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pH-Driven Co-encapsulation Strategy for Nano-Delivery of Bioactive Substances

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Abstract: The pH-driven method is a simple, effective, and solvent-free organic technique for encapsulating bioactive substances, with promising applications in the functional foods and pharmaceutical sectors. However, encapsulating a single bioactive has been the main focus of the majority of research on this technique. On the other hand, co-encapsulation and the simultaneous administration of multiple bioactives have become more popular recently, as they enable complementary and synergistic effects. The primary obstacles to pH-driven co-encapsulation are variations in bioactive properties across different pH levels and potential bioactive competition, which could lower encapsulation efficiency. To overcome these limitations, improvements to the preparation process and modifications to carrier systems through specific treatments or combinations with other techniques have been explored. This review provides a succinct overview of pH-driven co-encapsulation technology, including the molecular interactions among components within the carrier platform and strategies to enhance the efficiency process. Most investigations indicated that the encapsulation efficiency of bioactive substances typically ranges from 75% to 97%, with particle sizes generally remaining below 300 nm. These systems have also shown significant improvements in the stability and bioactivity of the encapsulated substances. The review's conclusions provide researchers with important insights for developing pH-driven technologies for industry.

Keywords: green method; pH adjustment; carrier systems; polyphenols; bioavailability.

1. Introduction

Bioactive substances are components of dietary materials, whether nutritional or non-nutritional, that confer physiological benefits beyond their nutritional value [1]. Numerous studies have shown that compounds such as peptides, phenolic compounds, essential oils, vitamins, polyunsaturated fatty acids (PUFAs), and probiotics can reduce the risk of chronic

diseases, including cardiovascular disorders, neurological conditions, cancer, and aging-related conditions [2-4]. In recent years, the use of bioactive substances in the fields of food, nutraceuticals, and biomedicine has been increasingly studied due to their many health benefits. However, throughout processing, distribution, and storage, the majority of these chemicals are vulnerable to structural degradation from exposure to heat, oxygen, and light [5-8]. Additionally, their effectiveness in the body is often hindered by low absorption rates and bioavailability [9-11]. An effective strategy to overcome these challenges is to encapsulate bioactive compounds in various carrier platforms such as nanoparticles, liposomes, emulsions, nanogels, and films [12-14]. Nanoparticles have attracted significant interest in these platforms due to their high surface-area-to-volume ratio, which confers unique properties such as toxicity, color, solubility, and diffusion characteristics [15-19].

The pH-driven method, which uses the structural and characteristic changes of components under particular pH conditions, is currently being developed for nanoencapsulation techniques. This novel method doesn't require specific equipment and is very eco-friendly, simple to use, effective, and energy-efficient [20-23]. With its advantages, pH-driven is regarded as one of the most promising methods for large-scale industrial production [24,25]. However, its application in designing systems capable of carrying multiple bioactive substances remains limited. On the other hand, the trend of co-encapsulating multiple bioactive compounds is gaining momentum, offering benefits such as loading compounds with different biological activities that can work synergistically, enhancing stability and bioavailability, and allowing simultaneous delivery of components according to the desired mechanism [2,26,27]. For example, co-encapsulation of tannic acid and resveratrol enhanced antioxidant activity in vitro, reduced oxidative stress in HepG2 cells, and altered the release profile of the compounds. In the gastric environment, encapsulation reduced the release of tannic acid while enhancing the release of resveratrol. In contrast, in the intestinal phase, it achieved remarkably high bioaccessibility values of 76% for resveratrol and 100% for tannic acid [28]. Ji *et al*. successfully developed a gelatin–sodium carboxymethyl cellulose coaservative for the co-encapsulation of L-ascorbic acid and quercetin, resulting in high stability and encapsulation efficiency of bioactive compounds [29]. Co-encapsulation of the polyphenols epigallocatechin-3-gallate (EGCG) and quercetin in liposomes also showed synergistic antioxidant effects and good storage stability, thus having potential for use in food fortification and antioxidant-based therapy [30].

Although co-encapsulation of multiple bioactive substances can offer numerous benefits over single encapsulation, this process is not straightforward. Accommodating bioactives with varying solubility and chemical stability within a single wall material poses a significant challenge [31]. Furthermore, very little research has been done on the interactions between various bioactive compounds and how they function within a single system; the reliability of the co-encapsulation system remains unknown. Another challenge that warrants further optimization research is competition among compounds for binding sites on the wall material, which reduces encapsulation efficiency [1,25,32]. As a result, numerous attempts have been made to enhance pH-driven co-encapsulation capabilities, including improvements to the preparation process and modifications to carrier systems via various chemical and/or physical treatments. Molecular-level exploration is also necessary to understand the behavior of components within the carrier platform, which is useful for designing better co-encapsulation systems. In this paper, we will briefly present the development of the pH-driven

technology for the co-encapsulation of multiple bioactive substances, along with a summary of significant and intriguing results from several investigations.

2. Basic Concepts of pH-driven Method

A technique for encapsulation known as pH-driven uses the differences in the properties of carrier materials and bioactive substances at specific pH levels. Using this technique, lipophilic polyphenols are frequently entrapped into protein-based carrier systems by changing the system's pH from alkaline to neutral or acidic [25]. In alkaline solutions, phenolic hydroxyl groups undergo deprotonation to form negatively charged phenolate ions (ArO^-). This process increases water solubility and changes the nature of polyphenols from hydrophobic to more hydrophilic, allowing them to be dispersed evenly in aqueous media [22,33]. At the same time, proteins at pH levels well above their isoelectric point (pI) undergo deprotonation of ionizable amino acid groups, such as the carboxylate groups of Asp and Glu and the amino groups of Lys and Arg, resulting in an increase in net charge. This results in increased electrostatic repulsion, which leads to partial unraveling of the protein structure, weakening internal hydrophobic interactions, and increasing the flexibility of the polypeptide chain. Under these conditions, hydrophilic residues are more exposed to the aqueous phase, while hydrophobic domains remain relatively protected internally, although some become more accessible. This open conformation facilitates the homogeneous mixing of polyphenols with proteins [12,34].

After homogeneous mixing, the pH of the system is gradually lowered towards neutral or slightly acidic to induce protonation. In polyphenols, the phenolate ions (ArO^-) accept a proton back to form a neutral hydroxyl group (ArOH), decreasing their water solubility and restoring their hydrophobic properties [22,24]. Meanwhile, proteins undergo reprotonation at ionizing groups (Asp, Glu, Lys, Arg, His), reducing the net charge, weakening electrostatic repulsion, and allowing refolding into a more compact structure [35]. The reorganization of hydrophobic domains and the reformation of intramolecular interactions, such as salt bridges and hydrogen bonds, enhance the structural stability of proteins. Under these conditions, hydrophobic polyphenols are pushed into the hydrophobic pockets of proteins. Non-covalent interactions, including hydrophobic interactions, hydrogen bonds, van der Waals forces, and π–π stacking with aromatic residues such as Phe, Tyr, and Trp, stabilize the formed complexes [36]. This process results in the self-assembly of proteins into nanoparticles encapsulating polyphenols, generally <200 nm in size, with high encapsulation capacity and physical and chemical stability. Over time, the pH-driven method has also been applied to encapsulate hydrophilic substances [12,25].

3. Preparation Approach

A number of variables, including preparation methods, mechanical features, operating circumstances, and how bioactive substances behave in acidic-basic environments, affect how well the pH-driven method works to incorporate numerous bioactives into carrier systems [12,25]. As a result, these elements must be carefully examined prior to the co-encapsulation procedure. Generally, there are three primary ways to apply pH-driven co-encapsulation techniques: one-step, two-step, and in combination with other techniques.

3.1. One-step process.

In a single process, pH-driven technology can readily co-encapsulate two or more bioactive compounds that are soluble and insensitive to alkaline conditions. One of the main factors that determines the stability of compounds, especially polyphenols, is the amount of hydroxyl groups (-OH) in their structure. Compounds that have more hydroxyl groups tend to be unstable in extreme basic environments [37]. Thus, substances such as apigenin, curcumin, resveratrol, and thymol can be co-encapsulated effectively by a one-step process. By dispersing the bioactive substances and carrier agents in an alkaline solution, this method gradually lowers the mixture's pH until it approaches or reaches neutral conditions while stirring [38-41].

3.2. Two-step process.

The two-stage preparation process was developed to address the shortcomings of earlier methods, accounting for the various properties of bioactive substances in both basic and acidic environments. Each bioactive ingredient is handled differently in solution using this approach based on its unique physicochemical characteristics. There are two primary routes that the preparation process takes: 1) Using a stirrer, the first bioactive molecule and the carrier material are combined with a buffer, and the pH is then neutralized or adjusted to nearly neutral. The pH then drops once the second bioactive and/or coating material is added to the suspension [41,42]. 2) The carrier platform is first assembled, followed by the incorporation of the alkaline bioactive substances. An acidifier is usually used to maintain or adjust the pH environment [24,43].

3.3. Combination with other methods.

The pH-driven method's great versatility, which enables it to be integrated with other methods, is one of its benefits [12]. The pH-driven procedure has been combined effectively with a range of techniques, including one-step emulsification [44], ionic gelation [45], and the antisolvent approach [46]. This approach enables the efficient loading of two or more bioactive substances with dissimilar properties onto various carrier platforms, opening up additional pH-driven uses. Nevertheless, this approach calls for additional materials and slightly more intricate techniques. Moreover, the use of a modest quantity of organic reagents becomes inevitable, especially when paired with the antisolvent technique.

4. Co-encapsulation Systems Created by pH-driven Technique

The investigations on pH-driven preparation techniques used to assemble several co-encapsulation systems are summarized in Table 1. As is evident, curcumin is primarily one of the bioactive compounds co-encapsulated with other substances in various protein-based carriers. This co-encapsulation system is achieved through methods such as one-step, two-step, or a combination of pH-driven techniques with other methods. Each system will be covered in detail in the sections that follow.

Table 1. Research on the pH-driven system to co-encapsulate multiple bioactive substances in different carrier platforms.

Preparation approach	Co-encapsulated bioactives	Carrier platform	Main results	Ref.
One-step process	Apigenin and curcumin	Protein nanoparticles	Curcumin and apigenin co-encapsulation produces synergistic anti-inflammatory actions.	[38]

Preparation approach	Co-encapsulated bioactives	Carrier platform	Main results	Ref.
	Egg white-derived peptide and curcumin	Protein-polysaccharide nanocomplexes	Curcumin's solubility, stability, and bioactivity might be enhanced through the interaction of peptides with protein-polysaccharide complexes.	[47]
	Phenolic extract	Protein nanoparticles	The digestion of the phenolic extract-loaded Tartary buckwheat protein was much lower than that of the protein by itself.	[48]
	Curcumin and Zn	Protein nanoparticles	A three-part structure including curcumin and zinc was formed in the aqueous solution thanks to the soy protein isolate acting as a connecting agent. This structure was propelled by hydrophobic, electrostatic, and coordination forces.	[49]
	Curcumin and diosmetin	Protein-protein nanocomposite	Protein architectures were changed by the simultaneous encapsulation of diosmetin and curcumin, which increased the number of binding sites available for diosmetin on zein nanoparticles.	[39]
	Resveratrol, quercetin, and curcumin	Colloidal dispersion of milk	The pH-driven approach worked well for effectively encapsulating many polyphenols at once, especially curcumin and resveratrol.	[50]
	Resveratrol (Res) and curcumin (Cur)	Protein-protein nanocomposite	The resultant zein–bovine serum albumin nanocomposites entrapped Res and Cur in discrete areas with certain binding sites.	[40]
	Eugenol (Eu), thymol (Thy), carvacrol (Car), and trans-cinnamaldehyde (TC)	Protein-polysaccharide nanocomplexes	The biological activity was enhanced by the phytoglycogen-zein (PZ) nanocomplexes, with PZ-Eu-Thy showing a significant increase in antioxidant qualities and being most efficient against Gram-negative bacteria.	[41]
Two-step process	Quercetin and avenanthramide 2c	Protein nanoparticles	Successful coencapsulation depends on the interaction between caseinate and ionized quercetin, as well as the increased hydrophobicity of avenanthramide 2c during acidification.	[42]
	Curcumin, resveratrol, and quercetin	Nanoemulsions	There were minor differences in each polyphenol's encapsulation efficiencies, stabilities, and bioaccessibilities. It's noteworthy that quercetin degraded more when exposed to extended alkaline environments.	[51]
	Anthocyanins and curcumin	Protein-polysaccharide nanocomplexes	The exterior and inner layers of the bovine serum albumin-fucoidan nanocomplex, which included anthocyanins and curcumin, were released at different rates.	[43]
	Caffeic acid and betanin	Protein nanoparticles	Betanin was well encapsulated by the ferritin-caffeic acid covalent complex, which improved its stability.	[52]
	Vitamin E (VE) and quercetin (QU)	Protein nanoparticles	Proteins were able to connect to VE or QU more effectively when the pH was changed in conjunction with ultrasonic processing, which changed the protein's structure.	[53]
The combination with other methods	Quercetin and curcumin	Protein-protein nanocomposite	Curcumin was more effectively encapsulated by the zein-caseinate composite, whereas quercetin was less effectively encapsulated. In the meantime, due to its greater binding ability, the zein-bovine serum albumin composite holds onto more curcumin over time.	[46]
	Curcumin and L-ascorbate	Protein-polysaccharide nanocomplex	Chitosan, which was later placed atop caseinate particles with hydrophobic curcumin encapsulated in them, established electrostatic connections with L-ascorbate.	[45]
	Quercetin and curcumin	Dual-compartments Emulsion	Ferritin and chitooligosaccharide were combined 2:1 to create a dual-compartment emulsion that demonstrated exceptional stability and improved physicochemical properties.	[44]
	Tannic acid (TA) and Fe^{3+}	High internal phase Pickering emulsions (HIPPEs)	HIPPEs stabilized by ovalbumin showed significant improvements in stiffness, thickness, stress resistance, and flexibility when pH-shifting and metal phenolic network (MPN) integration were coupled.	[54]
	Flavor compounds	High internal phase	Sweet orange essential oil scent components could be effectively captured by HIPPEs stabilized by soy protein	[55]

Preparation approach	Co-encapsulated bioactives	Carrier platform	Main results	Ref.
		Pickering emulsions	nanoparticles (SPN), which also delayed their dispersion into the surrounding air.	

4.1. Bioactive substances co-loaded protein nanoparticles.

The unique amphiphilic properties of the protein facilitate simpler interactions with lipophilic substances, thereby facilitating more effective encapsulation, in addition to its natural origin, varied availability, biocompatibility, and capacity for natural disruption [22,56,57]. Curcumin and apigenin were effectively co-encapsulated in sodium caseinate by dissolving them both in a basic solution (pH 12) and then stirring for 30 minutes at 21°C. Following HCl neutralization of the sample, high-speed centrifugation was used to separate the unbound polyphenolic compounds (Figure 1). The technique produced spherical nanoparticles that were highly stable and uniformly sized between 10 and 40 nm. According to bioactivity testing, the encapsulated curcumin and apigenin demonstrated synergistic anti-inflammatory effects. This was probably caused by greater solubility, molecular proximity, multitarget effects, and increased bioavailability [38]. Using a similar approach, curcumin and Zn were successfully co-encapsulated in soy protein isolate (SPI). The presence of Zn enhanced the body's ability to absorb curcumin and maintained its stability during simulated digestion. This complex also demonstrated synergistic protective effects against 6-OHDA-induced neuronal damage in PC12 cells [49].

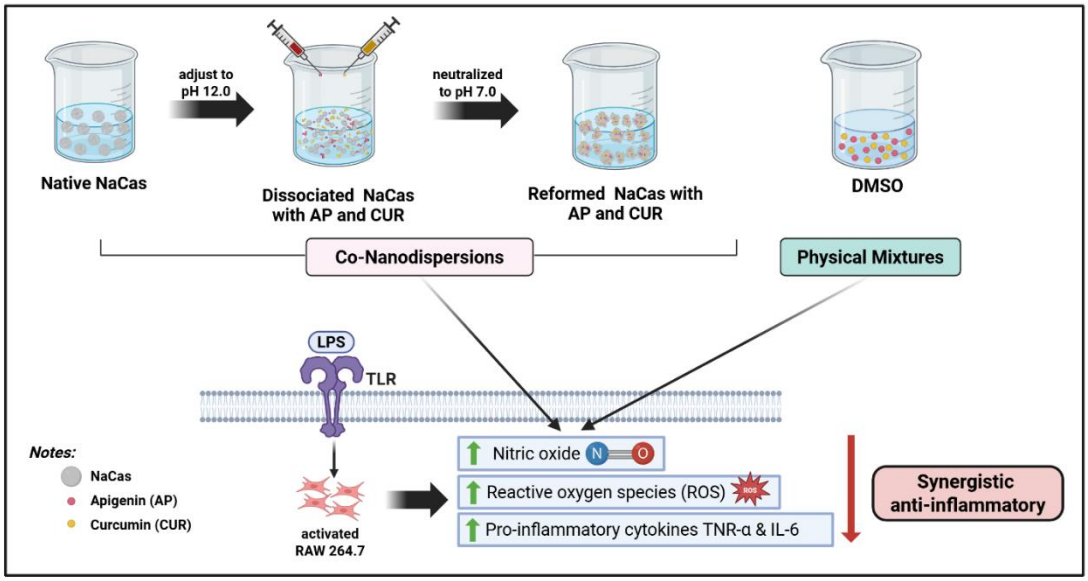


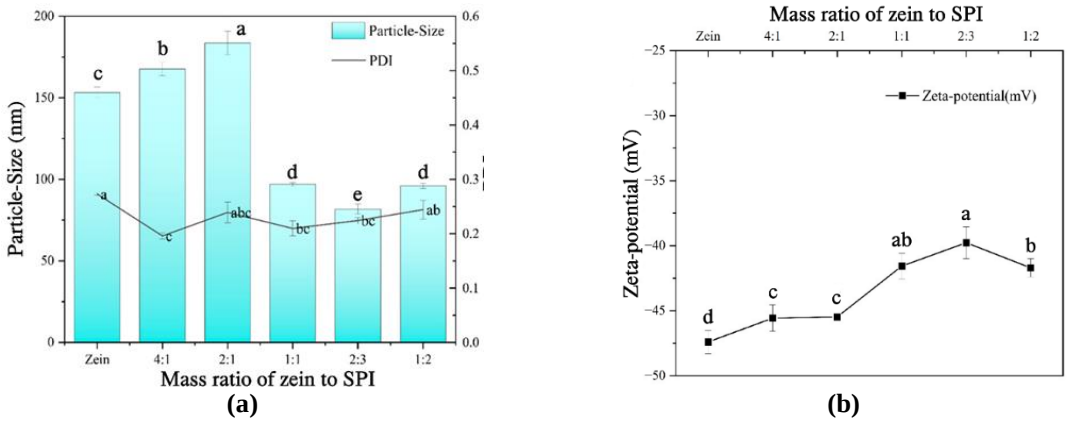
Figure 1. Co-encapsulation of curcumin-apigenin in sodium caseinate using a one-step process and its synergistic effect. Adapted from Hong *et al.* with modification [38].

The differences in solubility and stability of bioactives across different pH levels make single-step encapsulation challenging. For example, quercetin demonstrates high solubility and stability, whereas AV 2c is poorly soluble and prone to degradation at high pH. By employing the two-stage process, both compounds were successfully incorporated into caseinate nanoparticles. The nanoparticles containing quercetin-AV 2c (Q-2c-N) remained stable for 21 days at 21°C. The encapsulation efficiency of quercetin and AV 2c in Q-2c-N was relatively high, at 94.3% and 80.6%, respectively. In vitro studies stated that this combined encapsulation improved the bioavailability of both compounds and enhanced their uptake by Caco-2 cells [42]. Sha *et al*. [52], developed a ferritin-based nanostructure designed to bind caffeic acid on

its exterior while encapsulating betanin within. In addition to offering recommendations on how to employ betanin as a natural food coloring agent, this approach seeks to maximize the stability of protein and its function as a transport medium for bioactive substances. In the first step, caffeic acid and ferritin (CFRT) formed covalent connections in an alkaline environment by raising the pH to 9 with a NaOH solution. The complex was then dissociated by employing HCl to bring the pH down to 2. The ferritin structure was neutralized once betanin was added, which allowed betanin to become stuck inside. By assessing the preservation of betanin under high temperatures and UV exposure, CFRT's efficacy as a delivery device was assessed. The findings showed that betanin was successfully shielded against deterioration by CFRT, increasing its resilience to unfavorable environmental conditions.

4.2. Bioactive substances co-loaded protein nanocomplex/nanocomposite.

The main problem with using a single protein as a carrier is that it has a tendency to flocculate and precipitate when the pH of the surrounding environment approaches its isoelectric point or when ion concentration is high [58,59]. To address this issue, complexation with other biopolymers (polysaccharides, proteins) or surfactants has been shown to be an effective method for stabilizing the generated nanocapsules [60-62]. The stability and physicochemical performance in practical applications are largely determined by the type and composition of biopolymers. The resulting nanoparticles often exhibit a denser organization, superior bioactive binding capacity, and greater physicochemical stability when the mixing proportion is just right [59,63]. Building zein-soy protein isolate (SPI) nanocomposites with different ratios of 4:1, 2:1, 1:1, 2:3, and 1:2, for example, demonstrated a tendency to decrease particle size (Figure 2a) and increase zeta potential (Figure 2b) as the ratio of SPI to zein rose [39]. A similar result was reported by X. Chen *et al*. [40]; enlarging the BSA level from 2 to 10 mg/mL during co-assembly led to a decline in zein–BSA nanoparticle size, shrinking from 170.2 to 81.8 nm. This suggests that BSA and SPI molecules play a significant role in preserving system stability.



(a) **(b)**

Figure 2. (**a**) Mass ratio of zein to SPI Z-average; (**b**) Zeta-potential of zein-SPI NPs. (Retrieved from Yu *et al*. [39]).

The nanocomplex demonstrated effective encapsulation of many bioactives with varying solubility. Using a two-stage approach, hydrophobic curcumin was co-encapsulated with hydrophilic anthocyanins in a bovine serum albumin (BSA)–fucoidan nanocomplex. Curcumin (Cur) was incorporated into the core of BSA nanoparticles by adjusting the pH from alkaline to neutral, thereby triggering the formation of a BSA layer around the nanoparticles. Subsequently, when the pH was adjusted to the isoelectric point of BSA (pH 4.7), fucoidan bound to BSA and simultaneously adsorbed anthocyanins (ACN) onto the outer layer of the

Cur-BSA particles. Curcumin's assessed encapsulation effectiveness was 78.49%, while anthocyanin's was 76.9%. The investigation into the release behavior of the bioactive compounds revealed that the release profiles of CUR and ACN corresponded most accurately with the Weibull and Logistic kinetic models, as reflected by high determination coefficients (R^2 = 0.986, 0.996, and 0.982, 0.988, respectively) [43]. Comparable findings were observed in studies involving BSA nanoparticles carrying vitamin B12 and scutellarin. Consequently, these two models appear suitable for describing the release dynamics of bioactives encapsulated within BSA-based nanocarriers [64,65]. In a separate study, the release profiles of quercetin and curcumin from zein-based nanoparticles were more in line with the Gompertz model [46]. This result underscores the critical role of the encapsulating matrix in the release behavior of bioactive substances.

Curcumin and L-ascorbate have been employed in a caseinate-chitosan complex coacervation system. Ionic gelation and the pH-driven approach were combined to create the co-encapsulation system. L-ascorbate and chitosan interacted electrostatically during the co-encapsulation process, forming a coating around the caseinate particles containing curcumin. In addition to preventing structural alterations in caseinate, the L-ascorbate-containing chitosan layer enhanced curcumin's resistance to light and storage conditions. Compared with single-component encapsulation, co-encapsulation demonstrated higher antioxidant activity [45].

4.3. Bioactive substances co-loaded plant-based milk.

Plant-based milk is a perfect medium for encapsulating, preserving, and delivering various polyphenols, as it is a colloidal dispersion system with oil droplets (fat globules) dispersed in an aqueous phase [50,66]. Hydrophilic polyphenols can be dissolved by the surrounding aqueous medium, whereas hydrophobic polyphenols can be dissolved by the lipophilic part of the oil droplets. Furthermore, plant-based milk's protein content can interact with lipophilic polyphenols, shielding them from physical and chemical damage (Figure 3) [67,68].

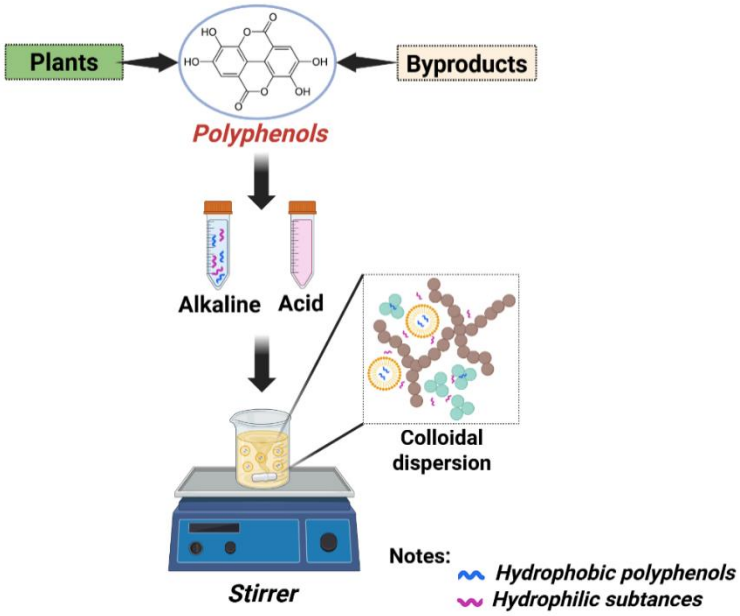


Figure 3. Schematic representation of the approach for incorporating polyphenols from plants or byproducts into colloidal dispersions. (Retrieved from X. Gong *et al*. [69].

A pH-driven process has been used to co-encapsulate and fortify quercetin, curcumin, and resveratrol in soy milk. The polyphenols were first dissolved in an alkaline solution before being combined with the soy milk colloidal dispersion to create the co-encapsulation system. Encapsulated polyphenols demonstrated more bioaccessibility than polyphenol crystals dispersed in water, according to in vitro research on gastrointestinal function. Due to their limited water solubility, which makes them difficult to dissolve in mixed micelles, polyphenol crystals were found to have low bioaccessibility. Nonetheless, the crystalline form of polyphenols showed superior chemical stability during passage through the digestive system, most likely because fewer molecules in the aqueous phase were directly exposed to stressors [50].

4.4. Bioactive substances co-loaded emulsion-based nanocarrier.

The food and pharmaceutical industries are increasingly using nanoemulsions, which are systems with droplets smaller than or equal to 100 nm. This is because nanoscale droplets have unique properties, such as a huge surface area [69-71]. A nanoemulsion system comprising multiple polyphenols (curcumin, resveratrol, and quercetin) was created using three protocols: 1) The three polyphenols are first solubilized in the same basic medium, then introduced into an emulsion with mild acidity; 2) Each polyphenol is individually dispersed in its own alkaline medium, and all solutions are subsequently combined into one nanoemulsion; 3) The pH-shift approach is used to separately create distinct nanoemulsions containing each polyphenol, which are then combined. These methods aid in the co-entrapment of diverse nutraceuticals or the inclusion of polyphenols with varying solubility properties into a range of droplets, including droplets with different compositions, sizes, or types of emulsifying agents. The gastrointestinal behavior (lipid digestion, chemical stability, and bioaccessibility) and physical features (droplet size and charge) of the three polyphenols were not significantly altered by the three processes, yielding findings that were equivalent [51].

In addition to conventional emulsions, other emulsion-based carrier platforms have been developed by integrating one-step emulsification with pH-responsive methods. Curcumin and quercetin have been co-encapsulated in ferritin/oligosaccharide-based dual-compartment emulsions using sunflower seed oil as the base oil. The proportion of Marsupenaeus japonicus ferritin (MF) to chitooligosaccharide (COS) was adjusted to 8:1, 4:1, 2:1, 1:1, 1:2, 1:4, and 1:8. Optical microstructural analysis revealed that all MF/COS emulsions displayed a spherical morphology with uniform droplet dispersion and no aggregation [44]. High internal phase Pickering emulsions (HIPPEs), characterized by oil contents exceeding 74% and using solid particles as stabilizers, have recently been developed [72-74]. HIPPEs represent compelling opportunities for innovation in the pharmaceutical and functional food sectors, as they have demonstrated enhanced loading capacity and faster biological absorption of lipophilic compounds compared to traditional emulsion systems [75,76]. As a HIPPE stabilizer for dysphagia treatment, a compound comprising ovalbumin and a tannic acid-Fe^{3+} network has been created [54]. To enhance fragrance qualities and consumer appeal, HIPPEs are also used as a carrier for flavor compounds and as a substitute for fat in plant-based or low-calorie food products [55,77].

5. Molecular Interaction

Molecular interactions affect the general properties of the co-encapsulation system and are essential to the formation and stability of carrier platforms. All components are involved in these interactions through covalent and non-covalent interactions, such as hydrogen bonds, hydrophobic forces, and electrostatic interactions. Proteins are frequently used as the primary wall material in co-encapsulation systems developed using the pH-driven approach. The carrier structure is formed and stabilized by intermolecular interactions enabled by the diverse amino acid residues found in proteins. Amino acid residues can also form networks with other components or interact with bioactive substances [1,78,79].

The production of zein-BSA nanoparticles loaded with curcumin and/or resveratrol was found to be influenced by hydrogen bonds and hydrophobic interactions. Proteins and polyphenols can create hydrogen bonds thanks to the hydroxyl groups found in curcumin and resveratrol. In contrast, hydrophobic interactions occur between the aromatic ring of polyphenol and hydrophobic amino acids found in proteins [40]. Non-covalent interactions are the primary mechanism underlying the production of protein-based nanoparticles, according to other research [38,42,45]. Treatment conditions can either increase or decrease the strength of interactions between proteins or with other components. Proteins may aggregate across these linkages, for instance, if the system's temperature increases [1,75]. The alkaline reaction conditions facilitated the protein's unfolding and structural reorganization, revealing normally concealed hydrophobic regions that enabled hydrophobic bioactives to bind. Thus, it is crucial to control variables such as pH and temperature to promote the desired interactions and avoid unintended reactions [80,81].

According to Li *et al*. [47], hydrophobic interactions between polyphenols and proteins resulted in a more compact curcumin–peptide–casein–chitosan complex structure with smaller particle sizes compared to casein–chitosan alone. Furthermore, the presence of hydrophilic groups in egg white-derived peptides (EWDP) facilitated interactions with water, while their negative charge enabled binding with positively charged chitosan. On the other hand, the hydrophobic groups of EWDP tended to avoid contact with water and interacted with the hydrophobic regions of the casein surface, leading to denser, more uniformly distributed nanoparticles. The co-encapsulation process of curcumin and diosmetin in zein-soy protein isolate nanoparticles revealed an intriguing phenomenon: with the addition of curcumin, the encapsulation efficiency (EE) of diosmetin improved dramatically from 43.07% to 73.41% [39]. An analogous phenomenon was noted in the research conducted by X. Chen and colleagues [40]. Using this co-entrapment technique, resveratrol and curcumin could be co-loaded into zein-BSA nanoparticles. The resveratrol EE% rose from 63.7% to 79.1%, indicating that curcumin helped encapsulate resveratrol. This is likely influenced by π–π stacking interactions within the benzene ring structure of phenolic compounds [82]. Furthermore, curcumin may alter protein structure in an alkaline environment, increasing the protein's ability to bind other polyphenols. In the presence of diosmetin/resveratrol, fluorescence spectrum analysis revealed a change in the binding location of curcumin from a more polar region to the more hydrophobic zein core, indicating that curcumin and diosmetin/resveratrol occupied distinct binding sites within the nanocomposite [39,40].

Numerous investigations have demonstrated that interactions on the carrier platform are significantly influenced by treatment conditions. Caffeic acid, for instance, forms covalent connections with soybean ferritin in alkaline circumstances (pH 9), as evidenced by an increase

in polyphenol binding equivalents and a decrease in free amino acid concentration [52]. Molecular docking analysis revealed that the binding sites of phenolic compounds (quercetin, rutin, and kaempferol) with 13S globulin (a buckwheat storage protein) differed significantly between basic and neutral pH conditions. The increased electronegativity of polyphenols, brought about by hydroxyl group deprotonation, may have contributed to the greater number of hydrogen bonds formed in an alkaline environment by enhancing interactions with amino groups in proteins (Table 2) [48]. Furthermore, the application of ultrasonic waves to soybean lipophilic protein (SLP) results in modifications to its molecular structure and greater exposure of its hydrophobic groups [53,83]. This state causes strong hydrophobic interactions between proteins and lipophilic compounds such as quercetin (QUE) and vitamin E (VE), making it easier for bioactive compounds to be encapsulated. While QUE was successfully entrapped in the inner region of SLP close to the surface, VE was successfully entrapped in the inner core of SLP using ultrasonic pretreatment [53].

Table 2. Hydrogen interaction sites between phenolic substances and 13S globulin across varying pH environments[48].

Polyphenol	pH 7	pH 12
Quercetin	Gln3, Asn152, Leu1064	Ser561, Arg 1326, Arg1580, Gln2258, Asn1349
Rutin	Leu1970, Asn1964, Gln1969 Asn2668, Asn2417, Gln2268,	Glu817, Thr184, Arg191, Ser209, Gln182, Arg185, Gly204, Asp197
Kaempferol	Asn1058, Asp1056, Asn609	Phe1060, Thr38, Asn152, Gln1063, Ser153

6. Techniques to Increase pH-Driven Process Efficiency

The pH-driven technique has shown effectiveness in co-encapsulating a variety of bioactive compounds with differing characteristics by developing preparation procedures and modifying carrier systems. The performance of the pH-driven technology is undergoing enhancements to achieve greater efficiency. To enhance efficiency, accelerate processing, and reduce resource consumption, researchers have recently modified this technology by integrating extraction and encapsulation into a more streamlined process. This technique enhances product sustainability, minimizes waste, and optimizes the utilization of raw materials. Moreover, employing sealed containers and regulating operational parameters, such as accelerating dissolution, mitigates degradation of bioactive compounds resulting from prolonged exposure to light, oxygen, and alkaline environments [69,84].

The research conducted by Gong *et al*. [69] indicates that the amalgamation of the pH-driven polyphenols extraction and encapsulation technique, under regulated operating parameters, markedly enhances process efficiency. This method was proven to extract polyphenols from peanut skins 1.8 times more effectively. Compared with the water-based technique, the antioxidant potential of polyphenols in nanoemulsion form was substantially tripled. The high encapsulation efficiency of quercetin, a molecule extremely sensitive to alkaline environments, reaching 95.9%, was another noteworthy finding from this study. This is in sharp contrast to earlier research, which found that, in the absence of process condition control, quercetin encapsulation efficiency in nanoemulsions was only 61% [51]. Using a similar approach, Suryamiharja and his associates were able to extract curcumin from turmeric powder and effectively encapsulate it in soy milk. The curcumin extraction process had a success rate of 96.4% ± 0.5%, while the curcumin encapsulation efficiency in soy milk was 94.2% ± 1.6%. The usage of raw turmeric as an alternative to pure curcumin supports raw material sustainability by reducing CO_2-eq emissions by up to 22-fold and saving energy consumption by up to 10-fold [84].

7. Advantages and Limitations of pH-Driven Co-encapsulation System

The use of pH-driven systems in the encapsulation of bioactive substances offers several advantages that make it very promising for food and health applications. This method is not only fast and simple but also avoids the use of potentially hazardous organic solvents and utilizes biopolymers, such as proteins and polysaccharides, which are more biocompatible [58,60,85]. Research by Yu *et al*. showed that zein-SPI nanoparticles (NPs) have L-O2 and HepG2 cell viability above 90% at various concentrations, indicating no toxic effects and high compatibility with the human body [39]. In addition to its excellent safety profile, the pH-based method has been shown to produce nanocarriers with high encapsulation efficiency (EE) for bioactive substances. For example, curcumin encapsulated using the pH-based method showed an encapsulation efficiency (EE) of 87.4%, higher than the 85.7% achieved by the anti-solvent method [86]. Co-encapsulation of resveratrol (Res) and curcumin (Cur) demonstrated that the presence of Cur significantly increased the EE of Res due to changes in protein configuration under alkaline conditions, which facilitated the binding of bioactive molecules to the nanoparticle structure. Meanwhile, the encapsulation of Cur has a marginally detrimental effect on the Res EE% using the anti-solvent technique. Furthermore, this method allows for the formation of nanoparticles with smaller sizes and greater loading capacities [40,87].

The pH-driven approach offers high flexibility in encapsulating a wide range of bioactive compounds, particularly polyphenols. A study by X. Chen, Qin, *et al*. [43] successfully co-encapsulated curcumin (hydrophobic compounds) and anthocyanins (hydrophilic compounds) utilizing BSA–fucoidan nanoparticles, further confirming its efficacy. Another notable advantage of the pH-driven system is its capability to encapsulate polyphenols directly from raw natural sources, including food waste materials such as fruit peels and plant roots. This not only broadens the method's application in the development of functional foods but also contributes to food industry sustainability by promoting the valorization of agricultural and food by-products [24,69].

Despite its promising prospects, pH-driven co-encapsulation systems are currently limited to the laboratory scale and are not yet ready for commercial production. This limitation is primarily due to a lack of comprehensive understanding of the mechanisms occurring at each stage of the encapsulation process [25]. Furthermore, most existing research has focused on in vitro testing; the effectiveness of these systems under complex biological conditions remains uncertain. To overcome these limitations, *in vivo* testing is needed to evaluate the bioaccessibility, bioavailability, and bioactivity of active compounds in biological systems, as well as to understand their release kinetics when applied internally. This *in vivo* data is crucial to ensure that bioactive substances are not only protected during processing but also effectively released and absorbed in the body. Furthermore, in-depth studies are needed on the molecular interactions between the encapsulant material and biological system components, for example, at the intestinal mucosal level. This includes studies on the compatibility and potential reactivity of the encapsulant material with body tissues, as well as thorough safety testing to ensure the system is safe for use in food and pharmaceutical applications.

8. Conclusion

Various preparation techniques, modifications of carrier systems, and control of operational conditions have been successfully applied to enable efficient co-encapsulation of multiple bioactive substances using pH-driven technology. This method facilitates the

encapsulation of diverse bioactives: easily soluble and chemically stable substances can be co-encapsulated via a straightforward one-step process, whereas substances with varying physicochemical properties and pH sensitivities necessitate a more sophisticated two-step approach, frequently in conjunction with additional supporting techniques. Moreover, the application of various preparation techniques facilitated the creation of diverse and effective carrier systems with enhanced physicochemical stability. The stability and efficacy of the co-encapsulation system are additionally affected by synergistic molecular interactions among the encapsulated bioactives, as evidenced by numerous molecular-level studies. These interactions can improve encapsulation efficiency and safeguard delicate molecules. Nevertheless, existing research remains confined to a limited range of bioactive compounds, necessitating more extensive inquiries to elucidate synergistic effects across various substance classes comprehensively. The binding behavior of bioactives within the carrier matrix is significantly influenced by the chemical properties of the bioactives, the features of the wall material, and the particular processing parameters used during encapsulation. To enhance the efficacy of the pH-driven co-encapsulation method, it is crucial to refine operational parameters and investigate integrating the extraction and encapsulation stages into a cohesive process. This modification could markedly enhance process efficiency and diminish production costs. The co-encapsulation of multiple bioactives via pH-driven technology offers significant potential for diverse applications, particularly in the pharmaceutical and functional food sectors.

Author Contributions

Writing—original draft preparation, R.R.; writing—review and editing, R.R., S.S., A.R.A., and A.A.; investigation (literature search), S.S.; supervision, L.A. and A.A.; co-supervision, L.A. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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