Therapeutic Potential of Encapsulated Probiotics in the Management of Inflammatory Bowel Disease

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Abstract

Probiotics play a vital role in human health and have a potential effect on composition of gastrointestinal (GI) microflora. Chronic inflammation is recognized as a major contributor to inducing chronic inflammatory bowel conditions due to an imbalance of dysbiosis of GI microflora. The inflammatory bowel disease (IBD) is prevalent and recoded in Western countries. Moreover, recent data depicted IBD also increased in other regions like Japan, Singapore, India, and Malaysia. There are many factors that contribute to developing this ailment including the interaction of environmental elements: gut microbiota composition and immune system. Oral therapy of probiotics gained popularity for various ailments including inflammatory bowel disease, intestinal barrier dysfunction, and colorectal cancer due to its safety and suitability. That few probiotics have the potential to survive in acidic and bile conditions in GIT. The probiotics and probiotic-based interventions had been depicted as having promising therapeutic potential as compared to conventional treatments. Therefore, encapsulation technology gained popularity in protecting the probiotics from the harsh environmental conditions of GIT. Some animal and clinical-based research have demonstrated that probiotic therapies can modulate GIT microbiota and alleviate inflammation of the gut. Moreover, certain prebiotics have been encapsulated with probiotics to achieve better results. This chapter contributed to adopting the advance techniques for effective delivery system of probiotics with increased efficacy against IBD.

Keywords: Probiotics, GIT microflora, IBD, Encapsulation techniques, advance interventions

Cite this Article as: Abid M, Iftikhar F, Munawar A, Javid M, Amin S, Sajjad F, Sajjad U, Aftab M, Fatima M and Arif S, 2025. Therapeutic potential of encapsulated probiotics in the management of inflammatory bowel disease. In: Aadil RM, Salman M, Mehmood K and Saeed Z (eds), Gut Microbiota and Holistic Health: The Role of Prebiotics and Probiotics. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 279-286. https://doi.org/10.47278/book.HH/2025.180

A Publication of Unique Scientific Publishers

Chapter No: 25-037

Received: 12-Jan-2025
Revised: 21-March-2025
Accepted: 12-May-2025

Introduction

The inflammatory bowel disease (IBD) is a chronic inflammatory condition of GIT. The functionality of GIT (food digestion, absorption, and excretion) is affected by inflammation (Darb Emamie et al., 2021). The symptoms of IBD include diarrhea, fatigue, abdominal pain, weight loss, and severe bleeding in the rectum. Additionally, the other inevitable convolutions linked to IBD include abscesses, stenosis, fistulas, and colorectal cancers (Asha & Khalil, 2020). The symptoms of IBS (irritable bowel syndrome) and IBD have confusion in a few cases. This disorder is related to gastrointestinal and worldwide prevalent were 7% (IBS) and 0.5% (IBD) affected (). Both diseases have adversely affected on patient's quality of living, increased financial burden and health care cost (Alatab et al., 2020). However, IBS affects the down area of GIT, especially small and large bowel (Darb Emamie et al., 2021). The patients suffering IBS frequently experience constipation, diarrhea and bloating. Meanwhile, gut inflammation contributed in worse symptoms including loss of appetite, bloody stool, and weight loss, could have a potential role in promoting colonic cancer). Recent data depicted that genetic factors of host play crucial role in the development of IBD either through weak immune system or microbiota dysbiosis (Darb Emamie et al., 2021). Moreover, gut microbiota is crucial microbial community inside the body comprising fungi, viruses, bacteria and microbes reside in GIT (Dzutsev et al., 2015). Overall human health is affected by GI microbiota including digestion and absorption as well as regulation of gut barrier function and maintenance of the immune system (Luo et al., 2022). The previous research depicted that microbiota play a significant role in the disease prevention and health promotion. There are two types of IBD Ulcerative colitis (UC) and Crohon's disease (CD) (Luo et al., 2022). The pathogenic factors involved in IBD is still unknown and considered often linked to microbial infections, inherited genes, diet, and environmental factors (Bajinka et al., 2020).

The important key factors are to maintain homeostasis especially in epithelial barrier function, interaction with microorganisms and innate immune system. However, the intestinal mucosal barrier is disrupted and the immune system is inactivated (Franzosa et al., 2019).

The first crohons disease associated gene was elaborated in 2001 and ulcerative colitis associated genes are ongoing to be described. The

GI microbiome of humans has to be recognized as therapeutic solution for inflammatory bowel disease (Hoffmann et al., 2016). Numerous studies have shown that alternative therapies utilizing probiotics and specific dietary supplements including prebiotic modulate the GI microbiome (Amoroso et al., 2020; Naseer et al., 2020). Furthermore, the other efficacy studies confirmed that using commensal microbiota to stimulate immune function and integrity of mucosa (Chen et al., 2020; Kim et al., 2020). The clinical trial demonstrated that probiotic, prebiotic, and synbiotic therapies have a potential positive impact on curing IBD in patients (Franzosa et al., 2019). However, there are still other drawbacks including ingestion of oral probiotics were affected by gastric acid as well as bile salt in the intestine that ultimately decrease the survival and functionality of these microbes (Razavi et al., 2021). Furthermore, there is dire need to introduce the most effective strategy to tackle these challenges. The encapsulation has an emerging technique and promising solution to address this problem of delivering probiotic to the colon (Cheng et al., 2021; Zheng et al., 2020). The microencapsulation system includes enzyme responsive release, pressure triggered release system and pH responsive release have been made various method such as extrusion, drying, complex coacervation and emulsification (Cheng et al., 2021; Zhu et al., 2021). Consequently, effective methods and strategies must be employed to protect probiotics in microcapsule for the treatment of IBD.

2. Global Prevalence of Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) i.e. crohn's disease and ulcerative colitis are idiopathic disorders caused by excessive inflammation of gastrointestinal tract (GIT) leading to rectal bleeding and weight loss. IBD are chronic and relapsing disorder of the gastrointestinal tract associated with major cause of illness in western countries. This can result in debilitating physical and physiological symptoms for patients that affect society by loss of schooling absenteeism and health care cost. (Patel et al., 2018).

These western countries have good economy i.e. Western Europe, United States, New Zealand, Australia and Canada. All of these revolutionized countries have same history of industrial revolution started in 18th century within Great Britain before spreading to the Europe. At the end of 20th century Sir Wilks reported the very first case of IBD in China. Systematic analysis revealed that the cases of ulcerative colitis and crohn's disease were recognized in Asia at the start of 21st century. In 2017, IBD had a highest prevalence rate along the globe mainly in Western world (Cominelli et al., 2017). There are only 10 to 25% cases of IBD in early childhood recorded that have been associated with genetic abnormalities which suggest that it's a complex polygenic disease.

In addition to having an effect on national economies, the frequency and prevalence of this illness also have an effect on individuals' emotional and social well-being (Rudbaek et al., 2024). The ratio of IBD peaked in Western nations in the 1950s but there were few instances documented in Asia, Africa, and Latin America. At the start of 21st century, there has been observed a decline rate in the prevalence of IBD but in developing industrialized countries i.e. Asia, South America and Middle East, the prevalence rate of IBD have continuously increased. . The overall incidence ratio of IBD in Western Europe in 2017 was 136.6 per million while in Eastern Europe it was lower at 104.5 per million. Similar trends were recorded in Wales, Hungary and Sweden. By 2030, the disease is estimated to affect 1% of individuals in the Western World (Wang et al., 2023).

3. Types of IBD

IBD has two types that is crohn's disease (CD) and ulcerative colitis (UC), both of these are characterized as chronic IBD. Crohn's disease affects the people between 15 to 35 years. IBD cannot be suppressed easily like other inflammatory diseases ultimately the immune system is stimulated and the particular part of intestine can be destroyed. CD affects the digestive tract, mouth, esophagus and stomach. On the other side, UC affects the entire layer of colon. One of the main symptom of CD is malnutrition as it destroy the small intestine thus hinder the absorption of nutrients (Khan et al., 2019). The symptoms of CD and UC include diarrhea, abdominal pain, weight loss and rectal bleeding. Both of these may occur in adolescent, adults and affect men and women equally. There are some similarities and differences between crohn's disease and ulcerative colitis. Clinical signs of diarrhea (with blood or mucus), fever, weight loss, and stomach pain are typically used for diagnosing CD. Mucosal ulcers are the initial stage of ileocolic infections which finally turn into fistulas. Approximately 80% of those suffering from CD have undergone some kind of intestinal surgery (Alinaghi et al., 2020).

The cites of CD ulcers are located in particular part of gut which includes 5% in perianal zone, 25% in only small intestine and 50% in both small and large intestine. Some genetic and immunological factors trigger the disease. UC is limited to some parts of large intestine, colon and rectum. The higher ratio of CD in developed nations is due to their life style. The clinical symptom of CD and UC differs significantly. CD is frequently transmural patchy and can affect any area of the GI tract from the mouth to the anus, UC is mainly caused by confluent inflammation of the colonic mucosa. UC associated with the bleeding in stool with severe pain but in several other cases there is chance of bleeding in crohn's disease. Rectal bleeding is not common in CD while it is associated with UC. The people suffering from crohn's disease mostly have vitamin D deficiency while iron deficiency promote the chances of UC (Le Berre et al., 2020). The pathophysiology of both subtypes involves the same risk factors. Since both subtypes share characteristics like persistent inflammation and a dysregulated immunological inflammatory response, the immune system has been the subject of a large portion of studies on the pathophysiology of IBD (Banerjee et al., 2021). Benign tumors polyps may form in the intestinal wall as UC becomes worse. Severe inflammation of the colonic mucus layers and the rectum, which may spread to the deeper parts of the gut, are two of the most noticeable signs of ulcerative colitis. The incidence of UC varied from 2.4 (Romania) to 432 (Scotland) per million. The incidence of CD ranged from 1.5 (Romania) to 331 (The Netherlands) per million. Although the causes of IBD are not fully understood yet but some comprehensive studies highlight the role of genetic and environmental factors. Any change in gut microflora and disturbance on epithelium function stimulates the pathogenic response in normal mucous system leads to IBD (Gajendran et al., 2019). Adult IBD incidence varied from 9.6 to 44.3 cases per 100,000 people (4.6 to 18.5 cases for CD and 3.4 to 26.5 cases for UC), with the most current estimate being 16.2 cases per 100,000people (7.4CDand8.1UC). In both CD and UC, the psychological comorbidities are common in IBD patients (Barreiro-de Acosta et al., 2023).

4. Probiotic and Prebiotic Mechanism in IBD

Probiotics are live bacteria when given in appropriate quantity deliver positive impact on host's health. Beneficial bacteria are delivered into intestinal flora results starvation in harmful bacteria through competition for nutrients. The strains of *Enterococcus faecium, Bifidobacterium, Bacillus, Saccharomyces boulardii, Lactobacillus* and *Pediococcus* are currently marketed as probiotics and have positive health effects. The beneficial of these probiotics includes production of immunoglobulin, short chain fatty acids (SCFA) and inhibits the release of pro-inflammatory cytokines. The prebiotics are non-digestible food that stimulates the growth of beneficial bacteria. A prebiotic is a specifically fermented substance that permits particular modifications in the GI microbiota's composition and activity which improves health of host (Akutko & Stawarski, 2021).

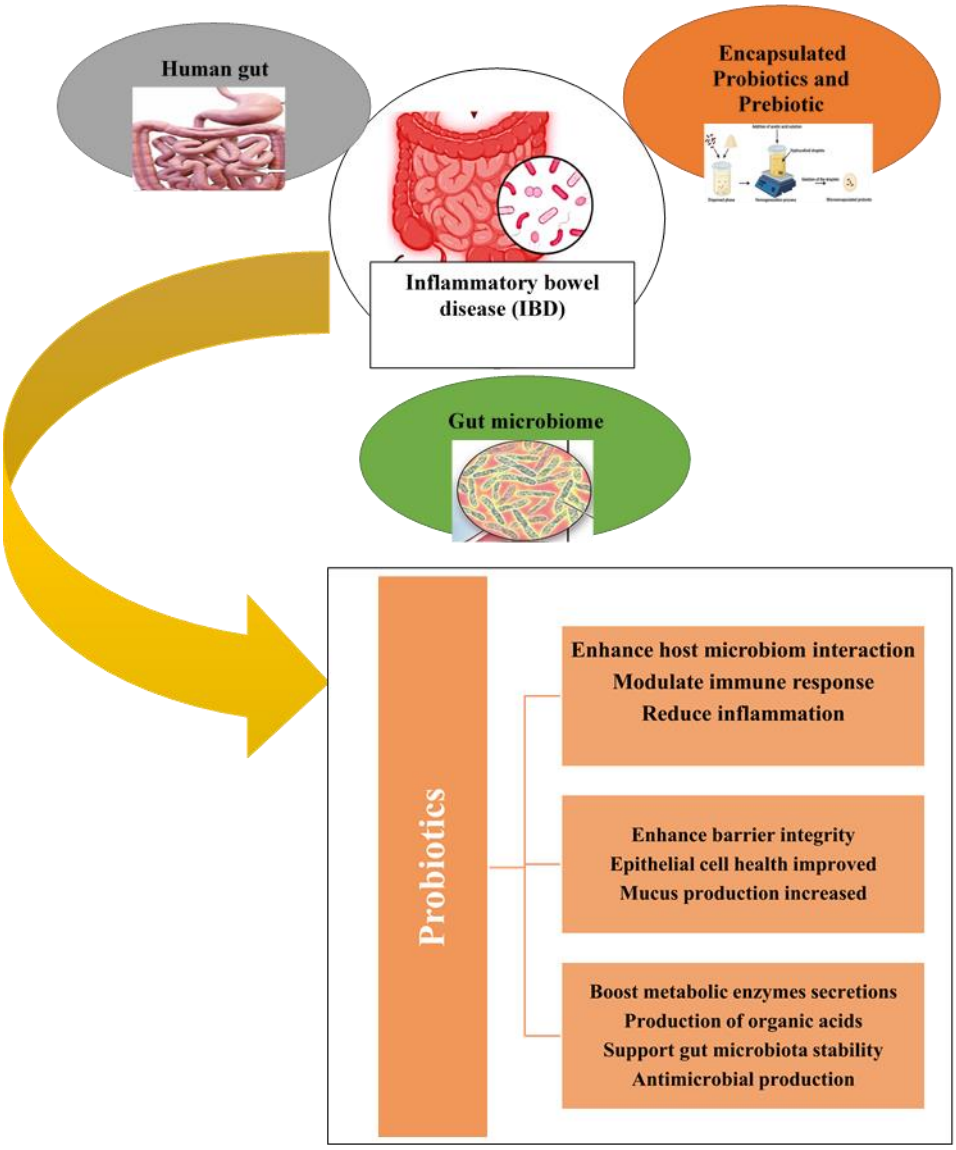

Fig. 1: Mechanism of action of probiotics against symptoms of IBD

There is growing interest in using probiotics to treat and prevent IBD. Many reports provide evidences that some probiotic strains are useful to cure IBD both in rat and murine models of the disease. Probiotics work by competing with both beneficial and harmful bacteria. They also influence immunological responses and epithelial function. They impede the growth of potentially harmful microbes by reducing the pH of the gut environment and through increasing the synthesis of SCFA. Some probiotics have immunological response through releasing cell wall fragments in the intestinal lumen. Additionally, they control the nuclear factor kappa light chain enhancer of activated B cells (NFκB) pathway's over activation, decrease the synthesis and release of pro-inflammatory cytokines (Xia et al., 2023). *Saccharomyces boulardii* treatment helped CD patients sustain remission and close their bowels. *Lactobacillus acidophilus, Escherichia coli* and *Bifidobacterium bifidum* appear to be beneficial in controlling ulcerative colitis disease. The restoration of microbial resident populations via introduction of specific microorganisms is supported by recent developments in the assessment of the therapeutic potential of microbiota in the treatment of IBD.. Oral administration of *Bifidobacterium infantis* 35,624 decreased C-reactive protein (CRP) level in inflammatory gastrointestinal illnesses but had no discernible effect on ulcerative colitis. As compared to the group without probiotic supplementation, the other groups with UC who took yakult supplemented with *Bifidobacterium breve* had higher endoscopic scores. Patients with UC disease were examined with the probiotic

mixture of *Bifidobacterium animalis* subsp. *lactis* and *Lactobacillus acidophilus* strain LA-5. The probiotic mixture inhibits the ulcerative colitis in 90% of patients (Roy & Dhaneshwar, 2023). Prebiotics have beneficial effects on IBD through several mechanisms as described in Figure 1. Non-carbohydrate constituents are also considered prebiotics and their applications are not constrained to the GIT only. These component's vast surface area and loose structure make them a superior breeding ground for helpful microbes while also preventing the growth of diseases. Consequently, it has been demonstrated that taking prebiotics improves intestinal integrity, lowers infection rates, increases host immunological function and suppresses allergic reactions (Zhang et al., 2021).

5. Fecal Microbiota Transplantation (FMT)

FMT is a therapy based on the microbiota reside in GIT acquired potential interest in recent years. It is a complicated procedure that helps in restoring a stable intestinal microflora through infusion of feces from healthy donors into unhealthy donors in order to cure a specific condition. Purpose of FMT is to restore colonic microbiota by introduction of fit bacterial population through infusion of gut microbiota for instance via orogastric tube, colonoscopy, enema or orally in the form of capsules that contain the freeze-dried mass to obtain an intestinal microbiota from a suitable donor (Zhu et al., 2021).

Absolute exclusion criteria are category that prevent a subject from participating in a study because of unfeasibility for the researcher to evaluate the subject. This is in contrast to relative exclusion criteria which make it difficult but possible for the researcher to evaluate the subject using a different methodology. Following table shows selection criteria for fecal microbiota transplantation.

Donor Selection Criteria for FMT	
Relative exclusion Criteria	Absolute Elimination Criteria
History of major GI surgery	Infections related to Systematic and local microbes
Neuropsychiatric diseases	Chronic GI disorders, Gastroesophageal reflux disease
Abnormal body mass index that is smaller or bigger than the normal value of 18-25	Chemotherapeutics administration and Malignant pathologies, chronic constipation
Diabetes mellitus (DM)	Irritable bowel syndrome (IBS)
Systemic autoimmune disease	Peptic ulcer ailment
asthma and eczema (Atopic disease)	Taking dose of antibiotics, Autoimmune disorders

5.1: IBD cases treated with FMT

133 patients were suffering Ulcerative colitis and crohon's diseases and treated with FMT via nasogastric or gastroscopy and naso-jejunal. 71% patience recovered from symptoms of UC and CD	(Ianiro et al., 2014)
555 patients suffered UC (42 studies reporting on FMT in 2017 and many cases were not reported) Clinical remission afterward FMT in 201 cases	(Paramsothy et al., 2017)
Eighty-one patients with ulcerative colitis in a double-blind group FMT for active UC and stool testers from donors FMT group was associated with specific metabolic pathways and bacteria with induction of remission	(Paramsothy et al., 2019)
73 adults who had the symptoms of UC FMT through colonoscopy followed by 2 enemas over period of seven days and thirty-eight Donor FMT thirty-five Autologous FMT	(Costello et al., 2019)
Sixteen patience with active UC enrolled 87.5% (n= 14) patients achieved clinical response to FMT	(Wang et al., 2020)

6. Postbiotics in IBD

The human gut housing approximately 70% of the immune system plays a vital role in protecting against pathogens. However, its constant exposure to intestinal contents can trigger an overactive immune response leading to inflammation, tissue damage and potentially towards inflammatory bowel disease (IBD). There are over 10 million people worldwide affected by this disease. Current treatments, such as 5-aminosalicylic acid and glucocorticoids, often cause unwanted side effects due to their broad anti-inflammatory properties. Novel biological therapies, though effective or costly and face significant challenges including a 30% non-response rate and growing drug resistance (Wang et al., 2024).

The gut microbiome comprising over 500 species of commensal bacteria significantly influences IBD pathogenesis. Research suggests that disruptions in microbial metabolite composition contribute substantially to IBD development. Fortunately, probiotic interventions have shown promise in alleviating symptoms by modulating the gut microbiota offering a potential therapeutic avenue. Despite the benefits of live probiotics, their administration raises safety concerns including the risk of transmitting harmful microorganisms, presence of virulence factors and antibiotic resistance gene transfer. Additionally, probiotics are vulnerable to environmental factors such as storage conditions, transportation and stomach acidity. To overcome these limitations, researchers have begun exploring alternative agents, including non-digestible fibers (prebiotics) and microbial-derived compounds (postbiotics). Emerging evidence suggests that the beneficial effects of gut microbiota may be largely attributed to their non-living byproducts, or postbiotics can replicate the health benefits of live cells through similar or distinct metabolic pathways. International Scientific Association for Probiotics and Prebiotics defined postbiotics in 2021 as non-living microbial products conferring health benefits (Chang, 2020).

Postbiotics comprise a diverse range of inactive microbial components including inactivated cells, cellular fragments (such as peptidoglycan, lipopolysaccharides and extracellular vesicles) and metabolic byproducts (like bacteriocins, short-chain fatty acids, biotin, enzymes, and organic acids). These compounds are typically produced through microbial fermentation or cellular lysis. Postbiotics offer a promising alternative to live probiotics replicating their health benefits without the need for viable bacteria. Postbiotics have been demonstrated

to mitigate inflammation, modulate immune response, regulate gut microbiota, Maintain intestinal barrier integrity. Notably, postbiotics boost several advantages including well-defined chemical composition, excellent safety profile, extended shelf life, non-toxicity, resistance to hydrolysis and stability in digestive conditions. These attributes make postbiotics attractive parameter for incorporation into functional foods and pharmaceuticals aimed at preventing and treating inflammatory bowel disease (IBD) (Zhou et al., 2023). Postbiotics have transformed the food and pharmaceutical landscape due to their exceptional stability, minimal interactions with other ingredients and flexible storage requirements. They also improve food quality, texture, and shelf life while exhibiting antimicrobial properties that extend the freshness of perishable items. Besides these benefits, postbiotics enhance gut health, immune function, and overall well-being (Wang et al., 2024).

Furthermore, postbiotics have shown remarkable potential in alleviating various health conditions including diarrhea, inflammatory bowel disease, cancer and respiratory infections. Their ability to regulate lipid metabolism and reduce cardiovascular risk has also been well-documented. Commercially available postbiotic products, such as CytoFlora, Hylak Forte and *Lactobacillus gasseri* CP2305 have been developed to harness these benefits that targeting immune enhancement, digestive health, mental well-being and gut microbiota balance. The postbiotics inhibit pathogenic bacteria by regulating intestinal pH providing nutrients for beneficial bacteria and producing antimicrobial substances. They also modulate the immune system by stimulating epithelial cells, influencing dendritic cells and activating innate immunity (Darb Emamie et al., 2021). Moreover, postbiotics maintain the intestinal barrier by enhancing tight junction proteins, promoting mucosal repair reducing oxidative stress and inhibiting pathogen attachment. The postbiotics offer advantages such as well-defined chemical structure, high safety profile, ease of storage and lower production costs. Future research should focus on understanding postbiotic mechanisms, establishing dose-effect relationships, assessing safety in specific populations and developing efficient separation and purification technologies. Postbiotics show promise in treating IBD improving cardiovascular health, preventing obesity, regulating blood glucose and promoting digestive health, presenting exceptional natural biomolecules for future food and medical applications (Wang et al., 2024).

7. Encapsulation Techniques

There are several encapsulation techniques that protect the live microorganism inside the hard shell and provide better delivery of probiotics. The different vital parameters include type of bacteria, living conditions, wall material, carrier size, carrier stability, mass transfer and mechanism of release in the human gut. The most important thing is that the encapsulation techniques must be ensure about safe delivery of probiotic to gut without altering their physiological properties. There are many technologies suggested for encapsulation of probiotic. These includes spray drying, freeze drying, extrusion, coacervation, gelation, spray chilling and electro hydrodynamic atomization. Few encapsulated techniques are described below;

7.1. Spray Drying

This is economical technology in which biological active ingredients (probiotics) are dispersed in a solution that have carrier and then injected to atomizer in heated air chamber. Afterwards, the dried microparticles with solid wall material are achieved. The spray drying conditions such as type of atomizer, flow rate, inlet and outlet temperature and humidity of chamber effect the size and microencapsulation efficiency as described in Figure 2 (Di Battista et al., 2017). This drying method is fast but due to high temperature the efficiency of probiotic might be decrease. As the high temperature in the chamber is used we must be choose thermostable carrier/wall material. Recently, research demonstrated that the encapsulation of probiotic through spray drying have been significantly increased the viability and stability of probiotics (Colín-Cruz et al., 2019; Pinto et al., 2019; Tao et al., 2019).

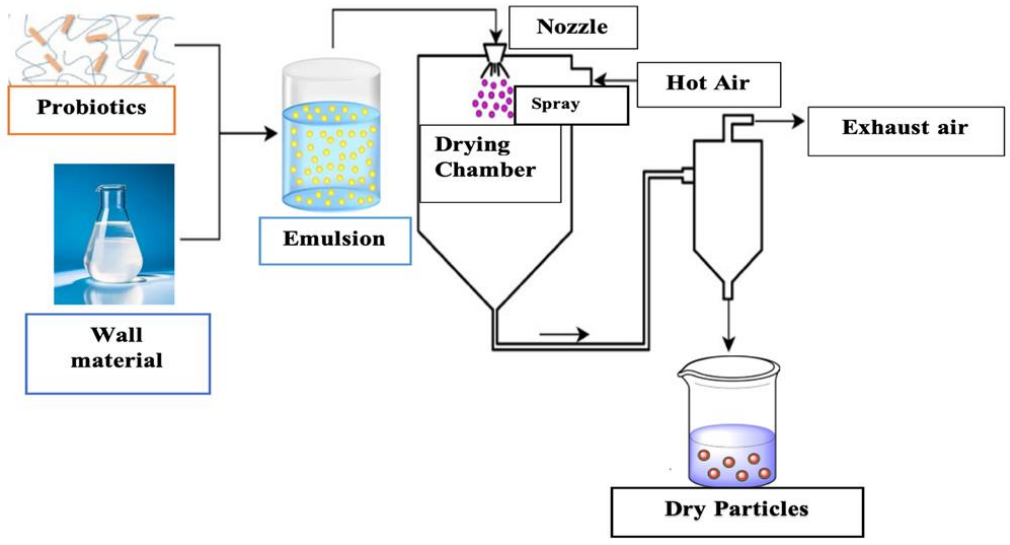

Fig. 2: Systematical Diagram of Spray Drying Chamber

7.2. Extrusion

Extrusion is a simple, economical and can be performed in gentle conditions as described in Figure 3. This encapsulated technique used to protect the bacteria and increased their viability of probiotic cells. In this procedure, hydrocolloid solution of probiotic is prepared and then injected into another hardening solution by using a syringes nozzle (24G, 25G and 28G) or encapsulator B-390 can also be used for this

procedure to make beads. The resulted microparticles are dried. The sodium alginate is the common wall material used for this method and $CaCl_2$ used as a hardening solution (Liu et al., 2019).

The *Lactobacillus plantarum* was encapsulated with sodium alginate through extrusion method. Afterwards, the viability of this probiotic was checked at two and four weeks, the viability was much higher than free cells. The acidification of microcapsules was less than free cells during storage in refrigerator. Therefore, these microcapsules can be used as food additives in yogurt and other products (Phoem et al., 2019).

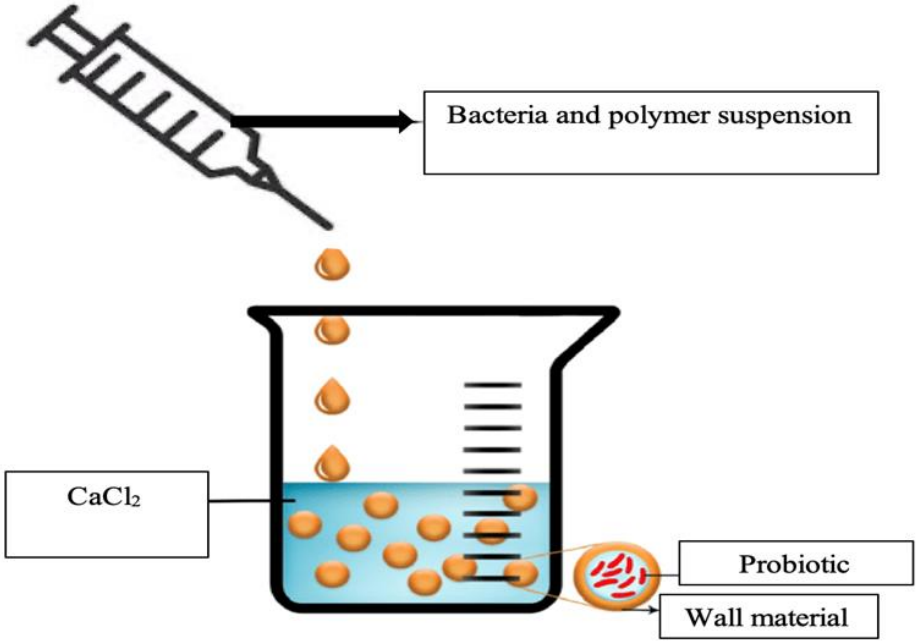

Fig. 3: Microencapsulated process of Bacteria via extrusion

7.3. Emulsification

The emulsification is an encapsulated technique in which low temperature can be used for encapsulation. This technique is super easy to scale up and significantly improved the viability of encapsulated probiotics as described in Figure 4. But the shortcoming or drawback of this technique is large particle size and the shape of microcapsules. Moreover, the size and shape can be changed by altering the ratio of water/oil and the agitation speed (Gaudreau et al., 2016). Generally, the emulsion contained one immiscible phase that is dispersed into another continuous phase with emulsifier. There are 3 methods used to encapsulate the bacterial cells in emulsification

1) Ionic gelation
2) Enzymatic gelation
3) Interfacial polymerization

These three methods for encapsulation with slightly modification in procedure.

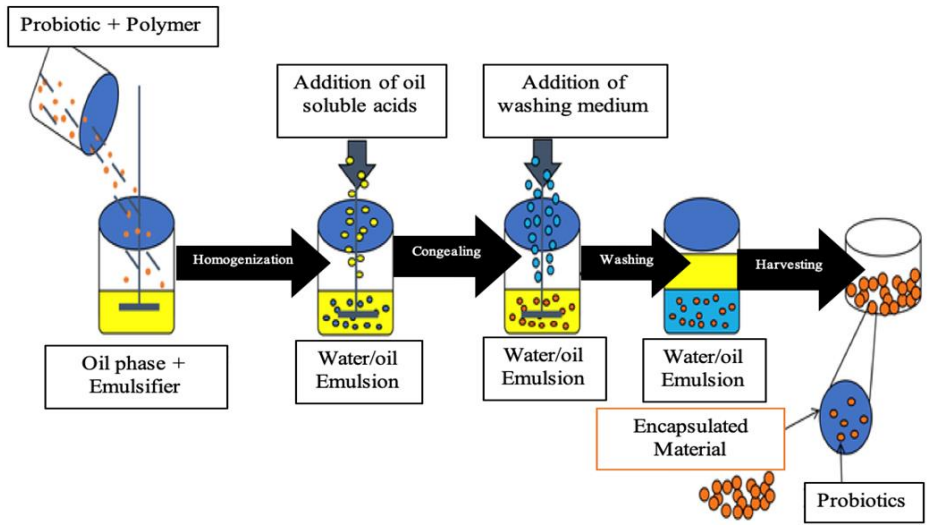

Fig. 4: Systematical Diagram of Emulsification

Conclusion

Inflammatory bowel disease is a condition involved with chronic inflammation of GIT. Many environmental risk factors such as smoking,

oral contraceptive pills (OCPs), imbalance diet and use of non-steroidal anti-inflammatory drugs promotes the IBD in population. The numerous researches have demonstrated that encapsulated probiotic have ability to restore the symptoms of inflammatory bowel disease. Therefore, the encapsulated bacterial cells have promising effect for prevention and treatment of IBD. Moreover, Additional studies needed to enhance the usage of several encapsulated probiotic techniques for their successful delivery to action site and that can be used in food products.

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