

LITERATURE REVIEW OF RESEARCH AND DEVELOPMENT OF PROBIOTIC TABLETS

Ngo Nguyen Quynh Anh^{1*}, Dam Thanh Xuan², Nguyen Ngoc Chien²

¹Hai Duong Central College of Pharmacy - 324 Nguyen Luong Bang, Hai Duong city, Vietnam

²Hanoi University of Pharmacy - 13-15 Le Thanh Tong, Hanoi, Vietnam

Received: 31/10/2023

Revised: 18/11/2023; Accepted: 08/12/2023

ABSTRACT

Probiotics are gaining increasing attention due to their significant benefits to the host. Despite their potential advantages, probiotic dosage forms have not been extensively studied, primarily because of their poor survival through the gastrointestinal tract. Probiotic tablets emerge as a promising delivery system utilized in nutritional products to supplement the natural intestinal flora. These tablets possess the capability to deliver live, functional bacteria in sufficiently large quantities, ensuring effectiveness, and providing protection against the harsh conditions of the gastrointestinal and biliary tract environment, thereby ensuring *in vivo* protection and maintaining viability during preparation. Various adverse effects that impact the effectiveness of probiotics are associated with preparation methods and user factors. This review primarily focuses on probiotic tablets, delving into factors influencing the existence of microorganisms and the development of formulations for probiotic tablets.

Keywords: Probiotic tablet; viability; factor; formulation.

*Corresponding author

Email address: qanhk63hup@gmail.com

Phone number: (+84) 988 185 505

<https://doi.org/10.52163/yhc.v64i13.865>



1. INTRODUCTION

1.1. Probiotic tablet

Probiotic microorganisms provide health benefits to patients when used in adequate amounts and in effective forms [1, 3]. Since their viability is essential, adequate storage stability and special precautions during processing are required to ensure effective dosage forms. Today, most probiotic products on the market are usually liquid or semi-solid, but they have limited cell viability after oral administration. This is mainly due to the difficult conditions in the stomach that make it difficult for bacteria to survive. Much current research is aimed at developing dry dosage forms that can enhance bacterial survival [1, 2, 5]. One expected benefit is that freeze-dried bacterial cells have low water activity so their viability can be maintained. The development of probiotic tablets is essential. Through careful selection of the tablet matrix, it is anticipated that the attached bacteria will be protected from the acidic environment in the stomach, increasing effectiveness [4, 6].

Probiotic tablets are one of the probiotic delivery systems widely used in nutritional products to supplement the natural intestinal flora. These delivery systems vary widely in their effectiveness in delivering health benefits to patients. Probiotic delivery systems can be classified into conventional pharmaceutical formulations and non-conventional products, mainly based on commercial foods. The extent of health benefits provided by these probiotic formulations varies in their ability to provide live, functional bacteria in sufficient (effective) quantities, providing protection against the harsh effects of the gastric and enterobiliary environment (*in vivo* protection), and to survive the formulation process (viability) [2]. Because tablets are convenient for patient administration, ensure safe dosing, and allow for cost-effective production on a large scale, they are the preferred dosage form for many active pharmaceutical ingredients as well as to use effective probiotic microorganisms. Tablets and capsules are convenient solid dosage forms for delivering probiotics. These formulations allow the application of various functional excipients to improve shelf life, gastrointestinal stability, cell viability and also to control release rate and target location of

probiotics [4, 8].

Tablets, a dosage form with a high market share in the global market, offer many advantages such as physicochemical stability, simple manufacturing process, low production costs and high consumer acceptance [9]. Although tablets are not the preferred dosage form for probiotic preparations, the properties of tablets make them an important avenue for probiotic drug development. Due to the adverse effects on the biological activity of probiotics due to the wet compression and granulation method, the general process to form probiotic tablets is to mix the powder with excipients after a drying process and then press pellets form directly [10]. However, processes such as drying, mixing and compacting will inevitably destroy many cellular components and biological activities of probiotics, which is a challenge that needs to be addressed in the design of probiotic tablets [11].

1.2. Ingredients of probiotic tablets.

1.2.1. Probiotic strain

Verify the identity of the probiotic strains used in the formulation. Accurate strain identification is crucial for ensuring that the intended strains are present and match the labeling. Measure the viable count of probiotic microorganisms in colony-forming units (CFUs) per dose. This indicates the concentration of live probiotics in each tablet and is a critical factor in achieving the intended health benefits. Conduct stability testing to assess the viability of probiotic strains throughout the product's shelf life. Assess the influence of temperature, humidity, and other environmental factors on probiotic viability to select the most suitable strain for the design [12].

1.2.2. Excipients

The majority of probiotic products available in the market contain various additives alongside the active probiotic ingredient. These additives, known as excipients, are integral to the performance of the product and are present in nearly all pharmaceutical formulations. The effectiveness of the product relies heavily on the physical and chemical characteristics of these excipients. Excipients serve various functional purposes, such as acting as diluents, lubricants,

colorants, binders, coating agents, sweetening agents, anti-caking agents, suppository bases, etc [13]. Commonly employed excipients for probiotic formulations, such as bulk powders, tablets, and capsules, include microcrystalline cellulose (used as a binder/diluent), rice maltodextrin (employed as a binder/diluent), silicon dioxide (utilized as a gliding/anti-caking agent), magnesium stearate (functioning as a lubricant), hydroxypropyl methyl cellulose (serving as a suspending/viscosity agent), and so on.

The Shu's research (2019) evaluated the effect of different excipient combinations of xylitol, erythritol, mannitol, sodium alginate, and microcrystalline cellulose on the quality of probiotic goat milk tablets on four indicators, namely, viable cell counts, friability, hardness, and sensory evaluation [6]. Tablet probiotic is frequently selected for the administration of viable probiotic microorganisms. *Saccharomyces cerevisiae* cells, granulated through a fluidized bed process, were tableted using a compaction simulator, employing dicalcium phosphate (DCP), lactose (LAC), and microcrystalline cellulose (MCC) as carrier materials. The compression stress was varied during the process. The tablets underwent analysis concerning physical properties, including porosity and tensile strength, along with an assessment of microbial survival. The survival rate and physical properties of the tablets were significantly influenced by the choice of carrier material and the applied compression stress. These dependencies were attributed to the specific deformation characteristics of the materials and were connected to mechanistic approaches aimed at explaining the observed variations in sensitivities [7, 8]. So, the influence of tableting speed on mechanical tablet properties was intensively studied for different materials.

1.3. Advantages

Tablets have several advantages over other dosage forms such as ease of production and administration, accurate dosage, good acceptance, and can be developed in order to allow delivery in the colon. Probiotics must colonize the distal ileum and colon in order to exert their action. Previous works designed and studied probiotic tablets using lyophilization as a way to obtain concentrated

probiotic powders [1, 14].

2. PROBIOTIC TABLET PREPARATION

2.1. Manufacturing Process

Optimize the tablet manufacturing process to ensure uniform tablet weight, content uniformity, and proper compression. Adjust processing parameters as necessary.

2.1.1. Preparation of Blend

Blend the probiotic strains with the selected excipients. This step ensures a homogeneous mixture, distributing the probiotics evenly throughout the tablet. Such as tablets were prepared by direct compression using a single punch tablet press connected to a computerized compression force analyzer, under constant environmental conditions (35% RH, 20–22 °C). An exactly weighed quantity of powder mixture containing LAB powder and HPMCP was filled into a die of 10 mm diameter and under a determined pressure ranging from 2 to 20 kN tablets with a plane surface were formed [4].

2.1.2. Granulation

Granulation may be performed to improve the flowability of the blend and facilitate the compression process. It involves the binding of powder particles into larger granules. In the granulation process, the carrier material is fluidized within the fluidized bed processor, and the cell suspension is sprayed onto these particles [15]. Depending on the process parameters, carrier particles can either be coated with the cells [16, 17], or the particles are granulated with cells [15, 19], and if necessary, additional binders are introduced. For instance, *Enterococcus faecium* M74 was coated on MCC pellets to enhance flowability compared to lyophilizate, facilitating proper further processing into solid dosages [19]. Typically, the coating procedure requires an extended process time since the spray rate must be low enough to prevent agglomeration. However, the prolonged process time could be a concern as it exposes the cells to potentially harmful temperatures. Hence, granulation is the primary focus of this study. Moreover, granules produced in this manner generally exhibit better tabletability than, for example, coated



MCC pellets [20]. The study investigates the influence of various process and formulation parameters, including the type and amount of protective additives in the spray suspension, spray rate, inlet temperature, post-drying time, and cell concentration. The outcomes will be utilized to determine process conditions that enhance the survival of cells during granulation.

2.1.3. Tablet Compression

Use a tablet press to compress the blend into tablets. The compression process should be gentle to avoid damaging the probiotic strains. The tablet size and shape depend on the specific requirements of the formulation. Compression is another process that can easily damage probiotics. Direct compression is regarded as the method of choice for manufacturing tablets with inhaled and moisture-sensitive active ingredients for industrial use [21]. As direct compression inevitably causes damage to bacterial morphology, it is essential to investigate the relationship between compression force and probiotic cell viability. One study showed that as the concentration of hypromellose phthalate increases, tablets made with high tensile and compressive strengths exhibit a slow release rate and greater than 80% bacterial cell viability [22]. Meanwhile, a similar issue was reported that when the cell density of the tablets increases, the particle gap is too small and high levels of mechanical stress may cause cell rupture and thus reduce the survival of probiotic bacteria [23]. The difference between these two results may be attributed to variations in drying processes and excipients. Notably, the species of the strain also affects the sensitivity of directly compressed probiotic tablets, as some strains have cell surface molecules, such as exopolysaccharides, that reduce cell damage during compression [24]. Due to strain specificity and the variability in excipients, the appropriate choice of compression force during the manufacturing of probiotic tablets can substantially improve strain survival.

2.1.4. Enteric Coating

Apply an enteric coating to protect the probiotics from the acidic environment of the stomach, ensuring their release in the intestines. Enteric coatings may use polymers like hydroxypropyl methylcellulose phthalate (HPMCP) or polyvinyl acetate phthalate (PVAP).

2.1.5. Drying

If the tablet formulation involves liquid components, such as probiotic suspensions, a drying step may be necessary to remove excess moisture and enhance stability. During tableting, stresses due to compression, shear and heat occur, showing detrimental effects on microbial survival. The fact that large cells are damaged more strongly suggests mechanical stress (shearing) as the significant factor [25]. Besides dependency on cell size, the degree of damage also seems to be dependent on the compaction stress [26, 27], compression speed [11], spatial distribution and mechanical as well as physical properties of the used excipients, e.g., deformation characteristics [26].

2.2. Influence of compression kinetics during tableting

The viability of microorganisms and the physical characteristics of the tablets, such as porosity and tensile strength, were assessed. Increased compression stresses led to decreased porosities. While this adversely affected microbial survival due to elevated pressure and shear stress during particle rearrangement/densification, it simultaneously resulted in higher tensile strengths. When comparing tablets under the same compression stress, a lengthened dwell time resulted in reduced porosity, leading to lower survival rates but increased tensile strength. Conversely, consolidation time did not exert a significant impact on the tablet quality attributes considered. Given the negligible changes in survival rates relative to tensile strength (due to opposing yet compensatory influences on porosity), high production speeds could be employed for granule tableting without compromising viability, as long as tablets with equivalent tensile strength are produced [28, 29].

3. Some of the major factors in the formulation development for probiotics

3.1. Biological Factors

Upon oral ingestion, probiotics confront the challenging conditions of the gastrointestinal (GI) tract, specifically in the stomach and upper intestine. The highly acidic gastric fluids with a pH range of 1–3 and a gastric emptying time of approximately 2 hours significantly diminish the viability of probiotics in the stomach. The

acidic gastric pH negatively impacts the cytoplasmic pH and glycolytic enzyme activity of probiotics, affecting the F1Fo-ATPase proton pump crucial for their survival in acidic conditions [30]. Therefore, acid resistance is a pivotal and desirable characteristic of oral probiotics [31, 32]. Factors such as high ionic strength, enzyme activity (pepsin), and gastric motility can further reduce probiotic viability [30].

In the small intestine, bile acids and various digestive enzymes, including lipases, proteases, and amylases, also influence probiotic viability. The increased secretion of bile acids, particularly in response to high-fat meals, creates an unfavorable environment for many probiotics, despite aiding in lipid digestion and absorption. Bile acids exhibit antimicrobial properties by acting as biological detergents, disrupting cell membranes and damaging DNA [16]. Consequently, elevated bile acid secretion may decrease probiotic viability in the small intestine. Proteolytic enzymes like trypsin and chymotrypsin can cause lysis of certain bacterial strains and hinder their growth [33].

While oral administration is the preferred route for probiotics, their significant instability in the GI tract necessitates alternative formulations. Consequently, non-GI routes have been actively explored in recent years. However, each route of administration has its own limitations. For instance, vaginal administration's efficacy can be influenced by factors like cervical mucus and variations in the vaginal microenvironment, including vaginal mucosa thickness and properties of the vaginal fluid [34]. Similarly, intranasal delivery faces challenges such as rapid mucociliary clearance, short retention time, small surface area, and enzymatic degradation [35, 36]. Additionally, the colonization of probiotic strains on the respiratory epithelium may be influenced by the presence of the nasal microbial community [37]. Therefore, the formulation strategy for effective probiotic delivery should be tailored to address the specific biological barriers encountered with each route of administration.

3.2. Pharmaceutical Factors

Throughout the manufacturing and storage phases, probiotics can be exposed to diverse stress conditions that impact their stability. Key stressors contributing

to the destabilization of probiotics include heat, oxygen levels, mechanical force, osmotic shock, and pH variations. For instance, common processes like spray drying, often used in manufacturing, introduce thermal stress that may denature proteins and cause cell damage in probiotics due to elevated temperatures. The drying process, as in spray drying, can induce osmotic shock by increasing intracellular osmolarity, leading to physiological changes in the outer cellular membrane [26, 38].

Freezing and thawing processes also influence probiotic viability [39]. Mechanical stress from the formation of ice crystals in the media or inside the cells can damage probiotic cell membranes during freezing. Osmotic stress may further diminish probiotic viability during thawing [40]. Under hypo- or hypertonic conditions, osmotic shock adversely affects cell viability, with low osmotic pressure causing an increase in internal cell pressure due to water absorption, resulting in cell lysis [41, 42, 43].

The formulation process subjects probiotic bacteria to mechanical stress. Compression force during tableting, for example, damages the bacterial cell wall and other bioactive components, reducing probiotic survival rates [44, 45]. Shearing force induced by inter-particulate movement also influences probiotic cell survival [46, 47]. Similarly, oxidative stress impacts probiotic survival during manufacturing and storage. While oxygen itself is not harmful, reactive oxygen species generated during its partial reduction to water can damage probiotic proteins, lipids, and DNA [48, 49]. Spray-dried cells may be more susceptible to oxidative stress due to cellular injuries during dehydration [50, 51]. Additionally, the cellular accumulation of toxic oxygen metabolites eventually leads to cell death, referred to as oxygen toxicity [52, 53]. The ability to endure oxidative stresses becomes crucial in selecting probiotic strains. Although genetic manipulation techniques have been employed to enhance microorganism stability under various stresses encountered during manufacturing and storage, safety concerns persist. Consequently, safeguarding probiotics against these stresses should be a primary objective in formulation development [54, 55].



4. CONCLUSION

Probiotic tablets constitute a widely utilized delivery system in nutritional products for supplementing the natural intestinal flora. These tablets have the capability to deliver live, functional bacteria in sufficiently large quantities (ensuring effectiveness), offering protection against the harsh conditions of the gastrointestinal and biliary environment (providing *in vivo* protection), and maintaining viability through the formulation process. The inherent advantages of tablets position them as a crucial avenue for the development of probiotic drugs. Given the potential adverse effects on the biological activity of probiotics due to the preparation method, careful consideration is essential in the design of probiotic tablet formulations. Probiotic tablets are gaining increased interest and finding applications in both pharmaceutical and food production practices, contributing to product diversification and addressing existing challenges related to the stability of biological products.

REFERENCES

- [1] E Silva JPS, Sousa SC, Costa P et al., Development of Probiotic Tablets Using Microparticles: Viability Studies and Stability Studies. *AAPS PharmSciTech*, 14(1), 121–127., 2012.
- [2] Govender M, Choonara YE, Kumar P et al., A review of the advancements in probiotic delivery: Conventional vs. non-conventional formulations for intestinal flora supplementation; *AAPS PharmSciTech*, 2014, 15, 29–43.
- [3] FAO/WHO, Guidelines for the evaluation of probiotic in food, Joint FAO/WHO working group report on drafting guidelines for the evaluation of probiotic in food, 2002.
- [4] Kim W-S, Cho C-S, Hong L et al., Oral delivery of probiotics using pH-sensitive phthalyl inulin tablets; *J Microbiol Biotechnol*; 2019; 29(2):200–208.
- [5] Gurram S, Jha DK, Shah DS et al., Insights on the Critical Parameters Affecting the Probiotic Viability During Stabilization Process and Formulation Development; *AAPS PharmSciTech*. 2021 May 18;22(5):156. doi: 10.1208/s12249-021-02024-8. PMID: 34008083.
- [6] Shu G, Tian M, Chen L et al., Probiotic goat milk tablets: Formulation optimization and stability evaluation. *LWT*, 2019, 108862. doi:10.1016/j.lwt.2019.108862
- [7] Huq T, Vu KD, Riedl B et al., Development of probiotic tablet using alginate, pectin, and cellulose nanocrystals as excipients. *Cellulose*, 23(3), 2016, 1967–1978. doi:10.1007/s10570-016-0905-2
- [8] Vorländer K, Bahlmann L, Kwade A et al., Tableting of fluidized bed granules containing living microorganisms, *European Journal of Pharmaceutics and Biopharmaceutics*, 2023.
- [9] Sierra-Vega NO, Romañach RJ, Méndez R, Feed Frame: The Last Processing Step before the Tablet Compaction in Pharmaceutical Manufacturing. *Int. J. Pharm*, 2019, 572, 118728.
- [10] Vorländer K, Kampen I, Finke JH et al., Along the Process Chain to Probiotic Tablets: Evaluation of Mechanical Impacts on Microbial Viability; *Pharmaceutics* 2020,12, 66.
- [11] Byl E, Bladt P, Lebeer S et al., Importance of Pressure Plasticity during Compression of Probiotic Tablet Formulations. *Eur. J. Pharm. Biopharm*, 2019,145, 7–11.
- [12] Vorländer K, Bahlmann L, Kwade A et al., Effect of Process Parameters, Protectants and Carrier Materials on the Survival of Yeast Cells during Fluidized Bed Granulation for Tableting, *Pharmaceutics*, 2023.
- [13] Breitenbach J, Beermann C, Esper GJ, Comparison of different methods for microencapsulation of probiotics. *Prog. Agric. Eng. Sci.* 2016,12, 63–80.
- [14] Yan J, Wu M, Zhao W et al., Effects of probiotics and its fermented milk on constipation: a systematic review, *Food Science and Human*

- Wellness, 2023.
- [15] Broeckx G, Vandenheuvel D, Claes IJJ et al., Drying techniques of probiotic bacteria as an important step towards the development of novel pharmabiotics. *Int. J. Pharm.* 2016,505, 303–318.
- [16] El Mafadi S, Picot A, Poncelet D, Modification/improvement of the Wurster process for drying or coating sensitive bioactive materials. *Minerva Biotechnol*, 2005,17, 231–235.
- [17] Zaghari L, Basiri A, Rahimi S, Preparation and characterization of double-coated probiotic bacteria via a fluid-bed process: A case study on *Lactobacillus reuteri*. *Int. J. Food Eng.* 2020,16, 108349.
- [18] Stummer S, Toegel S, Rabenreither MC et al., Fluidized-bed drying as a feasible method for dehydration of *Enterococcus faecium* M74. *J. Food Eng*; 2012,111, 156–165.
- [19] Sun CC, Decoding Powder Tableability: Roles of Particle Adhesion and Plasticity. *J. Adhes. Sci. Technol*; 2011, 25, 483–499.
- [20] Thoorens G, Krier F, Leclercq B et al., Microcrystalline Cellulose, a Direct Compression Binder in a Quality by Design Environment—A Review. *Int. J. Pharm.* 2014,473, 64–72.
- [21] Klayraung S, Viernstein H, Okonogi S, Development of Tablets Containing Probiotics: Effects of Formulation and Processing Parameters on Bacterial Viability. *Int. J. Pharm.* 2009,370, 54–60.
- [22] Allouche R, Dupont S, Charriau A et al., Optimized Tableting for Extremely Oxygen-Sensitive Probiotics Using Direct Compression. *Int. J. Pharm*, 2018, 538, 14–20.
- [23] Byl E, Jokicevic K, Kiekens S et al., Strain-Specific Differences in Behaviour among *Lactobacillus Rhamnosus* Cell Wall Mutants during Direct Compression. *Int. J. Pharm.* 2020,588, 119755.
- [24] Iswandana R, Putri KSS, Anisa HN et al., Formulation of various polysaccharides-based multicoated tablets containing dexamethasone and probiotics for inflammatory bowel disease, *Journal of Applied Pharmaceutical Science*, 2023.
- [25] Blair TC, Buckton G, Bloomfield SF, On the mechanism of kill of microbial contaminants during tablet compression. *Int. J. Pharm*; 1991, 72, 111–115.
- [26] Plumpton EJ, Gilbert P, Fell JT, The survival of microorganisms during tableting. *Int. J. Pharm*; 1986, 30, 241–246.
- [27] Fassihi AR, Parker MS, Inimical Effects of Compaction Speed on Microorganisms in Powder Systems with Dissimilar Compaction Mechanisms. *J. Pharm. Sci.* 1987, 76, 466–470.
- [28] Vorländer K, Bahlmann L, Kwade A et al., Influence of compression kinetics during tableting of fluidized bed-granulated microorganisms on microbiological and physical-mechanical tablet properties, *European Journal of Pharmaceutics and Biopharmaceutics*, 2023.
- [29] Gurram S, Jha DK, Shah DS et al., Insights on the Critical Parameters Affecting the Probiotic Viability During Stabilization Process and Formulation Development, *AAPS PharmSciTech*, 2021.
- [30] Yao M, Xie J, Du H et al., Progress in microencapsulation of probiotics: a review. *Compre Rev Food Sci.* 2020;19(2):857–874. doi: 10.1111/1541-4337.12532
- [31] Baral, Kshitis & Bajracharya, Rajiv & Lee et al., Advancements in the Pharmaceutical Applications of Probiotics: Dosage Forms and Formulation Technology. *International Journal of Nanomedicine*, 2021, Volume 16. 7535-7556. 10.2147/IJN.S337427.
- [32] Urdaneta V, Casadesús J, Interactions between bacteria and bile salts in the gastrointestinal and hepatobiliary tracts. *Front Med.* 2017;4:163. doi: 10.3389/fmed.2017.00163.
- [33] Grenier D, Effect of proteolytic enzymes on the lysis and growth of oral bacteria. *Oral Microbiol Immunol.* 1994;9(4):224–228. doi:



- 10.1111/j.1399-302X.1994.tb00062.x.
- [34] Pliszczak D, Bourgeois S, Bordes C et al., Improvement of an encapsulation process for the preparation of pro- and prebiotics-loaded bioadhesive microparticles by using experimental design. *Eur J Pharm Sci.* 2011;44(1):83–92. doi: 10.1016/j.ejps.2011.06.011.
- [35] Merkus FW, Verhoef JC, Schipper NG et al., Nasal mucociliary clearance as a factor in nasal drug delivery. *Adv Drug Deliv Rev.* 1998;29(1–2):13–38. doi: 10.1016/S0169-409X(97)00059-8.
- [36] Serralheiro A, Alves G, Sousa J et al., Nose as a route for drug delivery. In: Önerci TM, editor. *Nasal Physiology and Pathophysiology of Nasal Disorders.* 1st ed. Berlin: Springer; 2013:191–215.
- [37] De Rudder C, Garcia-Timmermans C, De Boeck I et al., Lacticaseibacillus casei AMBR2 modulates the epithelial barrier function and immune response in a donor-derived nasal microbiota manner. *Sci Rep.* 2020;10(1):16939. doi: 10.1038/s41598-020-73857-9.
- [38] Terpou A, Papadaki A, Lappa IK et al., Probiotics in food systems: significance and emerging strategies towards improved viability and delivery of enhanced beneficial value. *Nutrients;* 2019;11(7):1591. doi: 10.3390/nu11071591.
- [39] Stanbury PF, Whitaker A, Hall SJ, The recovery and purification of fermentation products. In: Stanbury PF, Whitaker A, Hall SJ, editors. *Principles of Fermentation Technology.* 3rd ed. Oxford: Butterworth-Heinemann; 2017:619–686.
- [40] Blair TC, Buckton G, Bloomfield SF, On the mechanism of kill of microbial contaminants during tablet compression. *Int J Pharm.* 1991;72(2):111–115. doi: 10.1016/0378-5173(91)90048-S.
- [41] Plumpton EJ, Gilbert P, Fell JT, The survival of microorganisms during tableting. *Int J Pharm.* 1986;30(2–3):241–246. doi: 10.1016/0378-5173(86)90086-4.
- [42] Mills S, Stanton C, Fitzgerald GF et al., Enhancing the stress responses of probiotics for a lifestyle from gut to product and back again. *Microb Cell Fact.* 2011;10(Suppl 1):S19–S19. doi: 10.1186/1475-2859-10-S1-S19.
- [43] Ketaubon P, Prapagdee B, Enhancing cadmium phytoremediation of Chlorophytum comosum (Thunb.) Jacques by applying cadmium-resistant bacterial tablet, *Environmental Science and Pollution Research, Article in Press* 2023
- [44] Kaur R, Simnani FZ, Singh S, Enhancement of Probiotics for Functional Food (Book Chapter), *Recent Advances in Food Biotechnology,* 2022.
- [45] Das NC, Patra R, Dey A et al., Probiotics as Efficacious Therapeutic Option for Treating Gut-Related Diseases: Molecular and Immunobiological Perspectives (Book Chapter), *Prebiotics, Probiotics and Nutraceuticals,* 2022
- [46] Sreeja V, Prajapati JB, Probiotic Formulations: Application and Status as Pharmaceuticals—A Review. *Probiotics and Antimicrobial Proteins,* 5(2), 2013, 81–91. doi:10.1007/s12602-013-9126-2
- [47] Plumpton EJ, Gilbert P, Fell JT, Effect of spatial distribution of contaminant microorganisms within tablet formulations on subsequent inactivation through compaction. *Int. J. Pharm,* 1986, 30, 237–240.
- [48] Chan ES, Zhang Z, Encapsulation of probiotic bacteria Lactobacillus acidophilus by direct compression. *Trans IChemE* 80 (part C), 2002, pp 78–82
- [49] Maggi L, Mastromarino P, Macchia S et al., Technological and biological evaluation of tablets containing different strains of lactobacilli for vaginal administration. *Eur J Pharm Biopharm* 50:389–395, 2000.
- [50] Mohd AA, Mimi SAM, Design and optimization of a probiotic tablet for gastrointestinal tolerance by a simplex-centroid mixture, *Drug Development and Industrial Pharmacy,* 2020.

- [51] Sierra-Vega NO, Romañach RJ, Méndez R, Feed Frame: The Last Processing Step before the Tablet Compaction in Pharmaceutical Manufacturing. *Int. J. Pharm*, 2019,572, 118728.
- [52] Vorländer K, Kampen I, Finke JH et al., Along the Process Chain to Probiotic Tablets: Evaluation of Mechanical Impacts on Microbial Viability; *Pharmaceutics* 2020,12, 66.
- [53] Byl E, Bladt P, Lebeer S et al., Importance of Pressure Plasticity during Compression of Probiotic Tablet Formulations. *Eur. J. Pharm. Biopharm.* 2019,145, 7–11.
- [54] Maggi L, Mastromarino P, Macchia S et al., Technological and biological evaluation of tablets containing different strains of lactobacilli for vaginal administration. *Eur J Pharm Biopharm*; 2000;50(3):389–395
- [55] Azhar MA, Munaim MSA, Design and optimization of a probiotic tablet for gastrointestinal tolerance by a simplex-centroid mixture. *Drug Development and Industrial Pharmacy*, 47(2), 2020, 189–196.

