

## Role of 3D Printing in Enhancing Drug Delivery and Patient Compliance in Parkinson's Disease

Mrs Ashwini D Murdare

*Assistant professor.*

*School of pharmacy, Indira University*

Ms Shreya Keshav Patil

*School of pharmacy, Indira University*

Mr Deepak Khatri

*School of pharmacy, Indira University*

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### Abstract:

Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by the loss of dopaminergic neurons, leading to motor symptoms such as tremor, rigidity, and bradykinesia, along with non-motor complications. Current treatment mainly focuses on symptomatic management using drugs like levodopa and other adjunct therapies. However, conventional drug delivery systems, especially oral formulations, face several limitations including variable absorption, frequent dosing, and motor fluctuations such as "on-off" phenomena, particularly in advanced stages of the disease. Three-dimensional (3D) printing has emerged as an innovative approach to overcome these challenges by enabling the development of personalized drug delivery systems. This technology allows precise control over drug dose, shape, and release characteristics, making it ideal for patient-specific therapy. Various techniques such as fused deposition modeling, semi-solid extrusion, stereolithography, and selective laser sintering enable the fabrication of complex dosage forms like multilayer tablets, polypills, and orally disintegrating systems. These advancements improve drug release control, enhance patient compliance, and support precision medicine. Overall, 3D printing offers a promising platform for optimizing drug delivery, reducing treatment variability, and improving therapeutic outcomes in Parkinson's disease management.

### KEYWORDS:

**Keywords:** Parkinson's disease, 3D printing, personalized drug delivery, patient-specific therapy, polypill.

Parkinson's disease (PD) is a chronic progressive disease of the central nervous system with both motor and non-motor symptoms<sup>(1,2)</sup>. One of the most common neurodegenerative diseases in the world, especially among older people, with the number of cases and prevalence rising significantly with age<sup>(1,3)</sup>. As a progressive disease with chronic disability, it is a significant public health problem and a significant contributor to illness<sup>(2,3)</sup>. The pathological characteristic of Parkinson's disease is the selective and progressive degeneration of dopaminergic neurones in the substantia nigra pars compacta, resulting in a significant reduction of dopamine in the striatum<sup>(1,2)</sup>.

This depleting of dopamine disrupts the proper functioning of basal ganglia circuits which play a crucial role in the regulation of voluntary movement<sup>(1,3)</sup>. In addition to the loss of neurones, protein aggregates inside cells (often called Lewy bodies) are also characteristic of the disease<sup>(2,3)</sup>. All these pathological changes have a cumulative effect on clinical symptoms and evolution of Parkinson's disease<sup>(1,2)</sup>. Resting tremor, bradykinesia, muscular rigidity and postural instability are the primary motor features of Parkinson's disease<sup>(1,3)</sup>. In the beginning, these motor symptoms usually show up on only one side of the body. As time goes by, they worsen and happen on both sides<sup>(1,2)</sup>.

The most common symptom is slowness of movement (bradykinesia), which is required for diagnosis. Tremor and rigidity also make it more difficult to function<sup>(1,3)</sup>. With the advancement of disease, patients can develop gait abnormalities, balance disorders and an increased risk of falls<sup>(2,3)</sup>. Although mainly a condition of motor symptoms, Parkinson's disease also presents in a variety of non-motor symptoms which have a significant effect on

### I. Introduction:

patients' lives <sup>(1,2)</sup>. These include neuropsychiatric symptoms such as depression, anxiety and cognitive dysfunction, sleep disturbances, autonomic dysfunction and sensory anomalies <sup>(2,3)</sup>. Interestingly, non-motor symptoms can appear years before the onset of classical motor symptoms, indicating that Parkinson's disease involves several neural systems in addition to the dopaminergic ones <sup>(2,3)</sup>.

These symptoms have been recognised and have contributed to a better understanding of Parkinsonism as a multisystem disorder not just a motor disorder <sup>(1,2)</sup>. Parkinson's disease is a complex and poorly understood condition, with both genetic and environmental factors playing a role <sup>(2,3)</sup>. Most cases are sporadic, but a handful of genetic abnormalities have been identified that cause the familial forms of the disease <sup>(2)</sup>. Neuronal degeneration has been linked with environmental stressors such as exposure to toxins and oxidative stress <sup>(2,3)</sup>. The resulting cellular dysfunction is believed to result in defective mitochondria, protein folding, and cellular homeostasis, ultimately

resulting in the death of neurones <sup>(2,3)</sup>. Although a definitive diagnostic test is not yet available, diagnosis of PD is largely clinical, based on the recognition of the typical motor symptoms and ancillary features <sup>(1,3)</sup>. Symptomatology often serves as a supportive criterion for diagnosis <sup>(1,2)</sup>, and is often used to confirm the diagnosis.

Possible enhancements are being investigated, such as neuroimaging and the use of biomarkers, but these are not used routinely in clinical practice <sup>(2,3)</sup>. Despite all of our current knowledge, there is no cure for Parkinson's disease, and the medications available so far are primarily targeted towards alleviating its symptoms <sup>(1,2)</sup>. Pharmacological treatments aim at restoring or mimicking the role of dopamine and thus reduce motor symptoms and improve the quality of life <sup>(1,3)</sup>. Treatment can often be complicated and disease activity continues after treatment <sup>(2,3)</sup>. Thus, ongoing studies are dedicated to finding disease-modifying strategies and improving early diagnosis and management <sup>(2,3)</sup>.

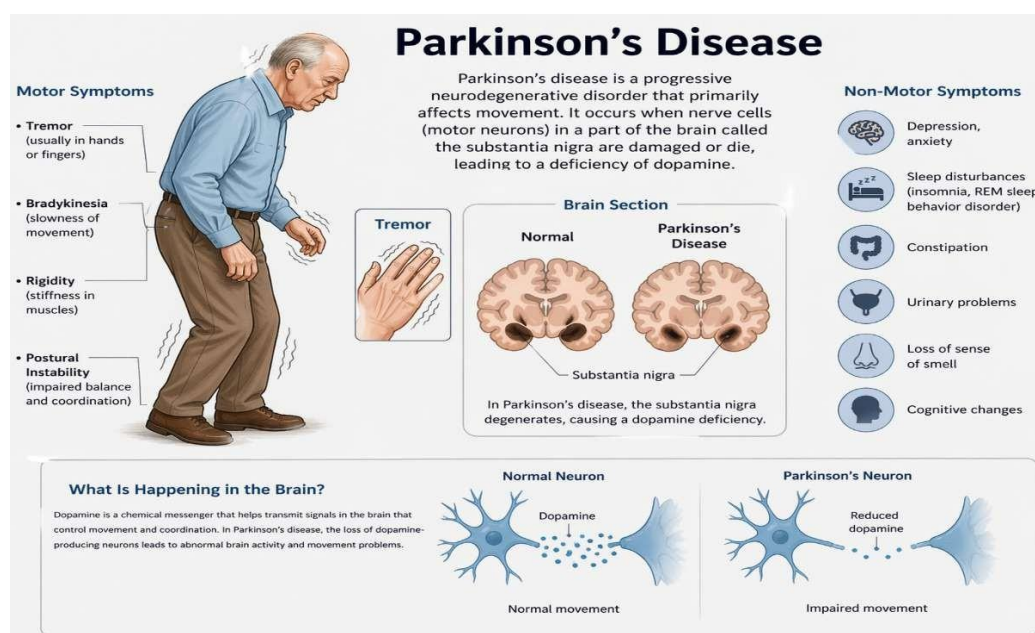


FIG: PARKINSON DISEASE

### Conventional Treatment of Parkinson's Disease with Pharmacological Drugs and their dosage forms. Conventional Treatment of Parkinson's Disease using Pharmacological Drugs & their dosage form.

#### Levodopa

Levodopa is the most effective and widely used drug

for the symptomatic treatment of Parkinson's disease (PD) and is the gold standard of therapy due to its high efficacy in motor symptom improvement <sup>(3,4)</sup>. A loss or degradation of the dopaminergic cells in the substantia nigra leads to a massive loss of dopamine in the striatum in a PD patient. This deficit causes a lack of control of movement and produces the classic signs of bradykinesia (slow movement),

rigidity, tremor and postural instability. Levodopa raises dopamine in the brain and can help restore motor function and significantly improve patients' quality of life <sup>(3)</sup>. Levodopa is a forerunner of the chemical dopamine. In contrast to dopamine, it can enter the brain through the large neutral amino acid transporters in the blood–brain barrier.

It crosses the blood-brain barrier and is converted to dopamine by an enzyme called aromatic L- amino acid decarboxylase and is then stored in the presynaptic neurons. The dopamine released activates postsynaptic receptors, which brings the neurotransmission back to normal and regulates movement. Levodopa is metabolized in the periphery, however, if administered alone this results in a significant amount being metabolized before it can enter the brain. This diminishes its activity, but also leads to side effects like nausea, vomiting and cardiovascular disturbances <sup>(3)</sup>. In order to get around peripheral metabolism, levodopa is typically combined with the decarboxylase inhibitors carbi-dopa or benserazide.

These drugs inhibit its breakdown outside the brain which results in higher levels of the drug in the central nervous system and less side effects. This combination is effective and allows reduction of doses <sup>(3,4)</sup>. Levodopa has a short half-life (1–2 hours) and results in a fluctuating level and response to the drug. It is predominantly absorbed in the small intestine and its absorption can be modulated by the gastric emptying and dietary amino acids. It is important to consider diet since high protein meals can impair its effectiveness <sup>(3,4)</sup>. Long-term use can lead to motor fluctuations also known as “wearing-off” and “on-off” effects” which occur because of irregular dopamine stimulation and disease progression, and dyskinesia (involuntary movements) also occur <sup>(3,4)</sup>. Eventually, the majority of patients with PD will need levodopa as the drug that offers the most symptomatic relief.

Earlier on, side-effects concerns delayed the use of the medication, but recent evidence has shown that early use helps with symptom control as well as quality of life <sup>(5)</sup>. Long-term complications are reduced using such strategies as dosage adjustments, controlled release drugs, and combination therapies (dopamine agonists, COMT inhibitors and MAO-B inhibitors). To keep the drug levels stable, continuous dopaminergic stimulation is necessary <sup>(3,4)</sup>.

In advanced cases, advanced delivery systems like levodopa–carbidopa intestinal gel infusion are used to deliver continuous medication directly to the intestine, thus enhancing motor

control. <sup>(3,4)</sup> There are newer technologies such as microtablets, gastroretentive systems, and inhaled levodopa that provide quicker response and improved control of OFF episodes <sup>(4,5)</sup>.

Available Dosage Forms of Levodopa:

**1. Oral Tablets (Immediate and Controlled Release):** Tablets taken by mouth are the most popular dosage form because they are easy to use and inexpensive. Immediate release tablets have immediate onset of action and controlled or extended release tablets have delayed release of the drug, thus reducing the need for frequent dosing and the rate of motor fluctuations. Gastric emptying and competition with dietary amino acids can cause variation in absorption however [3,4].

**2. Dispersible Tablets Dispersible formulations:** They are dissolved in water before use, thus offer more rapid onset of action and better bioavailability. They are especially useful for patients who have a swallowing problem (dysphagia), like elderly patients or those at a late stage of the disease <sup>[3]</sup>.

**3. Intestinal Gel Infusion (Duodenal Delivery):** Levodopa–carbidopa intestinal gel is given directly into the small intestine through a tube inserted into the gut via a hole in the abdomen. The benefits of this method are that it provides a sustained release of the drug, a steady level of the drug in the blood, and important decreases in motor fluctuations and dyskinesia. It is, however, an invasive, costly and requires specialized equipment and monitoring <sup>[3,4]</sup>.

**4. Subcutaneous Infusion Systems:** Continuous subcutaneous infusion systems are effective in providing a steady dopaminergic stimulation and minimising fluctuations in oral therapy. Such systems have been found as beneficial in the more advanced stages of Parkinson's disease, although they can have device associated complications and may trigger skin reactions <sup>[3,4]</sup>.

**5. Micro tablet and Pump-Based Systems:** Microtablets containing levodopa/carbidopa can be individually dispensed and provide more pharmacokinetic control using electronic dispensing devices. These systems enhance treatment accuracy and decrease symptom control variability <sup>[4]</sup>.

**6: Gastroretentive Drug Delivery Systems:** Gastroretentive formulations are developed to have an increased gastric residence time, and increase the absorption of levodopa in the upper gastrointestinal tract. Sustained drug release can be achieved for a long time with technologies like unfolding polymeric systems or accordion pills <sup>[4]</sup>.

**7. Transmucosal Delivery Systems Oral**

**disintegrating tablets (ODT):** Dissolve quickly in the mouth, beneficial for patients who are unable to swallow. Sublingual and buccal: Avoid first-pass

metabolism and are absorbed quickly These systems enhance compliance and provide quicker effect [4].

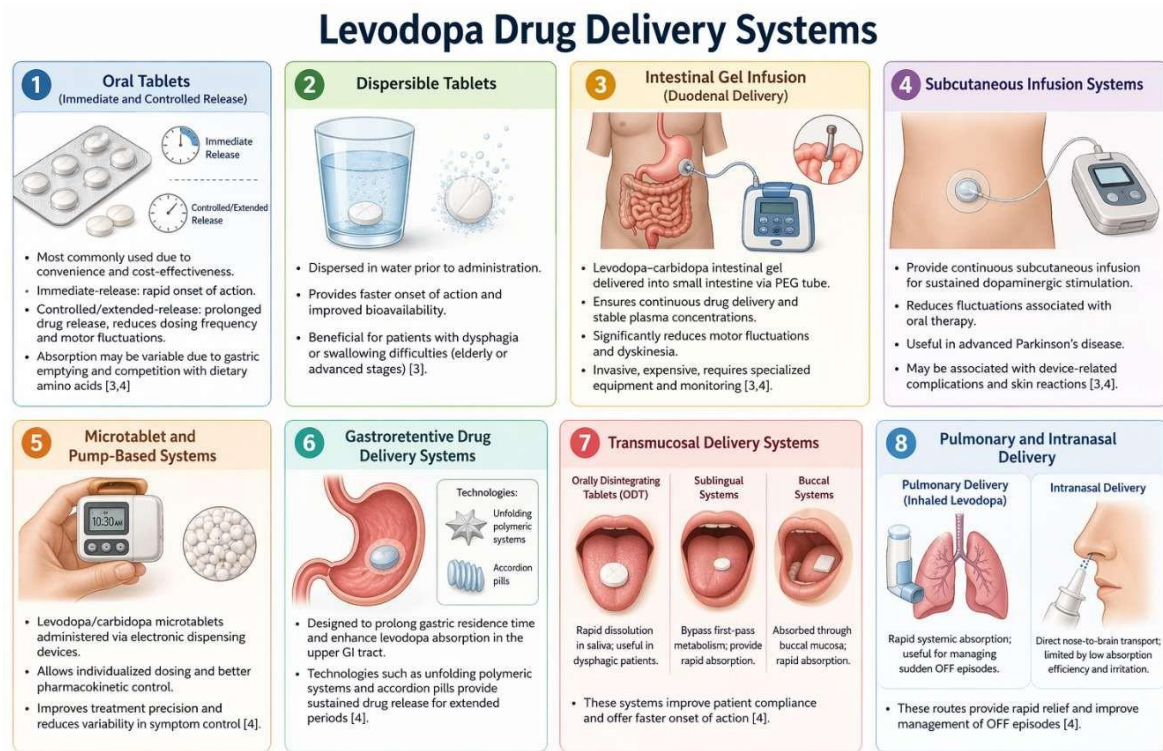


FIG:LEVODOPA DRUG DELIVERY

### Anticholinergic Drugs

Anticholinergic drugs are one of the most traditional therapies available for Parkinson's disease (PD) and, even with the advent of newer medications that are more effective, these drugs have a place in certain patients, especially those with tremor dominant PD (5,6). They restore the balance of dopamine and acetylcholine in the basal ganglia: With PD, there is an increase in cholinergic activity while the use of anticholinergic activity reduces it by blocking muscarinic receptors, thereby improving motor function (5,6). Common drugs used are trihexyphenidyl, bentsropine, biperiden and procyclidine, which are especially used in younger patients as monotherapy in early stages or used in combination with other medications, because older patients are at higher risk of adverse effects (5). In the clinic, these drugs are most effective in

diminishing tremors, whereas they have limited effects on bradykinesia and rigidity and are less effective than levodopa (6). They are limited in their use because of potential side effects such as peripheral effects: dry mouth, blurred vision, constipation and urinary retention, and central effects: sedation, hallucinations and confusion, particularly in elderly patients (5,6). Use these with caution because they can exacerbate memory loss and can make dementia symptoms worse and can also lead to neuropsychiatric side effects such as agitation and delirium, and should be discontinued slowly to prevent worsening of symptoms (5,6). In general, anticholinergics are now used in the treatment of younger patients with predominantly tremor and minimal cognitive impairment and are typically used as an adjunctive therapy instead of as first-line treatment (5).

### Dopamine Agonist

Dopamine agonists are an important component of the treatment of Parkinson's disease (PD) because they directly stimulate the dopamine receptors in the brain and can help to replace the loss of dopaminergic neurons in the substantia nigra. In contrast to levodopa, they are not converted into an active form and therefore have direct effects and are effective in providing symptomatic relief, particularly in the bradykinesia, rigidity and tremor<sup>(7,8)</sup>. These drugs primarily effect D2-like receptors and are used to restore motor function<sup>(6,7)</sup>. Dopamine agonists are divided into two groups: ergot and non-ergot derivatives; but the use of ergot drugs is now uncommon because they cause serious side effects like fibrosis and heart valve problems. At the present time, non-ergot dopamine agents (pramipexole, ropinirole, rotigotine and apomorphine) are more commonly used and seem to be safer and better tolerated<sup>(7,8)</sup>. Can be administered in early stages of PD alone and/or in the advanced stages in combination with levodopa to enhance symptom control and minimise motor fluctuations<sup>(6,7)</sup>. One of the best features of dopamine agonists is that they have a longer half-life than levodopa, which offers more sustained dopaminergic activity and reduces the likelihood of side effects such as dyskinesia and "wearing off" effects. Due to this, they are frequently employed in younger patients to postpone the time of levodopa treatment<sup>(7,8)</sup>. Convenient and effective formulations have been developed, including the rotigotine transdermal patch (which delivers the drug continuously over 24 hours), and injections of apomorphine (which can be used to relieve sudden "OFF" periods)<sup>(7,8)</sup>. However, central effects, such as hallucination, confusion and excessive sleepiness, as well as central effects, nausea, vomiting, dizziness and low blood pressure, can occur with these drugs, particularly in the elderly<sup>(7)</sup>. One issue that has been raised is impulsivity disorders such as compulsive gambling, over eating, and shopping, which can have an impact on behavior and quality of life<sup>(7,8)</sup>. Recent advances include the introduction of extended release and transdermal formulations, which offer the advantage of maintaining a stable drug level, decreasing dosing frequency and increasing long-term treatment effect in Parkinson's Disease<sup>(7,8)</sup>.

### COMT Inhibitors

Catechol-O-methyltransferase (COMT) inhibitors are added-on medications that are used in Parkinson's disease (PD) to enhance the effects of

levodopa. They act by inhibiting the enzyme COMT which converts levodopa into inactive metabolites. They block this pathway, which in turn makes more levodopa available, makes it active for longer and improves its activity in the brain<sup>(3,9)</sup>. These drugs are of no use, provided alone, and are always used in combination with levodopa and a decarboxylase inhibitor (carbidopa or benserazide). They are most useful for stabilizing levodopa levels and improve "ON time" and decrease "OFF time" in patients experiencing motor fluctuations<sup>(3,9)</sup>. The more common COMT inhibitors are entacapone, tolcapone, and opicapone. Both have been safe and widely used, and entacapone works peripherally, while tolcapone is more potent and has a dual central and peripheral action, but is limited by the liver toxicity risk<sup>(3,9)</sup>. Opicapone is a newer, long-acting medication that has once-daily dose administration and improved safety and efficacy with respect to reduction in OFF time<sup>(10)</sup>. Pharmacokinetically, these drugs are used for levodopa stability, fluctuations reduction and continuous dopaminergic stimulation and in this way they help to minimize the complications associated with levodopa use including dyskinesia and wearing-off<sup>(9,10)</sup>. They can also aggravate side effects of levodopa, including dyskinesia, nausea, hallucinations, diarrhea and hypotension. Liver monitoring is necessary because of the hepatotoxicity concern with tolcapone<sup>(3,9)</sup>. In general, COMT inhibitors are a valuable part of combination therapy and newer strategies centre on more efficient formulation and individualised treatment to enhance the long-term efficacy of treatment in Parkinson's disease<sup>(10)</sup>.

### MAO-B Inhibitors

Monoamine oxidase-B (MAO-B) inhibitors are important drugs used in Parkinson's disease (PD) as they block the MAO-B enzyme responsible for breaking down dopamine in the brain. They block this enzyme, increasing and prolonging the release of dopamine, which helps to relieve the symptoms of movement<sup>(9,11)</sup>. The inhibition of MAO-B would not only inhibit the degradation of dopamine but also inhibit the production of harmful oxidative byproducts, so its inhibition might also help prevent neuronal damage<sup>(11)</sup>. Other commonly used medications are selegiline, rasagiline and safinamide, used as monotherapy in early PD and as adjunctive therapy to levodopa in advanced PD to increase symptom control and decrease motor fluctuations<sup>(9,11)</sup>. These drugs are most effective in mild to moderate disease and may postpone levodopa treatment, and when combined with

levodopa that increases “ON time” and decreases “OFF time”<sup>(9,11)</sup>. They are generally safe, and often have side effects like nausea, insomnia, dizziness, and sometimes confusion or hallucination, particularly in older people<sup>(9)</sup>. Drug interactions must also be taken into account, as some drugs can interact with specific antidepressant medications, causing potentially dangerous reactions such as serotonin syndrome<sup>(9)</sup>. While they are safe and effective, and have neuroprotective potential, there are still not robust clinical studies to support slowing the progression of the disease<sup>(11)</sup>. In recent years, the focus has shifted to novel formulations and more selective inhibitors for this purpose, with the goal of enhancing treatment efficacy and safety and ensuring chronic drug delivery.

#### **Amantadine**

Amantadine is an antiviral agent that is more recently known to be of benefit in Parkinson's disease (PD) particularly for motor symptoms and levodopa induced dyskinesia. The mechanisms of action for its effects are not completely understood, but it does act through several mechanisms such as inhibiting NMDA receptors to prevent excess glutamate activity and boosting dopamine levels by encouraging its release and inhibiting its reuptake<sup>(11,12)</sup>. These influences have a beneficial impact on the symptoms such as bradykinesia, rigidity and tremor<sup>(11,12)</sup>. Amantadine can be used in early PD for mild relief, and it can also be combined with levodopa in advanced PD to specifically decrease levodopa-induced involuntary movements<sup>(11,12)</sup>. It might also be effective in decreasing motor variance with other treatments

<sup>(3)</sup>. Amantadine comes in oral and extended release preparations; newer ones can be taken once a day and provide more effective symptom control<sup>(12)</sup>. It is readily absorbed and predominantly excreted renally, and dose adjustments should be made in patients with renal impairment<sup>(11)</sup>. Side effects are nausea, dizziness, insomnia and hypotension, with central effects such as confusion and hallucinations being possible but rare, particularly in the elderly<sup>(11,12)</sup>. A unique side effect is livedo reticularis (skin discoloration), which is usually reversible<sup>(11)</sup>. There can be serious side effects such as psychosis, so it's necessary to monitor<sup>(3)</sup>. Overall, amantadine is a valuable supportive therapy especially for dyskinesia and current research aims at enhancing delivery and efficacy in the management of Parkinson's disease<sup>(3)</sup>.

#### **Oral and Advanced Dosage Forms in Parkinson's Disease**

Oral drug delivery is the most widely used method used in Parkinson's Disease (PD) due to its convenience, cost-effectiveness and patient-friendliness. Levodopa alone or with carbidopa or entacapone is the primary treatment, but “wearing-off” and “on- off” effects, related to fluctuations in the level of the drug in the system, can occur in advanced stages of the disease because of dysphagia and the delayed gastric emptying, and dietary interactions, that can cause irregular absorption of the drug<sup>(13,14)</sup>. Extended-release formulations are used to help avoid this and help maintain more drug stability, will also be dose with immediate release forms and added drugs (such as COMT inhibitors). There are newer methods of delivering drugs like microtablet pump systems that can give personalized dosing and control symptoms<sup>(13,14)</sup>. There are also other sophisticated systems which are designed to enhance absorption of the drug and its uniformity, such as gastroretentive formulations permitting a longer gastral residence time.

Patients with swallowing difficulties will benefit from alternative routes such as orally disintegrating tablets, sublingual and buccal, which act faster<sup>(14)</sup>. Transdermal patches release the drug continuously and intranasal and pulmonary routes have a fast onset of action, which is beneficial during sudden OFF episodes

<sup>(14)</sup>. In advanced PD, steady symptom control is provided by parenteral administration of apomorphine or continuous subcutaneous infusion (CSCI)<sup>(14)</sup>. Advanced therapy that is highly effective is intestinal gel infusion of levodopa/carbidopa that provides a sustained release of the drug in the intestine, thus maintaining more stable levels and improving motor control; this is an invasive and expensive procedure<sup>(13,14)</sup>. In general, the new approach of drug delivery aims to keep the dopamine levels stable, minimize fluctuations and enhance patient quality of life, and further research investigates more sophisticated therapies<sup>(14)</sup>.

#### **Advantages**

Oral drug delivery has been the most popular route of administration, as it is easy and appropriate for use at home without the need for medical supervision and would be suitable for long-term therapy in Parkinson's disease<sup>(13,14)</sup>. It is also cost effective as many generic formulations are available worldwide which will minimise the financial burden on patients. Immediate-release formulation has a rapid onset of action and is beneficial in rapidly relieving acute motor symptoms. This is a route that can be flexibly adjusted with respect to dose, so that treatment can be

customised with regard to disease progression and patient response. Oral drugs have been shown to be effective against core symptoms like tremor and rigidity, and are therefore effective in clinical practice. Oral bioavailability of most antiparkinsonian medications is high, with high absorption of the medications.

Furthermore, the oral forms are convenient to store and do not need to be refrigerated, which makes it easier to access and use. Patients are usually well-aware of tablets and capsules, and do not require special training and increase compliance. Multiple combination formulations (e.g., levodopa and carbidopa or entacapone) make treatment more convenient and effective. Oral dosage forms can be

manufactured in large quantities and can be manufactured in a consistent supply chain. They also can be used safely with most other medications for polypharmacy and are compatible with most comorbid conditions. Oral therapy is more acceptable than an injection or implant-based system, since it is not invasive.

In addition, these medicines have wide regulatory clearance and are frequently insurance-provided, making them more available. Doses can be readily titrated to reduce side effects in initial treatment and oral delivery is overall very effective, particularly for monotherapy in early stage Parkinson's disease. (13,14,15).



FIG: ADVANTAGES OF ORAL DRUG DELIVERY

**Disadvantages:**

Drug delivery via the oral route is also limited in a few respects in PD, which may influence the long-term treatment. Drugs such as levodopa have a short half-life, which can cause unpredictable “on-off” fluctuations, and they require multiple doses throughout the day (usually four), which decreases patient compliance (13,14). Sudden increases in plasma concentrations can lead to dyskinesia; swallowing problems are a significant problem in late-stage patients with dysphagia. Side effects include nausea and vomiting, and peripheral effects such as orthostatic hypotension, which are caused by first

pass effects. Variability in response (13) may occur due to food interactions, particularly when food is consumed with a high protein meal. After a few years of treatment, patients may find that the treatment is not as effective as their daily activities are disrupted by “wearing off” effects between doses. Central side effects, such as hallucinations or cognitive impairment, also may be experienced, especially in the elderly.

As disease progresses, the gastrointestinal function may become impaired, which may lead to less reliable therapy. In some cases, controlled-release products can result in "dose dumping" with a rapid

increase in blood levels of the drug. Appetite changes may lead to weight gain or loss, and repeated use can lead to irregular sleeping habits. Long-term use also poses concerns of cumulative toxicity. The challenges mentioned above

underscore the need to develop alternative drug delivery systems and optimized therapeutic interventions in the treatment of Parkinson's disease. (13,14,15).

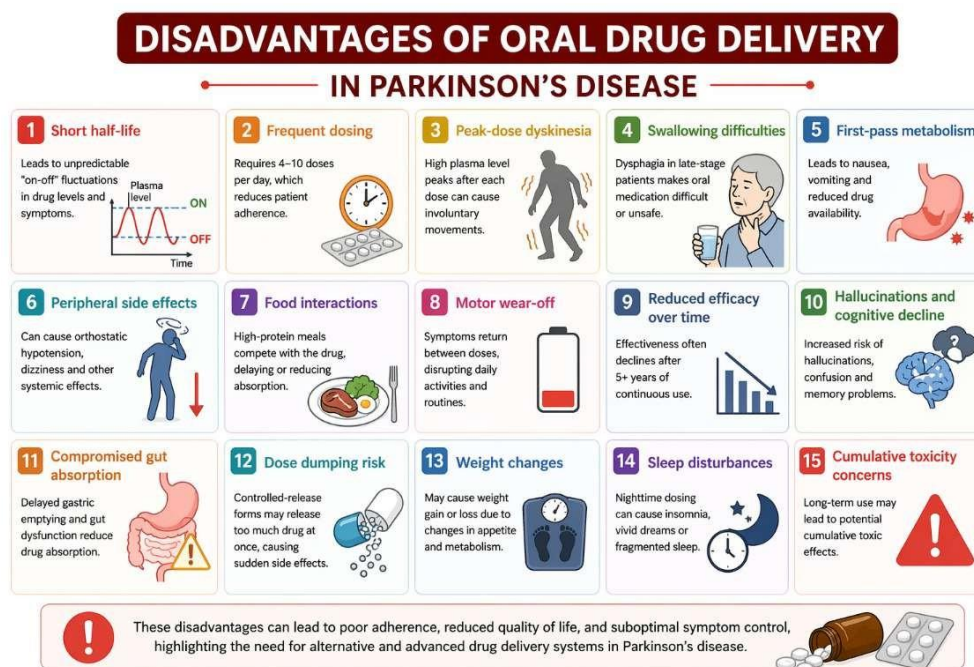


FIG:DISADVANTAGES OF ORAL DRUG DELIVERY

**Introduction to 3D Printing.**

Three-dimensional (3D) printing, or additive manufacturing, is an emerging digital fabrication technology that can create and print real-world objects from virtual designs by depositing materials in a controlled manner, layer by layer. In contrast to conventional subtractive manufacturing techniques such as cutting, drilling or milling out material from a bulk piece, 3D printing builds up objects only where they are needed. This is a key distinction that can help cut material waste, boost production profit, and allow for the creation of highly complex geometries that are less constrained (16,17).

The first step in the 3D printing process is to create a digital model, which can be done using computer-aided design (CAD) software or by scanning the object in 3D. A digital model is then created into a standard tessellation language (STL) file, which will approximate the surface geometry of the object in terms of triangles. The file is then sent to a slicing software program, which slices the model into thin horizontal layers and produces machine instructions (G-code) for the printer. The printer then follows these instructions to build the desired three

dimensional object (18,19) out of the same material, layer by layer. Many 3D printing technologies have been created, based on different working principles and material compatibility. Common shaping methods include fused deposition modeling (FDM), stereolithography (SLA), and selective laser sintering (SLS), which melts thermoplastic filaments, photopolymerizes liquid resins with ultraviolet light, and heats and fuses powdered materials with a laser beam.

These technologies enable the use of a variety of materials including polymers, metals, ceramics and composite materials, expanding the applications in various different industries (16,18). In the last ten years, 3D printing has developed from a prototype-making technology to a full manufacturing technology that has a great industrial application value. It's used in many industries, including construction, healthcare, automotive, and aerospace, due to its capabilities of producing complex and precise shapes. In healthcare, 3D printing is employed to create patient-specific drug delivery systems, prosthetics, and implants, embracing the concept of personalized medicine. In construction,

similarly, large-scale 3D printers are starting to be used to create parts and entire buildings more efficiently and with less manual labor<sup>(20)</sup>.

One of the main benefits of 3D printing is its "seamless integration with digital manufacturing and automation. Adopting these new technologies, including artificial intelligence, machine learning and computer-aided engineering, enables design, process and material optimization. This will not only help to ensure product quality and consistency, but also allow for quick prototyping and on-demand manufacturing. Furthermore, the 3D printing enabled decentralized production minimizes the need for intricate supply chains and transportation, thereby reducing carbon emissions and promoting sustainability<sup>(17,19)</sup>.

While 3D printing has many benefits, it has some drawbacks, such as the high cost of the initial equipment, the time it takes to print large products,

and the lack of standardized materials. Additionally, quality control, repro-ducibility and regulatory compliance problems are challenges for the broad use of the technologies in industry, in specific sensitive areas like pharmaceuticals and medical devices. Continued research and development in materials science, process optimization, and regulations should be able to overcome these obstacles, and propel the potential for this technology even further<sup>(16,18)</sup>.

Finally, 3D printing is a revolutionary technology in the manufacturing sector providing previously unseen design freedom, material usage and customization options. It has also the potential to become a part of Industry 4.0 with the integration of new digital technologies to be a pivotal element in the production process, healthcare solutions and sustainable practices in the near future<sup>(17,20)</sup>.



3D Printing techniques in treating Parkinson's Disease.

### Fused Deposition Modeling (FDM)

Among the most widely applied extrusion-based 3D printing technologies in the pharmaceutical industry, Fused Deposition Modeling (FDM) is a key technology. The first one is the thermoplastic method, which involves extruding drug-laden thermoplastic filaments through a nozzle until solid dosage forms are created, layer by layer, after heating the material above its glass transition temperature. This technique enables to control the geometry, infill density and inner structure of the tablet with high precision, directly affecting the drug release kinetics.

In Parkinson's, the FDM has been extensively studied in the area of sustained or modified release formulation of levodopa and other dopaminergic drugs<sup>(22,21)</sup>. With the change of the parameters like

infill percentage and shell thickness, the drug release behavior can be adjusted to obtain stable plasma drug levels, which is an important issue in controlling the motor fluctuations in Parkinson's patients<sup>(23,24)</sup>. Furthermore, FDM can be used to produce polypills consisting of several drugs combined into a single dosage form with compartmentalized release. This is especially beneficial when treating Parkinson's patients which typically need multiple medications, and therefore increased compliance and decreased dosing frequencies<sup>(21,22)</sup>.

### Semi-Solid Extrusion (SSE) / Pressure-Assisted

### Microsyringe (PAM) Semi- solid extrusion (SSE) or pressure-assisted microsyringe (PAM)

on the other hand, is a low-temperature printing method producing drug loaded gels, pastes or semi-

solid formulations. It is particularly useful for heat-sensitive drugs that can break down in the high-temperature processes such as FDM. SSE is especially beneficial for the manufacture of orally disintegrating tablets in Parkinson's disease (ODTs). Non-motor symptoms in Parkinson's patients that are common and which can impact medication adherence include dysphagia, or trouble swallowing. The newly developed SSE-based ODTs disintegrate rapidly in the oral cavity (without water) and improve patient compliance and therapeutic outcome. Moreover, the ability to control of the distribution of the drug and the possibility to fabricate personalized dosage forms with optimized drug loading and fast onset of action is of great importance to control sudden "off" periods in Parkinson's disease<sup>(23,24)</sup>

#### **Stereolithography (SLA)**

Stereolithography (SLA) is a laser-based 3D printing method which uses photopolymerization of liquid resins to create complex and precise structures. It has a higher resolution and surface quality than extrusion methods. In Parkinson's disease research, SLA is investigated for the development of advanced drug delivery systems such as microstructured devices and implantable drug delivery systems for targeted drug delivery. These systems can enable targeted and sustained drug delivery to targeted areas, which may allow better therapeutic efficacy and minimal side effects to the rest of the body. The extreme accuracy of SLA also allows fabrication of micro-scale platforms for drug delivery methods that are currently under investigation for use in neurodegenerative disorders, such as localized drug delivery and intracerebral drug delivery<sup>(24,25)</sup>.

#### **Selective Laser Sintering (SLS)**

Laser Sintering (SLS) is a powder based 3D printing method, in which powdered materials are fused together by the application of a high-energy laser. One of its important benefits is that it makes highly porous dosage forms without a need for any other excipients. For drugs which need fast onset such as

levodopa, SLS has been studied for the production of porous tablets which have been found to have improved dissolution rates in Parkinson's disease. The porosity of the structure may be accurately controlled and optimized drug release profiles can be obtained for both Selective and sustained drug delivery. Also, SLS does not require the use of solvents, which makes it applicable for moisture/chemical sensitive drugs<sup>(22,26)</sup>.

#### **Inkjet 3D Printing**

Droplet based inkjet printing is a method that is used to apply a precise amount of a drug solution onto the substrate or powder bed. This is a very accurate method for dosing, works well for low dose, high potency drugs. In Parkinson's disease, inkjet printing techniques have been investigated to prepare ropinirole and other dopaminergic drugs formulations, with an objective of controlling the dosage and spatial distribution of drugs. The method also enables the deposition of multiple drugs, making it an attractive option for the development of combination products with different drug release profiles. Additionally, because of the concept of personalized medicine<sup>(27)</sup>, on-demand and point-of-care manufacture are also positive traits of the inkjet printing technology<sup>(27)</sup>.

#### **3D Screen Printing (Multilayer Printing)**

The 3D screen printing is a novel process which can be used for the production of multi-layered pharmaceutical delivery systems with spatial separation between active pharmaceutical ingredients. This type of technology can be used to have multiple drugs in a single dosage form in separate sections or layers. This can be especially useful when developing combination treatments in Parkinson's disease, which might involve giving both immediate release and sustained release medications at the same time. This allows greater control of plasma levels of the drugs and decreases drug level fluctuations from conventional dosing. Additionally, the ability to compartmentalize drugs minimizes incompatibility issues and enhances formulation stability<sup>(28)</sup>

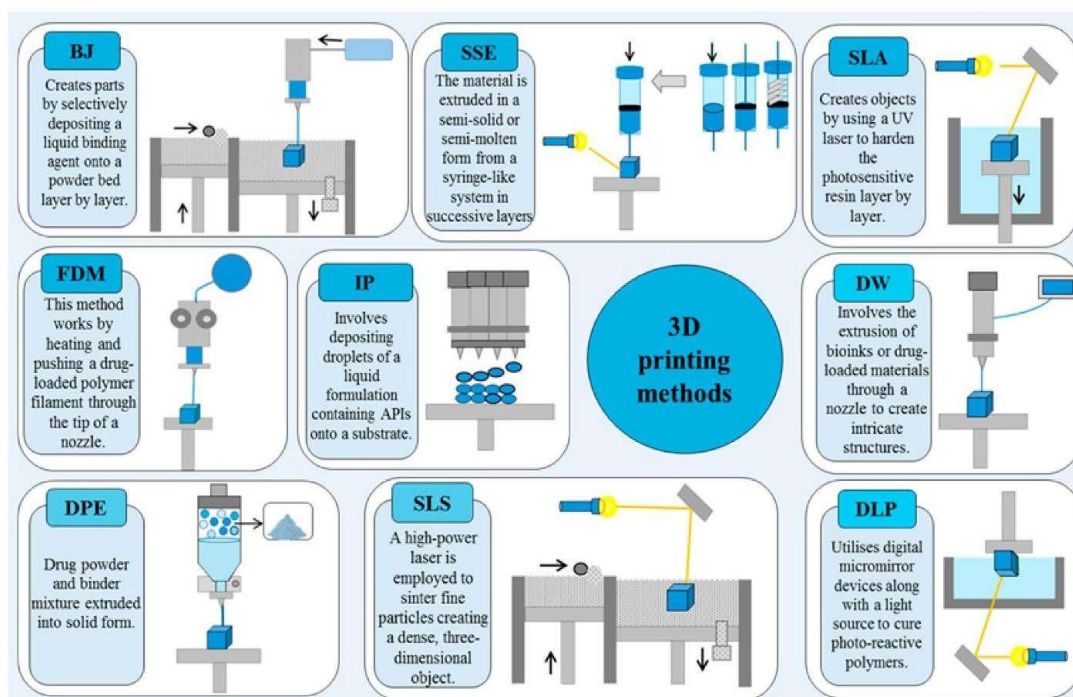


FIG: 3D PRINTING METHODS

### Advantages of 3D Printing Over Conventional Methods

Three dimensional (3D) printing or additive manufacturing has become a game-changing technology in the pharmaceutical and biomedical fields due to the fact that it overcomes some of the problems associated with traditional manufacturing technologies. Conventional drug manufacturing practices involve batch processing, fixed-dose formulations, and a series of sequential unit operations limiting flexibility and personalization. A contrastingly patient-centred, precise and adaptable approach in the creation of drugs and delivery is offered by 3D printing, which combines an automated production and fabrication process with a digital design <sup>(29,30)</sup>. 3D Printing offers a major benefit of personalized medicine. Standard dosage forms are made at predetermined dosages which may not be optimal for an individual patient. But 3D printing can enable the customization of dose, shape, size, and drug release characteristics as per patient-specific needs.

This is especially useful in disorders like Parkinson's disease where there is a need for dose titration and combination therapy. In addition, polypills with different drugs with different release profiles can be manufactured which will decrease pill burden and increase adherence to treatment

<sup>(31,32)</sup>. The other end benefit is the capability to generate complex geometries and inner make-up. Due to mechanical and tooling constraints, conventional techniques are not suitable for the production of complex designs.

By contrast, 3D printing can be used to create tablets with multiple layers, hollow systems, porous matrices and compartmentalized structures. The designs here enable spatial separation of active pharmaceutical ingredients and are suitable for advanced drug delivery systems like immediate release layers and sustained release cores <sup>(30,33)</sup>. The 3D printing technology also offers the ability to precisely control the release of the drugs, a crucial factor for any therapeutic application. Drug release dosage forms with immediate, delayed, pulsatile or sustained drug release can be designed by tuning the infill density, surface area, geometry and the material composition. Such accuracy cannot be obtained with conventional compression or coating technologies that do not have structural flexibility <sup>(31,34)</sup>.

Advantage of 3D printing in the field of manufacturing efficiency is that it has fewer processing steps. The production of traditional pharmaceuticals involves several processes, including blending, granulation, drying, compression, and coating, all of which add the

possibility of variability. Unlike this, in 3D printing formulation and fabrication are combined in a single automated process, which enhances reproducibility and minimizes human error<sup>(29,32)</sup>. The other major benefit is speedy prototyping and fast product development. According to conventional systems, the formulation change must involve changing molds, dies or processing factors which is time consuming and costly. Digital modifications can be made using 3D printing, which can speed the development and optimization of drug formulations. This is especially beneficial when it comes to early research and clinical development<sup>(30,35)</sup>.

In terms of the environment, 3D printing promotes material efficiency and eco- friendliness. Additive manufacturing is different from subtractive manufacturing because it requires only the amount of material necessary, which reduces material waste. Furthermore, the use of biodegradable polymers and recyclable materials promotes an environmentally friendly pharmaceutical production<sup>(33,36)</sup>. 3D printing also improves patient adherence and accessibility with novel dosage forms like chewable tablets, taste-masked medicines and orodispersible tablets. These are particularly useful for children and elderly people. Such dosage forms have been found to enhance the ease of administration and adherence to therapy in patients with PD, in which dysphagia is prevalent<sup>(31,37)</sup>. Furthermore, 3D printing facilitates decentralized and on-demand manufacturing, which makes it possible to manufacture medicines at the hospital or the pharmacy according to a prescription. It not only decreases the space needed to store drugs, but also cuts down on drug wastage and makes drugs available on time, a departure from the mass production of drugs in centralized locations and towards personalized healthcare systems<sup>(29,34)</sup>. However, there are some drawbacks: expensive equipment costs, regulatory restrictions and lack of productivity for large-scale manufacturing. Furthermore, there are no regulatory standards for 3-D printed drugs which may present quality control and validation issues. Continued progress in materials science, process optimisation and regulatory guidance is likely to resolve these problems and increase the use of 3D printing in the pharmaceutical industry<sup>(32,36)</sup>.

## II. Conclusion

Parkinson's disease (PD) is still a complicated and progressive neurological condition, which can be managed with long-term and individualized treatment. While traditional medications like levodopa and other additives are

beneficial in alleviating symptoms, they do have side effects that can limit their usefulness over the long term, including motor fluctuations, dyskinesia, and inconsistent drug response.

Although convenient and widely employed, traditional oral drug delivery systems are not able to achieve sustained plasma drug concentrations, particularly in late stages of the disease. Progress in drug delivery systems has led to better therapeutic effects, including increased bioavailability, decreased fluctuations, and more sustained dopaminergic stimulation. In these innovations, three-dimensional (3D) printing has proven itself to be a highly promising technology in modern pharmaceutical research. The ability to deliver personalized dosage forms with control of drug release, drug dose, and formulation design is a significant step towards patient-centred therapy. Moreover, 3D printing allows the production of complex structures, polypills and on-demand production of drugs that will enhance patient adherence to treatment and treatment efficiency. While there are some challenges to address, including regulatory, cost, and scalability, the continued innovation in the sector is expected to mitigate those issues. In conclusion, potential for drug delivery systems to be enhanced by advanced approaches such as 3D printing looks promising for the future of Parkinson's disease.

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