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Formulation strategies for the oral delivery of probiotics: a review

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ABSTRACT
Probiotics are live microorganism possessing significance health benefits ranging from the effect on immunological function, protection against pathogenic microorganism to treatment of wide variety of diseases including cancer and tumour. Probiotics are simple, cost effective, intrinsic and receptive alternative for achieving health benefits. The present review article focuses on the mechanism and application of probiotics in different diseases/disorders. Mechanism of probiotics and different formulations for oral delivery of probiotics have been discussed in detail. Different patents on probiotics for oral delivery have also been tabulated. Overall the aim of the study was to underline the input of oral delivery of probiotics for human health and better lifestyle.
Keywords: *Probiotics; microorganisms; oral delivery; formulations.*

1. INTRODUCTION
Oral route is a widely accepted channel for the delivery of drugs and probiotic microorganism for the treatment of a variety of diseases. According to WHO, probiotics are described as "live microorganisms that when ad-ministered in adequate amounts confer a health benefit on the host". Specifically, live microorganisms are used as probiotics to benefit animal hosts by normalizing their bacterial content [1]. There are different methods and strategies currently used to deliver probiotics orally, including incorporation into foods, capsules, oral films, nanoparticles, tablets, beads, and gels [2-5]. However, present delivery techniques have significant challenges when delivery of drug from oral route like a short period of residence in mouth, undesirable impacts on meal texture along with non-compliance of patient [6,7].

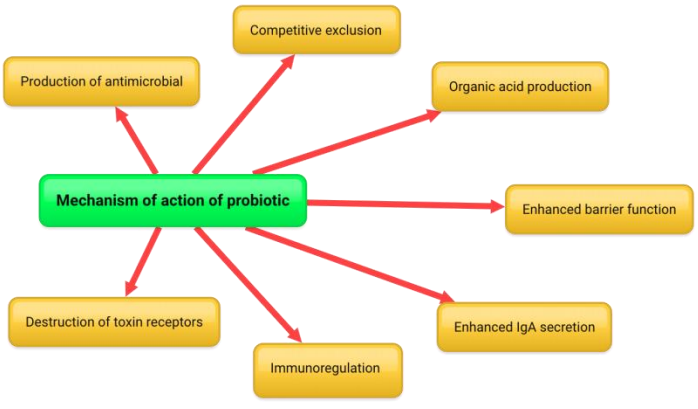

Figure 1. Mechanism of probiotic microorganism.

The system of distribution that can use to feed bacteria in mouth, the cavity of mouth is needed by oral microbiota to be precisely modulated. A delivery system should allow a controlled release into the oral cavity of feasible and metabolically active probiotic bacteria and possibly the remainder of the gastrointestinal tract. The mechanism of action of probiotics isunknown but it acts through the altering gut pH, antagonizing pathogens, competing on binding sites and receptor etc. by which it involves modulation of host microflora, microbial balance adjustment, modulation of host metabolic activity and stabilization of digestive enzyme patterns (as shown in Figure 1). All these activitiesare dependent on microbial strains of probiotics. It can further also modulate the immune power of the host, affect other microbs and act on microorganisms containing food products [8,9].

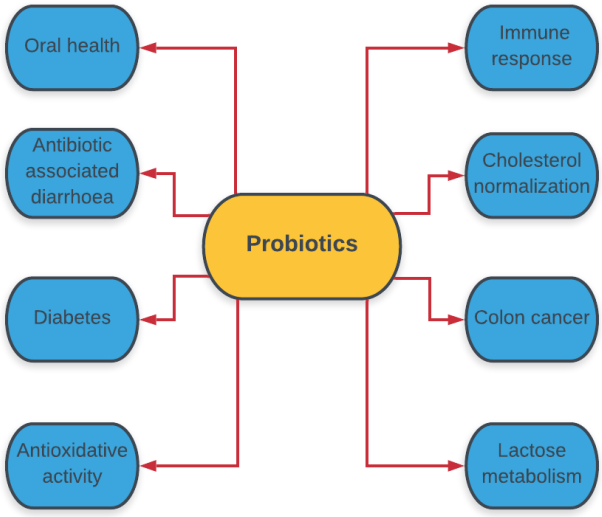

Figure 2. Therapeutic applications of probiotics.

Beneficial bacteria embedded drug like probiotics are used for the therapy and prohibition of the range of illnesses, including allergies [4], metabolic syndrome [4], liver diseases [10], hypercholesterolemia [11], and colon cancer [12], to name a few, some other uses of probiotics are shown in figure 2.
Probiotics may help to manage oral health, digestion, antibiotic associated diarrhoea and common cold etc. List of bacteria with their strains are used for management of some specific diseases are depicted in Table 1[13].

Table 1. Different probiotic microorganisms helpful in the management of various diseases.

Disease	Strain of bacteria
Oral health (periodontitis, Gingivitis etc.)	*Lactobacillus reuteri LR_2, Weissellacibaria*
Lactose intolerance	*Lactobacillus acidophilus, Lactobacillus bulgaricus, Streptococcus thermophilus*
Irritable bowel syndrome	*Lactobacillus plantarum 299v, Bifidobacterium bifidumMIMBb 75, Bifidobacterium infantis 35624, Lactococcus lactis, Lactobacillus salivarius CECT5713*
Digestion	*Lactobacillus salivarius*
Antibiotic induced diarrhoea	*Lactobacillus acidophilus*
Promotion of vitamin	*Lactobacillus rhamnosus*
Infant diarrhoea	*Lactobacillus rhamnosus GG (LGG)*
Common cold	*Lactobacillus acidophilus NCFM, Bifidobacterium animalis Bi-07*
Traveller'sdiarrhoea	*Saccharomyces boulardii*
Colon cancer inhibition with strong antitumor activity	*Bifidobacterium longum*
Decrease Serum cholesterol concentration	*Lactobacillus acidophilus (L1 and ATCC43211)*
Mucosal immune system activator	*Streptococcus salivarius, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus delbrueckii, Lactobacillus plantarum*
Against influenza virus infection	*Lactobacillus plantarum L137*
Intestinal microflora stabilizer	*Bifidobacterium breve*
IgE production with tumer inhibitor and cellular immune system activator	*Lactobacillus casei Shirota*
Protection against rotavirus and influenza infections with immune system activator	*Bifidobacterium breve YIT4064*

2. ORAL DELIVERY OF PROBIOTICS

Probiotic is the type of beneficial bacteria which play a vital role to maintain oral health. Probiotics in the oral cavity (Figure 3) can assist to combat harmful bacteria and help to keep healthy teeth and gums. In the field of dentistry, diseases like dental caries, periodontal diseases, gingivitis are used to treat by probiotics. Probiotics are also effective in some other diseases such as candidiasis, voice prosthesis and orthodontic [14-16]. Oral cavity hascomplex anatomy so the use of probiotics in oral cavity needs detail study about its activity, most of them are act through direct interaction, competitive exclusion and indirect action [17].

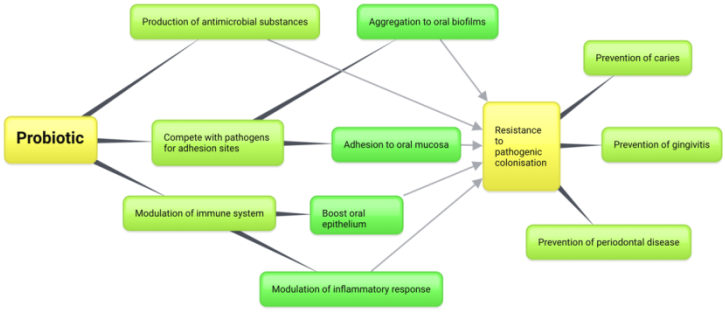

Figure 3. Activity of probiotics in the oral cavity.

In recent years, the use of probiotics isincreasing day by day, however the utilization of probiotics in various diseases iscomplicated because all the available strains cannot show the required properties for preparation of drug, the choice of probiotic strains for the treatment of diseases on the basis of strain of microorganism, its effectiveness, compatibility with ingredient and safety about patient [18-20]. A study shows that the nasal mucosa got changes when delivery of probiotic from oral route during occasional allergic rhinitis. [21]. Harsh conditions in the upper gastrointestinal tract(low pH), epithelial lining as physical barrier, enzymatic degradation aresome common barriers for the oral delivery of probiotics. Mechanical protection, entrapment and microencapsulation could protect the probiotic microorganism from the harsh conditions of the GIT for effective oral delivery.

2.1. Oral Probiotic Formulations.

Formulation is the process of development and discovery of new drugs and dosage form. Oral formulation is the one of the preferred and most used method for delivery of drug, various oral preparations are available for delivery of drug. Nowadays, probiotics are also prepared in oral dosage forms such as capsules, tablets, chewing gum, lozenges, powder, films etc., among them lozenges, films and chewing gum are effective for prevention of gingival, halitosis etc., in addition to tablets, capsule and powder are used as dietary supplements and treatment of diseases [22]. Some marked formulations for the delivery of probiotic microorganisms are represented below in table 2.

Oral films.

Mouth dissolving films are a type of dosage form for the delivery of drugs and probiotic microorganisms in the oral cavity. Properties of the film are guided by the type of polymer used in their manufacturing. There are two kinds of oral films which is mucoadhesive and non-mucoadhesive (oridispersible film) [24]. Orodispersible films are thin strip which when placed on tongue of the patient, immediate to release the drug in oromucosal area. Fast dissolving films are very useful for the patient who hasdifficulty in swallowing tablet. As it doesnot require water for swallowing these films one gives effective for patients who are traveller and are busy in daily hectic lifestyle. The onset of action of fast dissolving films isvery fast as compared to other dosage form except parenteral. These are very useful in disease like motion sickness, asthma, bronchitis etc. [25]. Probioticsareusually associated with natural protection from pathogens that contribute to oral health. Heinemann *et al*, 2013 developed that the orally disintegrating films were composed *Bifidobacterium animalis /*

Lactobacillus acidophilus sub sp lactis incorporated in a matrix (made of starch), carboxymethyl cellulose and gelatin. The probiotic shows increased viability during storage, the developed product which dissolves in simply and innovative for regular use [26]. Saha *et al* 2013 prepared oral thin films using carboxymethyl cellulose as polymer for treatment of oral disorder. *Lactobacillus fermentum* NCM 5221($6.75*10^8$kill/film) was incorporated into the film for the cure of dental caries and oral candidiasis. Films were successfully developed as oral health biotherapeutics [27]. Gagliarini *et al*. investigated whey protein and polysaccharide kefiran for preparing probiotic microorganism loaded films of*Kluyyeromycesmarxianus* CIDA 8154 and *Lactobacillus paracasei* CIDCA. The filmsexhibited increased viability of microorganisms during storage[28]. Kanmani *et al* developed edible probiotic film using pullulan/starch as polymers. More probiotic bacteria with their strain and blended starch from different origin in pullutan solution with different ratio were prepared and its parameter were investigated and found to be pillulan or potato starch films with high relative cell viability (70-80%) after 60 days of storage at 4 °C, pullulan/starch films can be utilized as probiotics for helpful delivery system as edible films [29]. Singh *et al*. developed edible films for probiotic, hydroxyethyl cellulose (HEC) & sodium carboxymethyl cellulose (CMC) with cross linker citric acid (CA) were utilized for probiotic film development under moderate conditions using *Lactobacillus rhamnosus GG*. Probiotic bacteria successfully incorporated into the films with sufficient viability for food protection and packaging [30].

Beads.

Beads are specially design medicine to delivery of drug to the targeted area in controlled way. Beads have almost uniformity in shape with great distribution in intestine, so the local irritation and retention of polymeric material are decreased. The advantageous ability of beads isincreased bioavaibility, patient compliance and decrease dose with side effect. The beads are prepared from alginate with calcium ion for oral delivery of probiotic [31]. Krasaekoopt *et al*. 2004 showed probiotic beads formed were comparable with salmon eggs, which retained the suggested counts of microorganism for a periodic time which enabling their manufacturing and marketing. In addition, there has been a decent index from market potential and acceptability. The product may, therefore, get a chance to introduce probiotics of non-dairy product, particularly in oriental meal. So the use of salmon eggs and probiotics loaded beads preparation are alternative dairy product [32]. Guimaraes *et al*. 2013 prepared extra probiotic beads very similar to fish eggs respectively an extrusion encapsulation method with Ca-alginate incorporated to *Bifidobacterium animalis*DN-173 010/*Lactobacillus rhamnosus* GG ATCC 53103 stored at 4 °C for 30 day. The probiotic exhibited 82.3% satisfactory level of entire features and worthiness market possibility as probiotic product [33]. Capela *et al*. showed that the homogenisation techniques for minimization of Ca- alginate beads size while the general microencapsulation using *Lactobacillus acidophilus, Lactobacillus casei&Lactobacillus rhamnosus as well as Bifidobacterium longum.* It was feasible to cut down the bead size under 100 ml employing the ultra-turrax homogeniser but silver-non mixture had a bad effect upon probiotic populations. However, homogenisation technique can reduce the bead size for viable bacteria [34]. Voo *et al* conducted comparative study of alginate plus pectine beads for manufactured of probiotic cells of poultry using MRS media in recurrent fermentation batches. The beads cores were made using Ca-alginate or pectinate and Ca-pectinate for comparative study. Pectine beads were found more stable than the alginate beads along with their stableness further progressed by using chitosan [35].

Nanoparticles.

Nanoparticles are 1 to 100nm in size, consisting of active ingredient which dissolves, trap, encapsulates or attach the drug to a matrix of nanoparticles [36]. The disease like inflammatory bowel disease that includes colitis and Crohn's illness are targeted using nanoparticles in colon region. Advantage in design of medicine to delivery have considerably enhanced the activity of drug in colon, but considerations must be made for modified gastrointestinal tract physiology connected with GI swelling, in order for a medication to have therapeutic effectiveness during illness. In the design of oral formulations, nanotechnology has been used as approaches to further improve the absorption of diseased tissue within the colon[37]. Yao M *et al*. 2018 showed, increased probiotics viability via enclose in microgels doped together with inorganic nanoparticles. The bacteria *Pediococcuspentosaceus*Li05 was incorporated in alginate-gelatin microgels with or without magnesium oxide nanoparticles and systems were characterized using transmission electron microscopy & atomic force microscopy. Nanoparticle indicated great benefits in enhancing probiotic viability for the period of long time storage, heat treatment, and GI transit [38]. Babitha *et al*. prepared TiO_2 nanoparticles from the bacteria (*Propionibacterium sp*.) isolated from the coal fly ash effluent. The bacterial strain was detected on the basis of character like 16 rDNA gene sequence (KC 545833), cell viability plus haemolytic studies sure the biocompatible and nontoxic nature of the nanoparticles. The synthesis of Tio2 nanoparticle showed non-toxic nanoparticles with improved wound healing property [39]. Ghibaudo *et al* investigated pectin furnished magnetite nanoparticles for iron delivery and safeguard of probiotic bacteria. The investigation for stability of iron-pectin nanoparticles and its use in delivery of probiotic strain (*Lactobacillus plantarum* CIDCA 83114). Iron oxide (Fe_3O_4) nanoparticle was prepared from o.25m FeCl2/0.5m, $FeCl_3.6H_2O$ and moreover covered with citrus pectins. The pectin decorated magnetite nanoparticles were used for delivery of probiotic in iron deficient population [40].

Table 2. List of probiotic formulationsavailable in the market [23].

Formulation – Capsule	Strain of probiotic microorganism	Example of brand	Use claim by label
	Bacillus coagulansnr	Probioslim(probioslim, Canada, USA)	"Promotes healthy digestion, helps you lose weight"
	Escherichia coli Nissle 1917	MUtaflor (pharma-Zentiale, Germany)	"For chronic constipation or ulcerative colitis"

		L. helveticus R52 (CNCM I-1722)+L. rhamnosus R11 (CNCM I-1720)	Florastor (Biocodex, France)	"Strengthens digestive balance" "Boosts immune response"
		L. acidophilus LB	Lacteol (Mirren south Africa)	"preserves intestinal peristalsis"
		S. boulardii CNCM I-745 (ATCC 74012)	Florastor (Biocodex, France)	"Strengthens digestive balance" "Boosts immune response"
		L. acidophilus nr + B. infantisnr	Infloran Berna(Berna, Switzerland)	"Helps restore balance of intestinalbacteria" "Used for diarrhoea, vaginal and urinary tract infections"
	Sachets	*L. helveticus R52 (CNCM I-1722)+L. rhamnosus R11 (CNCM I-1720)*	Florastor (Biocodex, France)	"Strengthens digestive balance" "Boosts immune response"
		L. acidophilus LB	Lacteol (Mirren south Africa)	"Preserves intestinal peristalsis"
		S. boulardii CNCM I-745 (ATCC 74012)	Florastor (Biocodex, France)	"Strengthens digestive balance" "Boosts immune response"
		L. helveticus (bulgaricus) 33409 + L. gasseri 4962	Lactinex (Becton, Dickinson Comp., USA)	"Replaces intestinal flora"
		Enterococcus faecium SF68	Bioflorin (Sanofi, Germany)	"To treat diarrhoea"
	Tablet	*Clostridium butyricum 588*	MIYA-BM(MIyarisan Pharm, Japan)	"Intestinal health"
		L. reuteri DSM17938 + L. reuteri PTA5289	Lactinex (Becton, Dickinson Comp., USA)	"Replaces intestinal flora"
	Powder	*Enterococcus faecium SF68*	Bioflorin (Sanofi, Germany)	"To treat diarrhoea"
		L. reuteri DSM17938 + L. reuteri PTA5289	Protectis (BioGaia, Sweden)	"Replaces intestinal flora"
	Lozenges	*L. reuteri DSM17938 + L. reuteri PTA5289*	Protectis (BioGaia, Sweden)	"Healps restore balance in digestive tract"

Abbreviations: *ATCC, American Type Culture collection; B, Bifidobacterium; CNCM, Collection Nationale de Cultures de Microorganisms; DSM, Deutsche Sammlung von Mikroorganismmen; L, Lactobacillus; S, Saccharomyces.*

Tablets.

Tablets are the most common type of dosage form, 3rd to 4th of the medicines are prescribe in this dosage form. Tablet is a compressed form of powder or granules that contains medicative products with or without excipients [41]. The primary objective of tablet production is to preserve the probiotic bacteria from stomach acidity for enhancing their stability and viability, which inturn is useful in fighting against various diseases. The microparticles of the *Lactobacillus paracasei* L26 with protein concentrate are generated by spray drying and integrated into tablets with phthalate cellulose acetate and croscarmellose sodium. Probiotic tablets created have disclosedthat they are potential vectors to deliver viable probiotic microorganisms. Paracasei L26 and likely other probiotics are beneficial for patient by probiotic treatment [42]. Klayraung *et al* 2009 exhibited the percentage excipients for tablets and the force of compression influenced the characteristics of probiotic, tensile strength and disintegration with bacterial cell viability were created through appropriate formulation design. These findings open the option of treating patients with tablet formulations who may benefit from probiotic treatment [43]. Poulin *et al* showed that the utilization of succinylatedβ-lactoglobulin as the new purposeful tablet content to protect probiotic bacterium from harmful stomachic environments and their survival of as much as 108 cfu to 107 cfu after 60 min. and 120 min GI incubation. Succinylatedβ-lactoglobulin was shown to be acceptable natural excipient for forming tablets featuring probiotic bacterium and promoting their life against gastric environments [44].

Powder/Granules.

Powder is a dry, majority solid which includes an enormous amount of very fine particles which can flow freely when agitated or tilted. Granules are class of powder which have different form used for encapsulation of probiotic. Probiotic powders are great supplement for the improvement of healthy digestion, maintain the intestinal lining and support gut mobility. Her *et al* 2015 prepared probiotic powder through spray freeze drying technique using *Lactobacillus casei* (IFO 15883). The survival rate of bacteria was measured employing plate agar counting technique. The biopharmaceutical powder preparations were successfully prepared and viability rate of spray freeze drying probiotic powder was found to be 97 percentage [45]. Weng *et al* showed that increased amylose maize (amylomaize) starch granules which effect the viability *of Bifidobacterium spp.* in mouse intestines. The probability of employing maximum amylose maize starch granules with *Bifidobacterium spp* for delivery of probiotic bacteria was considered, The *Bifidobacterium* Strains (Lafti™ 8b and Lafti™ 13b) were culture either with or without increase amylose maize starch granules, after that, blended with increased amylose maize starch granules in addition to introduced in acid buffers or solutions of bile acid. The growth and existence of increased amylose maize starch granules shows high survival of Lafti™ 8b and Lafti™ 13b strains [46]. González-Ferrero *et al*. encapsulated *Lactobacillus plantarum and Lactobacillus casei*

with soyabean protein concentrate by spray drying technique. The shelf life, probiotic viability and tolerance were found significantly enhanced after the encapsulation of probiotic microorganisms.[47].

3. PATENTS AND FUTURE PERSPECTIVE

The patent is one of the value forms of intellectual property right, filing a patient is the smart work by inventor or company. Patent will only protect the new innovations created by company and scientist[48]. The patent filing for probiotics in recent 20 years, drastically increasing in order, most of from United States, Europe and China. List of patent with their title, patent number, assignee and issue date on probiotics are selected for oral delivery are tabulated and shown in table 3. List of patents filed by the inventors depicted the application of oral delivery of probiotic as therapeutic agent for the treatment of various disease.

Table 3. List of patents filed by inventors depicting oral delivery of probiotics.

Patent Number	Inventor	Assignee	Title	Issue date
US 9, 907, 755 B2	Kabadi *et al.*	Therabiome, llc.	Targeted gastrointestinal tract delivery of probiotic organisms and / or therapeutic agents	Mar. 6, 2018
US 6,479,051 B1	Bruce *et al*	UrexBiotex, Inc.	Oral administration of lactobacillus for the treatment and prevention of urogenital infection	Nov. 12, 2002
US 9,511,102 B2	Castellana	AB-BIOTIcs S.A.	Probiotic composition for oral health	Dec. 6, 2016
US 6,706,287 B2	Ranganathan *et al.*	Kibow Biotech Inc.	Prebiotic and probiotic compositions and methods for their use in gut-based therapies	Mar. 16, 2004
US 9,629,883 B2	Fagerberg *et al.*	University of florida research foundation, inc.	Probioticarginolytics oral compositions and methods of making and using probiotic arginolytic compositions	May 23, 2017
US 9,629,883 B2	Mira Obrador	Centro superior de investigaconensaludpublica (CSISP)	Anticaries compositions and probiotics/prebiotics	Apr. 25, 2017
US 9,265,719 B2	Castiel *et al.*	L'OREAL	Cosmetic use of microorganism(s) for the treatment of scalp disorders	Feb. 23, 2016
US 8,926,952 B2	Trejo *et al.*	The procter and Gamble Company	Methods of use of probiotic bifidobacterial for human beauty Benefits	Jan. 6, 2015
US2019/01097A	Rudolph *et al.*	Merck patent	Oral administration form comprising probiotic bacteria	Apr. 18, 2019

4. CONCLUSIONS

Oral delivery of probiotic microorganisms has been a topic of interest with many challenges and regulatory complications for developing an acceptable delivery system. However, taking into consideration the factors affecting probiotic therapy and therapeutically beneficial effects of probiotic microorganism, effective oral delivery system have been developed and patented too. Genetic modification of microorganism for enhancing the existing probiotic properties of an organism is also attracting the researcher working in this area enabling them to develop specific and targeted probiotics. Synbiotic which are a combination of probiotics and prebiotics are also been used in combination, Probiotic is a non-digestible food ingredient that selectively stimulates the growth/activity of one or a number of microorganism. Hence, suitable combination of probiotic and prebiotic enhances the activity and survival of microorganism. The main focus should be on development and evaluation of new strains of probiotics and their application in biomedical and clinical research with an aim to improve human health.

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