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Review Article

Role of Sublingual Drug Delivery in Parkinson's Disease Management

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ABSTRACT

The aim of this study is to formulate and evaluate Pramipexole Sublingual Tablets using disintegrants to enhance the drug's dissolution, bioavailability, and rapid onset of action for the effective management of Parkinson's diseasePramipexole Dihydrochloride along with all selected excipients, including Croscarmellose sodium, Mannitol, microcrystalline cellulose, sodium lauryl sulphate, saccharin sodium, peppermint flavour and magnesium stearate, were individually weighed and passed through a 40-mesh sieve to eliminate agglomerates and ensure uniform particle size distribution. The sieved materials, excluding lubricants, were initially blended to achieve a homogeneous mixture. Subsequently, magnesium stearate was incorporated into the pre- mixed powder and gently blended for 2–3 minutes to ensure proper lubrication while minimizing the risk of over-lubrication, which could adversely affect tablet hardness and disintegration characteristics. The resulting blend was then subjected to compression using a rotary tablet compression machine equipped with flat-faced punches to produce uniform sublingual tablets. Preformulation studies assessed the flow properties, compressibility, and density of different formulations (F1-F9). Among these, F6 exhibited the best flow and compressibility characteristics. Post-compression evaluations included weight variation, hardness, friability, disintegration time, wetting time, and water absorption ratio. F6 showed the most promising results with the fastest disintegration time (38 sec) and high drug content uniformity. The In- vitro dissolution studies confirmed F6's superior drug release profile, making it the optimal formulation for rapid therapeutic action. The formulation of Pramipexole sublingual tablets showed at the enhancing rapid onset of action by optimizing disintegration and dissolution properties

INTRODUCTION

Oral Drug Delivery

The oral route remains the most commonly used and preferred method for drug administration due to its ease of use, patient compliance, cost-effectiveness, and flexibility in formulation. Oral

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drug delivery systems are designed to ensure effective drug absorption and prolonged therapeutic action while minimizing side effects. The optimization of drug formulation is crucial to achieving controlled drug release and maintaining consistent drug concentrations within the desired therapeutic range.

Oral dosage forms have evolved significantly over the years, with various strategies being developed to enhance the bioavailability and therapeutic effectiveness of drugs. One of the primaries focuses of pharmaceutical research is the development of controlled and sustained- release systems, which allow for a more consistent release of active ingredients over time. A recent review discussed various formulation strategies that enable controlled drug release, highlighting the importance of the dissolution profile and the release mechanisms that control the therapeutic outcome of oral dosage forms [1].

Mucoadhesive oral tablets, which offer prolonged drug retention at the site of absorption, have also gained significant attention. An evaluation of the effectiveness of mucoadhesive tablets in improving drug absorption by increasing the residence time in the gastrointestinal tract, ensuring better bioavailability for drugs with poor solubility, was presented in another study.[2] This strategy has been particularly useful for drugs that require sustained therapeutic levels over an extended period.

Extended-release oral tablets, which enhance the bioavailability of drugs by releasing them gradually, were the focus of another study. This research highlighted the development of formulations that provide a more controlled release and better patient compliance compared to conventional dosage forms.[3] Such advancements are crucial for managing chronic conditions where constant drug levels are required.

In addition, gastroretentive drug delivery systems (GRDDS) have emerged as a promising approach to enhance the bioavailability of drugs, particularly those that are poorly soluble in the intestinal tract. A recent review discussed floating and expandable oral dosage forms that

can remain in the stomach for an extended period, thereby improving the absorption of drugs.[4] Lastly, the development of orally disintegrating tablets (ODTs) has addressed the issue of ease of administration, particularly in patients with swallowing difficulties. A study demonstrated the optimization of ODTs using super disintegrants, ensuring rapid disintegration and drug release for immediate therapeutic effects.[5]

Advantages of Oral Drug Delivery Systems [6,7]

Ease of Administration: Oral formulations are non-invasive and easy to self-administer, increasing patient compliance.

1. **Cost-Effectiveness**: Compared to injectable or transdermal drug delivery systems, oral drug formulations are generally more affordable to produce and distribute.
2. **Versatility**: A wide range of drugs, from solid tablets to liquid suspensions, can be formulated for oral administration.
3. **Reduced Risk of Infections**: Unlike injectable formulations, oral drug delivery does not require sterile conditions or professional administration.[8]
4. **Sustained Drug Release**: Modified-release formulations can provide extended drug action, reduce the frequency of dosing and improve therapeutic outcomes.[9]

Challenges in Oral Drug Delivery [10,11,12]

Despite its advantages, oral drug delivery faces several challenges, including:

1. **Variable Drug Absorption**: Factors such as gastrointestinal pH, enzyme activity, and food intake can influence drug absorption and bioavailability.

2. **First-Pass Metabolism**: Some drugs undergo extensive metabolism in the liver before reaching systemic circulation, reducing their effectiveness.

3. **Short Half-Life Drugs**: Certain drugs are rapidly absorbed and eliminated, necessitating frequent dosing to maintain therapeutic levels.

4. **Gastrointestinal Irritation**: Some drugs can cause irritation or damage to the gastric lining, limiting their oral use.

5. **Limited Solubility and Permeability**: Poorly soluble drugs may have low bioavailability, requiring advanced formulation techniques to enhance dissolution and absorption.[13,14,15]

Types of Oral Drug Delivery Systems[16,17,18]

To address these challenges, various drug delivery systems have been developed:

1. Immediate-Release Systems

These formulations dissolve quickly in the gastrointestinal tract, allowing rapid drug absorption. Examples include conventional tablets, capsules, and oral solutions. They are suitable for drugs that do not require controlled release and have a short onset time.

2. Sustained-Release Systems

Sustained-release formulations are designed to release the drug gradually over an extended period, maintaining steady drug levels in the bloodstream and reducing dosing frequency. These systems include:

- **Matrix Tablets**: Incorporate polymers that control drug release.
- **Reservoir Systems**: Use coatings or membranes to regulate drug diffusion.
- **Hydrophilic and Hydrophobic Systems**: Modify drug release based on the polymer properties used.

3. Controlled-Release Systems

Controlled-release systems ensure a precise and consistent drug release rate, providing predictable pharmacokinetics. Examples include:

- **Osmotic Drug Delivery Systems (OROS)**: Utilize osmotic pressure to control drug release.
- **Gastroretentive Systems**: Designed to remain in the stomach for extended periods to enhance drug absorption.
- **Multi particulate Systems**: Include microspheres, nano particles, and beads to allow gradual drug dispersion.

4. Targeted Drug Delivery Systems[19,20]

These systems enhance drug bioavailability and minimize side effects by directing the drug to specific sites within the gastrointestinal tract. Examples include:

- **Colon-Specific Drug Delivery**: Utilizes pH-sensitive coatings that release drugs in the colon for the treatment of local conditions such as ulcerative colitis.
- **Mucoadhesive Systems**: Enhance retention time by adhering to the mucosal lining of the gastrointestinal tract.

Formulation Strategies for Optimized Oral Drug Delivery[13,14,15]

Several formulation strategies are employed to improve drug solubility, stability, and bioavailability:

1. **Pro drugs**: Chemically modified drugs that enhance absorption and are converted into their active form after administration.

2. **Lipid-Based Systems**: Utilize emulsions, liposomes, and self-emulsifying drug delivery systems (SEDDS) to improve solubility.

3. **Nanotechnology Approaches**: Nanoparticles and nano emulsions enhance drug dissolution and targeted delivery.

4. **Complexation Techniques**: Cyclodextrin inclusion complexes improve drug solubility and stability.

5. **Coating Technologies**: Protect drugs from degradation and modify release profiles.

Challenges in Oral Drug Delivery[21,22,23,24]

One of the major limitations of conventional oral drug delivery systems is the unpredictable gastric emptying time (GET) and short gastric retention time (GRT). These factors can lead to incomplete drug release, resulting in reduced efficacy and inconsistent therapeutic outcomes. Since the stomach and upper small intestine are the primary absorption sites for many drugs, those that pass through these regions too quickly may not be fully absorbed. Therefore, prolonging gastric retention time can significantly improve drug bioavailability and therapeutic efficacy.

Factors Affecting Gastric Retention Time[25,26,27,28]

Several physiological and formulation-related factors influence GRT. These include:

- **Gastric Motility**: The contractions of the stomach control the movement of food and drugs. Fast gastric emptying can lead to premature drug elimination, while slower emptying enhances absorption.
- **Density of the Dosage Form**: High-density formulations tend to sink and remain in the stomach longer, whereas low-density formulations may float and prolong retention.
- **Size and Shape of the Dosage Form**: Larger and non-spherical dosage forms tend to have a prolonged gastric residence compared to smaller ones.
- **Fed vs. Fasted State**: The presence of food in the stomach delays gastric emptying and increases retention time.
- **pH and Gastric Fluid Composition**: The acidic environment of the stomach can influence drug solubility and absorption.

Approaches to Improve Gastric Retention

To overcome the challenges of short GRT, various formulation strategies have been developed. These include:

Floating Drug Delivery Systems[29-33]

These systems have a lower density than gastric fluids, allowing them to float on the stomach contents and extend retention time. Floating dosage forms can be:

- **Effervescent Systems**: Use gas-generating agents like sodium bicarbonate to create buoyancy.
- **Non-Effervescent Systems**: Use polymers that swell upon contact with gastric fluids, maintaining flotation.

Mucoadhesive Drug Delivery Systems[34-38]

Mucoadhesive systems utilize bioadhesive polymers that adhere to the gastric mucosa, extending retention time. Common bioadhesive polymers include:

- Chitosan
- Carbopol
- Polycarbophil
- Hydroxypropyl methylcellulose (HPMC)

High-Density Systems[39]

These systems have a density greater than 2.5 g/cm³, making them settle in the lower part of the stomach and resist gastric emptying. Common materials used to increase density include:

- Barium sulphate
- Zinc oxide
- Titanium dioxide
- Iron powder

Swelling and Expanding Systems [40]

These dosage forms expand upon contact with gastric fluids, preventing passage through the pylorus and prolonging gastric residence. They can be:

- **Hydrogel-based systems**: Absorb large amounts of water and expand.
- **Super porous hydrogels**: Swell rapidly and maintain their structure in gastric fluids.

Advantages of Gastric Retention Systems [41-48]

- **Enhanced Bioavailability**: Drugs with narrow absorption windows remain in the absorption site longer, improving bioavailability.
- **Reduced Dosing Frequency**: Prolonged drug release allows for less frequent administration.
- **Improved Patient Compliance**: Extended drug release minimizes the need for multiple daily doses.
- **Better Control of Drug Release**: Controlled and sustained drug release optimizes therapeutic effects.

Challenges and Considerations [49-53]

Despite their advantages, gastric retention systems face several challenges:

- **Variability in Gastric Physiology**: Gastric motility varies among individuals, affecting drug retention and absorption.
- **Potential for Gastric Irritation**: Prolonged contact with the stomach lining may cause irritation in some drugs.
- **Formulation Complexity**: Developing gastric retention systems requires specialized formulation techniques and excipients.

By designing site-specific, controlled-release dosage forms, gastric retention can be increased, leading to several benefits, including:

- **Enhanced drug absorption** due to prolonged exposure to the gastric mucosa.
- **Reduction in drug wastage**, particularly for drugs that are poorly soluble at higher pH levels.
- **Localized action in the stomach,** this localization helps reduce systemic side-effects and drug interactions compared to agents that distribute widely through the body.
- **Improved patient compliance** by reducing dosing frequency and dose size.
- **Greater control over drug release** for predictable and sustained therapeutic effects.

Future Perspectives in Oral Drug Delivery [54-58]

The field of oral drug delivery continues to evolve, with ongoing research focused on developing innovative technologies to improve drug efficacy, safety, and patient adherence. Some emerging trends include:

1. **3D Printing of Oral Dosage Forms**: Personalized drug formulations can be created using 3D printing technology, allowing for tailored drug release profiles.
2. **Smart Drug Delivery Systems**: Integration of sensors and electronic components can enable real-time monitoring of drug levels and automated dose adjustments.
3. **Biodegradable and Natural Polymers**: The use of biodegradable materials in drug formulations enhances safety and reduces environmental impact.
4. **Artificial Intelligence in Drug Design**: AI-driven models are being used to optimize drug formulations and predict their behaviour in the human body.

Sublingual route [59-65]

The inclusion complex approach has proven beneficial in enhancing the solubility of tacrolimus, a drug known for its poor water solubility. However, this strategy alone does not overcome another significant barrier to its effective delivery the extensive first-pass metabolism that occurs when the drug is administered orally. Tacrolimus is characterized by complex and variable pharmacokinetics, which presents considerable challenges in achieving consistent and adequate systemic drug levels through conventional oral routes.

Given these limitations, there is a growing interest in exploring alternative routes of administration that can bypass hepatic first-pass metabolism and improve bioavailability. One such promising route is sublingual administration. The sublingual area is richly supplied with blood vessels, allowing the drug to be directly absorbed into the systemic circulation, thus avoiding hepatic degradation.

Combining the inclusion complexation technique with sublingual delivery offers a dual advantage: enhanced solubility and improved systemic absorption. This integrated approach can potentially lead to more predictable pharmacokinetics and better therapeutic outcomes, especially in clinical scenarios requiring precise immunosuppressant, such as in solid organ transplant recipients. Clinical studies have supported this concept, showing that sublingual administration of tacrolimus can achieve comparable or even superior bioavailability

compared to traditional oral dosing, making it a viable and effective alternative in transplant pharmacotherapy.

The sublingual mucosa consists of the following parts: [66,67,68]

1. The epithelium [66]

The sublingual region is lined by stratified, squamous, non-keratinized epithelium that is 100–200μm and 8–12 cells in thickness. The cells that make up the sublingual epithelium are essentially embedded in an intercellular material that is primarily made up of protein– carbohydrate complexes. The mucous layer that covers the surface is about 70 and 100μm thick on average. Epithelia contain a variety of intercellular junctions, primarily desmosomes, hemi-desmosomes, and gap junctions. The mechanical linkages between neighboring cells of epithelia and between basement membrane and epithelial layer are called desmosomes and hemi-desmosomes, respectively. The gap between neighboring epithelial cell membranes is between 2 and 5 nm; a gap this size would likely allow

molecules up to several thousand Daltons to get through. The sublingual region's average surface area measures about 25-30 cm^2. The sublingual artery provides the body's main blood supply to base of tongue and mouth.

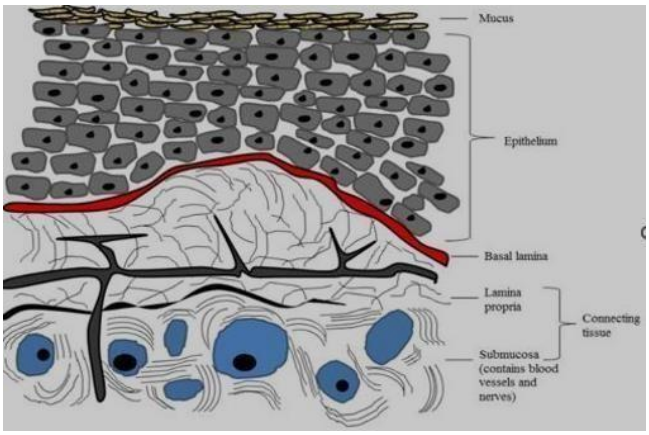

Figure 1: Anatomy of Sublingual Route

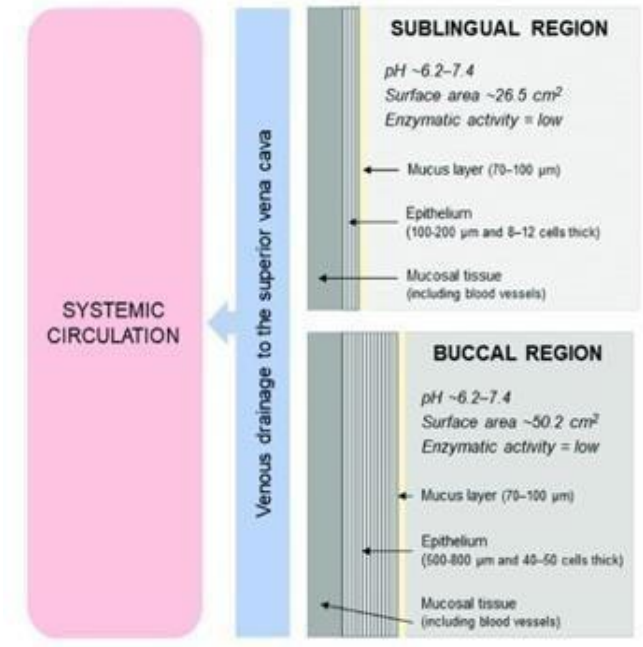

Figure 2: Comparison of Sublingual and buccal routes

2. The basement membrane [67]

It is a thin, sheet-like structure primarily composed of specialized proteins such as collagen, laminin, nidogen, and proteoglycans. It is a tri-laminar structure, consisting of an upper lamina lucida (40-80 nm in thickness), a central dense layer (lamina densa), and a wider fibrous material region beneath. Lamina densa and lamina lucida are connected across by hemi- desmosomes in the membranes of the basal cells.

The basement membrane facilitates cell adhesion and migration during tissue repair and regeneration processes, acts as a barrier separating the epithelium from the underlying connective

tissue, regulates the passage of molecules and cells between these two compartments, and contains signaling molecules and receptors that control cell behavior, including proliferation, differentiation, and survival.

3. The lamina propria and the sub mucosa [68]

These connective tissue layers contain blood and lymphatic arteries, nerve endings, and scattered inflammatory cells. Through venous drainage to the superior vena cava, drugs can quickly and immediately be absorbed into the blood circu

Mechanism of sublingual drug absorption

There are two suggested drug transport pathways: transcellular and paracellular. While lipophilic molecules will ideally be absorbed by passive diffusion, hydrophilic molecules are penetrated by the paracellular route.[35] The oral mucosa's ability to absorb a medicine is influenced by its permeability, which is based on its molecular weight, lipid solubility, and ionization p^H. Osmosis, a diffusion process, is also thought to allow for drug absorption into the circulatory system.

Polar medications are generally ineffectively absorbed. Medicaments having high partition coefficient becomes too insoluble in water to reach a high enough concentration in saliva fluids, however medication with an average lipophilicity is efficiently absorbed. In addition, drug absorption may be impeded by their binding to oral macromolecules.

Drugs are absorbed into capillaries, but they are also thought to be significantly absorbed into the lymph.

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Ideal properties of drugs for sublingual administration [69]

- Drugs which undergo first-pass metabolism resulting in the deprived bioavailability of their oral formulations are suitable candidates for sublingual administration.
- Ideally, the drugs having an unpleasant or bitter taste are unsuitable for this route, but taste masked formulations can be given.
- Low dose drugs are preferred because the area available for absorption is less and maintaining the entire dose within the sublingual area is difficult as there are chances for swallowing the doses.
- The likelihood of absorption is higher for drugs with small to moderate molecular weight and moderate lipophilicity.
- The drugs must have stability in water and saliva and they should be partly non- ionized in p^H of mouth.

Advantages of sublingual drug delivery[70,71]

- Due to the thin epithelium and rich supply of vascular and lymphatic drainage the sublingual route, which facilitates rapid drug absorption, the route is thought to have a quicker onset of action

- The medicament has the direct entry into the systemic circulation, circumventing first pass metabolism and thereby increasing the bioavailability of drugs which undergo higher hepatic clearance or decompose in the digestive tract.
- The saliva in sublingual regions has less mucin and limited number of enzymes.
- If a drug is administered sublingually instead of orally, the required dosage reduction to reach comparable target levels could lead to decreased medical expenses.
- There will be greater patient compliance, particularly in individuals who have trouble chewing and swallowing. Drug absorption can be easily terminated.
- The comparatively neutral ^{pH} in the mouth may make medications more stable.

Disadvantages of sublingual drug delivery [72]

- Maintenance of the formulation in the sublingual part is very crucial for the drug absorption. This differs between individuals and depends on the flow of saliva, formulation composition, dosage form disintegration, and rate of drug absorption.
- Not all drugs may be administered through this route and often only small doses are administered. Drugs may be bitter, unpleasant, or irritate the oral mucosa.
- For prolonged or sustained drug delivery, the route is normally less suitable.

Physiologic factors influencing sublingual drug delivery [73-77]

❖ **Blood Supply and Vascularity** [74]

The sublingual mucosa has a vast capillary network at the surface and is highly vascularized. Its abundant blood supply makes it easier for drugs to be absorbed quickly and enter the bloodstream.

❖ **pH and Ionic Composition of Saliva**[75,76,77]

Due to its ability to facilitate medication disintegration and transport via the mucosal epithelium, saliva is essential for sublingual drug absorption. Saliva's p^H and ionic makeup can affect a drug's permeability and solubility, which can impact absorption rates.

❖ **Drug absorption**

The drug's physicochemical characteristics, including its ionization state, lipophilicity, and molecular weight, affect its capacity to pass through the sublingual mucosa and into the bloodstream. Sublingual absorption of lipophilic drugs with low molecular weights and non- ionized forms is generally more successful.

❖ **Salivary Flow Rate and Composition**

Individual differences in these parameters can have an impact on medication absorption kinetics, drug solubility, and retention time in the sublingual cavity. Sublingual drug delivery maybe impacted by variables such oral health, drugs that change salivary flow, and degree of hydration.

❖ **Residence time of dosage form**

The drug's residence time in sublingual region can vary significantly depending on the formulations and patient. The many sublingual formulations available are pills, sprays, wafers, and films. Until the drug has been absorbed, patients should also refrain from eating, drinking, chewing, or swallowing. The effectiveness of the medication will be reduced if it is swallowed.

Strategies for Optimizing Oral and Sublingual Drug Formulations [78-80]

The development of effective oral and sublingual drug delivery systems requires careful

optimization of drug formulations. Some key strategies include:

1. **Enhancing Solubility and Permeability**: Techniques such as solid dispersion, lipid-based formulations, and cyclodextrin inclusion complexes can improve drug solubility and absorption.
2. **Use of Bioadhesive Polymers**: These polymers enhance drug retention in the GI tract or mucosal surfaces, increasing contact time and absorption.
3. **Targeted Drug Delivery**: Formulations designed to release the drug at specific sites in the GI tract or sublingual mucosa improve therapeutic efficacy and minimize side effects.
4. **Microencapsulation and Nanotechnology**: These approaches help protect drugs from degradation and enable controlled release mechanisms.

Formulation challenges & key design criteria for sublingual tablets [81-83]

1. Taste masking

 Importance: When placed under the tongue, APIs (active pharmaceutical ingredients) are in direct contact with taste buds. Bitter or unpleasant taste severely affect patient acceptance. Rapid disintegration/dissolution means drug will dissolve in saliva, exposing its taste unless masked.

2. Tablet Size

- **Why Size Matters**: The larger the tablet, the more difficult it may be to place under the tongue comfortably.
- Large tablets can increase discomfort, reduce patient compliance, and also make rapid disintegration harder (longer diffusion path, more mass to disintegrate).

3. Hardness & Friability (Mechanical Strength)

- **Hardness**: The tablet must be strong enough to survive handling, packaging, transport without breaking or crumbling. If too soft, tablets may damage during shipping or handling.
- **Friability**: This is a measure of how much weight loss the tablets suffer under mechanical agitation. High friability means too much material crumbles off, leading to dose variability, messy handling, and possible loss of integrity. Acceptable limits typically <1% friability.

4. Ensuring Adequate Contact Time Under the Tongue

Short Residence Time: In the sublingual region, the available time for the drug to dissolve, permeate, and be absorbed is limited. Patients may swallow saliva, drink, or move the tablet; this reduces the time the tablet or drug particles remain under the tongue.

If disintegration/dissolution is slow, much of the drug can be lost or swallowed, reducing bioavailability. The tablet should break apart fast in saliva to free the drug.

Use of superdisintegrants, optimized wettability and high porosity help. Materials which allow some binding to the mucosal surface under tongue can help retain drug at the absorption site. Some formulations use fine drug particles in bioadhesive matrix. units which adhere to sublingual mucosa after disintegration.

Formulations for sublingual drug delivery

- Tablets
- Films
- Sublingual vaccines (Immunotherapy)

- Sprays

Sublingual tablets (SLTs)[84-86]

The sublingual tablets are usually formulated as small, flat tablets which are lightly compressed. When positioned beneath the tongue, active ingredient is dissolved very quickly in the small volume of saliva and is absorbed directly through the sublingual mucosa.

The Sublingual tablets are usually formulated as fast disintegrating/dissolving dosage forms to aid rapid and complete drug solubility and hence absorption. The tablets essentially should dissolve rapidly permitting the quick absorption of API. Besides, bio adhesive and lipid matrix tablets have also been formulated for sublingual drug delivery.

It is feasible to achieve both a quick dissolving and bio adhesive drug retention in the oral cavity with the bio adhesive tablet method.

Sublingual and liposomal technology advancements are used in formulating lipid matrix tablets for the development of a dosage form which provides a quicker and more extensive absorption.

Ideal requirements of sublingual tablets

- Preferably, they should disintegrate or dissolve in the sublingual fluids with no need of water.
- Sublingual tablets should be palatable.
- Provide ease of administration to children, psychiatric and elderly patients.
- They should leave agreeable feeling in the oral cavity.
- Should leave no or minimal tablet residue in the mouth.

- When taken orally, there should be little to no tablet residue in the mouth.

Challenges in developing sublingual tablets

- Rapid/delayed disintegration of the tablet
- Formulating tablet of suitable size
- Desirable mechanical strength
- Leaves little to no traces in the mouth
- Compatible with various technologies for taste masking .

Common excipients in Sublingual tablets

The commonly used additives for the development of sublingual tablets [44,45] are presented in Table 1.

Table 1: Excipients for sublingual tablets manufacturing

SI No.	Excipient	Examples
1	Tablet diluent/ Binder	Microcrystalline cellulose Lactose monohydrate Hydroxy Propyl Methyl Cellulose (HPMC) Hydroxy Propyl Cellulose Poly Vinyl Pyrrolidone (PVP) Mannitol
2.	Lubricants	Aerosil Talc Magnesium stearate
3.	Sweeteners	Aspartame Sodium saccharin Sugar alcohols Sucralose
4.	Superdisintegrants	Sodium starch glycolate (SSG) Croscarmellose sodium (CCS) Crospovidone PVP Low substituted hydroxyl propyl cellulose

Manufacturing technologies of sublingual tablets [86]

Direct Compression

The direct compression technique of preparing tablets is very suitable to manufacture sublingual tablets of required hardness. The method usually incorporates super disintegrants and direct compressible and soluble ingredients to attain quick tablet disintegration. It is also the best technique for heat-labile compounds.

Although the approach is straightforward, affordable, and effective, it is very susceptible to variations in the form and number of excipients as well as in the compression forces. The high friability of quickly disintegrating pills may be compensated for by using novel packaging techniques like strip packing. The sublingual tablet method has now become more popular with the availability of improved tablet excipients.

Compression molding87

The formulations for the compression molding typically incorporate more quantity of water-soluble excipients to get rapid disintegration. In this process, using a compression molding machine or a die and punch set, the medicine mixture is molded into tablet shapes. Poor mechanical strength is the disadvantage of this technique. To improve the mechanical strength, binders such as acacia or PVP are usually added.

Spray drying88

In spray drying, the processing solvent quickly evaporates in the drying operation, thereby resulting in highly porous fine powders. The tablet blend usually consisting of diluents, super disintegrants, acidic and/or alkaline components, flavoring agents. The SLTs exhibits fast disintegration and improved dissolution.

Freeze drying89

Compared to other methods, this method is costly, and tedious but it produces tablets having high porosity and instant dissolution. It is appropriate for heat- sensitive medications. Sometimes the product produced by the freeze-drying process has an amorphous structure, which promotes a faster rate of dissolution.

The sublingual tablets prepared are brittle, possess low mechanical strength, exhibit poor stability on storage and hence difficult to handle. Therefore, proper packaging is very important. Strip packaging and blister packaging can ensure protection of the tablets.

Mass extrusion

To produce a continuous extrudate, a mixture of drug(s) and excipients is heated, pressed through a die, cooled, and cut into individual dosage units.

Technologies for oral fast dissolving sublingual tablets (patented)90

Several patented methods have been established by pharmaceutical companies to manufacture sublingual tablet.

Characterization of sublingual tablets

Characterization of sublingual tablets involves evaluating various physical, chemical, pharmaceutical and therapeutic properties to ensure that the tablets are of good quality, safe, and effective for sublingual administration. Some of the characterizations for sublingual tablets are as follows:

Table2: Patented sublingual tablets technologies

SI No.	Technology	Characteristic features	Limitations
1	Zydis (R.P. Scherer, Inc.)	First to market, lyophilized, self-preserved, increased bioavailability	Expensive, poor stability at higher Temperature & humidity, sensitive to degradation at humidity greater than 65%
2	Orasolv (Cima Labs, Inc.)	Incorporates taste-masking technology, used to develop over-the-counter formulations, contains an effervescent disintegrating agent, can accommodate high doses	Low mechanical strength, sensitive to moisture
3	Durasolv (Cima Labs, Inc.)	Improved mechanical strength	Not suitable for high amounts of active ingredients because
4	Wowtab (Yamanouchi Pharma, Inc.)	Superior mouthfeel due to the smooth melt action, adequate hardness and fast dissolution rate, more stable to the environment than the zydis and orasolv	Less stability to moisture and humidity
5	Flash Tab (Fuisz Technologies, Ltd.)	It utilizes a unique spinning mechanism to produce a floss-like crystalline structure, high surface area for dissolution	Not suitable for heat-sensitive drugs, sensitive to moisture and humidity, the tablets are friable, soft and moisture sensitive
6	Lyoc Technology (Aenova Group)	It uses a freeze-drying process to create porous tablets that disintegrate rapidly when exposed to saliva. It is versatile and can handle a wide range of APIs.	Since porous, susceptible to moisture which can lead to stability issues. Production process is expensive.
7	FDT Prozolv Technology (JRS Pharma)	It utilizes a combination of superdisintegrants and excipients providing rapid drug release.	Moisture-sensitive

Pre-compression studies:[91]

- **Solubility and permeability:** The information on the solubility of the API in sublingual conditions (saliva) and its permeability through the sublingual mucosa helps to determine the appropriate dosage strength and formulation.
- **Flow properties:** These properties of the blend are evaluated for ensuring the uniform flow and to confirm that it can be accurately dosed during tablet compression.
- **Bulk and tapped density:** These densities of powder mixture are measured to decide the suitable tablet compression force and die fill volume.
- **Angle of repose:** It provides an indication that how freely the tablet powder flows. A lesser angle of repose value suggests better flowability, while a higher value indicates poor flow properties. This information can be used

to make adjustments in the tablet formulation or processing steps for improving the powder blend flow properties.

Post-compression studies [92,93,94,95]

Physical appearance:

- **Visual inspection:** The tablets are examined for any defects, such as cracks, chips, or discoloration.
- **Surface texture:** The surface smoothness or roughness of the tablets is assessed.
- **Weight variation:** The weight of a specified number of tablets are recorded to check for uniformity. Weight uniformity is essential to ensure accurate dosing.
- **Thickness:** It is measured to confirm uniformity in tablet dimensions.
- **Hardness:** It is assessed by a hardness tester. The prepared tablets should be hard to survive handling and at the same time soft, enough to disintegrate rapidly under tongue.
- **Friability:** The friability is determined by subjecting the tablets to mechanical stress in a friability tester. Minimal friability is desirable to prevent tablet breakage during handling and storage.
- **Disintegration time:** It involves the determination of the time taken by SLT to completely disintegrate when positioned under tongue. Rapid disintegration is essential for SLT to facilitate drug absorption.
- **Surface p^H:** Surface p^H refers to the p^H of the surface of tablet when it comes into contact with saliva or suitable aqueous medium. It is essential to ensure that the p^H of the sublingual tablet is close to sublingual p^H that is comfortable and non-irritating to the sublingual region. Typically, neutral to slightly acidic p^H (around 5 to 7.5) is preferred to minimize irritation and provide patient comfort.
- **Wetting time:** Wetting time measures the rapidity with which a sublingual tablet absorbs moisture and becomes wet upon contact with saliva. Short wetting times are desirable because they indicate rapid disintegration and drug release, ensuring efficient absorption through the sublingual mucosa. The wetting time can be determined by placing a tablet on a moistened surface and measuring the time it takes to fully wet and disintegrate.
- **Water absorption ratio (WAR):** The WAR quantifies the extent to which the tablet absorbs water when placed in contact with saliva or an aqueous medium. It is established from the differences in weight of tablets before and after a specified period of contact with the medium. A higher water absorption ratio suggests that the tablet can rapidly absorb saliva and disintegrate for effective drug release.
- **Swelling index:** The swelling index is defined as the degree to which a SLT expands or swells when exposed to saliva or water. It is calculated by measuring the change in tablet dimensions (e.g., thickness or diameter) before and after exposure to the medium. A higher swelling index indicates that the tablet can rapidly increase in size, has good disintegration properties and can facilitate drug release and absorption.
- **Drug content uniformity:** Representative samples of tablets from different batches are analyzed to ensure that the drug content is consistent. Variability in drug content can lead to inconsistent dosing.
- **Dissolution rate:** Dissolution tests are performed to evaluate the rate at which the API dissolves from the tablet. This aids to decide the tablet's performance in releasing the drug for sublingual absorption. A complete or acceptable drug dissolution within a very short

time period is desirable because the residence time of fast dissolving SLT can be only short

- **Palatability and taste masking:** The taste and palatability of the SLTs are to be assessed in the case of bitter or unpleasant tasting drugs. Taste masking techniques may be employed to improve patient acceptability. Common methods used to evaluate taste masking are sensory analysis by human panels (*in vivo*), determination of the taste threshold for the active ingredient, electronic tongue, use of taste masking excipients etc.

Sublingual fast-dissolving tablets[96]

Fast disintegrating/dissolving films (FDFs) or strips are usually formulated for sublingual use. They are formulations that utilize a hydrophilic polymer which disintegrate quickly in saliva. The drug is then released for absorption when the strip is put under the sublingual area.

Advantages of FDFs over the fast-dissolving tablets[97]

- Useless excipients.
- Useless expensive materials for packaging and processing.
- Less laborious procedure.
- Offer a more substantial, efficient surface for disintegration.
- No loss of friability.
- More economical.

Disadvantages of FDFs

- It is not possible to include high dosages of drugs in the films.
- Technical limitations such as attaining dose uniformity, the correct thickness while casting the film, etc.
- Film packaging necessitates special considerations [55].

Composition of FDFs[98]

The composition of a typical FDF is given below:

API	25%
Film forming polymers	40 – 50%
Plasticizers	0 – 20%
Saliva stimulating agent	2 – 6%
Organoleptic additives	0 – 40%

- **API**

Drugs having low dose are the most suitable candidates to be loaded into the films. The bitter or unpleasant taste of the drugs, if any, needs to be masked before incorporating into the film formulation.

- **Film former polymers**

To develop these types of dosage forms, the selection of appropriate polymer is very important. An optimal functioning film may not be obtained with the use of single polymer but with the use of combination of different polymers. The general concentration employed is approximately 40-50% but, can be further increased to get the desired film strength.

Ideal properties of polymers

- Excellent film forming capability
- Do not obstruct the disintegration time of the films
- Non-irritant, Tasteless, Good wettability
- Must demonstrate sufficient tensile strength
- Must not result in infections in oral mucosa
- It should possess good mechanical properties. In most cases hydrophilic polymers are preferred but hydrophobic polymers are also employed. Both natural and synthetic polymers are employed for formulating films.
- Natural polymers: Starch, pullulan, sodium alginate, gelatin, pectin, and mal to dextrins.
- Synthetic: HPMC, polyvinyl pyrrolidone, Hydroxypropyl cellulose, and sodium CMC.

Table 4 gives the basic properties of the commonly used polymers.

Table 4: Film forming polymers: properties

SI. No.	Polymer	Characteristics
1	Hydroxy propyl methyl cellulose	Most commonly used film forming polymer-available in different grades, E3, E5 and E15 etc., lipophilic drugs can be incorporated in films formulated by HPMC
2	Hydroxy propyl cellulose	Water soluble, non-ionic, thermoplastic polymer, form flexible films
3	Polyvinyl pyrrolidone	Water soluble, non-ionic, good wetting characteristics, pH-stability, temperature-stability, and is colorless. Forms films with rapid and easy disintegration
4	Kollicoat	Hydrophilic having high aqueous solubility, a good film former, internal plasticizer provides good flexibility
5	Pullulan	Water soluble, neutral, non-immunogenic, non-carcinogenic, non-toxic, biodegradable, high adhesion and film forming abilities, non-ionic polysaccharide

➢ **Plasticizers**

They are used in films to improve its mechanical properties like percent elongation and tensile strength, and thus, also affects the flexibility and brittleness The plasticizers are usually employed in 0-20% of dry polymer weight and the commonly employed examples are propylene glycol, glycerol, PEGs etc.

➢ **Saliva stimulating agent**

These compounds usually possess acid nature which stimulates saliva formation and help in rapid film disintegration as well as the film dissolution. Citric, tartaric ascorbic, and malic acids are examples of common agents used for this purpose.

➢ **Organoleptic additives**
Sweetening agents

Both natural and synthetic agents are used including glucose, fructose, dextrose, saccharin, cyclamate, aspartame, sucrose, isomaltose, neotame etc.

Flavoring Agents The kind of drug to be used in the formulation will determine which flavoring agent is used, and the type and strength of flavoring will determine how much flavor is required to mask taste. Cooling agents can also be used to enhance the mouth feel and strength of the flavor.

Super disintegrants

Super disintegrants facilitate the disintegration and hence, dissolution of the films. These super disintegrants work by various mechanisms, including wicking action, swelling, and creating a porous structure that allows for rapid entry of saliva and subsequent disintegration of the film. The selection of super disintegrant depends on factors such as specific formulation, the drug being loaded, etc. Proper selection and optimization of super disintegrants are important to ensure the films disintegrate quickly, providing efficient drug delivery to the patient.

Types of Super disintegrants

Both natural super disintegrants like gums, mucilage etc., and synthetic super disintegrants are available.

Table 5: Synthetic super disintegrants and their properties

SI No.	Superdisintegrant	Commercial name	Properties
1	Crospovidone	Polyplasdone XL10	Cross-linked polyvinyl pyrrolidone, disintegration mechanism is simultaneous water absorption and swelling (wicking).
2	Sodium starch glycolate	Explotab Primogel	Sodium salt of cross-linked carboxy methyl starch, mechanism is fast water absorption and subsequent swelling
3	Croscarmellose Sodium	Primellose	Cross-linked carboxy methyl starch, mechanism is fast absorption of water followed by rapid swelling.
4	Polacrilin potassium	Amberlite IRP 88	An ion exchange resin, mechanism involves quick water uptake followed by rapid swelling

Methods for the preparation of film formulation[99]

There are diverse types of methods used for the manufacturing of oral film formulations. The methods mainly employed are:

1. **The Solvent casting method**

It is the mostly exploited method to prepare film-dosage forms. The method consists of dissolving water-soluble components including the polymers in an aqueous vehicle, making solution of drug and other excipients in appropriate solvents and then combining both the solutions and casting onto any smooth surface like petri plate, glass plate etc. and is dried (Figure 3).

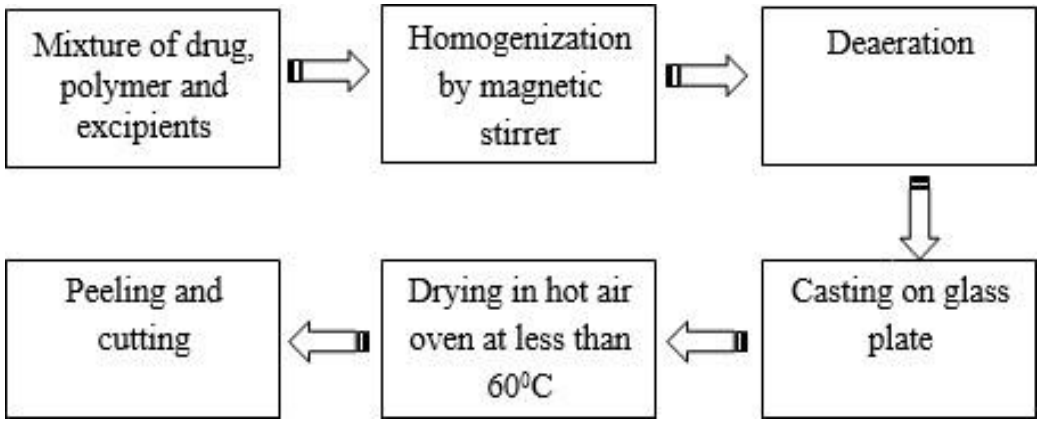

Figure 3: The solvent casting method

The solubility medications and excipients to be loaded determines the choice of solvent to be used. The properties of the drugs including its heat sensitivity, existence of various polymorphic forms, etc., should be taken into consideration. Moisture levels in the solution, another critical factor, can alter the mechanical characteristics of fast dissolving films.

Advantages

- Greater clarity, thickness uniformity and homogeneity of the prepared films when compared to other methods
- The physical properties and flexibility of film are better Limitations
- Stable solutions having low viscosity need to be produced
- The polymer needs to dissolve in the used solvent.

2. Semi solid casting

This technique is used with polymers insoluble in acids such as cellulose acetate phthalate. Here watersoluble film former polymeric solutions and ammonium or sodium hydroxide solutions of acid insoluble polymeric are combined and a gel mass are prepared by incorporating suitable plasticizers.

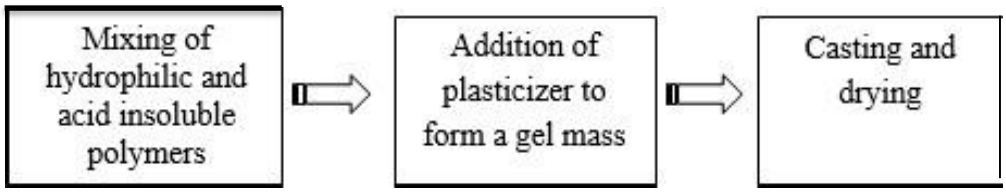

Figure 4: The semi solid casting method

3. Hot melt extrusion

It is a continuous manufacturing process, where the drug along with excipients are mixed, melted, and then extruded through a die to produce a continuous film, which is cooled, solidified, and then cut into individual dosage units.

4. Rolling method

The drug and the polymer solutions are thoroughly mixed and resulting mixture, is sent through the roller.

The formed film dried on rollers and then cut into the appropriate sizes and shapes.

5. Spray technique

To obtain a transparent solution, drugs, polymers, along with the added excipients are dissolved in an appropriate solvent. The appropriate surfaces, such as glass, polyethylene film, or teflon sheet, are then sprayed with this solution.

Characterization of sublingual Tablets[100, 101,102]

The important characterizations of sublingual films are as follows:

- **Organoleptic evaluation**: Visual inspection for color, homogeneity, suspended particles and clarity are done.
- **Mechanical properties:** They are used to measure the film's durability and integrity. The commonly evaluated properties are tensile strength, thickness, percent elongation etc.
- **Swelling test:** This test can provide information about the hydration and swelling properties of films, which are important for drug release.
- **Surface p^H:** This measurement is done to ensure that it is within a suitable range to avoid irritation or discomfort in the oral cavity.
- **Assay/ uniformity of content:** The analysis is performed to determine the content of drug in each film and also to evaluate the API distribution and uniformity between different batches. Ensuring that the film's drug content is consistent and meets the intended dose requirement is vital for patient safety and treatment efficacy.
- **Disintegration test:** Determination of disintegration time of fast- disintegrating film i.e., the time taken to disintegrate under the tongue. Is done typically using a disintegration testing apparatus, but other non- official methods are also widely employed.
- **In-House Disintegration Test:** These tests often involve placing the sublingual film in a beaker with the medium (usually water or artificial saliva) in a controlled temperature with stirring and recording the time it takes for the film to disintegrate.

-USP Disintegration Test: Done with official disintegration apparatus, and the time it takes for the film formulation to completely disintegrate is noted.

-Texture Analyzer: The sublingual film is placed on the analyzer's platform, and a probe is lowered onto the film. The force needed for the probe to pierce into or disintegrate the film is measured, and this gives information about its disintegration properties.

-Visual Observation: A sublingual film is placed in a controlled environment (such as a petri dish with a specified volume of water or saliva) at a defined temperature.

- ***In vitro* dissolution test:** The official *in vitro* dissolution tests measure the drug release from the film in a controlled environment, simulating the conditions inside the sublingual cavity. A suitable dissolution apparatus is usually used to evaluate the drug release; standard paddle or basket apparatus given in any of the pharmacopoeia can be employed.

Packaging

Packing issues have a big impact on dosage form stability, protection, and storage. Packaging choices for film formulations include barrier films, plastic pouches, blister packaging with multiple units, aluminum pouches, foil, paper, or plastic pouches.

Parkinson's Disease[103]

Parkinson's disease affects millions worldwide, causing significant disability. Levodopa, along with dopamine agonists and MAO-B inhibitors, remains the cornerstone of therapy. However, fluctuations in drug absorption and motor complications necessitate the development of alternative drug delivery systems. Sublingual tablets provide an efficient method of administration, ensuring faster therapeutic effects and improved patient compliance. This paper outlines the formulation techniques, benefits, and challenges associated with sublingual drug delivery for Parkinson's disease.

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that primarily affects movement. It is characterized by the loss of dopamine-producing neurons in the substantianigra, a part of the brain responsible for movement regulation. The deficiency of dopamine, a neurotransmitter essential for smooth and coordinated muscle activity, leads to a range of motor and non-motor symptoms. [104]

While Parkinson's disease is not directly life-threatening, its progressive nature significantly impacts a person's quality of life. Current treatments focus on symptom management, but ongoing research aims to find a cure and improve therapeutic options.

Causes and Risk Factors[105]

The exact cause of Parkinson's disease is unknown, but it is believed to be influenced by a combination of genetic and environmental factors.

Genetic Factors[105, 106]

- Certain gene mutations have been linked to Parkinson's disease, including **SNCA, LRRK2, PARK2, PINK1, and GBA**.
- Approximately **10-15%** of Parkinson's cases have a hereditary component.
- People with a family history of PD have a higher risk of developing the disease.

Environmental Factors:

- **Exposure to Pesticides & Herbicides**: Chemicals like **paraquat and rotenone** have been associated with an increased risk of PD.
- **Heavy Metal Exposure**: Long-term exposure to manganese, lead, or copper may contribute to neuronal damage.
- **Head Trauma**: Repeated head injuries, as seen in boxers and football players, have been linked to a higher risk of developing PD.
- **Rural Living & Well Water Consumption**: Some studies suggest a correlation between rural environments and PD, possibly due to pesticide exposure.

Aging:

- The risk of Parkinson's disease increases with age, with most cases diagnosed after **60 years**.
- Aging leads to natural dopamine decline, which may contribute to disease onset.

Other Risk Factors

- **Gender**: Men are more likely to develop Parkinson's than women.
- **Chronic Stress & Inflammation**: Long-term inflammation may increase neurodegeneration.
- **Diet & Lifestyle**: Poor diet, lack of physical activity, and smoking history may contribute to disease risk.

Symptoms of Parkinson's Disease[107]

Parkinson's symptoms vary in severity and can be

classified into motor symptoms and non- motor symptoms.

Motor Symptoms (Movement-Related Symptoms):

- **Bradykinesia (Slowness of movement)** – One of the hallmark symptoms, making everyday activities slow and difficult.
- **Tremors** – Typically begin in one hand (pill-rolling tremor) and occur at rest.
- **Rigidity (Stiffness)** – Muscle stiffness causing discomfort and reduced range of motion.
- **Freezing Episodes** – Sudden inability to move, often triggered by stress or narrow spaces.
- **Micrographia** – Small, cramped handwriting due to reduced motor control

Non-Motor Symptoms

- Cognitive Impairment (memory loss, difficulty concentrating, dementia in later stages)
- Depression and Anxiety
- Sleep Disturbances (REM sleep behaviour disorder, insomnia, restless legs syndrome)
- Constipation and Urinary Dysfunction
- Loss of Smell (Anosmia
- Orthostatic Hypotension (low blood pressure leading to dizziness and fainting)
- Excessive Sweating and Temperature Dysregulation.

Stages of Parkinson's Disease (Hoehn & Yahr Scale)[107]

- **Stage 1** – Symptoms appear on one side of the body, mild tremors, slight movement difficulty.
- **Stage 2** – Symptoms affect both sides but do not impair balance.
- **Stage 3** – Balance issues arise, falls become more common, but independence is maintained.
- **Stage 4** – Severe disability, needing assistance for daily activities.
- **Stage 5** – Wheelchair-bound or bedridden, requiring full-time care.

Diagnosis of Parkinson's Disease[108]

There is no definitive test for Parkinson's. Diagnosis is based on:

- **Clinical Examination** – Neurologists assess motor symptoms.
- **Dopamine Transporter (DaT) Scan** – Differentiates Parkinson's from other conditions.
- **Levodopa Challenge Test** – If symptoms improve after taking dopamine medication, it supports the diagnosis
- **MRI & CT scans** – Rule out other neurodegenerative disorders.

Treatment Options [109]

While there is no cure for Parkinson's, treatments aim to control symptoms and improve quality of life.

Medications

- **Levodopa/Carbidopa (Sinemet)** – Converts to dopamine in the brain, improving movement.
- **Dopamine Agonists** (Pramipexole, Ropinirole) – Mimic dopamine action.

- **MAO-B Inhibitors** (Selegiline, Rasagiline) – Prevent dopamine breakdown.
- **COMT Inhibitors** (Entacapone, Tolcapone) – Prolong Levodopa's effects.
- **Amantadine** – Helps reduce dyskinesia (involuntary movements).
- **Anticholinergics** – Reduce tremors but have side effects.

Deep Brain Stimulation (DBS)

- Electrodes are implanted in the brain to regulate abnormal movement signals.
- Used for patients whose symptoms no longer respond well to medications.

Physical and Occupational Therapy

- **Exercise** (walking, yoga, tai chi) helps maintain mobility.
- **Speech Therapy** – Assists with communication difficulties.
- **Occupational Therapy** – Helps adapt daily activities to improve independence.

Lifestyle Modifications

- **Healthy Diet** (Mediterranean diet rich in antioxidants) may slow progression.
- **Support Groups** – Provide emotional and social support.

Drugs and Formulations Used in Parkinson's Treatment.[110,111]

Treatment options focus on replenishing dopamine levels, improving motor function, and managing non-motor symptoms.

Medications

Levodopa/Carbidopa (Sinemet) – Converts to dopamine in the brain, improving movement.

Formulations: Immediate-release tablets, extended-release tablets, intestinal gel (Duopa), orally disintegrating tablets.

Dopamine Agonists (Pramipexole, Ropinirole) – Mimic dopamine action.

Formulations: Tablets, extended-release tablets, transdermal patches, injectable formulations.

MAO-B Inhibitors (Selegiline, Rasagiline) – Prevent dopamine breakdown.

Formulations: Oral tablets, orally disintegrating tablets, transdermal patches, liquid formulations.

COMT Inhibitors (Entacapone, Tolcapone, Opicapone) – Prolong Levodopa's effects.

Formulations: Tablets, combination formulations with Levodopa/Carbidopa.

Amantadine – Helps reduce dyskinesia (involuntary movements).

Formulations: Immediate-release and extended-release tablets, liquid formulations, extended-release capsules.

Anticholinergics (Trihexyphenidyl, Benztropine) – Reduce tremors but have side effects.

Formulations: Tablets, capsules, injectable solutions.

Other Medications:

Adenosine A2A Receptor Antagonists (Istradefylline) – Helps improve motor function.

Formulations: Tablets.

Glutamate Modulators – Used to manage dyskinesia.

Formulations: Extended-release capsules.

Neuro protective Agents – Under research for potential disease-modifying effects.

Formulations: Various investigational drug formulations, including infusions and implants.

Non-Pharmacological Approaches:

Deep Brain Stimulation (DBS) – A surgical treatment for patients with advanced Parkinson's disease.

Physical Therapy and Rehabilitation – Helps maintain mobility and function. Dietary Modifications – Antioxidant-rich diets may help slow disease progression.

Emerging Treatments and Research

Gene Therapy – Investigating targeted genetic modifications to slow disease progression. Stem Cell Therapy – Exploring the possibility of regenerating dopamine-producing neurons. Personalized Medicine – Tailoring treatment based on genetic and biomarker analysis.

New Drug Delivery Systems – Researching novel delivery mechanisms like nanoparticles and intranasal formulations to improve drug efficacy and reduce side effects.

Selection of Excipients for Sublingual Tablets [112].

A well-formulated sublingual tablet requires the careful selection of excipients to enhance dissolution, absorption, and patient acceptability. Each excipient plays a crucial role in ensuring the rapid disintegration, efficient drug absorption, and palatability of the final dosage form.

Superdisintegrants[113]

Fast-dissolving agents are essential to ensure the tablet disintegrates quickly upon contact with saliva.

Examples include:

- **Crospovidone**: Enhances water uptake and facilitates rapid tablet breakdown.
- **Sodium starch glycolate**: Swells upon hydration, promoting quick disintegration.
- **Croscarmellose sodium**: Provides superior wicking action, leading to faster dispersion of the drug.

Bioadhesive Polymers[114]

Bioadhesive agents help in prolonging the drug's retention time in the sublingual mucosa, allowing for enhanced absorption. These include:

- **Hydroxypropyl methylcellulose (HPMC)**: Increases mucoadhesion and controls drug release.
- **Chitosan**: Improves permeability and enhances mucoadhesion, leading to better drug retention.
- **Gums** (guar gum, xanthan gum, gellan gum, etc.): Good swelling; often used in blends; can contribute to mucoadhesion; relatively cheap; may have viscosity issues

Permeation Enhancers[115]

Since sublingual absorption bypasses the gastrointestinal tract, permeation enhancers are necessary to improve drug penetration across the mucosal barrier:

- **Sodium lauryl sulfate**: Increases drug solubility and enhances absorption.

- **Cyclodextrins**: Forms inclusion complexes with drugs, improving their solubility and permeability.

Flavouring and Sweetening Agents[116]

Taste plays a critical role in patient compliance, especially for long-term therapy. These agents mask the bitter taste of Parkinson's medications:

- **Aspartame**: Provides a sweet taste without affecting blood sugar levels.
- **Sucralose**: A high-intensity sweetener that improves palatability.
- **Menthol**: Imparts a cooling sensation, helping to mask bitterness.

Methods of Sublingual Tablet Formulation

Sublingual tablets can be formulated using various techniques, each offering unique advantages in terms of dissolution rate, stability, and drug release profile.

Direct Compression Method[117]

This is one of the most commonly used techniques due to its simplicity and cost- effectiveness.

- The active pharmaceutical ingredient (API) and excipients are blended uniformly.
- The mixture is compressed into tablets using a tablet press.
- This method is suitable for drugs with good flow and compressibility properties.

Freeze-Drying (Lyophilization)[118]

This technique produces tablets with a highly porous structure, leading to ultra-fast dissolution.

- The API is dissolved in a polymeric solution.
- The solution is frozen and subjected to sublimation under vacuum.
- The resulting porous structure ensures rapid disintegration upon contact with saliva.

Spray Drying[119]

This method ensures uniform drug dispersion and enhances solubility.

- The drug is dissolved in a solvent.
- The solution is sprayed into a drying chamber, where the solvent evaporates rapidly.
- The fine powder obtained is compressed into tablets, ensuring homogeneous drug distribution.

Quality Control and Evaluation

Ensuring the safety, efficacy, and stability of sublingual tablets requires rigorous quality control measures.

Disintegration and Dissolution Tests[120]

- Sublingual tablets should disintegrate within **one to two minutes** to ensure rapid drug release.
- Dissolution studies help assess how quickly the drug becomes available for absorption.

Bioavailability Studies[121]

- Pharmacokinetic studies compare **plasma drug levels** of sublingual versus oral administration.
- These studies confirm enhanced bioavailability and faster onset of action.

Stability Testing[122]

- Tablets are stored under different conditions (humidity, temperature) to evaluate them physical and chemical stability over time.
- Moisture-sensitive formulations require special packaging materials.

Patient Compliance and Sensory Evaluation

Taste-masking effectiveness, ease of administration, and patient preferences are assessed to improve **acceptability and adherence** to treatment.

Advantages of Sublingual Tablets in Parkinson's Disease[123]

- **Rapid onset of action**: Essential for managing sudden "off" episodes.
- **Bypassing first-pass metabolism**: Ensuring higher drug bioavailability.
- **Avoiding gastrointestinal side effects**: Reducing nausea and vomiting.
- **No need for water**: Making it easier for patients with dysphagia.
- **Better dose precision**: Compared to oral liquids or dispersible tablets.

Challenges and Future Developments[124]

Despite their advantages, sublingual formulations come with some limitations that require further research and innovation.

Limited Drug Absorption[125]

- Some Parkinson's drugs have **low permeability** across the mucosal membrane, reducing bioavailability.
- Strategies such as **nano particle-based drug carriers** are being explored to enhance absorption.

Taste Masking

- Many APIs used in Parkinson's disease have an inherently bitter taste.
- Advanced **microencapsulation** techniques and novel flavouring agents are being researched to improve palatability.

Stability Issues

- Moisture-sensitive drugs require specialized **packaging solutions** such as blister packs with desiccants.
- Stability-enhancing excipients can be incorporated to prevent degradation.

Innovative Approaches to Drug Delivery

1. **Nanotechnology-Based Drug Delivery[126]**
   Nanotechnology plays a crucial role in enhancing drug solubility, stability, and absorption. Advanced carriers such as lipid-based nanoparticles (liposomes, solid lipid nanoparticles, and nano emulsions) and polymeric nanoparticles (biodegradable and non- toxic polymers) enable targeted and controlled drug release.
   These systems protect drugs from degradation, increase their bioavailability, and facilitate penetration through biological barriers, making them highly effective for poorly soluble drugs.
2. **Micro needle-Assisted Drug Delivery[127]**
   Micro needles offer a revolutionary, minimally invasive method to enhance sublingual and transdermal drug absorption. These tiny, painless needles create micro channels in the skin or mucosal tissue, allowing drugs to bypass the first-pass metabolism and reach systemic circulation more efficiently.
   Micro needle patches can be designed to deliver small molecules, biologics, and vaccines with improved efficacy, reduced side effects, and enhanced patient compliance.
3. **Lipid Nanoparticles for Enhanced Drug Permeability[128,129]** Lipid nano particles, such as solid lipid nano particles (SLNs) and nanostructured lipid carriers (NLCs), provide an excellent platform for encapsulating hydrophobic and hydrophilic drugs. These lipid-based carriers improve drug solubility,

protect the active ingredient from enzymatic degradation, and enhance permeability across biological membranes.

Lipid nanoparticles are widely explored in pharmaceuticals, particularly for oral, topical, and injectable formulations, as they significantly improve drug absorption and therapeutic outcomes.

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