Review Article

BIOTECHINTELLECT, 2026, 3(1) e12 (1-19)
https://jbiotechintel.com/index.php/biotechintel

eISSN: 3115-7920

OPEN ACCESS

Food and Pharmaceutical Applications of Yeast Based Microencapsulation

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Article History:
Received 2026-04-14
Revised 2026-04-29
Accepted 2026-05-19
Published online 2026-05-29

Keywords: Drug delivery, Food, Microencapsula-tion, Pharmaceutical applications, *S. cerevisiae*, Yeast

How to cite this article: Mirbagheri Firoozabad MS., Karimi N, Hajihosseini M, Sharifi P, Shahi Z.. Food and pharmaceutical applications of yeast based micro-encapsulation, BiotechIntellect, 2026; 3 (1): e12 (1-19)
https://doi.org/10.66224/BiotechIntellect.3.1.50

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Abstract

Background and Aimes: Remarkable functional compounds endowed with nutraceutical properties, but are vulnerable to stressful conditions. Encapsulation may overcome this problem. This paper aims to introduce yeast cells as a desirable vehicle in the microencapsulation procedure.

Material and Method:
A narrative review was conducted using Web of Science, Scopus, PubMed, Science Direct, and Google Scholar. The literature search covered studies published in the last 7 years. The keywords were wide enough to cover all application in drug delivery (therapeutic medications including insulin) and food sectors.

Results and Conclusion: Yesat are suitable carriers for functional compounds due to their cost-effectiveness, simplicity in production, and distinctive architecture comprising a cell wall and two plasma membranes, possess. Anyway, yeast-based microencapsulation is an innovative platform with great industrial potential, but its practical success depends on overcoming technological, regulatory, economic, and safety challenges while providing more comparative and mechanism-based evidence.

What is "already known":	• Functional and pharmaceutical compounds (e.g., chlorogenic acid, curcumin, enzymes, purslane) are sensitive to heat, moisture, and light. • Microencapsulation is an established technology for protecting such compounds • Yeast cells are a suitable candidate for encapsulation of bioactive materials in food matrix.
What this article adds:	• Yeast-based microencapsulation for sensitive bioactive compounds is effective and varies by compounds. • Yeast cell possesses low cost, simple production and distinctive architecture comprising a cell wall and two plasma membranes, possess the potential to serve as a desirable vehicle in the microencapsulation procedure • The influencing factors are species, cell-wall composition, techniques, conditions • Standardized protocols and comparative/mechanism-based studies, and proposes integrating yeast encapsulation with precision fermentation, synthetic biology, and engineered yeast systems. • Practical barriers are scale-up, regulation, cost, sustainability

1. Introduction: Background and Aims

Encapsulation is a process in which one compound, due to enhancing its stability, is going to be entrapped into another material that acts as a carrier or wall. Encapsulation ensures that the active component is stabilized since the coating acts as a physical barrier to both oxygen and other substances, thus preventing any harmful interactions. Furthermore, through encapsulation, the substance being encapsulated can be delivered in a controlled manner in biological systems or products [1]. Several encapsulation systems are commonly used, such as spray-drying, fluidized-bed coating, coacervation, and liposome entrapment [2]. However, the wall materials used for this purpose usually are polymers or expensive lecithin [3-5]. Recently, due to the structure of yeast cells and their nutritional benefits, researchers have been interested in using yeast cells as a new carrier material in encapsulation. This technique is less expensive for encapsulating various food ingredients and flavors, and can also be used for compounds possessing different physicochemical properties (hydrophobic or hydrophilic) [6]. Yeast cells are regarded as a coating material which behaves as a protective capsule which regulates the osmotic pressure and exchange between the cell and its surroundings [2]. Microencapsulation methods have been extensively employed in different fields, such as the pharmaceutical, cosmetic, and food industries, and so forth [7]. Due to their unique structure, yeast cells are the primary choice for microencapsulation.

1.1. *Microencapsulation*

Encapsulation and microencapsulation are advantageous practices that can be employed in various methods and with varying substances, such as nanomaterials, chitosan, sodium alginate, carboxy methyl cellulose (CMC), methylcellulose, cellulose acetate, polycarbonate, polysulfide, polyacrylate, and collagen. The most crucial purpose is targeted delivery which is used to help the drug reach the desired organ or tissue. The protection of material properties comes second due to the possibility of materials losing their ability or decreasing and, in this way, the consumption of this substance is stored from overuse. The third reason is masking to improve taste and acceptability during and after swallowing food products.

1.2. Structure of the Yeast Cell

Yeasts are eukaryotic microorganisms and unicellular fungi. They have a nucleus and a few organelles consisting of Golgi apparatus, mitochondria, endoplasmic reticulum, vacuole, and cytoskeleton. Yeast reproduces in two ways: the primary way is budding and once in during fission. The global yeast population encompasses a wide range of varieties. Nevertheless, the most crucial yeast strain is *Saccharomyces* (*S.*) *cerevisiae*. *S. cerevisiae* and other different yeasts are distinguished by their ability to ferment individual sugars. Due to their extensive use in food products, it is possible that they are the masters of fermentation. Yeasts have a unique characteristic that they may be immune to antibiotics, sulfamides, and different antibacterial agents [8-10].

1.3. Microencapsulation Using Yeast Exploring the Crucial Role of Selective Permeability and Its Fluidity Connection

Cell walls and inner plasma membranes are the critical parts that used for microencapsulation. Yeast diameter usually is between 2-5 μm. The diameter of the wall is about 10% of the total diameter of the cell, and it is between 100 and 200 nm [11]. On both outer sides of the cell wall is a glycosylated mannoprotein layer whose role is to save the cell from external attack and make it hydrophilic. There are two other materials - chitin and β-1, 3-glucan. The β-1,3-glucans and the chitin are responsible for the mechanical rigidity of the cell wall. Generally, the cell wall provides mechanical strength to the cells [12].Its porosity for extra molecules is up to 760 Da and 40000Da with proper prior treatment [13]. The plasma membrane mainly consists of polysaccharides [11]. It has an important role, selective permeability, and is related to fluidity [14]. Protein-based carriers offer good film- and gel-forming, emulsifying, and solubility properties, while also providing nutritional benefits. However, their selection for peptide encapsulation can be challenging because of structural similarities between the carrier and the encapsulated peptides. Polysaccharide-based carrier such as gum arabic, chitosan, cyclodextrin, and

maltodextrin, are abundant, inexpensive, and structurally stable, but may undergo undesirable reactions with the encapsulated compounds under severe processing conditions. Lipid-based carriers, particularly liposomes, can improve the biostability and bioavailability of encapsulated compounds and accommodate both hydrophilic and hydrophobic substances; however, their limitations include relatively low encapsulation efficiency, thermal instability, lipid oxidation, and higher formulation complexity. Spray drying is widely used for protein- and polysaccharide-based systems, whereas film hydration is generally employed for liposome preparation [15]. Using yeasts for encapsulation is more accessible than other materials, which becomes a more critical point when encapsulation is used on an industrial scale. Using yeast reduces the cost of encapsulation which is an essential option. Other reasons for using yeast include its potential for being used for both hydrophobic and hydrophilic compounds having high loading capacity. Another advantage of yeast is that it increases the stability of the active compound. Some of the yeasts used for the encapsulation technique includes *S. cerevisiae* (baker's and brewer's yeast), *S. bayanus* (wine yeast), *Candida utilis, Kluyveromyces fragilis* (dairy yeast), *Torulopsis lipofera*, *Endomyces vernalis* and oleaginous yeast (*Cryptococcus curvatus*).

2. METHODS

2.1. Yeast cell encapsulation process

Water, yeast (or yeast wall), and active ingredients are needed. The mixture should be stirred for hours until diffusion happens. Temperature (40-60°C) and the stirrer speed should be under control. During this process, the cell loses its viability, particularly for 2 hours, but a loss of viability of yeast cells does not influence their ability of encapsulation [16]. The hydrophobic interaction, Van Der Waals attraction force, and hydrogen bonding between the components of the yeast cell and the active ingredient keep the element inside the cell. When the process is finished, the loaded non-viable cells should be washed with water or organic solvent to remove all non-encapsulated material. In the end, the product can be dried in three ways - spray drying, fluidized bed, or freeze-drying. This guarantees the safety of the encapsulation and prevents the loss of ingredients [8, 14, 17]. Each milligram of a freeze-dried powder contain4.7×10^7 of *S. cerevisiae* [18]. Figure 1 showed schematic of the encapsulation mechanism and controlled drug release in biomedical applications.

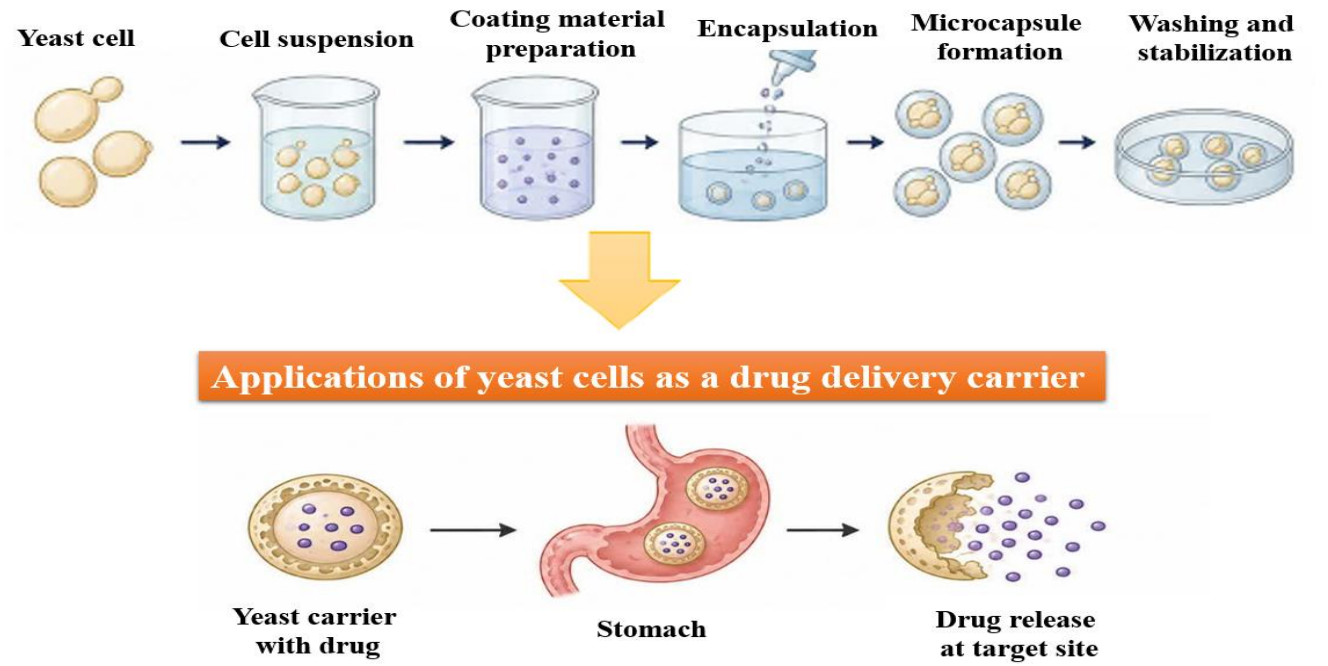

Figure 1. Schematic illustration of the encapsulation mechanism and controlled drug release, with an example of drug delivery in biomedical applications.

Yeast cells have emerged as versatile microcapsules for the encapsulation and controlled release of exogenous compounds. Depending on the intended application, yeast cells can be employed in living, dead, intact, permeabilized, or emptied forms. Passive diffusion is considered the predominant encapsulation mechanism, particularly in intact or permeabilized cells, involving sequential processes of adsorption onto the cell surface, permeation through the cell wall, and interactions with the cell membrane. The major advantages of yeast-based microcapsules include their low cost, biodegradability, biocompatibility, and sustainable origin. However, encapsulation efficiency and release behavior are affected by several factors, including yeast type, culture conditions, compound properties, and post-encapsulation treatment and storage. Despite their potential for food and pharmaceutical applications, the lack of standardized procedures remains a major limitation for quantitative comparison and prediction of encapsulation performance [19].

2.2. Enfluencing parameters on encapsulation

The parameters like the solubility of the hydrophobic compound in the cell wall, molecular size, shape, and polarity, the size of the active ingredient, the presence of hydroxyl or other polar groups influence encapsulation[16,20]. Two quantitative parameters are available to demonstrate loading capacity and encapsulation performance.

Encapsulation yield (%EY) is characterized as the proportion of encapsulates generated in relation to the overall weight of materials employed during the course of the procedure. Encapsulation Efficiency (%EE) represents the numerical value denoting the proportion of the enclosed substance compared to the original overall quantity available for encapsulation. The inclusion of hydroxyl or other polar moieties exerts a beneficial influence on both the encapsulation process and the efficiency of yield, denoted as %EY. Mass ratio is one of the most vital parameters and stands for the mass ratio of the active compound to the yeast cells involved in yeast microcapsules preparation process [21-23]. Several factors can influence the encapsulation performance of yeast cells, including yeast pretreatment, cell-wall structure, thephysicochemical properties of the active compound, and surface. Kavosi et al. (2018) investigated the encapsulation of purslane seed oil (PSO), a rich source of omega-3 fatty acids, in *S. cerevisiae* cells. The %EE and loading capacity (LC) were approximately 53–65% and 187–231 g/kg, respectively. Plasmolysis increased both EE and LC and reduced the peroxide value (PV) of the encapsulated oil. The lowest oxidation level was observed in plasmolyzed carboxymethyl cellulose (CMC)-coated yeast microcapsules (16.73 meq O_2/kg), whereas the highest oxidation was observed in non-plasmolyzed yeast cells (28.15 meq O_2/kg). These findings demonstrate that yeast pretreatment can improve encapsulation performance and oxidative stability, supporting its potential for food applications [24]. Karaman et al. (2021) investigated the encapsulation of gallic acid in *S. cerevisiae* cells and evaluated encapsulation efficiency, bioactive properties, and release behavior. The authors found that both solvent type and yeast pretreatment significantly affected encapsulation performance, while more than 80% of gallic acid was released within 2 h under simulated gastrointestinal conditions [25]. He et al. (2024) evaluated yeast cells and yeast cell wall (YCW) capsules as delivery systems for avenanthramide-C (AVN-C), a bioactive compound in oats. The YCW capsules showed higher encapsulation and loading capacities due to their larger internal space. Moreover, hydrophobic interactions and hydrogen bonding contributed to AVN-C loading, while the increased hydrophobicity inside the capsules improved its stability and enabled slow and sustained release under simulated gastrointestinal conditions [26].

2.3. Encapsulation conditions

A medium such as water or a solution consisting of water, an organic solvent, and an emulsifier is required for the encapsulation process. When the active ingredient is water-soluble, an aqueous medium is generally used. For hydrophobic ingredients, the organic solvent is first introduced into the solid hydrophobic material before being combined with the aqueous medium. The presence of water is essential because it causes yeast cells to swell, allowing larger hydrophobic molecules to penetrate

the cells due to the increased permeability of the cell wall [27]. The temperature typically ranges from 20°C to 60°C. However, several studies have reported that a temperature of approximately 40°C provides better performance because the membrane phase transition temperature of yeast, depending on the strain, is around 30–37°C. At this temperature, the membrane transitions from the gel phase to the more fluid liquid-crystalline phase, facilitating the penetration of active ingredients into the cells [16].

3. APPLICATION

3.1. Food industry

According to what is mentioned above, yeast cells have been used as natural micro-vesicles not only for water-soluble but also for insoluble molecules, such as essential oils, chlorogenic acid, curcumin, enzymes, and purslane. The naturally occurring bioactive substances have an unstable nature and are vulnerable to destruction due to various environmental effects such as exposure to oxygen, light, moisture, and heat. The substances in the pure and natural form are limited in their application in foods due to certain features such as fast release, poor solubility, poor bioavailability, and oxidation. The most important aspect in the application of the substance in foods is that it is safe for consumption and is permitted by the authorities, for example, Food and Drug Administration (FDA). There are several aspects of the core material that could be used in the choice of the encapsulating substances. These include, for example, its concentration, mechanism of release, stability, and price. The reasons for the encapsulation of sensitive substances, such as essential oils, vitamins, phenolic substances, etc., are: (i) the protection against the environmental factors or any other undesirable interaction; (ii) controlled release within the certain period of time in the required matrix; (iii) improved solubility; (iv) increased bio-accessibility/bioavailability. The yeast cell encapsulation technique is inexpensive, biocompatible, and biodegradable. The ability of the yeast cells to take up large quantities of hydrophobic substances is well understood, and the technique can be modified to create cells loaded with hydrophobic or yeast-based capsules. In truth, cell wall functions go beyond being merely mechanical; they are used for both controlled loading and release of the substance. The hydrophobic core substance diffuses through the process of encapsulation and is trapped passively within the cell, and released upon appropriate stimulation [28]. Fernandes de Souza et al. (2023) investigated the coacervation of yeast cells and xanthan gum for vitamin C encapsulation. The optimized microcapsules achieved a high encapsulation efficiency of approximately 86% and improved the thermal and storage stability of vitamin C. During simulated digestion, about 50% of vitamin C was retained in gastric conditions and up to 80% was released in intestinal conditions, demonstrating the potential of yeast–xanthan microcapsules for protecting and delivering water-soluble bioactives in food applications [29].

3.1.1. The effects of microencapsulation on black cumin

Black cumin, a seed possessing both aromatic and nutraceutical properties, finds itself with diverse applications in the food industry, particularly in the realm of pharmaceuticals. Furthermore, the growing fascination with cold-pressed oils has likewise exerted an influence on their utilization [30]. Thymoquinone, a bioactive compound, is one of the cardinal constituents of the black cumin seed and its oil. The numerous functions and effects of black cumin's seed and its oil can be attributed to the presence of this specific compound. The substance known as thymoquinone is derived from terpenoids, a class of organic compounds. The susceptibility of terpenoids to heat is quite significant. An investigation found that even after a brief exposure period, thymoquinone showed significant degradation in hydrous media and great susceptibility to light. Black cumin seed oil also bears a fatty acid composition, which makes it vulnerable to oxidative reactions, and also the level of thymoquinone will decrease owing to the weak stability of thymoquinone at unaffordable conditions, such as heat, humidity, or light presence [31]. One protective strategy for maintaining the phytoactive chemicals in the food matrix is microencapsulation by yeast cells. Because of their hydrophobic cell walls, yeast cells are a good encapsulation medium for hydrophobic compounds like oils when the first interaction occurs between the cell wall and molecules. Therefore, the

major encapsulation mechanism by the yeast cells is based on the electrostatic features, which result in the adhesion of the related compounds [32]. Black cumin seed oilwas encapsulated using both plasmolyzed (PYC) and nonplasmolysed (NPYC) cell walls in a study carried out using *S. cerevisiae* yeast cells [33]. According to this research, samples covered by plasmolyzed yeast cells had a higher encapsulation efficiency, higher loading capacity values, and higher oil content than nonplasmolysed ones (Table 1). However, the concentration level of thymoquinone for the native black cumin seed oil, as a control oil sample, was higher than Samples of plasmolyzed (PYC) and nonplasmolysed (NPYC) loaded yeast cells, respectively. Furthermore, compared to control black cumin seed oil, encapsulation—particularly when employing plasmolyzed yeast cells—found a protective effect on the thymoquinone level during storage. According to (Table 1), although radical scavenging activities of the BCSO in encapsulated samples were lower than the control BCSO due to the higher bioactive constituents like thymoquinone in the native BCSO, the reduction of radical scavenging activities in encapsulated samples, during storage, was lower than the control ones.

Table 1. Some physiochemical features of native and encapsulated black cumin seed oil

Sample	OC (%)	EE (%)	LC (g/kg)	DL (%)	RSA (%)
PYC	29.98 ± 1.85^{a}	59.97 ± 3.70^{a}	260.34 ± 6.83^{a}	41.4±2.6 ^{a}	5.45±1.31 ^{a}
NPYC	19.59 ± 2.98^{b}	39.18 ± 5.97^{b}	172.20 ± 14.5^{b}	51.61±3.9 ^{b}	55.9±3.22 ^{b}
BCSO	-	-	-	86.09±2.98	2.77±1.25

OC: oil content, EE: encapsulation efficiency, LC: loading capacity,BCSO: Black cumin seed oil, PYC: Plasmolysed loaded yeast encapsulate, NPYC: Nonplasmolysed loaded yeast encapsulate, RSA: Radical scavenging activity, DL: Degradation level. The small superscript letters in each column show significant differences ($p < 0.05$)

3.1.2. The effects of microencapsulation on chlorogenic acid

The naturally available phenolic compound is chlorogenic acid (CGA). Because CGA can interact with reactive oxygen species, it possesses many advantageous properties [34]. According to a study CGA is an OH scavenger; however, because of its chemical configuration, which is orthodihydroxy-phenolic, it is thought to be oxidized by oxidation stressors such as gamma irradiation. Additionally, although the photochemical oxidant properties of polyphenolics have been investigated to a great extent, in many cases, they have unpleasant tastes [35] as well as unstable properties [36]. Therefore, CGA stabilization is one of the most important issues for its function. Yeast-encapsulated chlorogenic acid has been observed to have a positive impact on stability [16, 37, 38]. The bilayer structure of the yeast cell wall membrane behaves like liposomes in microencapsulation of essential oils and stabilizes the oil droplets inside the yeast cells, and the yeast cells effectively protected CGA from degradation by oxygen and light during storage. Moreover, in conditions of heat and moisture, yeast-encapsulated CGA possessed superior stability, and the release profile indicated that the yeast cells were capable of protecting CGA from variations without significantly affecting its release.

3.1.3. The effects of microencapsulation on curcumin

One of the other components capsulated by yeast cells is curcumin (diferuloylmethane). Curcumin is a polyphenol that possesses various colors in different pHs. When it is in a powder state, it has a yellow-orange color, while, in a solution state, it bears a yellow color at pH 2.5-7 and a red one at pH > 7.0 [39]. This substance has a wide variety of uses in different industries, one of which is in the food industry as a stabilizer in commercial jellies or a natural colorant in many foods, such as yogurt, cheeses, soup, and ice cream, to name but a few. Furthermore, as curcumin has anticarcinogenic and anticancer properties, it is a substantial pharmacological compound. Additionally, curcumin acts against skin diseases (scleroderma, psoriasis], autoimmune ones [rheumatoid arthritis, psoriasis,

inflammatory bowel disease), Alzheimer's, and HIV-replication [40] in a protective way. Therefore, curcumin, owing to all benefits mentioned above, is commercially available in the forms of tablets, soft gels, capsules, or transdermal film. However, there are some obstacles in the food process of curcumin use, which impose constraints on its clinical action, such as its poor water solubility and it is being readily affected by alkaline conditions as well as light, oxidation, and heat [41]. Encapsulation has been implemented as a viable resolution for the majority of these issues through the utilization of diverse encasing mediums, inclusive of gelatin, cyclodextrins, liposomes, and modified starch. Research [18], using *S. cerevisiae* yeast cells as carriers for the encapsulation of curcumin, has been conducted in which plasmolyzed and non-plasmolyzed yeast cells, both freeze-dried and none-freeze-dried, have been employed. Plasmolysis is a phenomenon in which intracellular water is removed from the cell [42]. The coextraction of water soluble substances like proteins, sugars, enzymes, amino acids and nucleic acids during plasmolysis causes an expansion of the intracellular space thereby enabling the plasmolyzed yeast cells to use in several yeasts encapsulations because of being regarded as empty sacks which can be filled with active ingredients [18]. Several ways have been applied for plasmolysis, and recently, yeast cells plasmolyzed by NaCl were successfully employed for chlorogenic acid encapsulation [37]. According to [18], the process based on freeze-drying was fatal to virtually 97 percent of plasmolyzed and non-plasmolyzed yeast cell population. Considering this, using non-freeze-dried yeast cells would be better for the encapsulation of curcumin. Dadkhodazade et al. (2018) used *Saccharomyces cerevisiae* yeast cells as carriers for vitamin D3 encapsulation. They investigated the effects of vitamin concentration, yeast plasmolysis with NaCl, and drying method (spray drying and freeze drying). The %EE was obtained for plasmolyzed and spray-dried yeast cells, reaching 76.10 ± 6.92%. The encapsulated vitamin D3 also showed controlled release, with sustained release under gastric conditions and greater release in the intestinal medium. SEM images (a, b) showed nearly spherical yeast microcapsules without visible vitamin crystals on the surface. Spray-dried capsules showed a more compact and slightly indented surface, while freeze-dried capsules showed greater aggregation. TEM images (c, d) confirmed the presence of cholecalciferol inside the yeast cells and showed that the yeast cell wall remained intact after plasmolysis (Figure 2) [43].

3.1.4. The effects of microencapsulation on enzymes

The preparation and purification of Enzymes are usually expensive processes. Hence, different immobilization techniques can be employed to enable reusing of the enzymes [44]. However, these techniques also have some disadvantages including limitations of diffusion, loss of enzyme activity and stability [45]. Most of the recombinant or native enzymes are synthesized by microorganisms such as bacteria and fungi that contain cell walls. The advantages of these microorganisms include low cost of cultivation in high amounts, well-designed mechanisms for gene expression and harvest, provision of physical and osmotic shielding while growing due to having cell walls, and reducing the exposure of cells to external factors such as proteases. β-Galactosidase and pyruvate kinase were encapsulated in *S. cerevisiae* yeast cells in a study, which aimed to show how the microencapsulation affected the activity and retention of these enzymes [46]. The *S. cerevisiae* cell membranes were extracted, and (in some cases) the permeability of their cell walls was manipulated. The study displayed that the *S. cerevisiae* cell wall provides nearly complete retention of the enzymes β-galactosidase and pyruvate kinase and prevents adsorption onto surfaces. Even though the enzyme activity in encapsulated cells was lower than at the same concentration in free solution, the encapsulated enzyme was easily recovered and could be used in numerous reactions without experiencing a significant reduction in activity.

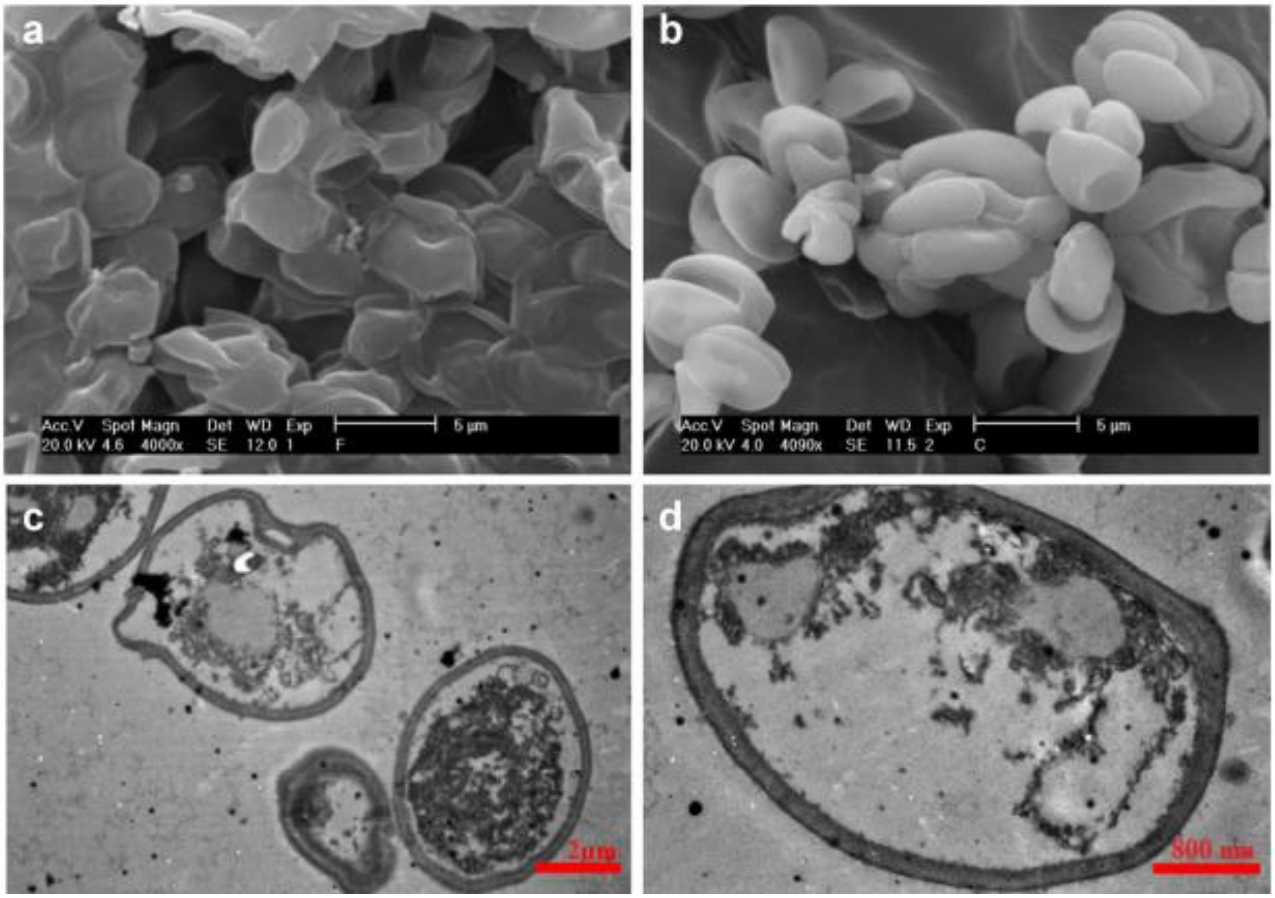

Figure 2. Morphology of cholecalciferol-loaded yeast microcapsules: (a) freeze-dried SEM image, (b) spray-dried SEM image, and (c, d) TEM images of spray-dried yeast microcapsules [43].

According to the study, large enzymes can be more easily kept by the cell wall, while small products diffuse more rapidly in and out of the cell. Therefore, the bigger size of enzymes and smaller size of their products bring about more benefits of enzyme microencapsulation.

3.1.5. The effects of microencapsulation on purslane

Portulaca oleracea, or Purslane, is the eighth most abundant plant across the globe; it can be regarded as a functional food owing to the unique composition of nutrients and biological active substances in it including antioxidant (tocopherol, ascorbic acid, *β*-carotene, glutathione), dopamine, noradrenaline, sterols, flavonoids, amino acids (phenylalanine, alanine, tyrosine, and aspartate) and plant acids (citric, malic, ascorbic, succinic, fumaric and acetic acids), etc. [47-50]. Further, the oil extracted from purslane is made up of unsaturated fatty acids which are the most abundant vegetables sources of omega-3 fatty acids [51], thus, it can be considered important in connection with the lowering of cholesterol levels, treatment of arthritis, healing of burns, inhibiting the development of cancer cells, and also in curing depression. Nevertheless, the high concentration of the unsaturated fatty acids together with copper and iron ions in the crude oil makes it susceptible to oxidation under the influence of oxygen and light [52]. The encapsulation process can be applied in the food industry. This process is a good technique for upgrading the delivery of bioactive compounds (essential fatty acids, antioxidant compounds and living cells “probiotics”). Furthermore, encapsulation can be used for the protection of volatile agents from radiation, light and oxygen [53].

3.2. Pharmaceutical Industry

Recent studies on the use of microencapsulation have contributed significantly to the pharmaceutical

industry. The advantages of using this method are improving the therapeutic effect of the molecule with the ability to deliver directly at the targeted site without destroying the enzyme, and low dosage requirements. Other benefits of microencapsulation include controlled drug release with four mechanisms - release, dissolution, permeation and corrosion- which protect the drug from destruction and protect the body from toxic effects of medicine [54]. Other studies also highlight that gastrointestinal barriers have a destructive effect on nanoparticle delivery systems. However, bioinspired yeast microcapsules help in delivering such nanoparticles as quantum dots, iron oxide nanoparticles, and different kinds of fluorescent nanoparticles. According to some observations, nanoparticles can be introduced into the yeast microcapsules through electrostatic interaction, layer by layer method, and surface derivation. Also, there are some studies showing that yeast can be applied for enhancing penetration. In various conditions, yeast can be autolyzed through different solvents [55].

3.2.1. Drug delivery

It is considered predominate that yeasts can be genetically tractable and share common features with humans [56]. Active pharmaceutical ingredients are delivered and encapsulated using current good production grade yeast (cGMP), which is also utilized to make vaccines and biopharmaceuticals [57]. A beneficial platform for the delivery of different therapeutic drugs is provided by yeast-based drug delivery. Additionally, it treats ailments like diabetes, cancer, inflammation, and cardiovascular diseases[55].

3.2.2. Drug delivery carrier

A double layer microcapsules the baker's yeast cells. Yeast cells are good biocarriers because they produce and stabilize metal nanoparticles without the need for chemical dispersants or stabilizers. Moreover, yeast cells can contain or have surfaces integrated with silver nanoparticles (Ag NPs) and palladium nanoparticles (Pd NPs). Using in situ metal ion reduction techniques, yeast cells' surfaces can be integrated with metal nanoparticles acting as carriers. There were a number of problems with adding metal nanoparticles, one of which was that the particles became trapped inside the yeast cell. A metal salt undergoes intracellular reduction to produce metal nanoparticles. They consist of three steps: the removal of extracellular salts, the passive diffusion of metal salt into cells, and lastly the transport of reducing agents into cells to initiate the reaction. It is simpler for polar metal salts to seep into cells. The cytoplasm volume or the thin membrane that encases the metal nanoparticles is another problem. The preparation procedures determine whether nanoparticles grow within the yeast cell or on the surface. Inside the yeast cell, UV irradiation with silver nitrate solution can form Ag NPs. Tollens' reaction may also be used to make Ag NPs on the cell envelope. Because of their biocompatibility and loading capacity, aerosols can be utilized as medication delivery vehicles [58]. To entrap liposomes and deliver water-soluble chemicals for a variety of theranostic applications, glucan particles function as a microcarrier [59]. Berberine was loaded into the cell owing to hydrophobic interactions with the yeast cell membrane and cell wall [58]. A novel medicinal carrier called berberine can be used to treat a variety of illnesses by being incorporated into *S. cerevisiae* yeast cells. The enhanced solubility and prolonged release lead to high stability and bio-availability [60].

3.2.3. How to encapsulate Insulin with yeast cells?

Due to the spontaneous deposition of differentially charged nanoparticles driven by electrostatic force, *S. cerevisiae* microcapsules have the ability to absorb them. It has been found that using yeast microcapsules (YMC) for extended periods of time has a very good safety record when treating chronic illnesses [61].Tight junctions may be opened by yeast cells in a time and dose-dependent manner. It's non-toxic and entirely reversible [62]. The porous wall of -1,3- D-glucan allows the nano-particles to be introduced into yeast capsules [63, 64]. YMC can be transported to the systemic circulation via lymphatic circulation via intestinal M cell-mediated endocytosis. It's worth mentioning that alginate's good biocompatibility, low cost, and natural abundance make it a good alternative for protecting insulin from the astringent conditions of the GIT [64]. Insulin may load onto YMCs, and 100 mg of YMC was put into a 10ml insulin solution [100 g/mL] [n Hcl

0.01 Normal]. They were stirred for 3 hours at 400 rpm in a magnetic stirrer. After that, the sample was centrifuged for 10 minutes at 2000 rpm. Finally, the concentration of the supernatant was determined using a spectrofluorophotometer [61, 65]. The process of insulin loading onto YMC was studied using fluorescence imaging [66].

3.2.4. Preparation of alginate-coated insulin-loaded yeast microcapsules

IYMC was dropped into a 1 percent sodium alginate solution and stirred gently for 10 minutes. The supernatant was then decanted after centrifugation at 3400 rpm for 10 minutes. The alginate layer on the surface of IYMC was crosslinked by dispersing the sediment into a calcium chloride aqueous solution (5 mL, 4%), which was prepared by mixing the sediment with 5 mL of water [67].

3.2.5. Applications of microencapsulation in the delivery of diverse nanoparticles for imaging and therapy

It has been demonstrated that the yeast-derived bioinspired microcapsule is an effective vehicle for the oral delivery of various nanotherapies and nanoprobes that are intended to target distant disease sites. The challenge of getting around physiological barriers to oral delivery of nanoparticles to remote locations can be solved with a Trojan horse technique based on a bioinspired yeast microcapsule. Electrostatic deposition can be used to insert a charged nanoparticle into a yeast microcapsule. Moreover, yeast cells were exposed to nanotherapies, which macrophages effectively endocytozed and stayed inside the cell for a long time. It is transcytosed by M cells after oral absorption and then endocytosed by macrophages. Typically, they travel to adjacent lymphoid tissue before reaching the location of the action [61]. Nanoparticle-based medication delivery has several obstacles, including a lack of appropriate techniques and successful cellular targeting. It was discovered that glucan absorption relies on dectin 1 under in vitro conditions. Due to the specific targeting capacity of phagocytic cells, glucan particles are a potential drug delivery strategy. Encapsulation, transport, delivery, and release of electrostatically bound payloads are all achievable because to the hollow and microporous structure. Cadmium telluride quantum dots generated by extracellular synthesis using *S. cerevisiae* can be used in optical imaging [68].

3.2.6. Applications of microencapsulation in oral delivery

In recent years, yeast glucan particles (YGPs) have garnered significant attention as novel oral drug delivery carriers, owing to their superior biocompatibility, specific targeting capabilities, and intrinsic immunomodulatory properties [70, 71]. In yeast microcapsules, the lipophilic active ingredients can be incorporated. The genetically engineered yeast can be used in the oral delivery method to deliver the ingredient directly to the gastrointestinal tract. The outer crust of the capsule makes the delivery of active ingredients to be targeted. The yeast microcapsule attaches itself to the mucous membrane and releases the components into the bloodstream [38]. The encapsulation strategy aids in the protection of medications from the acidic medium to the gut by allowing β -glucans to play a vital role. Additionally, it protects the stomach against ulcers induced by some medications [72-75]. There are extremely harsh environments when it comes to oral drugs, such as the presence of highly acidic environment (pH 1–3), pepsin attack, and other digestive enzymes, which include pancreatic enzymes and bile salts, in the small intestine. However, the most important constituent of the YGP is the β glucan, which cannot be digested in the gut. Thus, it serves as an “armor” to protect the encapsulated drugs [76, 77]. The concept of YGPs stems from the purification of the *S. cerevisiae* cell wall. Due to the process of particular extractions resulting in the removal of cytoplasmic content, hollow and porous microspheres, mostly comprising β-glucans, are isolated. The mentioned hollow structure provides a good means for the encapsulation of drugs, protecting them from the influence of stomach acid and digestive enzymes. Beyond physical protection, YGPs possess a dual functionality: they act not only as a protective barrier but also as an active targeting vector. β-glucan is specifically recognized and internalized by M cells in Peyer’s patches and by Dectin-1 receptors on macrophages and dendritic cells. Thus, this specific recognition mechanism makes YGPs intrinsically

targeted, providing the possibility to deliver drugs either to the gut associated lymphoid tissues (GALT) or to the inflamed areas containing many macrophages [70]. Li et al. (2024) developed an oral drug delivery system (YP-MPA-ZnO-DOX) consisting of yeast microcapsules and DOX-loaded ZnO nanoparticles modified with 3-mercaptopropionic acid. The system exhibited good resistance to gastrointestinal conditions and retained the drug during gastric and intestinal transit, while showing enhanced drug release under the acidic tumor-mimicking environment. In vitro studies demonstrated effective inhibition of cancer cell proliferation and induction of apoptosis. Moreover, pharmacokinetic analysis showed that the yeast-based system prolonged the in vivo retention of DOX and significantly improved its oral bioavailability, highlighting the potential of yeast microcapsules as protective and responsive carriers for oral anticancer drug delivery [78]. Zhou et al. (2019) developed a yeast-derived microcapsule platform for the targeted oral delivery of cisplatin. They prepared yeast microcapsules (YCs) and loaded them with cisplatin-derived precursor nanoparticles (PreCDDP). The resulting PreCDDP/YC system showed enhanced drug bioavailability, targeted accumulation in tumor tissue, antitumor activity, and improved safety compared with free cisplatin. Figure 3 shows the morphology, loading efficiency, and in vitro release profile of PreCDDP-loaded yeast capsules (PreCDDP/YC) under simulated gastrointestinal conditions [79].

3.2.7. The vaccine delivery system

Studies have indicated that microparticles possess the ability to facilitate the transportation of molecules into targeted cells [80]. Yeast cases have recently been explored as a novel vaccination platform for cancer immunotherapy. The cutaneous layer of yeast encapsulation operates as a potential vehicle for administering vaccines, as it connects the antigen to the encapsulating layer and stimulates an immune response specific to the antigen by presenting it to dendritic cells. This method can provide high drug loading and feasibility [81]. Antigen loading into yeast shells is limited due to the porosity and hydrophilic nature of the yeast microcapsule. It is of utmost importance to underscore that enhancing the immune response is achieved by linking the antigen to the surface instead of encapsulating them [82, 83]. One of the most difficult immunization methods is the oral vaccine. Increased immunological responses at both systemic and mucosal locations, as well as socio-economic benefits, are all advantages of this method. Based on cost-effectiveness and inherent adjuvanticity, β -glucan is known as a potent immune system activator [84]. Functionally, β-Glucan is an immune activator of the innate immune response that can act nonspecifically and specifically on the immune system with PAMPs (pathogen-associated molecular patterns) [85, 86].

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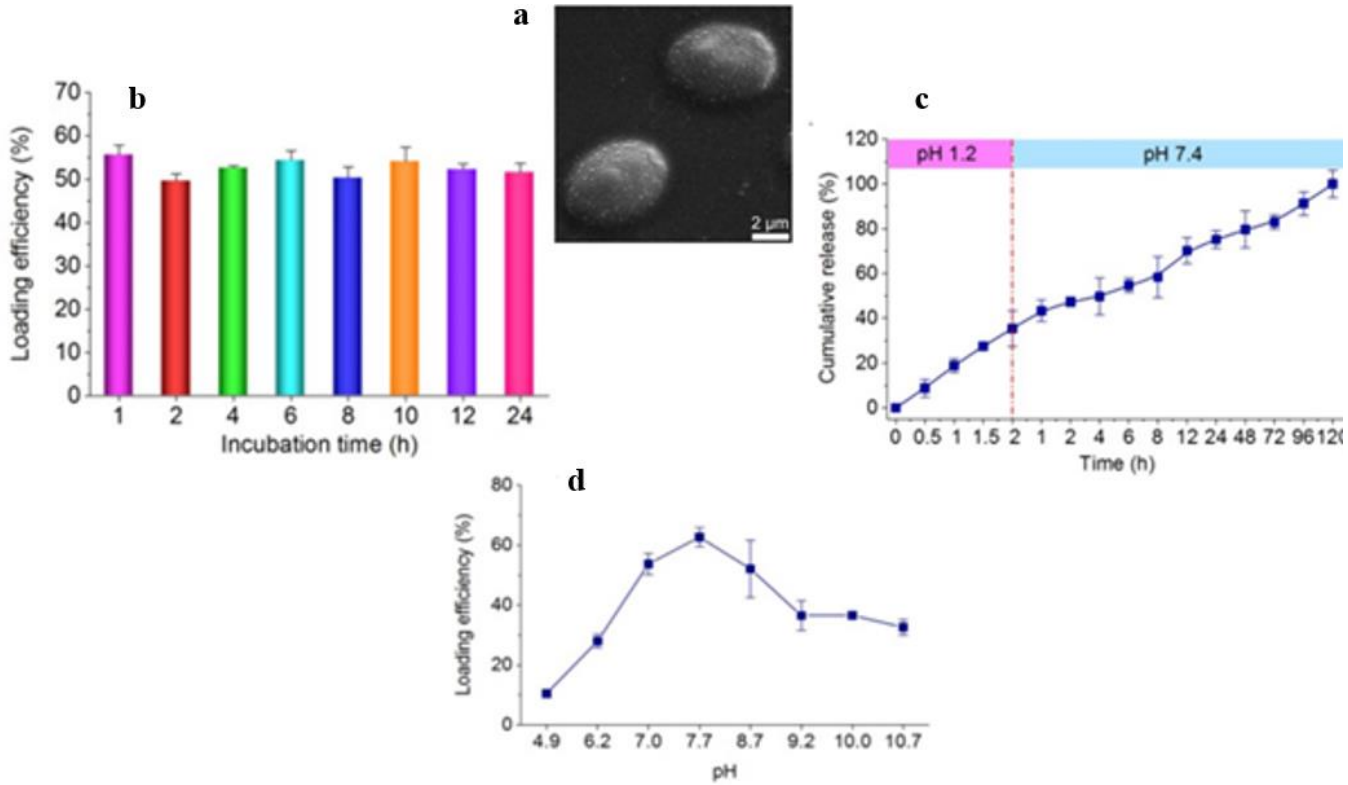

Figure 3. a) TEM of images of PreCDDP-loaded YC b) The effect of buffer pH values c) and incubation time on loading efficiency d) In vitro release profile of PreCDDP/YC in aqueous solutions simulating gastrointestinal conditions [79].

Using β -glucan as an antigen delivery platform improves immune response[84]. β-glucans are immune-modulating compounds that stimulate the immune system of the host, causing inflammation in return. Moreover, this mechanism is responsible for the anticancer effects and the therapy of infections. β -glucans do not have any antitumor activity but the β-glucans containing herbal compounds possess antitumor properties [87]. Studies have shown that delivering siRNA orally through yeast skins eliminates systemic inflammation by specifically targeting macrophages [64]. Du et al. (2024) developed recombinant yeast-cell microcapsules (YCMs) as oral carriers for a DNA vaccine against *Clostridium perfringens*. The researchers engineered yeast cells to carry DNA vaccine constructs encoding mutated α-toxin and administered the recombinant YCMs orally to mice. The results showed that oral YCM administration induced effective intestinal mucosal immunity, with the H126G construct showing superior performance compared with the C247–370 construct. In addition, YCM treatment modulated the gut microbiota and increased bacterial richness, highlighting the potential of yeast-cell microcapsules as oral carriers for DNA vaccines and mucosal immunization [88].

4. RESULTS AND CONCLUSION

Microencapsulation using yeast cells is one of the promising techniques that could be applied to enhance the stability, bioavailability, and controlled release of bioactive compounds. Yeast cells have specific properties that make them suitable for microencapsulation and delivery of different active compounds due to their low price, biocompatibility, easy production and scalability. Yeast-based micro-encapsulation technology can be used to protect bioactive compounds used in the food industry and probiotics, as well as pharmaceutical compounds. However, although yeast microencapsulation technique possesses many promising characteristics, there are still some issues that need to be addressed to improve its application. Differences in yeast species, cell wall composition, microencapsulation

techniques and conditions could significantly influence the efficiency of the process, as well as the stability and release characteristics of the compounds. Therefore, standard protocols and comparative studies are necessary to investigate these issues. Also, the stability, reproducibility, cost-efficiency, and compatibility with the manufacturing processes need to be studied. Future research should emphasize the integration of yeast-based micro-encapsulation with novel technologies like precision fermentation, synthetic biology, engineered yeast systems, and formulation optimization. This could allow for better regulation of encapsulation efficiency and targeted delivery of the microcapsules. In addition, issues related to scale-up production, regulatory requirements, commercialization, and environmental sustainability should also be taken into account to assist the adoption of yeast-based system from research to practice. In general, yeast-based microencapsulation can be regarded as an innovative platform with great application potential in the food and pharmaceutical industry. Nevertheless, the successful application of the system in industrial and clinical practice will highly depend on overcoming existing technological, regulatory, economic and safety issues as well as providing more comparative and mechanism-based evidence.

5.DECLARATIONS

5.1. Acknowledgments

We thank the research core of Yazd University for the financial support during the course of this project.

5.2.Conflict of Interest: The authors have no relevant financial or non-financial interests to disclose.

5.3. Author contributions

All authors contributed to the study's conception and design.

5.4. Ethical considerations

All ethical principles were adhered in conducting and writing this article.

5.5.Using artificial intelligent chatbots

No AI chatbot has been used in this study.

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