applied sciences

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*Review*

# Oral Health and Use of Novel Transbuccal Drug Delivery Systems in Patients with Alzheimer's and Parkinson's Disease: A Review

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**Abstract:** Neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are common age-related diseases responsible for high disability. Disease-modifying treatments for AD and PD are still lacking, but symptomatic therapies are available, although limited by difficult administration and patients' scarce compliance at later disease stages. Transbuccal Drug Delivery Systems (TDDSs) include chemical-physics biotechnologies and mechatronic approaches, allowing drug delivery via the transbuccal route, a strategy that may theoretically overcome the limitations imposed by conventional oral administration. In this review, we provided a snapshot of TDDSs, their mechanism of action, the existing subtypes, and their potential application in PD and AD patients. We found a variety of TDDSs, including tablets, solutions, sprays, patches, and the more sophisticated "mechatronic" IntelliDrug and OraFuse devices using a system of pumps and valves for continuous drug release. Several trials have been conducted either on models or patients to test the safety and efficacy of the antidementia and antiparkinsonian agents delivered by TDDSs, which produced encouraging results that suggest future application on a larger scale. Moreover, oral health has emerged as a fundamental prerequisite for the successful use of TDDSs. Accordingly, greater attention to oral hygiene is now due in patients with neurodegenerative disease.

**Keywords:** periodontal health; special care dentistry; new technology in dentistry; transbuccal drug delivery systems; oral diseases; neurodegenerative diseases; Parkinson's disease; Alzheimer's disease



**Citation:** Basilicata, M.; Grillo, P.; Tancredi, A.; Di Fiore, A.; Bollero, P.; Stefani, A.; Schirinzi, T. Oral Health and Use of Novel Transbuccal Drug Delivery Systems in Patients with Alzheimer's and Parkinson's Disease: A Review. *Appl. Sci.* **2023**, *13*, 4974. https://doi.org/10.3390/app13084974

Academic Editor: Gaetano Isola

Received: 9 February 2023
Revised: 3 April 2023
Accepted: 9 April 2023
Published: 15 April 2023



## 1. Introduction

The incidence of neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD), is progressively rising due to the natural increase in life expectancy [1–6].

AD is the most common neurodegenerative disease and the most frequent form of dementia. The neuropathological hallmarks of AD are the aggregates of amyloid-beta and tau proteins [7–9], whereas the clinical spectrum is characterized by progressive cognitive decline. Patients first suffer from loss of episodic memory, and later develop a multidomain deterioration with functional disability. Based on the aetiology, two forms

of AD can be distinguished: the familial, more rare, and the sporadic, which instead represents the vast majority of cases. Familial AD forms depend on pathogenic variants in three main genes, namely the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*). Conversely, sporadic AD has a multifactorial origin, due to the interaction between genetic risk factors (e.g., variants in genes implicated in cholesterol metabolism and neuroinflammation) and other acquired factors (e.g., mid-life hypertension or diabetes) [10]. In addition, more recently, a potential pathogenic role has been recognized for microwaves. Indeed, microwave radiation can affect the human brain, interfering with the neurochemical transmission in critical areas for memory and cognition, such as the hippocampus. Moreover, it may exert detrimental neuronal effects, as preclinical models have shown, that can account for an increased risk of neurodegeneration in exposed individuals [11].

PD, instead, is the second most common neurodegenerative disease whose core neuropathological features are the loss of dopaminergic neurons in the substantia nigra pars compacta and the brain accumulation of alpha-synuclein-positive Lewy bodies [12–14]. The clinical presentation of PD includes a triad of motor signs: bradykinesia, rigidity, and rest tremor. However, a wide spectrum of nonmotor symptoms (e.g., constipation, mood disturbances, sleep disorders, etc.) accompanies the disease course, from prodromal to advanced stages. As for AD, only a minority of PD cases are inherited, whereas the largest part depends on a complex interplay between genetic background and other risk factors (age, male sex, rural living, and exposure to certain pesticides).

Even if effective disease-modifying treatments are not available for these disorders, several symptomatic drugs can be used with a remarkable impact on the quality of life [15–18]. In particular, AD patients can benefit from medications potentiating cholinergic signaling and enhancing memory circuits. PD patients, conversely, take advantage from drugs that increase dopamine in the nigrostriatal pathway.

Oral, enteral, and parenteral administrations are considered the gold standard for drug delivery, although with some limitations and restrictions. In fact, at later disease stages of AD and PD, dysphagia and swallowing difficulties may provide an obstacle to the assumption of the tablets [19]. Moreover, in PD, a narrowing of the therapeutic window occurs along the disease progression, with consequent long-term side effects of Levo-Dopa treatment (i.e., motor fluctuations and dyskinesia) [20]. In this perspective, alternative delivery routes have been progressively tested and emphasized over the years either for AD or PD patients, including Transbuccal Drug Delivery Systems (TDDSs). Indeed, TDDSs represent a group of novel, different techniques to convey drugs through the oral mucosa both at the sublingual and genial level, theoretically overcoming the main bias of conventional oral assumption.

This review aims to provide an overview of the main TDDSs that are available, or in development, for AD and PD patients. Moreover, we highlight the relevance of oral health in patients with neurodegenerative disease, as an essential condition to successfully approach such a novel kind of therapy [21–24].

### *1.1. Oral Health, Alzheimer's Disease and Parkinson's Disease*

AD and PD patients are predominantly elderly individuals, and in most countries various preventive measures have been implemented to safeguard and monitor the general health condition of these patients. In this perspective, the assessment of oral health is critical, following the axiom that an individual's general health status is directly influenced by oral health. Periodontal disease and carious lesions do not only have local effects on the oral cavity, but can also have a number of negative systemic implications [25,26]. Oral health problems (such as higher incidence of caries, periodontal disease, and xerostomia) severely affect patients with these two neurodegenerative diseases because of the limited oral hygiene care due to aging [27–31]. In addition, PD and AD patients suffer from motor disturbances, which definitely increase the risk for dental complications because

of the inability to take care of oral hygiene or the impairment of oral musculature and lip movements [32,33].

Although a causal relationship between dental infections and neurodegenerative diseases has not been established yet, there is evidence that they may act as possible risk factors. There are studies showing that the blood invasion of oral microbiota, in particular the periodontal pathogenic bacteria from the various Sokransky complexes, may potentially trigger AD [34,35]. The passage into the bloodstream of oral microbiota bacteria (e.g., Porphyromonas gingivalis, Viridians Streptococci, bacteria of the HACEK group) could generate serious systemic infections, influencing the progression of neurodegenerative diseases, diabetes, and atherosclerosis [36,37]. In addition, the systemic antibody response to oral pathogens could promote AD progression, as suggested by Franciotti and collaborators. Specifically, these authors compared the prevalence of Porphyromonas gingivalis and the severity of periodontal disease in AD patients and healthy subjects [38–40], finding a significant increase in the AD group, which raised the hypothesis that the different oral microbiota or the presence of periodontal disease could play a role in the complex pathogenic mechanisms of AD onset and evolution [41], although the mechanisms still remain unclear [42–47]. Indeed, the same could be hypothesized for PD pathogenesis [48].

### *1.2. Transbuccal Drug Delivery Systems: Mechanism of Action and Nanosystems*

The oral mucosa is a 200 $cm^2$ tissue with a protective function against pathogenic microorganisms, enzymes, carcinogenic factors, and mechanical insults. It consists of a stratified squamous epithelium and a vascular layer, which drains directly into the jugular veins. Loose intracellular connections (i.e., gap junctions, desmosomes, and hemidesmosomes) make the oral mucosa more permeable than epidermidis even with regional differences. The degree of absorption, indeed, varies according to the presence of a horny layer in the squamous epithelium, being maximum at the sublingual level and lower in the gums, hard palate, and lingual dorsum [49]. TDDSs allow the administering of drugs through the oral mucosa. In detail, sublingual mucosa is the preferred route for a rapid onset effect of drugs; conversely, absorption via the genial mucosa is more suitable for long-release administration, limiting the fluctuation of the drug concentration. The main advantages of TDDSs include higher patient compliance, noninvasive administration, a reduced amount of drug administered with fewer side effects, higher bioavailability, and the elimination of hepatic first-pass metabolism. The disadvantages, instead, mostly depend on the high cost of some devices [50,51]. All the advantages of TDDSs are found with the use of innovative nanosystems. A nanosystem can consist of organic and/or inorganic nanoparticles (NPs) assembled from lipids, metal polymers, and metal oxides. Because of their physico-chemical characteristics (particle size, surface charge, and hydrophobicity), the system (drug + nanosystem) can interact efficiently with the biological targets, increasing the efficacy of the drug to which they are joined [52]. Moreover, nanosystems enable a reduction in the frequency of drug administrations and prevent dose fluctuations, thanks to the capability to bind reversibly with mucins within the oral cavity. The effectiveness of NPs in dentistry has been exploited in caries processes and hypersensitivity, periodontal disease, endodontic infections, and even oral carcinoma. In the conservative field, an adhesive rich in zinc-filled NPs was introduced to counteract the activity of matrix metalloproteinases and to promote remineralization between resin and tooth substance. Then, calcium and doxycycline were added to the nanosystems with zinc to increase the mineralization effect and the antibacterial effect. In endodontics, nanoparticles can be incorporated into root canal filling material, sealer, irrigating solutions, and intracanal medicaments. PLGA (polylactic-co-glycolic acid) nanoparticles loaded with chlorhexidine or chitosan nanoparticles have been developed.

To combat oral carcinoma, moreover, cisplatin has been exploited in combination with PEG-poly (glutamic acid) [53]. More clinical studies are required in the future in order to implement nanotechnology, a valuable aid in the delivery of various drugs [54–58].

### 1.3. Transbuccal Drug Delivery Systems: Subtypes

The spectrum of TDSSs currently available is wide and varied, and includes both chemical/physical biotechnology and a mechatronic approach (Figure 1). This review does not aim to provide a detailed description of each device and its functioning, but rather, to describe the current and potential application of TDSSs in the field of PD and AD. The list below contains the most common TDDSs available for PD and AD patients:

- Buccal tablets: a small flat disc to insert into the buccal vestibule, designed to dissolve slowly while releasing the active ingredient.
- Buccal patches: made of silicone foil, consisting of an impermeable carrier layer and a reservoir containing the drug that is released in a controlled manner over an extended period of time.
- Buccal spray: a uniform dispersion of active ingredient in a solvent along with propellant to generate a uniform spray during application.
- Therapeutic mouth rinse: viscous liquids used to coat the buccal surface either as protectors or as vehicles for drug delivery.
- Ointments: a semisolid dosage form in which the active ingredients are dispersed in a bioadhesive ointment base that is applied to the oral mucosa.
- Nanoparticle drug delivery systems: a multicomponent delivery system that includes a drug and biodegradable nanoparticles with bioadhesive properties that is able to penetrate regions that might be inaccessible by other delivery systems, such as periodontal pocket areas below the gingival margin. They can generally be incorporated into any suitable oral hygiene product, such as gels, chewing gum, toothpaste, and mouthwash [59].
- IntelliDrug (ID): ID is the most promising delivery system. Along with new therapeutic targets such as α-Klotho protein (KL), they could become alternative future therapeutic approaches in the field of PD and neurodegenerative diseases overall [60]. IntelliDrug is driven by electronics, mechanics, and computer science (mechatronic approach) and it has been designed to deliver the maximum amount of drug solution with a minimum amount of energy. It is implanted in the oral cavity—built on a prosthetic crown or incorporated within a larger prosthesis—and includes an osmotic pump for liquid propulsion and a normally-closed microvalve [61]. It is also equipped with a flow sensor and a fill-level sensor to monitor the dispensed amounts. The speed of drug release is regulated by the onboard electronics, which changes the duty cycle related to valve openings. The users can control the entire device via infrared remote control, which allows the operator to program the dosage and monitor the status of the device, such as the remaining drug level. The biggest disadvantage of ID is that the patient needs to have two missing adjacent teeth [62].

### 1.4. Transbuccal Delivery Systems for Dental Purposes and Periodontal Disease

Continuous-release devices are relatively recent tools in dentistry; several types of devices are commercially available or are being premarketed. Various delivery approaches have been developed: mouthwashes, lozenges, gels, chewing gum, lollipops, films, patches, tablets, and various specialized mechanical transmucosal devices. All of these delivery systems must be in close contact with the mucosa (mucoadhesive concept), resulting in a high concentration in a localized area and thus a high drug flow through the absorbing mucosa. These buccal mucoadhesive forms of delivery can be used to treat both local (mouth ulcers, oral cancer, aphthous stomatitis, etc.) and systemic conditions. Additionally, in patients with AD and PD where local oral problems are common, these forms of administration offer many advantages [63]. Numerous side effects, such as ulcers and xerostomia, are related to the main drugs used to treat these conditions. Increased masticatory muscle spasms can lead to temporomandibular disorders. Candida albicans overinfections can also be found, resulting in stomatitis, as well as in periodontal disease and premature loss of dental elements. Several mucoadhesive polymer delivery systems for the mouth have been developed in the latest years, encompassing drug-loaded polymer matrices for the

delivery of antimicrobics drugs, composite filling materials to release fluoride ions into dental caries, and bioerodible oligomers for the treatment of periodontal diseases.

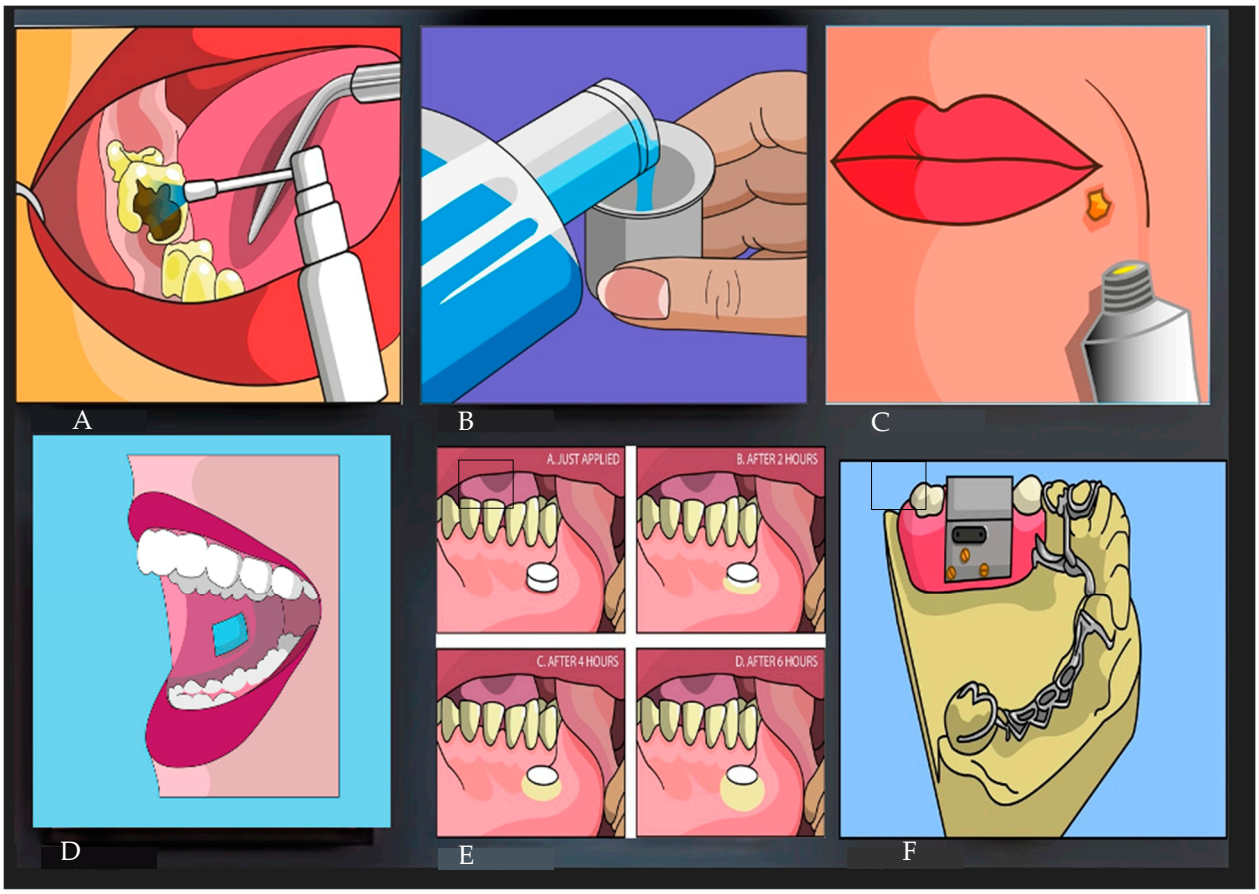


**Figure 1.** It shows different subtypes of Transbuccal Drug Delivery Systems: (**A**) buccal spray: a uniform dispersion of active ingredient in a suitable solvent along with propellant; (**B**) therapeutic mouth rinse: viscous liquid that contains drugs; (**C**) ointment: a semisolid dosage form in which the active ingredients are dispersed in a bioadhesive ointment base; (**D**) patch: made of silicone foil consisting of an impermeable carrier layer and reservoir containing the drug; (**E**) tablet: a small disc applied to the mucosa of the cheek; (**F**) IntelliDrug: a mechatronic approach, incorporated within a prosthesis.

## 2. Materials and Methods

This is a narrative review in which references have been included according to the authors' judgement. Regarding the identification of TDDSs-related articles, the existing literature has been reviewed (period: 2003–2023) by accessing the Medline database, Scopus and PubMed, Web of Science Embase, Cochrane Central, CINAHL, Lilacs, and searching the following keywords: "transbuccal drug delivery system" AND "neurology", "transbuccal drug delivery system" AND "neurodegenerative diseases", "transbuccal drug delivery system" AND "Parkinson's disease", "transbuccal drug delivery system" AND "Alzheimer's disease", "oral health" AND "neurodegenerative diseases", "oral health" AND "Parkinson's disease", "oral health" AND "Alzheimer's disease", "periodontal health" AND "neurodegenerative diseases", "periodontal health" AND "Parkinson's disease", "periodontal health" AND "Alzheimer's disease", "transbuccal drug delivery system" AND "oral health", "transbuccal drug delivery system" AND "periodontal health", "special care dentistry" AND "neurodegenerative diseases", "new technology in dentistry" AND "neurodegenerative diseases". Only papers in English have been selected and included after consultation between the authors.

## 3. Results

### 3.1. Transbuccal Drug Delivery Systems in AD

AD is the most common cause of dementia, and galantamine—a competitive and reversible acetylcholinesterase inhibitor—is one of the most commonly used drugs. Patients with AD suffer from swallowing problems and have low adherence to therapy. The investigational IntelliDrug system has been used to test the efficacy of Galantamine administration in vivo (Table 1). A study investigated the efficacy of a prototype IntelliDrug device in vivo in pigs, following a single administration of galantamine through the buccal mucosa, in comparison with an intravenous injection of the drug. The results suggest that transbuccal administration has the potential to generate controlled long-lasting blood levels of galantamine. Histologic analysis of the buccal mucosa did not reveal evidence of inflammation or tissue damage or significant cytologic changes. Transbuccal administration of galantamine by the IntelliDrug device proved to be an attractive, noninvasive, safe, and feasible route of administration for a sustained or controlled-release delivery approach that could maintain a steady release of the drug into systemic circulation. This mode of administration also promotes patient compliance and may make it feasible to use ultra-low doses of the drug according to tightly scheduled medications to optimize the efficacy of therapy ("chronotherapy") [64] (Table 2). However, further in vivo studies in humans are needed.

**Table 1.** Clinical features of Parkinson's disease.

| | Prodromal Stage | Early Stage | Advanced Stage |
|---|---|---|---|
| MOTOR SIGNS | \ | • Bradykinesia<br>• Rigidity<br>• Tremor | • Fluctuations<br>• Dyskinesia<br>• Dysphagia<br>• Postural Instability<br>• Freezing of Gait |
| NONMOTOR SYMPTOMS | • Constipation<br>• Sleep Disorders<br>• Depression<br>• Hyposmia | • Pain<br>• Fatigue | • Urinary Symptoms<br>• Orthostatic Hypotension<br>• Dementia<br>• Psychosis |

### 3.2. Transbuccal Drug Delivery Systems in PD

PD is a complex motor disorder due to the loss of dopaminergic neurons. Levodopa is the most frequently used therapy to restore dopaminergic transmission within the brain. While at early stages of PD, the therapeutic response could be full and effective, at later disease stages the response to levodopa could fluctuate, with alternating phases of akinesia and hyperkinesia (Table 1). Accordingly, keeping a stable level of dopamine in the brain, which implies a near-constant absorption of levodopa, is one of the main goals in the treatment of PD patients. Oral administration is not satisfactory in this perspective; elsewhere, the levodopa intestinal gel administered by the percutaneous endoscopic gastrojejunostomy is not tolerated, accepted, or admitted to all patients. In this regard, the TDSSs represent promising novel strategies that are under investigation in several trials.

#### 3.2.1. Synagile

In addition to the aforementioned new frontier initiated by the IntelliDrug system, which has not yet expressed its full potential in the context of PD, SynAgile's DopaFuse, which uses the OraFuse system to deliver levodopa noninvasively at a constant rate, is also in circulation, but for purely experimental use. The DopaFuse drug delivery system consists of a customized reusable dental device (a transparent retainer) and a prefilled disposable container that continuously releases the drug into the mouth. When worn, a carbidopa/levodopa paste is delivered very slowly into the mouth, swallowed with saliva, and absorbed through the gastrointestinal route. To store the system during meals or household hygiene, patients have to simply remove the device and lay it down in a

special case, thus interrupting the flow of medication. SynAgile is conducting a patient-based clinical study of the DopaFuse delivery system. The purpose of this study is to evaluate whether the DopaFuse system is able to reduce fluctuation in plasma levodopa levels compared to standard intermittent doses of oral LD/CD tablets given to patients. Whether the system is safe, well tolerated, and able to alleviate motor symptoms will also be evaluated [65]. To date, we have no compelling data on the current efficacy of this system.

#### 3.2.2. L-Dopa

Levodopa (L-DOPA) is the most beneficial pharmacological agent in PD and remains the gold standard. Taking advantage of the transbuccal administration, the propharmaceutical L-DOPA methyl ester hydrochloride (LDME) has been hypothesized as a good alternative method to keep plasma levels constant and to reduce unwanted effects. Several clinical studies are currently ongoing in the buccal mucosa of pigs. In detail, IntelliDrug can be used to deliver the drug in the proximity of buccal mucosa, obtaining a good bioavailability [66].

#### 3.2.3. Ropinirol

Ropinirol (ROP) is a dopamine receptor agonist molecule that is widely administered orally, subject to hepatic metabolism. The buccal mucosa is also considered an effective route for ROP administration, as reported by several trials. The results obtained from the administration of ROP discs, proposed as a new dosage form, have been evaluated. The aforementioned results show that after an ex vivo evaluation on a film with an area of 0.282 $cm^2$ and a dose of 2.29 mg, the amount of the drug, through the buccal mucosa, is closely comparable to the amount of ROP reaching the steady-state bloodstream after oral administration of 4 mg of ropinirol. Thus, a lower dose can be administered to achieve the same plasma concentration, because the hepatic metabolism is bypassed with the buccal method of administration. In addition, fluctuations in plasma concentration should be limited because buccal film administration allows rapid absorption of the drug [67–69]. According to these findings, the ROP film might improve treatment outcomes in terms of efficacy, safety, and quality of life.

**Table 2.** Trials investigating Transbuccal Drug Delivery Systems in Parkinson's Disease and Alzheimer's Disease.

| Delivery System | Drugs | In Vivo/In Vitro/Ex Vivo | Results |
|---|---|---|---|
| IntelliDrug | Galantamine | In vivo (in pigs) [64] | Positive, keeping plasma levels constant and reducing unwanted effects |
| SynAgile's DopaFuse | L-DOPA | In vivo (in humans) [65] | No hard data on the actual efficacy of this system |
| IntelliDrug | L-DOPA methyl ester hydrochloride | In vivo (in pigs) [66] | Positive, achieving and maintaining constant therapeutic blood levels for a long time |
| Discs | Ropinirole | Ex vivo [65–67] | Positive, the hepatic first-pass effect is avoided and fluctuations in plasma concentration are avoided |
| Tablets with Zydis technology | Selegiline | In vivo (in humans) [70] | Positive, bypassing presystemic metabolism and providing higher plasma concentrations and lower levels of undesirable metabolites |
| Tablets | Apomorphine | In vivo (in pigs) [71–73] | Positive, with relevant plasma levels and no significant safety issues |
| Mucoadhesive tablets | Rotigotine with hyaluronic acid and cysteine (HAC) | In vitro [74] | Positive, increasing permeation, controlling drug release and mucoadhesion |

#### 3.2.4. Selegiline/Zydis Formulation

Selegiline belongs to the category of oral monoamine oxidase B inhibitor and can be administered as a single or adjunctive therapy for the treatment of PD in various disease phases. However, oral selegiline undergoes extensive first-pass metabolism that reduces bioavailability and determines the production of amphetamine and other undesirable metabolites. In order to bypass presystemic metabolism and provide higher plasma concentrations and lower levels of undesirable metabolites, Zydis technology was applied to a selegiline tablet, which has been exploited to achieve a rapidly disintegrating dosage form with freeze-drying of the tablet, thus making it qualitatively different from conventional oral dosage forms [70]. This has been confirmed by several comparative clinical studies in patients.

#### 3.2.5. Apomorphine

Prolonged systemic administration of apomorphine by the sublingual route has proven to be a viable treatment of PD in place of subcutaneous infusions. In order to avoid hepatic metabolism, apomorphine is administered parenterally (subcutaneous injections). The disadvantages of parenteral administration are poor compliance and adherence to treatment. While the parenteral route bypasses the passage through the liver, the passage through the buccal mucosa gives greater safety, is free of discomfort and pain, is less expensive, and possesses excellent accessibility, thus, overall, increasing patient compliance. This administration through the buccal mucosa was investigated in vivo, in a porcine model. Clinically relevant plasma levels have been obtained for 8 h with a residual effect for additional hours, and no significant safety issues, such as irritative phenomena, have been found [71–73]. This study opens another avenue for clinical research of this approach in patients with PD.

#### 3.2.6. Rotigotine

One of the major problems associated with PD disease is dysphagia. Therefore, release through the mucosa is advantageous for patient compliance. A study aiming to synthesize mucoadhesive hyaluronic acid (HA) containing rotigotine for the treatment of PD has been conducted. The polysaccharide HA was chemically modified with the ethyl ester of the thiol ligand cysteine through the formation of an amide bond (HAC). HAC was assessed in terms of stability, cytotoxicity, increased permeation, controlled drug release and mucoadhesion [74]. The conclusion of this in vitro study is that HAC could be a keystone to release through the buccal mucosa in the treatment of PD.

## 4. Discussion

This review provided an overview of the potential of TDDSs, in particular for patients with AD and PD. Neurodegenerative diseases represent a major challenge for the future, because of the worldwide increase in prevalence and incidence, and the ever-higher socio-economic costs [75]. While waiting for disease-modifying treatments, the symptomatic control of motor and cognitive disturbances is the main therapeutic goal for these conditions [76]. However, because of the disease progression and growing disability, drug administration by the conventional oral route is not so easy and effective at later disease stages. For a long time in the oral cavity, drugs have been applied to solve diseases of the mouth itself. In this field, great improvements have been made in the long-term administration. Accordingly, TDDSs emerge as an excellent alternative to conventional oral administration [77,78]. Available data, indeed, show that TDDSs offer good clinical benefits in PD and AD patients, without affecting the cytoarchitecture of the mouth. Even more satisfying and encouraging are the results of the various in vivo and in vitro clinical trials of the innovative IntelliDrug and Orafuse systems. Therefore, in the future, they may become valid tools to deliver symptomatic therapy in neurodegenerative patients at later stages. The systems might improve patient compliance, which is particularly low in these individuals, also ensuring constant drug flow [79]. Likewise, the devices can help to keep

stable or even lower drug dosage, limiting the risk of side effects. Besides neurodegenerative disease, there is also evidence that TDDSs might be used for the treatment of local oral diseases, such as periodontal pockets and mucositis [80]. However, further studies are needed to confirm these encouraging but preliminary findings.

## 5. Conclusions and Future Directions

In the last years, there has been a growing interest in TDDSs, with a number of experimental trials especially dedicated to patients with neurodegenerative diseases. The initial results are encouraging and definitely demonstrate the safety of these delivery systems, thus opening the way for better therapeutic opportunities for AD and PD patients at later stages. However, research in the field has focused attention on the relevance of oral health in patients with neurodegenerative disease, as an essential condition to successfully approach novel TDDSs-based therapies. In fact, it seems clear that these patients may have poor oral hygiene with several active infectious foci and tooth loss because of the inability to perform usual daily activities, such as brushing their teeth. Accordingly, there is a need for early identification of these conditions—which seriously impact on the patient's prognosis [81,82]—and for attempting adequate preventive strategies. Neurodegenerative patients should perform regular dental checkups and receive frequent reminders for professional hygiene. Moreover, the patient's caregivers should be appropriately trained [83,84] but also dentists, social and health workers should be made aware of the importance of oral hygiene in these patients [85,86], developing preventive and rehabilitative measures aimed at ensuring a good standard of living, early targeted interventions, adequate timing for dental care, and tailored treatment plans [87–90]. All these aspects will be critical for the successful impact of the above-mentioned IntelliDrug and Orafuse systems. Moreover, it should be reminded that oral mucosa might represent a valuable source of disease biomarkers, as new studies suggest [91–94].

**Author Contributions:** Conceptualization, M.B., P.G., P.B., T.S. and A.D.F.; Methodology, M.B., P.G., T.S. and A.D.F.; Investigation M.B., P.G. and A.T.; Data Curation, M.B., P.G. and A.T.; Writing—Original Draft Preparation M.B., P.G. and A.T.; Writing—Review & Editing M.B. and P.G; Supervision A.S., M.B., P.G., P.B., T.S., M.B. and P.G. have contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** No new data were created or analyzed in this study. Data sharing is not applicable to this article.

**Acknowledgments:** We are in debt to Francesca Scaccia for English language revision and Adriano Mossa for image editing.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Soria Lopez, J.A.; González, H.M.; Léger, G.C. Alzheimer's Disease. In *Handbook of Clinical Neurology*, 3rd ed.; DeKosky, S.T., Asthana, S., Eds.; Elsevier: Boston, MA, USA, 2019; Volume 167, pp. 231–255. [CrossRef]
2. Jellinger, K.A. Parkinson's Disease. In *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders*, 2nd ed.; Wiley Blackwell Publisher: Hoboken, NJ, USA, 2011; pp. 194–223. [CrossRef]
3. Balestrino, R.; Schapira, A.H.V. Parkinson Disease. *Eur. J. Neurol.* **2020**, *27*, 27–42. [CrossRef]
4. Deng, H.; Wang, P.; Jankovic, J. The Genetics of Parkinson Disease. *Ageing Res. Rev.* **2018**, *42*, 72–85. [CrossRef]
5. Scheltens, P.; De Strooper, B.; Kivipelto, M.; Holstege, H.; Chételat, G.; Teunissen, C.E.; Cummings, J.; van der Flier, W.M. Alzheimer's Disease. *Lancet* **2021**, *397*, 1577–1590. [CrossRef]
6. Jankovic, J.; Tan, E.K. Parkinson's Disease: Etiopathogenesis and Treatment. *J. Neurol. Neurosurg. Psychiatry* **2020**, *91*, 795–808. [CrossRef]
7. Turner, R.S. Alzheimer's Disease. *Semin. Neurol.* **2006**, *26*, 499–506. [CrossRef] [PubMed]

8. Goedert, M.; Spillantini, M.G. A Century of Alzheimer's Disease. *Science* **2006**, *314*, 777–781. [CrossRef] [PubMed]
9. Mucke, L. Neuroscience: Alzheimer's Disease. *Nature* **2009**, *461*, 895–897. [CrossRef] [PubMed]
10. Lane, C.A.; Hardy, J.; Schott, J.M. Alzheimer's Disease. *Eur. J. Neurol.* **2018**, *25*, 59–70. [CrossRef] [PubMed]
11. Mumtaz, S.; Rana, J.N.; Choi, E.H.; Han, I. Microwave Radiation and the Brain: Mechanisms, Current Status, and Future Prospects. *Int. J. Mol. Sci.* **2022**, *23*, 9288. [CrossRef] [PubMed]
12. Ye, H.; Robak, L.A.; Yu, M.; Cykowski, M.; Shulman, J.M. Genetics and Pathogenesis of Parkinson's Syndrome. *Annu. Rev. Pathol.* **2023**, *18*, 95–121. [CrossRef]
13. Uwishema, O.; Onyeaka, H.; Badri, R.; Yücel, A.N.; Korkusuz, A.K.; Ajagbe, A.O.; Abuleil, A.; Chaaya, C.; Alhendawi, B.H.M.; Chalhoub, E. The Understanding of Parkinson's Disease through Genetics and New Therapies. *Brain Behav.* **2022**, *12*, e2577. [CrossRef] [PubMed]
14. Parkinson's Disease: Genetics, Pathogenesis and Emerging Therapeutics | Hindawi. Available online: https://www.hindawi.com/journals/bmri/si/426914/ (accessed on 4 March 2023).
15. Mayeux, R.; Stern, Y. Epidemiology of Alzheimer Disease. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a006239. [CrossRef]
16. Bolós, M.; Perea, J.R.; Avila, J. Alzheimer's Disease as an Inflammatory Disease. *Biomol. Concepts* **2017**, *8*, 37–43. [CrossRef] [PubMed]
17. Selkoe, D.J. Preventing Alzheimer's Disease. *Science* **2012**, *337*, 1488–1492. [CrossRef]
18. Price, D.L. New Perspectives on Alzheimer's Disease. *Annu. Rev. Neurosci.* **1986**, *9*, 489–512. [CrossRef]
19. Grillo, P.; Sancesario, G.M.; Mascioli, D.; Geusa, L.; Zenuni, H.; Giannella, E.; della Morte, D.; Mercuri, N.B.; Schirinzi, T. Constipation Distinguishes Different Clinical-Biochemical Patterns in de Novo Parkinson's Disease. *Park. Relat. Disord.* **2022**, *102*, 64–67. [CrossRef]
20. Tambasco, N.; Romoli, M.; Calabresi, P. Levodopa in Parkinson's Disease: Current Status and Future Developments. *Curr. Neuropharmacol.* **2018**, *16*, 1239–1252. [CrossRef]
21. Zhu, B.; Yin, D.; Zhao, H.; Zhang, L. The Immunology of Parkinson's Disease. *Semin. Immunopathol.* **2022**, *44*, 659–672. [CrossRef] [PubMed]
22. Chen, X.; Holtzman, D.M. Emerging Roles of Innate and Adaptive Immunity in Alzheimer's Disease. *Immunity* **2022**, *55*, 2236–2254. [CrossRef]
23. Schirinzi, T.; Grillo, P.; Di Lazzaro, G.; Zenuni, H.; Salimei, C.; Dams-O'Connor, K.; Sancesario, G.M.; Mercuri, N.B.; Pisani, A. Effects of Head Trauma and Sport Participation in Young-Onset Parkinson's Disease. *J. Neural Transm. (Vienna)* **2021**, *128*, 1185–1193. [CrossRef]
24. Schirinzi, T.; Maftei, D.; Passali, F.M.; Grillo, P.; Zenuni, H.; Mascioli, D.; Maurizi, R.; Loccisano, L.; Vincenzi, M.; Rinaldi, A.M.; et al. Olfactory Neuron Prokineticin-2 as a Potential Target in Parkinson's Disease. *Ann. Neurol.* **2023**, *93*, 196–204. [CrossRef] [PubMed]
25. Bakke, M.; Larsen, S.L.; Lautrup, C.; Karlsborg, M. Orofacial Function and Oral Health in Patients with Parkinson's Disease. *Eur. J. Oral. Sci.* **2011**, *119*, 27–32. [CrossRef] [PubMed]
26. Van Stiphout, M.A.E.; Marinus, J.; Van Hilten, J.J.; Lobbezoo, F.; De Baat, C. Oral Health of Parkinson's Disease Patients: A Case-Control Study. *Park. Dis.* **2018**, *2018*, 9315285. [CrossRef]
27. Martimbianco, A.L.C.; Prosdocimi, F.C.; Anauate-Netto, C.; dos Santos, E.M.; Mendes, G.D.; Fragoso, Y.D. Evidence-Based Recommendations for the Oral Health of Patients with Parkinson's Disease. *Neurol. Ther.* **2021**, *10*, 391. [CrossRef]
28. Hanaoka, A.; Kashihara, K. Increased Frequencies of Caries, Periodontal Disease and Tooth Loss in Patients with Parkinson's Disease. *J. Clin. Neurosci.* **2009**, *16*, 1279–1282. [CrossRef] [PubMed]
29. Verhoeff, M.C.; Koutris, M.; de Vries, R.; Berendse, H.W.; van Dijk, K.D.; Lobbezoo, F. Salivation in Parkinson's Disease: A Scoping Review. *Gerodontology* **2022**, *40*, 26–38. [CrossRef]
30. Barbe, A.G.; Deutscher, D.H.C.; Derman, S.H.M.; Hellmich, M.; Noack, M.J. Subjective and Objective Halitosis among Patients with Parkinson's Disease. *Gerodontology* **2017**, *34*, 460–468. [CrossRef]
31. Proulx, M.; de Courval, F.P.; Wiseman, M.A.; Panisset, M. Salivary Production in Parkinson's Disease. *Mov. Disord.* **2005**, *20*, 204–207. [CrossRef]
32. Friedlander, A.H.; Mahler, M.; Norman, K.M.; Ettinger, R.L. Parkinson Disease: Systemic and Orofacial Manifestations, Medical and Dental Management. *J. Am. Dent. Assoc.* **2009**, *140*, 658–669. [CrossRef]
33. Chen, Y.Y.; Fan, H.C.; Tung, M.C.; Chang, Y.K. The Association between Parkinson's Disease and Temporomandibular Disorder. *PLoS ONE* **2019**, *14*, e0217763. [CrossRef]
34. Fleury, V.; Zekeridou, A.; Lazarevic, V.; Gaïa, N.; Giannopoulou, C.; Genton, L.; Cancela, J.; Girard, M.; Goldstein, R.; Bally, J.F.; et al. Oral Dysbiosis and Inflammation in Parkinson's Disease. *J. Park. Dis.* **2021**, *11*, 619–631. [CrossRef] [PubMed]
35. Chen, C.K.; Wu, Y.T.; Chang, Y.C. Periodontal Inflammatory Disease Is Associated with the Risk of Parkinson's Disease: A Population-Based Retrospective Matched-Cohort Study. *PeerJ* **2017**, *2017*, e3647. [CrossRef] [PubMed]
36. Olsen, I. Update on Bacteraemia Related to Dental Procedures. *Transfus. Apher. Sci.* **2008**, *39*, 173–178. [CrossRef] [PubMed]
37. Ito, H.O. Infective Endocarditis and Dental Procedures: Evidence, Pathogenesis, and Prevention. *J. Med Investig.* **2006**, *53*, 189–198. [CrossRef]
38. Fiorillo, L.; Cervino, G.; Laino, L.; D'Amico, C.; Mauceri, R.; Tozum, T.F.; Gaeta, M.; Cicciù, M. Porphyromonas Gingivalis, Periodontal and Systemic Implications: A Systematic Review. *Dent. J.* **2019**, *7*, 114. [CrossRef]

39. Franciotti, R.; Pignatelli, P.; Carrarini, C.; Romei, F.M.; Mastrippolito, M.; Gentile, A.; Mancinelli, R.; Fulle, S.; Piattelli, A.; Onofrj, M.; et al. Exploring the Connection between Porphyromonas Gingivalis and Neurodegenerative Diseases: A Pilot Quantitative Study on the Bacterium Abundance in Oral Cavity and the Amount of Antibodies in Serum. *Biomolecules* **2021**, *11*, 845. [CrossRef]
40. Jeong, E.; Park, J.B.; Park, Y.G. Evaluation of the Association between Periodontitis and Risk of Parkinson's Disease: A Nationwide Retrospective Cohort Study. *Sci. Rep.* **2021**, *11*, 16594. [CrossRef]
41. Schwarz, J.; Heimhilger, E.; Storch, A. Increased Periodontal Pathology in Parkinson's Disease. *J. Neurol.* **2006**, *253*, 608–611. [CrossRef]
42. Alvarenga, M.O.P.; Frazão, D.R.; de Matos, I.G.; Bittencourt, L.O.; Fagundes, N.C.F.; Rösing, C.K.; Maia, L.C.; Lima, R.R. Is There Any Association Between Neurodegenerative Diseases and Periodontitis? A Systematic Review. *Front. Aging Neurosci.* **2021**, *13*. [CrossRef]
43. Cicciù, M. Neurodegenerative Disorders and Periodontal Disease: Is There a Logical Connection? *Neuroepidemiology* **2016**, *47*, 94–95. [CrossRef]
44. Auerbacher, M.; Gebetsberger, L.; Kaisarly, D.; Schmidmaier, R.; Hickel, R.; Drey, M. Oral Health in Patients with Neurodegenerative and Cerebrovascular Disease: A Retrospective Study. *Disabil. Rehabil.* **2022**. [CrossRef] [PubMed]
45. Rozas, N.S.; Tribble, G.D.; Jeter, C.B.; Machida, C.A.; Maier, T.J.; Said-Al-Naief, N. Oral Factors That Impact the Oral Microbiota in Parkinson's Disease. *Microorganisms* **2021**, *9*, 1616. [CrossRef] [PubMed]
46. Newadkar, U.; Khairnar, S.; Dodamani, A.; Newadkar, R. Oral Health Issues and Challenges in Parkinson's Disease. *Int. J. Nutr. Pharmacol. Neurol. Dis.* **2017**, *7*, 54. [CrossRef]
47. Auffret, M.; Meuric, V.; Boyer, E.; Bonnaure-Mallet, M.; Vérin, M. Oral Health Disorders in Parkinson's Disease: More than Meets the Eye. *J. Park. Dis.* **2021**, *11*, 1507–1535. [CrossRef] [PubMed]
48. van Vuuren, M.J.; Nell, T.A.; Carr, J.A.; Kell, D.B.; Pretorius, E. Iron Dysregulation and Inflammagens Related to Oral and Gut Health Are Central to the Development of Parkinson's Disease. *Biomolecules* **2020**, *11*, 30. [CrossRef]
49. Campisi, G.; Paderni, C.; Saccone, R.; Fede, O.; Wolff, A.; Giannola, L. Human Buccal Mucosa as an Innovative Site of Drug Delivery. *Curr. Pharm. Des.* **2010**, *16*, 641–652. [CrossRef]
50. Patel, V.F.; Liu, F.; Brown, M.B. Advances in Oral Transmucosal Drug Delivery. *J. Control. Release* **2011**, *153*, 106–116. [CrossRef] [PubMed]
51. Homayun, B.; Lin, X.; Choi, H.J. Challenges and Recent Progress in Oral Drug Delivery Systems for Biopharmaceuticals. *Pharmaceutics* **2019**, *11*, 129. [CrossRef]
52. Silvestre, A.L.P.; di Filippo, L.D.; Besegato, J.F.; de Annunzio, S.R.; Almeida Furquim de Camargo, B.; de Melo, P.B.G.; de Souze Rastelli, A.N.; Fontana, C.R.; Chorilli, M. Current Applications of Drug Delivery Nanosystems Associated with Antimicrobial Photodynamic Therapy for Oral Infections. *Int. J. Pharm.* **2021**, *592*, 120078. [CrossRef]
53. Mercadante, V.; Scarpa, E.; de Matteis, V.; Rizzello, L.; Poma, A. Engineering Polymeric Nanosystems against Oral Diseases. *Molecules* **2021**, *26*, 2229. [CrossRef]
54. Agrawal, U.; Sharma, R.; Gupta, M.; Vyas, S.P. Is Nanotechnology a Boon for Oral Drug Delivery? *Drug. Discov. Today* **2014**, *19*, 1530–1546. [CrossRef]
55. Ahuja, A.; Khar, R.K.; Ali, J. Mucoadhesive Drug Delivery Systems. *Braz. J. Pharm. Sci.* **1997**, *23*, 489–515. [CrossRef]
56. Russo, E.; Selmin, F.; Baldassari, S.; Gennari, C.G.M.; Caviglioli, G.; Cilurzo, F.; Minghetti, P.; Parodi, B. A Focus on Mucoadhesive Polymers and Their Application in Buccal Dosage Forms. *J. Drug. Deliv. Sci. Technol.* **2016**, *32*, 113–125. [CrossRef]
57. Pinto, S.; Pintado, M.E.; Sarmento, B. In Vivo, Ex Vivo and in Vitro Assessment of Buccal Permeation of Drugs from Delivery Systems. *Expert Opin. Drug Deliv.* **2020**, *17*, 33–48. [CrossRef] [PubMed]
58. Gilhotra, R.M.; Ikram, M.; Srivastava, S.; Gilhotra, N. A Clinical Perspective on Mucoadhesive Buccal Drug Delivery Systems. *J. Biomed. Res.* **2014**, *28*, 81. [CrossRef] [PubMed]
59. Pathan, S.; Iqbal, Z.; Sahani, J.; Talegaonkar, S.; Khar, R.; Ahmad, F. Buccoadhesive Drug Delivery Systems–Extensive Review on Recent Patents. *Recent Pat Drug Deliv. Formul.* **2008**, *2*, 177–188. [CrossRef]
60. Grillo, P.; Basilicata, M.; Schirinzi, T. Alpha-Klotho in Parkinson's Disease: A Perspective on Experimental Evidence and Potential Clinical Implications. *Neural Regen. Res.* **2022**, *17*, 2687. [CrossRef]
61. Moscicka, A.E.; Czarnecka, K.; Ciach, T. IntelliDrug Implant for Medicine Delivery in Alzheimer's Disease Treatment. *Macromol. Symp.* **2007**, *253*, 134–138. [CrossRef]
62. Scholz, O.A.; Wolff, A.; Schumacher, A.; Giannola, L.I.; Campisi, G.; Ciach, T.; Velten, T. Drug Delivery from the Oral Cavity: Focus on a Novel Mechatronic Delivery Device. *Drug. Discov. Today* **2008**, *13*, 247–253. [CrossRef]
63. Srivastava, N.; Aslam, S. Recent Advancements and Patents on Buccal Drug Delivery Systems: A Comprehensive Review. *Recent Pat Nanotechnol.* **2022**, *16*, 308–325. [CrossRef]
64. de Caro, V.; Giandalia, G.; Siragusa, M.G.; Paderni, C.; Campisi, G.; Giannola, L.I. Evaluation of Galantamine Transbuccal Absorption by Reconstituted Human Oral Epithelium and Porcine Tissue as Buccal Mucosa Models: Part I. *Eur. J. Pharm. Biopharm.* **2008**, *70*, 869–873. [CrossRef]
65. Assessing the Pharmacokinetics, Safety, Tolerability and Efficacy of Continuous Oral Levodopa Via the DopaFuse® Delivery System in Parkinson's Disease Patients—Full Text View—ClinicalTrials.Gov. Available online: https://clinicaltrials.gov/ct2/show/NCT04778176 (accessed on 3 January 2023).

66. Scaturro, A.L.; de Caro, V.; Campisi, G.; Giannola, L.I. Potential Transbuccal Delivery of L-DOPA Methylester Prodrug: Stability in the Environment of the Oral Cavity and Ability to Cross the Mucosal Tissue. *Drug. Deliv.* **2016**, *23*, 2355–2362. [CrossRef] [PubMed]
67. de Caro, V.; Giandalia, G.; Siragusa, M.G.; Sutera, F.M.; Giannola, L.I. New Prospective in Treatment of Parkinson's Disease: Studies on Permeation of Ropinirole through Buccal Mucosa. *Int. J. Pharm.* **2012**, *429*, 78–83. [CrossRef]
68. Lai, K.L.; Fang, Y.; Han, H.; Li, Q.; Zhang, S.; Li, H.Y.; Chow, S.F.; Lam, T.N.; Lee, W.Y.T. Orally-Dissolving Film for Sublingual and Buccal Delivery of Ropinirole. *Colloids Surf. B Biointerfaces* **2018**, *163*, 9–18. [CrossRef]
69. di Prima, G.; Campisi, G.; de Caro, V. Amorphous Ropinirole-Loaded Mucoadhesive Buccal Film: A Potential Patient-Friendly Tool to Improve Drug Pharmacokinetic Profile and Effectiveness. *J. Pers. Med.* **2020**, *10*, 242. [CrossRef] [PubMed]
70. Lew, M.F. Selegiline Orally Disintegrating Tablets for the Treatment of Parkinson's Disease. *Expert. Rev. Neurother.* **2005**, *5*, 705–712. [CrossRef] [PubMed]
71. Bilbault, T.; Taylor, S.; Walker, R.; Grundy, S.L.; Pappert, E.J.; Agro, A. Buccal Mucosal Irritation Studies of Sublingual Apomorphine Film (APL-130277) in Syrian Golden Hamsters. *Ther. Deliv.* **2016**, *7*, 611–618. [CrossRef]
72. Itin, C.; Komargodski, R.; Domb, A.J.; Hoffman, A. Controlled Delivery of Apomorphine Through Buccal Mucosa, Towards a Noninvasive Administration Method in Parkinson's Disease: A Preclinical Mechanistic Study. *J. Pharm. Sci.* **2020**, *109*, 2729–2734. [CrossRef]
73. Itin, C.; Komargodski, R.; Barasch, D.; Domb, A.J.; Hoffman, A. Prolonged Delivery of Apomorphine Through the Buccal Mucosa, Towards a Noninvasive Sustained Administration Method in Parkinson's Disease: In Vivo Investigations in Pigs. *J. Pharm. Sci.* **2021**, *110*, 1824–1833. [CrossRef]
74. Laffleur, F.; Wagner, J.; Barthelmes, J. A Potential Tailor-Made Hyaluronic Acid Buccal Delivery System Comprising Rotigotine for Parkinson's Disease? *Futur. Med. Chem.* **2015**, *7*, 1225–1232. [CrossRef]
75. Logroscino, G.; Tortelli, R. Epidemiology of Neurodegenerative Diseases. *Imaging Neurodegener. Disord.* **2015**, 3–19. [CrossRef]
76. Do, C.B.; Jaiswal, M.S.; Jang, Y.S.; Kim, U.K.; Kim, G.C.; Hwang, D.S. Non-Thermal Plasma Directly Accelerates Neuronal Proliferation by Stimulating Axon Formation. *Sci. Rep.* **2022**, *12*, 15868. [CrossRef]
77. Birudaraj, R.; Mahalingam, R.; Li, X.; Jasti, B.R. Advances in Buccal Drug Delivery. *Crit. Rev. Ther. Drug Carr. Syst.* **2005**, *22*, 295–330. [CrossRef] [PubMed]
78. Şenel, S.; Rathbone, M.J.; Cansz, M.; Pather, I. Recent Developments in Buccal and Sublingual Delivery Systems. *Expert. Opin. Drug. Deliv.* **2012**, *9*, 615–628. [CrossRef] [PubMed]
79. Kalia, L.V.; Lang, A.E. Parkinson's Disease. *Lancet* **2015**, *386*, 896–912. [CrossRef] [PubMed]
80. Schwach-Abdellaoui, K.; Loup, P.J.; Vivien-Castioni, N.; Mombelli, A.; Baehni, P.; Barr, J.; Heller, J.; Gurny, R. Bioerodible Injectable Poly(Ortho Ester) for Tetracycline Controlled Delivery to Periodontal Pockets: Preliminary Trial in Humans. *AAPS PharmSci* **2002**, *4*, 20. [CrossRef]
81. Dental Management of Parkinson's Disease: A Case Report—ProQuest. Available online: https://www.proquest.com/openview/69ede58a766cb511b9d77a2100e83242/1?pq-origsite=gscholar&cbl=41679 (accessed on 5 February 2023).
82. Watanabe, Y.; Arai, H.; Hirano, H.; Morishita, S.; Ohara, Y.; Edahiro, A.; Murakami, M.; Shimada, H.; Kikutani, T.; Suzuki, T. Oral Function as an Indexing Parameter for Mild Cognitive Impairment in Older Adults. *Geriatr. Gerontol. Int.* **2018**, *18*, 790–798. [CrossRef]
83. Spurthi, S.; Sridharan, S.; Hosadurga, R.; Rao, R.J.; Prabhu, S.; Pal, P.K.; Kamble, N.; Rakesh, K.; Kumar, A. Effectiveness of Oral Hygiene Educational Interventional Programs on Participants with Parkinson's Disease: A Randomized Controlled Study. *Quintessence Int.* **2023**. [CrossRef]
84. Baram, S.; Karlsborg, M.; Bakke, M. Improvement of Oral Function and Hygiene in Parkinson's Disease: A Randomised Controlled Clinical Trial. *J. Oral Rehabil.* **2020**, *47*, 370–376. [CrossRef]
85. Moorhouse, B. Understanding the Impact of Parkinson's Disease on Oral Health. *Dent. Nurs.* **2021**, *17*, 184–187. [CrossRef]
86. Pullishery, F. Oral Health-Related Quality of Life in Patients with Parkinson's Disease Wearing Fixed Partial Dentures—A Prospective Study. *Park. Relat. Disord.* **2016**, *22*, e62–e63. [CrossRef]
87. Pereira, P.A.B.; Aho, V.T.E.; Paulin, L.; Pekkonen, E.; Auvinen, P.; Scheperjans, F. Oral and Nasal Microbiota in Parkinson's Disease. *Park. Relat. Disord.* **2017**, *38*, 61–67. [CrossRef] [PubMed]
88. Nicholson, J.S.; Landry, K.S. Oral Dysbiosis and Neurodegenerative Diseases: Correlations and Potential Causations. *Microorganisms* **2022**, *10*, 1326. [CrossRef] [PubMed]
89. Farrow-Hamblen, A. Prostheses in Parkinson's Disease. *Br. Dent. J.* **2019**, *227*, 329. [CrossRef]
90. Rajeswari, C.L. Prosthodontic Considerations in Parkinson's Disease. *People's J. Sci. Res.* **2010**, *3*, 45–47.
91. Farah, R.; Haraty, H.; Salame, Z.; Fares, Y.; Ojcius, D.M.; Said Sadier, N. Salivary Biomarkers for the Diagnosis and Monitoring of Neurological Diseases. *Biomed. J.* **2018**, *41*, 63–87. [CrossRef] [PubMed]
92. Swarbrick, S.; Wragg, N.; Ghosh, S.; Stolzing, A. Systematic Review of MiRNA as Biomarkers in Alzheimer's Disease. *Mol. Neurobiol.* **2019**, *56*, 6156–6167. [CrossRef]

93. Elangovan, A.; Venkatesan, D.; Selvaraj, P.; Pasha, M.Y.; Babu, H.W.S.; Iyer, M.; Narayanasamy, A.; Subramaniam, M.D.; Valsala Gopalakrishnan, A.; Kumar, N.S.; et al. MiRNA in Parkinson's Disease: From Pathogenesis to Theranostic Approaches. *J. Cell. Physiol.* **2023**, *238*, 329–354. [CrossRef]
94. Li, S.; Lei, Z.; Sun, T. The Role of MicroRNAs in Neurodegenerative Diseases: A Review. *Cell Biol. Toxicol.* **2022**, *39*, 53–83. [CrossRef]