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Review Article

PROBIOTIC DELIVERY SYSTEMS: APPLICATIONS, CHALLENGES AND PROSPECTIVE

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ABSTRACT

Probiotic are bacteria that help to maintain the natural balance of the microorganism in the intestine. Probiotic is gaining its popularity as an alternate approach for the healthcare management and till now has proofed its therapeutic indication in many simple to complex diseases. Diverse mechanism of action and being a living organism are two main advantages. However there are several drawbacks also associated with this new emerging therapeutic area. Probiotic strain identification, characterization, screening, understanding its mechanism of action for particular disease which is seeking much attention. The primary aim associated with the probiotic delivery is maintaining bacteria viability during product manufacturing and during storage. Several approaches such as microencapsulation and use of suitable biocompatible material have been studied and still under continuous exploration. Along with the regulatory aspect associated with the probiotics in this review details on current research in the area of exploring indication and advancement in delivery technologies has been covered. Review concluded with rational recommendations of each aspect of probiotics.

Key words: Probiotics; therapeutic application; delivery technology; Regulatory aspects

INTRODUCTION

The Food and Agriculture Organization (FAO) and the World Health Organization (WHO) have defined Probiotics as "Live microorganisms which when administered in adequate amounts confer a health benefit on the host".[1] Probiotic are live microorganisms (in most cases bacteria) that are similar to beneficial microorganism found in human gut. The human digestive track has several kind of bacteria, out of which probiotics bacteria maintains the natural balance of the microorganism by reducing the growth of harmful bacteria and promotes the healthy digestive system.[2] So are called" friendly bacteria" or good bacteria.[3] In 1908 Metchinkoff suggested that people should consume fermented milk which contains lactobacilli for health benefit and to prolong their lives.[4] Accelerated aging is because of autointoxication which is due to toxins produced by some gut micro flora. The pathological reactions might be removed and life expectancy could be enhanced by implanting lactic acid bacteria from the food or consumable.[5]

In 1953 Kollath introduced the term Probiotics for such health beneficial microbes. The widely used definition of probiotics was suggested by the Fuller in the year of 1989 as "A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance".[6] For the regulatory purpose the US Food and Drug Administration (FDA) uses other terms for live microbes; live microbes used in animal feeds are called "direct fed microbials"[7] and when intended for use as human drugs, they are classified as "live biotherapeutics".[8] However, no legal definition of Probiotics exists in the United States or in other countries, which allows the marketing of products labelled as "Probiotics" that do not meet the fundamental criteria stipulated in the scientific definition.

The first recorded use of probiotics was human consumption of fermented milk. Although yeast is a Probiotics substance, the largest group of Probiotic bacteria is Lactobacillus acidophilus.[9] Probiotics are available in food and dietary supplements such as capsule, tablet and powder form. Food containing Probiotic are yogurt, fermented and unfermented milk, misco, some juices and soy beverages. In Probiotic food and supplements, the bacteria may have been present originally or added during the preparation.[2]

Efficacy of the probiotic and colonization of it can be improved by substances called 'prebiotics'. Probiotics are often supplemented with Prebiotic. The term prebiotic was coined by Gibson and Roberfroid who defined them as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon".[10] They stimulate bacterial growth and enhance fermentation leading to production of short chain fatty acids, but they neither absorbed nor degraded in the GIT.

The term 'synbiotic' applies to a product that has a mixture of probiotics and prebiotics. In general, the prefix 'syn' implies the synergism between probiotics and probiotics.[10] Several species of bifidobacteria have been found to show better growth rates with fructo-oligosaccharides than on inulin.

In current review article, various applications, research evolved around development of Probiotic delivery systems as well as challenges and prospective of Probiotic delivery systems are discussed.

Application of Probiotics

Probiotic are bacteria that help to maintain the natural balance of the microorganism (micro flora) in the intestine. Lactic acid bacteria (LAB) and Bifidobacteria are the most common types of microbes used as Probiotic: but certain yeast and bacilli may also be helpful. Probiotic are commonly consumed as part of fermented food with specially added active live cultures such in yogurt, soy yogurt or as dietary supplements. Probiotics are usually used by the patient of indigestion, diarrhea or heartburn. Several diseases and conditions have been proposed to be treatable with probiotics on the basis of animal studies, preliminary human studies, uncontrolled studies, anecdotal observations, or simply speculation. These uses can be classified as potential

applications of Probiotics in the future or that require ongoing research. There have been animal studies and one small human trial that indicate that Lactobacillus GG may be useful for alleviating joint symptoms among patients with rheumatoid arthritis.[11,12] There are several animal studies that show that Probiotics inhibit initiation or progression of colon and bladder cancers.[13,14] In vitro, cell culture, and animal studies have indicated that Probiotics bind and prevent the absorption of aflotoxins, which have been implicated in the etiology of liver cancer in humans.[15,16] A rat model of ethanol-induced liver damage has been used to demonstrate the protective effects of Probiotics.[17] An animal model of diabetes showed that Lactobacillus GG could lower levels of blood haemoglobin A1c and could improve glucose tolerance.[18] Probiotics studied in a mouse model have demonstrated a possible role for these agents in the prevention or treatment of graft-versus-host disease in transplant recipients.[19] Probiotic could also be used in the conditions like irritable bowel syndrome, inflammatory bowel disease, infections with helicobacter Pylori, tooth decay and periodontal disease, vaginal infections, stomach and respiratory infections and skin infections.

Advantages of Probiotics as therapeutic agent

Diverse Mechanisms of action: A unique advantage of with the Probiotic therapy is that they are 'living organisms incorporated delivery system' and they survive to the target organ. Probiotics suppress the effect of disease causing micro organism or suppress the growth. Potential mechanisms of action may include:

(1) Enhancing the natural barrier effect of normal intestinal micro flora,
(2) Modulation of the immune system,
(3) Direct anti-microbial effects and
(4) Regulation of intestinal enzymes and interactions with the enteric nervous system.[20,21-23]

Enhancement of natural barrier effect: It is documented that a typical human may carry over several thousands of bacterial species in the collective intestinal microbiome.[24] The normal intestinal flora has many functions, including digestion of food, but the one that is most germane for this discussion is called ''colonization resistance''.[25] This involves the interaction of many bacterial microflora and results in a barrier effect against colonization of pathogenic organisms. Normal microflora may act by competitive exclusion of nutrients or attachment sites, produce bacteriocins, or produce enzymes detrimental to pathogenic growth. Factors that disrupt this protective barrier, for example antibiotic use or surgery, results in host susceptibility to pathogen colonization until such time as the normal microflora can become re-established. Probiotics are uniquely qualified to fit into this window of susceptibility and may act as surrogate normal microflora until recovery is achieved. There are several avenues to preserve the barrier effect: probiotics have been shown to protect the integrity of the tight junction between enterocytes[26], or block the attachment sites for pathogens (including C. difficile) or their toxins.[13, 27] Some probiotics may directly destroy pathogenic toxins produced by C. difficile toxin A or B or suspected etiologies for some cases of antibiotic associated diarrhea (AAD).[28,29,30]

Modulation of immune system: Probiotics may also regulate immune responses, by increasing secretory IgA levels in the intestines[133], by either increasing or deregulating cytokines[14] or inducing higher levels of anti-toxin A/B antibodies[31] Probiotics may also alter amino acid metabolism, restoring protective levels of short chain fatty acids in the intestine.[32]

Regulation of intestinal enzymes: Probiotics also affect the regulation of the enteric nervous system[33] and reduce epithelial apothesis.[34] Not all probiotics have the ability to produce every mechanism of action described above, but many of the strains utilize multiple mechanisms, increasing the probability of probiotic effectiveness against a specific pathogen. The benefit of these multiple mechanisms is the rapid restoration of bacteria disrupted by inciting antibiotics.[35]

Survival to target site: Probiotics can act as their own delivery vehicle for anti-pathogenic enzymes or defensive mechanisms. Animal models or healthy human volunteers study finds that probiotic organisms survive through GIT and are detectable in the stool. One of the study suggested that although much of the oral dose is destroyed, where usually stool levels are hundred times lower than the oral dose given, the surviving dose is usually effective as a therapy as long as stool levels are over 108 organisms/g stool.[36]

As all of the protective mechanisms described above are an inherent component of the probiotic organism and the enzymes are pre-packaged in a living organism, delivery of the multiple mechanisms of action are carried along when the organism passes through the digestive system.

Drawbacks and Limitations of Probiotics

Most of the above information indicates only benefits of Probiotics. However, there is another side to this therapy. In fact, when they're not taken as per their prescription, they can easily lead to a lot of problems.

Side effects and drug interactions: Probiotics are usually used by the patient of indigestion, diarrhea or heartburn. While probiotics may alleviate some of these problems but may also cause similar kind of complications when it is not taken as per prescription. The National Center for Complementary and Alternative Medicine describes the potential gastrointestinal side effects of probiotics. The most common side effects of probiotics are gas and bloating. In more serious and more rare instances, probiotics can cause infections, especially in Immuno-compromised people.[37] According to researches carried out recently, probiotics are known to react with certain drugs like Sulfasalazine. Probiotics causes faster metabolism of these drugs and thereby causing higher quantities of them in the body. In some cases the genetically modified strains increases the mortality rate of patients with acute pancreatitis. In a clinical trial conducted at the University of Western Australia, aimed at showing the effectiveness of probiotics in reducing childhood allergies, those given the good bacteria were more likely to develop a sensitivity to allergens compare to placebo treatment.

Probiotic Efficacy: Many probiotics products claim for beneficial effects for digestive health and immunity further these claims are strengthen by the animal models, clinical studies and related studies. While there are some study and reports are there which raises the question of probiotic efficacy. A 2010 report in "The Independent" reports that the

European Food Safety Authority, Europe's equivalent of the FDA, had rejected all of the health claims by every probiotic manufacturer in Europe. According to this report, none of the health claims concerning probiotcs have been backed by sufficient scientific evidence. MayoClinic.com also explains that probiotic supplements may not be necessary for health as your body already contains plenty of this healthy bacteria.[37]

Price: One of the biggest drawbacks of probiotics is that they are not cheap. It is an developing segment of therapeutics which requires extensive research & exploration, further its manufacturing, packing and storage is not as simple as conventional products. In a discussion about probiotics on CNN.com, Dr. Otis Brawley points out that probiotics are expensive and not likely to be covered by insurance any time soon. Most probiotic supplements are sold in specialty stores or on nutrition websites for high prices. Some probiotic supplements are designed specifically for infants with colic and charge parents a premium for a potential colic cure.[37]

Handling and storage: The probiotic exerts its beneficial effect after colonization in the gut environment. Hence it is the primary requirement that it should reach to gut in viable condition. These are delicate organisms that require appropriate handling to maintain maximum activity. Probiotic products contain live cultures and require appropriate handling to maintain their maximum activity during storage. The potency of probiotics can be adversely affected by prolonged exposure to high temperature and humidity. Thus, refrigeration is recommended during storage. Although Probiotic strains vary in their sensitivity to heat, most studies show bacterial organisms lose viability over time at room temperatures. This can create significant product quality issues, especially in retail settings where probiotic products are often sold unrefrigerated. An industry study undertaken in the 1990s found that up to half of Probiotic products purchased from retail stores contained significantly fewer live organisms than claimed on the label. A more recent 2003 review by an independent laboratory found that over one-third of commercial probiotic products tested contained less than 1% of the expected number of viable organisms.

Probiotic Drug Delivery Technologies, their Advantages and Challenges

Presently, various kinds of probiotic formulations have been developed for the specific purpose which includes fermented milk, chewing gum, sachets and capsules.[38,39,40,41] Most of formulations are developed for the oral administration of the probiotics as site of action for these probiotics is gut micro flora.

While passing through the GIT the Gastric juice is generally the strongest barrier for such probiotics, whereas bile salts and pancreatic acid together causes around one third mortality of the cells which survived stomach transit. For effectiveness, orally administered probiotics should be efficiently implanted in the intestine and adhere to the intestinal mucosa where it proliferates and provides beneficial health effects. Reaching the intestine, these microorganisms should be able to establish themselves, remain viable and perform their beneficial actions. This means that they must tolerate the acidic and protease rich conditions of the stomach and survive and grow in the presence of bile acids. This feature is also strongly strain-dependent, but on average 10 to 25% of the ingested cells are able to survive and reach the gut, thus exerting their probiotic benefits.[42] Del Piano et al. studied seven *Lactobacillus plantarum* probiotic strains for their ability to survive in simulated gastric juice and human gastric juice. It was noted that less than 20% of the bacteria survived after an hour of exposure to simulated gastric juice, while human gastric juice allowed a survival rate between 15% and 45%.[43]

The traditional products show limited stability of the Probiotic microorganisms. Among several species of Probiotics, only one strain of *Bifidobacterium longum* could survive in fermented milk for 2 weeks. Moreover, the number of viable bacteria that enter the intestinal tract is not controlled with these formulations because the bacteria do not survive at low pH in the stomach.[44] Hence, there is a need for formulations that provide protection to the bacteria from the harsh conditions in the stomach. Probiotic survival in products is affected by a range of factors including pH, post-acidification during products fermentation, hydrogen peroxide production and storage temperatures.[28] Moreover, the process also determines the viability of these cells and significant concern also needed with respect to manufacturing process. There are various approaches studied for providing protection to probiotics and also targeting its delivery to the intestinal track.

Providing probiotic living cells with a physical barrier against adverse conditions is an approach currently receiving considerable interest.[29]

Microencapsulation of Probiotics

Microencapsulation of bacteria with a gastroresistant material may be applied to accelerate and amplify the onset of their beneficial effects. Microencapsulation is extensively used in the pharmaceutical industry for various applications. Generally microencapsulation is a process by which small particles or droplets are surrounded by a coating to produce microcapsules[301] The concept of microencapsulation allows the functional core ingredient (in this case the probiotic cells) to be separated from its environment by a protective coating. Separation of the functional core ingredient from its environment continues until the release of the functional ingredient is desired (post stomach for the probiotic).[45]

Probiotic encapsulation technology is an exciting field of pharmaceutics that has emerged and developed rapidly in the past decade. Based on this technology, a wide range of microorganisms have been immobilized within semipermeable and biocompatible materials that facilitate the efficient delivery of the living cells.[45] Encapsulation is the process of forming a continuous coating around an inner matrix that is wholly contained within the capsule wall as a core of encapsulated material, while immobilisation refers to the trapping of material within or throughout a matrix.[45] Encapsulation tends to stabilize cells, potentially enhancing their viability and stability during production, storage and handling. An immobilized environment also confers additional protection to probiotic cells during rehydration. As the technique of immobilization or entrapment became refined, the cell immobilization technology has evolved into cell encapsulation technology.[45]

The best application of encapsulation technology in the pharmaceutical field is the controlled and continuous delivery of cells in the gut with maintaining its viability while passing through the acidic environment. In their viable state, probiotics may exert a health benefice on the host.[31,32] One research group showed that alginate could pass through the stomach without any degradation. Gel beads formed from this

biomaterial were visualized in the human gut by nuclear magnetic resonance imaging.[33] The choice of the biomaterial is crucial because it determines the effectiveness of the probiotics. Beyond this protection, the probiotic containing system must withstand during the passage through the stomach, disintegrate in the gut to release the cells. Probiotics are currently encapsulated in polymer matrices for various applications. The physical retention of cells in the matrix and their subsequent separation is the consequence of the encapsulation technology used. Selecting the encapsulation technology is very important. Moreover other processing materials used should be non toxin and biocompatible.

Material attributes for encapsulation of probiotics

The biomaterials used for probiotics encapsulation include natural polymers and synthetic polymers.[34] These biomaterial needs to be biocompatible and biodegradable as these material are in direct contact with the living cells. The most common biomaterial used for probiotics encapsulation is alginate.[35,36,46] Other supporting biomaterials include carrageenan, gelatin, chitosan, whey proteins, cellulose acetate phthalate, locust bean gum and starches (Table 1). Locust bean gum and starches are usually mixed with alginate or carrageenan to develop gel beads or capsules. It appears that specific interactions occur during mixing of these polymers. The ratio between the proportions of each biomaterial before mixing is essential.[35]

Microencapsulation process attributes

Encapsulation technology requires techniques that are gentle and non-aggressive towards the cells. There several techniques which provide the entrapment of subjected material. Spray drying, freez-drying & fluidized bed drying techniques were utilized to entrap and provide protection to the probiotics. By this techniques the probiotic were converted into the concentrated powder form, which increases the shelf-life of probiotics. However there are recent studies done which shows the effectiveness of spray-drying techniques in providing protection to the probiotic cells.[57,58] Extrusion and emulsification are the other techniques which are better than the drying technology. These techniques were intended to develop gel beads (figure -a) or capsules (figure -b) which were made from hydrocolloids by means of extrusion or emulsification techniques.[69,60] Each technology has its own advantages, disadvantages and unique principle. The main intension of development and utilizing and carrying out continues development is to provide better delivery of probiotics with improved viability of cells, easy to implement, modification according to requirement.

Detailed comparison and aspects of each technique have been summarises in the following table 2.

Table 1: Excipient used for microencapsulation of Probiotic

Polymer	Chemistry	Specific Characteristic	Remark	Reference
Alginate	Acid α-L-guluronic (G) and acid β-D-mannuronic (M) linked by β (1–4) glycosidic bonds	Temperatures in the range of 60°C to 80 °C are needed to dissolve alginate in water. Insoluble in acidic media.	Provides protection to the cells against acidic environment.	[47,48,49, 50,51,52]
Carrageenan	Linear structure consisting of D-galactose units alternatively linked by α (1–3) and β (1–4) bonds **Types**: kappa (κ) carrageenan, iota (ι) carrageenan & lambda (κ) Carrageenan	Kappa (κ) carrageenan & Iota (ι) carrageenan has a gelation property due to their Structural conformation. At temperature 60 °C to 80 °C it dissolves and on cooling it solidifies.	Forms a gel and entraps cells.	[53,54,55]
Chitosan	Positively charged polysaccharide	Insoluble at pH higher than 5.4. Form negatively charges semipermeable membrane.	Can be used in combination with other polymer like alginate, Carrageenan for providing stability or can be tailored to get intended purpose.	[46,56]
Cellulose acetate pthalate	pH dependent cellulose derivative	Insoluble at a pH below 5 but and soluble when the pH is greater than 6.	The disadvantage of CAP is that it cannot form gel beads by ionotropic gelation; only capsules have been developed by emulsification using this biomaterial. CAP is widely used as a coating agent.	[35,46]
Locust bean gum & Starches	Polysaccharide	Specific interaction occurs by mixing with other polymers. The ratio between the proportions of each biomaterial before mixing is essential	Usually mixed with alginate or carrageenan to develop gel beads orcapsules. It appears that specific interactions occur during mixing.	[35]

Table 2: Details of microencapsulation process technologies

Technology	Principal Specific Feature	Advantages	Disadvantages	Reference
Spray drying, freez-drying & fluidized bed drying techniques	Drying of aqueous medium of probiotic and carrier material and getting concentrated powder form	Less complicated technique	Release of entrapped probiotics in the dosage form & less viability.	[61]
Extrusion	Gel bead formation by extrusion of hydrocolloidal- probiotic mixture in gel forming solvent	Simple, implementable, allowing the retention of a high number of cells. Process can be automated. Uniform size beads.	Size and shape of beads depends on the diameter of nozzle & distance between the nozzle and gelling solution. Produced beads has greater size compare to capsules	[61]
Emulsification	Dispersing probiotic containing disperse phase in to the continuous phase.	Produces very smaller size capsules compare to the beads.	Process complications. Expensive process. Use of oils in the process. Un-uniform size capsules	[62,63, 34,35]

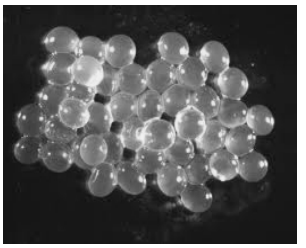

Figure -a (Beads)

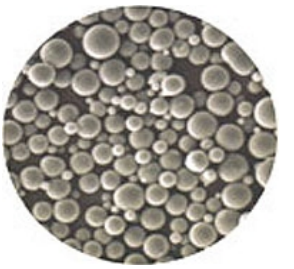

Figure -b (Capsules)

Providing protection by adjuvant excipients of dosage form

In the pharmaceutical field, acid labile drugs are formulated in tablets which are able to protect them from these harsh conditions and deliver the active substances into the intestinal tract for their intended purpose. Tablets can be easily designed to control the release and enhance the adhesion and colonization of the probiotic microorganisms to the epithelial mucosa of human host by using the proper kinds of tablet excipients.[64] Klayraunga et. al. designed a tablet formulation for Probiotics that protect them from the degradation at low pH and deliver them to the intestinal tract in viable form. They used hydroxypropyl methylcellulose phthalate (HPMCP) as tablet forming matrix because this polymer is insoluble in gastric fluids (pH ~1.5) but dissolves rapidly in the upper small intestine where the pH is around ~ 5.5. More over tablets have advantages above other dosage forms.[65] Chan and Zhang proposed the sodium alginate in combination with hydroxypropylcellulose matrix formulation where along with hydrophilic polymer alginate provides the specific gelling property which requires for providing protection ans entrapment of probiotics.[66,67] Stadler & Viernstein developed the tablet formulation using hydroxypropylmethylcellulose acetate succinate and reported to ensure high stability of Lactobacillus acidophilus in artificial gastric juice.[68] Calinescu et al. proposed Carboxymethyl high amylose starch (CM-HAS) as an excipient for bioactive agent transport in simulated gastrointestinal conditions[69,70] but due to its relatively fast and total dissolution, which can be further enhanced by enzymatic hydrolysis of alpha-amylase, CM-HAS alone may not be suitable in formulations of drugs aimed at colon delivery. Further they incorporated chitosan along with the Carboxymethyl high amylose starch (CM-HAS) as chitosan provides stability against the enzymes in duodenum and the lower intestinal tract but it can be degraded by colonic bacterial enzymes.[71] However, chitosan dissolves the gastric medium due to the protonation of amino groups. Further as a new approach they proposed a novel double-layer system based on CM-HAS:Chitosan tablets coated with CM-HAS polymer. Further for providing the better protection and to improve the percentage of delivered bacteria in intestine, they dry coated the CM-HAS:Chitosan based monolithic tablet with CM-HAS polymer which provides two step pH sensitive protection to bioactive agents.[72] Poulin et al. studied the use of succinylated Beta-lactoglobulin as a novel functional tablet excipient for the protection of probiotic bacteria against the adverse gastric conditions and their delivery in the intestine was studied succinylated beta-lactoglobuline as novel excipient which promoted the survival of actives upon compression and after simulated gastric passage.[73]

Other proprietary and patented delivery technologies

'PROBIO-TECH' technique involves the bacterial cultures to be coated with polysaccharides to ensure stability during manufacture and provide resistance to acids in stomach.

Stomach Acid Resistance (STAR) technique, developed by Institut Rosell, there is an enteric coating process to protect the probiotics during the passage through gastric barrier by preventing the solubilization in the stomach.

LIVEBAC - It is developed by Nutraceutix and provides protection by extending product shelf life even without refrigeration.

PROBIOCAP - It belongs to Balchem and Institut Rosell and claims to provide resistance to destruction in stomach and release only in intestine based on pH. Examples include L. acidophilus, L. rhamnosus, Bifidobacterium.

Starch encapsulation of LAB is being done so that bacterial production and capsulation can be done in one batch process. In this technique, a porous carrier is obtained from potato starch granules by enzymatic treatment. Finally amylase, after solubilization and cooling, is precipitated over these bacteria filled starch granules.[74] This technique is based on the adhesion between the probiotic bacteria and starch and offers several advantages like protection of bacteria from adverse environment conditions during processing, storage and its passage through upper GIT.[75]

Controlled delivery technology (CDT) process involves manufacture of tablets and capsules, which are 'programmed' to release active ingredients either at a constant rate or pulsed rate or at precisely, timed intervals. BIO-TRACT is the patented name for CDT. L.acidophilus can be released in upper small intestine, whereas Bifidobacteria targeted to release in lower large intestine with this technique.

Oil Matrix Complex technique is belongs to Natren Inc, USA, and involves the use of sunflower oil and vitamin E without oxygen and water to create a totally anaerobic environment, so the targeted organisms are separated and non-competitive.

Cryotabletting: In this technique, the tablets are quickly cooled after production to preserve microorganisms. It also belongs to Nutraceutix and does not require refrigeration during storage.

Qore Probiotic uses Trisphere™ technology, a proprietary triple-layered beadlet, to deliver bacteria to the intestines. Manufacturer claims that this delivery method is 100% more effective than traditional two-piece capsules and 50% better than enteric coated two-piece capsules at keeping the bacteria alive and usable, and delivering them to your intestinal tract.[76]

Bioadhesive vaginal tablets consisting of two layers containing different components have been formulated. One of the layers is effervescent immediate release of a fraction of the dose and the other is slow sustained release layer to

increase the residence time of the microorganism and releases organisms over a longer period of time. Hydroxypropyl methyl cellulose was used, as bioadhesive agent that produced required release-retarding effect of the Lactobacillus. These tablets found to have high molecular weight, viscosity, hydration capacity and gelling property in order to produce polymeric matrix with prolonged release characteristics. Carbopol was also attempted as a bioadhesive ingredient in vaginal tablets, decreased adhesion properties of Lactobacilli.[64]

Current research in probiotic delivery technologies

For providing better probiotic delivery there are several research is being going on and few recent innovation in the probiotic delivery technology have been summarised. Intestinal delivery systems resistant to gastric juice, loaded with the probiotic bacteria Lactobacillus acidophilus and Bifidobacterium lactis, were produced by the polyelectrolyte complexation.[20] Due to their ability to restore vaginal ecosystem, Pliszczak et al designed a new vaginal bioadhesive delivery system based on pectinatehyaluronic acid microparticles for Probiotics and prebiotics encapsulation. In this study Microparticles were produced by emulsification/gelation method using calcium as cross-linking agent.[25] Md. Athar Alli et al developed mucoadhesive microspheres of Bacillus coagulans for intestinal site specific delivery. Core mucoadhesive microspheres of Bacillus coagulans were prepared using hypromellose, following coacervation and phase separation technique and were then coated with hypromellose phthalate to achieve.[27]

Hence it can be summarise that, targeted drug delivery such as Intestinal/colon targeting, vaginal bioadhetion probiotic delivery and other such area of probiotic delivery can be explored.

Recommendations for improving probiotic delivery technology

Exploring other polymers or biocompatible material which are more suitable for purpose of providing protection to the cells and improve the viability of the cells. These materials must meet the requirements of non-toxicity, resistance to gastric acidity and compatibility with respect to probiotic cells. As stated in the previous sections there are several research has been going on with respect to exploring novel excipient for efficient delivery of probiotic as well as improving the current manufacturing technology.

Exploring new biocompatible material: The selection of excipient is a critical thing as it directly comes in the contact with the probiotic. The primary requirement is provide the protection to probiotics during the processing and storage and after ingestion by patient. These excipients can either be used in microencapsulation technology or matrix tablet formulation technology.

Manufacturing process: Also there is a need to find new manufacturing technologies which may provide better solutions for probiotic delivery. The prospective area of improvement includes use of other excipients which are suitable for the process as well as provide biocompatibility and cause less cell viability. Incorporation of other process technologies to combat the process related issue such as use of cryoprotectants in the mixture[77] in the composition.

Other site of administration: As stated in the previous section targeted drug delivery such as intestinal/colon targeting, vaginal probiotic delivery may provide a new scope and probiotics can be efficiently utilized for the health benefits.

Regulatory Aspects

Most of the available Probiotic products either come under the category of food / dietary supplement or medicinal product. Although selling of such product are being done via health food stores or internet, the strain of the microorganism used for the preparation of corresponding product is generally not mentioned on the product label. The Probiotic concept should be accepted by regulatory bodies and authorities only after their mechanism are elucidated and appropriate selection criteria is established.[78] Due to lack of regulation and standardization of probiotic agents there is difficulty in recommendation of these products for clinical application.[79] Many over the counter products are available in health food stores but they are generally neither reliable nor efficacious, and moreover many make false claims.[80] However, now considerable scientific evidence for probiotics has established regarding the safety and utility and thus appropriate regulatory guidelines are being framed.[81] Consumers should be clearly and explicitly informed and protected against the misguiding statements about the products. The indications on the labels include various conditions such as immunomodulation, urogenital infection, and skin, etc.[82] It is the responsibility of manufacturers to give due consideration to the safety aspects. But there are many limitations associated with it. A general view may be reached on the selection of the strains and probiotics but what should be the other criteria, which enable a product to be labeled as pro/prebiotic. It would be the evidence of its presence in faeces or causing changes in the host microflora or the establishment of health promoting effects? This may be the reason that as of now probiotics have not been included into any of the official compendia. All these issues should be addressed keenly requiring expertise from the field of microbiology, nutritional sciences, food technology and medical areas, so that uniform criteria for these products is set.[83] Regulations need to be revised in order to improve the overall therapy and safety with the probiotic formulations and then only their credibility will be established.

It is often misstated that Probiotics products are unregulated. Clearly, the FDA has regulatory authority over Probiotic products and regulates manufacturers' responsibilities, including the labeling and safety of these products, whether in food, supplement, or drug form. Of note, on 24 August 2007, the FDA issued regulations that require current good manufacturing practices for dietary supplements to be phased in over the next few years. Although these regulations do not address verification of efficacy claims, hopefully they will improve the compositional quality (identity, purity, and strength) of Probiotic supplements in the US market. However, manufacturers of foods and supplements are not required to obtain premarket approval of claims of efficacy or safety. In practice, the FDA has never challenged the labeling or safety of a Probiotic product except in cases where the product is represented as a drug (i.e., to treat, cure, prevent, mitigate, or diagnose disease) and lacks approval as a drug.

A reasonable approach for manufacturers marketing a product that contains a Probiotic is to use guidelines established by a working group convened jointly by the Food

and Agriculture Organization of the United Nations and the World Health Organization, which include the following.

- Proper identification to the level of strain of all Probiotics in the product, with deposit of all strains in an international culture collection.
- Characterization of each strain for traits important to its safety and function.
- Validation of health benefits in human studies, including identification of the quantity of the microorganism required to provide the benefit.
- Truthful and not misleading labeling of efficacy claims and content through the end of shelf life.

As a practical matter, the intended use of a Probiotic product will determine its regulatory categorization under the FDC Act. This categorization, in turn, will determine the regulatory status of the product. For example, depending on its intended use, a Probiotic product can be categorized as a drug or biological product, as a dietary supplement, or as a food or food ingredient (including medical food). Depending on which of these regulatory categories applies, a Probiotic product is subject to different requirements with respect to the conduct of medical tests, premarket versus postmarket authorization requirements, and evidentiary burdens to establish safety and to substantiate claims.[82]

Current Research and Potential Future Indications of Probiotics

Several diseases and conditions have been proposed to be treatable with Probiotic on the basis of animal studies, preliminary human studies, uncontrolled studies, simply speculation. These uses can be classified as potential applications of probiotics in the future or that require ongoing research.

In Liver Diseases: Studies were carried out to evaluated the effect of *Lactobacillus plantarum* alone or in conjunction with arginine for the treatment of endotoxin-mediated liver injury in rats[23] Other group also evaluated the hepatoprotective effect of *Lactobacillus casei Zhang* using rat model and results indicated that this probiotics provide liver protection by its anti-oxidative and anti-inflammatory capacities.[84]

In Immune modulation: Rodriguez et al. evaluated the capacity of *Lactobacillus reuteri CRL1098* soluble factors to modulate TNF-α production in peripheral blood mononuclear cells and to study lipid rafts participation in this response. This study demonstrated for the first time the lipid rafts participation in a response induced by a beneficial bacterium. Also, these results open new possibilities for investigating the molecular mechanisms involved in the interaction of Probiotic bacterial extracellular compounds with immune cells.[85]

As a Gene carrier for cancer therapy: Wang et al studied that the *Escherichia coli Nissle 1917* as probiotic vector can act as a gene carrier to deliver TAT-Apoptin fusion gene to the colorectal cancer.[77] Takeda et al, assessed the immuno-modulatory activity of 10 lactic acid bacteria on influenza virus infection in relation to their efficacies in infected mice.[21]

Intestinal colitis: Garrido-Mesa et al showed that *Escherichia coli Nissle 1917* as probiotic supplementation to minocycline treatment improves the recovery of the intestinal damage and prevents the reactivation of experimental colitis in mice.[26]

In Food supplement: Jones et al evaluated safety and of microencapsulated Lactobacillus reuteri NCIMB 30242 in a yogurt formulation and found safe for its application in food.[24] Gil-Campos et al, evaluated the safety and tolerance of an infant formula supplemented with Lactobacillus fermentum CECT5716, a probiotic strain isolated from breast milk, in infants of 1–6 months of age and found its safety as food supplement.[23]

CONCLUSION

Presently the use of probiotic as an alternate therapeutic approach is in initial stage. Probiotics is continuously proving its potential candidature as an important and alternate approach for the healthcare management and finds numerous applications in various diseases from simple digestive problem to cancer. Probiotic as an alternate therapeutic approach requires much more emphasis at clinical stage to prove the significance of mentioned findings and their implication for the therapeutic effectiveness. There are several aspects such as probiotic strain identification, characterization, screening, Understanding its mechanism of action for particular disease which are seeking much attention. The probiotic delivery is another area which needs much improvement and exploration as probiotics are very susceptible to process and environment. As part of probiotic delivery it is needed to explore new excipient and exploring new technologies along with improving the current techniques for the delivery of probiotic. Efforts are also to be made for developing suitable and efficient in vitro and in vivo techniques so that safe suitable and efficacious products, which have also evaluated on the ground of risk-benefit comparison with existing treatment, can reach the market.

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