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Review Paper

# Quercetin in Drug Carriers: Polymer Composite, Physical Characteristics, and *In vitro* Study

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**Abstract**
Quercetin is a highly prevalent flavonoid commonly found in a wide variety of fruits and vegetables. This compound has various biological actions, indicating great potential in preventing diseases and promoting health but the disadvantages include low solubility and instability. The disadvantages can be overcome by using a polymer composite in the form of microspheres in the formulation. Therefore, this study aimed to review various uses of polymers in delivering quercetin compounds. The results showed that various polymers in microspheres have been formulated with quercetin to minimize the weaknesses. The delivery systems developed and reported from several related studies include microencapsulation, microcapsules, microparticles, microspheres, solid lipid microparticles (SLM), and nanoparticles. Polymers including Gelatine, Maltodextrin and Inulin, Carnauba wax, Poly (lactic-co-glycolic acid) (PLGA), Gyceryl behenate, Pectin, Nano-hydroxyapatite, Polycaprolactone, Starch, Chitosan, Eudragit S 100, Sodium Alginate, Ethyl cellulose, and Alumina efficiently improved the properties of quercetin, enabling the utilization as a controlled drug delivery agent. Therefore, developing a quercetin delivery system using composite polymers presents both an opportunity and a challenge for future applications.

**Keywords**
Quercetin, Polymer, Microspheres, Physical Characteristic, *In vitro*

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## 1. INTRODUCTION

Quercetin is a prominent bioflavonoid, the structural foundation for numerous other flavonoids. This compound is a significant component in multiple food supplements and other nutraceutical products (Karuppusamy et al., 2021), functioning as a potent antioxidant that effectively neutralizes highly reactive biological substances, including peroxynitrite and hydroxyl radicals. It is categorized as a Biopharmaceutics Classification System (BCS) II compound because of the high permeability and low solubility, which affects the bioavailability. The biological action is determined by the five hydroxyl groups (Madaan et al., 2016).

The quercetin molecule is hydrophobic, with poor solubility at average room temperature, a pH of 3, and a concentration of 0.4 $\mu$g/mL. Therefore, the bioavailability is exceedingly limited, approximately 1% in humans and less than 17% in rats. Quercetin experiences fast metabolism, and about 99.4% binds to plasma proteins. It is currently being promoted as a dietary supplement, with a suggested daily dosage ranging from 200 to 1200 mg. The stability as a flavonoid is due to the significant melting point of approximately 326 °C (Setyawan et al., 2017). Quercetin also has a high sensitivity to oxygen, and following a 2-hour bubbling process, the molecule degrades significantly with about 91% being broken down (Chaaban et al., 2017). The degradation mechanism through oxidation is illustrated in Figure 1.

Quercetin has a restricted solubility in water and is prone to spontaneous oxidation as well as decay in the upper gastrointestinal tract (GIT), greatly diminishing the amount and efficacy reaching the colon. There is a growing interest in enclosing quercetin within different carriers to achieve targeted delivery to the colon. One particularly significant approach entails using natural biopolymers, such as dietary fibers, due to the inability to be digested in the upper GIT. However, these fibers can be broken down by enzymes produced from colonic microbes, which release quercetin at the desired location (Liu et al., 2023).

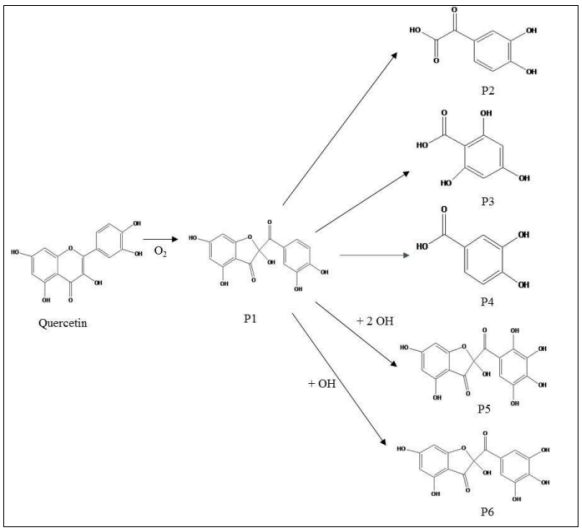


**Figure 1.** Oxidative Degradation Mechanism of Quercetin (Chaaban et al., 2017)

Diverse techniques have been used to enhance the solubility and durability of quercetin, including formulation into microcapsules, microparticles, microspheres, solid lipid microparticles (SLM), nanoparticles, and microemulsion preparations as shown in Figure 2. Microspheres are one of the most widely formulation types.

Microspheres are spherical materials with hollow interiors and diameters ranging from the nano to micro-scale, containing material on the surfaces or not. These materials play a crucial role in biotechnology. Microspheres typically range in size from 1 to 1000 micrometers ($\mu$m) and function by encapsulating substances, providing protection from external factors. In this context, drug release is directly correlated to the breakdown of the matrix in bodily fluids (Saavedra Leos et al., 2022).

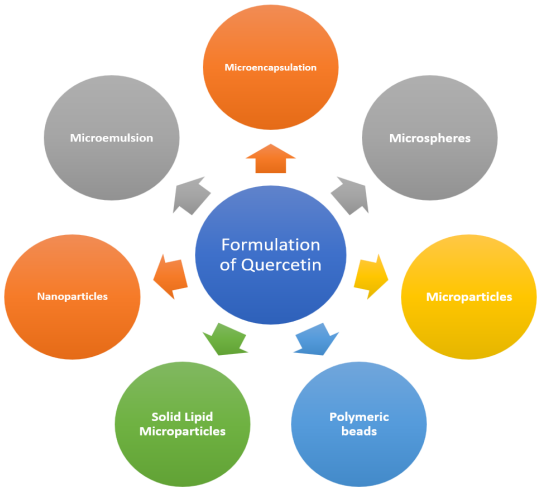


**Figure 2.** Various Quercetin Formulations Using Polymers

The film-forming polymer in microparticles may dissolve in the medium or function as a permeable, semipermeable, or water-insoluble membrane. The release of the active ingredient is primarily responsible for the diffusion in the cases of permeable membranes. Meanwhile, it is important to consider the osmotic phenomenon when working with semipermeable coatings. Another option is to use a water-soluble membrane, which speeds up the dissolution profile by forming pores (Lengyel et al., 2019). The methods of release from microencapsulated formulations are shown in Figure 3.

Microencapsulated preparations use a polymer composite in the formulation. Carbohydrate polymers are naturally occurring compounds analogous to synthetic types, with qualities including glass transition and melting temperatures, as well as molecular weight distribution. These polymers mainly consist of polysaccharides such as glucose, sucrose, dextrose, arabinose, and galactose as well as starch, chitosan, maltodextrins, inulin, and gum Arabic. Polysaccharides have been extensively used as standalone carrier agents for preserving and microencapsulating active components in food and medicinal goods (Saavedra Leos et al., 2022). Carbohydrate polymers, formed by condensation of monosaccharide units through glycosidic bonds, are abundant in nature and found in various cell structures including plant cell walls, arthropod exoskeletons, bacteria cell walls, and animal extracellular space. These compounds have reactive groups and can experience chemical as well as biochemical modifications (Ansari et al., 2020). Using biopolymers derived from plants, animals, or microorganisms offers advantages, while semi-synthetic cellulose derivatives and synthetic polymers either biodegradable or not, are also used. Although proteins or polysaccharides are typically the foundation of the formulation, lipids, and waxes are also important to the structure. Non-polymer excipients help build and harden the polymer network of drug delivery systems by crosslinking chains, such as those in $CaCl_2$. The type of polymer and method used determine the stability and solubility of quercetin.

Studies have been conducted on quercetin, a naturally occurring flavonoid with anti-inflammatory and antioxidant qualities. The stability, bioavailability, and targeted administration can all be improved by using polymers as carriers. The utilization of polymers as quercetin transporters presents several benefits, including enhanced bioavailability, safeguarding against deterioration, and regulated release. This article discusses the various uses of polymers in delivering quercetin compounds, with drug carrier polymers shown in Figure 4.

## 2. EXPERIMENTAL SECTION

### 2.1 Methods

This study used a systematic review method for scientific journals published on Scopus with the keyword "microspheres polymers for quercetin" and a publication period of 2015-2024. The literature search used the software Harzing's Publish or Perish (Windows GUI Edition) 8.9.4554.8721. A total of 40 relevant titles were produced, then to visualize the topics re-

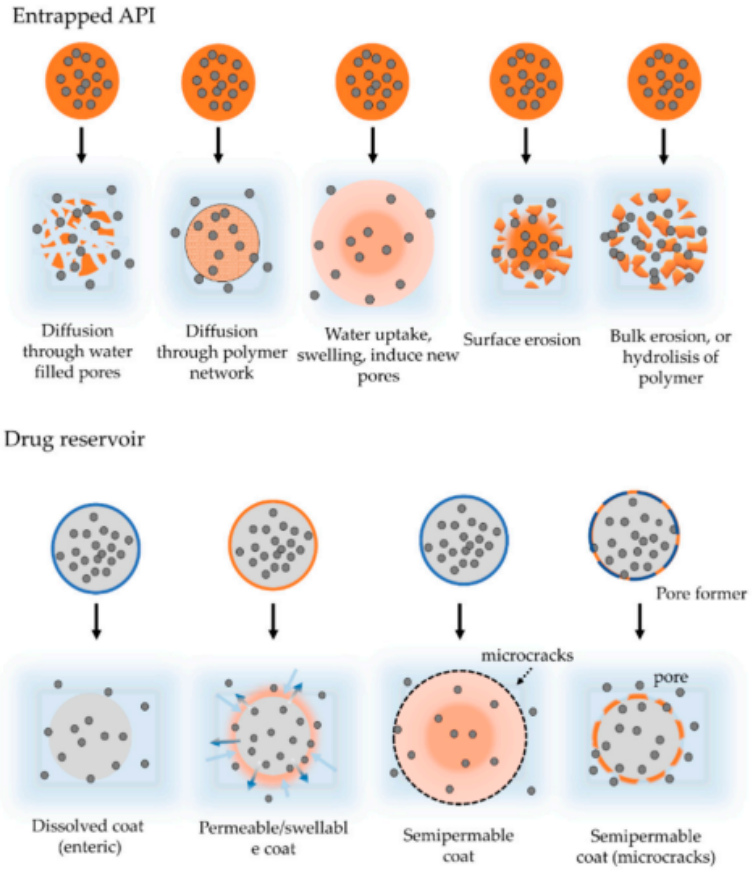


**Figure 3.** Microencapsulated Products: Methods of Release (Lengyel et al., 2019)

viewed, VOSViewer software version 1.6.20 was used (Wibowo et al., 2023). This study used content analysis to develop a comprehensive understanding of using polymers in the quercetin drug delivery system.

## 3. RESULTS AND DISCUSSION

A systematic literature review strategy, in conjunction with content analysis, offers a rigorous process for performing thorough investigations to generate comprehensive insights. Integrating these two methodologies enables effective collection, examination, and amalgamation of diverse data from various origins to completely comprehend a particular subject matter. A systematic literature review entails a methodical and organized approach to find and retrieve relevant studies from several databases, ensuring a thorough examination of the available literature. This methodology reduces prejudices and assures clarity by adhering to predetermined criteria and rules for selecting studies. In addition, methodical analysis of diverse literature enables the discovery of recurring patterns, new trends, and valuable insights (Wibowo et al., 2023).

Figure 5 shows the citation metrics of search results using Harzing's Publish or Perish software. Meanwhile, Figure 6 provides a visualization of the total number of papers from the Scopus database related to the keyword "microspheres polymers for quercetin ."The data shows an increasing trend in the number of papers published from 2015 to 2023. Based on the results, the total number of Scopus papers found was 40, with an average of 4.4 per year. This suggests that studies on the use of polymers in the formulation of quercetin drug delivery systems have yet to be widely conducted, presenting opportunities for future investigations. However, an increasing trend was observed between 2022 and 2023, with eight and 11 papers respectively compared to 2015 and 2021, in which only an average of three papers were published per year. This implies a growing interest in studies focused on using polymers in the drug delivery system to increase the stability and bioavailability of the quercetin compound.

Figure 7 showed that quercetin was always strongly correlated with the subject of polymers and microspheres, according to the keywords used in the search, namely "microsphere polymers for quercetin," suggesting the three topics were frequently used as main ideas in writing articles. The topics of polymers and microspheres were in the same cluster, indicating that the design of microspheres was closely related to optimizing the use of polymers to meet specific criteria. Meanwhile, the topic of quercetin was not in the same cluster as polymers and microspheres, suggesting the possibility of using other active substances aside from quercetin to make microspheres.

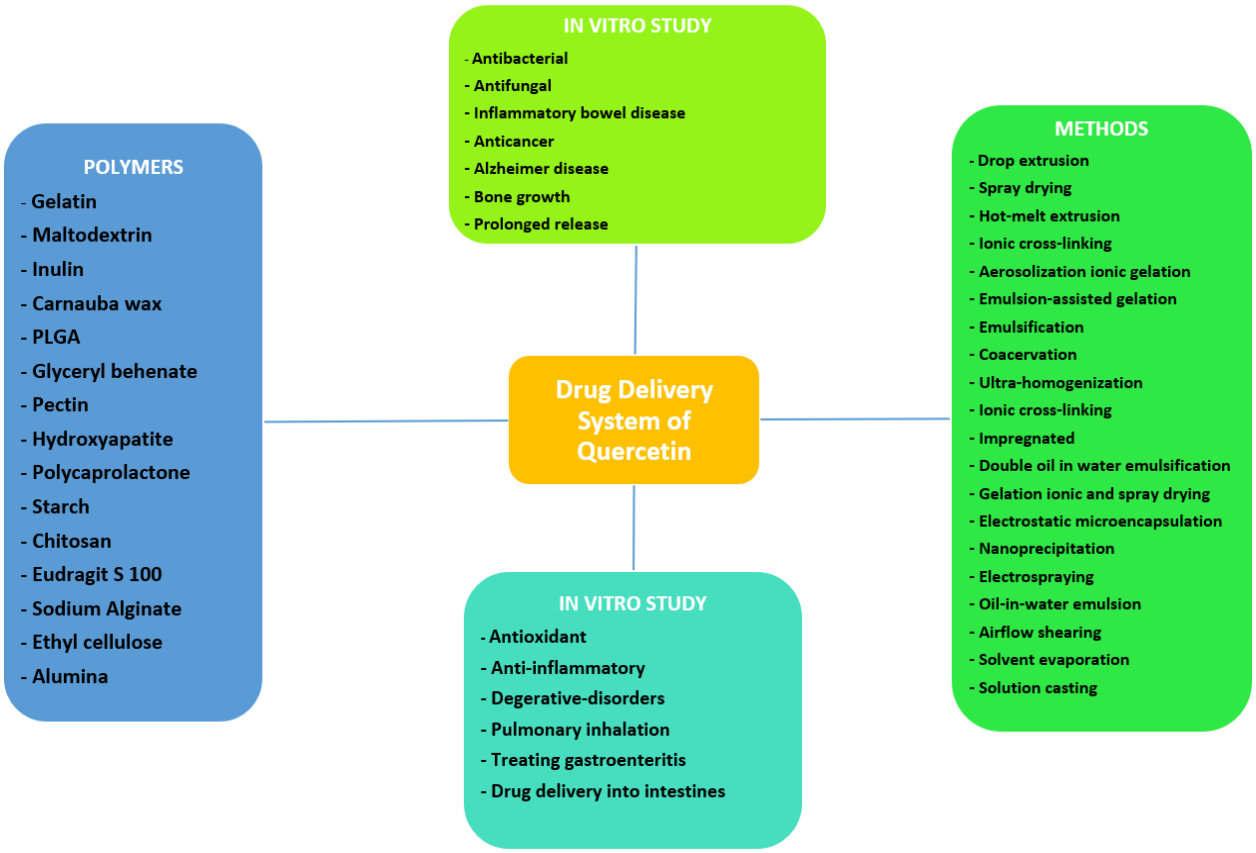


**Figure 4.** Drug Carriers Polymer for Quercetin

| Citation metrics | Help |
|---|---|
| Publication years: | 2015-2023 |
| Citation years: | 9 (2015-2024) |
| Papers: | 40 |
| Citations: | 491 |
| Cites/year: | 54.56 |
| Cites/paper: | 12.28 |
| Cites/author: | 491.00 |
| Papers/author: | 37.99 |
| Authors/paper: | 0.95 |
| h-index: | 13 |
| g-index: | 21 |
| hI,norm: | 13 |
| hI,annual: | 1.44 |
| hA-index: | 7 |
| Papers with ACC >= 1,2,5,10,20: | 28,20,9,0,0 |

**Figure 5.** Citation Metrics from Software

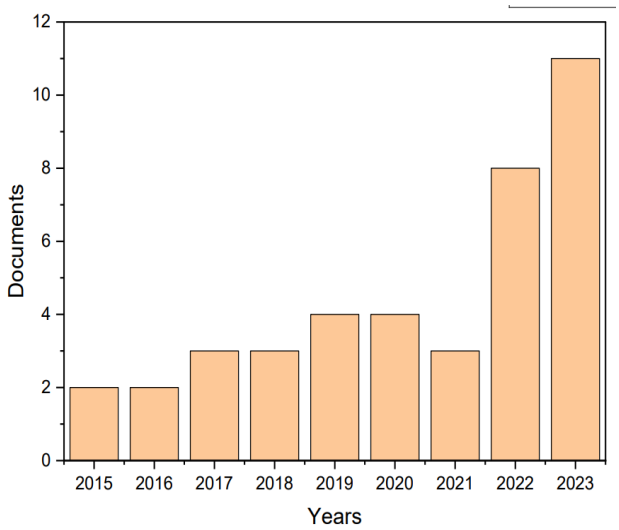


**Figure 6.** Scopus Database Documents

Figure 8 shows the authors who contributed to the 40 papers retrieved, with the most significant contribution stemming from Chinese publications. This indicates that China has dominated investigations on using polymers to produce quercetin microspheres in the last nine years.

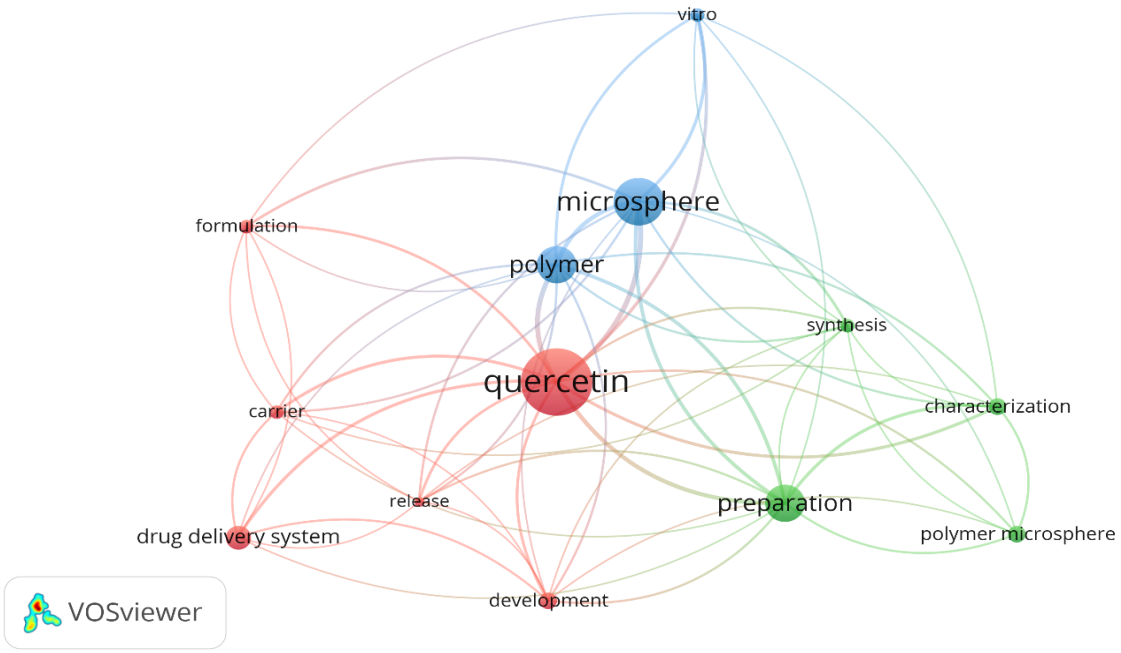


**Figure 7.** Keywords of Relevant Published Papers

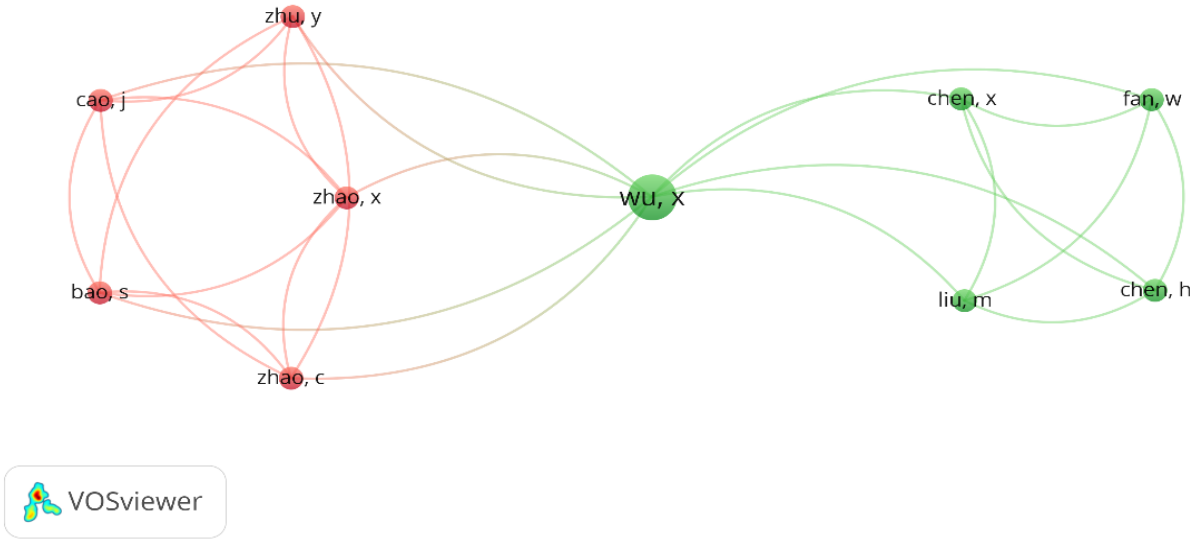


**Figure 8.** Authors Names and Significant Contributions to the Published Papers

### 3.1 Physical Characteristics of Quercetin Carriers

Microspheres can be manufactured using several types of natural and synthetic polymers. Possible options for synthetic polymers include polyester, namely PLGA and polylactide (PLA), while natural polymers include collagen, gelatin, albumin, starch, dextran, cellulose, and alginate. Several applications of composite polymers are shown in Table 1 while Table 2 presents the method used in producing the preparation.

**Table 1.** Applications of Polymer Composites-Quercetin

| Polymers | Results | References |
|---|---|---|
| Gelatine-Alginate | Increases swelling degree, mechanical parameters, and denaturation enthalpy; exhibited antioxidant and antibacterial properties that depended on the rate at which quercetin was released; a entrapment and controlled release of quercetin molecules. | (Rubini et al., 2020); (Ezati and Rhim, 2021); (Dhasmana et al., 2022); |
| Maltodextrin-inulin | Quercetin nanocrystals, both free and film-loaded, showed a dissolution rate similar and significantly greater than that of bulk quercetin; superior encapsulation efficiency, and minimal drying temperature impact. | (Lai et al., 2015); (Saavedra Leos et al., 2022); |
| Pectin-Casein | Reduce oxidative stress in arthritis-infected rats; enhancing drug release and stability. | (Souza et al., 2021); (Jing et al., 2023) |
| Carnauba Wax | Proved effective in flavor masking | (Khor et al., 2017) |
| Sodium Alginate -chitosan | High-bioavailability drug delivery; wrinkled surface, compact structures, and thermal stability; enhanced quercetin bioactivity, increased smoothness, and roughness; absorption of albendazole and its active metabolite was enhanced | (Hazra et al., 2015); (Frenț et al., 2022); (Frent et al., 2023); (Bhadraiah et al., 2023) |
| Sodium Alginate | Increased sodium alginate concentrations reduce drug loading; great promise for the combined therapy of depressive disorder when quercetin nanogels were administered intranasally; showed favorable physico-mechanical characteristics and durability. | (Kalalo et al., 2022); (Xu et al., 2023); (Szulc Musioł et al., 2023) |
| Inulin-Chitosan -sodium alginate | An effective carrier for enclosing hydrophobic bioactive compounds with a safe profile; superior gel strength and encapsulation efficiency; facilitates bacterial activity modulation and potentially mitigates gut dysbiosis. | (Nalini et al., 2019); (Liu et al., 2022); (Liu et al., 2023) |
| Glyceryl Behenate | Showed significantly superior effectiveness compared to conventional antihistamine medications; spherical with smooth surfaces, demonstrated good flowability; prolonging quercetin release duration | (Chakraborty et al., 2017); (Rosita et al., 2022); (Hariyadi et al., 2022) |
| Chitosan-Polycaprolactone | Promising potential for wound dressings and medication delivery carriers in wound management; synergistic antibacterial and antioxidant capabilities have a 30-month shelf life; the delayed release of quercetin in an acidic environment | (Zhou et al., 2021); (Azeem et al., 2022); (Viscusi et al., 2023) |
| Chitosan | Superior therapeutic effects in rabbit colitis models; effective approach for developing antibiotic -releasing coatings for medical purposes; the bactericidal activity has been improved. | (Helmy et al., 2020); (Wiggers et al., 2022); (Azeem et al., 2023) |

### 3.1.1 Gelatin

Gelatin is a type of biopolymer extensively used in various industries, particularly in the production of culinary, pharmaceutical, cosmetic, and photographic items, due to the distinctive functional characteristics. It is a tasteless, transparent, solid

| Polymers | Results | References |
|---|---|---|
| Chitosan-Alumina -PLGA-Oleic Acid | Slow-release properties, high concentration in the lung medicines; increased alkaline phosphatase medications; spherical with smooth surfaces, activity, Runx2 protein expression; potential cancer treatment system due to its pH-sensitive nature | (Liu et al., 2017); (Lee et al., 2018); (Nematollahi et al., 2021) |
| Alginate-Hydroxyapatite | The release of quercetin reached equilibrium within one day for all coatings; has great potential as a drug and cell delivery vehicle; maintains the color and smell of fresh pork meat with satisfactory quality until the end of the storage period. | (Malvano et al., 2021); (Kim et al., 2022); (Montone et al., 2023) |
| Eudragit S100 | Drug entrapment and oral bioavailability confirmed through stability studies, high drug loading and efficiency; efficient in creating a nanomedicine for treating colon cancer; formulating quercetin with | (Jat, 2018) ; (Sunoqrot and Abujamous, 2019); (Patel and Patel, 2022); (Elizondo Luevano et al., 2023) |
| PLGA | Improve cognitive and memory deficits without any adverse effects; minimal burst release and no harmful effects when exposed to INS-1 cells; demonstrating anticancer potential. | (Sun et al., 2016); (Nguyen and Jeong, 2018); (Karthick et al., 2019) |
| Nano-Hydroxyapatite | High efficiency and continuous release behavior; show anti-inflammatory effects, and repair *in vivo*; quercetin and bone morphogenetic protein-2 act as osteoconductive carriers. | (Han et al., 2022); (Ren et al., 2022); (Lee et al., 2023) |
| Chitosan-Fluorescein Isothiocyanate - Zein | Demonstrate antioxidant properties, encapsulation effectiveness, and drug-loading efficiency; promising tissue engineering material; recommended establishing a viable platform for delivering to the colon | (Zhou et al., 2022); (Al-Musawi et al., 2023); (Elmowafy et al., 2023) |
| Ethyl Cellulose-Eutragit S 100-HPMC-Zein | Improved prophylactic action can be used for drug colon targeting; conserved rifampicin release in the stomach and improved tuberculosis care; efficient method to enhance the targeted distribution of active chemicals to the colon. | (Jat et al., 2014); (Pingale and Amrutkar, 2021); (Lee et al., 2023) |
| Starch | Increased resistance to changes in temperature; antioxidant and antibacterial properties were considerably enhanced; the microcapsules containing porous starch and inulin exhibited greater DPPH and ABTS scavenging capabilities compared to free quercetin. | (Farrag et al., 2018); (Yong et al., 2020); (Davoudi et al., 2023) |

compound produced from the hydrolysis of collagen, the predominant protein in skin, tendons, connective tissue, cartilage, and bones. Heating collagen beyond transition temperature produces a combination of protein and peptide fragments of varying sizes. Therefore, gelatin can also be described as collagen experiencing partial hydrolysis (Lv et al., 2019), given the close similarity in the composition. The manufacturing process is responsible for specific alterations in the composition. Collagen synthesis from gelatin occurs by altering many amino acid content (Thakur et al., 2017). Gelatin comprises 18 distinct complex amino acids, with glycine, proline, and hydroxyproline making up around 57% of the composition as the primary constituents. The remaining 43% consists of additional significant amino acid groups, including alanine, arginine, glutamic, and aspartic acid. Gelatin also comprises 25.2% oxygen, 6.8% hydrogen, 50.5% carbon, and 17% nitrogen, while the structure consists of single and double unfolded chains with a hydrophilic character (Alipal et al., 2021).

Similar to collagen, gelatin is typically identified by the repeated triplet (Gly-XY)n. Glycine constitutes one-third of the

**Table 2.** Methods of Application Polymers-Quercetin

| Polymers | Methods | References |
|---|---|---|
| Gelatine-Alginate | Drop-extrusion | (Rubini et al., 2020); (Ezati and Rhim, 2021); (Dhasmana et al., 2022) |
| Maltodextrin-Inulin | High-pressure homogenization; spray drying | (Lai et al., 2015); (Saavedra Leos et al., 2022) |
| Pectin-Casein | Spray drying | (Souza et al., 2021); (Jing et al., 2023) |
| Carnauba Wax | Hot-melt extrusion | (Khor et al., 2017) |
| Chitosan-Fluorescein Isothiocyanate- Zein | Oxidative degradation and ionic cross-linking; coacervation | (Zhou et al., 2022); (Al-Musawi et al., 2023); (Elmowafy et al., 2023) |
| Sodium Alginate | Aerosolization ionic gelation | (Kalalo et al., 2022); (Xu et al., 2023); (Szulc Musioł et al., 2023) |
| Inulin-Chitosan- | Emulsion-assisted gelation, ionic gelation Sodium Alginate | (Nalini et al., 2019); (Liu et al., 2022); (Liu et al., 2023) |
| Glyceryl Behenate | Emulsification | (Chakraborty et al., 2017); (Rosita et al., 2022); (Hariyadi et al., 2022) |
| Chitosan-Polycaprolactone | Ultra-homogenization | (Zhou et al., 2021); (Azeem et al., 2022); (Viscusi et al., 2023) |
| Chitosan | Ionic cross-linking | (Helmy et al., 2020); (Wiggers et al., 2022); (Azeem et al., 2023) |
| Chitosan-Alumina-PLGA-Oleic Acid | Double oil in water emulsification; gelation ionic and spray drying | (Liu et al., 2017); (Lee et al., 2018); (Nematollahi et al., 2021) |
| Alginate-Hydroxyapatite | Gelation method; electrostatic microencapsulation | (Malvano et al., 2021); (Kim et al., 2022); (Montone et al., 2023) |
| Eudragit S100 | Emulsion-solvent diffusion; nanoprecipitation; solvent evaporation | (Jat, 2018); (Sunoqrot and Abujamous, 2019); (Patel and Patel, 2022); (Elizondo Luevano et al., 2023) |
| PLGA | Electro spraying; the double emulsion; oil-in-water emulsion | (Sun et al., 2016); (Nguyen and Jeong, 2018); (Karthick et al., 2019) |
| Nano-Hydroxyapatite | Airflow shearing; electrostatic spraying; | (Han et al., 2022); (Ren et al., 2022); (Lee et al., 2023) |

| Polymers | Methods | References |
|---|---|---|
| Sodium Alginate-Chitosan | Ionic cross-linking; coacervation | (Hazra et al., 2015); (Frenț et al., 2022); (Frent et al., 2023); (Bhadraiah et al., 2023) |
| Ethyl Cellulose-Eutragit S 100-HPMC-Zein | Oil/water emulsification; solvent evaporation | (Jat et al., 2014); (Pingale and Amrutkar, 2021); (Li et al., 2023) |
| Starch | Solution casting | (Farrag et al., 2018); (Yong et al., 2020); (Davoudi et al., 2023) |

chain, while proline or hydroxyproline makes up the other third. The posttranslational alteration of proline and lysine residues into 4-hydroxyproline and $\epsilon$-hydroxylysine, respectively is exclusive to collagen. Gelatin possesses hydrophobic, cationic, and anionic groups in a ratio of 1:1:1. Therefore, positively charged amino acid residues (lysine and arginine residues) constitute approximately 13% of the polypeptide chain in gelatin, negatively charged amino acid residues (glutamic and aspartic acid) make up about 12%, and hydrophobic residues (leucine, isoleucine, methionine, and valine) accounts for 11% (Milano et al., 2023). Figure 9 shows the chemical structure of gelatin.

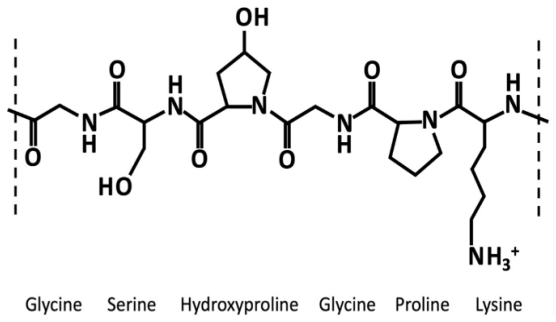


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**Figure 9.** Chemical Structure of a Gelatin $\alpha$-Chain Fragment, Where X and Y Are Typically Proline and Hydroxyproline, Respectively, and the Triplet (Gly-X-Y)n Is Repeated.

Gelatin possesses a distinctive arrangement of amino acids and is derived from hydrolyzing collagen, the primary constituent of connective tissues such as skin, tendon, and bone. Collagen consists of interlinked protein chains and hydrolysis disassembles the complex three-dimensional arrangement to generate gelatin, which both possess a fundamental arrangement of up to 20 distinct amino acids in varying amounts. The amino acid content and sequence of gelatin vary among different sources but always consist of non-polar and polar amino acids. For instance, pig skin and bone gelatin lack cysteine, which is found in fish scales and bones. Conversely, both have a lesser amount of glycine compared to mammalian sources

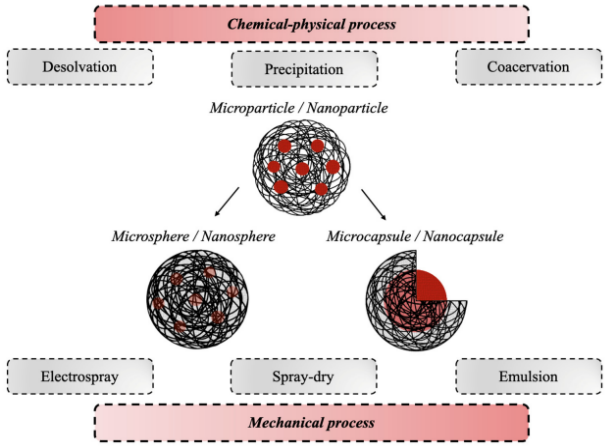


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**Figure 10.** Diagram Showing the Most Popular Production Methods for Gelatin-Based Micro- and Nano-Drug Delivery Systems Synthesis.

(Su and Wang, 2015).

According to the 2011 IUPAC recommendations, polymeric particles of any shape with a diameter of around 0.1–100 $\mu$m and 1–100 nm, are referred to as microparticles and nanoparticles respectively. The two morphological classes that comprise both systems are spheres and capsules, respectively. The drug is physically and uniformly dispersed in the first set of polymeric particles, which are spherical in shape. The second set of polymeric particles consists of at least two-phase domains, with the drug nucleus (fluid or solid) that can be released subsequently and enclosed in an outer layer. Gelatin-based micro- and nano-DDSs can be prepared using a variety of methods, categorized into physico-chemical and mechanical procedures. The precipitation or flocculation of colloidal substances serves as the foundation for the physico-chemical procedures, which also include coacervation, precipitation, and desolvation. On the other hand, mechanical procedures such as electrospray, spray drying, and emulsion rely on the use of certain machin-

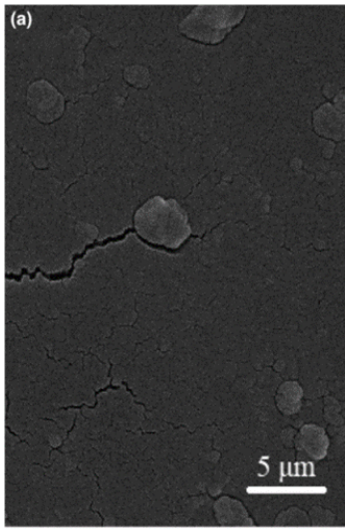


**Figure 11.** Picture of SEM from Pure Gelatin (Mohseni Shahri and Moeinpour, 2023)

ery to create particles (Milano et al., 2023). Figure 10 shows a frequently used method of gelatin utilization, while Figure 11 presents the SEM structure from pure gelatin.

### 3.1.2 Maltodextrin and Inulin

Maltodextrin, a polysaccharide composed of $\beta$-D-glucose units connected primarily by glycosidic linkages is derived by hydrolysis of certain starches such as corn, rice, potato, or wheat using acid or enzymes. Differences in dextrose equivalent (DE) values lead to powders with distinct physico-chemical characteristics, such as bulk density, water absorption, water solubility, hygroscopicity, and porosity. Maltodextrin possesses several significant attributes, including pronounced water solubility, minimal viscosity even at high solid content, lack of flavor and color in solutions, as well as easy accessibility. The application is predominant in products with high moisture content, aiming to mitigate problems related to adhesion and clumping during the storage phase (Lourenço et al., 2020).

Regarding the structure, maltodextrin is composed of D-glucose units linked by an $\alpha$ (1 → 4) glycoside bond. These units are joined in chains of varying lengths, and the DE is less than 20, resulting from the partial hydrolysis of native starch (Figure 8). In water, maltodextrin dissolves quickly and readily, but in alcohol, it becomes practically completely insoluble to barely soluble. The DE value serves as a benchmark for the overall ability of all reducing sugars in the hydrolysate material relative to glucose, which is estimated at 100. High molecule weight maltodextrin, which promotes elasticity and inhibits cracking, is indicative of low DE levels. Additionally, a variety of physical and functional characteristics, including taste and solubility, are influenced by the DE level. Maltodextrin, a nutritious saccharide molecule consisting of polymers made of D-glucose units, has a DE of less than 20. Higher DE rates result in greater hygroscopicity and solubility but decreased viscosity, anti-crystallizing power, and solidification point. In contrast, maltodextrin with a lower DE offers better film-forming qualities and increased viscosity (Olechno et al., 2021). Chemical structure and SEM images of maltodextrin are shown in Figures 12 and 13.

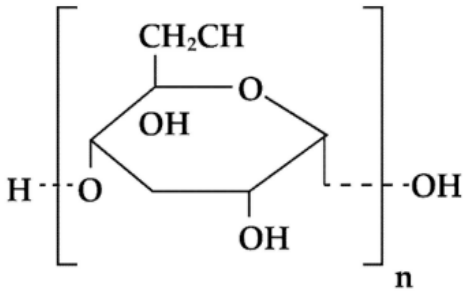


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**Figure 12.** A Schematic Representation of Maltodextrin Structure

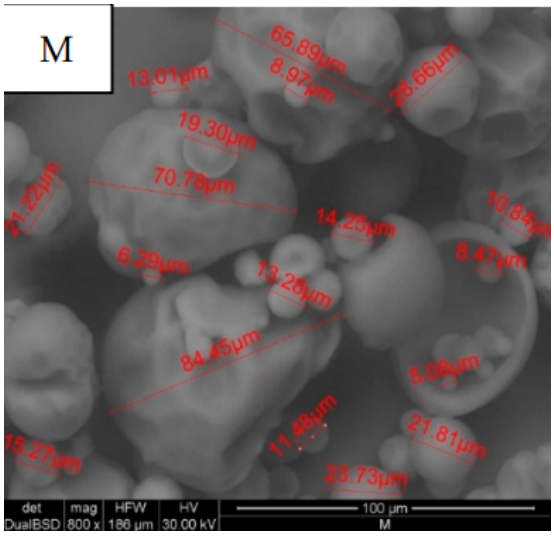


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**Figure 13.** SEM Images of Pure Maltodextrin

Inulin is a storage polysaccharide synthesized by numerous plants and is commonly obtained through industrial extraction from chicory. It is a fructose polymer with a glucose unit at the end of the chain and is widely known for functional activities, such as enhancing the availability of calcium and biological effects, including anti-cytotoxic and immunomodulatory potential. Furthermore, inulin acts as a prebiotic, improving the function of microorganisms favorable to health in the colon. Due to the exclusive release in the intestine, this polymer can safeguard bioactive substances prone to destruction throughout the human digestive tract (Lourenço et al., 2020). Inulin is

categorized as either an oligosaccharide or a polysaccharide, depending on the chain length. It is a member of the fructan carbohydrate subgroup and the structure consists of ß-d-fructose subunits connected by (2 → 1) glycosidic bonds, with a $\beta$-d-glucosyl group typically bound at the end of the molecule through a (1 ↔ 2) linkage. The fructose chains have varying lengths, ranging from 2 to 60 monomers. Oligofructose, which refers to inulin containing a maximum of 10 fructose units is frequently used as a substitute for sweeteners in food, while longer-chain inulin is mainly utilized to replace fats and modify texture. Both inulin and oligofructose are used as dietary fiber and prebiotics in functional meals. However, inulin is more pharmacologically advantageous due to the extended chain length as a distinctive oligo- or polysaccharide without any sugar ring in the backbone. The core component is essentially polyethylene oxide, resulting in a more significant degree of flexibility for the molecule. In addition, inulin is primarily composed of furanose groups, which have greater flexibility than pyranose rings (Mensink et al., 2015).

### 3.1.3 Carnauba Wax

Carnauba wax, with a high melting point, is widely used in food due to the inert and stable components. Currently, various studies are exploring new applications and technologies to improve existing ones, such as microencapsulating flavors, preparing edible films, and creating biodegradable packaging. Carnauba wax is also used in conservation and food processing, with studies focusing on safety aspects, national and international laws, and permitted uses (de Freitas et al., 2019)

Derived from leaves of the Brazilian palm tree (Copernica cerifera), Carnauba wax is commonly applied to fruits as a protective coating for prevention of moisture loss and extension of fruit shelf life. Meanwhile, shellac resin is obtained from the excretions of the Laccifer lacca insect. When combined with other waxes, shellac resin creates a glossy surface. Carnauba-shellac wax can control respiration rate by reducing gas permeability of the fruit surface. Consequently, this leads to a reduction in the amount of weight loss and a glossy surface. Studies have been conducted on edible coatings made of wax for apple slices, but investigations on whole apples are limited. Shellac and aloe-gel-based surface coatings efficiently delay the deterioration of apple-slice characteristics. Additionally, cassava starch-carnauba wax coatings proved effective for preserving freshly sliced apples. A coating of candelilla wax containing ellagic acid demonstrated antifungal barrier properties and prevented any apparent harm to the apple fruits (Jo et al., 2014). This preparation serves a variety of purposes in food, including glazing, body or bulking, acidity regulation, carrier, and anti-caking during surface treatment. Several studies have been conducted to increase the potential applications of Carnauba wax, including the use for flavor microencapsulation and as a source of molecules for the treatment of diabetes, dyslipidemia, or other conditions. Wax is a substance with several potential applications in the food production chain (Figure 10). (de Freitas et al., 2019). The application of carnauba wax is shown in Figure 14, while the chemical structure and SEM images are presented in Figures 15 and 16.

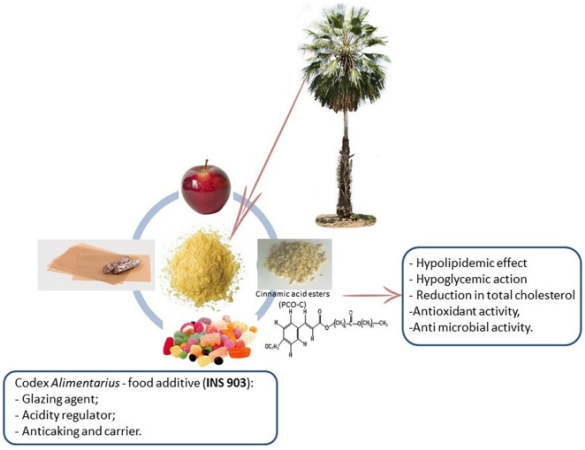


**Figure 14.** Applications of Carnauba Wax in Food and the Pharmacological Effects of the Constituent Ingredients (de Freitas et al., 2019)

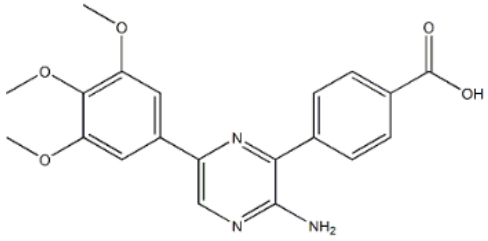


**Figure 15.** Chemical Structure of Carnauba Wax

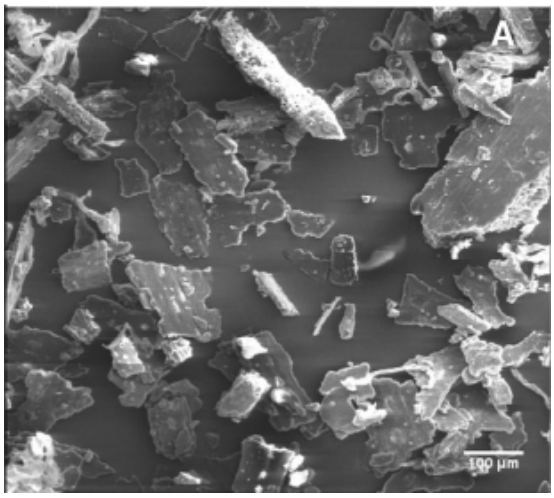


**Figure 16.** SEM Images of Carnauba Wax (Freitas et al., 2016)

### 3.1.4 Poly (Lactic-co-Glycolic Acid) (PLGA)

PLGA, a copolymer composed of repeating units of lactic and glycolic acids is structured as either a block copolymer or a statistical polymer. It has a wide range of molecular weights and can be produced by directly combining lactic and glycolic acids through polycondensation. The rate of biodegradation is contingent upon the composition and microstructure. In this context, the 50:50 ratio of lactic and glycolic acids has the highest degradation rate, leading to the frequent application in nanomedicine. PLGA is soluble in various solvents, with higher amounts of lactic and glycolic acids dissolved in chlorinated and fluorinated solvents respectively. Moreover, the glass transition temperature of PLGA can be leveraged to enhance the release rate. The particles experience functionalization with poly(ethylene glycol) (PEG) to form a "stealth" surface, which enhances blood circulation duration and decreases reticuloendothelial clearance (Swider et al., 2018).

Different varieties of PLGA can be formed depending on the ratio of lactide to glycolide acids used in the polymerization process (Figure 11). These varieties are often recognized based on the ratio of monomers used, for example, PLGA 75:25 indicates a copolymer consisting of 75% lactic acid and 25% glycolic acid. Furthermore, many synthesis methods are used, and the process parameters have a significant impact on the physicochemical properties of the final product. Low molecular weight (MW < 10 kDa) PLGA can be synthesized by solution poly-condensation of GA and LA at temperatures over 120 °C under water-removal conditions (Gentile et al., 2014). The chemical structure and SEM image of pure PLGA are shown in Figures 17 and 18.

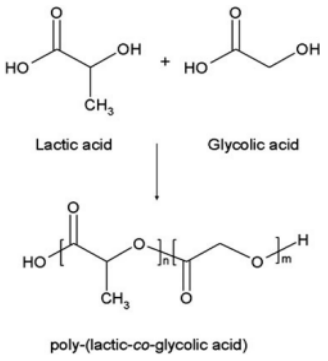


**Figure 17.** Poly(lactic-co-glycolic acid) and Chemical Structures of the Monomers (Gentile et al., 2014)

### 3.1.5 Glyceryl Behenate

Glyceryl behenate is a pharmaceutically approved compound comprising a mixture of glycerol esters of 1-docosanoic or behenic acid, with approximately half of the weight being glyceryl dibehenate. In the liquid phase above melting point, this material can effectively trap both lipophilic and hydrophilic compounds, which are then incorporated into the solid phase upon cooling. The solid mixture is highly water-insoluble, delaying the release of the trapped compounds by a diffusion mechanism controlled by the porosity of the matrix and solubility of loaded substances (Pivette et al., 2014).

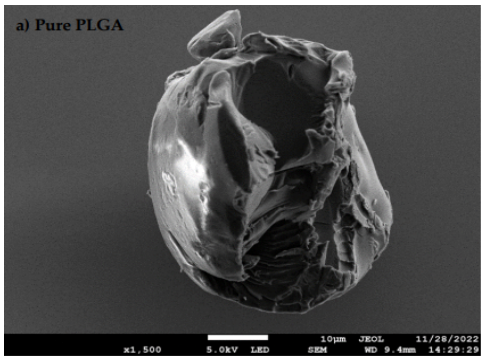


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**Figure 18.** SEM of Pure PLGA

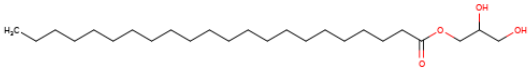


**Figure 19.** Structure of Glyceryl Behenate

Glycerides are a group of compounds used in the field of pharmaceutics for the production of solid dosage forms. Compritol® 888 ATO, a powdered blend of mono-, di-, and tribehenate glycerol, was initially developed as a lubricant for tablet formulations. Over the last ten years, it has been used for controlled-release purposes such as direct compression, hot-melt coating, melt granulation, pelletization, and solid-lipid nanoparticle creation. The complex polymorphism of glyceride mixtures depends on parameters such as crystallization rate and storage temperature. Understanding the thermal and structural behaviors of these mixtures is crucial for pharmaceutical science, food, and cosmetics. Moreover, glycerides are naturally abundant and have biological importance, underscoring the potential as ideal candidates for controlled drug release (Yasir et al., 2023). The structure of glyceryl behenate is shown in Figure 19.

### 3.1.6 Petin

Specific natural polysaccharides, such as pectin and chitosan, maintain stability in the gastrointestinal tract (GIT) but experience colon degradation due to microbes and enzymes. Pectin is a soluble polysaccharide generated from fruits and contains many galacturonic acid (GalUA) units. It experiences gelation as an acidic polymer by interacting with the carboxyl groups in GalUA units and divalent cations such as calcium ions. For example, $Ca^{2+}$ ions bind to both the carbonyl group of two adjacent pectin molecules (intermolecular contact) and the two hydroxyl groups of one molecule (intramolecular interaction), leading to the formation of an "egg-box" gelation structure.

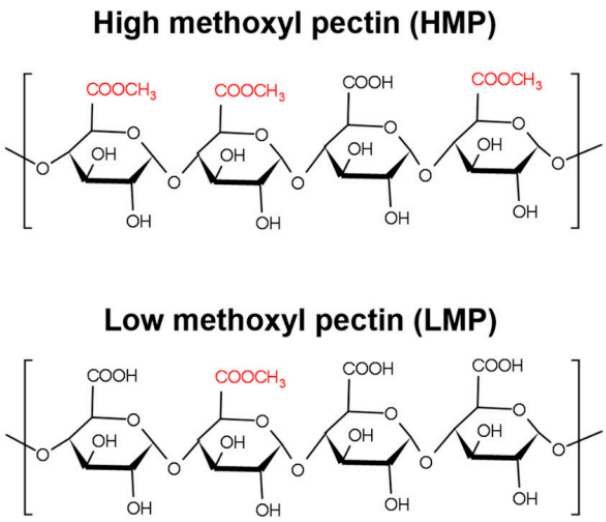


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**Figure 20.** Structure of Pectin

Pectin gels have decreased susceptibility to the acidic pH levels in the stomach (pH 1–2), facilitating slow release and deterioration of drugs in the GIT. However, as the pH in the colon increases, and the anhydrogalacturonate residues become ionized, pectin expands, causing the drug to be released earlier (Jing et al., 2023).

Pectin accumulates in the primary cell walls and middle lamella of higher plants. Dicotyledonous plants have more pectin in the primary cell walls compared to monocotyledonous serving as a cementing material and hydrating agent. This polymer typically has a backbone comprising xylogalacturonan (XGA), homogalacturonan (HG), rhamnogalacturonan-I (RG-I), and rhamnogalacuronan-II (RG-II). The HG areas are composed of $\alpha$-(1-4)-linked-D-galacturonic acid (GalA) units, which may be methyl-esterified at position C-6 and acetylated at position C-2, C-3, or carboxyl groups. The degree of esterification (DE) measures the proportion of methyl-esterified GalA to total GalA groups. Low methoxyl pectin (LMP) has DE less than 50%, while high methoxyl pectin (HMP) has a value greater than 50% (Steigerwald et al., 2021). The chemical structure of HMP and LMP is shown in Figure 20. SEM images of commercial pectin are presented in Figure 21.

### 3.1.7 Nano-Hydroxyapatite

Hydroxyapatite is the primary biomineral constituent present in the hard tissues of humans, such as teeth and bones. The stoichiometry is denoted by the formula ($Ca_{10}(PO_4)_6(OH)$), comprising calcium and phosphorus in a ratio (Ca/P) of 1.67. Hydroxyapatite has garnered significant attention as a biomaterial for prosthetic purposes because it resembles human hard tissue in crystallography and chemical composition (Kantharia et al., 2014).

As the main component of the enamel, hydroxyapatite

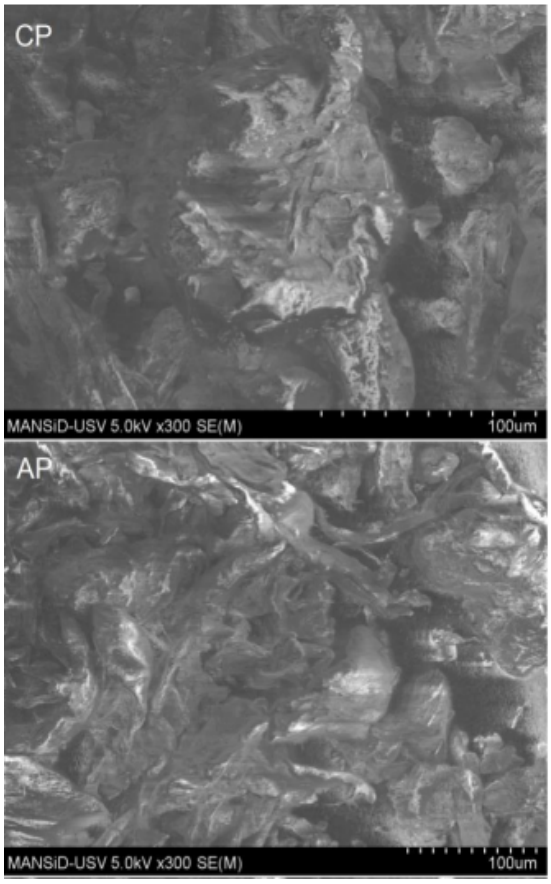


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**Figure 21.** SEM Images from Commercial Citrus Pectin (CP) and Commercial Apple Pectin (AP)

(HA) provides a bright white appearance and eliminates light reflectivity. It is a biocompatible biomaterial and a key source of calcium and phosphate, essential for remineralizing demineralized enamel areas. Meanwhile, nanotechnology is advancing nano-hydroxyapatite application in dentistry, with crystals ranging from 50 to 1000 nm. These nanoparticles bond with proteins, plaque fragments, and bacteria, acting as fillers to repair small holes and depressions on enamel surfaces (Pepla et al., 2014).

Nano-HA crystals are readily dissolved and absorbed in the body due to the extensive surface areas and fragile intercrystalline connections. Moreover, the extensive surface area enhances sintering at elevated temperatures, leading to improved mechanical strength and fracture toughness. Nanocrystalline HA shares a structure comparable to bone apatite with favorable bioactivity, osteoblast adhesion, proliferation, and osseointegration. Furthermore, the particles have attracted significant interest in recent years (Yasir et al., 2023). Chemical structure and SEM images of nano-hydroxyapatite are shown in Figures 22 and 23.

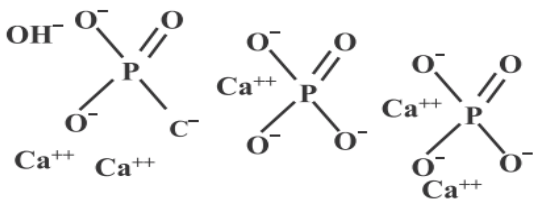


**Figure 22.** Chemical Structure of Hydroxyapatite (Yazdani et al., 2018)

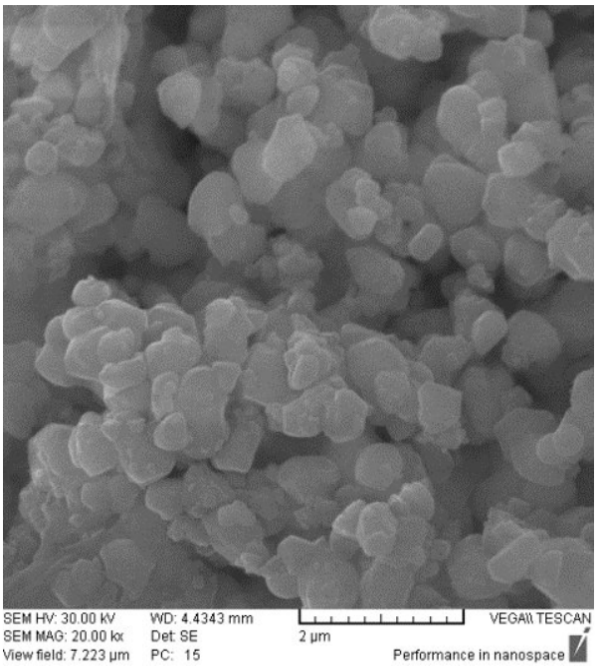


**Figure 23.** SEM mages of Nano-Hydroxyapatite (Sedighi et al., 2017)

### 3.1.8 Polycaprolactone

Polycaprolactone (PCL) is a biodegradable polymer commonly used in biomedical applications and environmentally friendly packaging. The documentation and investigation of the mechanisms behind PCL degradation are inconsistent due to the potential impact of various factors on the polymer behavior over time. These factors include synthesis, end-group chemistry, molecular weight, crystallinity, as well as both pre and post-melt processing. This study examined the various factors contributing to PCL degradation in biomedical applications including polymer structure and shape, radical interactions, temperature, pH, enzyme activity, as well as cellular phagocytosis on degradation (Bartnikowski et al., 2019).

Poly($\epsilon$-caprolactone) (PCL) is an aliphatic polyester that degrades slowly and is commonly used in biomaterial and sustainable packaging applications. Due to the moderate disintegration rate and chemical structure, PCL is well-suited for packaging and medicine, effectively reducing physiological complications. It has a low melting point and favorable rheological characteristics, allowing for the maintenance of stability throughout the range of melting temperatures for extended periods. However, PCL experiences swift thermal deterioration when exposed to temperatures above 170 C °. Other significant aliphatic polyesters, such as poly(lactic acid) and poly(glycolic acid), are susceptible to a heightened possibility of deterioration when subjected to melt processing due to higher melting temperatures (Bartnikowski et al., 2019).

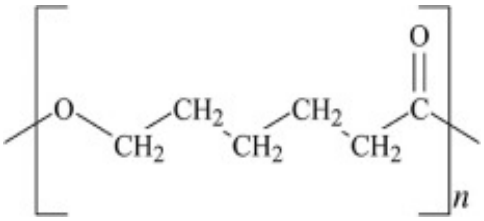


**Figure 24.** Structure of Polycaprolactone

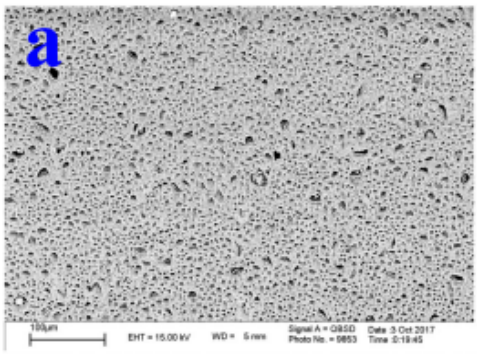


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**Figure 25.** SEM Images of Polycaprolactone (Yaghoubi et al., 2015)

As a member of biodegradable polyesters including polyglycolic acid and poly-L-lactide, PCL is an aliphatic semi-crystalline polymer. The melting temperature ranges from 59 to 64 °C, higher than the average human body temperature. Additionally, it has a glass transition temperature of -60 °C. When exposed to moderate body temperature, the semi-crystalline PCL becomes rubbery, contributing to exceptional toughness and excellent mechanical characteristics such as high strength and elasticity, which vary depending on the molecular weight. Due to the nontoxic nature and compatibility with tissues, PCL is extensively used as resorbable sutures, scaffolds in regenerative medicine, and drug delivery applications. This compound has a prolonged disintegration period of 2-3 years and is broken down by bacteria or through hydrolysis of aliphatic ester bonds in physiological environments. PCL has the slowest degradation rate among all polyesters due to five hydrophobic $-CH_2$ groups in the repeating units. The degradation rate of nano-fiber matrices constructed from polyesters follows the order of polyglycolic acid > polylactic, glycolic acid > poly-L-lactide > polycaprolactone (Dwivedi et al., 2020). Structure

and SEM images of PCL are shown in Figures 24 and 25.

### 3.1.9 Starch

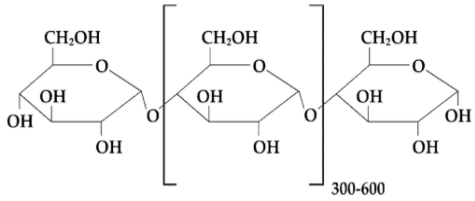




**Figure 26.** Schematic Representation of Starch Structure

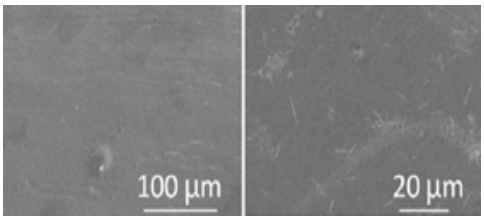


**Figure 27.** SEM Results of Starch (Ali et al., 2017)

Starch and cellulose derivatives can be categorized based on structure, chemical composition, and origin. Natural polysaccharides are extracted from plants, algae, lichens, fungi, and certain microorganisms using various methods for extraction, purification, and separation. The finished products are analyzed for molecular weight, monosaccharide composition, and total sugar concentration. Polysaccharides often possess a high molecular weight and can form numerous inter- and intramolecular interactions due to the available hydroxyl groups. These properties facilitate the ability to greatly enhance the thickness of the substance and induce solidification. Starch and cellulose are crucial in the formation of particles for drug-loaded microstructures and the mechanism by which the polymer matrix/shell expands/degrades as well as release the active component (Lukova et al., 2023). Starch granules consist of three distinct regions, including an amorphous area, crystalline lamellae, and amorphous growth ring. Due to the semicrystalline structure, water at normal temperatures does not dissolve granules but leads to swelling. The branching and open structure allows solvent molecules with hydrogen bonds to access the composition. Furthermore, starch is more disrupted in water than amylose, reacting differently with hot water to cause gelatinization. Due to the low mechanical strength and barrier against low-polarity compounds, the use of starch is limited. For oral films, plasticizers such as sorbitol and glycerol are preferred. Starch dissolves at high temperatures and low concentrations, but the solubility in water presents challenges due to large molecular size and strong hydrogen bonding (Olechno et al., 2021). Schematic representation and scanning electron microscopies (SEM) of starch are shown in Figures 26 and 27.

### 3.1.10 Chitosan

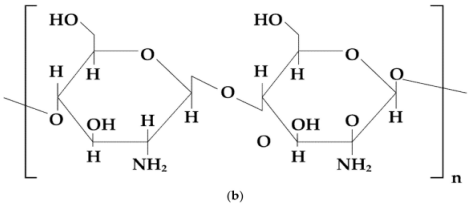




**Figure 28.** Chemical Structure of Chitosan

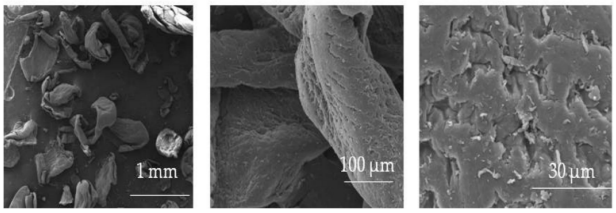




**Figure 29.** Particles of Chitosan Magnified at (a) 100×, (b) 1000×, and (c) 5000×

Chitosan is obtained through the alkaline deacetylation of chitin, a polysaccharide that occurs naturally and may be easily found in marine crustaceans. Due to primary amine groups derived from 2-amino-2-deoxy-$\beta$-D-glucan monomers, the polymer chains possess a cationic character. Chitosan is not soluble in neutral or basic pH but in acetic acid solutions, while the primary benefits include exceptional biocompatibility and minimal toxicity. The beads can release drugs in a regulated manner, underscoring the potential for continuous administration. Microspheres, chitosan beads, and nanoparticles are produced through the utilization of various cross-linking agents, such as glutaraldehyde, trisodium polyphosphate, and sodium lauryl sulfate (SLS) (Muniyandy et al., 2020). Chitosan, a highly adhesive polysaccharide, has been extensively studied for colon delivery due to mucoadhesion and tight-junction regulation. It binds to negatively charged polymers such as pectin and alginate to form polyelectrolytes, which reduce solubility in the GIT. The molecular weight affects microsphere surface coating, with high-Mw chitosan causing steric hindrance and low penetration. Oligochitosan, degraded by colon-specific enzymes and bacteria, can be used as a carrier material for colonic drug delivery, improving the stability and controllability of microspheres (Jing et al., 2023). As a cationic polymer with mucoadhesion properties, chitosan enhances drug penetration through the intestinal mucosa and facilitates transport. Although this polymer offers controlled drug release, gels in situ, nontoxic, and safe for the human body, it disintegrates rapidly in acidic gastric juice, necessitating other anionic poly-

mers for safe, stable, and efficient drug release (Frenț et al., 2022). The chemical structure of chitosan is shown in Figure 28, while SEM images are presented in Figure 29.

### 3.1.11 Eudragit S 100

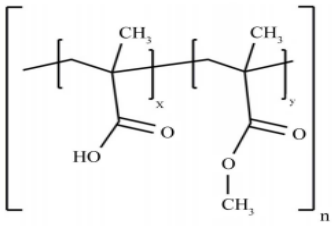

**Figure 30.** Eudragit S100 Structure (Sakhno et al., 2016)

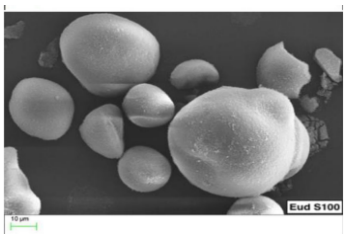


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**Figure 31.** SEM Images from Eudragit S100 (Mustafa et al., 2022)

Eudragit® polymers, which are methacrylic acid copolymers, are frequently used in the pharmaceutical industry to create modified-release film coatings for tablets and capsules. In particular, Eudragit® S100 is the most appropriate form for targeting the colon, with a methacrylic acid to methyl methacrylate ratio of 1:2. In acidic environments such as the stomach, the carboxyl groups of the methacrylic acid units become protonated, while the side chains remain uncharged, causing the polymer to become insoluble. When exposed to neutral or basic pH values, the carboxyl groups become ionized. Consequently, the presence of carboxylate side groups generates unfavorable electrostatic forces, leading to a rise in the ability of the polymer to dissolve in water (Sunoqrot and Abujamous, 2019). The chemical structure and SEM images of Eudragit S100 are shown in Figures 30 and 31.

### 3.1.12 Sodium Alginate

Sodium alginate, a naturally occurring polymer used in the production of microparticles has several benefits, including nontoxicity, biodegradability, biocompatibility, and cost-effectiveness. Hydrogels can be formed by cross-linking sodium alginate in an aqueous solution using divalent cations such as $Ca^{2+}$, $Ba^{2+}$, and $Sr^{2+}$. Among these cations, $Ca^{2+}$ is commonly used due to the nontoxic characteristics [9]. Quercetin-loaded ca-alginate microspheres were created using the aerosolization ionic gelation process and subsequently subjected to freeze drying. The

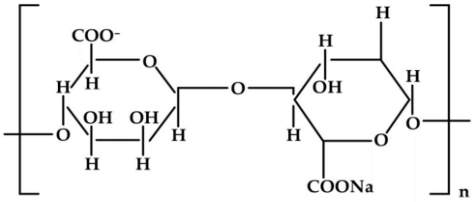

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**Figure 32.** Chemical Structure of Sodium Alginate

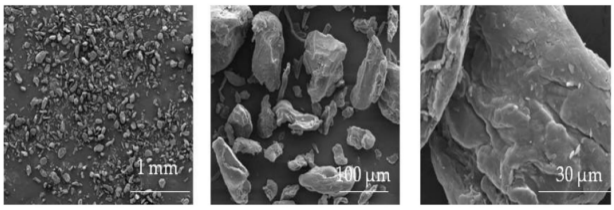


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**Figure 33.** Particles of Sodium Slginate Magnified at (a) 100×, (b) 1000×, and (c) 5000×

results showed that higher concentrations of sodium alginate including 1%, 1.5%, 2%, and 2.5% resulted in reduced drug loading but increased particle size, yield, and entrapment efficiency as well as delayed release of quercetin from the microspheres. During the 28-day stability test, the drug loading levels and entrapment efficiency decreased while the particle size increased with higher concentrations of sodium alginate (Kalalo et al., 2022).

Alginate is a natural polysaccharide safe for the human body and can easily break down over time. It has several benefits in the pharmaceutical industry, including being inexpensive and readily accessible, forming stable gels that can be reversed when needed. Furthermore, alginate can rapidly absorb water to form a thick and sticky substance. The application as a material for microencapsulation creates tiny spheres that release drugs in a controlled manner (Frenț et al., 2022). *In vitro* inflammatory cytokine levels were elevated by quercetin nanogels, which also showed protective properties against protein degradation and antioxidant activity without impairing cell viability, proliferation, or immune response. Quercetin nanogels ingested quickly spread throughout the brain in less than 30 minutes and increased the drug bioavailability by almost 50 times at a lower dosage (Xu et al., 2023). The chemical structure of sodium alginate is shown in Figure 32, while the SEM images are presented in Figure 33.

### 3.1.13 Ethyl Cellulose

Polysaccharides are a significant focus among natural polymers due to the renewable nature as raw materials. Ethyl cellulose is a linear polysaccharide belonging to the semi-synthetic cellu-

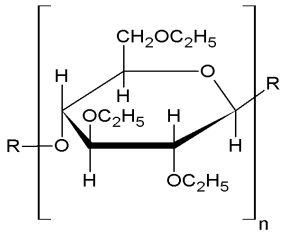


**Figure 34.** Chemical Structure of Ethyl Cellulose

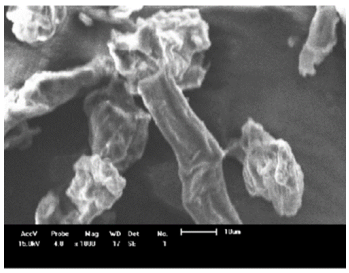

**Figure 35.** SEM Images of Pure Ethyl Cellulose (Bezerra et al., 2014)

lose derivative family. This is an inert polymer that is insoluble in water and hydrophobic, with a relatively cheap cost. The exceptional biocompatibility and biodegradability make ethyl cellulose a promising option for various applications in the food industry, packaging materials, cosmetics, as well as biomedical and pharmaceutical technologies. This hydrophobic polysaccharide has been widely used in biomedical and pharmaceutical industries for over 50 years, with excellent performance in adhesives, fillers, and films, making it valuable in cosmetics, food, and medicine for drug microencapsulation (Alekseeva et al., 2022). Ethyl cellulose has resistance to light, heat, oxygen, moisture, and chemicals, facilitating compatibility with a wide range of plasticizers and resins. This property enables the production of durable and waterproof films (Su et al., 2020). Furthermore, ethyl cellulose is a polymer that is biocompatible, non-irritating, non-toxic, and non-biodegradable. These qualities account for the widespread application as a polymer for oral controlled medication administration (Davidovich Pinhas et al., 2015). The chemical structure and SEM images of ethyl cellulose are shown in Figures 34 and 35 respectively.

### 3.1.14 Alumina

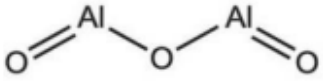


**Figure 36.** Structure of Alumina (Ghalme et al., 2020)

Alumina is extensively utilized as a fundamental substance for catalytic support due to the exceptional chemical inertness,

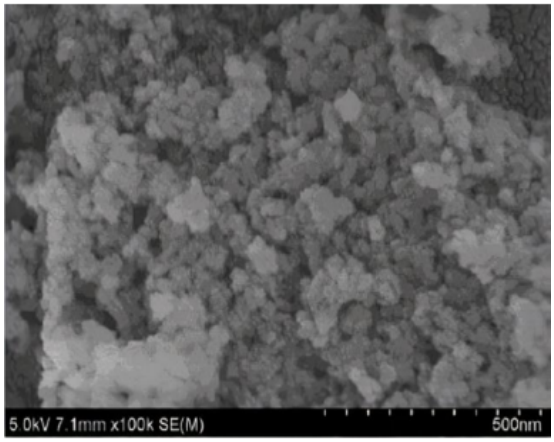


**Figure 37.** SEM Images of Alumina Ghalme et al. (2020)

strength, and hardness. Specifically, $\gamma$-Alumina has excellent surface area due to the small particle size, leading to a high level of surface activity as catalyst support. The exceptional characteristics of mesoporous alumina include consistent channels, a substantial surface area, and a tightly confined dispersion of pore sizes. This material has been extensively used for adsorbent and catalyst support as well as in various ceramic applications. Alumina can be derived from bauxite or kaolin in different stages, and the most stable type, namely $\alpha$-alumina is commonly used as a ceramic material. Transitional alumina, which refers to several forms, is extensively used as catalysts, catalytic supports, or adsorbents. Gamma-alumina is the most often used type for catalysis and adsorption applications due to the superior surface area and favorable porosity characteristics (Paranjpe, 2017). The chemical structure and SEM images of alumina are shown in Figures 36 and 37.

### 3.2 *In vitro* Study of Carriers Containing Quercetin

The capability of polymer composites to improve and assist *in vitro* testing of quercetin was tested. Chitosan is most widely used in quercetin drug carrier systems, either independently or in combination with other types of polymers due to the mucoadhesive property, high permeability, and ability to create a barrier to protect the drug. The nanoparticles have great potential for the penetration of mucous barrier (Mohammed et al., 2017) as well as sustained drug release, and illness detection (Li et al., 2018). The materials also have the capacity to regulate drug release and minimize dosages. Altogether, these actions lead to reduced adverse effects and enhanced drug stability, ultimately leading to increased effectiveness and bioavailability (Jafernik et al., 2023). The *in vitro* test results are shown in Table 3.

### 3.2.1 Gelatin

Quercetin-loaded scaffolds, made from bioactive chemicals and natural biogenic polymers, have been developed for improved tissue regeneration and cell proliferation. These beads, produced from gelatine-alginate-quercetin possess anti-inflammato

**Table 3.** *In vitro* Study of Carriers Containing Quercetin

| Polymers | *In vitro* results | References |
|---|---|---|
| Gelatine-Alginate | Decrease in swelling, an improvement in mechanical properties, and a decrease in denaturation enthalpy; demonstrated significant inhibitory effects on *L. monocytogenes* and *E. coli*; effectively trapped and released quercetin molecules | (Rubini et al., 2020); (Ezati and Rhim, 2021); (Dhasmana et al., 2022) |
| Maltodextrin-Inulin | Produced a dissolution rate similar and significantly greater than bulk quercetin; increased antioxidant activity and viability of quercetin nanocrystals | (Lai et al., 2015); (Saavedra Leos et al., 2022) |
| Pectin-Casein | Anti-inflammatory properties are not yet potent enough to be targeted by paw edema approaches; enhances adhesion and release, making it a viable therapeutic approach | (Souza et al., 2021); (Jing et al., 2023) |
| Carnauba Wax | Lower dissolution rates in salivary pH 6.8 medium | (Khor et al., 2017) |
| Sodium Alginate-chitosan | Enhance bioavailability for various degenerative disorders; entraps 86.07% of quercetin, allowing 24-hour drug delivery into the intestines; show antibacterial and antifungal effects on various strains; the absorption of albendazole and its active metabolite was enhanced. | (Hazra et al., 2015); (Frenț et al., 2022); (Frent et al., 2023); (Bhadraiah et al., 2023) |
| Sodium Alginate | High sodium alginate concentrations increase particle size, yield, and entrapment efficiency; effectively prevent monoamine neurotransmitter depletion and have antidepressant effects on rats, reducing depressive behavior, anhedonia, weight loss, and improving inflammatory cytokine levels; efficiently transport quercetin to the pig skin in an ex vivo setting. | (Kalalo et al., 2022); (Xu et al., 2023); (Szulc Musioł et al., 2023) |
| Inulin-Chitosan-Aodium Alginate | Show no immediate toxicity in animal studies and improves the protective effects of quercetin;. suitable for colonic fermentation; facilitates bacterial activity modulation and potentially mitigates gut dysbiosis | (Nalini et al., 2019); (Liu et al., 2022); (Liu et al., 2023) |
| Glyceryl Behenate | Suppressed the histamine secretion from the mast cells; sustained release, with no impact on lipid amount, and showed potential as an inhalation delivery system; conforming to pulmonary inhalation route specifications. | (Chakraborty et al., 2017); (Rosita et al., 2022) (Hariyadi et al., 2022) |
| Chitosan-Polycaprolactone | Excellent biocompatibility and antioxidant/bactericidal properties; alternative to antioxidant/bactericidal properties; alternative to antibiotics in treating gastroenteritis; the capacity of quercetin-loaded membranes to decrease cell viability in human cell lines under two distinct situations. | (Zhou et al., 2021); (Azeem et al., 2022) (Viscusi et al., 2023) |

| Polymers | *In vitro* results | References |
|---|---|---|
| Chitosan | Potent for treating acute inflammatory bowel disease due to appropriate pharmacological properties; modulating the release kinetics of the loaded trimethoprim while preserving its bactericidal properties; antioxidant characteristics have been verified. | (Helmy et al., 2020); (Wiggers et al., 2022); (Azeem et al., 2023) |
| Chitosan-Alumina-PLGA-Oleic Acid | Prolonged circulation duration suggests potential pulmonary delivery strategies for hydrophobic anticancer medicines; prolonged release profiles of quercetin; enhanced cytotoxicity and anticancer properties | (Liu et al., 2017); (Lee et al., 2018); (Nematollahi et al., 2021) |
| Alginate-Hydroxyapatite | Rapid and uniform release of the quercetin glycoside molecule through the coatings, achieving equilibrium after 24 hours; potential as drug and cell delivery vehicles; high effectiveness in inhibiting the increase of total viable bacterial count, psychoactive bacteria count, *Pseudomonas* spp., and *Enterobacteriaceae* over a 15-day period at 4 °C | (Malvano et al., 2021); (Kim et al., 2022); (Montone et al., 2023) |
| Eudragit S100 | Effectively counteract sulfur mustard-induced toxicity; demonstrated higher potency in CT26 colon cancer cells; delays the release of quercetin in the upper gastrointestinal system, showing efficient targeting of the medication to the colon; the hemolytic activity of polymer and quercetin was evaluated in human red blood cells, showed no significant cytotoxic effects as compared to the control group. | (Jat, 2018); (Sunoqrot and Abujamous, 2019); (Patel and Patel, 2022); (Elizondo Luevano et al., 2023) |
| Nano-Hydroxyapatite | Potentially contribute to drug delivery platforms and clinical applications; sustain quercetin release, regulate osteogenesis genes, promote bone marrow stem cell migration; and regeneration in a rat model | (Han et al., 2022); (Ren et al., 2022); (Lee et al., 2023) |
| Chitosan-Fluorescein Isothiocyanate-Zein | Potentially valuable for physical therapy and chemotherapy; offering dense, mechanical, high porosity, thermal stability, and antioxidant activity; recommended as a viable platform for colon drug delivery. | (Zhou et al., 2022); (Al-Musawi et al., 2023); (Elmowafy et al., 2023) |
| Ethyl Cellulose-Eutragit S 100 -HPMC | Enhance absorption, bioavailability, specific drug targeting, reduced dose, and patient compliance; conserve rifampicin release in the stomach and improve tuberculosis care; demonstrate comparable antioxidant properties and ability to inhibit HCT-116 cells like unbound quercetin. | (Jat et al., 2014); (Pingale and Amrutkar, 2021); (Li et al., 2023) |

ry, anti-oxidative, and nontoxic properties, which are significantly influenced by the concentration of quercetin. *In vitro* studies show successful entrapment and controlled release of quercetin molecules (Dhasmana et al., 2022). The antibacterial activity of the films was tested *in vitro* against *S. aureus* (ATCC 25923) with *E. coli* (ATCC25922), selected as controls and representative strains for Gram-positive and Gram-negative bacteria.

| Polymers | *In vitro* results | References |
|---|---|---|
| Starch | Increased resistance to changes in temperature; increased reducing power, free radical scavenging activity, and antibacterial action against *E. coli, S. aureus, Salmonella,* and *L. monocytogenes*; the twofold encapsulation of quercetin by porous starch and inulin resulted in a more consistent release of quercetin in the colon. | (Farrag et al., 2018); (Yong et al., 2020); (Davoudi et al., 2023) |

The gelatin-quercetin films in this investigation showed no action against *S. aureus* and *E. coli*, regardless of the assay method used. The outcome may be attributed to the low quercetin content of the films. Among the film samples, none contained a quercetin concentration sufficient to reach the Minimum Inhibitory Concentration (MIC) required to stop bacterial growth, despite having 3.8% quercetin loaded and weighing 5.39 mg. The highest concentration of quercetin in the PBS solution used in the broth microdilution assay was 20 $\mu$g/mL. The MIC values for pure quercetin are 125 $\mu$g/mL for *S. aureus* and 500 $\mu$g/mL for *E. coli* (Rubini et al., 2020). Furthermore, the films with additional quercetin showed antioxidant and antibacterial properties depending on the release rate. The gelatin/quercetin films showed considerable inhibitory effects on *L. monocytogenes* and *E. coli* (Ezati and Rhim, 2021). The *in vitro* test results using gelatine-alginate as polymers are shown in Table 4.

### 3.2.2 Maltodextrin and Inulin

A functional food powder was created by blending carbohydrate polymers, such as maltodextrin and inulin, with active chemicals that have probiotic and antioxidant characteristics. The powders comprised microorganisms encapsulated at a microscopic level and particles that were not agglomerated. The inclusion of inulin and maltodextrin increased both antioxidant activity and viability. The inulin-maltodextrin blends demonstrated superior encapsulation efficiency, and the drying temperature had a minimal impact on the yield. This study underscored the advantages of using carbohydrate polymer blends for the microencapsulation and conservation of active molecules containing furanose groups, which had greater flexibility than pyranose rings (Lourenço et al., 2020). Bulk quercetin had the slowest dissolve rate, but quicker dissolution profiles were achieved by testing both free and film-loaded nanocrystals. After five minutes, the percentages of quercetin dissolved from the fast-dissolving films, freeze-dried quercetin nanocrystals, and quercetin raw material were 66.73%, 54.65%, and 5.20%, respectively (Lai et al., 2015). The antioxidant activity and viability showed synergistic effects when combined with inulin-maltodextrin blends. Inulin enhanced antioxidant activity, while maltodextrin improved viability (Saavedra Leos et al., 2022). The *in vitro* test results of using maltodextrin-inulin as polymers are shown in Table 5.

### 3.2.3 Carnauba Wax

The microencapsulated powders showed a considerably reduced dissolving rate in the simulated saliva with a pH of 6.8 compared to the non-encapsulated quercetin. Therefore, zein, carnauba wax, and shellac were considered most efficient in concealing the flavor. The electronic tongue bitterness test *in vitro* showed that the microencapsulated powders could effectively mask the flavor. Based on the *in vitro* digestion results, the rates at which carnauba wax and shellac-microencapsulated powders, as well as pure quercetin, dissolved were similar in a medium with a pH of 1.0 and 6.8, representing the gastric and intestinal environment respectively. Conversely, the rate at which zein-microencapsulated powders dissolved was significantly slower than the other powders. The chemical structure of quercetin remained the same, but the crystallinity decreased with microencapsulation. This implies that the hot-melt extrusion microencapsulation technique can be attractive for producing bioactive powders (Khor et al., 2017). The *in vitro* test results using carnauba wax as polymers are shown in Table 6.

### 3.2.4 Poly (lactic-co-glycolic acid) (PLGA)

The study found that quercetin effectively encapsulated 74 ± 1.2% of PLGA microspheres, showing anticancer potential. The biodegradable PLGAq microspheres, assessed using cytotoxicity and flow cytometric studies, showed significant inhibition of cancer cells at higher doses. These biodegradable microspheres have the potential to be a promising therapeutic approach for cancer (Karthick et al., 2019).

The loading capacity of the microspheres was 7.77 ± 0.15%, while the drug encapsulation efficiency was 81.84 ± 1.60%. There was no indication of sudden release during a 30-day long-lasting release pattern of quercetin in a laboratory setting. Furthermore, a cytotoxicity analysis showed that the exposure of INS-1 cells to PLGA microspheres had no detrimental consequences. This study suggests that the electrospray technique can manufacture quercetin-loaded PLGA microspheres (Nguyen and Jeong, 2018).

Quercetin was encapsulated within microspheres made of poly(lactic-co-glycolic acid) and subsequently analyzed using a scanning electron microscope. Silicon elastomer-based concave microwells were utilized to create three-dimensional cell spheroids. The results showed that quercetin-loaded microspheres increased alkaline phosphatase activity, Runx2 protein

**Table 4.** *In vitro* Study of Gelatine-Alginate Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Gelatine-Alginate | Decrease in swelling, an improvement in mechanical properties, and a decrease in denaturation enthalpy | (Rubini et al., 2020) |
| Gelatine-Alginate | Significant inhibitory effects on *L. monocytogenes* and *E. coli* | (Ezati and Rhim, 2021) |
| Gelatine-Alginate | The gelatine-alginate-quercetin beads were designed to effectively trap and release quercetin molecules | (Dhasmana et al., 2022) |

**Table 5.** *In vitro* Study of Maltodextrin-Inulin Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Maltodextrin-Inulin | Showed a dissolution rate similar and significantly greater than that of bulk quercetin | (Lai et al., 2015) |
| Maltodextrin-Inulin | Increased antioxidant activity and viability of quercetin nanocrystals | (Saavedra Leos et al., 2022) |

**Table 6.** *In vitro* Study of Carnauba Wax Polymers Containing Quercetin

| Polymer | *In vitro* Results | References |
|---|---|---|
| Carnauba Wax | Lower dissolution rates in salivary pH 6.8 medium | (Khor et al., 2017) |

expression, and mineralization. These biodegradable microspheres could enhance osteoblastic differentiation in cell therapy (Lee et al., 2018).

Intraperitoneal administration of PLGA-quercetin nanoparticles to APP/PS1 mice improved cognitive and memory impairments, with no harmful effects from systemic toxicity. This suggests that PLGA-quercetin nanoparticles are suitable for safe biomedical applications, particularly in treating Alzheimer's disease. The results have significant implications for investigations and practical use of nanoparticles in disease treatment (Sun et al., 2016).

Microparticles composed of L-lactide and 1,3-dioxolane demonstrated sensitivity to acidic pH and accelerated release of quercetin due to the restricted solubility. The antiradical activity and hydrophilic-hydrophobic characteristics enable microparticles to inhibit all tested bacteria strains. The antibacterial action of quercetin was enhanced through encapsulation (Kost et al., 2022). The *in vitro* test results of using PLGA as polymers are shown in Table 7.

### 3.2.5 Glyceryl Behenate

The formation of Solid Lipid Microparticles (SLM) comprises the combination of lipids and surfactants, namely Glyceryl Behenate and Poloxamer 188 respectively. The SLM was manufactured using the melt oil-in-water emulsification method and dehydrated using a freeze dryer. This study examined the system's potential for delivering lipophilic active drugs, such as quercetin, into the lungs. Due to the inclusion of lipids in the formulation, this approach offers several advantages, such as excellent tolerability, regulated release, protection against severe conditions, and minimized risk of adverse effects. The results showed that the physical and chemical characteristics of the SLM and the drug's release pattern were affected by the composition of the formulation and the manufacturing technique used. Future studies should prioritize examining tests related to mass median aerodynamics and *in vivo* investigation (Rosita et al., 2022).

A lipid microparticle system was created by using glyceryl behenate and poloxamer 188 as the lipid and surfactant polymers respectively. Quercetin was synthesized as a desiccated powder. The solid lipid microparticle (SLM) delivery system demonstrated favorable physical properties, including moisture

**Table 7.** *In vitro* Study of PLGA Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| PLGA | Potentially impacted Alzheimer's disease treatment when administered intraperitoneally to APP/PS1 mice | (Sun et al., 2016) |
| PLGA | Minimal burst release and no harmful effects when exposed to INS-1 cells | (Nguyen and Jeong, 2018) |
| PLGA | Effectively inhibited cancer cells at higher concentrations | (Karthick et al., 2019) |

content, yield, high drug loading, and entrapment efficiency. In addition, the augmentation of the surfactant concentration in poloxamer 188 from formula 1 to 5 (0.2% to 2%) led to the anticipated formation of smooth and spherical particles, as well as enhanced flow characteristics. The surfactant poloxamer 188 concentration was increased to extend the period when quercetin was released. The SLM quercetin yielded particles with a size of less than 5µm, which met the requirements for pulmonary inhalation. Furthermore, aerodynamic mass median (MMAD) testing has been conducted to ascertain the proportion of powder deposited on the alveolar surface, validating the ability of SLM quercetin to penetrate the alveoli (Hariyadi et al., 2022). An *in vitro* investigation was carried out to measure the cumulative drug release percentage over a prolonged duration. The parameter is crucial as it impacts both the quantity of medicine released over a set period and the release pattern. The results showed that 88.7±1.5% of quercetin was liberated from the formulation after 504 hours (Chakraborty et al., 2017). The *in vitro* test results of using glyceryl behenate as polymers are shown in Table 8.

### 3.2.6 Pectin

During the acute phase, quercetin-based inflammatory bowel disease treatment relies on local colon activity. An oral microsphere system was developed for colon-specific administration, which responded to the microenvironment, producing drug release as well as better stability and less stomach swelling than chitosan-treated microspheres. The oligochitosan coating improved colon adhesion and release, suggesting the value for surface modification applications in colon delivery and disease treatment. The long-term use and food-derived components make the microsphere a viable therapeutic approach (Jing et al., 2023).

Quercetin is efficiently enclosed within the polymeric matrix composed of pectin and casein. Administering quercetin encapsulated in oral form at 10 mg per kilogram substantially reduced oxidative stress in the liver and brain of rats with adjuvant-induced arthritis during an extended treatment period. The administration in this manner also did not cause any harm to the liver or mitochondria. However, the anti-inflammatory properties were insufficiently strong to be detected by the paw edema approach. The phenomenon illustrates that the existence of pectin/casein microcapsules loaded with quercetin can alter levels of oxidative stress without significantly affecting inflammation. This discovery provides evidence for the continued utilization of quercetin as a long-term treatment for rheumatoid arthritis, specifically as a supplement with antioxidant properties (Souza et al., 2021). The *in vitro* test results of using pectin as polymers are shown in Table 9.

### 3.2.7 Nano-Hydrohepatite

Microspheres with an eyeball-shaped structure composed of quercetin, nano-hydroxyapatite, and poly(glycolide-co-epsilon-caprolactone) were successfully manufactured through airflow shearing. These materials have exceptional encapsulation efficiency and a consistent release pattern. The application of microspheres resulted in a beneficial immunological milieu, as demonstrated by laboratory studies and animal investigations. Microspheres had a significant impact on successful bone repair by influencing the polarization of M2 macrophages and enhancing osteo-differentiation in Bone Marrow Stem Cells. The airflow shearing method had a potential role in constructing a drug delivery platform. Moreover, the combination of quercetin, nano-hydroxyapatite, and poly(glycolide-co-epsilon-caprolactone) in composite microspheres showed potential as cutting-edge materials for bone-filling purposes. The precise control of osteogenesis was proposed as a novel approach to bone regeneration (Han et al., 2022).

A recent investigation used electrostatic spraying to generate hydroxyapatite microparticles of uniform dimensions ranging from 50 to 150 $\mu$m without requiring intricate arrangements or additional stages. Laboratory experiments conducted *in vivo* and *in vitro* further confirmed that the newly developed hydroxyapatite microbeads could carry quercetin and bone morphogenetic protein-2, promoting bone growth. Furthermore, the concurrent administration of bone morphogenetic protein-2 and quercetin using hydroxyapatite beads resulted in a synergistic impact on the regrowth of bone in a rat model with calvarial abnormalities. The study showed that electrostatic spraying was an effective technique for producing ceramic granules. Hydroxyapatite microbeads containing quercetin and bone morphogenetic protein-2 also reportedly

**Table 8.** *In vitro* Study of Glyceryl Behenate Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Glyceryl Behenate | Suppressed the histamine secretion from the mast cells | (Chakraborty et al., 2017) |
| Glyceryl Behenate | Sustained release, with no impact on lipid amount, and shows potential as an inhalation delivery system | (Rosita et al., 2022) |
| Glyceryl Behenate | Conformed to pulmonary inhalation route specifications. | (Hariyadi et al., 2022) |

**Table 9.** *In vitro* Study of Pectin Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Pectin-Casein | Anti-inflammatory properties were less sufficient to be targeted by paw edema approaches. | (Souza et al., 2021) |
| Pectin | Enhanced adhesion and release, making it a viable therapeutic approach. | (Jing et al., 2023) |

**Table 10.** *In vitro* Study of Nano-Hydroxyapatite Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Nano-Hydroxyapatite | Potentially contributed to drug delivery platforms and clinical applications. | (Han et al., 2022) |
| Nano-Hydroxyapatite | Sustain quercetin release, regulate osteogenesis genes, and promote bone marrow stem cell migration. | (Ren et al., 2022) |
| Hydroxyapatite | Promote bone growth and regeneration in a rat model. | (Lee et al., 2023) |

**Table 11.** *In vitro* Study of Polycaprolactone Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Chitosan-Polycaprolactone | Excellent biocompatibility and antioxidant/bactericidal properties | (Zhou et al., 2021) |
| Chitosan-Polycaprolactone | Alternative to antibiotics in treating gastroenteritis | (Azeem et al., 2022) |
| Chitosan-Polycaprolactone | The capacity of quercetin-loaded membranes to decrease cell viability in human cell lines under two distinct situations. | (Viscusi et al., 2023) |

functioned as highly efficient implants for the treatment of bone abnormalities (Lee et al., 2023). A novel composite material consisting of quercetin-alpha-calcium sulfate hemihydrate and nano-hydroxyapatite has been developed for quercetin

**Table 12.** *In vitro* Study of Starch Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Starch | Increased resistance to changes in temperature; increased reducing power; | (Farrag et al., 2018) |
| Starch | Free radical scavenging activity, and antibacterial action against *E. coli, S. aureus*, *Salmonella*, and *L. monocytogenes* | (Yong et al., 2020) |
| Starch | The twofold encapsulation of quercetin by porous starch and inulin resulted in a more consistent release of quercetin in the colon. | (Davoudi et al., 2023) |

delivery and controlled release. This material can increase the expression of genes specific to the formation of bone tissue, effectively enhancing the migration, mineralization, proliferation, and maturation of bone marrow stem cells. Significant anti-inflammatory effects were also found when tested in a laboratory setting. Furthermore, quercetin-alpha-calcium sulfate hemihydrate/nano-hydroxyapatite showed substantial reparative properties in living organisms, showing superior ability to induce bone growth and exceptional compatibility with biological systems. These results suggest potential application as an ideal substitute for natural bone grafts. Quercetin and calcium ions modified the microenvironment of the modeling region and enhanced the expression of RUNX2, OSX, and OCN (Ren et al., 2022). The *in vitro* test results of using nano-hydroxyapatite as polymers are shown in Table 10.

### 3.2.8 Polycaprolactone

Ultra-homogenization was used to create three distinct types of microspheres namely chitosan-polycaprolactone (CS-PCL-Ms), quercetin-polycaprolactone (QT-PCL-Ms), and chitosan-quercetin-polycaprolactone (CS-QT-PCL-Ms). These microspheres were loaded with levofloxacin, and the antibacterial effects against *Pseudomonas aeruginosa* 15692, *Staphylococcus aureus* 12600, and *Escherichia coli* 25922 were assessed by measuring the particle size, charge, antioxidant, hemolytic, and *in vitro* drug release. The antibacterial effect of the loaded microspheres was confirmed by evaluating histological alterations, weight loss, and diarrhea scores in an *in vivo* antidiarrheal model. Based on the results, CS-QT complex and its levofloxacin-loaded microspheres (CS-QT-PCL-Levo-Ms) demonstrated an increase in bactericidal activity against *E. coli* and *P. aeruginosa* of more than twofold, while against *S. aureus*, it was only 1.5 fold.

The synergistic effects of quercetin (QT) and chitosan (CS) also improved the antioxidant properties of the CS-QT complex. All microspheres used at 5 $\mu$g/100 $\mu$L on albino rats did not cause any skin discomfort, yielding < 5% hemolytic effect and < 0.5 PDI value. Based on the first-order release behavior, CS-QT-PCLLevo-Ms had less than 50% release within 16 hours in phosphate buffer pH 6.8.

Stability experiments indicated a 30-month shelf life for the CS-QT-PCL-Levo-Ms complex. The microsphere-shaped CS-QT complex, which possesses synergistic antibacterial and antioxidant capabilities, can serve as a viable substitute for currently available antibiotics in the treatment of gastroenteritis (Azeem et al., 2022). Quercetin was gradually released, promoting wound healing and prolonged bacteriostasis. A faster decline was also demonstrated compared to rutin due to high instability and easy decomposition in neutral and alkaline environments. Limited release and rapid breakdown of quercetin may hinder the use in burn treatments (Zhou et al., 2021). The release rate of quercetin was studied in PBS and pH = 3 solutions to mimic the conditions of a skin lesion. The data were analyzed using the Gompertz model, showing that quercetin was released more slowly in an acidic environment, as shown by the diffusion coefficients. The photostability of quercetin-loaded membrane was assessed by exposure to UV-A lamp irradiation for up to 10 hours, showing stability of the encapsulated compound in the fibers even under prolonged treatment. The quercetin released from membranes retained the biological activity, as indicated by the cytotoxic effects on cultured cells (Viscusi et al., 2023). The *in vitro* test results of using polycaprolactone as polymers are shown in Table 11.

### 3.2.9 Starch

Experiments were conducted to investigate the release of quercetin through the films in a mixture of water and ethanol. The release reached equilibrium after 1-4 days for films constructed from cereal starch, while those made from legumes required more than a week to achieve the same equilibrium. The data was analyzed using the Peppas-Sahlin model, indicating that the release kinetics were governed mainly by fiction diffusion. The main applications of the produced biofilms are active food packaging (Farrag et al., 2018). Corn starch was effectively modified with quercetin through an acid-catalyzed condensation process. The resulting conjugate was soluble in water and showed optimal grafting efficiency. All instrumental investigations verified that quercetin was well attached to starch aldehyde. The conjugate demonstrated distinct structural features compared to native and starch aldehyde. The antioxidant

 

**Table 13.** *In vitro* Study of Chitosan Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Chitosan-Sodium Alginate | Entraps 86.07% of quercetin, allowing 24-hour drug delivery into the intestines. | (Frenț et al., 2022) |
| Chitosan-Sodium Alginate | Show antibacterial and antifungal effects on various strains. | (Frent et al., 2023) |
| Chitosan | Potential for treating acute inflammatory bowel disease due to appropriate pharmacological properties. | (Helmy et al., 2020) |
| Chitosan | Antioxidant characteristics have been verified. | (Azeem et al., 2023) |
| Chitosan | Modulates the release kinetics of the loaded trimethoprim while preserving the bactericidal properties | (Wiggers et al., 2022) |
| Chitosan-Zein | Offering dense, mechanical, high porosity, thermal stability, and antioxidant activity. | (Al-Musawi et al., 2023) |
| Chitosan- PLGA | Prolonged release profiles of quercetin. | (Lee et al., 2018) |
| Chitosan-Fluorescein Isothiocyanate | Potentially valuable for physical therapy and chemotherapy. | (Zhou et al., 2022) |
| Chitosan-Alginate | The absorption of albendazole and its active metabolite was enhanced | (Bhadraiah et al., 2023) |
| Chitosan-Oleic Acid | Prolonged circulation duration suggests potential pulmonary delivery strategies for hydrophobic anticancer medicines. | (Liu et al., 2017) |
| Chitosan-Inulin | Show no immediate toxicity in animal studies and improve the protective effects of quercetin | (Nalini et al., 2019) |
| Inulin-Chitosan-Sodium Alginate | Suitable for colonic fermentation. | (Liu et al., 2022) |
| Chitosan-Zein | Recommended establishing a viable platform for delivering to the colon. | (Elmowafy et al., 2023) |

and antibacterial properties of starch aldehyde significantly increased upon conjugation with quercetin. The results showed that an acid-catalyzed condensation procedure was appropriate for producing starch aldehyde-polyphenol conjugates (Rubini et al., 2020), with potent antibacterial effects against *E. coli* and *S. aureus*. The antibacterial activity was significantly increased by integration with quercetin, which has strong antimicrobial properties (Yong et al., 2020). Incorporating inulin into the porous starch effectively safeguards quercetin during the process of digestion. Biologically active compounds with poor water solubility have limited bioavailability, hindering the effective transport of the desired molecule. Based on the results, the porous starch-inulin matrix is a suitable carrier for regulating the release of quercetin in simulated gastrointestinal settings (Davoudi et al., 2023). The *in vitro* test results of using starch as polymers are shown in Table 12.

### 3.2.10 Chitosan

Chitosan is often combined with Na alginate in microsphere formulations, forming microparticles with varying sizes. The highest chitosan concentration entraps 86.07% of quercetin, enabling regulated drug delivery into the intestines. These microspheres possess a textured surface, dense structures, and creases, with thermal stability facilitating the application for delivering drugs at physiological temperatures (Frenț et al., 2022).

Polymeric microspheres, with a size range of 1 to 5 $\mu$m, may be easily dispersed in water and have controlled release characteristics at pH 4.5 and 7.4. These microspheres have a high concentration in the lung and a prolonged circulation time, indicating prospective use as a pulmonary delivery method for hydrophobic anticancer drugs (Liu et al., 2017). Inulin filling and chitosan coating in the alginate polymer network increase gel strength and encapsulation efficiency. Alginate+inulin+chitosan+quercetin performed better than other formulations, leading to the selection for colonic fermentation. Quercetin release was delayed but occurred within 3 hours and was entirely metabolized by the microbiota within 24 hours. Alginate+inulin+chitosan+quercetin microspheres showed promise for targeted quercetin transport to the colon (Liu et al., 2022). Furthermore, quercetin was entrapped by chitosan-sodium alginate-quercetin microspheres (Caq-MS), releasing 71.46 ± 0.25˜91.06 ± 0.15% *in vitro*. The smoothness and roughness of the microspheres increased with higher polymer concentration. Caq-Ms demonstrated antibacterial and antifungal properties against several strains, resulting in broader inhibition zones against *Escherichia coli*, and *Candida albicans*, as well as smaller zones against Staphylococcus aureus (Frent et al., 2023).

Fluorescein isothiocyanate was successfully used to label chitosan-quercetin drug-loaded nanoparticles, demonstrating antioxidant qualities, encapsulation effectiveness, and drug-loading efficiency. The drug-loaded rate was 8.39%, and encapsulation rate was 83.65%. The fluorescence aperture matched the antibacterial circle, providing a method for tracking medication release and activity. This new encapsulation structure could be used in physical therapy and chemotherapy (Zhou et al., 2022). The administration of albendazole and quercetin-impregnated chitosan alginate microspheres enhanced the absorption of albendazole and increased the bioavailability of the active metabolite, albendazole sulphoxide (Bhadraiah et al., 2023).

Quercetin microparticle formulations were tested for the pharmacological, morphological, and compatibility properties. A significant proportion was released in the IBD colon-mimicking medium and therapeutic effects were assessed using a rabbit colitis model. The results showed that quercetin microparticles had better therapeutic effects than simple medication and untreated animals, suggesting potential use in acute inflammatory bowel disease treatment (Helmy et al., 2020).

Chitosan-quercetin-polycaprolactone-Levofloxacin-Ms sho wed increased bactericidal activity against *E. coli* and *P. aeruginosa*, reaching up to 1.5 times against S. aureus. The antioxidant properties were confirmed through green-colored phosphate molybdate complexes. Furthermore, the use of maleic acid, *in vitro*, and *in silico* antimicrobial studies confirmed the potential as a treatment strategy (Azeem et al., 2023). Gallic acid is incorporated into chitosan-basil seed gum hydrogel, forming hydrogen bonds. The hydrogel possesses a compact microstructure, favorable mechanical characteristics, substantial porosity, thermal durability, and a notable swelling ratio. Due to the elevated antioxidant activity and biocompatibility, the hydrogel has great potential as a material for tissue engineering. Cell culture tests confirmed the nontoxic and biocompatible nature (Al-Musawi et al., 2023). The drug release from the microparticles showed reduced loss in the simulated stomach and intestine fluids as well as fast, specific release in environments mimicking Inflammatory Bowel Disease colon (Helmy et al., 2020). However, the release rate of quercetin reduced in pH 5.5 and 6.5 compared to 7.4, eventually reaching maximum capacity (Nalini et al., 2019). The *in vitro* test results of using chitosan as polymers are shown in Table 13.

### 3.2.11 Eudragit S 100

Quercetin microspheres can mitigate the harmful effects caused by exposure to Sulfur mustard. The drug release profile of Eudragit-based microspheres was highly favorable, with a release rate of up to 99% and an optimal particle size of 60.89 ± 1.91 $\mu$m. The drug was wholly assimilated in the polymer, with 73% drug entrapment, and a previous study has confirmed the oral bioavailability (Jat, 2018). A nanoprecipitation method was used to create an optimized formulation of quercetin loaded in Eudragit® S 100 nanoparticles, resulting in good drug loading and efficiency encapsulation values. The nanoparticles formed intermolecular H-bonding between quercetin and the polymer, releasing the drug at neutral pH after ionizing carboxylate moieties in the polymer. The nanomedicine candidate showed significantly higher potency in CT26 colon cancer cells (Sunoqrot and Abujamous, 2019). Furthermore, Eudragit-coated nanoparticles can inhibit premature drug release before reaching the colon, indicating a bright outlook for targeted drug delivery (Patel and Patel, 2022). A method was created to effectively encapsulate non-water-soluble biomolecules, such as flavonoid quercetin, using the nanoprecipitation technique and Eudragit® polymers for pharmaceutical purposes (Elizondo Luevano et al., 2023). The *in vitro* test results of using Eudragit S 100 as polymers are shown in Table 14.

### 3.2.12 Sodium Alginate

The study showed that alginate microspheres coated with chitosan can provide controlled quercetin drug delivery, increasing therapeutic bioavailability for various degenerative disorders. The aerosolization ionic gelation method was used to create quercetin-loaded ca-alginate microspheres, which were freeze-dried. The results showed that increasing sodium alginate concentrations decreased drug loading but enhanced particle size, yield, and entrapment efficiency (Kalalo et al., 2022). The ALINCH-Q microspheres, containing alginate, inulin, chi-

**Table 14.** *In vitro* Study of Eudragit S100 Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Eudragit S100 | Effectively counteract Sulfur mustard-induced toxicity | (Jat, 2018) |
| Eudragit S100 | Demonstrated higher potency in CT26 colon cancer cells | (Sunoqrot and Abujamous, 2019) |
| Eudragit S100 | Delayed the release of quercetin in the upper gastrointestinal system, showing efficient targeting of the drug to the colon | (Patel and Patel, 2022) |
| Eudragit S100 | The hemolytic activity of polymer and quercetin was evaluated in human red blood cells, showing no significant cytotoxic effects compared to the control group. | (Elizondo Luevano et al., 2023) |

**Table 15.** *In vitro* Study of Sodium Alginate Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Sodium Alginate-Chitosan | Enhanced bioavailability for various degenerative disorders. | (Hazra et al., 2015) |
| Sodium Alginate | Higher sodium alginate concentrations increased particle size, yield, and entrapment efficiency. | (Kalalo et al., 2022) |
| Alginate-Hydroxyapatite | Demonstrate potential as drug and cell delivery vehicles. | (Kim et al., 2022) |
| Sodium Alginate-Chitosan-Inulin | Facilitate bacterial activity modulation and potentially mitigate gut dysbiosis. | (Liu et al., 2023) |
| Sodium Alginate | Effectively prevented monoamine neurotransmitter depletion and had antidepressant effects on rats, reducing depressive behavior, anhedonia, weight loss, and improving inflammatory cytokine levels; | (Xu et al., 2023) |
| Sodium Alginate | Efficiently transport quercetin to the pig skin in an *ex vivo* setting. | (Szulc Musioł et al., 2023) |
| Alginate-Hydroxyapatite | Rapid and uniform release of the quercetin glycoside molecule through the coatings, achieving equilibrium after 24 hours. | (Malvano et al., 2021) |
| Alginate-Hydroxyapatite | High effectiveness in inhibiting the increase of total viable bacterial count, psychoactive bacteria count, *Pseudomonas* spp., and *Enterobacteriaceae* over a 15-day period at 4 °C | (Montone et al., 2023) |

**Table 16.** *In vitro* Study of Ethyl Cellulose Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Ethyl cellulose-Eutragit S 100-HPMC | Enhanced absorption, bioavailability, specific d rug targeting, reduced dose, and patient compliance | (Jat et al., 2014) |
| Ethyl Cellulose-Eutragit S 100 | Conserved rifampicin release in the stomach and improved tuberculosis care | (Pingale and Amrutkar, 2021) |
| Ethyl cellulose-HPMC | Demonstrated comparable antioxidant properties and ability to inhibit HCT-116 cells like unbound quercetin. | (Li et al., 2023) |

**Table 17.** *In vitro* Study of Alumina Polymers Containing Quercetin

| Polymers | *In vitro* Results | References |
|---|---|---|
| Chitosan-Pleic Acid | Prolonged circulation duration suggests potential pulmonary delivery strategies for hydrophobic anticancer medicines | (Liu et al., 2017) |
| Chitosan-PLGA | Prolonged release profiles of quercetin; | (Lee et al., 2018) |
| Chitosan-Alumina | Enhanced cytotoxicity and anticancer properties | (Nematollahi et al., 2021) |

tosan, and quercetin, showed a significant increase in the production of 3-hydroxyphenyl propionic and 3-hydroxyphenyl acetic acids during *in vitro* batch colonic fermentation. This indicates that the microspheres promote the metabolism of 4-hydroxyphenyl acetic and 3,4-dihydroxyphenylacetic acid. ALINCH-Q also enhanced the production of all short-chain fatty acids, except isovaleric acid, possibly due to the promotion of short-chain rich acid production by quercetin. These results suggest ALINCH-Q may help mitigate gut dysbiosis by enhancing the richness and diversity of bacteria community (Liu et al., 2023). A new method has been developed to produce quercetin and hydroxyapatite-filled hybrid microspheres in a two-step pretreatment process, resulting in a controlled size range of 290 to 330 $\mu$m. The microspheres showed excellent cell viability and release of hydrophobic medication as a viable bone substitute, demonstrating great potential as drug and cell delivery vehicles (Kim et al., 2022). The *in vitro* test results using sodium alginate as polymers are shown in Table 15. Quercetin nanogels, a protein drug carrier, prevented the depletion of monoamine neurotransmitters and had antidepressant effects on rats given reserpine. Moreover, these materials effectively reversed depressive behavior, reduced anhedonia and weight loss, as well as improved inflammatory cytokine levels and dramatic pyramidal cell damage in the hippocampal CA1 and CA3 subregions of a rat model. Quercetin nanogels also improved CUMS-induced cell apoptosis and proliferation in the hippocampal region (Xu et al., 2023).

### 3.2.13 Ethyl Cellulose

Ethyl cellulose and Eudragit S100 can be used for drug colon targeting, resulting in efficient absorption, enhanced bioavailability, specific drug targeting, reduced dose, and side effects, as well as patient compliance. The FT-IR spectra showed no chemical interactions between the drug and carriers. The particle sizes of the prepared microspheres increased with polymer concentration and decreased with stirring speed. *In vivo* studies on male Wistar rats showed that Quercetin-microspheres demonstrated more effective prophylactic action than conventional dosages, potentially reducing the dose and reducing adverse effects (Jat et al., 2014).

Recent studies have developed floating microspheres with quercetin-loaded rifampicin to improve tuberculosis treatment and preserve release in the stomach. These microspheres are made of HPMC and ethyl cellulose. The application resulted in extended-release patterns and improved trapping, demonstrating significant stability. Previous reports state that drug solubility inversely affects dissolution time, underscoring the importance of the delivery method in drug immersion. Quercetin loading may enhance the bioavailability of rifampicin, a crucial factor in treating tuberculosis. The microspheres can be pulverized into tablets, encapsulated, or transformed into oral solutions for reconstitution. In addition, the stability of the formulation was compared to that of microspheres without

quercetin. The results showed that microspheres containing quercetin remained intact even after six months of stability testing, with an entrapment efficiency of 76.50 percent. The buoyancy percentage was measured to be 61.50% after 8 hours. The microspheres produced in the stomach environment demonstrated extended drug release, indicating great potential application for the prolonged delivery of antitubercular drugs (Pingale and Amrutkar, 2021). The *in vitro* test results of using ethyl cellulose as polymers are shown in Table 16.

### 3.2.14 Alumina

The use of $\gamma$-Alumina nanoparticles led to a substantial enhancement in the encapsulation effectiveness, achieving a value of 95%. In addition, the examination of swelling and quercetin release pattern showed that $\gamma$-Alumina increased the pH responsiveness of the nanocomposite, enabling an accurate and targeted release. To investigate the mechanism of drug release, different release kinetic models were used to interpret the experimental data. The nanocomposite containing quercetin demonstrated significant cytotoxic effects on MCF-7 breast cancer cells, as evidenced by the MTT experiment and flow cytometry. Furthermore, the increased rate of apoptotic cell death provided evidence for the anticancer properties of $\gamma$-Alumina. The chitosan/polyvinylpyrrolidone/$\gamma$-Alumina nanocomposite demonstrated significant pH sensitivity and great potential as a drug delivery system for cancer therapy (Nematollahi et al., 2021). The *in vitro* test results of using alumina as polymers are shown in Table 17.

## 4. CONCLUSION

In conclusion, quercetin, a flavonoid with antioxidant, anti-inflammatory, antiviral, anticancer, and cardiovascular properties, has been studied for drug delivery systems using polymer composites including alginate, pectin, chitosan, starch, and hydroxyapatite. The stabilization, bioavailability, and targeted administration can all be improved by using polymers as carriers. These polymers are designed to improve the stability and dissolution of quercetin, with various delivery methods being investigated. To maximize the therapeutic potential, several delivery methods are being investigated, including drop-extrusion, spray drying, hot-melt extrusion, ionic cross-linking, aerosolization ionic gelation, emulsion-assisted gelation, emulsification, coacervation, and ultra-homogenization. These innovative methods have the potential for customized medicine and medication development, with the ability to be adjusted to target tissues, routes of delivery, and safety requirements. The benefits of using polymers as quercetin carriers include controlled release, resistance to degradation, and enhanced bioavailability. However, when designing polymer-based delivery systems, it is important to consider factors such as biocompatibility, toxicity, and reason for use. The efficacy and safety of these polymer-based delivery technologies still require additional investigation and clinical trials. Collaboration between pharmaceutical corporations, academic institutions, and regulatory authorities is essential for transforming promising results into real medical discoveries.

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## REFERENCES

Al-Musawi, M. H., M. Rashidi, V. Mohammadzadeh, S. Albukhaty, E. Mahmoudi, and M. Ghorbani (2023). Development of a Novel Scaffold Based on Basil Seed Gum/Chitosan Hydrogel Containing Quercetin-Loaded Zein Microshphere for Bone Tissue Engineering. *Journal of Polymers and the Environment*, **31**(11); 4738–4751

Alekseeva, O. V., A. V. Noskov, and A. V. Agafonov (2022). Structure, Physicochemical Properties, and Adsorption Performance of the Ethyl Cellulose/Bentonite Composite Films. *Cellulose*, **29**(7); 3947–3961

Ali, A., L. Yu, H. Liu, S. Khalid, L. Meng, and L. Chen (2017). Preparation and Characterization of Starch-Based Composite Films Reinforced by Corn and Wheat Hulls. *Journal of Applied Polymer Science*, **134**(32); 45159

Alipal, J., N. M. Pu'Ad, T. Lee, N. Nayan, N. Sahari, H. Basri, M. Idris, and H. Abdullah (2021). A Review of Gelatin: Properties, Sources, Process, Applications, and Commercialisation. *Materials Today: Proceedings*, **42**; 240–250

Ansari, R., S. M. Sadati, N. Mozafari, H. Ashrafi, and A. Azadi (2020). Carbohydrate Polymer-Based Nanoparticle Application in Drug Delivery for CNS-Related Disorders. *European Polymer Journal*, **128**; 109607

Azeem, M., M. Hanif, K. Mahmood, N. Ameer, N. Ramzan, U. Abid, H. Latif, and F. R. S. Chughtai (2022). Enhanced Antibacterial and Antioxidant Properties of Chitosan-Quercetin Complex Containing Polycaprolactone Microspheres for the Treatment of Gastroenteritis: An *in-vitro* and *in-vivo* Analysis. *Materials Today Communications*, **31**; 103780

Azeem, M., M. Hanif, K. Mahmood, F. Siddique, H. E. Hashem, M. Aziz, N. Ameer, U. Abid, H. Latif, and N. Ramzan (2023). Design, Synthesis, Spectroscopic Characterization, *In-vitro* Antibacterial Evaluation and *In-silico* Analysis of Polycaprolactone Containing Chitosan-Quercetin Microspheres. *Journal of Biomolecular Structure and Dynamics*, **41**(15); 7084–7103

Bartnikowski, M., T. R. Dargaville, S. Ivanovski, and D. W. Hutmacher (2019). Degradation Mechanisms of Polycaprolactone in the Context of Chemistry, Geometry and Environment. *Progress in Polymer Science*, **96**; 1–20

Bezerra, R. D., M. M. Silva, A. I. Morais, J. A. Osajima, M. R. Santos, C. Airoldi, and E. C. Silva Filho (2014). Phosphated Cellulose As an Efficient Biomaterial for Aqueous Drug Ranitidine Removal. *Materials*, **7**(12); 7907–7924

 

Bhadraiah, A., G. D. Reddy, K. Bharavi, V. R. Devi, and P. R. Kumar (2023). Albendazole Encapsulation along with Quercetin in Chitosan-Alginate Microspheres Enhances Bioavailability and Sustained Release in Broilers. *The Pharma Innovation Journal*, **12**(5); 3717–3723

Chaaban, H., I. Ioannou, C. Paris, C. Charbonnel, and M. Ghoul (2017). The Photostability of Flavanones, Flavonols and Flavones and Evolution of Their Antioxidant Activity. *Journal of Photochemistry and Photobiology A: Chemistry*, **336**; 131–139

Chakraborty, S., N. Kar, L. Kumari, A. De, and T. Bera (2017). Inhibitory Effect of a New Orally Active Cedrol-Loaded Nanostructured Lipid Carrier on Compound 48/80-Induced Mast Cell Degranulation and Anaphylactic Shock in Mice. *International Journal of Nanomedicine*, **3**(2); 4849–4868

Davidovich Pinhas, M., S. Barbut, and A. Marangoni (2015). The Gelation of Oil Using Ethyl Cellulose. *Carbohydrate polymers*, **117**; 869–878

Davoudi, Z., M. H. Azizi, M. Barzegar, and A. Bernkop-Schnürch (2023). Porous Starch-Inulin Loaded Quercetin Microcapsules: Characterization, Antioxidant Activity, *in-vitro* Release, and Storage Stability. *Journal of Pharmaceutical Sciences*, **000**; 1–11

de Freitas, C. A. S., P. H. M. de Sousa, D. J. Soares, J. Y. G. da Silva, S. R. Benjamin, and M. I. F. Guedes (2019). Carnauba Wax Uses in Food–A Review. *Food chemistry*, **291**; 38–48

Dhasmana, A., S. Malik, A. Ranjan, A. Chauhan, H. M. Tashkandi, S. Haque, R. Al-Raddadi, S. Harakeh, and G. Zengin (2022). A Bioengineered Quercetin-Loaded 3D Bio-Polymeric Graft for Tissue Regeneration and Repair. *Biomedicines*, **10**(12); 3157

Dwivedi, R., S. Kumar, R. Pandey, A. Mahajan, D. Nandana, D. S. Katti, and D. Mehrotra (2020). Polycaprolactone As Biomaterial for Bone Scaffolds: Review of Literature. *Journal of Oral Biology and Craniofacial Research*, **10**(1); 381–388

Elizondo Luevano, J. H., R. Castro Ríos, R. Parra Saldívar, H. Larqué García, M. Garza Tapia, E. M. Melchor Martínez, and A. Chávez Montes (2023). Influence of the Polymer and Solvent Variables on the Nanoencapsulation of the Flavonoid Quercetin: Preliminary Study Based on Eudragit® Polymers. *Applied Sciences*, **13**(13); 7816

Elmowafy, M., K. Shalaby, M. H. Elkomy, O. A. Alsaidan, H. A. Gomaa, O. M. Hendawy, M. A. Abdelgawad, H. M. Ali, Y. M. Ahmed, and K. M. El-Say (2023). Exploring the Potential of Quercetin/Aspirin-Loaded Chitosan Nanoparticles Coated with Eudragit L100 in the Treatment of Induced-Colorectal Cancer in Rats. *Drug Delivery and Translational Research*, **13**; 1–21

Ezati, P. and J. W. Rhim (2021). Fabrication of Quercetin-Loaded Biopolymer Films As Functional Packaging Materials. *ACS Applied Polymer Materials*, **3**(4); 2131–2137

Farrag, Y., W. Ide, B. Montero, M. Rico, S. Rodríguez-Llamazares, L. Barral, and R. Bouza (2018). Starch Films Loaded with Donut-Shaped Starch-Quercetin Microparticles: Characterization and Release Kinetics. *International Journal of Biological Macromolecules*, **118**; 2201–2207

Freitas, C. A. S., Í. G. P. Vieira, P. H. M. Sousa, C. R. Muniz, M. L. da Costa Gonzaga, and M. I. F. Guedes (2016). Carnauba Wax *p*-Methoxycinnamic Diesters: Characterisation, Antioxidant Activity and Simulated Gastrointestinal Digestion Followed by *in-vitro* Bioaccessibility. *Food Chemistry*, **196**; 1293–1300

Frent, O. D., D. M. Duda-Seiman, L. G. Vicas, N. Duteanu, N. S. Nemes, B. Pascu, A. Teusdea, C. M. Morgovan, M. E. Muresan, and T. Jurca (2023). Study of the Influence of the Excipients Used for the Synthesis of Microspheres Loaded with Quercetin: Their Characterization and Antimicrobial Activity. *Coatings*, **13**(8); 1376

Frenț, O. D., N. Duteanu, A. C. Teusdea, S. Ciocan, L. Vicaș, T. Jurca, M. Muresan, A. Pallag, P. Ianasi, and E. Marian (2022). Preparation and Characterization of Chitosan-Alginate Microspheres Loaded with Quercetin. *Polymers*, **14**(3); 490

Gentile, P., V. Chiono, I. Carmagnola, and P. V. Hatton (2014). An Overview of Poly (Lactic-co-Glycolic Acid) (PLGA)-Based Biomaterials for Bone Tissue Engineering. *International Journal of Molecular Sciences*, **15**(3); 3640–3659

Ghalme, S., P. Koinkar, and Y. J. Bhalerao (2020). Effect of Aluminium Oxide ($Al_2O_3$) Nanoparticles Addition into Lubricating Oil on Tribological Performance. *Tribology in Industry*, **42**(3); 494–502

Han, C., M. Guo, J. Bai, L. Zhao, L. Wang, W. Song, and P. Zhang (2022). Quercetin-Loaded Nanocomposite Microspheres for Chronologically Promoting Bone Repair Via Synergistic Immunoregulation and Osteogenesis. *Materials & Design*, **222**; 111045

Hariyadi, D. M., I. Prestisya, G. Suhariyono, A. Miatmoko, N. Rosita, and M. Rahmadi (2022). Characterization of Dry Powder Inhaler Quercetin Solid Lipid Microparticle (SLM) As Lung Delivery System: Effect of Polymer Concentration. *Egyptian Journal of Chemistry*, **65**(11); 281–289

Hazra, M., D. D. Mandal, T. Mandal, S. Bhuniya, and M. Ghosh (2015). Designing Polymeric Microparticulate Drug Delivery System for Hydrophobic Drug Quercetin. *Saudi Pharmaceutical Journal*, **23**(4); 429–436

Helmy, A. M., M. Elsabahy, M. Abd Elkareem, E. A. Ibrahim, and G. M. Soliman (2020). High-Payload Chitosan Microparticles for the Colonic Delivery of Quercetin: Development and In-Vivo Evaluation in a Rabbit Colitis Model. *Journal of Drug Delivery Science and Technology*, **58**(June); 101832

Jafernik, K., A. Ładniak, E. Blicharska, K. Czarnek, H. Ekiert, A. E. Wiącek, and A. Szopa (2023). Chitosan-Based Nanoparticles As Effective Drug Delivery Systems—A Review. *Molecules*, **28**(4); 1963

Jat, R. (2018). Formulation and *In vitro-In vivo* Evaluation of Quercetin Loaded Eudragit S100 Microspheres. *Asian Journal of Pharmaceutics (AJP)*, **12**(01); 31–37

Jat, R. C., S. Jain, and K. Arora (2014). Preparation and Eval-

 

uation of Quercetin Microsphere As Antidotes of Sulphur Mustard to Overcome the Poor Bioavailability and Frequent Dose Administration of the Drug. *World Journal of Pharmaceutical Research World*, **4**(2); 574–603

Jing, S., H. Chen, E. Liu, M. Zhang, F. Zeng, H. Shen, Y. Fang, B. Muhitdinov, and Y. Huang (2023). Oral Pectin/Oligochitosan Microspheres for Colon-Specific Controlled Release of Quercetin to Treat Inflammatory Bowel Disease. *Carbohydrate Polymers*, **316**(March); 121025

Jo, W. S., H. Y. Song, N. B. Song, J. H. Lee, S. C. Min, and K. B. Song (2014). Quality and Microbial Safety of 'Fuji' Apples Coated with Carnauba-Shellac Wax Containing Lemongrass Oil. *LWT-Food Science and Technology*, **55**(2); 490–497

Kalalo, T., A. Miatmoko, H. Tanojo, T. Erawati, D. M. Hariyadi, and N. Rosita (2022). Effect of Sodium Alginate Concentration on Characteristics, Stability and Drug Release of Inhalation Quercetin Microspheres. *Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia*, **9**(2); 107–114

Kantharia, N., S. Naik, S. Apte, M. Kheur, S. Kheur, and B. Kale (2014). Nano-Hydroxyapatite and Its Contemporary Applications. *Bone*, **34**(15.2); 1–71

Karthick, V., S. Panda, V. G. Kumar, D. Kumar, L. K. Shrestha, K. Ariga, K. Vasanth, S. Chinnathambi, T. S. Dhas, and K. U. Suganya (2019). Quercetin Loaded PLGA Microspheres Induce Apoptosis in Breast Cancer Cells. *Applied Surface Science*, **487**(May); 211–217

Karuppusamy, N., V. Mariyappan, S.-M. Chen, M. Keerthi, and R. Ramachandran (2021). A Simple Electrochemical Sensor for Quercetin Detection Based on Cadmium Telluride Nanoparticle Incorporated on Boron, Sulfur Co-Doped Reduced Graphene Oxide Composite. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, **626**(June); 127094

Khor, C. M., W. K. Ng, P. Kanaujia, K. P. Chan, and Y. Dong (2017). Hot-Melt Extrusion Microencapsulation of Quercetin for Taste-Masking. *Journal of Microencapsulation*, **34**(1); 29–37

Kim, J., Y. J. Choi, H. Park, and H. s. Yun (2022). Fabrication of Multifunctional Alginate Microspheres Containing Hydroxyapatite Powder for Simultaneous Cell and Drug Delivery. *Frontiers in Bioengineering and Biotechnology*, **10**(August); 827626

Kost, B., A. Kunicka-Styczyńska, A. Plucińska, K. Rajkowska, M. Basko, and M. Brzeziński (2022). Microfluidic Preparation of Antimicrobial Microparticles Composed of L-Lactide/1, 3-Dioxolane (co) Polymers Loaded with Quercetin. *Food Chemistry*, **396**(June); 133639

Lai, F., I. Franceschini, F. Corrias, M. C. Sala, F. Cilurzo, C. Sinico, and E. Pini (2015). Maltodextrin Fast Dissolving Films for Quercetin Nanocrystal Delivery. A Feasibility Study. *Carbohydrate Polymers*, **121**(1); 217–223

Lee, H., T. Nguyen, M. Kim, J. H. Jeong, and J. B. Park (2018). The Effects of Biodegradable Poly (Lactic-co-Glycolic Acid)-Based Microspheres Loaded with Quercetin on Stemness, Viability and Osteogenic Differentiation Potential of Stem Cell Spheroids. *Journal of Periodontal Research*, **53**(5); 801–815

Lee, S., H. Park, J. S. Oh, K. Byun, D. Y. Kim, H. s. Yun, and B. J. Kang (2023). Hydroxyapatite Microbeads Containing BMP-2 and Quercetin Fabricated Via Electrostatic Spraying to Encourage Bone Regeneration. *BioMedical Engineering Online*, **22**(1); 15

Lengyel, M., N. Kállai Szabó, V. Antal, A. J. Laki, and I. Antal (2019). Microparticles, Microspheres, and Microcapsules for Advanced Drug Delivery. *Scientia Pharmaceutica*, **87**(3); 20

Li, J., C. Cai, J. Li, J. Li, J. Li, T. Sun, L. Wang, H. Wu, and G. Yu (2018). Chitosan-Based Nanomaterials for Drug Delivery. *Molecules*, **23**(10); 2661

Li, S. F., J.-H. Wu, T.-G. Hu, and H. Wu (2023). Encapsulation of Quercetin into Zein-Ethyl Cellulose Coaxial Nanofibers: Preparation, Characterization and Its Anticancer Activity. *International Journal of Biological Macromolecules*, **248**(July); 125797

Liu, K., W. Chen, T. Yang, B. Wen, D. Ding, M. Keidar, J. Tang, and W. Zhang (2017). Paclitaxel and Quercetin Nanoparticles Co-Loaded in Microspheres to Prolong Retention Time for Pulmonary Drug Delivery. *International Journal of Nanomedicine*, **12**; 8239–8255

Liu, S., Z. Fang, and K. Ng (2022). Incorporating Inulin and Chitosan in Alginate-Based Microspheres for Targeted Delivery and Release of Quercetin to Colon. *Food Research International*, **160**(July); 111749

Liu, S., Y. T. Loo, Z. Li, and K. Ng (2023). Alginate-Inulin-Chitosan Based Microspheres Alter Metabolic Fate of Encapsulated Quercetin, Promote Short Chain Fatty Acid Production, and Modulate Pig Gut Microbiota. *Food Chemistry*, **418**(February); 135802

Lourenço, S. C., M. Moldão Martins, and V. D. Alves (2020). Microencapsulation of Pineapple Peel Extract by Spray Drying Using Maltodextrin, Inulin, and Arabic Gum As Wall Matrices. *Foods*, **9**(6); 718

Lukova, P., P. Katsarov, and B. Pilicheva (2023). Application of Starch, Cellulose, and Their Derivatives in the Development of Microparticle Drug-Delivery Systems. *Polymers*, **15**(17); 3615

Lv, L. C., Q. Y. Huang, W. Ding, X. H. Xiao, H. Y. Zhang, and L. X. Xiong (2019). Fish Gelatin: The Novel Potential Applications. *Journal of Functional Foods*, **63**(January); 103581

Madaan, K., V. Lather, and D. Pandita (2016). Evaluation of Polyamidoamine Dendrimers As Potential Carriers for Quercetin, a Versatile Flavonoid. *Drug Delivery*, **23**(1); 254–262

Malvano, F., A. M. I. Montone, R. Capparelli, F. Capuano, and D. Albanese (2021). Development of a Novel Active Edible Coating Containing Hydroxyapatite for Food Shelf-Life Extension. *Chemical Engineering Transactions*, **87**(March); 25–30

 

Mensink, M. A., H. W. Frijlink, K. van der Voort Maarschalk, and W. L. Hinrichs (2015). Inulin, a Flexible Oligosaccharide I: Review of Its Physicochemical Characteristics. *Carbohydrate Polymers*, **130**; 405–419

Milano, F., A. Masi, M. Madaghiele, A. Sannino, L. Salvatore, and N. Gallo (2023). Current Trends in Gelatin-Based Drug Delivery Systems. *Pharmaceutics*, **15**(5); 1499

Mohammed, M. A., J. T. Syeda, K. M. Wasan, and E. K. Wasan (2017). An Overview of Chitosan Nanoparticles and Its Application in Non-Parenteral Drug Delivery. *Pharmaceutics*, **9**(4); 53

Mohseni Shahri, F. S. and F. Moeinpour (2023). Development of a pH-Sensing Indicator for Shrimp Freshness Monitoring: Curcumin and Anthocyanin-Loaded Gelatin Films. *Food Science & Nutrition*, **11**(7); 3898–3910

Montone, A. M. I., F. Malvano, R. Taiano, R. Capparelli, F. Capuano, and D. Albanese (2023). Alginate Coating Charged by Hydroxyapatite Complexes with Lactoferrin and Quercetin Enhances the Pork Meat Shelf Life. *Foods*, **12**(3); 553

Muniyandy, S., L. M. Yi, A. Santhagunam, and L. H. Chuah (2020). Chitosan-Sodium Lauryl Sulfate/Eudragit S100 Beads Loaded with 5-Fluorouracil: Influence of Solvent and Duration of Crosslinking the Crosslinking on Physicochemical Properties. *Materials Research Express*, **7**(11); 115402

Nalini, T., S. K. Basha, A. M. M. Sadiq, V. S. Kumari, and K. Kaviyarasu (2019). Development and Characterization of Alginate/Chitosan Nanoparticulate System for Hydrophobic Drug Encapsulation. *Journal of Drug Delivery Science and Technology*, **52**(April); 65–72

Nematollahi, E., M. Pourmadadi, F. Yazdian, H. Fatoorehchi, H. Rashedi, and M. N. Nigjeh (2021). Synthesis and Characterization of Chitosan/Polyvinylpyrrolidone Coated Nanoporous $\gamma$-Alumina As a pH-Sensitive Carrier for Controlled Release of Quercetin. *International Journal of Biological Macromolecules*, **183**; 600–613

Nguyen, T. T. and J. H. Jeong (2018). Development of a Single-Jet Electrospray Method for Producing Quercetin-Loaded Poly (Lactic-co-Glycolic Acid) Microspheres with Prolonged-Release Patterns. *Journal of Drug Delivery Science and Technology*, **47**(July); 268–274

Olechno, K., A. Basa, and K. Winnicka (2021). "Success Depends on Your Backbone"—About the Use of Polymers as Essential Materials Forming Orodispersible Films. *Materials*, **14**(17); 4872

Paranjpe, K. Y. (2017). Alpha, Beta and Gamma Alumina As Catalyst. *The Pharma Innovation Journal*, **6**(11); 236–238

Patel, P. and T. Patel (2022). Design and Development of Dual Functional Colon Targeted Eudragit/Chitosan Nanoparticles: A QbD Approach. *Indian Journal of Pharmaceutical Education and Research*, **56**(4); 1063–1075

Pepla, E., L. K. Besharat, G. Palaia, G. Tenore, and G. Migliau (2014). Nano-Hydroxyapatite and Its Applications in Preventive, Restorative and Regenerative Dentistry: A Review of Literature. *Annali Di Stomatologia*, **5**(3); 108

Pingale, P. L. and S. V. Amrutkar (2021). Quercetin Loaded Rifampicin-Floating Microspheres for Improved Stability and *In-vitro* Drug Release. *Pharmacophore*, **12**(3); 95–99

Pivette, P., V. Faivre, J. B. Brubach, G. Daste, M. Ollivon, and S. Lesieur (2014). Polymorphism of Glyceryl Behenates: From the Individual Compounds to the Pharmaceutical Excipient. *Chemistry and Physics of Lipids*, **183**; 191–203

Ren, M., X. Wang, M. Hu, Y. Jiang, D. Xu, H. Xiang, J. Lin, and B. Yu (2022). Enhanced Bone Formation in Rat Critical-Size Tibia Defect by a Novel Quercetin-Containing Alpha-Calcium Sulphate Hemihydrate/Nano-Hydroxyapatite Composite. *Biomedicine & Pharmacotherapy*, **146**(October); 112570

Rosita, N., N. Ambarwati, T. Erawati, and D. M. Hariyadi (2022). Characterization and *In vitro* Release of Inhalation Quercetin Solid Lipid Microparticles: Effect of Lipid. *Journal of Advanced Pharmaceutical Technology & Research*, **13**(1); 11

Rubini, K., E. Boanini, A. Menichetti, F. Bonvicini, G. A. Gentilomi, M. Montalti, and A. Bigi (2020). Quercetin Loaded Gelatin Films with Modulated Release and Tailored Anti-Oxidant, Mechanical and Swelling Properties. *Food Hydrocolloids*, **109**(March); 106089

Saavedra Leos, M. Z., M. Román Aguirre, A. Toxqui Terán, V. Espinosa Solís, A. Franco Vega, and C. Leyva Porras (2022). Blends of Carbohydrate Polymers for the Co-Microencapsulation of Bacillus Clausii and Quercetin As Active Ingredients of a Functional Food. *Polymers*, **14**(2); 236

Sakhno, T. V., N. N. Barashkov, I. S. Irgibaeva, S. Pustovit, and Y. E. Sakhno (2016). Polymer Coatings for Protection of Wood and Wood-Based Materials. *Advances in Chemical Engineering and Science*, **6**(2); 93–110

Sedighi, M., N. Omidi, and A. Jabbari (2017). Experimental Investigation of FGM Dental Implant Properties Made from Ti/HA Composite. *Mechanics of Advanced Composite Structures*, **4**(3); 233–237

Setyawan, D., S. Febrianti, A. Zainul, and R. Sari (2017). PEG 8000 Increases Solubility and Dissolution Rate of Quercetin in Solid Dispersion System. *Marmara Journal of Pharmaceutical Sciences*, **22**(2); 259–266

Souza, K. S., L. S. Moreira, B. T. Silva, B. P. Oliveira, A. S. Carvalho, P. S. Silva, W. A. Verri Jr, A. B. Sá-Nakanishi, L. Bracht, and J. N. Zanoni (2021). Low Dose of Quercetin-Loaded Pectin/Casein Microparticles Reduces the Oxidative Stress in Arthritic Rats. *Life Sciences*, **284**(June); 119910

Steigerwald, H., F. Blanco-Perez, M. Albrecht, C. Bender, A. Wangorsch, H.-U. Endreß, M. Bunzel, C. Mayorga, M. J. Torres, and S. Scheurer (2021). Does the Food Ingredient Pectin Provide a Risk for Patients Allergic to Non-Specific Lipid-Transfer Proteins? *Foods*, **11**(1); 13

Su, K. and C. Wang (2015). Recent Advances in the Use of Gelatin in Biomedical Research. *Biotechnology Letters*, **37**(11); 2139–2145

Su, X., Z. Yang, K. B. Tan, J. Chen, J. Huang, and Q. Li (2020).

 

Preparation and Characterization of Ethyl Cellulose Film Modified with Capsaicin. *Carbohydrate Polymers*, **241**(April); 116259

Sun, D., L. Nuan, W. Zhang, Z. Zhao, Z. Mou, D. Huang, J. Liu, and W. Wang (2016). Design of PLGA-Functionalized Quercetin Nanoparticles for Potential Use in Alzheimer's Disease. *Colloids and Surfaces B: Biointerfaces*, **148**; 116–129

Sunoqrot, S. and L. Abujamous (2019). pH-Sensitive Polymeric Nanoparticles of Quercetin As a Potential Colon Cancer-Targeted Nanomedicine. *Journal of Drug Delivery Science and Technology*, **52**(April); 670–676

Swider, E., O. Koshkina, J. Tel, L. J. Cruz, I. J. M. de Vries, and M. Srinivas (2018). Customizing Poly(Lactic-co-Glycolic Acid) Particles for Biomedical Applications. *Acta Biomaterialia*, **73**; 38–51

Szulc Musioł, B., W. Siemiradzka, and D. Barbara (2023). Formulation and Evaluation of Hydrogels Based on Sodium Alginate and Cellulose Derivatives with Quercetin for Topical Application. *Applied Sciences*, **13**(13); 7826

Thakur, S., P. P. Govender, M. A. Mamo, S. Tamulevicius, and V. K. Thakur (2017). Recent Progress in Gelatin Hydrogel Nanocomposites for Water Purification and Beyond. *Vacuum*, **146**; 396–408

Viscusi, G., G. Paolella, E. Lamberti, I. Caputo, and G. Gorrasi (2023). Quercetin-Loaded Polycaprolactone-Polyvinylpyrrolidone Electrospun Membranes for Health Application: Design, Characterization, Modeling and Cytotoxicity Studies. *Membranes*, **13**(2); 242

Wibowo, Y. G., M. F. Imron, S. B. Kurniawan, B. S. Ramadan, T. Taher, A. H. Sudibya, H. Syarifuddin, and K. Khairurrijal (2023). Emerging Strategies for Mitigating Acid Mine Drainage Formation and Environmental Impacts: A Comprehensive Review of Recent Advances. *Science and Technology Indonesia*, **8**(4); 516–541

Wiggers, H. J., P. Chevallier, F. Copes, F. H. Simch, F. da Silva Veloso, G. M. Genevro, and D. Mantovani (2022). Quercetin-Crosslinked Chitosan Films for Controlled Release of Antimicrobial Drugs. *Frontiers in Bioengineering and Biotechnology*, **10**(March); 814162

Xu, D., L. N. Gao, X. J. Song, Q. W. Dong, Y. B. Chen, Y. L. Cui, and Q. Wang (2023). Enhanced Antidepressant Effects of BDNF-Quercetin Alginate Nanogels for Depression Therapy. *Journal of Nanobiotechnology*, **21**(1); 379

Yaghoubi, A., M. Ghojazadeh, S. Abolhasani, H. Alikhah, and F. Khaki Khatibi (2015). Correlation of Serum Levels of Vitronectin, Malondialdehyde and Hs-CRP with Disease Severity in Coronary Artery Disease. *Journal of Cardiovascular and Thoracic Research*, **7**(3); 113

Yasir, M., I. Chauhan, A. Zafar, M. Verma, N. K. Alruwaili, K. Noorulla, A. P. Singh, and A. J. Tura (2023). Glyceryl Behenate-Based Solid Lipid Nanoparticles As a Carrier of Haloperidol for Nose to Brain Delivery: Formulation Development, *In-vitro*, and *In-vivo* Evaluation. *Brazilian Journal of Pharmaceutical Sciences*, **58**; 1–18

Yazdani, J., E. Ahmadian, S. Sharifi, S. Shahi, and S. M. Dizaj (2018). A Short View on Nanohydroxyapatite As Coating of Dental Implants. *Biomedicine & Pharmacotherapy*, **105**(April); 553–557

Yong, H., R. Bai, F. Bi, J. Liu, Y. Qin, and J. Liu (2020). Synthesis, Characterization, Antioxidant and Antimicrobial Activities of Starch Aldehyde-Quercetin Conjugate. *International Journal of Biological Macromolecules*, **156**; 462–470

Zhou, J., N. Li, P. Liu, Z. Liu, L. Gao, and T. Jiao (2022). Preparation of Fluorescently Labeled Chitosan-Quercetin Drug-Loaded Nanoparticles with Excellent Antibacterial Properties. *Journal of Functional Biomaterials*, **13**(3); 141

Zhou, L., L. Cai, H. Ruan, L. Zhang, J. Wang, H. Jiang, Y. Wu, S. Feng, and J. Chen (2021). Electrospun Chitosan Oligosaccharide/Polycaprolactone Nanofibers Loaded with Wound-Healing Compounds of Rutin and Quercetin As Antibacterial Dressings. *International Journal of Biological Macromolecules*, **183**; 1145–1154

 