Chapter

Retrospective, Perspective and Prospective of B-Complex Vitamins: Encapsulation of Vitamins and Release from Vitamin-Loaded Polymers

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Abstract

Vitamins are regarded as vital nutrients because, when combined, they performed hundreds of functions in the body. They strengthen bones, heal wounds, and boost your immune system. In addition, they transform food into energy and heal cellular damage. In this regard, B-complex vitamins, such as thiamine, riboflavin, and niacin are soluble vitamins that serve as coenzymes in energy metabolism enzymatic activities which building blocks of a healthy body. However, B-complex vitamins are sensitive to light, pH conditions, and temperature. Consequently, they must be encapsulated before they may be used in pharmaceuticals. Recently, it is mainly focused on reducing drug degradation or loss, increase drug bioavailability, limit adverse effects, and improve drug accumulation in the targeted location. To maintain optimum bioavailability during a defined term of therapy, the fraction of drug dosage released from a controlled release product must be significant enough to adjust for the quantity of active drug metabolized and/or eliminated from the body over the same period. Drug release systems also aim to increase the effectiveness of the drug and treat the damaged area. In this chapter, it is aimed to study the production of the vitamin-loaded polymer systems in various forms, such as micro/nanoparticles, micelle, hydrogel, liposome, and nanofiber, as well as release studies in pharmaceutical and biomedical applications.

Keywords: encapsulatin, vitamin release, vitamin-loaded polymer, B-complex vitamins, nutrients

1. Introduction

Vitamins are a category of chemical substances that are not synthesized naturally by the body and therefore must be supplied in small amounts from food. The B-vitamins are a group of eight water-soluble vitamins that play important, interconnected functions in cellular activity, acting as co-enzymes in a wide range of catabolic and anabolic enzymatic processes [1]. Thiamine (B_1), riboflavin (B_2), niacin (B_3, also known as nicotinamide or nicotinic acid amide), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), folic acid or folate (B_9), and cobalamin are the

B vitamins (B_{12}) [2]. Their combined effects are especially significant in many areas of brain function, including energy generation, DNA/RNA synthesis/repair, genomic and non-genomic methylation, and the formation of various neuro-chemicals and signaling molecules [3]. B-complex vitamins are known as energy vitamins and stress fighters. Furthermore, the B-Complex vitamins are usually referred to as "beauty vitamins" since they are necessary for healthy hair, skin, and nails.

Polymeric materials have been regarded as the most effective drug delivery vehicles due to their superior pharmacokinetic characteristics. Several new drug delivery methods have been suggested with the rapid advances of nanotechnology. Polymeric drug delivery is described as a formulation or a technology that allows a therapeutic material to be introduced into the body. The nano-sized drug delivery system, in particular, can be built to overcome the current limitations of some drugs, such as poor bioavailability and significant cytotoxic side effects.

Polymers combined with B-complex vitamins can be bioactive to offer therapeutic effect on their own, or biodegradable, to enhance release kinetics and reduce carrier aggregation. Thus, B-vitamins encapsulated with polymer are protected

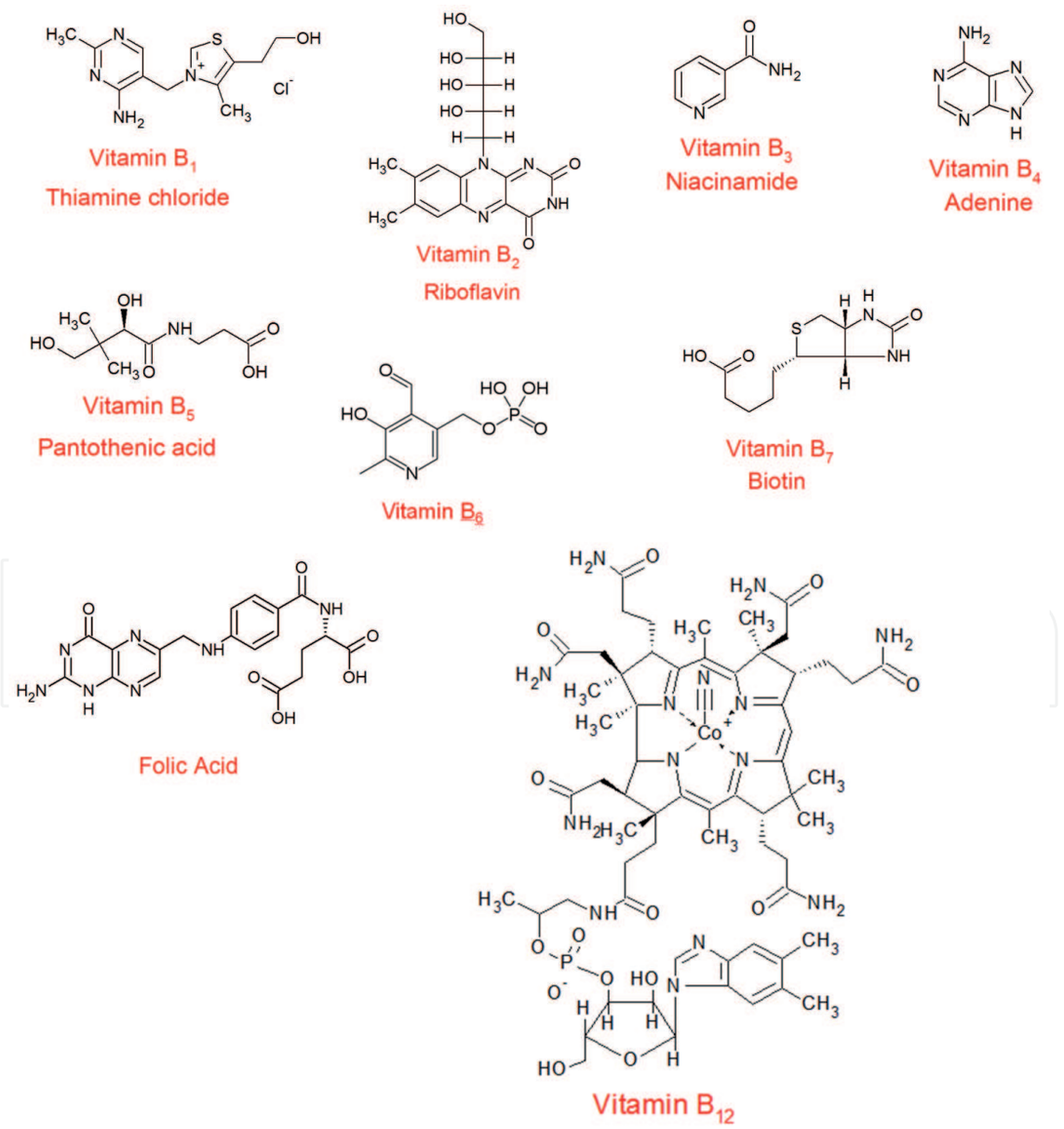

Figure 1.
Chemical structure of the B-complex vitamins.

from degradation caused by environmental effects. Several natural polymers, such as chitosan, starch, dextran, albumin, gelatin, alginate, gums, and also synthetic polymers, such as polylactic acid (PLA), poly-(lactide-co-glycolide) (PLGA), polyanhydrides, and polycaprolactone (PCL), have been utilized in the therapeutic delivery systems [4]. The majority of vitamin B-complex delivery of polymers can be broadly classified as hydrogels, films, nanofibers, beads or micro/nanoparticles, and polymer-drug conjugates, which are discussed in further detail in later sections.

This chapter explains polymer-based materials containing B-complex vitamins briefly and reviews studies in food, biomedical, drug delivery, tissue engineering, wound dressing, cosmetics, and other applications. The importance of vitamin-loaded polymers with unique features in different forms such as outstanding, pH and thermal sensitivity, bioactivity, swelling character, controlled release behavior, biodegradability, good *in vitro* and *in vivo* biocompatibility, and so on is discussed in detail. Finally, future problems and several ideas regarding the production of vitamin-loaded polymers as well as commercial applications have been highlighted (**Figure 1**).

2. Vitamin-loaded polymers

Liposomes, sponges, foams, micro/nanoparticles, fibers, hydrogels, and emulsions have been developed to increase pharmaceutical absorption, stability, penetration, half-life, and bioavailability [5, 6]. From this point, vitamin-loaded polymers have been encapsulated via different techniques such as layer by layer, solvent casting, spray drying, electrospinning/electrospraying, freeze-drying, emulsion polymerization, and complex coacervation. In this regard, vitamin B-complex is encapsulated in different forms with various polymer combinations, enhancing their controlled release and bioavailability. The following sections describe the many applications of vitamin B-complex-releasing polymer forms.

2.1 Hydrogels

Superabsorbent polymers (SAPs) or hydrogels are three-dimensional cross-linked networks of hydrophilic polymers (3D) that can absorb and retain a substantial proportion of liquid (>20%) within their weight [7, 8]. Hydrogels can be used to encapsulate medicines while still preserving bioactivity during gelation and release. Injectable methods can ensure that these medicines are administered locally to the location of the lesion in a continuous and controlled approach.

Natural polymers (e.g., sodium alginate, carboxymethyl cellulose, cellulose, chitosan, gelatin, pectin, starch), synthetic polymers (polyacrylamide, polyacrylic acid, polymethacrylic acid, polyethylene glycol, polyvinyl alcohol), and different acrylates can all be utilized to construct 3D networks [9]. The main factors involved in reversible swelling are based on chemical interactions and physical contact.

There have been several attempts to mix B-complex vitamins with hydrogels for use in medical applications. In this scope, Liu et al. [10] prepared B_{12} vitamin-loaded smart magnetic hydrogels to be utilized in bio-separation, and drug carrier applications. In their study, gelatin has been used as a matrix and Fe_3O_4 nanoparticles are used as magnetic agents. *In vitro* test results showed the crosslinked density of the hybrid gel affected porosity, pore size, and B_{12} release profile, as well. According to UV–VIS analysis, the increased crosslinking of the gelatin matrix via genipin crosslinker led to more vitamin B_{12} absorption at 361 nm [10].

Bajpai and Dubey [11] synthesized VB_{12}-loaded poly(N-vinyl-2-pyrrolidoneco-acrylic acid) hydrogels and evaluated swelling and *in vitro* release behavior. It has been reported pH conditions influence the gel swelling and controlled release profile of vitamins. The gels exhibited nearly 47.8 ± 4.9% swelling in the medium of pH 1.2, while nearly 2164.6 ± 21.8% swelling was observed in the phosphate buffer medium of pH 6.8 due to the functional COO^- groups in acrylic acid [11].

Gong et al. [12] engineered poly(ethylene glycol)-poly(e-caprolactone)-poly(ethylene glycol) (PEG-PCL-PEG) and Pluronic F127 copolymer via sol–gel transition to utilized in biomedical applications as injectable *in situ* gel-forming drug carrier. Because of its high water solubility, VB_{12} was rapidly released from the composite hydrogel. The release results showed that VB_{12} release slowed down due to an increased amount of hydrogel, and there was a 10% decrease in total release with an increased amount of VB_{12} in the hydrogel. The higher Pluronic F127 content caused the higher VB_{12} release amount. Furthermore, cell viability tests revealed that the obtained composite hydrogel copolymers were biocompatible and had low cell cytotoxicity [12].

Ozey [13] synthesized the biocompatible poly(2-hydroxylethyl methacrylate-co-N-allylsuccinamic acid)/B_{12} vitamin hydrogels. *In-vitro* release study indicated around the total release of B_{12} vitamin has 96.9%, 95.8%, and 93.7% release amount in three different media (pH 1.2, PBS and NaCl isotonic serum). As a result, different release media have been found to partially effect the B_{12} release profile. However, it has not seriously affected the total release amount [13].

In a similar study, Maheswari et al. [14] synthesized poly(N-isopropylacrylamide-co-N-vinyl-2-pyrrolidionone) with B_{12} vitamin via radical polymerization. In this study, increased N-vinyl-2-pyrrolidionone (NVP) concentration had led to an increase in pore structure and interconnectivity with pores. The swelling ratio changed with temperature due to using thermo-responsive N-isopropyl-acrylamide (NIPA) monomer. The composite hydrogel had 85% VB_{12} release at 30°C for 10 h. In last, the kinetic results showed the VB_{12}-loaded polymer templates had a non-Fickian diffusion mechanism [14].

Nath et al. [15] developed gelatin-g-poly(acrylic acid-co-acrylamide)/montmorillonite (MMT) clay composite hydrogel containing B_{12} vitamin and they investigated the utility of these materials in pH-responsive drug delivery systems. It was observed that the vitamin B_{12} released from the hybrid hydrogels with 40% (in pH 1.2) and 80% (in pH 7.4) of release amount over 6 h, respectively. Moreover, in comparison to the neat hydrogel, the biodegradability of the vitamin-loaded increased. All samples had no cyctotoxicity effects [15]. Another study of the same research group is about pH- responsive controlled VB_{12} release. It was found almost 50% and 70% VB_{12} were released in two different pH media (1.2 and 7.4) from the hydrogels for 48 h [16]. Fast VB_{12} diffusion was reported in artificial intestinal fluid (AIF, pH 1.2) indicating the pH-dependent cumulative release percentage of VB_{12}. This phenomenon is due to the protonation of a higher number of carboxylic acid (-COOH) groups in VB_{12}at a pH of 7.4. It was revealed to influence the degree of gel swelling, which enhances VB_{12} release, as well as an increase in electrostatic repulsion between the increased amount of ionized -COOH and -OH groups, which leads to increased space expansion inside the network structure.

CMC-xylan/VB_{12}hydrogels had been prepared in different molar ratios by Kundu and Banerjee [17]. According to in-vitro studies, the composite gels indicated a minimum cumulative VB12 release of 28% in pH 1.2. Moreover, 88% in pH 6.8 and 98 in pH 7.4 media, respectively.

Another study contributed to the development of VB_{12} loaded-alginate (Alg) scaffolds by the microfluidic method [18]. In this study, alginate and $CaCl_2$ are used as a template of vitamin, and crosslinker, respectively. The vitamin-loaded hydrogel

scaffolds in various alginate concentrations indicated a zero-order kinetic model with more than 80% drug release in 4.5 h.

Gum arabic cross-linked PVA/FA hydrogels were also reported to be a drug delivery carrier with high blood compatibility, good porosity, pH sensitivity and high mechanical properties [19]. The crosslinked hydrogels had a higher swelling ratio at higher pH. Further, *in vitro* release tests indicated the optimized hydrogel had the release FA amount of 78% and 32% at pH 7.4 and 2.1, respectively. It was found the PVA-based hydrogels prevent FA from UV degradation, and therefore, researchers evaluated the hydrogels could be UV-photoprotect material.

In topical/transdermal drug release, active substances have advantages such as localized at the site of infection and reducing their systemic effects [20]. Jung et al. [21] reported that liposomal hydrogels containing VB_{12} could be a candidate for the treatment of atopic dermatitis. VB_{12} derivative adenosyl cobalamin (AdCbl) was loaded into liposomes via a filmhydration method. The results showed the liposomal hydrogels have between 11.5–38.8% loading efficiency of AdCbl. The permeability tests also demonstrated liposomal gel form of AdCblhad 17 times more permeability than in only gel form of AdCbl after 24 h. Consequently, as AdCbl-loaded liposome structures were used, the release amount significantly increased [21].

Folic acid ($C_{19}H_{19}N_7O_6$) is an important member of the B-complex vitamin which also known as vitamin B_9. It consists of the conjugation of one or more L-glutamate units of 4-((pteridine-6-methyl)-amino) benzoic acid [22]. Besides, folic acid is an important factor in the physiological processes of cell metabolism; it is a coenzyme involved in cell growth and development, DNA synthesis and repair, and many metabolic reactions [23].

Folates in their reduced state (without glutamic acid) are chemically unstable and expose oxidatively breakdown at the C-9 and N-10 bonds, resulting in substituted pteridine and p-amino benzoyl glutamate (PABA) moieties. Camacho et al. [24] studied encapsulation of folic acid in copper-alginate hydrogels. This organometalic hydrogels performed as a gastro-resistant material, and slow folic acid release occurred only at pH > 5, particularly under simulated intestinal media (pH 8.2). Besides, the successful materials showed more release in alkaline media (>80 ppm) compared to acidic media (pH 5.4) (~8 ppm) with a zero-order kinetic model [24].

Moreover, in certain commercially available compounds, such as Fruit & Passion Boutiques Inc.'s Hydro Gel Face Masks, the moisturizing effect of these organic polymeric gels is combined with more complex drug-delivery systems designed to release biomolecules such as vitamin C or B_3 [25].

2.2 Films

The film is commonly used in food packaging applications. The edible films and edible coatings are usually used similarly in this field, however, they differ in preparation form [26]. Edible films are formed initially like a solid sheet and then applied to the product surface or between food components, whereas edible coatings are produced directly onto food surfaces once the product makes contact with them. These films and coatings are usually utilized to provide extra barrier protection to increase the shelf life of the food product [27]. Meanwhile, they can also be engineered as vitamin carriers. In this regard to biomaterials, where biopolymers are important due to their biodegradability and biocompatibility, particularly with free-standing devices for wound dressing applications. Coating and film coating are frequently used in applications involving bone implants, cardiovascular devices, wound control and treatment, and oral dissolving strips, as well.

van Dijkhuizen-Radersma et al. [28] have reported polymer composition and crystallinity directly affect the drug release behavior. In the study, VB_{12}-loaded poly(ethylene glycol)/poly(butylene terephthalate) films were synthesized by emulsion polymerization. The release rates and amounts of the resulting films vary between 20% and 100% depending on the copolymer ratios used. Moreover, they determined the total release of $VB_{12}$from the films with 50–100 μm in one day and a sustained release for more than 12 weeks [28].

In recent decades, the importance of thin films in biology and biomaterials research has increased rapidly. Thin films can be coated on a variety of surfaces depends on their physicochemical properties such as wettability, reactivity, conductivity, and corrosion resistance. Thin films are currently being used in the fields of tissue engineering and biomedical industries for osseointegration in dental and orthopedic implants, biodegradable/biobased scaffolds, and biomimetic materials [29]. In this context, Mallakpour and Hatami [30] prepared chitosan nanocomposite films containing folic acid to utilize in tissue engineering as bone and teeth additives. Contact angle measurements showed that the produced films had improved wettability and were more hydrophilic. Furthermore, the bioactivity of these NC films by soaking them in simulated bodily fluid (SBF, pH 7.4), and the pH changes for this solution were observed for 1 month [30].

Banerjee and Ganguly [31] studied on encapsulation of VB_{12} in layered biocomposite films to use in drug delivery, wound healing, and tissue repair applications [31]. In this study, alginate and chitosan was prepared by freeze-dry method as inner and outer layers, respectively. The macrovoids were formed by gas bubbles. Although lyophilized composite films have a high absorption capacity, this form of structure dissolves fast in releasing media. SEM images exhibited the bubbles were homogeneous, having a diameter of almost 0.5 mm, and bubbles were also obtained in multiple layers. Two polymer gel substrates were thought to be different, but the release test showed the diffusivity of biocomposite solute is much lower in crosslinked chitosan than in calcium alginate. In addition, the voids in films did not affect drug release behavior but affect the release amount of drug. Films with void have been found to release more drugs than non-void films.

Orodispersible Film (ODF) is a new progressive dosage form that can provide patients with excellent drug delivery benefits. They are the most revolutionary alternative to conventional dosage forms like pills and capsules [32]. Among all oral drug delivery methods, Oral Film Technology (OFT) has attracted a lot of interest. This dosage form is also known as rapid dissolving film, fast-dissolving film, and orodispersible film [33]. In this scope, Suryawanshi et al. [34] fabricated cyanocobalamin-loaded orodispersible films via a hot-melt extrusion process [34]. The choice of polymer for this process is an important step in the development of ODFs. In this study, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) was utilized as a solvent for drugs that were insoluble in water. Morphological analysis showed the surface of the cyanocobalamin-loaded films was smooth and homogeneous. Besides, 3D micrographs of the film surfaces had a uniform structure. The resulting VB_{12} loaded-films have thickness values varied from 0.21 ± 0.02 to 0.33 ± 0.03 mm. However, the thicknesses of optimized film 0.24 ± 0.02. The average tensile strength of VB_{12} films ranged from 1.53 ± 0.84 to 15.75 ± 0.47 N/cm^2, The optimized film's tensile strength was measured 15.45 ± 0.32 N/cm^2. Contact angle measurement confirmed the optimized films had superior wettability with 24.21°. Moreover, the optimized films have the amount of 99% cyanocobalamin release for 10 hour period.

PVA is a hydrophilic-based synthetic polymer [35]. It includes a carbon chain backbone with hydroxyl groups (-OH); these OH groups can act as a source of hydrogen bonding and therefore assist in the production of polymer composites [36].

Because of its biodegradability, non-toxicity, good film-forming ability, water processability, quick availability, and low cost, PVA is one of the most commonly biodegradable polymers used for different fields of industry [37]. Furthermore, the fabrication of inorganic nanoparticles in polymer matrices has attracted a great deal of interest. Especially, vitamins are used as a biocompatible modifier to form more functional groups on the surfaces of nanoparticles. Many studies on polymer-based metal oxide nanocomposites have been conducted. In this respect, Mallakpour and Shafiee synthesized ZrO_2/PVC nanocomposite films via the solvent casting method [38]. Vitamin B_1 (thiamin) has been used as a ligand for ZrO_2 NPs due to the many functional groups such as amino and hydroxyl groups. The results showed VB_1 is an excellent bioactive agent which provides good dispersion and enhances the interface between NPs and polymer matrix. The modification increased both the surface area of NPs and prevent the formation of zirconium aggregates in films. TEM analysis showed the particle size of ZrO_2-VB_1 NPs has around 36 nm. UV–Vis spectrum revealed that NC films more UV absorption than neat PVC films. The modification did not influence on the crystalline structure of ZrO_2, according to the XRD analysis. Moreover, mechanical testing demonstrated that NC films were more flexible than neat PVC ones. As a result, adding these NPs to hydrophobic materials like PVC increases surface free energy while decreasing contact angle.

In a similar study, Mallakpour and Mansourzadeh fabricated PVA films including CuO nanoparticles modified with vitamin B_1 (thiamine) [39]. In the study, thiamine improved polymer-metal compatibility by creating active regions on the surfaces of metal particles. FTIR analysis showed the new peaks were formed in CuO NPs. The addition of NPs to the PVA matrix further enhanced the optical and mechanical properties.

Buccal delivery has been studied as an alternative to traditional oral delivery for several drugs with limited oral bioavailability. The buccal route also offers the benefit of low enzymatic activity and acceptability by certain sensitizers [40]. The buccal route for drug delivery has received a lot of attention to solve the problem of pre-systemic metabolism caused by gastrointestinal degradation and first pass metabolism [41]. Buccal mucosa has a higher blood supply and is more permeable than oral mucosa. Mohamad et al. [42] designed chitosan/PVA containing VB_{12} buccal hydrogel films. Vitamin-polymer interactions are confirmed by FTIR analysis [42]. According to SEM images, all film samples had homogenous structures without drug agglomeration. In general, the obtained film formulations demonstrated fast drug release due to water absorption by the hydrophilic-based polymers, chitosan, and PVA, which improved wetting, swelling, and penetration of water into the matrix of the film, and therefore increasing drug diffusion phenomena. At the end of 40 minutes, the amount of drug released was 98.59%. Consequently, Higuchi kinetic model has been determined to be the best model for drug release kinetics for films.

Thiamine hydrochloride (THCl) and nicotinic acid (NA)-loaded propyleneglycol (PG) buccal films have been developed using a two-dimensional (2D) inkjet printing method [43]. The rough surface and formation of a pore network in the films were revealed by SEM images. The in vitro release tests revealed that both vitamins were released in a burst in 10 minutes. Additionally, 85%, 98%, and 100% THCl and 78%, 85%, and 100% NA are released from the 1, 5, and 9 print film in 7.5 minutes. The profiles of all formulations for both THCL and NA release were better suited to the first-order kinetic model, with the highest R^2 values.

Acevedo-Fani et al. developed folic acid/polysaccharide-based nanolaminate films [44]. The topology of the nanolaminates improved as folic acid was added, resulting in a uniform and smooth layers. After 7 hours, only 22% of the FA was released from the films at pH 3, however, almost 100% of FA was released at pH 7. This is related

to be entrapped folic acid in nanolaminates due to its poor dissolution in an acidic environment. Although researchers have utilized the highly bio-functional folic acid as a great factor for anticancer drug delivery, antibacterial agents, and fluorescence endoscopic detection, there are also studies for usage in electronic applications. Apart from the studies, folic acid has been used in energy storage applications [45]. It was found that FA as the bio-polymeric ligand which was present in different amounts in PVDF, was an effective modifying agent. The results pointed FA particles increased the interaction of β-phase from PVDF's energy storage capability.

2.3 Nanofibers

Nanofibers play a significant role in tissue engineering and drug delivery applications due to their unique properties including low density, high specific surface area, high porosity with<1 μm. Many studies on drug delivery systems indicated nanofibers can be a robust carrier system for therapeutics among other types of nanocarrier systems like hydrogels, beads, films, or others owing to high drug-loading ability, high encapsulation efficiency, target-specific, sustained drug delivery, and ease of processing [46].

Drug release systems are mainly concerned with minimizing drug degradation or loss, enhancing drug bioavailability, avoiding adverse effects, and improving drug accumulation in the targeted site [47]. It is expected to improve the drug's efficacy and treat the damaged site.

A study on increasing the bioavailability of folic acid was conducted by Fonseca et al. [48]. In the study, starch was used as a matrix, and the morphology and release behavior of nanofibers containing varying amounts of FA (5, 10, and 15%) were investigated. Although the diameters of nanofibers formed below 100 nm did not change substantially, it was observed some beads in FA-loaded fibers (5%) higher than in other samples. Moreover, TGA and UV-A radiation results have shown that starch is an effective matrix for FA encapsulation.

Evangelho et al. used an electrospray method to create vitamin B_9-loaded zein nanofibers and vitamin B_9-loaded zein capsules [49]. In the study, thermal and radiation resistance of the VB_9 to determine its availability in food applications. According to SEM micrographs, the addition of VB_9 did not affect on the morphology of the nanofibers and capsules; nevertheless, samples were generated at three different amounts (0.5, 1, and 1.5%, w/w) changed the fiber and capsule diameters. VB_9-loaded zein nanofibers exposed to UV-A radiation for 1 and 24 hours shown significant resistance compared to non-exposed nanofibers. Zein capsules containing 1% VB_9 were also found to be resistant to UV-A. As the mentioned previous section, folic acid is sensitive to UV radiation due to stimulation of the bond between C_9 and N_{10} and this causes the breakdown of the bond and the production of photodegradation products such as P aminobenzoyl-L-glutamic acid, 6-formylpterin, or 6-carboxypterin. It has been presumed that the resistance of VB_9 in both zein fibers and capsule structures may be related to the interaction of vitamins with amino acids in the structure of Zein protein, such as Proline, isoleucine, alanine, phenylalanine, methionine, valine, and leucine, and that this interaction makes it difficult to break down the C_9-N_{10} bond of folic acid. Additionally, TGA analysis revealed that pure folic acid in powdered form degrades considerably faster than folic acid in nanofiber and capsule form.

Amaranth protein/pullulan electrospun/VB_9 fiber structures were fabricated by Aceituno-Medina et al. [50]. The study aimed encapsulate and photoprotection of VB_9, a model bioactive molecule. It has been suggested that the photostability of VB_9 in nanofibers may have better than that produced capsules via conventional

techniques such as ionic gelation, coacervation, and spray drying. Optical and electron microscope results showed that VB_9 causes an increase in viscosity, resulting in thicker fibers. VB_9 was extracted from electrospun fibers using PBS for UV–Vis analysis. After UV exposure of non-encapsulated pure VB_9, some changes have occurred in the UV–Vis spectrum, and some characteristic UV absorption peaks of VB_9 are broken down into shorter peaks. It has been associated with p-aminobenzoyl glutamic acid (PGA) and 6-formylpterine (FPT), which are the degradation products of peaks at 275, 278, 310 and 365 nm, relatively.

Some efforts also performed in the incorporation of VB_9 and modified PVA-polyethyleneimine electrospun fibers to use in electronic applications as cancer diagnosis and treatment [51]. The same group prepared polydopamine-VB_9 complexes and the morphological structures of the obtained nanofibers due to the interactions between the polymer and bioactive material. The morphological structures of nanofibers produced by preparing polydopamine-folic acid complexes are predicted to use as graphene-like structures in energy applications such as organic semiconductor material due to ¶-¶ interactions formed between the polymer bioactive material [52]. The same research group also developed multifunctional folic acid-functionalized dendrimers onto electrospun cellulose acetate nanofibers for the specific capture of cancer cells [53].

Other nanofibrous structures based on PVP/dextran octadecyl amine/montmorillonite/VB_9 conjugates have been fabricated by Şimşek et al. [54]. The cytotoxicity results of nanofibers revealed that VB_9 has no negative effect on Vero cells (liver cells), and these fibers could be a pioneer for cancer studies and tissue engineering applications. The electrical properties of the functional nanofibers composed of dextran, PVP, and VB_9 were also investigated by the same study group [55]. As a result, amorphous structures of lower crystallinity and colloidal form of polymer mixtures tend to form the intermolecular hydrogen bond.

Hydrophilic drugs might cause a rapid burst release in the PBS buffer or in vivo conditions due to their high solubility [56]. Madhaiyan et al. prepared cyanocobalamine(vitamin B_{12})-loaded biocompatible PCL nanofibers and carried out plasma treated to nanofibers for periods of 5, 20, 40, and 60 seconds [57]. Contact angle measurements revealed a decrease in surface hydrophilicity from 139° to 108° due to the hydrophilic nature of VB_{12}. Unmodified nanofibers exhibited 18% sudden release in the first 4 hours in the PBS environment and 39% release after 48 hours. Moreover, modified nanofibers with a period of 60 seconds had the highest release value, with a total rate of 95%.

Soy proteins have been used to develop biodegradable and biocompatible nanofibers containing rhodamine B and riboflavin in order to study controlled drug release and desorption processes [58].

Llorens et al. prepared polylactic acid (PLA) nanofibers containing vitamin B_6 and evaluated their release in a hydrophilic Sörensen-ethanol release media and a hydrophobic Tris/Borate/EDTA (TBE) release medium [59]. It was found that within the first 8 hours in the TBE environment, the drug was released quickly from nanofibers; however, in the hydrophilic environment, the drug was released slowly and sustain behavior for several days. From the SEM micrographs, some aggregates formed in PLA nanofibers were related to the presence of vitamin B_6 crystals. As vitamin loading increases, nanofiber diameters increase from 921 nm to 1013 nm, and porosity increases from 69–85%. Cell proliferation results have also shown that these nanofibers have a high antioxidant activity which were produced against free radicals that cause cell damage.

Agarwal et al. produced films with cellulose acetate nanofibers containing nano-ZnO, vitamins B_2 and C for use in oral applications [60]. According to UV–Vis

analysis, the release amount of vitamins B_2 and C from nanofibers were measured to be 25% and 95%, respectively. It has been observed that vitamin B_2 is stable in the environment, while vitamin C has a reversible reaction to dehydroascorbic acid and then oxidized to 2,3-diketo-L-gulonic acid via irreversible reaction. Consequently, the study pointed out that cellulose acetate can be used as a carrier in the use of vitamin B_2, which is important for skin disorders, and vitamin C, which supports collagen formation.

Solar UV radiation is the major cause of skin damage owing to the production of reactive oxygen species (ROS), which causes skin collagen imperfection, roughness, allergies, and, therefore, premature aging [61]. Topical formulations have lately attracted great attention as a drug delivery system to the human skin. One approach to combating skin aging is to apply herbal phenolics and antioxidants to the skin. Folic acid (FA) is a significant antioxidant-rich B-complex vitamin that aids in the formation of healthy skin cells [62]. The utilization of folic acid as a beauty patch has been investigated by spraying it onto nanofiber surfaces. However, PVA-based polymers reduced the slow release of folic acid, allowing the process to be completed in a short time. In addition, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and neutral red uptake (NRU) assays in L929 have indicated that FA has 120% and 109% cell growth [63]. In a similar study, FA has been directly blended with hydrophilic polymers (PVA, PVP, and gelatin). Micron-seized VB_9 combinations have been created by the electrospraying method for topical applications. The total vitamin release percentages in different polymer matrix including PVA/FA, gelatin/FA, and PVP/FA fibers were 86.88%, 80.20%, and 76.66%, respectively [64].

Vitamin B_2 (riboflavin) is essential for normal reproduction, cell growth and repair, and tissue formation. Furthermore, the vitamin is used by the body to maintain tissues healthy and to repair wounds. The VB_2 (riboflavin)-loaded PCL/gelatin-loaded electrospun fibers have been fabricated to use in biomedical applications [65]. From the same perspective, Heydari et al. [66] developed hydrophobic peracetyl-cyclodextrin (AcCDP) nanofibers containing Vitamin B_2. As expected, the nanofibers exhibited two-phase release profiles involving burst and sustain release in two different release environments (pH 1.2 and pH 7.4). Besides, it was found that they had a 60% and 40% release, respectively, for 170 hours [66].

Vitamins are necessary for cosmetics and other purposes, and transdermal vitamin delivery systems are widely available. Nanoparticulatecombinations offer nearly unlimited delivery possibilities via oral, pulmonary, transdermal, and ocular routes. Vitamins their nano-based combinations would definitely assist in tissue regeneration as well as pharmaceutical delivery [64].

2.4 Beads

Microcapsules or beads produced of biopolymers are of scientific and technical interest, and they have a wide range of potential medical uses, including usage as controlled drug delivery systems. The development of stimuli-responsive microcapsules, especially those composed of biopolymers, is still in its early stages [67].

With relation to hydrogel studies, Bajpai and Tankhiwale [68] prepared vitamin-loaded multilayered polymeric beads using the complex coacervation method. Chitosan and calcium alginate was used as matrix, and VB_2 was used as a model drug, as well. It was found that the beads released around 54% of the drug in the first 3 hours in the artificial gastric fluid (AGF) (pH 1.0), while the remaining drug was released in the mimicking intestinal fluid of pH 7.4 in 6 hours. At last,

the concentration of alginate solution used to form the outer layer, as well as the concentration of the ionic crosslinker $CaCl_2$, affects the release profile [68].

Puguan et al. [69] prepared calcium alginate/VB_{12} beads using the dripping technique. In the study, VB_{12} was entrapped in polymers during the gelation process. The in vitro study indicated the total release of VB_{12} complete within 2 hours, and the vitamin loaded-beads had burst release in 30 min. The authors claimed the amount of calcium (crosslinker) ionic strength, and pH factors influence the kinetics of gel formation, as well as the volume and stability of the beads [69].

Vitamins are extremely sensitive, resulting in losing bioactivity during food processing, and storage. Thus, microencapsulation may be used to reduce vitamin loss, allow for a controlled release procedure, and improve their stability. Spray-drying process is versatile and generates high-quality microparticles, and it is superior to other methods in that the product quality in terms of homogenous and cheap [70]. VB_2 has been loaded into 3 different matrix (chitosan, modified chitosan, and sodium alginate) using spray drying method. The total amount of vitamins was released in around 120 min for microparticles produced with chitosan, 15 min for microparticles produced with alginate, and 10 min for microparticles produced with modified chitosan. SEM images and release study showed were associated with a slow release to a rougher surface. For all of the biopolymer-based microparticles with a mean diameter of almost 3 μm were detected [71]. The same group reported to VB_{12}-chitosan microparticles have controlled release behavior in gastric conditions (pH 1.2). The highest release of VB_{12} reached in 10 min. Microstructure of the materials revealed average diameter of particles vary from 3 to 8 μm with a smooth surface and an uniform round shape [72]. Similar to the spray drying of vitamin B_{12}/alginate beads conducted by Abubakr et al. [73]. In the study, as addition of chitosan into the alginate matrix, the release of VB_{12} slowed down. Further chitosan effect the alginate stability and decrease bead permeability. Estevinho and Rocha [74] studied the kinetic models of encapsulated VB_{12} bioactive compounds. Chitosan, modified chitosan, and also sodium alginate were utilized for capsulating matrix [74]. The findings indicated zero-order model was the best fitted for chitosan/VB_{12} particles. Recently, encapsulated the vitamins B_2 and B_3 into six different biopolymers performed using the spray drying method by Carlan et al. [75]. Moreover, encapsulation efficiency reached values higher than 99% for all vitamin-based microcapsules. SEM images demonstrated VB_2 and VB_3 particles had a varying range between 0.10–0.84 mm. Weibull kinetic model was determined suitable model for both vitamin NPs.

The selection of appropriate wall material is critical for achieving the optimum release rate and high encapsulation efficiency of bioactive compounds during the spray drying process. It has been reported that a wall material mixture of polysaccharide-based like gum acacia, cashew nut gum, sodium alginate, sodium carboxymethyl cellulose, and Eudragit RS100 has affected the release kinetics of encapsulated vitamin B_{12} [76]. Bajaj et al. [76] used carbonhydrate-based wall materials to co-encapsulate the vitamin B_{12} and D_3 for the food industry. In the study, the size of smooth microcapsules ranged between 3 and 7 μm without cracking. After the encapsulation process, both vitamins demonstrated higher stability and a change in release rate. Further, the *in vivo* studies showed the maximum concentration of VB_{12} was recorded at 240 min [77].

Madziva et al. [70] produced microcapsules containing folic acid varying in size from 300 to 650 m with a shell material composed of alginate and pectin that may be utilized in food. It was observed that these biopolymers encapsulating the core exhibit significant stability and high encapsulation efficiency in food products for folic acid [70].

Azevedo et al. [78] encapsulated vitamin B_2 into alginate/chitosan matrix by pre-gelation ionotropic method and investigated release behavior in different conditions. The size of nanoparticles has around 120 nm with 56% encapsulation efficiency. The vitamin B_2-loaded nanoparticles are more stable than vitamin B_2-free nanoparticles for 5-week periods [78].

Vitamin compounds, including vitamin B_1 and B_6, have been investigated for controlled drug delivery utilizing various clays to enhance encapsulation efficiency [79–81]. In recent years, gellan gum/laponite clay beads containing $VB_{12}$was fabricated by the ionotropic gelation method [82]. The composite beads had a smoother and regular surface with 2.1 mm. The incorporation of laponite in the bead formulation enhanced drug encapsulation efficiency and delayed the kinetics of the drug in the gastric media. It has been suggested that laponite could be a useful addition in the production of gellan gum beads for long-term drug release.

Several VB_2delivery systems for oral absorption have been developed to solve health problems [83–85]. Riboflavin delivery from ethyl-cellulose-coated barium alginate beads was reported by Bajpai and Sharma [86]. In a pH 1.2 media, the uncoated beads released faster than coated one. Stops et al. observed that calcium alginate beads had fast release VB_2 profile [87]. In another study, Kaygusuz et al. investigated the release of VB_2 from alginate-montmorillonite clay biocomposites [88]. The results showed two different crosslinkers (barium and calcium) utilized had no significant effect on drug release amount, however, barium-alginate beads were more stable than the others. Besides, the *in vitro* study indicated almost 50% VB_2 released from both (barium and calcium) composite beads. In brief, MMT-incorporated calcium and barium alginate beads were appropriate for VB_2 oral applications. The novel biomineralized alginate beads were also designed by Yang et al. [89, 100] to release VB_2. In the study, aliphatic poly(urethane-amine) (PUA) provides thermal sensitivity. Therefore, the VB_2 release was higher at 55°C than at 37°C due to the shrinking of aliphatic PUA at its lower critical solution temperature (LCST) [89].

Carlan et al. [90] researched microencapsulation of VB_1 into different polymers such as carrageenan, chitosan, maltodextrin, modified chitosan, modified starch, pectin, sodium alginate, and xanthan gum. The size of beads ranged from 0.11 to 1.32 μm. The modified starch beads had VB_1 release in 10 min, while VB_1-loaded xanthan gum had in 24 hours. The Weibull kinetic model performed the best on the experimental data [90].

2.5 Others

Carbon nanotubes (CNTs) are made up of micrometer-scale graphene sheets folded into nanoscale cylinders and topped with spherical fullerene [91]. CNTs have found widespread application from optoelectronics and energy storage to drug delivery and biosensor [92, 93]. In recent years, polymer nanocomposites have a worldwide focus to obtain novel polymer materials for practical applications by improving the properties of neat polymers. To improve the reinforcing effect of CNTs in polymer nanocomposites, good dispersion and effective interfacial adhesion between CNTs and the polymer matrix are required (NCs). However, it takes some effort to disperse effectively the CNTs in the composites due to ¶-¶ interactions and strong van der Waals forces between the tubes that cause CNT aggregation in the composites [94]. Therefore, CNT hybrids are used to aid CNTs in disperse inside polymer matrices [95]. A research group decided to improve CNTs functionality and prevent aggregation in composites by treatment with VB_1 [96]. The results showed VB_1 is a biosafe molecule for poly(ester-imide) matrix and CNTs, and it

enhanced the morphological properties of polymeric composites. Moreover, the diameter of CNTs increased too, when compared to CNTs-COOH, indicating that a thin coating of VB_1 was bonded to the CNTs via strong interactions.

Cancer is currently one of the most challenging diseases to treat, and its prevalence is on the increase [97, 98]. Targeted anticancer treatments have been widely developed for the past three decades to eliminate cancer cells. Various colloidal carriers, such as lipid nanoparticles, nanofibers, and nanocapsules, nanogels, and polymer-drug conjugates have been investigated for anti-cancer treatments [99]. The application of specific nanomaterials such as CNTs, gold nanoparticles (GNPs), and graphene nanosheets have been considered in the majority of reviews in this field [100]. Due to its low cost, non-toxic, non-immunogenic, low molecular weight, and ease of modification, folic acid (FA) is one of the most widely acknowledged cancer-targeting agents among the different targeting agents. Folate receptors are commonly utilized in epithelial, ovarian, cervical, breast, lung, kidney, colorectal, and brain cancers compared to other agents and B-complex vitamins. Many approaches have been reported for the chemical conjugation of FA to a variety of therapeutic drugs and imaging agents [101]. Yang et al. [89, 100] prepared a folate-conjugated PCL-PEG copolymer to obtain hydrophobic doxorubicin (DOX)-encapsulated active targeting micelles and they combined these micelles with PVA. In conclusion, core-shell nanofibers are produced for the treatment of solid tumors [100]. A study on liver cancer treatment was conducted by Fan and co-workers (2019) [102]. In the study, doxorubicin (DOX)-loaded folic acid-polyethylene glycol-β-cyclodextrin (FA-PEG-β-CD) nanoparticles (NPs) synthesized and this material showed 11.9% drug loading efficiency and 95.2% encapsulation efficiency with 30–60 nm. In another study, folic acid was conjugated with curcumin-encapsulated gum arabic microcapsules in order to drug delivery it to breast cancer cells [103]. Poltavets et al. [101] synthesized docetaxel-loaded PLGA nanoparticles with a folate modification via an emulsion solvent-evaporation. The *in vitro* study revealed these nanoparticles performed non-functionalized nanoparticles and free docetaxel in vitro anticancer activities against HeLa cervical carcinoma cells [104].

3. Future insights

The use of vitamin B-loaded polymers presents a serious progress in the above-mentioned applications and ensures a positive advancement in the upcoming years. Treatments will be more effective and safer owing to the design and functionalization of the various polymeric materials. The potential applications show that the polymeric carriers will progress to a specific active substance to the point where it can be customized to best adapt to a specific component or environment. However, it is important to note that vitamin-loaded polymers have some challenges. First, the number of vitamin-loaded polymers presently accessible for use as the industrial scale is still limited, despite the fact that R&D has advanced from the micro to nano-size scale in the previous decade, exceeding expectations. Secondly, the majority of the tests were improved *in vitro* studies with promising findings, however, the conversion from *in vitro* outcomes to clinical success have been restricted. More clinical trials and data are required to properly understand the mechanism of these polymer carriers. Further, these polymer-carriers must also be biodegradable or have a high capacity to be removed outside the body to minimize accumulation, as well as being non-toxic and non-immunogenic. It is notable to highlight the effect that copolymers or polymer blends might play in adjusting or modifying interactions with the human body in order to control their *in vivo* studies.

In sum, various disadvantages or drawbacks must still be overcome by multiple efforts and focused multidisciplinary scientific collaboration in order to achieve the desired results.

4. Conclusion

Since the beginning of the 2000s, B-complex vitamins have been produced in polymeric materials. Vitamin-loaded polymeric materials have been produced in various structures, such as gel, film, bead, liposome, and fiber forms. Each of these materials containing vitamins has become interesting for many industrial applications. Vitamin-loaded polymer materials have been utilized in medical applications such as implants, additives, tissue engineering, drug carriers, wound dressing, cosmetic applications as a skin-care mask, cancer diagnostic agent, and food applications as food supplements, as well. On the other hand, bioactive polymers are available in smart electronic applications. Some studies also pointed that B vitamins are utilized to obtain nanocomposite materials by modification of certain inorganic nanoparticles. In the studies, it was aimed to increase the bioavailability of B-vitamins by incorporating them in polymers and to develop controlled release behaviors. Furthermore, as the vitamin is introduced to polymer, the morphological, biological and thermal properties of polymeric materials have improved.

Conflict of interest

The authordeclare no conflict of interest.

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