Fucoidan in Pharmaceutical Formulations

Subjects: Others

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Fucoidan is a heterogeneous group of polysaccharides isolated from marine organisms, including brown algae and marine invertebrates. The physicochemical characteristics and potential bioactivities of fucoidan have attracted substantial interest in pharmaceutical industries. These polysaccharides are characterized by possessing sulfate ester groups that impart negatively charged surfaces, low/high molecular weight, and water solubility. In addition, various promising bioactivities have been reported, such as antitumor, immunomodulatory, and antiviral effects. Hence, the formulation of fucoidan has been investigated in diverse pharmaceutical dosage forms to be able to reach their site of action effectively. Moreover, they can act as carriers for various drugs in value-added drug delivery systems.

drug delivery formulation pharmaceutical industry

1. Introduction

Fucoidan encompasses a heterogenous class of polysaccharides found in the extracellular matrix and cell wall of brown seaweeds (Phaeophyta) and marine invertebrates with potential physiological functions. It acts as cellulose and hemicellulose cross-linkers, playing a crucial role in cell wall integrity, in addition to preventing algae dryness during summer and low tide periods, among others [1][2]. Chemically, fucoidan is composed of a sulfated backbone of diverse sugar monomers, mainly L-fucose, as well as galactose, glucose, xylose, mannose, and uronic acids. However, some proteins and minerals such as calcium, magnesium, manganese, copper, potassium, selenium, sodium, and zinc can be also found [3]. The heterogeneity in fucoidan's chemical composition regarding monomeric composition, glycosidic linkages, sulfation pattern and content, presence of other constituents, and molecular weight has been investigated extensively in the past few years. These variations are mostly associated with different factors, including algae species, season of harvesting, extraction processes, geographical origin, and vegetative phase [4][5][6][7]. The diversity in fucoidan's biochemical composition has enriched various scientific fields with investigations of potential bioactivities and applications. For instance, fucoidan either with low, intermediate, or high molecular weight has gained much interest recently due to its promising biological and pharmacological properties such as heparin-like anticoagulant, antitumor, anti-angiogenic, anti-inflammatory, anti-hyperglycemic, antiviral, and immunomodulatory bioactivities [8][9][10][11]. As a result, fucoidan-containing products are consumed widely for nutraceutical and health-promoting benefits based on unique molecular mechanisms.

Fucoidan also offers some attractive physical properties enabling its use in diverse pharmaceutical formulation techniques (**Figure 1**). These physical characteristics include, for instance, mucoadhesion, pH, temperature, and enzyme response. In addition, fucoidan has a strong ability to bind to numerous compounds and macromolecules.

The binding affinity is mainly resulting from the negatively charged surface, the degree of sulfation, and molecular weight. Additionally, fucoidan has low apparent viscosity with a pseudoplastic flow, preventing its use as a gelling or thickening agent. On the other hand, upon mixing fucoidan with oppositely charged polymers, gel, matrices, and films can be formed. Moreover, fucoidan is known for its high stability under acidic and alkaline conditions [12].

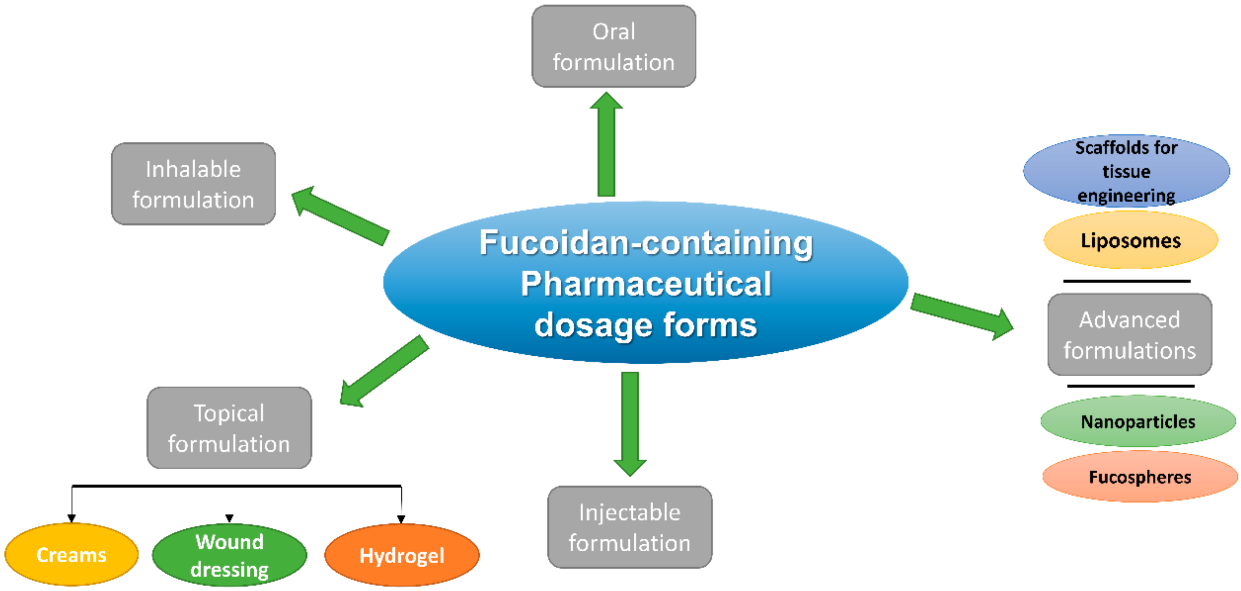

Figure 1. A summary of recently developed pharmaceutical formulations containing fucoidan.

In the past few decades, considerable progress has been achieved in designing suitable formulations of fucoidan as a therapeutic agent, polymeric drug carrier, excipient, and matrix-forming system. However,

2. Biopharmaceutical Properties of Fucoidan

2.1. Mucoadhesive Properties

Mucoadhesive pharmaceutical formulations are designed to ensure intimate contact between the formulation and the human mucosal membranes and the extended release of the drug in the desirable tissue. The mucoadhesion mechanism occurs in three successive stages. Firstly, the mucoadhesive polymer becomes wet and swollen by engulfing an aqueous proportion from the surrounding environment. Secondly, the swollen polymer exposes more relaxed polymer chains. Lastly, these relaxed polymer chains form van der Waals attractions or hydrogen bonds with mucin protein and the mucus layer. Mucoadhesive drug delivery systems can be used for targeting different mucus membranes in the body (e.g., conjunctiva, nasal cavity, buccal cavity, esophagus, upper and lower gastrointestinal tract, rectum, and vagina) [13]. Based on the mucoadhesive properties of fucoidan when mixed with chitosan at pH above 6 to allow the interaction with the acid glycoproteins of mucus (as fucoidan itself does not have mucoadhesive properties), some researchers started to prepare mucoadhesive fucoidan-containing formulations [14].

2.2. pH Response

Among all the explored advanced drug delivery systems (DDS), stimuli-responsive DDS is considered a promising strategy for delivering a drug right to the site of action through targeted delivery. Stimuli applied in this form of drug delivery may be endogenous or exogenous triggers. Endogenous triggers depend on physiological differences between unhealthy and normal tissue. These physiological differences include pH, hypoxia, redox state, enzymes, and regional difference in pressure. On the other side, exogenous triggers include light, magnetic field, ultrasound waves, and electrical and mechanical stimuli. The pH sensitivity is one of the promising and easily applied stimuli-based drug delivery approaches. The physiological pH varies along the gastrointestinal tract and, most importantly, it varies distinctly between healthy cells and tumor cells. Tumor cells possess acidic pH compared to normal cells due to their poor lymphatic drainage and high accumulation of waste product [15][16]. For any polymer to have a pH response, it should have ionizable functional groups interacting with the surrounding medium. Fucoidan is reported to have pH sensitivity owing to its high total number of negatively charged sulfonic acidic groups. However, for pH-responsive tumor targeting, it is crucial to incorporate a basic positively charged polymer (i.e., chitosan) that undergoes ionization upon encountering the tumor's acidic micro-environment, leading to repulsion among similar charges freeing the core drug content [14].

Chitosan itself has poor aqueous solubility at physiological pH. Therefore, to achieve an optimum pH-sensitive polymer coat composition, chitosan is incorporated with fucoidan, taking advantage of its anti-tumor, antioxidant, and immunomodulatory effects. It is important to note that a pH-responsive formula targeted to the tumor site should be injected intravenously to prevent premature release of the drug in the acidic environment of the stomach [17][18].

2.3. Temperature Response

Most natural polysaccharides exhibit thermo-responsive properties on their own or after synthetic modification. Many thermo-responsive polymers can respond to thermal change differently. Some polymers have a physical characteristic called lower critical solution temperature (LCST), while others have upper critical solution temperature (UCST). The difference here is that polymers with LCST are present in the form of a solution at room temperature and form chemical cross-linking upon increasing temperature (physiological temperature). On the contrary, polymers with UCST liquefy at high physiological temperatures and form gels below it. Polymers with a transition temperature (~20–40 °C) resembling room and physiological temperature are of immense importance in the biomedical field. This behavior enables researchers to utilize thermo-responsive hydrogels in various biomedical applications, including "smart" stimuli-responsive drug delivery systems, tissue engineering scaffolds (regenerative medicine), and gene therapy [19][20].

Fucoidan has a non-gelling nature due to its low viscosity. The rheological behavior of fucoidan is greatly dependent on multiple variables such as seaweed species, molecular weight, number of sulfate groups, and uronic acid positions [3]. Unfortunately, no studies have reported whether fucoidan itself exhibits upper or lower critical solution temperature. However, previous studies indicated that fucoidan, when mixed with other natural polysaccharides, can form synergistic interaction either via hydrogen bonds, van der Waals forces, and electrostatic interactions by the presence of charged sulfate and hydroxyl groups. Analogously, xanthan

polysaccharides cannot form a gel on their own, but gel formation occurs after its synergistic incorporation with another gelling agent such as gelatin and glucomannan [21].

2.4. Enzymatic Response

Fucoidan is a non-starchy polysaccharide at which the sugar monomers composed mainly of fucose are linked via α-(1,3) glycosidic linkage. Nevertheless, some other glycosidic linkages occasionally contribute, such as α-(1,4), α-(1,2), or α-(1,6). In addition, trace amounts of galactose, xylose, and glucuronic acid have been reported, and hence, it shows little to no degradation by digestive glycosidase enzymes [22]. The presence of glycosidic bonds in polysaccharides makes them labile to degradation by enzymes such as hyaluronidase and matrix metalloproteinases (MMPs), which act on the dissociation of the cells' extracellular matrix [23][24]. On the other hand, like most polysaccharides, fucoidan may be labile to degradation by some other enzymes and in analogy to its interaction with MMPs abundant at tumor sites, where fucoidan is reported to inhibit their over-expression [25].

2.5. Targeting Ligand

Ligand-mediated endocytosis is a promising mechanism for achieving targeted drug delivery. The endocytosis process is important to concentrate the highest possible effective concentration of chemotherapeutic agent into cancer cells, avoiding its cytotoxic adverse effect on normal cells [19]. Previous studies have reported that multiple sulfated oligosaccharides and polysaccharides (i.e., fucoidan, heparin, and dextran sulfate) can effectively bind to lectin receptors such as p-selectin [26]. The p-selectin receptor is overexpressed on activated platelets and is responsible for leukocyte rolling and trapping on platelet aggregates and the extravasation process. Additionally, p-selectin is found to be overexpressed by tumor cells and is responsible for promoting the adhesion process of cancer cells to endothelium and hence facilitating metastasis [27].

3. Pharmaceutical Dosage Forms of Fucoidan and Their Different Routes of Administration

Fucoidan-containing pharmaceutical formulations are classified and summarized in **Figure 2** based on the route of administration. In addition, they are discussed in detail in the following subsections. Previous literature reported that fucoidan exerts many interesting biological, pharmacological, and antimicrobial characteristics; for instance, Krylova et al. studied the antiviral activity of naïve and an enzymatically modified fucoidan derivative of high molecular weight isolated from *Fucus evanescens* against herpes viruses (HSV-1, HSV-2), and the results showed that the introduction of both types to the tested cells in vitro produced the highest antiviral activity as a protective effect before infection, while the in vivo tests using HSV-2 vaginally infected mice treated with intraperitoneal fucoidan at a dose of 10 mg/kg/d showed a significant reduction in virus replication (HSV-2 titer was decreased by 2 to 3 lg TCID50/mL) and significantly prevented lethal infection outcomes [28].

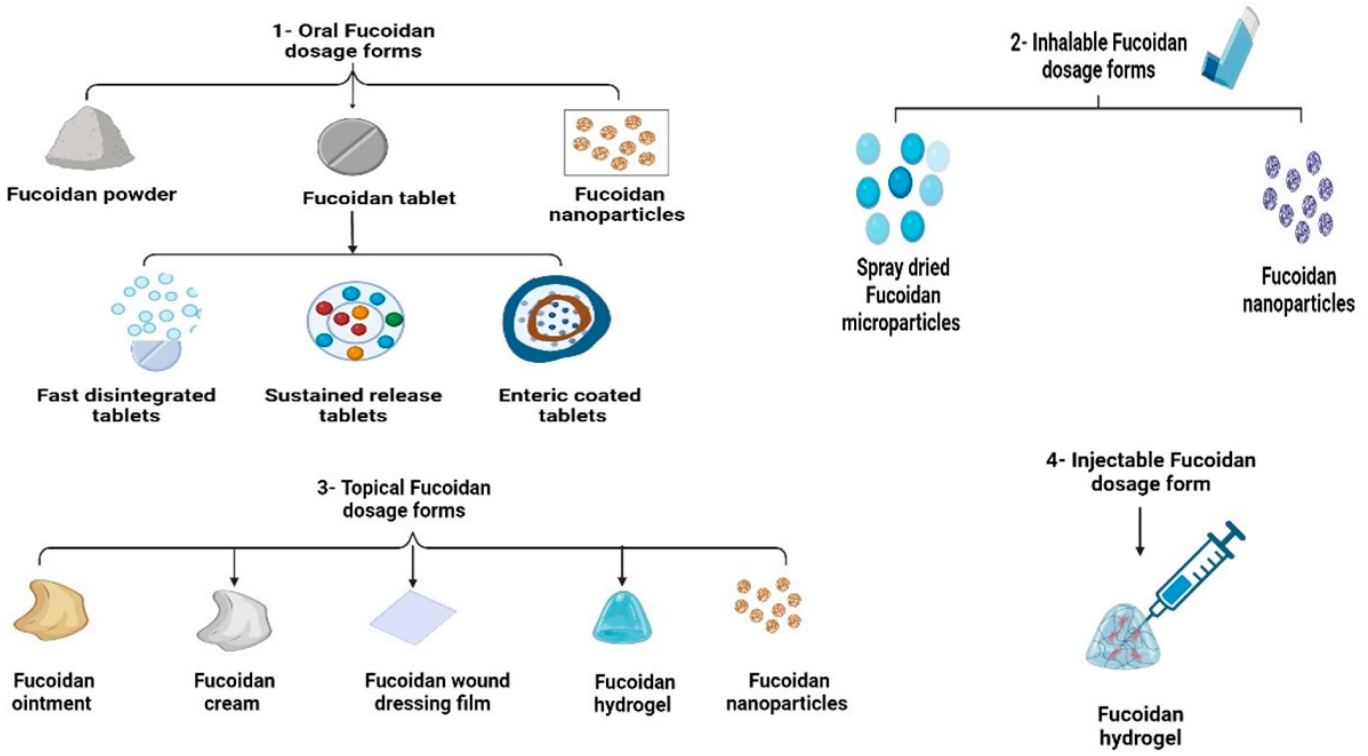

Figure 2. Different dosage forms and pharmaceutical formulations containing fucoidan.

Furthermore, fucoidan from different species is proven effective against different bacterial strains; for instance, fucoidan extracted from *Sargassum polycystum* demonstrated significant inhibition of the in vitro bacterial growth of *E. coli*, *S. aureus*, and *S. mutans*, with the highest inhibitory effect observed with *Pseudomonas aeruginosa* (21 ± 1.0 mm at the concentration of 50 µg/mL). The in vivo tests performed on *P. aeruginosa*-infected zebrafish treated with 15 mg/0.1 kg fucoidan pre- and post-exposure to the pathogen revealed that the fucoidan-pretreated fish showed lower mortality (10%) than fucoidan-post-treated fish (16.6%), while the control group showed total mortality within 20 days [29].

Antifungal activity of fucoidan extracted from *Undaria pinnatifida* was investigated by testing fucoidan against three fungal species, namely *Aspergillus flavus*, *Aspergillus fumigatus*, and *Mucor* species, and showed a larger diameter of inhibition zone for *A. fumigatus* (11.83 ± 1.0 mm) followed by *A. flavus* (8.5 ± 0.87 mm), with *mucor* species showing the least response, indicating its resistance to fucoidan treatment [30].

Interestingly, fucoidan as a marine polysaccharide possesses a prebiotic activity on gut microbiota as it can enhance the growth of beneficial gut flora and modulate gut dysbiosis resulting from the transformation of beneficial bacteria into harmful pathogens. Furthermore, fucoidan was reported to modulate cellular immunity, support the intestinal epithelial barrier, and reduce the expression of inflammatory mediators such as TNF-α and IL-6, and it can also directly promote the growth of the beneficial *Lactobacillus* species [31].

3.1. Oral Fucoidan Formulations

Although fucoidan has high solubility in water, it has poor gastric solubility and limited absorption from the stomach and upper gastrointestinal tract. In addition, it experiences degradation by normal flora in the lower gastrointestinal tract, producing oligosaccharides and short-chain fatty acids which are rapidly eliminated from the bloodstream by reticuloendothelial clearance. Taking advantage of the poor solubility and low gastric absorption of orally administered fucoidan from the stomach, it can be used as a gastro-protective dietary supplement. Fucoidan can be used orally as a physical barrier and as an anti-inflammatory and oxidative stress suppressor for managing gastric ulcers. In addition to the gastro-protective effect, fucoidan is useful for maintaining the chemical stability of acid-labile drugs in the stomach. In addition, fucoidan can control the release of active pharmaceutical ingredients via pH-sensitive behavior, allowing the release of the drug only in the slightly basic medium of lower GIT [32][33][34].

The formulation of fucoidan powder in oral tablet dosage form has some challenges based on fucoidan's physicochemical properties [24]. For example, fucoidan powder is hygroscopic with low flowability due to its irregular particle surfaces and wide size distribution ranging from 10 to 500 µm. The other formulation challenge is the long disintegration time associated with tablets with high dry powder extract content. Therefore, researchers used some tablet excipients such as sodium croscarmellose, crospovidone, lactose monohydrate, and microcrystalline cellulose to improve the disintegration and flowability, engaging the wet granulation technique [35].

3.2. Inhalable Fucoidan Formulations

The pulmonary route of administration has gained much attention as a non-invasive administration route for deep local alveolar delivery of different drugs. Pulmonary drug delivery can also be used for systemic absorption due to the high alveolar absorptive surface area (~100 m^2). This route of administration is characterized by the presence of a thin absorptive layer, rich blood supply, and minimal degradation enzyme activity. Furthermore, pulmonary drug delivery offers the advantages of bypassing proteolytic gastrointestinal degradation and hepatic first-pass metabolism. Therefore, the pulmonary route is more suitable for the systemic delivery of proteins and/or peptides [36].

Natural polysaccharides can act as a carrier for micro/nano aerodynamic particles and aerogels intended for pulmonary delivery [37]. The sulfated fucose polysaccharides can be easily docked in the surface receptors of alveolar macrophages, which host mycobacterium tuberculosis (TB). Researchers investigated the use of spray-dried fucoidan microparticles using fucoidan from *Laminaria japonica* as an inhalable formulation containing both isoniazid (INH) and rifabutin (RFB) [38]. This dosage form containing combined therapy for TB improved the patient compliance with treatment due to targeted drug delivery [38]. The aerodynamic properties of this formula were evaluated, and the erratic surface morphology of the microparticles showed favorable flowability and dispersibility, indicated by low tapped density. The aerodynamic diameter of these microparticles was around 2–4 µm, producing favorable deposition into alveoli [39].

3.3. Topical Fucoidan Formulations

The topical drug delivery systems include ointments, creams [40], nanogels and hydrogels [41], wound dressings [42], thin films [43], and smart stimuli-responsive systems [44]. There is a growing tendency by the Food and Drug

Administration (FDA) to reformulate different drugs such as anti-inflammatories, analgesics, wound healing enhancers, etc., to be in topical dosage forms. The reason for this is to improve these drugs' efficacy at the site of action while reducing their possible side effects. The incorporation of active pharmaceutical ingredients (APIs) into a carrier for the topical application provides substantial merits, for instance, enhanced transdermal permeation, protection against first-pass metabolism, ease and convenience of administration, non-invasive drug delivery, and localization of therapeutic effects at the target site of action [40][41].

Fucoidan, as a fucose-rich polysaccharide, is known to exert anti-inflammatory, immune-modulatory, and heparin-like anticoagulant action. Furthermore, it has been proven to mediate fast skin regeneration and re-epithelialization by enhancing the migration and build-up of fibroblasts. Fucoidan is used for inhibiting enzymes responsible for the hydrolysis of dermal elastic fibers (elastase, tyrosinase, and collagenase) and the suppression of IgE associated with allergic and inflammatory reactions [42][43]. As a result of the relatively high molecular weight, negatively charged sulfate groups, and hydrophilicity, fucoidans generally have a low skin permeation coefficient. It was also found that the anti-inflammatory effect of fucoidan, especially that based on the inhibition of protein denaturation, is dependent on the fucose and sulfate content of the extract obtained from five different brown seaweed species, which are *Saccharina japonica, F. vesiculosus, Fucus distichus, Fucus serratus,* and *Ascophyllum nodosum* [45].

The pharmacokinetic behavior of fucoidan ointment after topical application was studied using carrageenan-induced paw inflammation in a rat model compared to intravenous administration [44]. The tested formulation contained fucoidan, transcutol as a penetration enhancer, and polyethylene glycol (PEG 400) as a surfactant. The plasma levels of topical fucoidan (100 mg/kg) exhibited a longer half-life of 20.75 ± 9.43 h compared to 9.47 ± 2.34 h after IV administration. This prolonged half-life is attributed to the quick drug penetration and retention of the formula in the form of skin and striated muscle reservoirs [44].

The effect of topical application of fucoidan extracted from two different sources (*Undaria pinnatifida* extract, containing 85% fucoidan, and a *F. vesiculosus* co-extract, containing 60% fucoidan and 30% polyphenol) on the skin was evaluated [46]. Both extracts showed inhibition of enzymes responsible for the hydrolysis of dermal elastic fibers (elastase, tyrosinase, and collagenase). In addition, both extracts increased the expression of the human Sirtuin 1SIRT1 protein, counteracting the effect of UV radiation and oxidative stress. Furthermore, both extracts activated Toll-like receptors 2 and 3 with the expression of antimicrobial peptides and wound healing signals by 387% and 229%, respectively [46].

3.3.1. Fucoidan Creams

Obluchinskaya et al. prepared a fucoidan-based cream with anti-inflammatory action [47]. Formulations contained fucoidan (from *F. vesiculosus* with M.W of 735 kDa), olive oil, hydrogenated castor oil, and a surfactant such as poloxamer 407, geleol, gelucire, lanolin, or cremophor®. The highest fucoidan release in vitro was observed with the formulation containing poloxamer 407 as a surfactant. Moreover, poloxamer 407 increased the colloidal stability and enhanced the rheological properties of the formulation. In the same context, the effect of several penetration enhancers, such as dimethyl sulfoxide DMSO, transcutol P, and polysorbate 80, on fucoidan release was

assessed. The use of transcutol P increased the diffusion of fucoidan into the agar plate with superior spreadability of the formulation containing transcutol P over polysorbate 80. On the contrary, the formulation containing DMSO showed the slowest release and the poorest spreadability [47].

3.3.2. Fucoidan Wound Dressing Films

Wound dressing films are a simple, low-cost, and non-invasive choice for the management of wounds and promotion of healing. These films should include some major features such as flexibility, mechanical strength, and a physical barrier. These topical films show the ability to absorb wound exudates and evaporate moisture content. Furthermore, wound dressing films can act as a drug delivery system for antibacterial and tissue regeneration promoter genes [48][49][50].

3.3.3. Fucoidan Topical Hydrogels

Hydrogels are materials that have the ability to absorb water and swell upon embedding in an aqueous environment. Pharmaceutical hydrogels are composed of physically or chemically cross-linked water-insoluble polymers with hydrophilic functional groups and incorporated high water content of 90% *w/w*. Hydrogels provide a variety of physically and biologically interesting characteristics that simulate the physiology of natural tissues. These hydrogels are characterized by softness, flexibility, and a high surface area, along with swelling behavior and high loading capacity of drugs [3][51].

Fucoidan is a hydrophilic polysaccharide having some interesting physical characteristics needed for dermal burns and wound treatment. These characteristics are high exudate absorption capacity (high swelling index), mucoadhesion, adequate hygroscopicity, and oxygen permeability. In addition, its pharmacological activity includes heparin-like anti-coagulant, anti-thrombotic, and anti-inflammatory effects [52].

3.4. Injectable Fucoidan Formulations

Injectable hydrogels should have the ability to undergo a phase transition in response to temperature changes, particularly from ambient temperature to physiological temperature. These systems permit in situ hydrogel injection in a convenient minimally invasive solution form with subsequent solidification inside the body. Hydrogel formation occurs immediately after temperature change without the need for chemical initiators [20]. As previously mentioned, fucoidan cannot form an injectable thermo-responsive gel matrix unless mixed with another thermo-responsive polymer, i.e., chitosan, hyaluronic acid (HA), gelatin, xyloglucan, etc. [53].

3.5. Advanced Fucoidan Formulations

Advanced fucoidan formulations include liposomes, nanoparticles, fucospheres, and scaffolds, as illustrated in **Figure 3**.

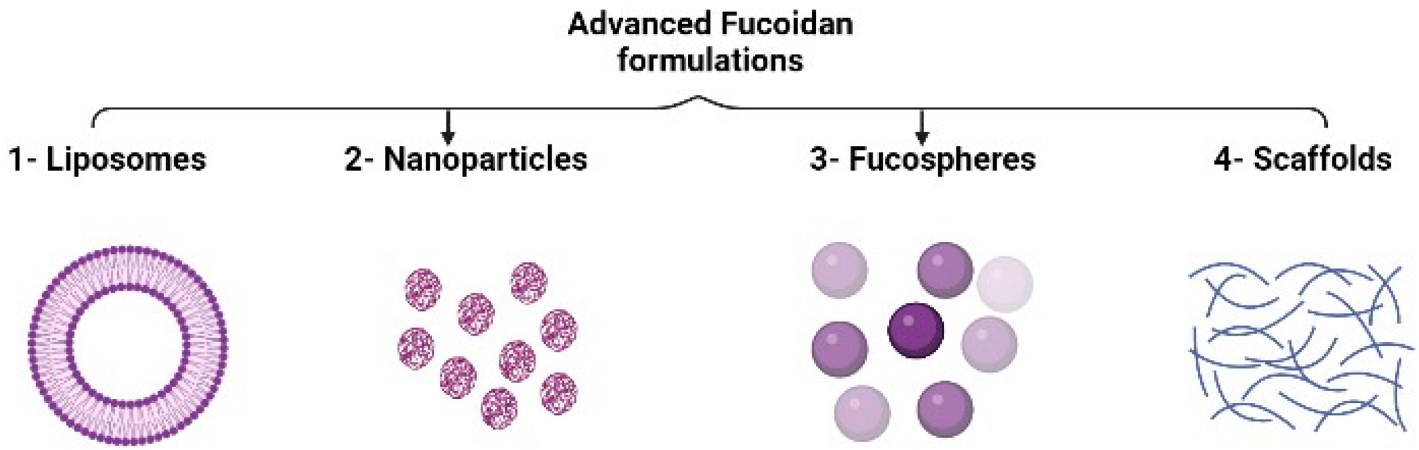

Figure 3. Advanced fucoidan formulation approaches.

3.5.1. Liposomes

Liposomes have several beneficial properties, especially in cancer treatment, when compared to other nanosystems. These properties include improving drug solubility, stability, and delivery to specific target sites [54].

Fucoidan extracted from *F. vesiculosus* was encapsulated into a nano-sized liposomal carrier composed of lecithin (phosphatidylcholine) and tested for anticancer and immunomodulatory effects. The results of this study showed increased anticancer activity as well as a reduction in the levels of interleukin-6 and tumor necrosis factor-α compared to fucoidan nanoparticles [55].

3.5.2. Nanoparticles

Nanotechnology-based drug carriers are highly prominent in the area of targeted drug delivery for the treatment of various diseases [56][57][58][59]. Targeted delivery of chemotherapeutics is greatly beneficial because these drugs suffer from low aqueous solubility, rapid clearance, and high toxicity. All these delivery limitations can be overcome by the use of biocompatible and biodegradable polymeric nanocarriers [60][61][62].

Recently, fucoidan has played a key role in nanotechnology-based medicine for different biomedical applications. Fucoidan in nanomedicine can be used as a nanocarrier for many drugs or it can be combined with different cationic polymers to encapsulate different cargos, besides being used as an effective therapeutic agent on its own [10][63].

Fucoidan is a promising carrier for nanoparticle formulation. The formulation of fucoidan nanoparticles by the self-assembly technique enables fucoidan particles to arrange themselves into a capsule structure that is ready for drug entrapment. The ionotropic cross-linking of fucoidan with polymers having opposite net charge (e.g., chitosan, Polyallyamine hydrochloride, Polyethyleneimine, Hexadecylamine, isobutyl cyanoacrylate) is a common technique for the preparation of drug-loaded nanoparticles [17].

3.5.3. Fucospheres

A conventional way of processing fucoidan and chitosan polymers for the construction of microsphere-based drug delivery systems is by cross-linking fucoidan and chitosan to form “fucospheres” [64][65]. The drug loading and encapsulation efficiency inside fucospheres are mainly affected by the concentrations and molecular weights of fucoidan and chitosan, as well as drug properties [66].

Sezer et al. prepared bovine serum albumin (BSA)-loaded fucospheres composed of cross-linked chitosan and fucoidan with particle sizes ranging from 0.61 to 1.28 µm and smooth, poreless, spherical morphology [67]. The particle size depended on the concentration of fucoidan, chitosan, and BSA. The encapsulation efficiency of BSA varied between 51.8% and 89.5%. Increasin

3.5.4. Scaffolds for Tissue Engineering

Fucoidan as a biomacromolecule can be used as a building block to produce self-assembling biomaterials, which can resemble the natural extracellular matrix necessary for cell culture and tissue engineering. Protein–polysaccharide hybrid hydrogels arranged via co-assembly or conjugation between peptides and polysaccharides provide a promising approach to tissue engineering [68]. This hybrid hydrogel can overcome the formerly reported problems such as lack of mechanical strength and low biological functionality associated with applying self-assembling polymers and synthetic peptides separately [68].

A thermodynamically driven hydrogel based on co-assembly between fucoidan and self-assembled peptide (SAP) was applied as a scaffold for skeletal muscle progenitor cells [69]. The myoblasts cultured on fucoidan scaffolds were smaller in size and had less multinucleated synthetia, with limited spreading and no observed toxicity. The scaffold matrix showed a 10-fold increase in stiffness compared to polysaccharide-free scaffolds [69].

4. Fucoidan Pharmacokinetics

Pharmacokinetics (PK) generally describes the pathway of the drug into the body and how the body reacts to it in four main processes: absorption, distribution, metabolism, and elimination (ADME system). Comprehending the pharmacokinetic behavior of fucoidan is crucial for determining dosage recommendations and the most suitable dosage form for each condition to achieve effective therapeutic outcomes.

The pharmacokinetic behavior of fucoidan from variable species was evaluated using experimental animals such as mice, rats, and rabbits after oral, topical, and parenteral administration. Recently, a group of researchers investigated the pharmacokinetic parameters of fucoidan extracted from *Laminaria japonica* after an intravenous injection of (50 mg/kg) in rabbits. The PK results showed a maximum plasma concentration (C_{max}) of 110.53 µg/mL after a maximum time (T_{max}) of 5 min [70][71].

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