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Oral pharmabiotic tablet formulations

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ABSTRACT: Pharmabiotic is a unique and recent term used to describe formulations containing probiotics. Pharmabiotics are probiotics prepared in a pharmaceutical form used to treat diseases and disorders by making physicochemical changes in human health. Probiotics, prebiotics, and synbiotics are included in this scope, and enzobiotics, which are a rising class of supplements, should be evaluated in this context, as they are a subspecies of synbiotics. Pharmabiotics, unlike nutribiotics, do not necessarily contain live microorganisms. The best examples of these are paraprobiotics and postbiotics. Tablet formulations are suitable dosage forms for pharmabiotics due to their redundant superiority over other solid dosage forms. Tablets are frequently preferred because they can be produced at low cost, are easily transported, and modified, are suitable for large-scale production, and are more stable than other dosage forms. Considering the examples in the literature and the definition of pharmabiotic, several tablet formulations can be mentioned as pharmabiotics. They can be divided into conventional uncoated tablets, chewable tablets, and effervescent tablets. With recent studies, this classification has expanded, and buccal mucoadhesive tablets, ODTs (orally disintegrating tablets) and FDTs (fast disintegrating tablets), layered/multi-layered tablets, and tablets within tablets have also taken their place in the classification. This article focuses on oral tablet formulations that can be classified as pharmabiotics.

KEYWORDS: pharmabiotic; probiotic; prebiotic; types of tablets; formulation

1. INTRODUCTION

In 2002, WHO (World Health Organization) and FAO (Food and Agriculture Organization) defined probiotics as "living microorganisms that are beneficial to human health when given in adequate amounts" [1,2]. Since this definition was adopted by The International Scientific Association of Probiotics and Prebiotics, it has been used in various publications as the definition of probiotics [3]. A comprehensive glance at recent publications reveals the concept of probiotics is divided into two as pharmabiotic and nutribiotic. The essential goal of nutribiotics is obtaining a final product that is nutritious for humans. Probiotics in nutribiotics are introduced to humans through food as it undertakes the task of regulating nutritional deficiencies. Nutribiotics can be prepared in solid (tablet and chewable tablet) and liquid (syrup, oil, and drops) dosage forms. Pharmabiotics, on the other hand, are probiotics prepared in pharmaceutical form, which are used to treat diseases and disorders through physicochemical changes in human health [4]. Current studies suggest that probiotic microorganisms can be effective even after they lose their vitality [5,6] , which is why the definition of pharmabiotics includes not only living microorganisms, but also their dead forms, the products they secrete, and the cellular structures of the microorganisms [6–8]. Concepts related to probiotics are summarized in Table 1.

Table 1. The definitions regarding probiotics

	Definitions	Reference
Pharmabiotic	Formulations that are presented to patients for various purposes by being turned into a pharmaceutical dosage form containing live microorganisms, microorganism secretions or organs of microorganisms that have proven beneficial effects for health.	[4–6]
Nutribiotic	Supplements or foods that offer the use of probiotics through diet.	[4]

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Probiotic	Living microorganisms that are beneficial to human health when given in adequate amounts.	[1,2]
Synbiotic	Combinations of probiotics and prebiotics which enable probiotics to multiply and improve their impact in the region.	[9,10]
Enzobiotic	A combination that includes a synbiotic and an enzyme.	[7,11]
Prebiotic	Components that are generally not digested by humans, increase the number of probiotic bacteria, are non-living, are the substrate in the gastrointestinal tract microbiota, positively affect the microbiota activity in the host, and are temporarily used by host microorganisms.	[10,12,13]
Postbiotic	Substances secreted by probiotics as a result of metabolic events.	[6–8]
Paraprobiotic	Probiotics that have become dead as a result of certain processes or fragmented probiotic parts.	[6–8]

1.1. Some mechanisms of action of probiotics

Studies on probiotic bacteria explain their mechanism with many diseases. Probiotic bacteria exert immunomodulatory effects by affecting various cytokine and interleukin activities in the intestinal lumen. At the same time, they create positive effects on the immune system by stimulating dendritic cells, macrophages, B and T lymphocytes in the intestine. In studies, it has been observed that they produce an immune-modulatory effect in the form of an increase in cytokines and Ig-A producing cells [14]. In a study examining the effect of probiotics on lipopolysaccharide (LPS)-induced acute liver injury, a decrease in the negative effects of LPS was observed in mice given *Bifidobacterium pseudolongum*.

At the same time, it showed a high antioxidant effect by changing the levels of tumor necrosis factor, interleukin-1 and interleukin-6. For this reason, it has been emphasized that probiotics can help to improve acute liver injury [15]. Some probiotic bacteria alter purine and urate metabolism by providing the formation of short-chain fatty acids, secondary bile acid, vitamins B and K, γ-amino butyric acid, choline and conjugated fatty acid. Thus, they constitute an alternative for the treatment of hyperuricemia and gout [16]. In addition to their immunomodulatory effects, probiotic bacteria also show immediate-inflammatory and anti-pathogenic activity by actively producing their own substances such as bacteriocin, forming hydrogen peroxide and organic acids, competing with the binding sites of pathogenic bacteria, and using the nutrients of pathogenic microorganisms [17].

1.2. Use of pharmabiotics

Pharmabiotics can be administered by oral [18], topical [19], vaginal [20], rectal, nasal, and even ocular [2] routes. There are various formulations for oral use such as powder, granule, pellet, tablet, and capsule. Preparations such as creams [21], lotions [22] for topical application; vaginal tablets, capsules, and suppositories for vaginal administration [23]; rectal enema and suppositories [24] for rectal administration; nasal sprays for nasal administration have also been studied. In addition, Kıvanç et al. conducted a study on a probiotic-containing biofilm applied to the eye [25].

Recently, with the increase in the use of probiotics in treatment, advanced technological methods have been started to be developed to ensure the survival of probiotic microorganisms in the human body. Among these, encapsulation, extrusion, ionic gelation, emulsion, fluidized bed drying, spray drying, and freeze drying are among the most preferred methods [26-28].

Up to 80% of commercial products commonly available on the market consist of solid dosage forms [29]. Tablet formulations are the most preferred solid dosage forms [30,31] because of the advantages they exhibit (Table 2).

Table 2. Advantages of the tablet formulations

Benefits of the tablet dosage forms
Tablets have the lowest price of all dosage forms.
Their transportation can be rapid and effortless.
Their properties can be improved using various techniques. Tablet features can be made convenient according to the desired situation.
They are suitable for large-scale production.
They are more stable in many respects compared to other pharmaceutical formulations.

In this article, the properties of various oral probiotic tablet formulations and current studies are reviewed.

2. TYPES OF ORAL PHARMABIOTIC TABLETS

2.1. Conventional Oral Pharmabiotic Tablets

Conventional tablets are the simplest form of tablets containing one or more active pharmaceutical ingredients (API) and several sufficient excipients [32]. Tablets can be prepared through the direct compression method, wet granulation-compression, or dry granulation-compression techniques. The excipients and their proportions are determined depending on the production method applied. Excipients used in tablet production can be fillers, binders (wet granulation), lubricants, glidants, anti-adherents, colorants, and/or flavourings [33]. In tablet formulations containing probiotics; microcrystalline cellulose (as binder/diluent), rice maltodextrin (as binder/diluent), silicon dioxide (as lubricant/anti-caking agent), magnesium stearate (as lubricant), and hydroxypropyl methyl cellulose (as coating agent/viscosity agent) are some of the most common excipients used [34].

When the literature and the products available in the market are examined, it is seen that most of the probiotics are given orally. Capsules, tablets, sachets, drops, straws, chewable tablets, lozenges, and are some of the formulations [34]. Oral tablets are deemed appropriate as pharmaceutical preparations due to their production rate, low cost, and ease of use in delivering probiotic bacteria to humans [35].

Oral tablet formulations were prepared to examine the effect of excipients and cryoprotectants by Vorländer et al. where *Saccharomyces cerevisiae* was used as probiotic bacteria. In order to examine the cryoprotectant effect, no additional cryoprotectant was included and the suspensions were formed after the cells were formed. Various types of sugar (dextran, lactose, trehalose), milk powder, glutamic acid, glycerine, and their various ratios or mixtures were used as cryoprotectants. When a cryoprotectant was added to the formulation, higher survival rates were observed from the formulations. Among the cryoprotectants used, the highest 3 cell viability was observed with 40% milk powder, 25% trehalose + 25% milk powder, 25% trehalose + 15% milk powder, respectively. The powders were then directly compressed using lactose, microcrystalline cellulose (MCC) and dicalcium phosphate (DCP). Compression forces of 100, 150, 200, 300, and 400 MPa were tested. Among the excipients, DCP was found to be the most suitable material for preparing a probiotic-containing tablet [36].

Both spray-drying and freeze-drying methods have their own advantages and draws. The quality of the products prepared in freeze-drying is much better than spray-drying method. However, the cost and energy expenditures are higher in the freeze-drying process. In spray-drying, the efficiency is lower, and the cost is also lower. For this reason, Mukprasirt et al., aimed to prepare fermented milk tablets and preferred the spray-drying method to this end. Jerusalem artichoke (*Helianthus tuberosus L.*) tubers were chosen as prebiotics because they contain prebiotic species (such as fructooligosaccharides, galactooligosaccharides and inulin), which are frequently used in the literature, and *Lactobacillus casei* TISTR 1463 as probiotic bacteria and a synbiotic formulation was made. Fermented milk was prepared by adding artichoke tubers and distilled water to reconstituted milk powder, followed by the addition of *L.casei*. Prepared fermented milk was dried by spray drying method and then tablets were prepared with this powder by applying 100 kg force for 20 seconds. Artichoke tubers and *L. casei* showed a synergistic effect and spray drying was possible at lower temperatures. However, a more detailed study is needed [37].

Researchers produced probiotic tablets from rice that was broken during production in China. *Brettanomyces custersii* ZSM-001 and *Lactobacillus plantarum* ZSM-002 were used as probiotics. In the study, the content of rice and its effect on probiotic bacteria were investigated. It has been reported that even after tabletting, the bacterial density was above the effective values stated in the literature. It was also evaluated that the antioxidant property was better compared with than the tablet on the market [38].

The subject of probiotics is a highly studied topic on oral and dental health which is why there are many studies on pharmabiotics in oral and dental health are available in the literature. In a study where goat milk tablets containing probiotics were prepared, an optimization study was carried out for the tablet formulation. To find suitable cryoprotectant for lyophilization of *Bifidobacterium bifidum* BB01, response surface methodology was used. According to this study, the optimum cryoprotectant content was glycine of 5.5%, sodium bicarbonate of 0.8%, xylo-oligosaccharides of 7%, arginine of 4.5% and skimmed milk of 25% [39]. In another study, the content of the optimum probiotic-containing tablet formulation was found to be 84.90% goat milk powder, 0.1% probiotic powder, 9% xylitol, 3% mannitol, 2.85% erythritol and 0.15% microcrystalline cellulose. Through this formulation 10^6 CFU/g bacteria were able to survive in room temperature storing for 210 days [40]. In another study conducted at Istanbul Yeditepe University on healthy young adult patients, the effect of 10^8 CFU *Lactobacillus reuteri* ATCC 55730 strain on oral flora was evaluated with placebo in terms of two different pharmaceutical dosage forms. Straw (BioGaia probiotic straw) and lozenge (BioGaia probiotic lozenge) forms were compared against placebo in the study. Both dosage forms showed a statistically significant effect on flora. When the two formulations were compared, it was found that

the lozenge form was more effective than the straw form. The study also showed that *L. reuteri* ATCC 55730 strain affected *Streptococcus mutans* rather than Lactobacilli [41]. Chuang et al. investigated the effect of *Lactobacillus paracasei* GMNL-33 strain on the oral flora. In this double-blind, randomized and placebo-controlled study with healthy subjects, tablets containing probiotics were used. Tablets contained 4% *L. paracasei* GMNL-33 (3x10) as probiotic and 11% xylitol as excipient. The saliva samples taken from the subjects showed no significant differences compared to the placebo group [42]. In another research Iniesta et al., carried out a study in which they evaluated the effect of probiotics in the mouth on subjects with gingivitis. Chewable tablets containing *L. reuteri* DSM-17938 and ATCCPTA 5289 strains were selected as probiotics and 8 weeks of treatment was applied to the gingival flora in healthy volunteers. As a result of the study, it was seen that *L. reuteri* reduced the total amount of pathogen on the gingiva, but the findings were not statistically significant [43]. In a study examining the effect of probiotics on halitosis, tablets containing 1×10^8 CFU *Weissella cibaria* CMU as probiotics and isomalt, sucralose, peppermint-flavored powder, maltodextrin, magnesium stearate as excipients were tested on volunteers for 8 weeks. As a result of the study, a statistically significant decrease in the number of sulfur compounds causing bad breath and an increase in the number of *W. cibaria* were observed in the group using probiotics [44].

Tablets containing *Bifidobacterium infants*, *Lactobacillus acidophilus, Enterococcus faecalis*, and *Bacillus cereus* were used in a study that wanted to correlate the gastrointestinal complications experienced by patients diagnosed with colorectal cancer and received postoperative chemotherapy (Capecitabine + Oxaliplatin) with probiotic use. It was observed that especially diarrhea complaints decreased significantly in patients using probiotics compared to the placebo group. In addition, researchers have considered the use of probiotics as an alternative treatment for these patients that can reduce complications by correcting the deteriorated intestinal microbiota and contributing to the synthesis of propionate, butyrate and acetate and short-chain fatty acids that they secrete [45].

2.2 Pharmabiotic Chewable Tablets

Chewable tablets are orally used pharmaceutical dosage forms for drugs and food supplements. Prior to digestion it is broken down into smaller pieces through physical forces exerted by the teeth and the tablet begins to show its effect in the mouth. Chewable tablets are advantageous over other oral formulations taken with water in that they are convenient for a wide range of patients; it is suitable for children and the elderly. In addition, it is more practical in day-to-day life as it can be applied with ease even in complex scenarios that may prevent taking the drug with water, such as traveling. They are also preferrable for patients with swallowing difficulties. Since it always contains a flavouring agent in its composition, it tends to taste very good. Due to their nature, chewable tablets dissolve before swallowing, which increases the solubility of the active substance, hence its bioavailability. Generally, dry, and wet granulation along with direct compression methods are applied to produce chewable tablets. Binder, filler, lubricant, anti-adhesive, flavouring, sweetener, and colour agent are used as excipients [46-48].

Since the chewable tablets are organoleptic, they should be both pleasing to the eye and suitable for the patients. The appearance of the tablet, its taste, aftertaste texture, and odour it creates in the mouth are crucial parameters to be considered. It is necessary to mask the bad taste and to this end combinations of sugars (such as polyols) are used in bulk and high-density. It should be noted that sweeteners have synergistic effects. Some sugars may reveal their flavours later and keep them longer, or their taste may become bitter when used in large quantities. Considering these complications, an ideal combination should be provided. In chewable tablets, flavouring agents are also used as fillers, binders, acid regulators, preservatives, and sweeteners. Various odours or tastes such as mint, fruity or sugar gum, can be provided through flavourings. Flavourings are generally used in dry powder form to reduce the loss of the volatile aromatic compounds they contain, and for this reason, the direct compression method is preferred in chewable tablets. If wet granulation is to be used, flavourings should be used in extra granular form. Flavour can also be altered by adding substances that can correct acidity, such as citric acid [48,49].

The most important advantage of chewable tablets is their ease of use for patients. However, there can be some issues such as hardness, disintegration, dissolution. Complications that chewable tablets can cause in the GI tract due to their physical properties and their effect on teeth and dentures; has forced FDA to come up with regulations such as performance simulations in physiological environment, use of *in vitro* bioequivalence data and post-approval considerations [50].

A clinical study was conducted using probiotic chewable tablets to examine the effect on dental caries in preschool children. Chewable tablets containing a total of $1x10^8$ CFU *Streptococcus uberis* KJ2, *S. oralis* KJ3, *S. rattus* JH145 (Evora Kids) were used as probiotics, and erythritol were utilised as sweetener. The prepared placebo tablets had the same properties as the other tablets, except for the probiotic content. Children used probiotic chewable tablets once a day for 3 months, after brushing their teeth with toothpaste containing 1100

ppm fluoride. At the end of the study, the researchers deduced that the use of probiotic chewable tablets together with tooth brushing could prevent dental caries, but further research was needed [51]. In another clinical study on cavities in children, Evora Kids (*S. uberis* KJ2, *S. oralis* KJ3, *S. rattus* JH145) chewable tablet and PerioBalance (*L. reuteri*) lozenge were compared. The comparisons were evaluated according to their effects on pathogenic bacteria commonly found in the mouth by using Caries Risk Test (CRT). Both EvoraKids and Periobalance reduced the levels of *S. mutans* and Lactobacilli in the saliva sample to a statistically significant degree [52]. Çağlar et al., on the other hand, conducted a clinical study to see how long the *L. reuteri* ATCC 55730, could be effective in the oral cavity after application. BioGaia containing *L. reuteri* ATCC 55730 was given to 25 healthy volunteers. The probiotic chewable tablet (10^8 CFU/tablet) was used for 2 weeks. The study was divided into 3 parts, each over a period of 2 weeks, the first of which is the pre-treatment clearance part, and no probiotics were used in this part. After the 2-week treatment period, the 2-week post-treatment period was included. In this process, the number of colonies in the salivary fluid of probiotic bacteria was evaluated. It was observed that the concentration of *L. reuteri* ATCC 55730 decreased in the salivary fluid within 2 weeks. Therefore, it was concluded that it would not be possible to establish a permanent colony of *L. reuteri* in the mouth within 2 weeks [53]. Shetty et al. studied the effects of probiotics on periodontitis patients. For this, they formed the control group that received only non-surgical treatment and the test group that received both treatment and probiotics. The probiotic chewable tablets given to the patients throughout the experiment contain a total of $2x10^9$ CFU *L. acidophilus, L. plantarum, L. rhamnosus, B. breve, L. salivarus, B, lactis, L. casei, L. paracasei, S. thermophilus and B. longum*. As a result of the clinical study, it was seen that the use of probiotics in addition to the treatment has an important place in improving the result [54].

The effects of synbiotics and products that we can describe as pharmabiotics based on the above definitions are known to have effects on the GI tract and have been supported by many publications [55-58]. Altun et al. studied the effect of synbiotic chewable tablets on 36 patients with mild to moderate ulcerative colitis. As a chewable tablet, NBL Probiotic Optima containing $3x10^9$ CFU/tablet *Enterococcus faecium*, *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Bifidobacterium longum* combined with 250 mg of fructooligosaccharides (FOS) as a prebiotic was used. Volunteers were divided into placebo and synbiotic groups, and the placebo tablet used was the same as the synbiotic tablet in appearance and taste. Volunteers in the synbiotic group used chewable tablets containing synbiotics twice a day for 8 weeks. Blood tests and related parameters were analysed before and after treatment. When the two groups were compared, it was concluded that the clinical recovery of the group receiving the synbiotic was better. C-reactive protein levels showed a statistically significant decrease in patients using synbiotics [59].
In order to examine the effects of probiotics on *Clostridium difficile*, in a study conducted on elderly patients in nursing homes, chewable tablet formulations containing synbiotics were used. All information about the patient, such as age, gender, and disease history, was obtained from the patient by conducting a questionnaire. The chewable tablet used contained a total of $8.5x10^9$ CFU/tablet *Saccharomyces boulardii* and *Bacillus coagulans* as probiotics. The tablet contained 500 mg of FOS as a prebiotic. From the patients that used the synbiotic, 95% did not have diarrhea caused by antibiotics and 97% of them did not exhibit diarrhea caused by *C. difficile*. In addition, according to the data obtained from the patients, mild gastrointestinal complaints were observed in very few of the patients, and most of them described the use of chewable tablets as an easy way of administration [60].

In a study focused on younger patients with irritable bowel syndrome (IBS), chewable tablets containing *Bacillus coagulans* Unique IS2 were used to evaluate its effect on it. This study focused on children between the ages of 4 and 12 who were diagnosed with IBS, which were divided into two groups: those taking probiotics and those taking a placebo. The data was evaluated according to the ROMA III criteria. There was a statistically significant reduction in the symptoms of IBS and the patients' pain in the group receiving probiotic treatment compared to the group receiving placebo [61].

In the study of Gan et al., a clinical trial was conducted using the ROMA III criteria in children aged 4-12 years. Chewable tablets containing $5x10^9$ CFU *Lactobacillus acidophilus* DDS-1 R and *Bifidobacterium animalis subsp. lactis* UABla-12 were given twice a day for 4 weeks. Compared to the placebo group, evacuation decreased, and the number of defecations returned to normal in children taking probiotics [62].
There are studies in the literature that probiotics are also effective in respiratory diseases [58]. In Finland, the effects of chewable tablets containing a combination of probiotics on viruses that cause respiratory tract infections, which are frequently seen among soldiers, were investigated. The chewable tablet used contained same ratio of xylitol and sorbitol, approximately 8% microfibrous cellulose, 3.0% magnesium stearate, 1.9% citrus flavour, *L. rhamnosus* GG (ATCC 53103) and *B. lactis* BB-12 (DSM 15954). The viruses studied were influenza A and B viruses, respiratory syncytial viruses (RSV) A and B, parainfluenza viruses 1-4 (PIV1-4), adenovirus (AdV), human metapneumovirus (hMPV), coronaviruses 229E, OC43, NL63 and HKU1, picornaviruses (EV/RV) and human bocavirus (HBoV). As a result, viral formation in soldiers did not

decrease, but after 3 months of probiotic use, the incidence of picornavirus decreased. Further trials were required [63].

A clinical study was conducted to evaluate probiotic therapy in allergic rhinitis and to compare it with cetirizine. Chewable tablets containing $2x10^9$ CFU *Lactobacillus paracasei*-33 were given in the study conducted on infants with allergic rhinitis aged 6 to 60 months. In the control group, 2.5 mg tablets were given to children under the age of 2 and 5 mg of cetirizine tablets were given to children between the ages of 2 and 5 years for 6 weeks. In the treatment of probiotics and cetirizine, both treatments successfully suppressed the initial symptoms of allergic rhinitis. Probiotic treatment was able to show identical effects as cetirizine treatment in allergic rhinitis with children under the age of 5 [64].

2.3 Pharmabiotic Effervescent Tablets

Effervescent tablets are uncoated solid dosage forms, which have the stability of solid dosage forms as well as the rapid action of liquid dosage forms. It is very suitable for active substances that can show their effect or maintain their stability in liquid. Prior to oral administration, it is dissolved in a sufficient amount (about 200 ml) of water or another suitable solvent, and the active substance is dispersed in the liquid. During the dissolution of the tablet, carbon dioxide release is observed due to the acidic and basic excipients present in its structure. Commonly citric, fumaric, malic, adipic, and/or tartaric acid are used however, acid salts may also be preferred. Carbonate and its derivatives are generally used as an alkaline component. Along with these, sweeteners and lubricants are also included in the formulation [65–72].

Effervescent tablets have several advantages over other dosage forms. The fact that it is administered after dissolving in the liquid media, minimizes the side effects of the drug on the stomach and ensures the rapid onset of the effect. Dissolving in liquid also creates an opportunity to mask the undesirable taste of the active ingredient in the formulation. It is also patient friendly; the application can be provided with ease, and the patient can take the exact required dose [65,67,69–71].

The reason why effervescent tablets may be chosen for probiotics is that they can be stored as a solid dosage form and dissolved in water allowing it to be taken daily. Due to its solubility in water, absorption will begin quickly and thanks to the carbon dioxide gas formed due to the nature of the formulation, the effects of stomach acid stabilise, creating a suitable environment for probiotics.

In a study where *Saccharomyces boulardii* and *Lactobacillus acidophilus* were used as probiotics, effervescent powders and tablets were used. The effects of probiotics and excipients in the dosage forms created were examined. Bacterial viability and formulation tests were also evaluated simultaneously. Accordingly, during dissolution studies, the resistance of *S. boulardii* to gastrointestinal system fluids was found to be better than *L. acidophilus*. Although the effects of excipients were not statistically significant, the flavouring (orange flavour) and selected acids (tartaric and citric) used in the formulation for *L. acidophilus* negatively affected the growth of bacteria, while sodium bicarbonate, lubricants, and sweeteners (sucrose and stevia) used had positive effects. In addition to these, bacterial viability decreased considerably at the forces of 20 Newton and above applied for probiotics that were used to prepare effervescent tablets. For this reason, it was thought that effervescent powders would provide better bacterial viability than effervescent tablets [73].

In a study on mice, the effect of synbiotic effervescent tablets in mice with a diabetes model was examined. In the study, *L. casei* FNCC 0090 was used as a probiotic, and glucomannan and gum Arabic were used as prebiotics. Each of the mice had blood glucose higher than 135 mg/dL. Mice were divided into 4 groups for synbiotic treatment. These were the control group, regular dose group, half dose group, and double dose group. To evaluate the effect, the blood glucose of the mice was measured, and their weight was evaluated. According to the study, more successful results were obtained in mice given a double dose of synbiotic effervescent tablets. It was also evaluated that normal blood sugar levels were achieved within the month with normal dose intake [74].

2.4 Different Approaches to Oral Pharmabiotic Tablets

Orally dispersing tablets and fast disintegrating tablets differ from other solid dosage formulations thanks to their inherent advantageous properties allowing them to become suitable for probiotics. They can be dispersed as soon as they are taken into the mouth, they act fast, require no additional liquid, and the dose can be tailored to be exact, making them patient friendly for all ages. Rapid release of probiotics within the mouth can cause an issue since bacteria can be dragged along with saliva without the assistance of food or beverage to carry them. To get ahead of this potential hurdle, some ODTs and FDTs have been developed specifically for probiotics. Currently, the main preferred method used to develop these tablets is, to impart mucoadhesive properties to them, allowing the probiotics to disperse in a more controlled manner over a longer period of time [75–77].

In 2019, Hoffman and Daniel prepared ultra-fast disintegrating tablets containing probiotics with mucoadhesive properties and examined their effects. In the study, HPMC-granulated or non-granulated versions of *Lactobacillus plantarum* 299v (Lp299v) and *Lactobacillus paracasei* 8700:2 were used as probiotics. The hydroxypropyl methylcellulose used for granulation was added to give mucoadhesive properties to the bacteria. The same excipients were used in each formulation of tablets made with granulated and non-granulated bacteria. The contact of ungranulated bacteria with HPMC was ensured only by mixing, granulation was not done. As a result, it was observed that the adhesion properties of the granulated bacteria improved considerably. They also found that methacrylic acid used during granulation, rather than HPMC, reduced the negative effects on bacterial viability and distribution that HPMC can cause. Researchers have demonstrated that probiotics can be administered with mucoadhesive orodispersible tablets [76].

In 2020, Hoffmann et al. tried an innovative approach for probiotic bacteria by preparing 3 different buccal mucoadhesive orodispersible tablet formulations and compared their effects. Anionic Carbopol 971P NF, non-ionic Metolose 65SH50, and cationic chitosan were used as polymers. Lp299v was chosen as probiotic. Tablets were prepared using two different methods, namely granulation, and direct compression. The prepared formulations were examined in terms of tablet properties, the viability of probiotics, and mucoadhesive capacity. The obtained results showed that all formulations were able to maintain their bacterial viability for a period of 30 months in refrigerator conditions, while only carbopol could preserve its mucoadhesive property [75].

Recently, a novel method has been trending in literature and among researchers, to encapsulate the outer part of the probiotic using various polymers in order to increase their viability under external stress such as stomach acid, or osmotic pressure and to target the intestine [78]. Bilayer, multilayer, or enteric layered tablets are other techniques that are widely used for preserving the viability of probiotics. Table 3 lists the most widely used polymers in pharmabiotic formulations.

Tablo 3. Different usages of polymers in pharmabiotic formulations

Polymer type	Probiotics	Effect of polymer	Formulation	Reference
Alginate	*L. plantarum* NCDC201, *L. casei* NCDC297	Coating to protect probiotics from GI conditions	Microcapsule	[79]
Carbopol 971P NF	*L. plantarum* 299v	Provides mucoadhesion properties	Buccal mucoadhesive tablet	[75]
Metolose 65SH50	*L. plantarum* 299v	Provides mucoadhesion properties	Buccal mucoadhesive tablet	[75]
Chitosan	*L. plantarum* 299v	Provides mucoadhesion properties	Buccal mucoadhesive tablet	[75]
HPMC	*L. plantarum* 299v, *L. paracasei* 8700:2, *L. acidophilus, E. faecalis*	Provides mucoadhesion properties, enteric coating	Ultra-FDT Pellets and multi-unit tablets	[76,80]
Alginate-Ca-EDTA	*L. plantarum*	Allows a pH-specific targeting	$W_1/O/W_2$ double emulsion	[81]
Eudragit	*L. acidophilus*	Coating to protect probiotics from GI conditions	Bilayer tablet-in-tablet	[82]
Gum Arabic	*L. acidophilus (NCDC 016)*	To increase the flowability	Powder	[83]

A multi-unit tablet has been developed to protect the bacteria from ambient conditions. Lyophilized *L. acidophilus* and *E. faecalis* were used as probiotics in this study. For the developed multi-unit tablet, probiotic powders were first pelleted (enteric coating using HPMC-AS) and then compressed into tablets using appropriate excipients. This tablet was able to provide bacterial viability for 6 months at room conditions and was able to withstand ambient conditions better than uncoated strains. It was also found that the tablets exhibited sufficient tablet hardness and disintegration time [80].

Govender et al., on the other hand, aimed to deliver probiotics specifically to the colon and small intestine by developing a bilayer tablet-in-tablet formulation. Both layers contained a tiny tablet that includes *L. acidophilus* and powdered ovalbumin obtained from raw egg whites. Ovalbumin forms a matrix system for probiotics that protects them from the stomach conditions. After this first process, layer containing the small tablet was treated with lactose and the other layer with Eudragit for an appropriate amount and time to obtain a double-layered tablet which allowed the formulation to dissolve in small intestine and colon respectively. A

luminescent substance was also placed within the small tablet to examine the release profiles of probiotics, which were measured using MRI. Examined by molecular docking studies, it has been proven that ovalbumin can form a suitable matrix to transport and protect the probiotic bacteria. It has also been revealed that there may be an interaction in the targeted areas with use of artificial environments and docking studies [82].

In a study to examine the effects of enteric coating on probiotics, a specific gastrointestinal model (TMI-1) was used to focus on different parts of the gastrointestinal tract. It was aimed to make an enteric-coated tablet by using 3 different probiotics, *L. gasseri* PA 16/8, *B. longum* SP 07/3, and *B. bifidum* MF 20/5. To this end, the researchers compared probiotic powder formulations and the uncoated tablet formulations containing 3 probiotic shushes and excipients. When bacterial viability was observed by using TMI-1, it was observed that the viability was decreasing dramatically. Survival rates increased more than 20 times after enteric coating [84].

In a study performed by Villena et al., probiotic tablet formulations containing a series of polymers were prepared. *L. fermentum* CECT 5716 was chosen as probiotic, and methocel K-15-sodium alginate combination [A], Eudragit L-100–sodium alginate combination [B], and cellulose acetate phthalate [C] were used as polymers, respectively. The initial bacterial count was 10^9 CFU/tablet. Each tablet with a weight of approximately 300 mg was prepared by hydraulic press in 60 seconds by applying a compression force of 25 kN for formulations A and B and 15 kN for formulation C. By the end of the study, the viability of bacteria decreased by approximately 2 log CFU. Eudragit L-100–sodium alginate was determined as an ideal polymer to overcome gastrointestinal conditions [85].

Huq et al, developed a probiotic tablet using pectin, alginate, and cellulose nanocrystals (CNC) as polymers and *L. rhamnosus* ATCC 9595 as probiotic bacteria. Probiotic tablets were formed in different categories (CNC, pectin, alginate individually and different ratios of these polymers). The optimized formulation containing alginate, pectin, and CNC of 134, 164, and 155 mg/tablet, respectively showed highest viability of probiotic bacteria (approximately 85%) in gastric pH condition. In addition, the decrease in viability of the optimized formulation at 25°C and 4°C after 42 days did not exceed 0.5 log (CFU)/tablet [86]. In order to protect probiotics from acid in the stomach, probiotic tablets containing phthalyl inulin and *L. reuteri* LRT18 have been developed. The developed tablets were tested under 3 different compression forces. The formulation most resistant to stomach acid was the formulation with the highest compression force (15kp). When examined in terms of viability, no significant difference was found between the 3 formulations [87].

Similarly, the simplex-centroid mixture design, which aims to avoid gastrointestinal conditions, was prepared using carboxymethyl cellulose and alginate. The probiotic in the centre was chosen as *Saccharomyces boulardii*. As a result of all the investigations, this new design trial with polymer was able to keep probiotic yeast away from gastrointestinal-related problems. At the same time, the probiotic viability contained in these new tablets, which were kept at 4°C for 6 months, remained above 10^6 CFU/tablet [88].

Fluid bed spray granulation dryers (FBGD) are one of the techniques developed for the survival of probiotic microorganisms throughout their shelf life. FBGDs provide a better drying compared to lyophilization, while it provides drying at lower temperatures compared to spray drying technique. Vorländer et al. evaluated the effects of *Saccharomyces cerevisiae* dried by fluid bed spray granulation on bacterial viability using different preservatives. As preservatives, starch, lactose, inulin, dextran, sorbitol, trihalose, two different ratios of milk powder, maltrodextrin, xylose and two different ratios of trihalose + milk powder mixture were compared, respectively. It was observed that trihalose + milk powder mixture used in equal proportions had a significant effect on bacterial viability compared to tablets without preservatives (89). The same research group examined the parameters in the tablet pressing process of the granules of *S. cerevisiae* formed by spray drying technique. It has been observed that there is an inverse relationship between the force applied during tablet compression and bacterial viability [90].

3. CONCLUSION

Due to the increase in studies and the proven effectiveness of probiotics, their use has increased in recent years. As probiotics are studied, novel terms such as "pharmabiotic" and "nutribiotic", have arised with different concepts of their application areas are discovered.

Pharmabiotics are formulations that are presented to patients for various purposes by being turned into a pharmaceutical dosage form containing live microorganisms, microorganism secretions, or organs of microorganisms that have proven beneficial effects on health. Postbiotics and paraprobiotics are also examined under this heading since they do not need to contain live microorganisms by definition.

Tablet formulations are frequently used in the pharmaceutical industry due to some of their superior properties. These superior properties of probiotics combined with the suitable dosage form, may be the reason why a lot of research has been performed. Tablets with probiotic and synbiotic content are divided into several

types; conventional tablets, chewable tablets, effervescent tablets, coated tablets, tablets within a tablet, multilayer or bilayer tablets, targeted tablets. Chewable tablets are frequently encountered in the market and in the literature due to their convenient application route, the suitability of their organoleptic properties, their availability to the people of all ages, and the fact that the production steps are suitable for probiotics.
The number of studies on probiotics are increasing day by day. The discovery of novel probiotics and the search for improved formulations for probiotics will be an alternative to the use of chemicals, especially in treatment.

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