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Review

Absorption of Vitamin B12 in Older Adults: Advances and Challenges in Sublingual Administration

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Abstract

The aim of this review is to analyze current routes for the administration and absorption of vitamin B12 in older adults, with a special focus on the sublingual route using orodispersible films, and evaluate the advances, materials, and challenges associated with this method of administration. Thus, the review aims to provide an updated overview of safe and effective alternatives for preventing and treating vitamin B12 deficiency in this age group. Vitamin B12 deficiency predominantly affects older adults. After the age of 70, absorption decreases, and deficiency occurs most frequently due to age-related gastric atrophy, decreased gastric acid production, reduced intrinsic factor secretion, and inadequate dietary vitamin B12 intake. This narrative review examines traditional and current treatments for vitamin B12 administration in older adults, with a focus on sublingual administration (SL) via orodispersible films (ODFs) to enhance absorption, adherence, and accessibility. SL vitamin B12 bioavailability, advantages versus disadvantages, ODF formulations (polymers such as pregelatinized starch, HPMC, and chitosan), and pharmaceutical process challenges (solvent casting and hot-melt extrusion) were explored in the reviewed in vitro and in vivo studies. According to the collected evidence, the sublingual route appears to offer rapid absorption directly into the bloodstream, with efficacy comparable to/superior to intramuscular (IM)/oral (OP) routes of administration, representing a patient-centered innovation for older adults that overcomes painful treatments and gastrointestinal/swallowing barriers. Future longitudinal clinical trials should validate long-term efficacy, standardize materials, and scale up to viable industrial production, addressing issues related to chemical stability and polypharmacy.

Keywords: elderly adults; vitamin B12; sublingual administration; intramuscular administration; oral administration; orodispersible films; bioavailability

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1. Introduction

Aging is a normal process that occurs during a person's life cycle. By 2050, 22% of the global population will be over 60, and 426 million people will be 80 or older [1]. Considering this demographic shift, it is crucial to comprehend the physiological changes in the gastrointestinal (GI) system that occur during aging [2,3]. These changes can compromise GI function, contributing to the risk of malnutrition. Loss of enteric neurons and interstitial Cajal cells affects GI motility, causing slower gastric emptying and altered intestinal transit. At the same time, there is an increase in gastric pH due to reduced acid secretion, in addition to degeneration and shortening of intestinal villi, which reduces the absorptive surface area

and increases the risk of malnutrition in the geriatric population [3,4]. For example, vitamin B12 (B12) absorption decreases, and deficiency occurs most frequently in older individuals (after age 70) due to age-related gastric atrophy, decreased gastric acid production, reduced intrinsic factor secretion, and inadequate dietary vitamin B12 intake [4,5]. The use of drugs like proton pump inhibitors and histamine H2 receptor antagonists has been associated with low vitamin B12 levels and deficiency. This is due to decreased gastric acid secretion in the stomach and the fact that vitamin B12 must be released from dietary proteins by gastric enzymes that require hydrochloric acid (HCl) [6]. Metformin use has also been associated with decreased serum vitamin B12 levels, defined as <400 pg/mL, depending on both time and dose, with the most significant risk of deficiency associated with prolonged use and high doses of the drug [7].

The Recommended Dietary Allowance (RDA) for vitamin B12 is based on the amount required for maintaining hematological status and normal serum values. The RDA for adults is 2.4 μg/day of vitamin B12. Severe deficiency is characterized by megaloblastic anemia and neurological changes, including cognitive loss, sensory disorders, and peripheral neuropathy, subacute combined degeneration of the spinal cord, psychiatric disorders, hearing loss, bone diseases, and macular degeneration, reflecting the importance of vitamin B12 in maintaining normal neurological, hematological, and metabolic function, especially in the elderly population [8,9].

2. Methods

2.1. Search Strategy

Searches were conducted in the PubMed, Web of Science, Scopus, Google Scholar, and Consensus AI databases. Review articles and original research were reviewed, beginning with a search of publications from the last five years. To improve the quality and quantity of the relevant literature, a second review was conducted using articles from 1999 to 2024. The following keywords and concepts were used for the search: vitamin B12; bioavailability; elderly adults; gastrointestinal absorption of vitamin B12; sublingual administration; intramuscular administration; oral administration; orodispersible films. Physicochemical characterization studies (e.g., FTIR, DSC) and clinical trials evaluating bioavailability and adherence in populations with comorbidities were prioritized, and only primary literature articles were included.

2.2. Methodology and Use of Artificial Intelligence Tools

In addition to traditional databases, the AI-powered search engine Consensus was utilized during the literature search to streamline the extraction of key findings and ensure comprehensive bibliographic coverage.

During the drafting phase, Gemini 3 Flash (Paid tier) and free version of Perplexity AI was used (www.perplexity.ai, open access) were employed as assistants to enhance grammatical coherence, stylistic clarity, and the manuscript's logical structure. Furthermore, data synthesis for tables and the design of the graphical abstract were supported by Gemini 3 Flash (Paid tier) and ChatGPT (OpenAI, version GPT-5, 2026). All content generated or refined by these tools underwent rigorous supervision, verification, and critical editing to ensure scientific accuracy and originality.

3. Innovative Approach for Vitamin B12 Delivery in Older Adults

3.1. Conventional Treatments for Vitamin B12 Deficiency

Vitamin B12 deficiency is commonly treated or prevented through monthly intramuscular (IM) or oral (OP) routes. Several studies have compared the effectiveness of IM and OP vitamin B12 treatments in older adults; however, in terms of adherence to treat-

ment, *patients' preferences can be a decisive factor for determining the administration route* [10]. According to Obeid et al., 2024 [11], in cases of patients without severe malabsorption, long-term management with a high dose of OP vitamin B12 (1000–2000 mcg daily) is effective and may be considered as an alternative to injections due to improved convenience and adherence. Meanwhile, IM injections of vitamin B12 are often expensive, invasive, and require trained healthcare personnel [12,13]. A study conducted by Lacombe et al., 2024 [14], showed that in 23 of 26 patients with pernicious anemia, an OP vitamin B12 supplementation of 1000 µg/d improved deficiency and normalized serum levels of vitamin B12 after one month of OP supplementation, with sustained improvement over 12 months. A randomized trial in 283 patients ≥65 years with vitamin B12 deficiency found that oral (1 mg/day) and IM administration were highly effective at normalizing vitamin B12 serum levels at 8 weeks (>90% in both groups). At 52 weeks, IM was slightly more effective in normalizing vitamin B12 levels (80.4%) when compared with the OP route (73.6%). The difference in adherence to treatment was only 4.2% in favor of the OP route; however, 83.4% of patients preferred this route due to convenience [10]. However, OP administration has low bioavailability (1–5%) and is not a suitable option in patients with absorption disorder or who are unable to take oral medication [15,16]. This treatment is usually administered in tablet form, which can be difficult for older adults to swallow or chew, affecting 20–50% of this population [17–19].

Intranasal (IN) administration may be an effective and safe alternative for restoring vitamin B12 levels in elderly people. Tillemans et al., 2024 [20], studied 60 vitamin-B12-deficient individuals over 65 years randomly assigned to a daily dose of vitamin B12 for 14 days followed by weekly administration (loading dose) or administration every 3 days (no loading dose) for 90 days, concluding that the combination of loading dose and no loading dose seemed the most appropriate dosage regimen for the treatment of vitamin B12 deficiency in elderly patients. Although IN administration might be a convenient alternative to IM and OP, due to the limited knowledge about this route and the possible variability in absorption affected by nasal pathology or improper use, the suitable loading dose remains uncertain. Table 1 provides a multidimensional comparison of IM, OP, and IN administration, summarizing the main methodological characteristics, main outcomes, advantages, and disadvantages associated with each administration route used (IM, OP, and IN), as well as the limitations inherent in each study. Overall, while the IM route remains the gold standard for long-term efficacy, the S and OP routes show equivalent efficacy in normalizing serum levels in short periods, with a significantly higher patient preference due to their non-invasive nature.

Table 1. Comparison of vitamin B12 administration routes in older adults.

Study	Study Population	Administration Route/Intervention	Main Outcomes	Route Advantages/ Disadvantages	Study Limitations
Sanz-Cuesta et al. (2020) [10].	283 patients aged ≥65 years with vB12 deficiency.	OP versus IM.	At 8 weeks, OP administration was noninferior to IM administration. At 52 weeks, a slight difference favored IM (80.4% vs. 73.6% normalization for OP), but the OP route remained comparable.	OPA: High patient preference (83.4%). Avoids injections; lower risk in patients with coagulation disorders. OPD: Slightly lower long-term normalization rate (52 weeks) vs. IM. IMA: Slightly higher long-term maintenance efficacy. IM D: Less preferred by patients and higher dropout rate.	The study design did not allow patient blinding. High dropout rates at 52 weeks (common in pragmatic trials). Higher data loss in the IM arm.

Table 1. *Cont.*

Study	Study Population	Administration Route/Intervention	Main Outcomes	Route Advantages/ Disadvantages	Study Limitations
Lacombe et al. (2024) [14].	26 patients aged 18 and older, with vB12 deficiency secondary to PA.	OP (Cyanocobalamin 1000 µg/day).	OP supplementation was highly effective in correcting vB12 deficiency in PA patients. 88.5% of patients achieved non-deficient status after 1 month. Improvement was sustained over 12 months.	OPA: Highly effective even with compromised absorption (PA). OPD: Clinical adoption may be limited by traditional use of IM and historical skepticism about OP efficacy in PA.	Open-label study (no blinding). Lacked a comparator group (e.g., IM route). Limited sample size (26 patients).
Tillemans et al. (2024) [20].	60 patients aged ≥65 years with vB12 deficiency.	IN (comparison of two dosing regimens).	Both dosing regimens were effective and adequate for replenishing and sustaining vB12 levels in elderly patients. The loading dose regimen resulted in the fastest increase.	INA: Convenient and safe, avoiding IM route drawbacks (pain, risk of infection/bruising, difficulty of self-administration in elderly people). IND: Optimal long-term maintenance regimen (loading vs. constant dose) requires further definition.	Recruitment challenges and difficulty completing the 90-day period. The study lacked a comparison with IM or OP routes.
Delpre et al. (1999) [21].	18 consecutive patients with cobalamin deficiency (mean age 48.1, range 23–80).	SL (2000 µg/day) for 7–12 days (loading phase).	Rapid restoration/ normalization of serum cobalamin concentration in all patients. Mean serum vB12 increased ~4-fold (from 127.9 pg/mL to 515.7 pg/mL).	SLA: Effective, safe, and convenient treatment. Preferred over IM injections. SLD: Evaluation was limited to the short-term loading phase (7–12 days), which precluded conclusions on long-term maintenance efficacy.	Prospective open-label study. Small sample size (n = 18). Short-term assessment (loading phase only).
Sharabi et al. (2003) [22].	30 subjects with low serum cobalamin concentrations (<138 pmol/L).	SL (500 µg/day) vs. OP (500 µg/day) vs. OP B-Complex.	A 500 µg dose administered via SL or OP routes is effective in correcting the deficiency. No significant difference in serum vB12 levels was found between the vB12 groups at 4 weeks.	SL/OPA: Both routes are equally effective, overcoming IM disadvantages (pain, difficulty, cost). SL/OP: Efficacy confirmation is based on short-term follow-up (only 4 weeks), limiting long-term stability assessment.	Small sample size (n = 30). Short follow-up (4 weeks).
Bensky et al. (2019) [23].	4281 patients older than 18 years with vitamin B12 deficiency.	SL vs. IM (retrospective comparison).	SL treatment was significantly superior to IM in restoring serum vB12 levels (higher mean increase, $p < 0.001$). SL is sufficient and superior to IM.	SLA: Superior to IM, overcomes injection challenges, and is suggested as a first-line option. SLD: Efficacy comparison was based only on serum vB12; functional markers (MMA/HCy) were not measured to confirm route superiority.	Retrospective analysis. Functional metabolites (MMA, HCy) could not be measured. Etiology and age/gender were not addressed.

Table 1. *Cont.*

Study	Study Population	Administration Route/Intervention	Main Outcomes	Route Advantages/ Disadvantages	Study Limitations
Del Bo' et al. (2019) [24].	40 vegan and vegetarian subjects with marginal vB12 deficiency, Ld aged 43 ± 12 and Hd aged 42 ± 13	SL (Ld, 350 µg/week) vs. (Hd, 2000 µg/week).	Both Ld and Hd supplements restored adequate serum concentrations and improved metabolic markers (HoloTC ↑, MMA/HCy ↓). No difference in efficacy was detected between the two doses.	SLA: Simple supplementation method, a low dose is sufficient. SLD: Lack of post-supplementation follow-up to assess long-term stability.	No true placebo group (ethical reasons). Lack of post-supplementation follow-up.

Decrease: ↓ high dose (Hd); homocysteine (HCy); holotranscobalamin (HoloTC); increase ↑; intramuscular advantage (IMA); intramuscular disadvantage (IMD); intranasal (IN); intranasal advantage (INA); intranasal disadvantage (IND); intramuscular (IM); low dose (Ld); methylmalonic acid (MMA); oral (OP); oral advantage (OPA); oral disadvantage (OPD); pernicious anemia (PA); sublingual (SL): sublingual advantage (SLA): sublingual disadvantage (SDA); vitamin B12 (vB12).

Depending on the supplementation route, the treatment option may depend on individual preference or specific medical conditions, such as absorption issues or difficulty swallowing. In this regard, sublingual (SL) vitamin B12 delivery via orodispersible films (ODFs) is a novel, convenient, and non-invasive method, offering rapid disintegration in the mouth and ease of administration, especially for populations with swallowing difficulties.

3.2. Advantages of Sublingual Supplementation of Vitamin B12

The sublingual (SL) route is a novel form of vitamin B12 treatment that offers several advantages compared to conventional administration (OP and IM treatments), including convenience, safety, potential for good adherence, and reduced cost [25].

The administration of compounds via the SL route is highly effective, as they are rapidly absorbed through blood vessels and directly enter the bloodstream [26]. When chemical compounds come into contact with the mucous membrane under the tongue, they diffuse through it because of the connective tissue beneath the thin epithelium that contains a profusion of capillaries. The compounds diffuse into them and enter the venous circulation [27]. For vitamin B12, the SL veins allow for bypassing the complex vitamin B12 absorption process in the GI system and directly reach the SL bloodstream [28]. Vitamin B12 absorption route was early tested by Delpre et al., 1999 [21], where 18 patients (mean age 48.1 years) with cobalamin deficiency (defined as serum cobalamin lower than 200 pg/mL) were treated with a daily doses of 2000 µg of SL cobalamin for 7–12 days, resulting in an increase in cobalamin serum concentration as much as four-fold compared with pretreatment serum concentration, providing rapid restoration of serum cobalamin. Sharabi et al. (2003) [22] compared the efficacy of 500 mg of cobalamin administered in an SL tablet and an OP preparation for 8 weeks in 30 subjects with mild vitamin B12 deficiency. The results showed that cobalamin concentrations returned to the normal range within 4° weeks of treatment and were maintained after 8 weeks of treatment, demonstrating that SL and OP administration were equally effective in correcting vitamin B12 deficiency. Del Bo et al. (2019) [24] evaluated the ability of two different doses of SL vitamin B12 tablets to improve vitamin B12 status in forty vegans and vegetarians with marginal deficiency, randomly assigned into two groups for a 12-week period. One group received the low dose (*Ld*; 50 µg/day, 350 µg/week), while the control received the high dose (*Hd*; single dose of 2000 µg/week). Both supplementation strategies successfully achieved adequate vitamin B12 serum concentrations. In another study conducted by

Bensky et al. (2019) [23], computerized pharmacy records from the Maccabi Health Service (MHS), Israel, of patients aged 18 years and older who were prescribed vitamin B12 via IM injection (1 mg/mL) or SL tablets (1 mg of cyanocobalamin, dextrose, croscarmellose, Na and Ca stearate) were retrospectively analyzed. The SL route was more effective than IM in elevating vitamin B12 levels (OR 1.85). Furthermore, the SL preparation was also significantly more effective in elevating vitamin B12 (>300 ng/L) in patients with low vitamin B12 levels (<300 ng/L) than IM (OR 2.7). Finally, Abdelwahab et al. (2024) [25] conducted a systematic review and network meta-analysis to evaluate the efficacy of IM, OP, and SL vitamin B12 administration. The results showed that all three routes can increase vitamin B12 levels without significant clinical differences. However, considering patient tolerance and the advantages and disadvantages of each route, the SL route is preferred over the IM and OP routes, for example, in people with swallowing difficulties.

In this regard, ODFs are an innovative alternative delivery form for the SL absorption of active pharmaceutical ingredients or food supplements. They consist of a water-soluble polymeric film that moisturizes quickly, adhering and dissolving immediately when placed on the tongue or the oral cavity (e.g., buccal, palatal, gingival, lingual, or sublingual), with no need for water or chewing [29–31]. ODFs offer advantages in terms of patient adherence, acceptability, and ease of administration, making them a particularly attractive option for improving treatment adherence in older adults [32].

In summary, the SL route using ODFs may represent a therapeutic alternative that overcomes critical gastrointestinal barriers associated with aging, such as gastric atrophy, increased luminal pH, and reduced intrinsic factor secretion [3–5]. By bypassing first-pass hepatic metabolism and overcoming swallowing difficulties that affect 20% to 50% of the geriatric population [17–19,29], these devices allow the compound to be delivered directly into the bloodstream, improving treatment adherence and reducing reliance on invasive and costly procedures, such as IM injections.

3.3. Synthesis of Orodispersible Films

Typical ODFs include one or more bioactive/therapeutic compounds, comprising approximately 30% of the total film mass, plus film-forming agents (backbone of the films), which constitute approximately 40% to 50% of the total film mass. Plasticizers that improve mechanical properties are also incorporated, reaching up to 20% *w*/*w* of the polymer's dry weight [33,34]. Film-forming agents, plasticizers, and other additives used as flavorings and sweeteners must be inert, food-grade, or approved for use in OP formulations and must belong to the "generally considered safe" category [19].

ODFs are typically produced using solvent casting, hot-melt extrusion, electrostatic spinning, inkjet, or flexographic printing [19]. In the solvent casting method, the polymer and the active ingredient are dissolved or dispersed in a solvent, and a film is formed by solvent evaporation [33].

Polymers that form ODFs must be non-toxic, highly hygroscopic, and exhibit a high capacity for disintegration [33,35]. Various polymers have been employed in film synthesis, including polyvinyl alcohol, polyvinylpyrrolidone, maltodextrin, microcrystalline cellulose, hydroxypropyl methylcellulose (HPMC), chitosan, gums, and modified starch, or blends thereof. For example, HPMC can enhance the flexibility and mechanical properties of natural polymers, such as starch, which exhibit rapid disintegration in the oral cavity but poor mechanical properties [34,36].

3.4. Orodispersible Films: Innovation in Sublingual Vitamin B12 Delivery

Oral thin films are polymeric films that rapidly hydrate and adhere to the oral mucosa, disintegrating and releasing bioactive molecules. There are two types of oral thin films:

oral mucosal films for transmucosal administration of substances and orodispersible films (ODFs) [34]. Specifically, ODFs are thin, mechanically resistant, and flexible polymeric films designed to rapidly dissolve or disintegrate in the oral cavity [37,38]. ODFs have been widely used to deliver drugs, thus facilitating the treatment of various diseases [39]. ODFs possess several advantages in terms of delivery of nutraceutical compounds (plant extracts, bioactive molecules, vitamins, minerals, and protein/peptides), such as gastrointestinal and first-pass hepatic metabolism bypassing with rapid onset of action, ease of administration, rapid disintegration/absorption, accurate dosing, increased stability, portability, discretion, dose flexibility, and user acceptance [29,34,40]. From a nutritional perspective, this strategy has already been utilized to deliver various nutrients, including iron [41,42], vitamin D [43–45], vitamin C [46,47], and vitamin B12 [48].

For instance, in the treatment of vitamin B12 deficiency, Mohamad et al. (2017) [49] synthesized and evaluated a vitamin-B12-loaded mucoadhesive buccal film as a non-invasive alternative to the IM route for treating vitamin B12 deficiency. Film composition consisted of chitosan used as a natural retarding polymer, polyvinyl alcohol (PVA) as the film-forming agent, and glycerol and PEG 400 as plasticizers. A mucoadhesive-optimized formulation of 1.24% *w*/*w* cyanocobalamin, 1.86% *w*/*w* chitosan, and 93.16% *w*/*w* PVA displayed acceptable mechanical and mucoadhesion properties, with a moisture content of 3.2% and a drug release of 98.59% in 40 min. Fourier transform infrared spectroscopy (FTIR) analysis revealed drug–polymer interactions, while differential scanning calorimetry (DSC) indicated molecular dispersion of cyanocobalamin in an amorphous state within the polymers. In vivo pharmacokinetics studies in Albino New Zealand rabbits demonstrated that the bioavailability of cyanocobalamin from the optimized formulation was 1.5 times higher than that of the IM route, suggesting that buccal films may be an effective and non-invasive alternative to IM injection. This complete amorphization of vitamin B12 within the polymers improved the vitamin's solubility and dissolution rate, facilitating its rapid in vitro release (98.59% in 40 min) and absorption. Furthermore, the in vivo studies indicated that the optimized film showed 1.5 times greater bioavailability than the IM injection, reflecting sustained release, attributable to increased mucosal permeability and mucoadhesive retention, enhanced by the amorphous form.

Another study performed by Suryawanshi et al. (2021) [48] developed and optimized the synthesis of vitamin-B12-loaded ODFs by the hot-melt extrusion (HME) method using Soluplus® (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer) as a film-forming agent and glycerin and menthol as plasticizer agents, and compared the pharmacokinetics of vitamin-B12-loaded ODFs and a commercial orally disintegrating strip in New Zealand White rabbits. The films obtained showed complete disintegration and dissolution within less than 10 min. The optimized ODFs, analyzed by scanning electron microscopy (SEM) and atomic force microscopy (AFM), revealed a uniform surface distribution of cyanocobalamin. Raman spectroscopy confirmed the stability of the drug during HME and long-term stability studies indicated that the ODFs did not undergo appreciable physicochemical changes over a period of up to six months. Finally, pharmacokinetic studies in vivo demonstrated that the optimized ODFs were bioequivalent to the commercial strip, as evidenced by similar plasma concentration–time profiles. The optimization process demonstrated that the major factors influencing mechanical properties, disintegration time, in vitro dissolution, and ex vivo permeation rate were the Soluplus®, glycerine, and menthol concentrations. In this research, the critical factors that directly influenced the film's flexibility and the rate of drug release were the polymer and plasticizer concentrations. Another critical factor was the cyanocobalamin absorption. As a class III (BCS) molecule (high solubility and low permeability), the inclusion of menthol in the film structure acts as a permeation enhancer, increasing the fluidity of mucous membranes and facilitating

more efficient drug penetration across the epithelial barrier than in a conventional solution. Furthermore, absorption is enhanced because the film's large surface area provides greater contact with the oral mucosa, allowing for rapid absorption and partially avoiding first-pass metabolism and gastric degradation.

These studies highlight the importance of the polymers used to synthesize ODFs and the drug to be administered. It is essential that such films disintegrate rapidly upon contact with the mucosa to ensure immediate capillary absorption. This would represent an advantage for the elderly population, which has reduced salivary secretion (xerostomia) and an aging digestive system, characterized by increased gastric pH and a reduced intrinsic factor.

Table 2 details the technical formulations of the ODFs and summarizes the main outcomes of the in vivo and in vitro experimental models. The key data on the relationship between polymer composition and disintegration times, dissolution, or bioavailability are presented in the main outcomes of each study.

Table 2. Experimental in vivo and in vitro release models of vitamin B12, route of administration, and film composition.

Study	Experimental Model/Participants	Type of Film Administration	Composition of the Films	Main Outcomes
Mohamad et al. (2017) [49].	In vitro: Mucoadhesion properties (Mucin adhesion) and release (USP Type I (Basket) apparatus). In vivo: Animal Model (New Zealand Albino Rabbits) for bioavailability and pharmacokinetics (compared to IM injection).	Optimized buccoadhesive films formula	Main Components: Chitosan (polymer), PVA (primary film-forming polymer), glycerin or PEG 400 as plasticizers, and propylene glycol as a penetration enhancer. Prepared by solvent casting.	1.5-fold increase in bioavailability from the optimized film (F11) compared to IM injection.
Suryawanshi et al. (2021) [48].	In vitro: Evaluation of mechanical properties, disintegration time, and USP II (Paddle apparatus) for dissolution. Ex vivo: Franz Diffusion Cell with chicken pouch mucosa for permeation. In vivo: Animal Model (New Zealand Albino Rabbits) for pharmacokinetics.	ODFs	Main Components: Soluplus® (film-forming polymer), glycerine (plasticizer), menthol (cooling agent, glycol, and enhancer). Processed by hot-melt extrusion.	Hot-melt extruded films: Complete dissolution within 10 min. Similar in vivo bioavailability between optimized ODFs and the commercial reference film.
van Dijkhuizen-Radersma et al. (2002) [50].	In vitro: Swelling, degradation, and controlled permeability/release studies of vB12 in copolymer matrices (determination of D).	PEGT/PBT film matrices for studying the controlled release system	Main Components: PEGT/PBT multiblock copolymers. The key variable was the PEG segment length (300 to 4000 g/mol).	Release could be tailored from 1 day to over 12 weeks of constant release. Films with 300 g/mol PEG segments followed zero-order kinetics (constant).
Patel et al. (2021) [51].	In vitro: Dissolution profile (USP Type I (Basket) apparatus). Drug Release Kinetics Analysis Using Mathematical Models.	Optimized the ODFs' formula	Main Components: Dehydrated Banana Starch and Gelatin (film-forming and binding polymers). Prepared by solvent casting.	The best-fitting model for drug release was first-order (R^2 = 0.9701).

Table 2. *Cont.*

Study	Experimental Model/Participants	Type of Film Administration	Composition of the Films	Main Outcomes
Polonini et al. (2023) [31].	In vitro: Stress stability tests (HCl, NaOH, UV Light, Heat, Humidity) and quantification by HPLC.	ODFs	Main Components: OrPhyllo™ (water-soluble polymers pullulan and xanthan gum) as a film-forming agent, PEG 400 as a plasticizer, polysorbate 80 as a surfactant, and simethicone emulsion as an adjuvant.	Cyanocobalamin was sensitive to stress conditions in the film vehicle, except thermal stress. ODFs disintegration time is 46.22 s, and the chemical stability of vB12 is maintained for at least 180 days at room temperature.

Active pharmaceutical ingredients (APIs); diffusion coefficient (D); High-Performance Liquid Chromatography (HPLC); intramuscular (IM); orodispersible films (ODFs); polyethylene glycol 400 (PEG 400); polyvinyl alcohol (PVA); poly (ethylene glycol) (PEG); poly (ethylene glycol)-terephthalate/poly (butylene terephthalate) (PEGT/PBT).

These studies show the feasibility of using polymers that exhibit favorable disintegration and release characteristics as a matrix for synthesizing ODFs, thereby enhancing the bioavailability and stability of vitamin B12 and facilitating effective and convenient administration for patients with vitamin B12 deficiency.

Matrix composition and formulation strategies allow for the definition of in vitro and in vivo vitamin B12 release profiles. In vitro studies, which generally use simulated salivary fluids, show that the rapid or controlled release of vitamin B12 depends on the design of the ODF matrix [50].

A study from van Dijkhuizen-Radersma et al. (2002) [50] investigated the effect of PEGT (hydrophilic poly (ethylene glycol)-terephthalate)/PBT (poly (butylene terephthalate)) composition, the length of the PEG segment, and the PEGT/PBT ratio on vitamin B12 release and diffusion behavior from the films formed by these copolymers, finding that the longer the PEG segment, the greater the rate and amount of vitamin B12 release, due to increased matrix swelling and permeability. Factors influencing the permeability and diffusion coefficient of vitamin B12 (10^{-12} to 10^{-14} cm^2/s) include composition, PEG segment size, and film matrix crystallinity. Crystalline regions act as impermeable barriers, reducing the space available for vitamin B12 diffusion. Therefore, by mixing copolymers with different PEG segment lengths, the release rate can be adjusted from 1 day to 12 weeks, allowing for effective control of the release system. A study conducted by Patel et al. (2021) [51] analyzed the in vitro release of 1,5 mg/film of cyanocobalamin from rapidly dissolving SL films formulated with dehydrated banana starch and gelatin as a film-forming agent and PEG 400 as a plasticizer through the solvent casting method. Release was assessed by dissolution testing in phosphate buffer (pH 6.8) under controlled conditions, and the data were modeled using several mathematical models of release kinetics, including zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models. The cyanocobalamin release profile fits the Higuchi square root model better (r^2 = 0.9636), indicating that release is a time-square-root-dependent diffusion-controlled process. Furthermore, the Korsmeyer–Peppas model showed a release exponent greater than 0.68, suggesting that release follows a non-Fickian diffusion mechanism. This study helps to understand and predict the release kinetics of vitamin B12 in SL formulations, which is valuable for designing controlled-release systems that optimize bioavailability and therapeutic efficacy. Polonini et al., 2023 [31], evaluated the disintegration times of ODFs using the commercial base OrPhyllo™ (formulated with the water-soluble polymers pullulan and xanthan gum) as a film-forming agent and polyethylene glycol 400 as a plasticizer, containing several

active pharmaceutical ingredients (APIs), including vitamin B12 (1 mg/film). The films were characterized by their rapid disintegration (approximately 46 s) in vitro, conducive to rapid sublingual release and absorption. The study demonstrated that the average ODF disintegration time was 46.22 s, allowing for the rapid in vitro release of vitamin B12, which is essential for its effective absorption. The study also showed the chemical stability of vitamin B12 for at least 180 days at room temperature, suggesting a suitable rapid onset of effects in vivo.

4. Conclusions

This review demonstrates that ODFs are not simply a more convenient alternative for vitamin B12 administration, but a necessary technological innovation to address the physiological limitations of geriatric patients, which lead to variability in gastric absorption. While PO administration faces barriers related to gastrointestinal aging, such as gastric atrophy and intrinsic factor deficiency, as well as pharmacological barriers, such as chronic use of proton pump inhibitors and metformin, sublingual ODFs leverage the oral mucosa's permeability to ensure direct absorption. Evidence suggests that formulating ODFs with polymers that allow for amorphous distribution, uniform distribution on a smooth surface, and high permeability can offer rapid disintegration and absorption. Absorption also depends on other physiological factors, such as the condition of the oral mucosa, including permeability, thickness, and secretions. Furthermore, clinical gaps have been identified in some in vivo trials, such as the need for future clinical trials to move beyond reliance on serum vitamin B12 and also use methylmalonic acid (MMA) and homocysteine (HCy) as more accurate indicators of functional deficiency at the metabolic level. Addressing these gaps will entail significant future challenges, including developing films with long-term physical and chemical stability, ensuring consistent bioavailability, and achieving affordable industrial-scale manufacturing. It is also critical to address practical barriers, such as patient tolerance and adherence, while establishing pharmaceutical regulations and clinical protocols tailored to geriatric populations with comorbidities and polypharmacy. Therefore, although this review underlines the potential of ODFs to transform clinical management and reduce reliance on invasive procedures, definitive progress toward their implementation in medical practice requires robust longitudinal clinical trials that confirm their stability and efficacy in real-world contexts, ensuring accurate and safe dosing of vitamin B12 in patients with an aging digestive system, dysphagia, or severe xerostomia.

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