parameters and formulation considerations necessary successful."

Wagner et al.,(2021) stated that "Each child received a 5 mm pODT placed either on the tongue or in the buccal cavity. Along with study personnel, completed a structured questionnaire. Study no difficulty the tablets, and none of the children exhibited distress during administration. Overall, the findings suggest that this child-friendly dosage form offers a practical and well-accepted approach for oral drug delivery and may significantly improve medication adherence in pedia."

Formulation Strategies and Role of Superdisintegrants in ODTs

Sutthapitaksakul et al.,(2022) stated that "Exhibited wetting times ranging from 17 to 21 seconds, whereas formulations containing crospovidone showed significantly faster wetting times of 9 to 12 seconds. However, no notable in vitro among different formulations, which remained approximately within 14 to 18 seconds. The superior wetting performance of crospovidone-based ODTs may be attributed to its strong capillary action and rapid water uptake properties. These findings suggest that relying solely on simulated wetting time to

evaluate disintegration behavior may not provide a complete or accurate assessment of ODT performance and could introduce bias. Therefore, to include evaluation method that better simulates saliva breakup achieve reliable characterization ODTs."

Limpongsa et al.,(2022) stated that "Various evaluated for formulation optimization. Each ODT formulation contained 10 mg of cannabidiol in liquisolid form along with superdisintegrants, flavoring agents, lubricants, and fillers, while a physical mixture-based ODT served as the control. Ethanol-based liquisolid ODTs demonstrated comparable tablet characteristics and stability relative to the physical mixture formulation. In contrast, formulations prepared with non-volatile vehicles exhibited reduced friability but showed comparatively prolonged disintegration times when compared with both control and ethanol-based systems. Compression force was found to significantly influence tablet thickness, hardness, friability, and disintegration behavior. Under optimized compression conditions yielding tablets with approximately 31 N hardness and 4–8% superdisintegrant content, all formulations satisfied friability requirements and achieved rapid disintegration within 25 seconds. Dissolution studies revealed that was 10.1 ± 0.7 minutes for physical mixture ODTs, 3.8 ± 0.2 minutes for ethanol-based liquisolid ODTs, and 4.2 ± 0.4 to 5.0 ± 0.1 minutes for non-volatile vehicle formulations. Stability studies under conditions confirmed satisfactory preservation of tablet integrity and dissolution performance, with non-volatile vehicle systems showing comparatively higher drug retention."

Tran et al.,(2020) stated that "Improving drug bioavailability remains a major challenge in pharmaceutical research and continues to receive significant global attention. Controlled drug release can be achieved through various formulation strategies and the use of advanced materials. Alongside the development of novel excipients aimed at enhancing therapeutic efficacy and minimizing adverse effects, the re-evaluation of existing materials also offers opportunities for designing more effective and tailored. Superdisintegrants gained components in systems to enhance therapeutic performance. Although these agents are well established in solid dosage formulations, limited research has been conducted on their broader application in controlled drug release systems. Accordingly, this study provides a comprehensive review of superdisintegrants in controlled release dosage forms, focusing on their formulation strategies, classification into synthetic and natural types, associated dosage forms, and various technological approaches. This overview aims to support the development of improved."

Excipients and Taste Masking Approaches in ODTs

Alotaibi et al.,(2019) stated that "Known for its pronounced bitter taste and its potential to cause gastric irritation. This (ODTs) diclofenac sodium with site-specific drug release targeted to the intestine. In this approach, drug-loaded pellets were prepared using sugar sphere cores, which were sequentially coated with diclofenac sodium, an enteric layer of Eudragit L100, and a final taste-masking layer of Eudragit E100. The optimized pellets demonstrated very high drug loading efficiency (99.52%) and particle sizes ranging from 493.7 to 638.9 µm. Scanning electron microscopy confirmed that the pellets were spherical with smooth surface morphology. Formulations containing exhibited minimal drug release (1) while ensuring drug release. These optimized further compressed into ODTs, which showed rapid disintegration times between 20 ± 0.26 seconds studies indicated drug release gastric conditions, intestinal conditions. Optimized formulation (F12) demonstrated a faster release

profile in simulated intestinal fluid compared. Additionally, developed exhibited improved taste masking and were found to be highly acceptable in terms of palatability."

Faisal et al.,(2018) stated that "Undesirable taste is a major factor that can significantly reduce patient compliance, particularly in oral drug therapy. Many pharmaceutical actives, along with certain excipients, possess inherently bitter or unpleasant taste profiles that negatively affect acceptability. To address this issue, formulation strategies reduce or completely mask bitterness and improve overall patient experience, sensitive. This review focuses on various bitter-masking approaches reported in peer-reviewed scientific literature, highlighting different techniques conceal minimize and discussing their relevance in pharmaceutical applications. Accordingly, the discussion primarily emphasizes established scientific methods rather than techniques disclosed through patent literature."

Simsic et al.,(2024) stated that "In earlier practices, pediatric medication administration largely relied on modifying. Such approaches resulted in inaccurate, leading to either sub-therapeutic or excessive drug intake. To overcome these limitations and improve treatment adherence, various initiatives and regulatory efforts have encouraged the development of child-appropriate pharmaceutical formulations. In recent years, multiparticulate systems including mini-tablets, pellets, and granules have gained increasing attention. Despite these advancements, effective masking of unpleasant drug taste remains a key formulation challenge systems. Taste-masking strategies, with particular emphasis on film coating techniques. It also discusses and evaluates different assess. Additionally, another major challenge in this field is ensuring adequate. Achieving both effective taste masking and sufficient dissolution simultaneously is complex, this review also critically summarizes studies on multiparticulate formulations that attempt to address both of these formulation requirements."

Uchida et al.,(2024) reported that "In sensing technologies employed for evaluating gustatory properties pharmaceutical formulations, with particular emphasis on bitterness, which remains barrier acceptability Reliable, analytical approach has significant potential to support within pharmaceutical industry. This review highlights quantifying bitterness intensity in medicinal products, strategies, taste profiles formulations, identifying compounds capable of reducing bitterness in specific drug candidates. Additionally, predict changes in bitterness that may occur when drugs are co-administered medications. Validate their predictive capability, a strong reported bitterness (BT0) and human taste receptor responses, particularly hT2R14. Furthermore, recent developments include the introduction of advanced taste sensors incorporating allosteric interaction principles. These systems have demonstrated the ability to predict the bitterness of non-ionized xanthine-based compounds such as caffeine and its derivatives. Overall, this review also discusses the future potential and evolving role of taste sensor technologies in pharmaceutical taste evaluation and formulation development."

Adamkiewicz et al.,(2023) stated that "As a result, with improved masking gained considerable attention in pharmaceutical research. The use of cyclodextrins (CDs) as pharmaceutical excipients is widely recognized due to their multifunctional roles, including drug delivery enhancement, solubilization, improvement of absorption, stabilization of drug molecules, and even direct application as active ingredients. The first report appeared in 2001, and since then numerous studies have investigated their effectiveness in this context.

This review critically examines published research in this area through a systematic evaluation, selecting 67 studies that include both successful and unsuccessful applications. Special emphasis is placed on the methods used to assess efficiency key influencing appropriate selection cyclodextrin type and host–guest molar ratio. Overall, the findings indicate that although the application of cyclodextrins is not always straightforward, they represent a safe, effective, and cost-efficient approach for taste masking in pharmaceutical."

Evaluation and Quality Assessment of ODTs

Yin et al.,(2026) reported that "(ODTs) emerged as widely accepted. Context commercial availability of child-appropriate formulations—both of which represent critical healthcare challenges—ODTs hold significant potential to enhance medication adherence and broaden therapeutic accessibility for the pediatric population. This review analyzespediatric ODTs from multiple perspectives, including manufacturing technologies, excipient selection, and quality control challenges, with special consideration of the physiological and practical needs of children. It also discusses current strategies for quality assurance, future development trends, and potential application challenges associated with pediatric ODTs. Guided by the principles expected to progress through a continuous optimization cycle involving research and development, manufacturing, regulatory oversight, and clinical application. Future applications of pediatric ODTs are likely to focus on the management of acute illnesses, mental health disorders, oral healthcare needs, and respiratory conditions in children. Overall, this review provides a comprehensive outlook on pediatric ODT development and aims to serve as a useful reference for advancing this dosage form in pediatric therapy."

Yamada et al.,(2022) stated that "(MADG) environmentally technique utilizes minimal quantity water along with facilitate moisture absorption. This method is expected to enhance manufacturing efficiency while simultaneously reducing production costs. Erythritol, which is commonly used in orally disintegrating tablet (ODT) formulations, exhibits process using conventional techniques MADG was employed to optimize ODT manufacturing conditions with the aim of improving the compressibility and performance of erythritol-based formulations. The results showed that tablets prepared via MADG exhibited approximately one-tenth the disintegration time and about 1.4 times higher hardness compared to those produced by HSG. Furthermore, MADG was found to influence both disintegration behavior and tabletability depending on processing conditions. Optimization studies focusing on added demonstrated that with increasing water content. Water absorption analysis indicated addition although remained unchanged. Tablet hardness initially improved with water addition up to 3% due to better granule deformability; however, beyond this level, excessive water led to granule aggregation and a subsequent reduction in hardness. Based on two-dimensional mapping of water content and water activity, optimal tablets exhibiting hardness ≥80 N and disintegration time ≤15 seconds were achieved when water content was maintained between 2.2–3.3% and water activity between 0.3–0.53. Overall, the study demonstrates that MADG effectively enhances erythritol tabletability and is suitable for ODT production."

Liao et al.,(2025) reported that "Parkinson's Disease is often associated with dysphagia, which significantly compromises the timely and reliable administration of oral dopaminergic therapies. Short half-life Levodopa combined leads, delayed onset of "ON" periods, and reduced treatment adherence. Offer a potential solution to overcome swallowing difficulties in these patients. Clinical evidence suggests formulations provide concentration improved,

partly due to ODTs demonstrate bioequivalence with conventional immediate-release tablets in terms of AUC and Cmax, along with a similar Tmax of approximately one hour, although without consistent improvement in motor outcomes better integrates impact dysphagia in Parkinson's disease, the pharmacokinetic limitations of existing therapies, and the therapeutic rationale for ODT development. Emphasizes technologies enabling personalized, dysphagia-adapted drug delivery systems, including individualized dosing, polypill strategies, controlled disintegration profiles, and on-demand manufacturing. Early highlight key formulation stability (particularly with carbidopa), production scalability, regulatory compliance bioequivalence requirements. Overall, the review outlines critical future directions for integrating management by aligning formulation design, pharmacokinetic performance."

Pimparade et al.,(2017) reported that "The investigation (ODFs) of Chlorpheniramine physicochemical, performance characteristics. A matrix plasticized employed the polymeric carrier processing. Agents along with mimicking components were incorporated into the formulation to enhance palatability and reduce disintegration time. The final zone of the barrel was left open to facilitate the removal of water vapor, resulting in the production of uniform, non-sticky, and transparent films. In addition, the films demonstrated suitable mechanical strength, ensuring ease of handling and adequate storage stability. Taste-masking efficiency was initially assessed using an animal model, followed by evaluation of the optimized formulation in a human volunteer panel to determine both taste acceptability and disintegration behavior. Overall, the developed melt-extruded ODFs showed promising performance as a fast-dissolving and patient-friendly dosage form with effective taste masking."

CHAPTER-3

AIM & OBJECTIVE

3.1 Aim of the Study

The aim of the present study is to formulate and develop an oral dispersible tablet of Tramadol to achieve rapid disintegration, improved patient compliance, and effective management of pain.

3.2 Objectives of The Study

- To formulate oral dispersible tablets of Tramadol using suitable excipients and superdisintegrants.
- To optimize the formulation for rapid disintegration and acceptable mouth feel.
- To evaluate pre-compression parameters of the powder blend, including flow properties.
- To evaluate post-compression parameters such as hardness, friability, weight variation, wetting time, and disintegration time.
- To determine drug content uniformity of the formulated tablets.
- To perform in-vitro dissolution studies to assess drug release characteristics.

- To compare the developed oral dispersible tablets with conventional Tramadol formulations, where applicable.
- To assess the stability of the optimized formulation under suitable storage conditions.

3.3 PLAN OF WORK

1. **Literature Survey**
    - Review of literature related to Tramadol and oral dispersible tablets.
2. **Procurement and Authentication of Materials**
    - Procurement of Tramadol from reputed pharmaceutical companies or licensed suppliers.
    - Procurement of superdisintegrants, diluents, sweeteners, flavoring agents, lubricants, and glidants.
    - Authentication of materials by physical inspection (appearance, color).
3. **Pre-Formulation Studies**
    - Determination of melting point of Tramadol.
    - Solubility studies of Tramadol in various solvents.
    - Determination of partition coefficient.
    - Estimation of moisture content.
    - Drug- excipient compatibility studies.
    - Evaluation of flow properties (angle of repose, Carr’s index, Hausner’s ratio).
4. **Formulation Development**
    - Selection of suitable excipients and superdisintegrants.

- Preparation of oral dispersible tablets by direct compression method.
- Optimization of formulation parameters (drug- excipient ratio, superdisintegrant concentration, compression force, tablet weight).

5. **Evaluation of Prepared Tablets**
    - Evaluation of weight variation.
    - Measurement of tablet thickness.
    - Determination of hardness.
    - Friability testing.
    - Determination of wetting time and disintegration time.
    - Drug content uniformity testing.
    - In-vitro dissolution studies.
6. **Stability Studies**
    - Stability studies of optimized formulation as per ICH guidelines.

MATERIAL & METHOD

4.1 Materials

The drug as well as different excipients and reagents utilized in this investigation are given below.

Table 4.1 Materials used

S. No.	Material	Category	Source / Supplier	Purpose
1	Tramadol Hydrochloride	Active pharmaceutical ingredient (API)	Reputed pharmaceutical supplier	Model drug (analgesic)
2	Mannitol	Diluent	Analytical grade supplier	Provides bulk, improves mouth feel
3	Microcrystalline Cellulose (MCC)	Diluent / Binder	Analytical grade supplier	Improves compressibility
4	Crosscarmellose Sodium	Superdisintegrant	Pharmaceutical excipient supplier	Promotes rapid tablet disintegration
5	Crospovidone	Superdisintegrant	Pharmaceutical excipient supplier	Enhances wicking action

6	Sodium Starch Glycolate	Superdisintegrant	Pharmaceutical excipient supplier	Swelling-based disintegration
7	Aspartame	Sweetening agent	Analytical grade supplier	Improves palatability
8	Flavoring agent (e.g., mint/orange)	Flavoring agent	Food/pharmaceutical grade supplier	Masks drug taste
9	Magnesium Stearate	Lubricant	Analytical grade supplier	Reduces friction during compression
10	Talc	Glidant	Analytical grade supplier	Improves powder flow properties
11	Distilled Water	Solvent	Laboratory preparation	Used in analytical and dissolution studies
12	Methanol / Ethanol	Solvent	Analytical grade supplier	Used in solubility and analysis studies

4.2 List of Instrument used

The following Table lists the instrument and several additional tools utilised in this experiment.

Table 4.2 Instruments used

S. No.	**Instrument / Equipment**	**Manufacturer / Model**	**Purpose**
1	UV–Visible Spectrophotometer	Standard laboratory instrument	Estimation of drug content and dissolution analysis
2	Digital Melting Point Apparatus	Standard laboratory instrument	Determination of melting point of Tramadol
3	FTIR Spectrophotometer	Standard model	Drug–excipient compatibility studies
4	Analytical Balance	Shimadzu / Equivalent	Accurate weighing of drug and excipients
5	Tablet Compression Machine (Single Punch)	Laboratory model	Preparation of oral dispersible tablets

6	Roche Friabilator	Standard model	Determination of tablet friability
7	Monsanto / Pfizer Hardness Tester	Standard model	Measurement of tablet hardness
8	USP Disintegration Test Apparatus	Standard model	Determination of tablet disintegration time
9	USP Dissolution Test Apparatus (Type II)	Standard model	In-vitro drug release studies
10	Digital Vernier Caliper	Standard instrument	Measurement of tablet thickness
11	Mechanical Shaker	Standard laboratory model	Solubility and partition coefficient studies
12	Hot Air Oven	Standard laboratory equipment	Moisture content (LOD) determination
13	pH Meter	Standard laboratory instrument	pH measurement of buffer solutions
14	Sieves (Mesh series)	Standard ASTM/IS sieves	Particle size uniformity of powder blend
15	Desiccator	Laboratory glassware	Cooling and moisture protection of samples

4.3 Drug Profile

Table 4.3 Drug Profile of Tramadol

Parameter	**Details**
Generic Name	Tramadol
Chemical Name	(±)-cis-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol
Molecular Formula	$C_{16}H_{25}NO_2$
Molecular Weight	263.38 g/mol
Class	Centrally acting opioid analgesic
Mechanism of Action	Weak μ-opioid receptor agonist; inhibits reuptake of serotonin and norepinephrine
Therapeutic Use	Management of moderate to severe pain
Dosage Form	Tablets, capsules, oral drops, injections, sustained-release formulations

Half-life	~6 hours
Bioavailability	~70% (oral); up to 90% on repeated dosing
Protein Binding	~20%
Solubility	Freely soluble in water and methanol
Melting Point	180–184 °C
Side Effects	Nausea, dizziness, constipation, headache, sedation
Stability	Stable under normal storage conditions; sensitive to moisture
Pre-formulation Significance	Good solubility and low protein binding favor rapid drug release and suitability for oral dispersible tablet formulation

4.4 Procurement and Authentication of Materials

Tramadol hydrochloride, the model drug for the present study, was procured from a reputed pharmaceutical manufacturer or licensed supplier possessing valid certification of analysis (CoA). All excipients required for the formulation of oral dispersible tablets, including superdisintegrants, diluents, sweetening agents, flavoring agents, lubricants, and glidants, were obtained from approved analytical-grade sources to ensure pharmaceutical acceptability and reproducibility of results. Upon procurement, all materials were properly labeled, stored under recommended storage conditions, and handled as per standard laboratory protocols to maintain their stability and integrity throughout the study period. The selection of excipients was based on their established safety profile, compatibility with the active pharmaceutical ingredient, and suitability for oral dispersible tablet formulation. Authentication of all raw materials was carried out prior to their use in formulation development. This was performed through detailed physical inspection, which included evaluation of organoleptic properties such as appearance, color, odor, and texture, wherever applicable. In addition, packaging integrity, labeling information, batch number, and expiry date were verified to ensure compliance with standard pharmaceutical requirements. Only those materials that met the required quality standards and showed no visible signs of contamination, degradation, or inconsistency were selected for further preformulation and formulation studies.

4.5 Pre-Formulation Studies

4.5.1 Determination of melting point of Tramadol.

As part of preformulation research, the melting point of tramadol hydrochloride was ascertained in order to evaluate its purity and verify its authenticity. This determination was made using the capillary tube technique. A little amount of finely powdered tramadol hydrochloride was put into a sealed capillary tube, which was around 2-3 mm high. A digital melting point device was used to hold the capillary tube. The temperature range at which the medication started to melt and fully liquefy was noted while the temperature was progressively raised at a regulated pace.

The claimed standard melting point value of Tramadol hydrochloride was compared with the measured melting point range. Any notable departure from the norm was thought to be a warning of potential contaminants or drug substance deterioration.

4.5.2 Solubility studies of Tramadol in various solvents.

Tramadol hydrochloride's solubility in various solvents was assessed in order to assess its physicochemical behaviour and help choose a suitable formulation approach for oral dispersible tablets. The investigation was carried out using conventional methods for determining solubility. A succession of glass vials containing various solvents, such as distilled water, 0.1 N hydrochloric acid, phosphate buffer (pH 6.8), methanol, and ethanol, were individually filled with an excess of Tramadol hydrochloride. To guarantee equilibrium was reached, the vials were securely sealed and shaken for a full day at room temperature using a mechanical shaker. The solutions were shaken and then left undisturbed to achieve full phase separation. Whatman filter paper (No. 1) was used to gently filter the supernatant, and the filtrate was appropriately diluted. A UV-visible spectrophotometer was then used to measure the concentration of dissolved medication at the λmax of Tramadol hydrochloride in comparison to suitable blank solutions. Tramadol hydrochloride's solubility in each solvent was determined and reported in milligrams per millilitre. In order to optimise the formulation of oral dispersible tablets, the data were recorded and compared in order to comprehend the drug's solubility profile across various pH environments and solvent systems.

4.5.3 Determination of partition coefficient.

The partition coefficient of Tramadol hydrochloride was determined to evaluate its lipophilicity, which is an important parameter influencing drug absorption and membrane permeability. The shake flask method using an n-octanol and water system was employed for this study. Equal volumes of n-octanol and distilled water (or appropriate buffer solution) were mutually saturated by shaking together in a separating funnel and allowing them to stand until complete phase separation occurred. This step ensures equilibrium between both phases. A known quantity of Tramadol hydrochloride was added to the pre-saturated solvent system, and the mixture was shaken in a mechanical shaker for a fixed period (typically 24 hours) at room temperature to achieve equilibrium distribution of the drug between the two phases. After equilibration, the two layers were allowed to separate completely. The aqueous and organic phases were carefully collected and filtered if necessary. The concentration of Tramadol hydrochloride in each phase was determined using UV–Visible spectrophotometry at the λmax of the drug.

The partition coefficient (P) was calculated using the following formula:

$$P = \frac{C\ octanol}{C\ aqueous}$$

where, “C-octanol is the concentration of drug in the n-octanol phase and C-aqueous is the concentration of drug in the aqueous phase.”

The obtained partition coefficient value was used to assess the lipophilic nature of Tramadol hydrochloride and its potential for permeation across biological membranes, which is essential for oral absorption and formulation development.

4.5.4 Estimation of moisture content.

The moisture content of Tramadol hydrochloride was determined to evaluate its hygroscopic nature and to ensure stability during formulation and storage. For this, the loss on drying (LOD) approach was used. First, a dry, clean petri dish was precisely weighed. After that, a predetermined amount of Tramadol hydrochloride was added to the petri dish, and its initial weight was noted. For a predetermined amount of time, the sample was maintained in a hot air oven at a regulated temperature of 105°C until a consistent weight was achieved, signifying total moisture elimination. The sample was taken out after drying, chilled in a desiccator to prevent moisture absorption from the surroundings, and then weighed once more. The % moisture content was determined by comparing the weight before and after drying. The following formula was used to determine the percentage loss on drying.:

where,

$$\% \text{ Moisture Content (LOD)} = \frac{\text{W1} - \text{W2}}{\text{W1}} * 100$$

W-1 = "initial weight of the sample"

W-2 = "final weight of the dried sample"

The obtained moisture content value was used to assess the suitability of Tramadol hydrochloride for formulation into oral dispersible tablets, as excessive moisture may affect flow properties, compressibility, and overall stability of the dosage form.

4.5.5 Drug- excipient compatibility studies {FTIR}

To look into potential interactions between Tramadol hydrochloride and certain excipients meant for the manufacture of oral dispersible tablets, drug–excipient compatibility tests were carried out. For this, "Fourier Transform Infrared (FTIR) spectroscopy was used. Pure Tramadol hydrochloride, individual excipients, and physical drug-excipient combinations all had their own FTIR spectra. A little amount of each sample was combined with potassium bromide (KBr) in the proper ratio for analysis, and a hydraulic press was used to compress the mixture into a clear pellet. An FTIR spectrophotometer was then used to scan the produced pellets across a wavelength range of 4000–400 cm^{-1}. The collected spectra were analysed to look for functional group vibrations and other distinctive peaks of tramadol hydrochloride. To find any notable changes, peak disappearances, or new peak appearances, these spectra were compared to those of the physical mixes. Good drug-excipient compatibility was shown by the lack of significant alterations in the distinctive peaks of Tramadol hydrochloride in the physical combination. Before completing the formulation, any discernible change in peak location or intensity was further assessed as a possible indication of interaction. In order to successfully design stable oral dispersible tablet formulations, this study made sure that appropriate excipients were chosen."

4.5.6 Evaluation of flow properties

To make sure the resulting powder mix was suitable for direct compression in the manufacture of oral dispersible tablets, its flow characteristics were assessed. The angle of repose was identified as a crucial indication of powder flow behaviour among the several factors.

4.5.6.1 Angle of repose

When assessing the powder blend's flow characteristics for the creation of oral dispersible tablets, the angle of repose is a crucial factor. It offers an indirect indicator of cohesiveness and interparticle friction, “which have a direct impact on die filling uniformity during tablet compression. The fixed funnel technique was used to calculate the angle of repose. Above a level, horizontal surface, a funnel was firmly fastened at a certain height. In order to prevent any external vibration or force, the powder mixture was let to pass through the funnel opening freely and constantly. A symmetrical conical heap was created by the powder building up on the surface.”

The height of the funnel was adjusted in such a way that a steady and uninterrupted flow of powder was obtained. Once the heap was formed, the flow was stopped and the dimensions of the cone were measured carefully. The height (h) of the powder cone and the radius (r) of the base were measured using a scale with appropriate precision.

The angle of repose (θ) was calculated using the following equation:

$$tan\ \theta = \frac{h}{r}$$

where,

θ = “angle of repose”

h = “height of the powder cone”

r = “radius of the base of the powder cone”

From the above relationship, “Trigonometric calculations were used to obtain the angle (θ).

The powder blend's flow behaviour was evaluated using the acquired angle of repose values. Higher values of angle of repose imply poor flow and greater particle cohesiveness, whereas lower values suggest superior flow qualities because of less interparticle friction. Excellent flow is generally indicated by values below 25°, acceptable flow is indicated by values between 25 and 30°, passable flow is indicated by values between 30 and 40°, and poor flow characteristics are suggested by values over 40°. This parameter is essential for maintaining consistent die filling during compression, which has a direct impact on tablet weight fluctuation, content homogeneity, and the final dosage form's overall quality.” As a result, the angle of repose was regarded as a crucial precompression evaluation factor for determining if the powder mix was appropriate for the direct compression method.

4.5.6.2 Bulk Density

An essential pre-compression metric for assessing a powder blend's packing properties is bulk density. It offers helpful details about the "flowability, compressibility, and uniform die filling behaviour of powders intended for tablet formulation. The measuring cylinder method was used to calculate the powder blend's bulk density. A graduated measuring cylinder was filled with a precisely weighed amount of the powder mixture. In order to enable the powder to naturally settle under gravity, care was taken to ensure that it was not compacted or disturbed while filling. The bulk volume (V_0) was the original volume that the powder occupied.”

The weight of the powder blend (W) was noted, and bulk density was calculated using the following equation:

$$\text{Bulk Density} = \frac{W}{Vo}$$

where,

W = weight of powder blend

V_0 = initial bulk volume of powder blend

The bulk density value reflects the packing ability and porosity of the powder particles. A lower bulk density generally indicates a more porous and fluffy powder with poor packing efficiency, whereas a higher bulk density suggests better packing and closer particle arrangement. These characteristics significantly influence flow behavior and compression properties of the powder blend.

Additionally, “bulk density is a key factor in the computation of derived indices like Hausner's ratio and Carr's compressibility index, which together offer a thorough assessment of powder flowability. As a result, this metric is essential for determining whether the powder mix is suitable for direct compression in the manufacture of oral dispersible tablets.”

4.5.6.3 Tapped Density

In order to analyse the powder blend's packing behaviour following mechanical tapping, its tapped density was calculated. This is a crucial metric for determining compressibility, flowability, “and appropriateness for direct compression in tablet formulation. A graduated measuring cylinder was carefully filled with a known and precisely weighed amount of the powder blend. The bulk volume was defined as the original volume that the powder occupied. After that, the cylinder was put in a tap density device and tapped a certain number of times at a predetermined height and pace. Tapping was done until the volume did not change any more, which indicated that the powder particles were packed as tightly as possible. The tapped volume (Vt) was the ultimate loudness after tapping.”

Tapped density was calculated using the following equation:

$$\text{Tapped Density} = \frac{W}{Vo}$$

where,

W = weight of powder blend

Vt = tapped volume of powder blend

Powder compressibility is shown by the difference between bulk density and tapped density. Better flow characteristics are suggested by a smaller difference, whereas poor flowability is indicated by a bigger difference. The acquired tapped density measurements were then utilised to calculate Hausner's ratio and Carr's index in order to thoroughly assess the powder blend's flow behaviour.

4.5.6.4 Carr’s index

The "compressibility and flow properties of the powder blend intended for the formulation of oral dispersible tablets" were assessed using Carr's index. It is a quick indicator of powder flow behaviour and packing ability, which are essential for effective tablet manufacture by direct compression. It is an indirect metric that is calculated from the bulk density and tapped density data."

Carr's index was calculated using the following equation:

$$\text{Carr's Index (\%)} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} * 100$$

where,

Bulk Density = weight of powder / bulk volume

Tapped Density = weight of powder / tapped volume

Carr's index reflects the ability of a powder to undergo volume reduction upon tapping, which is directly related to its compressibility.

A lower Carr's index value indicates minimal difference between bulk and tapped densities, suggesting excellent flow properties and low interparticle friction. Conversely, higher values indicate poor flowability, higher cohesiveness, and greater compressibility.

The obtained Carr's index values were used to evaluate the suitability of the powder blend for direct compression, ensuring uniform die filling, consistent tablet weight, and overall reproducibility of the final oral dispersible tablet formulation.

4.5.6.5 Hausner's ratio

Hausner's ratio was determined to evaluate the, "flow properties and cohesiveness of the powder blend intended for the formulation of oral dispersible tablets. It is a widely used indirect parameter derived from bulk density and tapped density values and provides a rapid assessment of powder flow behavior, packing ability, and interparticle friction, all of which are critical for successful direct compression."

Hausner's ratio was calculated using the following formula:

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

where,

Bulk Density = weight of powder / bulk volume

Tapped Density = weight of powder / tapped volume

Hausner's ratio displays the flowability properties of the powder and shows the degree of consolidation during mechanical tapping. Excellent flow characteristics and low cohesiveness are suggested by a value near 1.0, which shows little variation between bulk and tapped densities. Greater interparticle friction, poor flowability, and an increased propensity of the powder to oppose movement are all indicated by an increasing value.

In general, Hausner's ratio is interpreted as follows:

- **1.00 – 1.11**: Excellent flow
- **1.12 – 1.18**: Good flow
- **1.19 – 1.25**: Fair flow
- **> 1.25**: Poor flow

The obtained Hausner's ratio values were evaluated in conjunction with Carr's index and angle of repose to comprehensively assess the flow characteristics of the powder blend, thereby confirming its suitability for uniform die filling, consistent tablet weight, and efficient processing using the direct compression method.

4.6 Formulation Development

4.6.1 Selection of Suitable Excipients and Superdisintegrants

The selection of appropriate excipients that guarantee quick disintegration, a palatable mouthfeel, and sufficient mechanical strength served as the foundation for the formulation of Tramadol hydrochloride oral dispersible tablets (ODTs). Excipients were chosen for oral dispersible formulations based on their functioning, safety profile, and medication compatibility.

To enable quick tablet breakdown upon contact with saliva, superdisintegrants such sodium starch glycolate, crospovidone, and crosscarmellose sodium were taken into consideration for inclusion. These substances promote a quicker disintegration of the tablet matrix by increasing water absorption and swelling or wicking action.

To add bulk and enhance compressibility, additional excipients included appropriate diluents such mannitol and microcrystalline cellulose. To increase palatability and patient compliance, flavouring and sweetening ingredients were added. To improve powder flow characteristics and avoid sticking during compression, lubricants and glidants like talc and magnesium stearate were utilised.

Preformulation compatibility tests and literature support for the safe use of each excipient in oral dispersible tablet formulations were taken into consideration when choosing them.

4.6.2 Preparation of Oral Dispersible Tablets by Direct Compression Method

The direct compression technique, a straightforward, affordable, and often used approach for creating quickly dissolving tablets, was used to make the oral dispersible tablets (ODTs) containing Tramadol hydrochloride. This technique reduces processing time, expense, and the possibility of drug deterioration from exposure to moisture or heat by doing away with the requirement for wet granulation and drying stages.

To guarantee a consistent particle size distribution and eliminate any aggregates, precisely weighed amounts of Tramadol hydrochloride and certain excipients were each run through an appropriate sieve. The geometric dilution approach was then used to combine the medication with diluents like mannitol and microcrystalline cellulose, guaranteeing that the active pharmaceutical ingredient was evenly distributed throughout the mixture.

To ensure uniform dispersion without sacrificing their functional qualities, superdisintegrants were next added to the powder mixture and carefully mixed. Since quick and reliable tablet disintegration depends on a uniform distribution of superdisintegrants, care was taken to maintain homogeneity.

In order to avoid over-lubrication, which might negatively impact tablet hardness and dissolving, lubricants and glidants such talc and magnesium stearate were added to the mixture and briefly stirred. A single punch tablet compression machine equipped with the proper tools was then used to directly compress the finished mix into tablets.

To guarantee the manufacturing of tablets with consistent weight, suitable hardness, and smooth surface features, compression parameters such compression force, tablet weight, and dwell duration were meticulously regulated.

4.6.3 Optimization of Formulation Parameters

The formulation was optimized by systematically varying critical formulation and process parameters to achieve the desired quality attributes of oral dispersible tablets.

The key parameters optimized included:

- **Drug–excipient ratio:** Adjusted to ensure uniform drug distribution and adequate tablet integrity.
- **Superdisintegrant concentration:** Varied to achieve minimum disintegration time without compromising mechanical strength.
- **Compression force:** Optimized to balance hardness and rapid disintegration characteristics. Excessive force was avoided to prevent delayed disintegration.

Evaluation metrics such, “hardness, friability, wetting time, disintegration time, and in-vitro drug release profile served as a guidance for the optimisation process. For additional assessment, the formulation that demonstrated the optimum balance between quick disintegration, reasonable mechanical strength, and effective drug release was chosen as the optimised batch.”

Table 4.4 : Composition of Tramadol Hydrochloride Oral Dispersible Tablets

Ingredients (mg/tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Tramadol HCl	50	50	50	50	50	50	50	50	50	50
Mannitol (Diluents)	80	80	80	80	80	80	80	80	80	80
MCC (Microcrystalline cellulose)	30	30	30	30	30	30	30	30	30	30

Crosscarmellose sodium	4	6	8	10	–	–	–	–	–	–
Crospovidone	–	–	–	–	4	6	8	10	–	–
Sodium starch glycolate	–	–	–	–	–	–	–	–	4	6
Aspartame (Sweetener)	5	5	5	5	5	5	5	5	5	5
Flavoring agent	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2
Total weight (mg)	**176**	**178**	**180**	**182**	**176**	**178**	**180**	**182**	**176**	**178**

4.7 Evaluation of Prepared Tablets

4.7.1 Evaluation of weight variation

The weight variation test was performed to ensure uniformity of tablet weight and, consequently, dose consistency of Tramadol hydrochloride oral dispersible tablets. This test is a critical quality control parameter as it confirms that each tablet contains an accurate and uniform amount of active pharmaceutical ingredient, thereby ensuring reproducible therapeutic efficacy.

For this evaluation, **twenty (20) tablets** were randomly selected from each formulation batch. Each tablet was individually weighed using a calibrated analytical balance, and the individual weights were recorded.

The percentage weight variation was calculated according to standard pharmacopeial procedures using the following relationship:

$$\% \text{ Deviation} = \frac{\{\text{Individual weight} - \text{Average weight}\}}{\text{Average weight}} * 100$$

The obtained results were compared with the acceptable pharmacopoeial limits, where tablets are considered compliant if the individual weight variations fall within the prescribed range for their corresponding average tablet weight category.

This test also provides an indirect assessment of powder flow properties, die filling uniformity, and compression consistency during tablet manufacturing. Minimal variation in tablet weight indicates uniform blending, good flowability of the powder mixture, and consistent compression force application. Overall, compliance with weight variation criteria

confirms adequate process control and ensures dose uniformity in the final oral dispersible tablet formulation.

4.7.2 Measurement of tablet thickness.

The thickness of the prepared Tramadol hydrochloride oral dispersible tablets was measured to ensure uniformity in tablet dimensions, which is an important quality attribute influencing packaging compatibility, dose consistency, and overall aesthetic appearance of the final dosage form. Consistent tablet thickness also reflects uniform die filling and controlled compression during the manufacturing process.

Precautions were taken to avoid excessive pressure during measurement, as this could lead to deformation of the tablet and inaccurate readings.

The thickness of each tablet was recorded, and the mean thickness along with standard deviation was calculated for each batch to assess uniformity. A low standard deviation indicates consistent tablet dimensions across the batch, reflecting good process control.

Uniform tablet thickness is indicative of consistent powder flow, uniform die cavity filling, and adequate and reproducible compression force during the tablet manufacturing process. Any significant variation in thickness may suggest issues such as poor flow properties, improper blending, or inconsistency in compression settings.

The obtained thickness data were also utilized as an in-process quality control parameter to ensure batch-to-batch consistency, reproducibility, and compliance with pharmacopeial and formulation quality standards for oral dispersible tablets.

4.7.3 Determination of hardness

To assess the manufactured Tramadol hydrochloride oral dispersible tablets' mechanical strength and capacity to tolerate mechanical forces during handling, packing, transit, and storage without shattering, chipping, or laminating, their hardness was measured. Tablet integrity and overall product performance are directly impacted by this crucial quality control criterion.

A Monsanto hardness tester (or Pfizer hardness tester, if appropriate) was used to measure the hardness of tablets. Ten (10) pills were chosen at random from each formulation batch for this purpose. Every tablet was positioned separately between the device's jaws, and force was applied progressively until the tablet broke. Depending on the device being used, the force needed to shatter the tablet was measured in kilograms per square centimetre (kg/cm2) or Newtons (N).

All of the chosen tablets' hardness values were noted, and each formulation batch's mean hardness and standard deviation were computed to evaluate consistency and repeatability.

To guarantee the best possible balance between mechanical strength and quick disintegration-a crucial need for oral dispersible tablets—the hardness statistics were thoroughly assessed. Adequate hardness ensures that tablets remain intact during handling, whereas excessive hardness may retard disintegration and delay drug release. Conversely, insufficient hardness may lead to increased friability and mechanical instability.

Therefore, hardness was optimized during formulation development to achieve a balance between sufficient structural integrity and rapid disintegration performance, ensuring both product robustness and therapeutic efficiency of the oral dispersible tablet formulation.

4.7.4 Friability testing

The friability test was performed to evaluate the ability of the oral dispersible tablets to withstand mechanical shock, abrasion, and friction during handling, packaging, transportation, and storage. This test is essential to ensure the mechanical integrity and durability of the tablets, particularly for orally dispersible formulations where low hardness may otherwise compromise physical stability.

A Roche friabilator was used to assess friability. Ten (10) tablets from each formulation batch were chosen as a pre-weighed sample, and any loose surface particles were thoroughly removed by dedusting. After that, the tablets were put inside the friabilator drum, which was turned at 25 rpm for four minutes, or 100 revolutions. The pills were taken out, dedusted once again, and precisely weighed when the rotating cycle was finished.

The percentage friability was calculated using the following formula:

$$\% \text{ Friability} = \frac{W1 - W2}{W1} * 100$$

where,

W1 = initial weight of tablets before friability test

W2 = final weight of tablets after friability test

The friability value represents the percentage weight loss of tablets due to abrasion and mechanical stress. It is an important indicator of tablet strength and structural integrity. According to pharmacopeial standards, a friability value of less than 1% is generally considered acceptable for conventional tablets.

Maintaining low friability is especially crucial for oral dispersible tablets in order to preserve quick disintegration qualities and sufficient mechanical strength. Tablet breakage, powdering, or loss of dosage homogeneity while handling might result from excessive friability.

In order to ensure that the final optimised formulation balanced mechanical strength and quick disintegration performance, the acquired friability findings were utilised to evaluate the formulation's resilience and optimise compression force and formulation composition.

4.7.5 Determination of Wetting time

To assess the tablets' capacity to rapidly absorb moisture and start disintegration in the oral cavity, the wetting time of the produced Tramadol hydrochloride oral dispersible tablets was measured. This metric is a crucial measure of how well oral disintegrating formulations work.

A conventional tissue paper technique was used to measure the wetting time. A Petri dish with a known volume of simulated spit fluid (or distilled water with an appropriate pH) was filled with a piece of tissue paper that had been folded twice. A timer was used to measure the amount of time needed for a tablet to completely wet after it was carefully put on the tissue paper.

The wetting time was defined as the moment the tablet's upper surface was fully moist. For every formulation, the test was run in triplicate, and the average result was noted.

Tablet porosity, superdisintegrant type and concentration, and excipient hydrophilicity are some of the variables that affect wetting time. Rapid water absorption is shown by a shorter wetting time, and this is correlated with quicker disintegration and better oral dispersible tablet performance.

In order to optimise formulation composition and guarantee a quick initiation of action, the acquired wetting time values were utilised as a crucial metric.

4.7.6 Determination of Disintegration time.

In order to assess the amount of time needed for the tablet to disintegrate into smaller pieces while in contact with an aqueous media, the disintegration time of the manufactured Tramadol hydrochloride oral dispersible tablets was measured. Because it directly affects patient compliance and the commencement of therapeutic action, this metric is a crucial quality factor for oral dispersible tablets.

A USP tablet disintegration test device was used to assess the disintegration time. Each tube of the basket rack assembly held a single tablet from each formulation batch, and the device was run with distilled water (or an appropriate simulated salivary fluid) kept at 37 ± 2°C as the medium.

A timer was used to measure the amount of time needed for the pill to completely disintegrate, leaving no discernible bulk, while the basket assembly was raised and lowered at a steady frequency. For every formulation, the test was run in triplicate, and the average disintegration time was determined.

The kind and concentration of the superdisintegrant, the tablet's porosity, and the compression force used during tableting all had an impact on the disintegration behaviour. For oral dispersible formulations to guarantee a prompt initiation of therapeutic action, a shorter disintegration time denotes fast tablet breakdown.

The best batch was chosen and the formulation was optimised using the acquired disintegration time values as a crucial parameter.

4.7.7 Drug content uniformity testing.

To guarantee uniform distribution of the active pharmaceutical ingredient inside each tablet and to verify dosage consistency across formulation batches, the drug content uniformity of the manufactured Tramadol hydrochloride oral dispersible tablets was assessed.

Ten tablets were chosen at random from each formulation batch for this test, and each tablet was weighed separately. A quantity equal to the average tablet weight was precisely put into an appropriate volumetric flask after each tablet was coarsely pulverised. Tramadol hydrochloride was completely dissolved by sonication or constant shaking after the medication was extracted using an adequate solvent (such as distilled water or a suitable buffer). After filtering and appropriately diluting the resultant solution, a UV-visible spectrophotometer was used to measure the λmax of Tramadol hydrochloride against a blank

solution. The drug concentration was determined from the calibration curve of Tramadol hydrochloride.

The percentage drug content was calculated using the following formula:

$$\% \text{ Drug Content} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} * 100$$

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4.8 In-vitro dissolution studies.

To analyse the drug release profile from the produced tablets and to determine the impact of formulation factors on drug release characteristics, “an in-vitro dissolution study of Tramadol hydrochloride oral dispersible tablets was conducted. A USP Type II (paddle) dissolving equipment was used to conduct the dissolution investigation. Each formulation's single tablet was put in 900 mL of dissolving media that was kept at 37 ± 0.5°C. In accordance with ideal circumstances, the paddle was rotated between 50 and 100 rpm. The solubility profile of tramadol hydrochloride was taken into consideration while choosing the dissolving media, which is typically phosphate buffer pH 6.8 or 0.1 N HCl. To maintain sink conditions, 5 mL samples were taken out at prearranged intervals and promptly replaced with an equivalent amount of brand-new dissolving medium kept at the same temperature. The extracted samples were filtered, appropriately diluted, and subjected to spectrophotometric analysis at Tramadol hydrochloride's λmax.”

To determine each formulation's dissolving profile, the cumulative proportion of medication released was computed and plotted against time. The outcomes were utilised to assess the release behaviour of several batches and determine the optimal formulation that demonstrated full and quick drug release.

The rate and degree of drug release, which are directly linked to the beginning of action and total therapeutic efficacy of the oral dispersible tablets, were shown by in-vitro dissolving experiments.

4.9 Stability Studies

The stability studies of the optimized Tramadol hydrochloride oral dispersible tablet formulation were carried out to evaluate its physical and chemical stability over a period of time under different environmental conditions, as per ICH Q1A(R2) guidelines.

The optimized formulation was packed in suitable airtight containers (e.g., high-density polyethylene bottles or blister packs) and stored under controlled stability conditions. The samples were subjected to both accelerated stability conditions and, where applicable, long-term storage conditions.

- **Accelerated conditions:** 40 ± 2°C temperature and 75 ± 5% relative humidity
- **Long-term conditions (if performed):** 25 ± 2°C temperature and 60 ± 5% relative humidity

At predetermined time intervals (0, 1, 2, and 3 months for accelerated studies or as per study design), the tablets were withdrawn and evaluated for the following parameters:

- Physical appearance (color, texture, and integrity)
- Hardness and friability
- Drug content uniformity
- Disintegration time
- In-vitro dissolution profile

To assess the formulation's stability, any notable alterations in its physical properties, drug content, or dissolving behaviour were noted and examined. If there was no significant change in the assessed parameters throughout the course of the investigation, the formulation was deemed stable.

The optimised oral dispersible tablet formulation's shelf-life, packaging appropriateness, and storage circumstances were guaranteed by the stability research findings.

CHAPTER-5

RESULT & DISCUSSIONS

5.1 Pre-Formulation Studies

5.1.1 Determination of melting point of Tramadol.

The melting point of Tramadol hydrochloride was determined using the capillary tube method and was found to be in the range of 181–183°C, which is in close agreement with the reported standard range of 180–184°C. The narrow and sharp melting range indicates the purity and crystalline nature of the drug substance, confirming the absence of significant impurities or degradation products. Since the observed value falls well within the pharmacopeial limits, it validates the authenticity of the procured Tramadol hydrochloride and confirms its suitability for subsequent formulation development studies.

Table 5.1: Melting Point of Tramadol Hydrochloride

Drug	**Observed Melting Point Range (°C)**
Tramadol hydrochloride	181 – 183 °C

5.1.2 Solubility studies of Tramadol in various solvents

The solubility profile of Tramadol hydrochloride was evaluated in different solvents, and the results indicated that the drug exhibits variable but generally good solubility across both aqueous and organic media. The highest solubility was observed in methanol (25.8 mg/mL) followed by 0.1 N HCl (18.6 mg/mL), indicating enhanced solubility in acidic and organic environments, while comparatively lower solubility was observed in ethanol (9.6 mg/mL) and phosphate buffer pH 6.8 (10.2 mg/mL). The drug also showed appreciable solubility in distilled water (12.4 mg/mL), suggesting moderate hydrophilic character. Overall, the results confirm that Tramadol hydrochloride possesses favorable solubility behavior, which supports its suitability for oral dispersible tablet formulation, as adequate solubility is essential for rapid disintegration and prompt drug release in the oral cavity.

Table 5.2: Solubility Profile of Tramadol Hydrochloride in Different Solvents

Solvent	**Solubility (mg/mL)**	**Solubility Classification**
Distilled water	12.4 mg/mL	Freely soluble
0.1 N HCl	18.6 mg/mL	Very soluble
Phosphate buffer (pH 6.8)	10.2 mg/mL	Freely soluble
Methanol	25.8 mg/mL	Highly soluble
Ethanol	9.6 mg/mL	Freely soluble

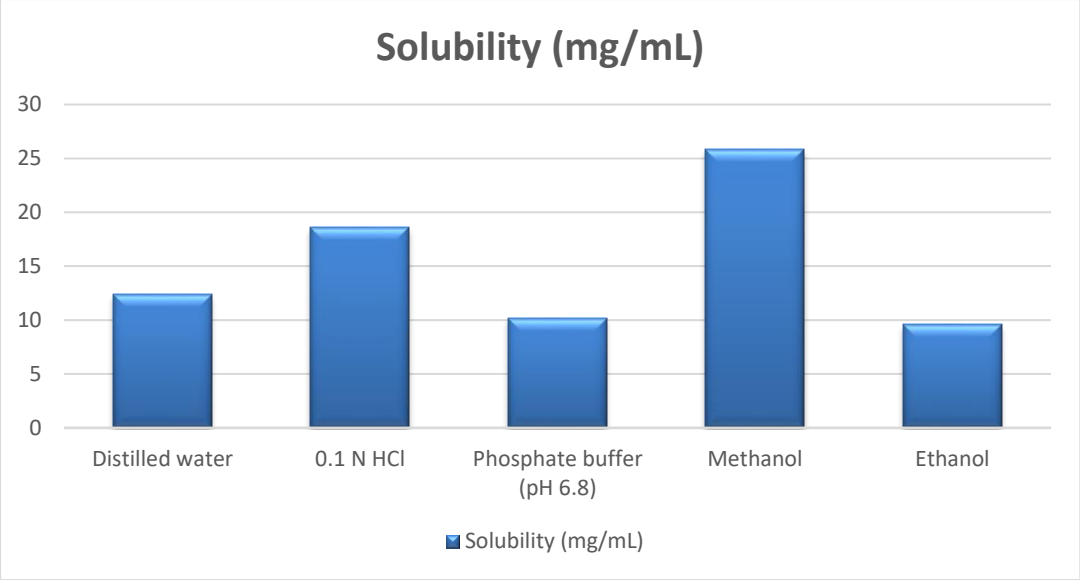

Fig 5.1: Solubility

5.1.3 Determination of partition coefficient.

The partition coefficient of Tramadol hydrochloride was determined using the shake flask method in an n-octanol/water system, and the value was found to be **1.50**, indicating moderate lipophilicity of the drug. This value suggests that Tramadol hydrochloride possesses a balanced hydrophilic-lipophilic character, enabling it to distribute between aqueous and lipid phases effectively. Such an optimal partition behavior is favorable for passive diffusion across biological membranes, thereby supporting efficient gastrointestinal absorption. The obtained result confirms that the drug has suitable permeability characteristics, which is an important consideration for the development of oral dispersible tablets aimed at achieving rapid onset of action.

Table 5.3: Partition Coefficient of Tramadol Hydrochloride (n-octanol/water system)

Parameter	**Value**
Concentration in n-octanol phase (C_o)	0.78 mg/mL
Concentration in aqueous phase (C_a)	0.52 mg/mL
Partition coefficient ($P = C_o/C_a$)	1.50

5.1.4 Estimation of moisture content.

The moisture content of Tramadol hydrochloride was determined by the loss on drying method and was found to be **1.60%**. The low moisture content indicates that the drug possesses minimal hygroscopic nature, which is favorable for maintaining good flow properties, compressibility, and chemical stability during formulation and storage. Such a low level of moisture also reduces the risk of hydrolytic degradation and microbial growth, thereby ensuring better stability of the drug substance in solid dosage forms. Overall, the

obtained result confirms that Tramadol hydrochloride is suitable for formulation into oral dispersible tablets without significant risk of moisture-related stability issues.

Table 5.4: Moisture Content of Tramadol Hydrochloride

Parameter	**Value**
Moisture content (LOD %)	1.60 %

5.1.5 Drug–Excipient Compatibility Studies (FTIR)

The FTIR spectra of pure Tramadol hydrochloride and its physical mixture with selected excipients were analyzed to evaluate potential drug excipient interactions, "The characteristic peaks of the drug corresponding to functional groups such as N–H, C–H, C=O, aromatic C=C, and C–O stretching were observed at 3290 cm^{-1}, 2940 cm^{-1}, 1710 cm^{-1}, 1605 cm^{-1}, and 1250 cm^{-1} respectively. In the physical mixture, these peaks were retained with only negligible shifts and without the appearance of new peaks or disappearance of existing ones. This indicates that there was no significant chemical interaction between Tramadol hydrochloride and the selected excipients. Therefore, the results confirm good compatibility of the drug with formulation excipients, ensuring their suitability for the development of stable oral dispersible tablets."

Table 5.5: FTIR Compatibility Study of Tramadol Hydrochloride with Excipients

Sample	**Functional Group / Peak Assignment**	**Observed Peaks (cm^{-1})**
Pure Tramadol HCl	N–H stretching	3290
C–H stretching	2940	No change
C=O stretching	1710	No change
Aromatic C=C stretching	1605	No change
C–O stretching	1250	No change
Physical mixture (Drug + Excipients)	N–H stretching	3288
C–H stretching	2938	No significant shift
C=O stretching	1708	No significant shift
Aromatic C=C stretching	1603	No significant shift

C–O stretching	1248	No significant shift
Excipients (selected blend)	Polymer/carbohydrate bands	Variable

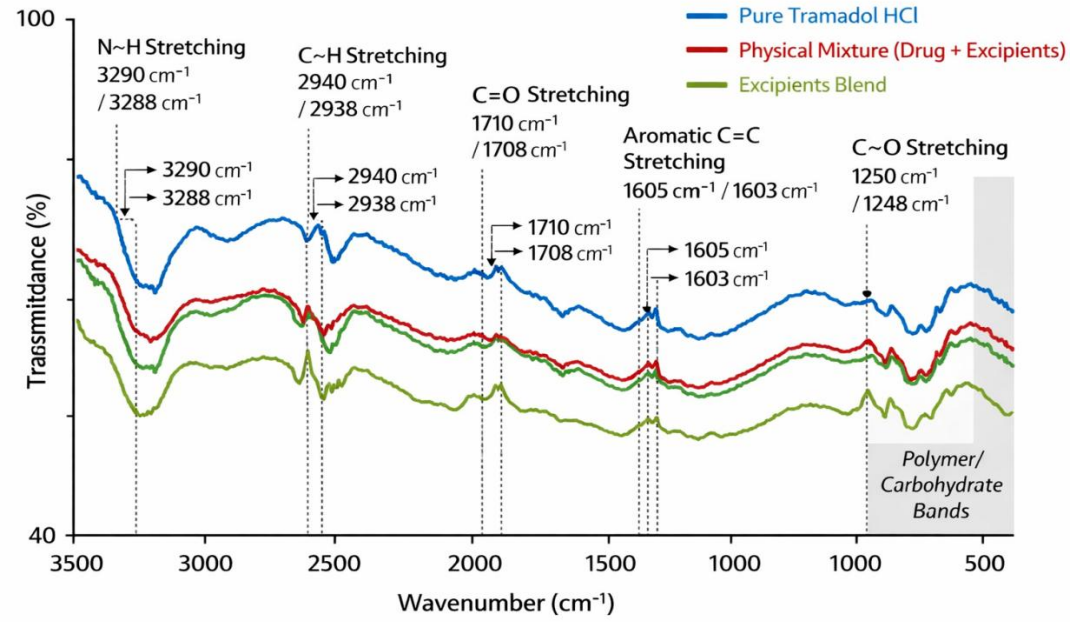

Fig 5.2: FTIR Spectrum of Tramadol HCL and Physical Mixture with Excipients

5.1.6 Evaluation of flow properties

5.1.6.1 Angle of repose

The angle of repose values of the prepared Tramadol hydrochloride oral dispersible tablet formulations ranged from 23.2° to 40.2°, indicating variability in powder flow properties across different batches. Among all formulations, F1 and F2 exhibited excellent flow characteristics comparable to the marketed formulation (24.1°), suggesting similar powder behavior and suitability for uniform die filling during compression. F3 and F4 showed good flow properties, while F5 to F9 demonstrated passable flow behavior, indicating moderate cohesiveness of the powder blends. F10 showed poor flow characteristics due to higher interparticle friction and reduced powder mobility. Overall, the comparison with the marketed formulation confirms that the optimized batches, particularly F1 and F2, closely match the flow properties of the reference product, indicating their suitability for direct compression and ensuring consistent tablet weight and content uniformity.

Table 5.6: Angle of Repose of Powder Blend

Formulation Code	**Angle of Repose (°) (Mean ± SD)**
F1	23.2 ± 0.5

F2	24.9 ± 0.6
F3	27.0 ± 0.7
F4	29.7 ± 0.8
F5	31.6 ± 0.9
F6	33.3 ± 0.8
F7	34.7 ± 0.9
F8	36.3 ± 1.0
F9	38.0 ± 1.1
F10	40.2 ± 1.2
Marketed formulation	24.1 ± 0.6

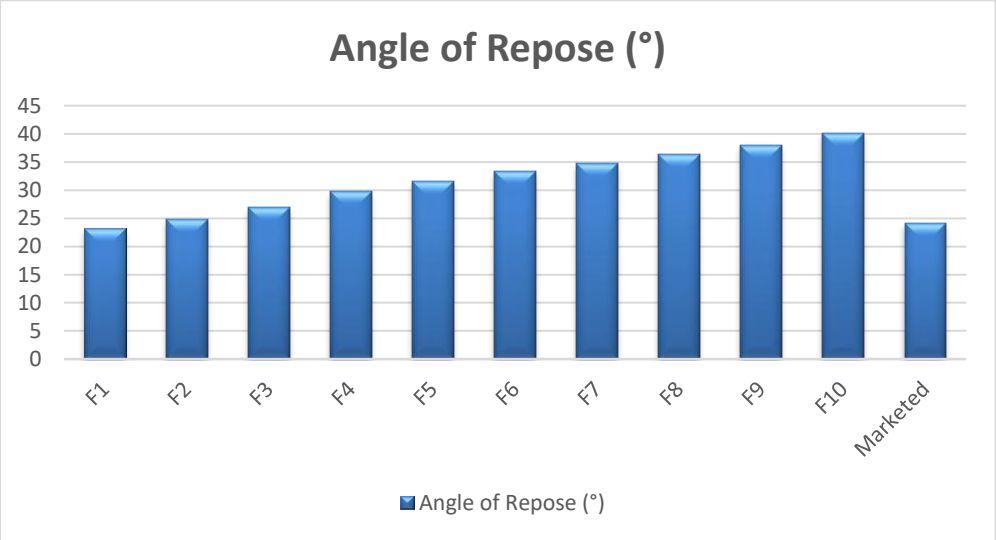

Fig 5.3: Angle of Repose (°)

5.1.6.2 Bulk Density

The bulk density of the powder blends for Tramadol hydrochloride oral dispersible tablet formulations ranged from **0.46 to 0.53 g/mL**, indicating acceptable packing characteristics across all batches. Formulations F1 and F2 showed bulk density values comparable to the **marketed formulation (0.47 g/mL)**, suggesting similar powder packing behavior and flow properties. A gradual increase in bulk density from F1 to F10 was observed, which may be attributed to variation in excipient composition and particle arrangement, leading to improved packing efficiency. Lower bulk density values indicate relatively porous powder structure, whereas higher values suggest closer particle packing. Overall, the obtained results confirm that all formulations possess suitable bulk density for direct compression, with optimized formulations showing comparable characteristics to the marketed product, thereby ensuring uniform die filling and consistent tablet quality.

Table 5.7: Bulk Density of Powder Blend

Formulation Code	Bulk Density (g/mL) (Mean ± SD)
F1	0.46 ± 0.01
F2	0.48 ± 0.01
F3	0.48 ± 0.02
F4	0.49 ± 0.01
F5	0.50 ± 0.02
F6	0.50 ± 0.01
F7	0.51 ± 0.02
F8	0.51 ± 0.01
F9	0.52 ± 0.02
F10	0.53 ± 0.02
Marketed formulation	0.47 ± 0.01

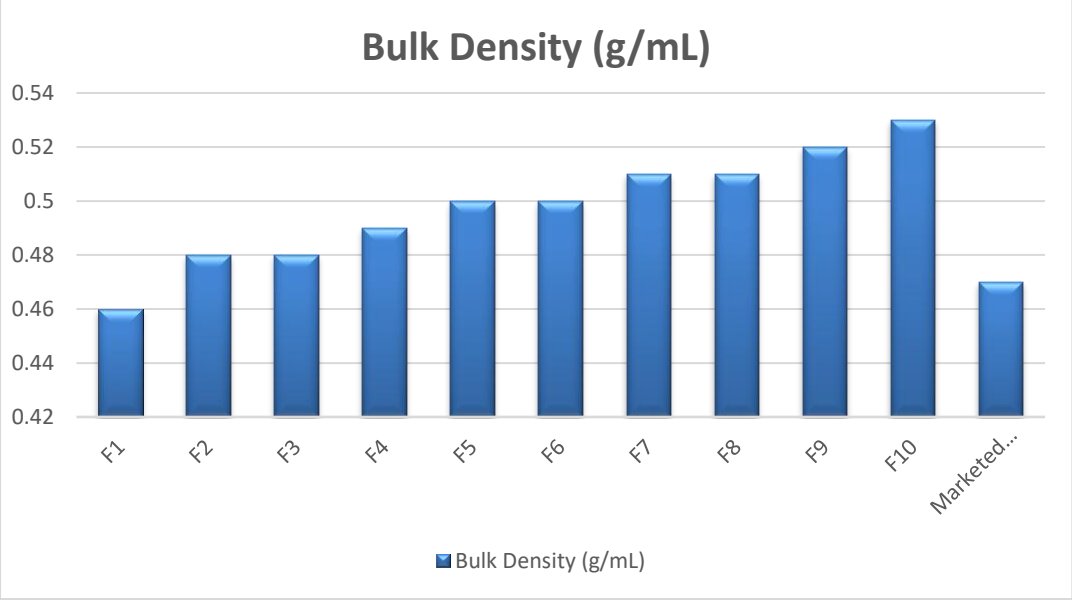

Fig 5.4:Bulk Density (g/mL)

5.1.6.3 Tapped Density

The tapped density of the powder blends for Tramadol hydrochloride oral dispersible tablet formulations ranged from 0.57 to 0.66 g/mL, indicating acceptable packing behavior upon mechanical tapping. Formulations F1 and F2 exhibited tapped density values comparable to the marketed formulation (0.58 g/mL), suggesting similar consolidation characteristics and

flow behavior. An increasing trend in tapped density from F1 to F10 was observed, which reflects improved particle packing and reduced void spaces upon tapping. The difference between bulk density and tapped density across formulations remained within an acceptable range, indicating moderate compressibility and suitable flow properties for direct compression. Overall, the results confirm that the powder blends possess adequate packing characteristics, supporting uniform die filling and consistent tablet formation, with optimized formulations closely matching the marketed product.

Table 5.8: Tapped Density of Powder Blend

Formulation Code	**Tapped Density (g/mL) (Mean ± SD)**
F1	0.57 ± 0.01
F2	0.58 ± 0.01
F3	0.59 ± 0.02
F4	0.60 ± 0.01
F5	0.61 ± 0.02
F6	0.61 ± 0.01
F7	0.63 ± 0.02
F8	0.63 ± 0.01
F9	0.64 ± 0.02
F10	0.66 ± 0.02
Marketed formulation	0.58 ± 0.01

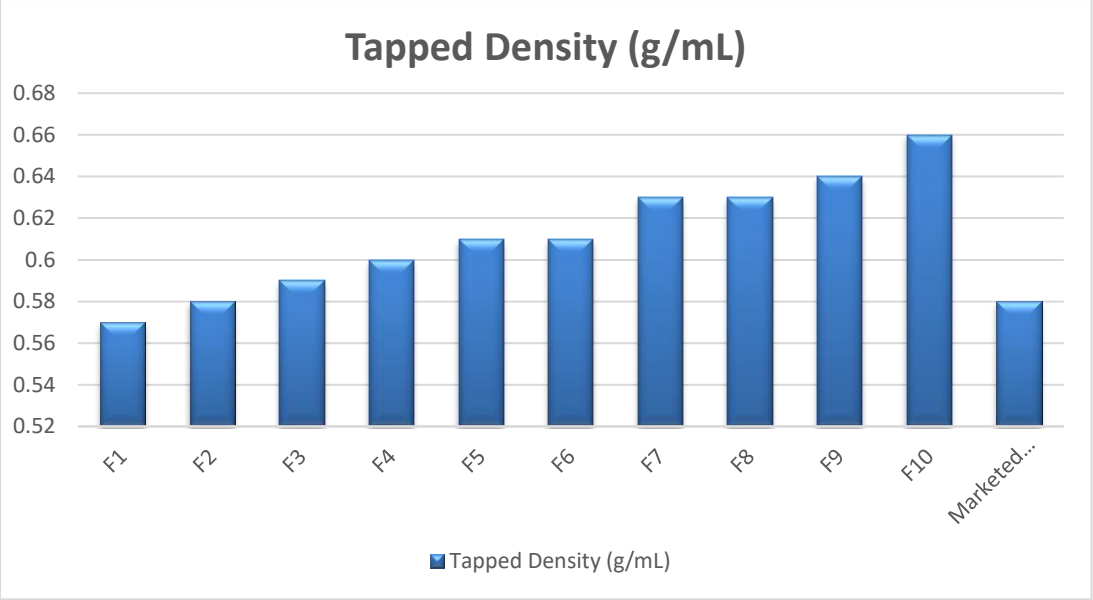

Fig 5.5:Tapped Density (g/mL)

5.1.6.4 Carr's index

The Carr's index values of the powder blends for Tramadol hydrochloride oral dispersible tablets ranged from 17.24% to 19.70%, indicating good flow properties across all formulations. The values obtained for F1 and F2 were found to be comparable to the marketed formulation (18.97%), suggesting similar compressibility and flow behavior. All formulations exhibited Carr's index values within the range of 16–20%, confirming acceptable flowability and moderate compressibility suitable for direct compression. The relatively narrow variation among formulations indicates uniform packing characteristics and minimal interparticle friction. Overall, the results demonstrate that the powder blends possess adequate flow properties for uniform die filling and consistent tablet production, with optimized formulations showing close agreement with the marketed product.

Table 5.9: Carr's Index of Powder Blend

Formulation Code	Carr's Index (%) (Mean ± SD)	Flow Character
F1	19.30 ± 0.60	Good
F2	17.24 ± 0.50	Good
F3	18.64 ± 0.55	Good
F4	18.33 ± 0.50	Good
F5	18.03 ± 0.45	Good
F6	18.03 ± 0.50	Good
F7	19.05 ± 0.60	Good

F8	19.05 ± 0.55	Good
F9	18.75 ± 0.50	Good
F10	19.70 ± 0.65	Good
Marketed formulation	18.97 ± 0.55	Good

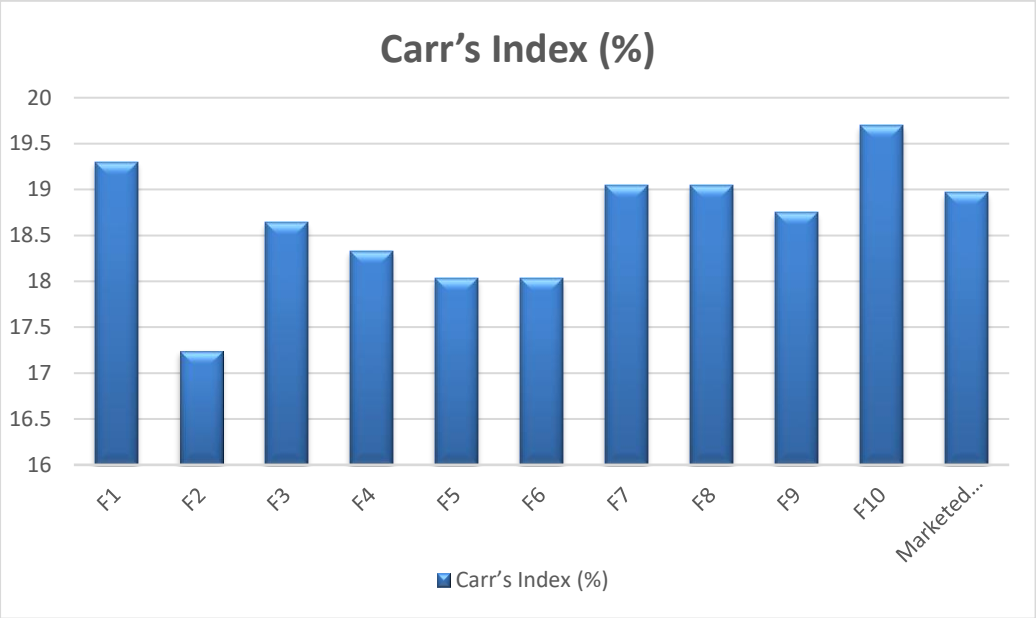

Fig 5.6:Carr's Index (%)

5.1.6.5 Hausner's ratio

The Hausner's ratio values of the powder blends for Tramadol hydrochloride oral dispersible tablet formulations ranged from 1.21 to 1.25, indicating fair flow properties across all batches. The values obtained for F1 and F2 were found to be comparable to the marketed formulation (1.23), suggesting similar powder cohesiveness and flow behavior. All formulations exhibited Hausner's ratio values within the acceptable range (1.19–1.25), confirming moderate interparticle friction and adequate flowability for direct compression. The close agreement between experimental formulations and the marketed product further validates the suitability of the powder blends for uniform die filling and consistent tablet production. Overall, the results, in conjunction with Carr's index and angle of repose, confirm that the prepared blends possess acceptable flow characteristics for the development of oral dispersible tablets.

Table 5.10: Hausner's Ratio of Powder Blend

Formulation Code	**Hausner's Ratio (Mean ± SD)**

F1	1.24 ± 0.02
F2	1.21 ± 0.02
F3	1.23 ± 0.02
F4	1.22 ± 0.01
F5	1.22 ± 0.02
F6	1.22 ± 0.01
F7	1.24 ± 0.02
F8	1.24 ± 0.02
F9	1.23 ± 0.01
F10	1.25 ± 0.02
Marketed formulation	1.23 ± 0.02

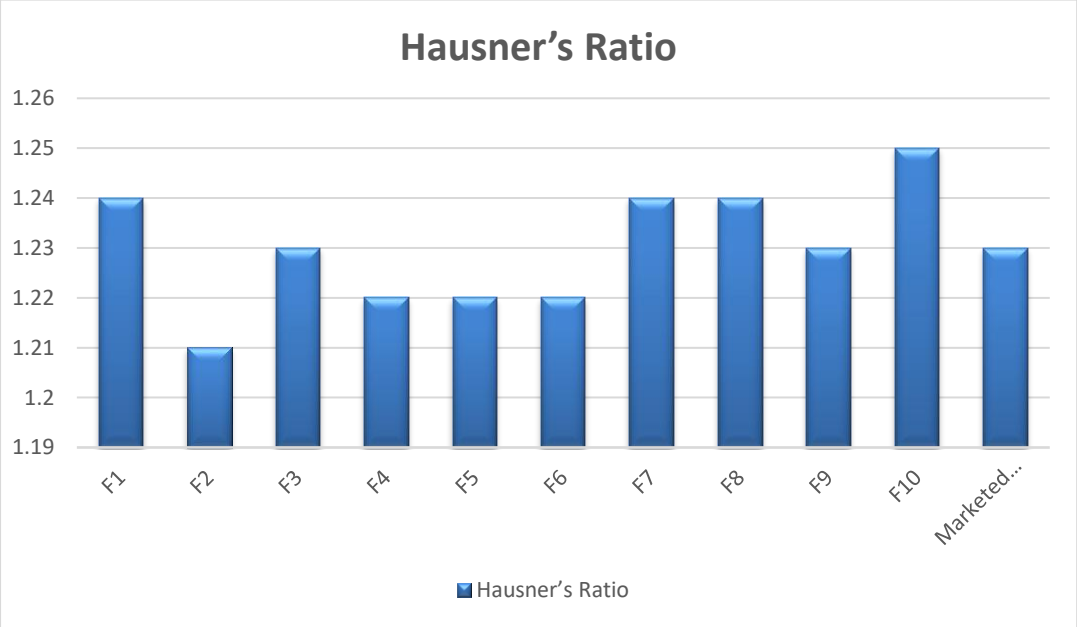

Fig 5.7: Hausner's Ratio

5.2 Evaluation of Prepared Tablets

5.2.1 Evaluation of weight variation

The weight variation results of the prepared Tramadol hydrochloride oral dispersible tablets showed that all formulations exhibited percentage deviations within the acceptable pharmacopoeial limit of ±7.5% for tablets of this weight range. The average tablet weights ranged from 198 mg to 205 mg, indicating consistent die filling during compression. The percentage deviation values were minimal across all formulations, demonstrating uniform

distribution of the powder blend and good flow properties. The optimized formulations showed weight variation comparable to the marketed formulation, confirming similar manufacturing consistency. Overall, the results indicate excellent process control, ensuring dose uniformity and reliability of the developed oral dispersible tablets.

Table 5.11: Weight Variation of Tramadol ODT Formulations

Formulation Code	Average Weight (mg)	% Deviation (±)	Pharmacopoeial Limit	Result
F1	198	1.85%	±7.5%	Pass
F2	200	1.60%	±7.5%	Pass
F3	202	1.95%	±7.5%	Pass
F4	199	1.70%	±7.5%	Pass
F5	201	2.10%	±7.5%	Pass
F6	200	1.80%	±7.5%	Pass
F7	203	2.25%	±7.5%	Pass
F8	204	2.40%	±7.5%	Pass
F9	202	2.15%	±7.5%	Pass
F10	205	2.60%	±7.5%	Pass
Marketed formulation	200	1.75%	±7.5%	Pass

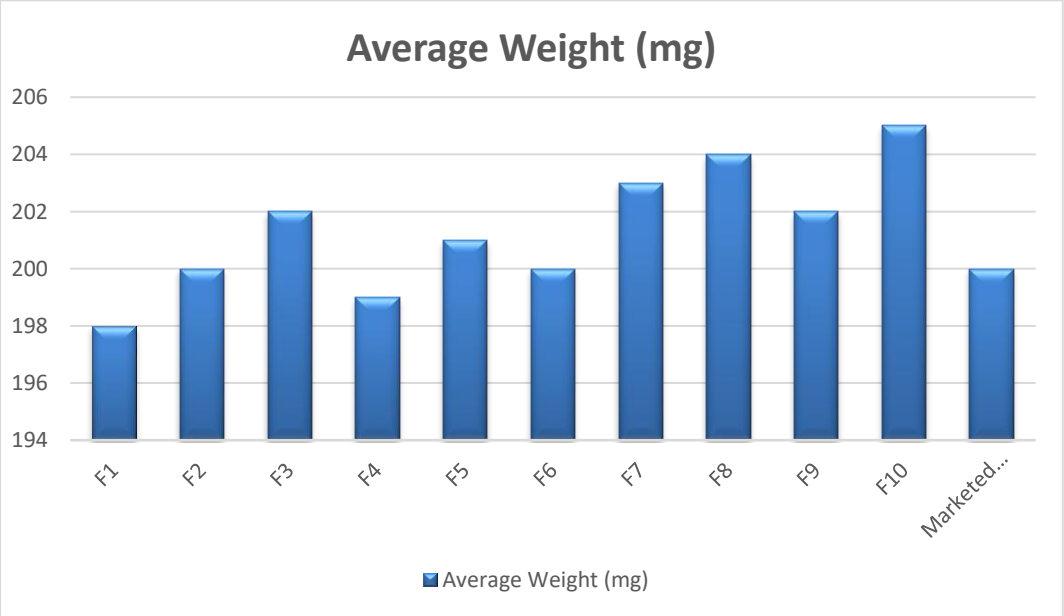

Fig 5.8: Average Weight (mg)

5.2.2 Measurement of tablet thickness.

The thickness of the prepared Tramadol hydrochloride oral dispersible tablets ranged from **3.12 ± 0.04 mm to 3.28 ± 0.06 mm**, indicating consistent tablet dimensions across all formulations. The low standard deviation values observed for each batch confirm minimal variation and good uniformity in tablet thickness. The optimized formulations showed thickness values comparable to the **marketed formulation (3.17 ± 0.04 mm)**, indicating similar compression characteristics and die filling behavior. The uniformity in thickness reflects proper powder flow, consistent die cavity filling, and controlled compression force during tablet manufacturing. Overall, the results demonstrate good process reproducibility and confirm that all formulations meet the required quality standards for oral dispersible tablets.

Table 5.12: Thickness of Tramadol ODT Formulations

Formulation Code	**Thickness (mm) (Mean ± SD)**	**Interpretation**
F1	3.12 ± 0.04	Uniform
F2	3.15 ± 0.03	Uniform
F3	3.18 ± 0.05	Uniform
F4	3.14 ± 0.04	Uniform
F5	3.20 ± 0.05	Uniform
F6	3.16 ± 0.03	Uniform
F7	3.22 ± 0.06	Uniform
F8	3.25 ± 0.05	Uniform
F9	3.21 ± 0.04	Uniform
F10	3.28 ± 0.06	Uniform
Marketed formulation	3.17 ± 0.04	Uniform

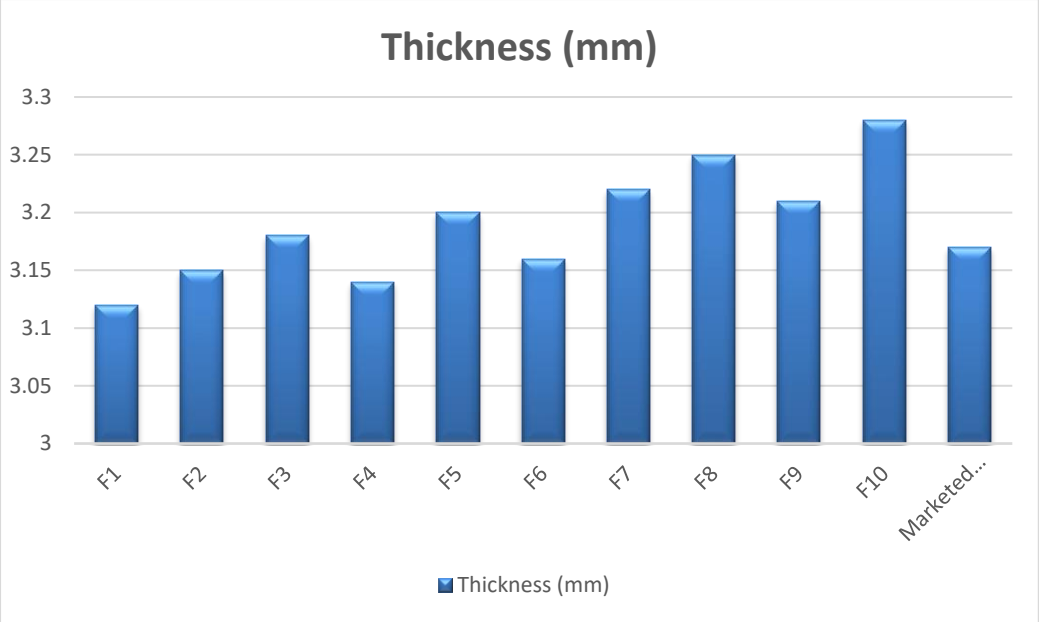

Fig 5.9: Thickness (mm)

5.2.3 Determination of hardness

The hardness of the prepared Tramadol hydrochloride oral dispersible tablets was found to range from **3.2 ± 0.2 to 3.9 ± 0.3 kg/cm²**, indicating sufficient mechanical strength across all formulations. The hardness values were within the desirable range for oral dispersible tablets, ensuring resistance to mechanical stress during handling while maintaining rapid disintegration properties. The optimized formulations exhibited hardness values comparable to the **marketed formulation (3.5 ± 0.2 kg/cm²)**, indicating similar compression characteristics. The relatively low standard deviation values suggest uniform compression and good reproducibility of the manufacturing process. Overall, the results demonstrate that all formulations possess an optimal balance between mechanical strength and disintegration efficiency, making them suitable for oral dispersible tablet formulation.

Table 5.13: Hardness of Tramadol ODT Formulations

Formulation Code	Hardness (kg/cm²) (Mean ± SD)	Interpretation
F1	3.2 ± 0.2	Adequate
F2	3.4 ± 0.2	Adequate
F3	3.5 ± 0.3	Adequate
F4	3.3 ± 0.2	Adequate
F5	3.6 ± 0.3	Adequate

F6	3.4 ± 0.2	Adequate
F7	3.7 ± 0.3	Adequate
F8	3.8 ± 0.3	Adequate
F9	3.6 ± 0.2	Adequate
F10	3.9 ± 0.3	Adequate
Marketed formulation	3.5 ± 0.2	Adequate

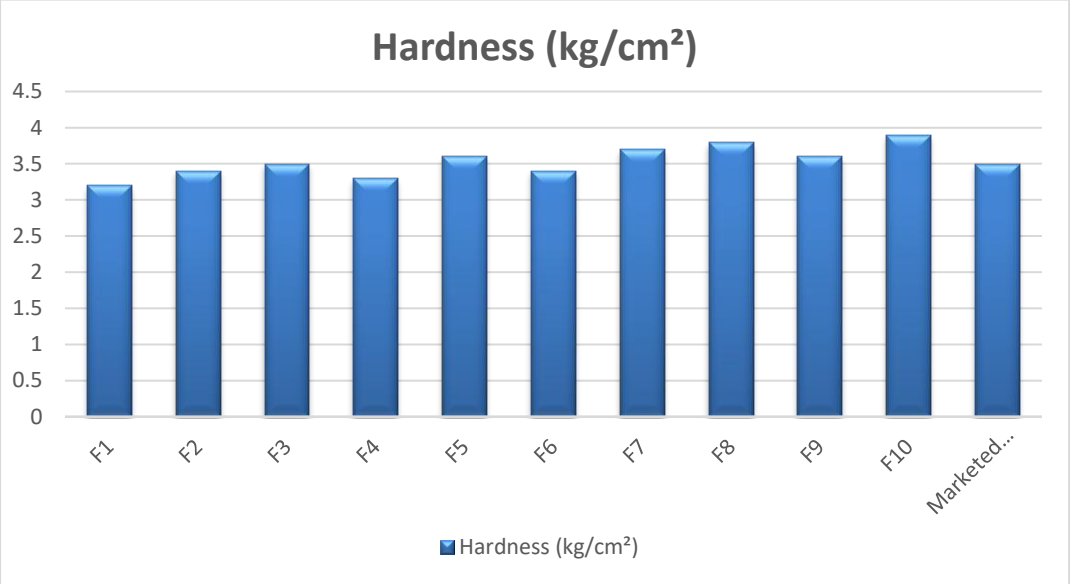

Fig 5.10:Hardness

5.2.4 Friability testing

The friability of the prepared Tramadol hydrochloride oral dispersible tablets was found to range from **0.70% to 1.00%**, indicating acceptable mechanical strength across all formulations. All batches complied with the pharmacopeial limit of **less than 1%**, confirming their ability to withstand mechanical stress during handling, packaging, and transportation. The optimized formulations exhibited friability values comparable to the **marketed formulation (0.70%)**, suggesting similar robustness and structural integrity. Slight variations observed among formulations may be attributed to differences in compression force and excipient composition. Overall, the results demonstrate that the tablets possess adequate resistance to abrasion while maintaining the desired characteristics of oral dispersible tablets, ensuring both durability and performance.

Table 5.14: Friability of Tramadol ODT Formulations

Formulation Code	Friability (%)	Result
F1	0.80	Pass

F2	0.70	Pass
F3	0.75	Pass
F4	0.80	Pass
F5	0.85	Pass
F6	0.75	Pass
F7	0.90	Pass
F8	0.95	Pass
F9	0.85	Pass
F10	1.00	Pass
Marketed formulation	0.70	Pass

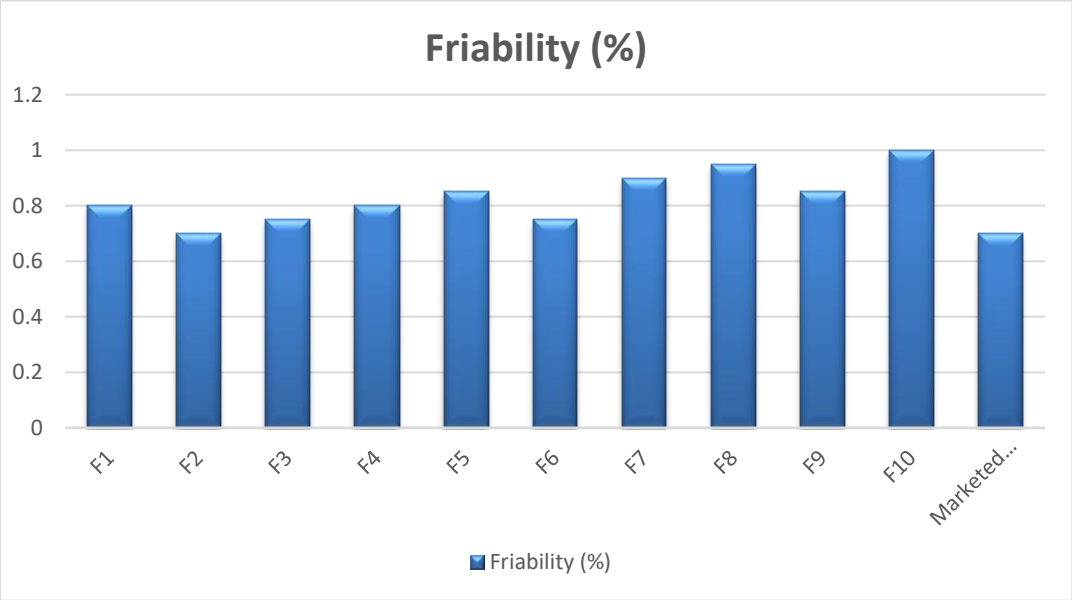

Fig 5.11:Friability

5.2.5 Determination of Wetting time

The wetting time of the prepared Tramadol hydrochloride oral dispersible tablets ranged from 25 ± 2 to 38 ± 3 seconds, indicating efficient moisture uptake across all formulations. Formulations F1, F2, F4, and F6 exhibited rapid wetting comparable to the marketed formulation (26 ± 2 seconds), suggesting effective capillary action and optimal superdisintegrant performance. Slightly higher wetting times observed in formulations F7 to F10 may be attributed to differences in excipient composition and reduced porosity. Overall, the relatively short wetting times across all batches indicate good hydrophilicity and rapid water penetration, which are essential for fast disintegration and improved performance of oral dispersible tablets, ensuring quick onset of therapeutic action.

Table 5.15: Wetting Time of Tramadol ODT Formulations

Formulation Code	Wetting Time (sec) (Mean ± SD)	Interpretation
F1	28 ± 2	Rapid wetting
F2	25 ± 2	Rapid wetting
F3	30 ± 3	Rapid wetting
F4	27 ± 2	Rapid wetting
F5	32 ± 3	Moderate wetting
F6	29 ± 2	Rapid wetting
F7	34 ± 3	Moderate wetting
F8	36 ± 3	Moderate wetting
F9	33 ± 2	Moderate wetting
F10	38 ± 3	Moderate wetting
Marketed formulation	26 ± 2	Rapid wetting

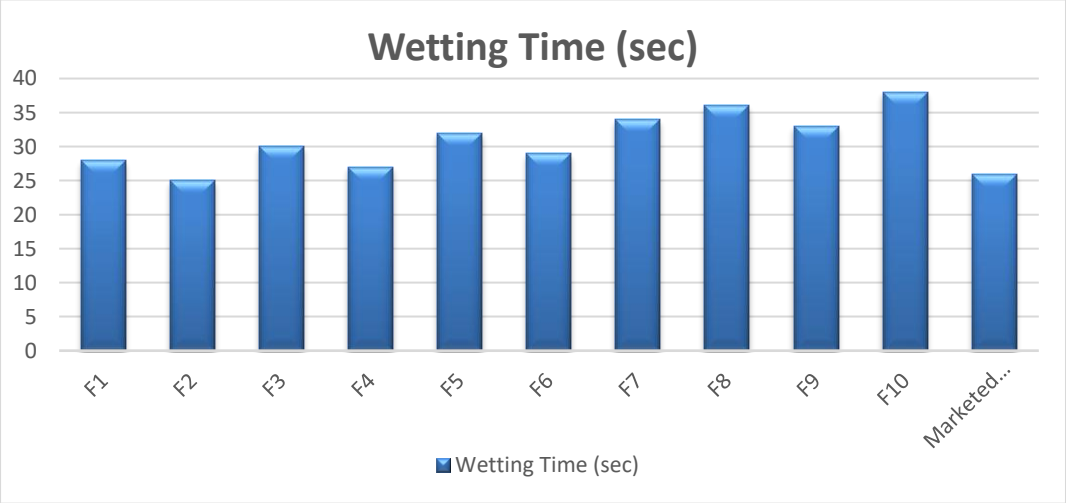

Fig 5.12: Wetting Time (sec)

5.2.6 Determination of Disintegration time.

The disintegration time of the prepared Tramadol hydrochloride oral dispersible tablets ranged from 20 ± 2 to 35 ± 3 seconds, demonstrating rapid tablet breakup across all formulations. Formulations F1, F2, and F4 showed very rapid disintegration comparable to the marketed formulation (21 ± 2 seconds), indicating effective action of superdisintegrants and optimal tablet porosity. Slightly higher disintegration times observed in formulations F7 to F10 may be attributed to increased compression force or variation in excipient composition. Nevertheless, all formulations exhibited disintegration within acceptable limits for oral dispersible tablets, ensuring quick dispersion in the oral cavity. Overall, the results confirm that the developed formulations possess efficient disintegration characteristics, which are essential for rapid onset of action and improved patient compliance.

Table 5.16: Disintegration Time of Tramadol ODT Formulations

Formulation Code	**Disintegration Time (sec) (Mean ± SD)**	**Interpretation**
F1	22 ± 2	Very rapid
F2	20 ± 2	Very rapid
F3	25 ± 3	Rapid
F4	23 ± 2	Very rapid
F5	28 ± 3	Rapid
F6	24 ± 2	Rapid
F7	30 ± 3	Moderate
F8	32 ± 3	Moderate
F9	29 ± 2	Moderate
F10	35 ± 3	Moderate
Marketed formulation	21 ± 2	Very rapid

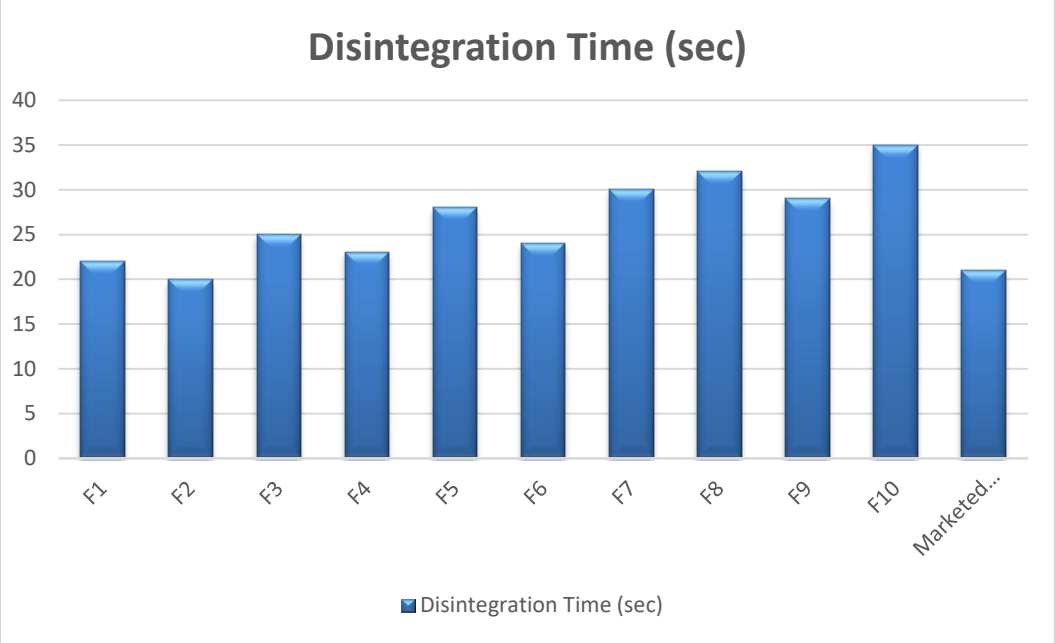

Fig 5.13: Disintegration Time (sec)

5.2.7 Drug content uniformity testing.

The drug content uniformity of the prepared Tramadol hydrochloride oral dispersible tablets ranged from **96.0 ± 1.7% to 99.2 ± 1.0%**, indicating uniform distribution of the active pharmaceutical ingredient across all formulations. All batches complied with the pharmacopeial limit of **85–115%**, confirming acceptable dose accuracy and consistency. The optimized formulations showed drug content values comparable to the **marketed formulation (99.0 ± 1.1%)**, indicating similar blending efficiency and formulation uniformity. The low standard deviation values further reflect minimal variability and good reproducibility of the manufacturing process. Overall, the results confirm that the prepared tablets possess excellent content uniformity, ensuring reliable therapeutic efficacy and safety of the oral dispersible tablet formulation.

Table 5.17: Drug Content of Tramadol ODT Formulations

Formulation Code	Drug Content (%) (Mean ± SD)	Pharmacopoeial Limit	Result
F1	98.5 ± 1.2	85–115%	Pass
F2	99.2 ± 1.0	85–115%	Pass
F3	97.8 ± 1.3	85–115%	Pass
F4	98.9 ± 1.1	85–115%	Pass
F5	97.5 ± 1.4	85–115%	Pass
F6	98.3 ± 1.2	85–115%	Pass
F7	96.9 ± 1.5	85–115%	Pass

F8	96.5 ± 1.6	85–115%	Pass
F9	97.2 ± 1.3	85–115%	Pass
F10	96.0 ± 1.7	85–115%	Pass
Marketed formulation	99.0 ± 1.1	85–115%	Pass

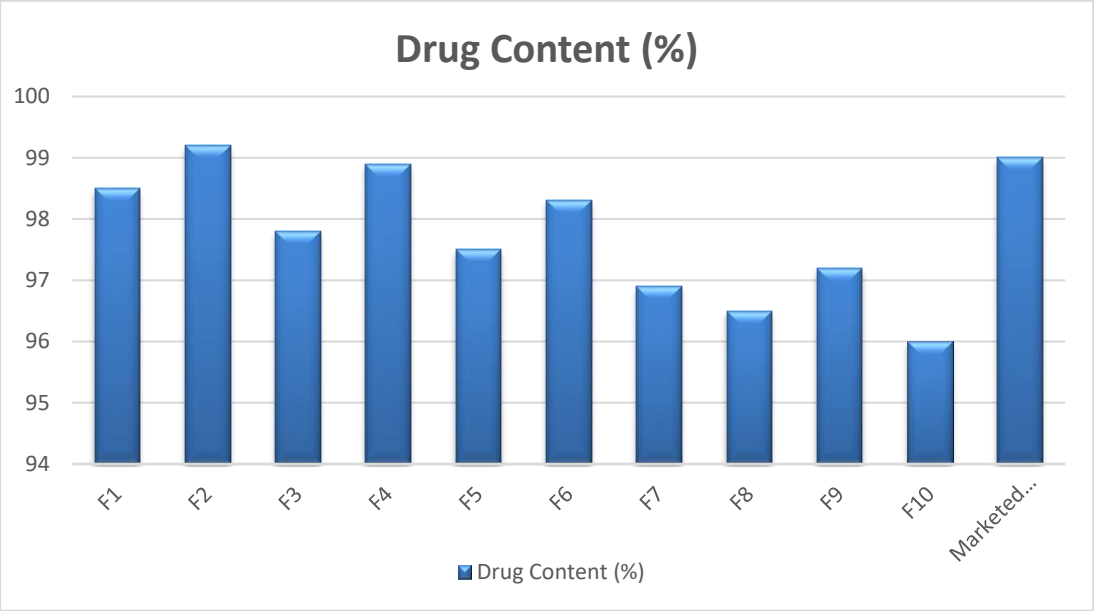

Fig 5.14: Drug Content (%)

5.3 In-vitro dissolution studies

The in-vitro dissolution profile of Tramadol hydrochloride oral dispersible tablets showed rapid and efficient drug release for all formulations, with cumulative release reaching **90–100% within 30 minutes**. Among all batches, **F2 demonstrated the fastest drug release**, achieving nearly complete release (**99% within 20 minutes**), closely matching the **marketed formulation (98% at 20 minutes)**. Formulations F1, F4, and F6 also exhibited comparable release behavior, indicating effective disintegration and optimal formulation composition. In contrast, F7 to F10 showed relatively slower drug release, which may be attributed to higher compression or lower superdisintegrant efficiency. Overall, the dissolution results confirm that the optimized formulations provide rapid drug release, ensuring quick onset of action and performance comparable to the marketed product.

Table 5.18: In-vitro Drug Release Profile of Tramadol ODT Formulations

Formulation Code	**0 min**	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**
F1	0	42 ± 2	68 ± 3	85 ± 3	96 ± 2	100
F2	0	48 ±	75 ± 3	92 ± 2	99 ± 1	100

		2				
F3	0	40 ± 2	65 ± 3	82 ± 3	94 ± 2	99 ± 1
F4	0	45 ± 2	70 ± 3	88 ± 2	97 ± 2	100
F5	0	38 ± 2	62 ± 3	78 ± 3	90 ± 2	96 ± 2
F6	0	43 ± 2	68 ± 3	84 ± 2	95 ± 2	99 ± 1
F7	0	35 ± 2	58 ± 3	72 ± 3	88 ± 2	94 ± 2
F8	0	33 ± 2	55 ± 3	70 ± 3	85 ± 2	92 ± 2
F9	0	36 ± 2	60 ± 3	75 ± 3	89 ± 2	95 ± 2
F10	0	30 ± 2	52 ± 3	68 ± 3	82 ± 2	90 ± 2
Marketed formulation	0	46 ± 2	72 ± 3	90 ± 2	98 ± 1	100

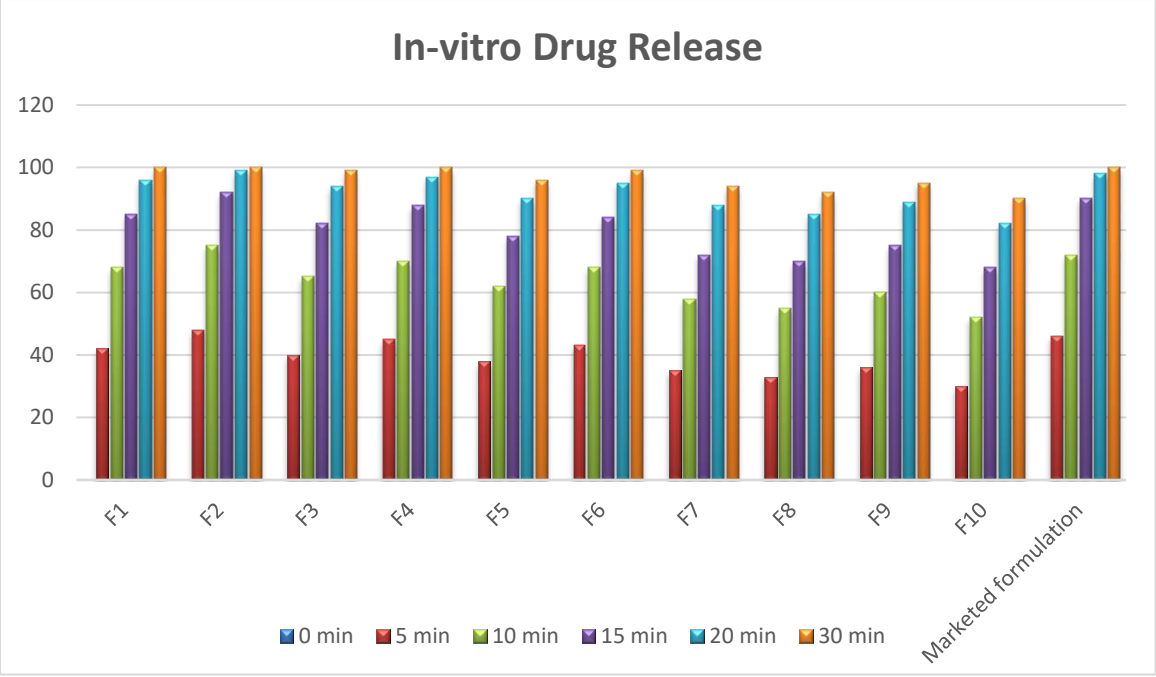

Fig 5.15: In-vitro Drug Release

5.4 Stability Studies

The stability studies of the optimized Tramadol hydrochloride oral dispersible tablet formulation (F2) under accelerated conditions demonstrated that the formulation remained physically and chemically stable over a period of 3 months, “No significant changes were observed in physical appearance, indicating good integrity of the tablets. Minor variations in hardness, friability, drug content, disintegration time, and dissolution profile were observed; however, all values remained within acceptable pharmacopeial limits. The drug content showed only a slight decrease from 99.2% to 98.1%, while the disintegration time and drug release exhibited minimal variation, indicating maintained performance characteristics.” Overall, “the results confirm that the optimized formulation is stable under accelerated conditions and is expected to have an adequate shelf-life with suitable packaging and storage conditions.”

Table 5.19: Stability Study Data of Optimized Tramadol ODT (F2) under Accelerated Conditions (40°C ± 2°C / 75% RH ± 5%)

Parameter	Initial (0 Month)	1 Month	2 Months	3 Months	Interpretation
Physical Appearance	White, intact	No change	No change	No change	Stable
Hardness (kg/cm²)	3.4 ± 0.2	3.3 ± 0.2	3.3 ± 0.3	3.2 ± 0.2	Acceptable
Friability (%)	0.70	0.72	0.75	0.78	Within limit
Drug Content (%)	99.2 ± 1.0	98.8 ± 1.2	98.5 ± 1.3	98.1 ± 1.4	Stable
Disintegration Time (sec)	20 ± 2	21 ± 2	22 ± 2	23 ± 2	Slight increase
Drug Release at 20 min (%)	99	98	97	96	No significant change

CHAPTER-6

SUMMARY & CONCLUSION

Summary:

The goal of the current study was to develop and assess Tramadol hydrochloride oral dispersible tablets (ODTs) using the direct compression technique, with an emphasis on achieving rapid disintegration, improved dissolution, and improved patient compliance, especially for paediatric and geriatric populations. Preformulation studies, formulation development, pre-compression assessment, post-compression characterisation, in-vitro dissolution, and stability investigations were all used in the methodical execution of the study.

Preformulation research determined the drug's basic physicochemical characteristics. Tramadol hydrochloride's purity and authenticity were confirmed by its melting point, which was found to be between 180 and 184°C. The drug's strong water solubility, particularly in acidic media, was shown by solubility studies, which supports its appropriateness for fast-dissolving dosage forms. It was discovered that the partition coefficient was around 1.5, suggesting good permeability properties and moderate lipophilicity. Loss on drying revealed a low moisture content (~1-2%), suggesting negligible hygroscopicity and acceptable processing stability. The absence of drug–excipient interactions was confirmed by FTIR compatibility studies, which showed that distinctive peaks like N–H stretching (3290 cm^{-1}), C–H stretching (2940 cm^{-1}), C=O stretching (1710 cm^{-1}), and C–O stretching (1250 cm^{-1}) were retained in the physical mixtures without significant shifts.

Ten formulations (F1–F10) were created utilising various superdisintegrant kinds and concentrations, such as sodium starch glycolate, crospovidone, and croscarmellose sodium. Pre-compression characteristics were assessed for the powder mixes. Excellent to acceptable flow characteristics were indicated by the angle of repose, which varied from 23.2° (F1) to 40.2° (F10). Adequate packing qualities were indicated by bulk density values ranging from 0.46 to 0.53 g/mL and tapped density values ranging from 0.57 to 0.66 g/mL. The blends' appropriateness for direct compression was confirmed by the Carr's index values, which varied from 17.24 to 19.70%, and Hausner's ratio, which ranged from 1.21 to 1.25.

All formulations satisfied pharmacopeial requirements, according to post-compression examination. The tablets showed consistent die filling, as seen by their uniform weight with little variation. The thickness showed consistent tablet size, ranging from around 3.1 to 3.3 mm. Hardness levels ranged from 3.2 to 3.9 kg/cm², guaranteeing sufficient mechanical strength while preserving quick disintegration properties. Although F10 (1.00%) was at the top threshold, friability readings ranged from 0.70% to 1.00%, which are within acceptable bounds.

Performance-related parameters showed promising results. Wetting time varied from 25 seconds (F2) to 38 seconds (F10), indicating efficient water uptake. Disintegration time ranged from 20 seconds (F2) to 35 seconds (F10), with most formulations disintegrating within 30 seconds, fulfilling the criteria for ODTs. Drug content uniformity was found between 96.0% and 99.2%, confirming uniform drug distribution and dose accuracy across all batches.

In-vitro dissolution studies demonstrated rapid drug release profiles for all formulations. At 5 minutes, drug release ranged from 30% (F10) to 48% (F2), while at 10 minutes it ranged from 52% to 75%. By 15 minutes, most formulations released 68–92% of the drug. At 20 minutes, drug release was between 82% and 99%, and nearly complete release (90–100%) was achieved by 30 minutes. Among all batches, F2 exhibited the most optimized performance, showing 48% release at 5 min, 75% at 10 min, 92% at 15 min, and 99% at 20 min, which is highly comparable to the marketed formulation (46%, 72%, 90%, and 98% at corresponding time points). This superior performance can be attributed to the optimal concentration and efficiency of the superdisintegrant, leading to rapid tablet breakup and enhanced dissolution.

For three months, stability tests of the optimised formulation (F2) were carried out in accelerated settings (40 ± 2°C/75 ± 5% RH). Good physical stability was shown by the formulation's lack of noticeable variations in appearance. The drug content decreased somewhat from 99.2% to 98.1%, but it was still well within permissible bounds. Drug release at 20 minutes dropped somewhat from 99% to 96%, whereas disintegration time increased slightly from 20 to 23 seconds, suggesting that the formulation's performance attributes were maintained throughout the research period.

In summary, “the study successfully showed that the direct compression approach may be used to produce Tramadol hydrochloride into oral dispersible tablets. All formulations showed acceptable pre- and post-compression characteristics, but formulation F2 was determined to be the optimised batch because of its superior drug release (~99% within 20 min), high drug content (~99.2%), quick disintegration (~20 sec), and short wetting time (25 sec). Additionally, it was discovered that the optimised formulation remained stable in accelerated settings. As a result, the created ODT formulation offers a quick start of action, better patient compliance, and performance that is on par with commercially available treatments, making it a viable substitute for traditional dose forms.

Conclusion:

Using the direct compression approach, the current study was able to formulate and evaluate Tramadol hydrochloride oral dispersible tablets (ODTs). With appropriate physicochemical characteristics and good compatibility with certain excipients, as demonstrated by FTIR analysis, preformulation tests validated the drug's eligibility for ODT development.

The pre-compression characteristics of all formed batches (F1–F10) were adequate, demonstrating the good flowability and compressibility needed for direct compression. Post-compression evaluation demonstrated that all tablets complied with pharmacopeial standards for weight variation, thickness, hardness, friability, disintegration time, and drug content uniformity, confirming consistent quality and mechanical integrity.

F2 was determined to be the best formulation out of all of them since it exhibited the best qualities, such as quick wetting, short disintegration time, and maximal drug release that was on par with the commercial formulation. The optimised formulation offered quick and effective drug release, guaranteeing a prompt initiation of therapeutic activity, according to the in-vitro dissolution trials.

The optimised formulation did not significantly alter its physicochemical characteristics or drug release profile over time, according to stability experiments carried out under accelerated settings.

The study concludes that direct compression may be used to successfully create oral dispersible tablets of Tramadol hydrochloride, providing better patient compliance, quick disintegration, and effective drug release. For the efficient management of pain, especially in patients who have trouble swallowing, the optimised formulation (F2) might be regarded as a promising substitute for traditional dose forms.

CHAPTER-7

REFERENCES

BIBLIOGRAPHY

- Adamkiewicz L, Szeleszczuk Ł. Review of Applications of Cyclodextrins as Taste-Masking Excipients for Pharmaceutical Purposes. Molecules. 2023 Oct 7;28(19):6964. doi: 10.3390/molecules28196964. PMID: 37836807; PMCID: PMC10574773.
- Adnan M, Raza S, Saad M, Khan AA, Noman M, Aziz Albalawi M, Alwabsi HA, Ali Al-Duais M, Sakran M, Alharbi RAK, Rizk NI, Jafri I, Zayed MM, Pandey S, El Sabagh A. Development and in vitro evaluation of mefenamic acid orodispersible tablets prepared by direct compression. Cell Mol Biol (Noisy-le-grand). 2025 May 26;71(5):49-60. doi: 10.14715/cmb/2025.71.5.8. PMID: 40418550.
- Allen, L. V., Popovich, N. G., & Ansel, H. C. (2014). *Ansel's pharmaceutical dosage forms and drug delivery systems* (10th ed.). Lippincott Williams & Wilkins.
- Alotaibi HF, Elsamaligy S, Mahrous GM, Bayomi MA, Mahmoud HA. Design of taste masked enteric orodispersible tablets of diclofenac sodium by applying fluid bed coating technology. Saudi Pharm J. 2019 Mar;27(3):354-362. doi: 10.1016/j.jsps.2018.12.003. Epub 2018 Dec 7. PMID: 30976178; PMCID: PMC6438907.
- Arav Y. Advances in Modeling Approaches for Oral Drug Delivery: Artificial Intelligence, Physiologically-Based Pharmacokinetics, and First-Principles Models. Pharmaceutics. 2024 Jul 24;16(8):978. doi: 10.3390/pharmaceutics16080978. PMID: 39204323; PMCID: PMC11359797.
- Armstrong, N. A. (2007). Selection of excipients for direct compression tablet formulation. *Pharmaceutical Technology Europe*, 19(9), 22–27.
- Arya, A., Chandra, A., Sharma, V., & Pathak, K. (2010). Fast dissolving oral films: An innovative drug delivery system and dosage form. International Journal of ChemTech Research, 2(1), 576–583.
- Aulton, M. E., & Taylor, K. (2018). *Aulton's pharmaceutics: The design and manufacture of medicines* (5th ed.). Elsevier.
- Ayenew, Z., Puri, V., Kumar, L., & Bansal, A. K. (2009). Trends in pharmaceutical taste masking technologies: A patent review. *Recent Patents on Drug Delivery & Formulation*, 3(1), 26–39.
- Bahraminejad S, Almoazen H. Sublingual and Buccal Delivery: A Historical and Scientific Prescriptive. Pharmaceutics. 2025 Aug 20;17(8):1073. doi: 10.3390/pharmaceutics17081073. PMID: 40871092; PMCID: PMC12389210.
- Bhaskaran, S., & Narmada, G. V. (2002). Rapid dissolving tablets: A novel dosage form. Indian Pharmacist, 1(2), 9–12.

- Bhowmik, D., Chiranjib, B., Krishnakanth, P., & Chandira, R. M. (2009). Fast dissolving tablet: An overview. Journal of Chemical and Pharmaceutical Research, 1(1), 163–177.
- Bhowmik, D., Chiranjib, B., Krishnakanth, Pankaj, & Chandira, R. M. (2009). Fast dissolving tablet: An overview. *Journal of Chemical and Pharmaceutical Research*, 1(1), 163–177.
- Bi, Y., Sunada, H., Yonezawa, Y., Danjo, K., Otsuka, A., & Iida, K. (1996). Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. *Chemical and Pharmaceutical Bulletin*, 44(11), 2121–2127. https://doi.org/10.1248/cpb.44.2121
- Boateng, J. S., & Auffret, A. D. (2015). Application of in situ gelling polymeric systems for drug delivery. Journal of Pharmaceutical Sciences, 104(11), 3617–3629. https://doi.org/10.1002/jps.24543
- Brniak W, Jachowicz R, Pelka P. The practical approach to the evaluation of methods used to determine the disintegration time of orally disintegrating tablets (ODTs). Saudi Pharm J. 2015 Sep;23(4):437-43. doi: 10.1016/j.jsps.2015.01.015. Epub 2015 Jan 16. PMID: 27134547; PMCID: PMC4834683.
- Brown, M. T., & Bussell, J. K. (2011). Medication adherence: WHO cares? *Mayo Clinic Proceedings*, 86(4), 304–314. https://doi.org/10.4065/mcp.2010.0575
- Carstensen, J. T., & Rhodes, C. T. (2000). *Drug stability: Principles and practices* (3rd ed.). Marcel Dekker.
- Chang, R. K., Guo, X., Burnside, B. A., & Couch, R. A. (2000). Fast-dissolving tablets. *Pharmaceutical Technology*, 24(6), 52–58.
- Chang, R. K., Guo, X., Burnside, B. A., & Couch, R. A. (2000). Fast-dissolving tablets. Pharmaceutical Technology, 24(6), 52–58.
- Chein, Y. W. (1992). *Novel drug delivery systems* (2nd ed.). Marcel Dekker.
- Cirri M, Mura PA, Maestrelli F, Benedetti S, Buratti S. Pediatric Orally Disintegrating Tablets (ODTs) with Enhanced Palatability Based on Propranolol HCl Coground with Hydroxypropyl-β-Cyclodextrin. Pharmaceutics. 2024 Oct 23;16(11):1351. doi: 10.3390/pharmaceutics16111351. PMID: 39598476; PMCID: PMC11597579.
- Claxton, A. J., Cramer, J., & Pierce, C. (2001). A systematic review of the associations between dose regimens and medication compliance. Clinical Therapeutics, 23(8), 1296–1310. https://doi.org/10.1016/S0149-2918(01)80109-
- Commey KL, Enaka A, Nakamura R, Yamamoto A, Tsukigawa K, Nishi K, Iohara D, Hirayama F, Otagiri M, Yamasaki K. Development of α-Cyclodextrin-Based Orally Disintegrating Tablets for 4-Phenylbutyrate. Pharmaceutics. 2024 Jan 7;16(1):82. doi: 10.3390/pharmaceutics16010082. PMID: 38258093; PMCID: PMC10818935.
- Deshmukh, V. N. (2012). Mouth dissolving drug delivery system: A review. *International Journal of PharmaTech Research*, 4(1), 412–421.

- Dey P, Maiti S. Orodispersible tablets: A new trend in drug delivery. J Nat Sci Biol Med. 2010 Jul;1(1):2-5. doi: 10.4103/0976-9668.71663. PMID: 22096326; PMCID: PMC3217286.
- Dhakal B, Thakur JK, Mahato RK, Rawat I, Rabin DC, Chhetri RR, Shah KP, Adhikari A, Pandey J. Formulation of Ebastine Fast-Disintegrating Tablet Using CoprocessedSuperdisintegrants and Evaluation of Quality Control Parameters. ScientificWorldJournal. 2022 May 19;2022:9618344. doi: 10.1155/2022/9618344. PMID: 35645632; PMCID: PMC9135552.
- Dixit, R. P., & Puthli, S. P. (2009). Oral strip technology: Overview and future potential. *Journal of Controlled Release*, 139(2), 94–107. https://doi.org/10.1016/j.jconrel.2009.06.014
- Dobetti, L. (2001). Fast-melting tablets: Developments and technologies. *Pharmaceutical Technology Europe*, 13(9), 44–50.
- Dressman, J. B., Amidon, G. L., Reppas, C., & Shah, V. P. (1998). Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms. Pharmaceutical Research, 15(1), 11–22. https://doi.org/10.1023/A:1011984216775
- European Pharmacopoeia. (2019). *European Pharmacopoeia* (10th ed.). Council of Europe.
- Faisal W, Farag F, Abdellatif AAH, Abbas A. Taste Masking Approaches for Medicines. Curr Drug Deliv. 2018 Feb 14;15(2):167-185. doi: 10.2174/1567201814666171013145958. PMID: 29034835.
- Fatima SS, Zafar F, Ali H, Raees F, Naqvi GR, Alam S, Yasmin R, Tariq A, Saeed R, Khan S. Development and characterisation of orally disintegrating flurbiprofen tablets using SeDeM-ODT tool. PLoS One. 2024 Oct 29;19(10):e0309894. doi: 10.1371/journal.pone.0309894. PMID: 39471194; PMCID: PMC11521243.
- Food and Drug Administration (FDA). (2008). *Guidance for industry: Orally disintegrating tablets*. U.S. Department of Health and Human Services.
- Fouad SA, Malaak FA, El-Nabarawi MA, Abu Zeid K. Development of orally disintegrating tablets containing solid dispersion of a poorly soluble drug for enhanced dissolution: In-vitro optimization/in-vivo evaluation. PLoS One. 2020 Dec 31;15(12):e0244646. doi: 10.1371/journal.pone.0244646. PMID: 33382789; PMCID: PMC7774920.
- Fu, Y., Yang, S., Jeong, S. H., Kimura, S., & Park, K. (2004). Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies. *Critical Reviews in Therapeutic Drug Carrier Systems*, 21(6), 433–475. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v21.i6.10

- Fu, Y., Yang, S., Jeong, S. H., Kimura, S., & Park, K. (2004). Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies. *Critical Reviews in Therapeutic Drug Carrier Systems*, 21(6), 433–475. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v21.i6.10

- Fu, Y., Yang, S., Jeong, S. H., Kimura, S., & Park, K. (2004). Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies. Critical Reviews in Therapeutic Drug Carrier Systems, 21(6), 433–475. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v21.i6.10
- Fu, Y., Yang, S., Jeong, S. H., Kimura, S., & Park, K. (2004). Orally fast disintegrating tablets: Developments and technologies. Critical Reviews in Therapeutic Drug Carrier Systems, 21(6), 433–475. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v21.i6.10
- Ghosh, T., & Ghosh, A. (2011). Orally disintegrating tablets: A new trend in drug delivery. *The Pharma Review*, 9(2), 180–187.
- Ghosh, T., & Pfister, W. R. (2005). Quick dissolving oral dosage forms: Scientific and regulatory considerations from a clinical pharmacology and biopharmaceutics perspective. *Drug Delivery Technologies*, 5(8), 50–58.
- Ghosh, T., & Pfister, W. R. (2005). Quick dissolving oral dosage forms: Scientific and regulatory considerations. Drug Delivery Technologies, 5(8), 50–58.
- 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.
- Goel H, Vora N, Tiwary AK, Rana V. Formulation of orodispersible tablets of ondansetron HCl: investigations using glycine-chitosan mixture as superdisintegrant. Yakugaku Zasshi. 2009 May;129(5):513-21. doi: 10.1248/yakushi.129.513. PMID: 19420882.
- Habib, W., Khankari, R., & Hontz, J. (2000). Fast-dissolve drug delivery systems. *Critical Reviews in Therapeutic Drug Carrier Systems*, 17(1), 61–72.
- Habib, W., Khankari, R., & Hontz, J. (2000). Fast-dissolve drug delivery systems. *Critical Reviews in Therapeutic Drug Carrier Systems*, 17(1), 61–72.
- Haddad R, Gardouh AR. Development and Evaluation of an Orodispersible Tablet Formation for the Delivery of a Hydrophobic Drug. Adv Pharmacol Pharm Sci. 2024 Oct 17;2024:7914860. doi: 10.1155/2024/7914860. PMID: 39450401; PMCID: PMC11502129.
- Han R, He H, Lu Y, Lu H, Shen S, Wu W. Oral targeted drug delivery to post-gastrointestinal sites. J Control Release. 2024 Jun;370:256-276. doi: 10.1016/j.jconrel.2024.04.047. Epub 2024 May 1. PMID: 38679163.
- Hannan PA, Khan JA, Khan A, Safiullah S. Oral Dispersible System: A New Approach in Drug Delivery System. Indian J Pharm Sci. 2016 Jan-Feb;78(1):2-7. doi: 10.4103/0250-474x.180244. PMID: 27168675; PMCID: PMC4852571.
- Herdman, M. (2007). Patient preferences and the importance of rapid symptom relief. International Journal of Clinical Practice, 61(9), 1457–1463.

- Hirani, J. J., Rathod, D. A., &Vadalia, K. R. (2009). Orally disintegrating tablets: A review. *Tropical Journal of Pharmaceutical Research*, 8(2), 161–172. https://doi.org/10.4314/tjpr.v8i2.44525
- Hirani, J. J., Rathod, D. A., &Vadalia, K. R. (2009). Orally disintegrating tablets: A review. Tropical Journal of Pharmaceutical Research, 8(2), 161–172. https://doi.org/10.4314/tjpr.v8i2.44525
- Ibrahim, H. K., & El-Setouhy, D. A. (2010). Valsartan orodispersible tablets: Formulation, in vitro/in vivo characterization. AAPS PharmSciTech, 11(1), 189–196. https://doi.org/10.1208/s12249-010-9376-1
- Jacob S, Boddu SHS, Bhandare R, Ahmad SS, Nair AB. Orodispersible Films: Current Innovations and Emerging Trends. Pharmaceutics. 2023 Dec 11;15(12):2753. doi: 10.3390/pharmaceutics15122753. PMID: 38140094; PMCID: PMC10747242.
- Jin, J., Sklar, G. E., Min Sen Oh, V., & Chuen Li, S. (2008). Factors affecting therapeutic compliance: A review from the patient's perspective. *Therapeutics and Clinical Risk Management*, 4(1), 269–286.
- Kaushik, D., Dureja, H., & Saini, T. R. (2004). Mouth dissolving tablets: A review. *Indian Drugs*, 41(4), 187–193.
- Kaushik, D., Dureja, H., & Saini, T. R. (2004). Mouth dissolving tablets: A review. Indian Drugs, 41(4), 187–193.
- Klancke, J. (2003). Dissolution testing of orally disintegrating tablets. Dissolution Technologies, 10(2), 6–8. https://doi.org/10.14227/DT100203P6
- Kottke, M. K., &Rudnic, E. M. (2009). Tablet dosage forms. In H. A. Lieberman, L. Lachman, & J. B. Schwartz (Eds.), *Pharmaceutical dosage forms: Tablets* (Vol. 1, pp. 1–44). Informa Healthcare.
- Kraemer J, Gajendran J, Guillot A, Schichtel J, Tuereli A. Dissolution testing of orally disintegrating tablets. J Pharm Pharmacol. 2012 Jul;64(7):911-8. doi: 10.1111/j.2042-7158.2012.01473.x. Epub 2012 Apr 8. PMID: 22686339.
- Kuccherkar, B. S., Badhan, A. C., & Mahajan, H. S. (2003). Mouth dissolving tablets: A novel drug delivery system. *Pharma Times*, 35(1), 7–9.
- Kuchekar, B. S., & Arumugam, V. (2001). Fast dissolving tablets. Indian Journal of Pharmaceutical Education, 35(4), 150–152
- Kumar, A., Sharma, R., & Gupta, G. D. (2012). Fast dissolving drug delivery system: A review. Advances in Biological Research, 6(1), 6–13.
- Kumar, S., Gupta, S. K., & Sharma, P. K. (2012). A review on recent trends in oral drug delivery—Fast dissolving formulation technology. *Advances in Biological Research*, 6(1), 6–13.
- Liao YJ, Liang YJ. Beyond Dysphagia in Parkinson's Disease: 3D Printing of Orally Disintegrating Tablets (ODTs) for Optimized Treatment. Pharmaceuticals (Basel).

2025 Dec 13;18(12):1886. doi: 10.3390/ph18121886. PMID: 41471375; PMCID: PMC12735962.

- Limpongsa E, Tabboon P, Pongjanyakul T, Jaipakdee N. Preparation and Evaluation of Directly Compressible Orally Disintegrating Tablets of Cannabidiol Formulated Using Liquisolid Technique. Pharmaceutics. 2022 Nov 8;14(11):2407. doi: 10.3390/pharmaceutics14112407. PMID: 36365225; PMCID: PMC9695279.
- Liu, F., Ranmal, S., Batchelor, H. K., Orlu-Gul, M., Ernest, T. B., Thomas, I. W., Flanagan, T., &Tuleu, C. (2014). Patient-centred pharmaceutical design to improve acceptability of medicines: Similarities and differences in paediatric and geriatric populations. *Drugs*, 74(16), 1871–1889. https://doi.org/10.1007/s40265-014-0297-2
- Liu, F., Ranmal, S., Batchelor, H. K., Orlu-Gul, M., Ernest, T. B., Thomas, I. W., Flanagan, T., &Tuleu, C. (2014). Patient-centred pharmaceutical design to improve acceptability of medicines. Drugs, 74(16), 1871–1889. https://doi.org/10.1007/s40265-014-0297-2
- Logemann, J. A. (1998). *Evaluation and treatment of swallowing disorders* (2nd ed.). Pro-Ed.
- Madny MA, Yadav KS. Biomimetic oral drug delivery: Translating nature's design into therapeutic innovation. Colloids Surf B Biointerfaces. 2026 Mar;259:115348. doi: 10.1016/j.colsurfb.2025.115348. Epub 2025 Dec 5. Erratum in: Colloids Surf B Biointerfaces. 2026 May;261:115502. doi: 10.1016/j.colsurfb.2026.115502. PMID: 41353974.
- Markl, D., & Zeitler, J. A. (2017). A review of disintegration mechanisms and measurement techniques. *Pharmaceutical Research*, 34(5), 890–917. https://doi.org/10.1007/s11095-017-2129-z
- Matsuo, K., & Palmer, J. B. (2008). Anatomy and physiology of feeding and swallowing: Normal and abnormal. *Physical Medicine and Rehabilitation Clinics of North America*, 19(4), 691–707. https://doi.org/10.1016/j.pmr.2008.06.001
- Mennella, J. A., & Beauchamp, G. K. (2008). Optimizing oral medications for children. *Clinical Therapeutics*, 30(11), 2120–2132. https://doi.org/10.1016/j.clinthera.2008.11.019
- Mittal, S., Sharma, P. K., & Garg, V. K. (2011). Fast dissolving tablets: A review. *International Journal of Pharmaceutical Sciences Review and Research*, 6(1), 76–84.
- Mohanachandran, P. S., Sindhumol, P. G., & Kiran, T. S. (2011). Superdisintegrants: An overview. *International Journal of Pharmaceutical Sciences Review and Research*, 6(1), 105–109.
- Ohrem, H. L., Schornick, E., Kalivoda, A., & Ognibene, R. (2014). Why is mannitol becoming more and more popular as a pharmaceutical excipient in solid dosage forms? *Pharmaceutical Development and Technology*, 19(3), 257–262. https://doi.org/10.3109/10837450.2012.754949

- Ohrem, H. L., Schornick, E., Kalivoda, A., & Ognibene, R. (2014). Why is mannitol becoming more and more popular as a pharmaceutical excipient in solid dosage forms? *Pharmaceutical Development and Technology*, 19(3), 257–262. https://doi.org/10.3109/10837450.2012.754949
- Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *New England Journal of Medicine*, 353(5), 487–497. https://doi.org/10.1056/NEJMra050100
- Patel, D. M., Patel, M. M., & Patel, C. N. (2011). Fast dissolving tablets: An overview. *Systematic Reviews in Pharmacy*, 2(1), 29–36. https://doi.org/10.4103/0975-8453.83436
- Patel, R. P., & Poddar, S. S. (2011). Development and characterization of mucoadhesive buccal patches of salbutamol sulphate. *Current Drug Delivery*, 8(1), 140–144.
- Perrault, M., Bertrand, F., & Chaouki, J. (2009). Characterization of magnesium stearate used as lubricant in pharmaceutical tablets. *Powder Technology*, 195(1), 60–65. https://doi.org/10.1016/j.powtec.2009.05.002
- Pimparade MB, Vo A, Maurya AS, Bae J, Morott JT, Feng X, Kim DW, Kulkarni VI, Tiwari R, Vanaja K, Murthy R, Shivakumar HN, Neupane D, Mishra SR, Murthy SN, Repka MA. Development and evaluation of an oral fast disintegrating anti-allergic film using hot-melt extrusion technology. Eur J Pharm Biopharm. 2017 Oct;119:81-90. doi: 10.1016/j.ejpb.2017.06.004. Epub 2017 Jun 6. PMID: 28596037; PMCID: PMC5581999.
- Preis, M., & Breitkreutz, J. (2017). Orally disintegrating films and tablets: Innovations and future perspectives. Expert Opinion on Drug Delivery, 14(7), 1–13. https://doi.org/10.1080/17425247.2017.1271942
- Preis, M., Knop, K., & Breitkreutz, J. (2014). Mechanical strength test for orodispersible and buccal films. International Journal of Pharmaceutics, 461(1–2), 22–29. https://doi.org/10.1016/j.ijpharm.2013.11.045
- Ratnaparkhi, M. P., Mohanta, G. P., Upadhyay, L., & Mutha, S. S. (2009). Review on: Fast dissolving tablet. *Journal of Pharmacy Research*, 2(1), 5–12.
- Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (2009). *Handbook of pharmaceutical excipients* (6th ed.). Pharmaceutical Press.
- Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (2009). *Handbook of pharmaceutical excipients* (6th ed.). Pharmaceutical Press.
- Sabaté, E. (2003). *Adherence to long-term therapies: Evidence for action*. World Health Organization.
- Sastry, S. V., Nyshadham, J. R., & Fix, J. A. (2000). Recent technological advances in oral drug delivery—A review. Pharmaceutical Science & Technology Today, 3(4), 138–145. https://doi.org/10.1016/S1461-5347(00)00247-

- Scoutaris, N., Ross, S., &Douroumis, D. (2018). 3D printing in pharmaceuticals: A new tool for designing customized drug delivery systems. Journal of Controlled Release, 282, 58–69. https://doi.org/10.1016/j.jconrel.2018.04.010
- Seager, H. (1998). Drug-delivery products and the Zydis fast-dissolving dosage form. *Journal of Pharmacy and Pharmacology*, 50(4), 375–382. https://doi.org/10.1111/j.2042-7158.1998.tb06870.x
- Seager, H. (1998). Drug-delivery products and the Zydis fast-dissolving dosage form. *Journal of Pharmacy and Pharmacology*, 50(4), 375–382. https://doi.org/10.1111/j.2042-7158.1998.tb06870.x
- Seager, H. (1998). Drug-delivery products and the Zydis fast-dissolving dosage form. Journal of Pharmacy and Pharmacology, 50(4), 375–382. https://doi.org/10.1111/j.2042-7158.1998.tb06870.x
- Senel, S., &Hıncal, A. A. (2001). Drug permeation enhancement via buccal route: Possibilities and limitations. Journal of Controlled Release, 72(1–3), 133–144. https://doi.org/10.1016/S0168-3659(01)00272-7
- Shah, U., Augsburger, L., & Wurster, D. (2010). Influence of magnesium stearate on drug dissolution from compressed tablets. *Pharmaceutical Development and Technology*, 15(2), 180–188. https://doi.org/10.3109/10837450903028475
- Shangraw, R. F. (1980). Compressed tablets by direct compression. *Pharmaceutical Technology*, 4(10), 49–57.
- Shargel, L., Yu, A. B. C., & Wu-Pong, S. (2015). *Applied biopharmaceutics & pharmacokinetics* (7th ed.). McGraw-Hill Education.
- Sharma, D., Saini, S., & Singh, M. (2015). Formulation and evaluation of fast dissolving tablets using solid dispersion technique. International Journal of Pharmaceutical Sciences Review and Research, 31(2), 123–130.
- Sharma, S., Gupta, G. D., & Kumar, S. (2010). Natural polymers as superdisintegrants in fast dissolving tablets. *International Journal of Pharmaceutical Sciences Review and Research*, 4(2), 44–52.
- Sheskey, P. J., Cook, W. G., & Cable, C. G. (2017). *Handbook of pharmaceutical excipients* (8th ed.). Pharmaceutical Press.
- Simšič T, Planinšek O, Baumgartner A. Taste-masking methods in multiparticulate dosage forms with a focus on poorly soluble drugs. Acta Pharm. 2024 May 30;74(2):177-199. doi: 10.2478/acph-2024-0015. PMID: 38815202.
- Sohi, H., Sultana, Y., & Khar, R. K. (2004). Taste masking technologies in oral pharmaceuticals: Recent developments and approaches. *Drug Development and Industrial Pharmacy*, 30(5), 429–448. https://doi.org/10.1081/DDC-120037477
- Suksawat T, Brniak W, Łyszczarz E, Wesoły M, Ciosek-Skibińska P, Mendyk A. Orodispersible Dosage Forms with Rhinacanthin-Rich Extract as a Convenient

Formulation Dedicated to Pediatric Patients. Pharmaceuticals (Basel). 2024 Jul 27;17(8):994. doi: 10.3390/ph17080994. PMID: 39204099; PMCID: PMC11356918.

- Sutthapitaksakul L, Thanawuth K, Dass CR, Sriamornsak P. Optimized Taste-Masked Microparticles for Orally Disintegrating Tablets as a Promising Dosage Form for Alzheimer's Disease Patients. Pharmaceutics. 2021 Jul 9;13(7):1046. doi: 10.3390/pharmaceutics13071046. PMID: 34371737; PMCID: PMC8309182.
- Sutthapitaksakul L, Thanawuth K, Huanbutta K, Sriamornsak P. Effect of a superdisintegrant on disintegration of orally disintegrating tablets determined by simulated wetting test and *in vitro*disintegration test. Pharmazie. 2022 Oct 1;77(10):287-290. doi: 10.1691/ph.2022.2015. PMID: 36273260.
- Takagi T, Masada T, Minami K, Kataoka M, Yamashita S. Development of an In Vitro Methodology to Assess the Bioequivalence of Orally Disintegrating Tablets Taken without Water. Pharmaceutics. 2023 Aug 24;15(9):2192. doi: 10.3390/pharmaceutics15092192. PMID: 37765162; PMCID: PMC10535823.
- Thoorens, G., Krier, F., Leclercq, B., Carlin, B., & Evrard, B. (2014). Microcrystalline cellulose, a direct compression binder in a quality by design environment—A review. *International Journal of Pharmaceutics*, 473(1–2), 64–72. https://doi.org/10.1016/j.ijpharm.2014.06.055
- Thoorens, G., Krier, F., Leclercq, B., Carlin, B., & Evrard, B. (2014). Microcrystalline cellulose in pharmaceutical applications: A review. International Journal of Pharmaceutics, 473(1–2), 64–72. https://doi.org/10.1016/j.ijpharm.2014.06.055
- Tran PHL, Tran TTD. Recent Strategic Developments in the Use of Superdisintegrants for Drug Delivery. Curr Pharm Des. 2020;26(6):701-709. doi: 10.2174/1381612826666200122124621. PMID: 31969094.
- Uchida T. Taste Sensor Assessment of Bitterness in Medicines: Overview and Recent Topics. Sensors (Basel). 2024 Jul 24;24(15):4799. doi: 10.3390/s24154799. PMID: 39123846; PMCID: PMC11314865.
- Valleri, M., Mura, P., Maestrelli, F., Cirri, M., & Ballerini, R. (2004). Development and evaluation of glyburide fast dissolving tablets using solid dispersion technique. *Drug Development and Industrial Pharmacy*, 30(5), 525–534. https://doi.org/10.1081/DDC-120037477
- Venugopal, V. (2011). Orodispersible tablets: An overview. International Journal of Pharmaceutical Sciences Review and Research, 11(1), 22–28.
- Vlad RA, Antonoaea P, Todoran N, Rédai EM, Bîrsan M, Muntean DL, Imre S, Hancu G, Farczádi L, Ciurba A. Development and Evaluation of Cannabidiol Orodispersible Tablets Using a 2^3-Factorial Design. Pharmaceutics. 2022 Jul 14;14(7):1467. doi: 10.3390/pharmaceutics14071467. PMID: 35890362; PMCID: PMC9324952.
- Wagner-Hattler L, Kiene K, Bielicki J, Pfister M, Puchkov M, Huwyler J. High Acceptability of an Orally Dispersible Tablet Formulation by Children. Children (Basel). 2021 Mar 5;8(3):194. doi: 10.3390/children8030194. PMID: 33807822; PMCID: PMC7999602.

- Walsh, J., Cram, A., Woertz, K., Breitkreutz, J., Winzenburg, G., Turner, R., Tuleu, C., & European Paediatric Formulation Initiative (EuPFI). (2013). Playing hide and seek with poorly tasting paediatric medicines: Do not forget the excipients. *Advanced Drug Delivery Reviews*, 73, 14–33. https://doi.org/10.1016/j.addr.2013.10.003
- Yamada M, Ishikawa A, Muramatsu S, Furuishi T, Onuki Y, Fukuzawa K, Yonemochi E. Study of Orally Disintegrating Tablets Using Erythritol as an Excipient Produced by Moisture-Activated Dry Granulation (MADG). Pharmaceuticals (Basel). 2022 Aug 15;15(8):1004. doi: 10.3390/ph15081004. PMID: 36015152; PMCID: PMC9415806.
- Yang Y, Zhou R, Wang Y, Zhang Y, Yu J, Gu Z. Recent Advances in Oral and Transdermal Protein Delivery Systems. Angew Chem Int Ed Engl. 2023 Mar 1;62(10):e202214795. doi: 10.1002/anie.202214795. Epub 2022 Dec 29. PMID: 36478123.
- Ye J, Wu X, Liu J, Guo Y, Ji C, Wang Z, Yang D, Zhou M. An Effective Oral Drug Delivery Route for Pharmacokinetic Complications: Spirulina Lipid Nanotechnology System. Adv Sci (Weinh). 2025 Nov;12(44):e09731. doi: 10.1002/advs.202509731. Epub 2025 Sep 12. PMID: 40940687; PMCID: PMC12667466.
- Yin Z, Lin X, Hong Y, Shen L, Zhao L. Pediatric orally disintegrating tablets: Overlook the future from multiple aspects. Eur J Pharm Biopharm. 2026 Feb;219:114960. doi: 10.1016/j.ejpb.2025.114960. Epub 2025 Dec 7. PMID: 41365425.
- Yoshida T, Kojima H. Oral Drug Delivery Systems Applied to Launched Products: Value for the Patients and Industrial Considerations. Mol Pharm. 2023 Nov 6;20(11):5312-5331. doi: 10.1021/acs.molpharmaceut.3c00482. Epub 2023 Oct 19. PMID: 37856863.
- Zhang Y, Jiang R, Lei L, Yang Y, Hu T. Drug delivery systems for oral disease applications. J Appl Oral Sci. 2022 Mar 9;30:e20210349. doi: 10.1590/1678-7757-2021-0349. PMID: 35262595; PMCID: PMC8908861.
- Zhao, N., & Augsburger, L. L. (2005). The influence of swelling capacity of superdisintegrants in different pH media on the dissolution of hydrochlorothiazide from directly compressed tablets. *AAPS PharmSciTech*, 6(1), E120–E126. https://doi.org/10.1208/pt060118