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REVIEW ARTICLE

From Insoluble to Injectable: Role of Natural Polymers Based Nanocarriers Game Changer for Solubility and Bioavailability in Oncology

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Abstract

Any pharmaceutical formulation contains two ingredients one is the active ingredient and other is an excipient. Excipients help in the manufacturing of dosage form, and it also improves physicochemical parameters of the dosage form. Polymers play an important role as excipients in any dosage form. They influence drug release and should be compatible, non-toxic, stable, economic *etc*. They are broadly classified as natural polymers and synthetic polymers. They have wide range of applications, so selection of polymer is the main step in designing any dosage form. Nowadays, due to many problems associated with drug release and side effects, manufacturers are inclined towards using natural polymers. Natural polymers are basically polysaccharides, so they are biocompatible and without any side effects. The increasing research interests in this group of materials are indications of their increasing importance. It is believed that as technology and testing techniques advance, more understanding of their physicochemical nature would be gained that can enable them to be tailored for wider pharmaceutical applications than their synthetic counterparts.

Major Findings: Natural polymers such as chitosan, alginate, cellulose derivatives, gelatin, and cyclodextrins are widely applied in cancer drug delivery, because they enhance solubility, prevent crystallization, and provide biocompatible stabilization of formulations. They are integrated into systems like polymeric micelles, cyclodextrin nanosponges, and lipid nanocarriers, which have successfully improved the solubility and bioavailability of anticancer agents such as paclitaxel and curcumin. These approaches enable more effective targeting, sustained release, and better therapeutic outcomes in oncology.

Keywords: Bioavailability, Cancer, Chitosan, Natural Polymer, Polymers, Solubility

1. Introduction

The numerous biological functions of the human body depend upon natural polymers which include polysaccharides proteins and nucleic acids. The multiple scientific fields and industrial industries utilize these biopolymers due to their diverse natural origins alongside their unique structural features and properties. Polymeric strands known as cellulose occur in plants and chitin exists in arthropods providing them mechanical durability but lysozyme functions as an antimicrobial defence protein[1-3]. The adaptable physicochemical features and biological traits in natural polymers result in their extensive use throughout different scientific sectors. These natural compounds play a vital role in papermaking along with textile manufacturing and chemical formulations for food processing and cosmetic development as well as nutraceutical designs.

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Their natural compatibility with human tissue and susceptibility to biological breakdown makes them appropriate for biomedical applications that include drug delivery methods and wound closure solutions as well as tissue regeneration strategies and cosmetic creation[4,5]. Sustainability concerns have elevated interest in natural polymers because they represent renewable materials that result in minimal environmental impact. Research teams develop next-generation materials through various forms of natural polymers including films, membranes, coatings and hydrogels and micro- or nanoparticle systems. Forecasted sustainable technological improvements in healthcare along with environmental science and material engineering applications result from natural polymers which supply functional advantages alongside synthetic material reduction possibilities[4-5].

Natural polymers function as primary components for solubility enhancement in pharmaceuticals as well as foods because bioavailability and effectiveness depend on solution dispersal. The wide application of hydrophilic polysaccharides including alginate alongside chitosan and cellulose derivatives (specifically Hydroxypropyl Methylcellulose known as HPMC) exists because these components form gels or viscous solutions while providing solubility enhancement capabilities. The solubility of difficult-to-dissolve drugs improves because these polymers serve as protective agents in solid dispersions while increasing drug wettability and stopping crystallization of drugs. The colloidal dispersion formations of proteins including gelatine and whey protein enhance solubility by delivering better hydrophobic compound dissolution. The solubility and stability of lipophilic molecules increase because cyclic oligosaccharides known as cyclodextrins form inclusion complexes with these molecules which enhance their ability to dissolve in water. Food technology uses natural polymers pectin and gum arabic for emulsifying and stabilizing water-based bioactive compound and flavour and essential oil solutions in food systems. Major food supplements and pharmaceutical compounds benefit from natural polymers because these compounds improve dissolution rates and bioavailability which leads to better therapeutic and nutritional outcomes. The characteristics of being biocompatible along with being easily degraded and non-toxic make these natural polymers excellent sustainable options for synthetic solubility enhancers[6-9].

Solubility occurs when solute components from solid, liquid or gaseous states combine with solvent components from solid, liquid or gaseous states to produce clear homogeneous solutions. The definition of solubility includes two parts: First it means the quantity of dissolved solute constituting a saturated solution at a definite temperature and second the automatic formation of distinct compounds from multiple substances when they create uniform dispersions. IUPAC defines solubility as the mechanism to generate widespread solute distribution within a particular solvent. Recent research shows that solubility acts as a drawback for 75 to 80% of newly created drugs (NCE) among all developing pharmaceutical products in the market. BCS classifies drugs into 4 distinct groups based on their solubility and permeability rates which are shown in Figure 1. Drugs belonging to Class I present both high permeability and high solubility. Class II contains drugs with high permeability but low solubility. The same pattern repeats for drugs in Class III with low permeability and high solubility, whereas Class IV drugs exhibit both low permeability and low solubility[10-11].

It is clear from the BCS that, dissolution becomes a rate limiting step for Class II and IV due to its low solubility (Table 1).

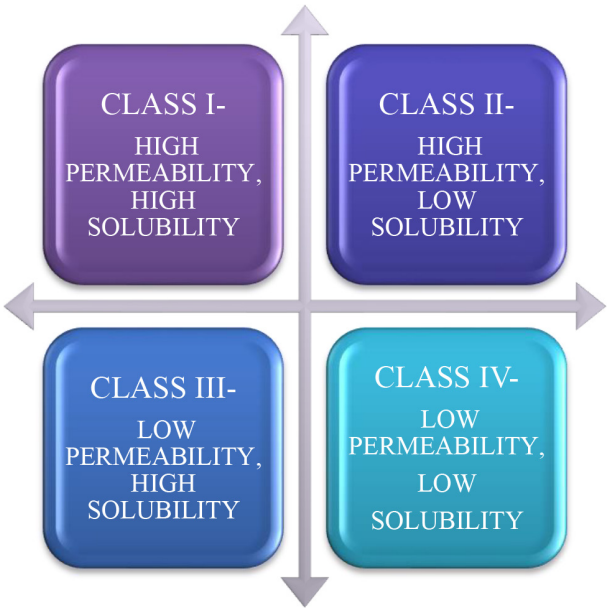


Figure 1. Bio pharmaceutics classification system.

2. Reasons for Improving Solubility of Poorly Soluble Drugs

Drug solubility stands as an essential component which determines both bioavailability and therapeutic effectiveness along with pharmacologic behaviour. Drugs with limited solubility properties struggle during dissolution and this produces poor drug absorption together with decreased therapeutic outcomes. Multiple methods (Figure 2) have emerged to boost drug solubility through particle size minimization alongside amorphous state conversion and wettability alteration and porous material development techniques[12-18].

Table 1. Solubility criteria according to USP

Descriptive Term	Part of Solvent Required Per Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Sparingly soluble	From 10 to 30
Soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

2.1 Reduction in Particle Size

The drug's surface area expands when its particle dimensions reduce, thus the dissolution rate improves based on Noyes-Whitney equation. Drug particles that present a smaller size pattern generate higher surface area-to-volume relationships which enhance dissolution contact between the drug and fluid (Figure 3). Wet milling together with high-pressure homogenization and supercritical fluid technology use this approach as a common strategy in micronisation and nanosizing processes. The combination of nanocrystals has resulted in successful

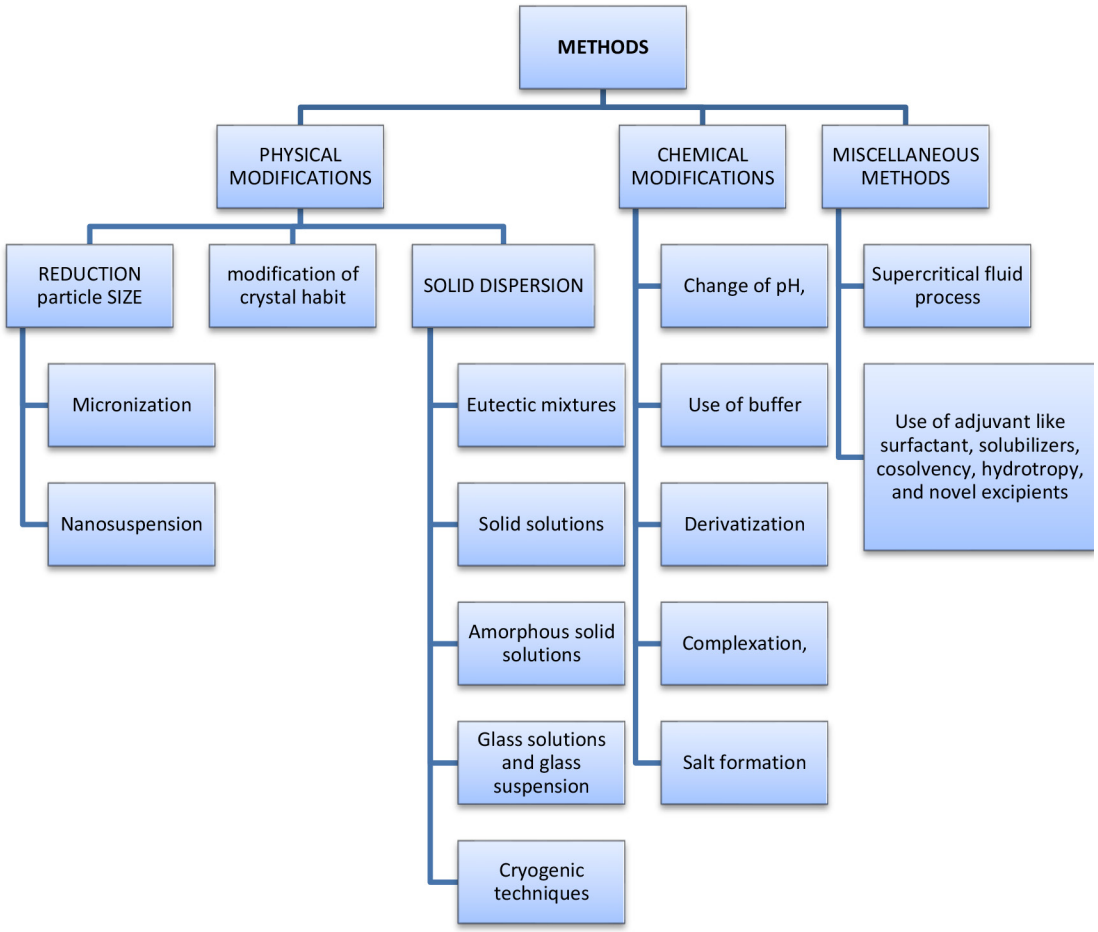


Figure 2. Different methods for enhancing solubility.

drug implementations of itraconazole and fenofibrate by enhancing their solubility and bioavailability levels[18-24].

2.2 Drug in Amorphous Form

Pharmaceutical substances tend to exist either as crystalline solids or amorphous solids where the latter shows better solubility because its disordered molecular organization and elevated energy promotes enhanced dissolution rate. Although the crystalline structure represents a more stable thermodynamic state it usually displays inadequate solubility properties. The dissolution properties of a drug can improve through its transformation into Amorphous Solid Dispersion (ASD). The production of amorphous drug formulations utilizes three common fabrication techniques: Spray drying together with hot melt extrusion alongside freeze-drying. Half-liquid solid mixtures from ritonavir and lopinavir showed superior dissolving properties than their regular crystal forms[25-27].

2.3 Particles with Increased Wettability

Drug particles become more soluble when wettability increases because it enhances their contact with the dissolving water solution. The wettability improvement happens through hydrophilic carriers combined with surfactants together with surface modification methods. The dispersal of hydrophobic drug particles benefits from SLS and polysorbates because they lower surface tension. Two techniques known as solid dispersion together with co-crystallization help drugs become more wettable. Celecoxib becomes more soluble after its formulation with Polyvinylpyrrolidone (PVP) resulting in improved wettability[29-31].

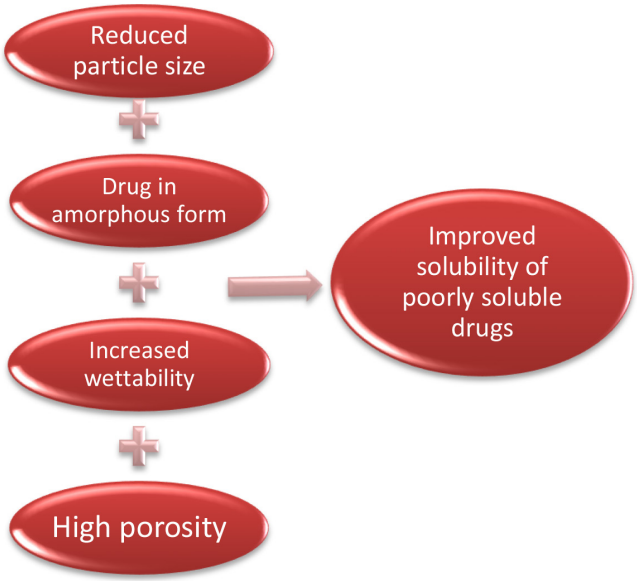


Figure 3. Reasons for improving solubility of poorly soluble drugs.

2.4 Particles with High Porosity

Drugs with a highly porous structure exhibit greater solubility due to their larger surface area and improved solvent penetration. Porous drug particles allow for faster dissolution as they facilitate the entry of dissolution media into their structure. Techniques such as spray drying, freeze drying, and supercritical fluid processing are employed to generate highly porous drug particles. For instance, porous mannitol-based formulations have been used to improve the solubility of poorly water-soluble drugs such as itraconazole and griseofulvin. Beyond the primary approaches of reducing particle size, converting drugs to amorphous forms, enhancing wettability, and increasing porosity, several other advanced strategies are employed to improve the solubility and bioavailability of poorly soluble drugs. These strategies are designed to address the thermodynamic and kinetic barriers to dissolution and absorption. The following are additional methods:

2.5 Use of Solubilizing Excipients (Co-solvents and Surfactants)

Medical practitioners frequently use co-solvents along with surfactants to boost the dissolving capacity of hydrophobic medications. The drugs that show limited water solubility can be dissolved using co-solvents including ethanol, propylene glycol, Polyethylene Glycol (PEG), and Dimethyl Sulfoxide (DMSO). These co-solvents lower the solvent mixture's polarity level and create an appropriate drug solubilization environment. Drugs with low solubility benefit from surfactants since these agents lower surface tension and prevent patients from experiencing aggregation issues. The wetting and dissolution of drugs with limited solubility can be enhanced through the implementation of surfactants such as Sodium Lauryl Sulfate (SLS), Polysorbates and Tween which carry anionic, cationic, and non-ionic properties. The surfactants have two applications: They enable the formation of micelles as drug-encapsulating

carriers that improve drug solubility in water-based solutions. The solubility of taxol received an improvement through its solubilization with Polyethylene Glycol (PEG)-based surfactants[32-34].

2.6 Self-Emulsifying Drug Delivery Systems (SEDDS)

The Self-Emulsifying Drug Delivery Systems (SEDDS) combine lipids together with surfactants and co-solvents that automatically shape small emulsions or microemulsions when they encounter water-based gastrointestinal fluids. The drug's water solubility gets enhanced through these delivery systems that make micellar structures or emulsions which boost the drug surface area and help enhance dissolution rate. SEDDS serve as effective drug delivery systems used to enhance the bioavailability of low-water-soluble drugs including cyclosporine and danazol[22,35].

2.7 Inclusion Complexation with Cyclodextrins

Cyclodextrins represent cyclic oligosaccharides which develop inclusion complexes with hydrophobic drugs. Drug solubility enhancement through cyclodextrin complexes occurs when drugs enter the hydrophobic pocket of the cyclodextrin which protects drugs from crystallization while maintaining stability in solution. The 3 main types of cyclodextrins used for drug solubilization include β-cyclodextrin, Hydroxypropyl-β-Cyclodextrin (HPβCD), and Methyl-β-Cyclodextrin (MβCD). The inclusion of drugs with cyclodextrin allows for enhanced product stability and solubility in water particularly in cases of griseofulvin and ibuprofen and diazepam administration[36-38].

2.8 Salt Formation

Drug salt formation represents a standard method to enhance insoluble weak acid or base medications. Drug conversion to its salt form results in greater water solubility since salts tend to be more soluble than plain compounds do. The conversion of drugs into salts works effectively on compounds whose dissolution depends on pH levels. The anti-epileptic drug phenytoin gains increased water solubility when pharmacologists convert it into its sodium salt form. The solubility of ibuprofen sodium exceeds that of free ibuprofen acid[39-42].

2.9 Lipid-based Formulations

Poorly soluble drugs find a solution through lipid-based formulations which involve liposomes and Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) to increase drug solubility by using lipid matrices. Liposome-based drug encapsulation systems accept drugs of any hydrophilic or hydrophobic nature while improving drug solutions through enhanced stability mechanisms and lower particle aggregation rates. SLNs and NLCs serve the purpose of drug bioavailability enhancement by delivering controlled drug release while protecting drugs from gastrointestinal degradation. The use of liposomal amphotericin B formulations provides enhanced solubility properties as well as lowered toxicity levels and superior therapeutic benefits compared to standard formulations[32,43,44].

2.10 Use of Supercritical Fluid Technology

The process of Supercritical Fluid (SCF) technology uses carbon dioxide or another substance above its critical point which creates conditions between gas and liquid properties. The dual characteristics of SCFs between liquids and gases enable their use as an ideal system for manufacturing drug particles on a micron scale. Superficial Antisolvent (SAS) precipitation as a part of SCF technology generates drug particles with high dispersal and exceptional fineness so they present increased surface areas available for dissolution. The process has yielded effective results for naproxen and tamoxifen drugs as it enhances their dissolving potential and delivery capability[19,23].

2.11 Nanocrystals and Nanoparticles

Formulating nanocrystals and nanoparticles stands as an optimal method to boost the solubility levels of poorly aqueous drugs. Drug particles called nanocrystals receive reduction to sizes within the nanometer domain (1-1000 nm) which expands surface area and boosts dissolution speed. Drugs become more soluble through dispersion in water solutions when using polymeric nanoparticles together with lipid nanoparticles as nanoparticle systems. The nanometric danazol and griseofulvin drug formulations have shown notable increases in solubility and bioavailability benefits[45,46].

2.12 Solid Dispersions

Solid Dispersion (SDs) combines drug substances with hydrophilic carrier polymers including PVP, HPMC, PEG to make SDs that enhance solubility. Drug delivery through a solid dispersion process involves the use of an amorphous state distribution of the drug that optimizes its dissolution potential over crystalline forms. Medical personnel use hot melt extrusion, solvent evaporation and spray drying methods to develop SDs. The formulation of carbamazepine drugs and poorly soluble anticancer drugs has been effectively achieved using this approach[47,48].

2.13 Polymer-based Nanocarriers (Polymeric Micelles)

The self-assembling system of polymeric micelles forms by amphiphilic block copolymers in aqueous solutions which result in stable micellar structures. Polymeric micelles contain an interior hydrophobic core that absorbs poorly soluble drugs while their exterior hydrophilic shell maintains stability when they are dissolved in water. The core of micelles seeks hydrophobic drugs to dissolve them so their dissolution rate improves. Scientists have achieved successful Paclitaxel formulation through polymeric micelles which improve drug solubility and stability together with therapeutic performance. The drug solubility of hydrophobic anticancer drugs reaches improvement using Polyethylene Glycol (PEG)-based micelles[32].

2.14 Biopharmaceutical Classification System (BCS) Modulation

Drugs obtain their classification from the Biopharmaceutical Classification System (BCS) through analysis of their absorption properties and solubility characteristics. The solubility of poorly soluble drugs (BCS Class II) can be enhanced through techniques which include the conversion of salts together with particle size reduction while adding solubilizers for improved bioavailability classification. The enhancement of dissolution rate represents the main goal for achieving better drug permeation. Carbamazepine and felodipine receive solubility-enhancing treatment through formulations like solid dispersions and lipid-based delivery systems since both drugs belong to BCS Class II[10,11,18].

2.15 Use of Prodrugs

A prodrug functions as a transformation of a chemically altered medication that transforms into its active form through body metabolism after drug administration. The drug design process creates prodrugs which elevate drugs absorbability as well as dissolving capacity through water-resistant modification. The chemically modified prodrug enhances drug molecule solubility in aqueous solutions which results in better absorption before activating the active drug. The solubility improvement of valacyclovir as a prodrug of acyclovir allows it to achieve better bioavailability. Similarly, talampanel, a prodrug of 2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-yl) acetic acid, exhibits better solubility and efficacy[49,50].

2.16 Salt of Hydrophobic Acids

Creating salts of hydrophobic drugs by pairing them with hydrophilic counterions is another strategy to improve solubility. These salts exhibit significantly better solubility compared to their free acid form. This method is typically applied to weakly acidic or weakly basic drugs. By altering the ionization properties of the compound, the solubility in water can be significantly increased. For instance, aspirin (acetylsalicylic acid) has been converted into sodium aspirin to enhance its water solubility, improving its bioavailability for oral administration[51-53].

2.17 Cyclodextrin-based Nanosponges

Nanosponges emerge from chemical cyclodextrin modification to three-dimensional polymeric systems that establish drug solubility through cavity-based drug encapsulation. Nanosponges create highly soluble pharmaceuticals that release medications in a controlled manner. Drug solubilization with nanosponges reveals better stability and dynamic capabilities to manage drugs with poor solubility instead of basic cyclodextrin complexation methods. Scientists have used cyclodextrin nanosponges to formulate ketoconazole alongside curcumin thus improving their therapeutic effectiveness and solubility[54,55].

2.18 Bioavailability Enhancing Lipid Nanocarriers

The solubility of lipophilic drugs improves when they integrate into lipid-based systems through using lipid nanocarriers such as Lipid-Core Micelles (LCM) and

Nanostructured Lipid Carriers (NLCs). The lipid carriers enhance drug solubility and stability levels in poorly soluble drugs while providing controlled drug release mechanisms shown in Table 2. The delivery of hydrophobic drugs to Gut-Associated Lymphoid Tissue (GALT) and exact body sites becomes possible through these systems. Scientists improve curcumin pharmaceutical properties by creating lipid nanocarriers which expand its water-insoluble nature and increase its bioavailability level[10,11,32].

2.19 High-pressure Homogenization (HPH)

High-pressure homogenization functions as a mechanical method for developing nanosuspensions of pharmaceutical drugs with limited dissolving capacity. Homogenising drugs at high pressures turns drug particles into nanoscale sizes while also raising their surface area for quicker dissolution. HPH technology enables the creation of nanocrystals as well as nanosuspensions or lipid-based nanosystems. HPH technology successfully enhances the solubility along with bioavailability of griseofulvin and carbamazepine medications[13,42].

2.20 Use of *In-situ* Gelation Systems

The *in-situ* gelation process uses polymers which transform from solution to gel state after activation through defined triggers such as temperature and pH fluctuations and ionic strength changes. The systems find their most suitable application in drug delivery because they enable localized drug release mechanisms. *In-situ* gelation systems benefit poorly soluble drugs through 2 functions: They encapsulate drugs in gel matrices to boost solubility while simultaneously managing drug release patterns. Methotrexate and diclofenac appear in *in-situ* gel formulations that increase their solubility while offering extended-release capabilities[10,11, 56,57].

3. Role of Polymers to Enhance Solubility and Bioavailability

Polymers are multiple units of homologous monomers that plays a role of backbone to majority of dosage forms like tablets, suspensions, ointment, *etc*. Also, among above techniques, the recent investigations have lead to estimate that polymers also play a major role in enhancing solubility of poorly water soluble drugs by controlling the drug release from different formulations by various mechanisms. Even has taken great place in novel drug delivery. These achievements of polymers have been due to its unique properties[1-8,20,21,25-27].

3.1 Natural Polymers

They are plant and animal derivatives, also due to its better desired properties, they have replaced synthetic polymers. Classification of polymers shown in Figure 4.

3.1.1 Classification of Polymers

3.2 General Mechanism of Polymers in Drug Release and its Solubility

There are 3 main mechanisms involved in drug release that leads to a better solubility which is shown in Figure 5.

Table 2. Role of natural polymers in nanocarriers with examples and advantages

Natural Polymer	Carrier Type(s)	Mechanism of Solubility Enhancement	Example Application	Key Advantages
Chitosan	NPs, micelles, liposome coatings.	Mucoadhesion, permeability enhancement, anti-aggregation.	Paclitaxel-CS micelles	Enhances solubility, enhances tumor uptake.
Alginate	Nanogels, beads, NLC coatings.	Ca^{2+} crosslinked gels maintain supersaturation.	ALG-5-FU nanogels	Colon targeting, sustained release.
Hyaluronic acid	Drug conjugates, decorated NPs/liposomes.	CD44 receptor targeting, hydrophilic corona.	HA-doxorubicin conjugates.	Active tumour targeting.
Gelatin	Nanoparticle, depots.	Hydrophilic matrix, enzymatic degradation.	Gelatin-cisplatin NPs.	Sustained release, injectability.
Dextran	Conjugates, nanocrystal stabilizer.	Solubility *via* conjugation, steric stabilization.	Dextran-doxorubicin.	Improved PK, reduced RES uptake.
Pullulan	Amphiphilic micelles.	Hydrophobic core + stealthy shell.	Pullulan-cholesterol/PTX micelles.	High loading, extended circulation.
Pectin/Xanthan/ Cellulose	Nanogels, matrices.	Precipitation inhibition, colon-specific release.	Pectin-5-FU nanogels.	Site-specific targeting.
Cyclodextrins	Inclusion complexes, nanosponges.	Host-guest encapsulation, controlled release.	Curcumin/CD nanosponge.	High payload, stability.

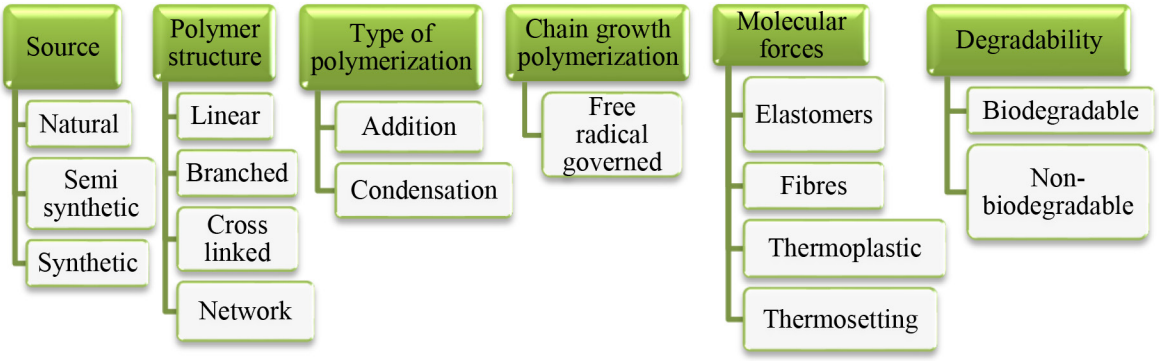


Figure 4. Classification of polymers.

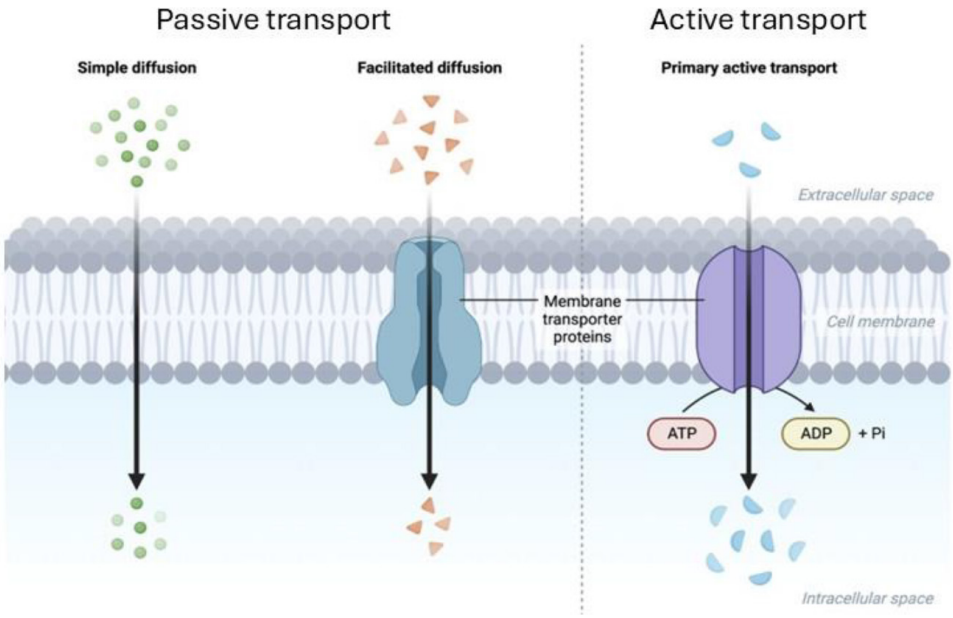


Figure 5. Different types of membrane transport.

3.2.1 *Diffusion*

The delivery of drugs from polymers as delivery systems depends on diffusion because drug molecules need to move by diffusion through the polymer matrix at specific release rates. Both drug diffusion speed and external environmental influences are determined by polymer nature and structure together with drug-polymer interactions. Drug dissolves and diffuses from matrix-based diffusion systems through the polymer because water penetrates to dissolve medications throughout the entire polymer structure. The drug release pattern demonstrates Higuchi kinetics because drug content continuously lowers inside the polymer material. The drug placement within a polymeric membrane during reservoir-based diffusion systems enables prolonged and consistent delivery of medication which follows zero-order kinetics. The diffusion rate of pharmaceutical products depends on multiple aspects that include the properties of polymers along with their interactions with drugs, their degradation characteristics and environmental conditions that involve pH levels as well as temperature measurements. Hydrophilic polymers augment diffusion because they can expand and take up water molecules, but hydrophobic polymers support prolonged release through their water-impermeable structure. Diffusion-controlled drug delivery mechanisms are fundamental in pharmaceutical engineering because they enable sustained drug release in sustained-release tablets and transdermal patches along with biodegradable implants

and nanoparticle carriers. Drugs release at steady rates from these systems both supports therapeutic drug monitoring and enhances patient medication adherence while minimizing adverse reactions[1-8,58,59].

3.2.2 Degradation

The drug delivery system depends on degradation as a fundamental mechanism because biodegradable polymers suffer gradual breakdown allowing polymer matrix breakdown without surgical intervention. The polymers degrade through hydrolysis and enzymatic processes which result in biocompatible substance byproducts that get safely processed and eliminated through metabolic pathways of the body. The degradation period and process of biodegradable polymers depend on molecular weight, polymer composition and hydrophilicity along with environmental conditions. The degradation of certain biodegradable polymers like Poly(Lactic-co-Glycolic Acid) (PLGA) and Polylactic Acid (PLA) causes systematic breakdown of the material structure which results in an extended drug release as the dissolving polymer matrix degrades. The degradation process of surface-eroding polyanhydrides occurs progressively from the exterior into the interior which creates a precise drug release profile. Surface erosion serves as a valuable release technique primarily used for medications that need to release according to specific timelines. Medical treatments using biodegradable polymers eliminate the necessity of surgical removal techniques which lowers healthcare expenses as well as improves patient comfort. These polymers provide many applications including biodegradable implants which pairs with microspheres and nanoparticles for controlling drug delivery systems that produce safe delivery methods without accumulating foreign materials within the body[1-8,32,58,59].

3.3.3 Swelling

Drug release depends heavily on the swelling process when drugs are formulated with polymers serving as protective layers or suspension materials. Drugs embedded inside polymeric systems enter biological fluids such as gastric or intestinal fluids where polymers show an ability to absorb water along with other chemicals. The absorption process expands the polymer network structure which leads to swelling. The swelling polymer expands its volume to allow more water molecules inside the matrix to dissolve drugs embedded in the dosage form which enables their diffusion to occur. The drugs release process is strengthened through this method which delivers steady and extended therapeutic benefits. The swelling ability of a polymer depends on the combination of hydrophilicity and molecular weight as well as the density of polymer cross-links. The drug diffusion process becomes faster when using hydrophilic polymers like Hydroxypropyl Methylcellulose (HPMC) alongside sodium alginate and chitosan because these polymers expand strongly after absorbing water. The extent of swelling in polymers depends on their cross-linking density and hydrophobic properties since these factors influence how much they absorb water and determine their drug release patterns. This drug delivery strategy provides exceptional benefits for hydrogels, matrix tablets and bio-adhesive drug carriers because polymer expansion controls drug bioavailability and avoids sudden drug release known as dose dumping. The mechanism drives drug formulations to achieve maximum efficiency and security because it enhances their therapeutic benefits[1-8,58,59].

4. Natural Polymers

It was found from many *in-vitro* dissolution studies that on addition of natural polymer, dissolution of drugs has been enhanced to a wide range as compared to drug alone or with the physical mixture. The enhancement in the rate of dissolution may be explained based on an increase in solubility and decrease in crystallinity of drug due to addition of polymers. Some polymers also have surface activity (like WSG- Water soluble Gelatin), it may improve the wettability of drug particles by water through dispersion of drug particles in polymers[1-8].

4.1 Classification of Natural Polymers

Classification of natural polymers show in Figure 6.

4.2 Natural Gums

4.2.1 Guar Gum

Guar gum, also known as guaran, gum cyamposis, Cyamopsis gum, Guarina, Glucotard, Guyarem, cluster bean, and Calcutta lucerne, is a naturally occurring

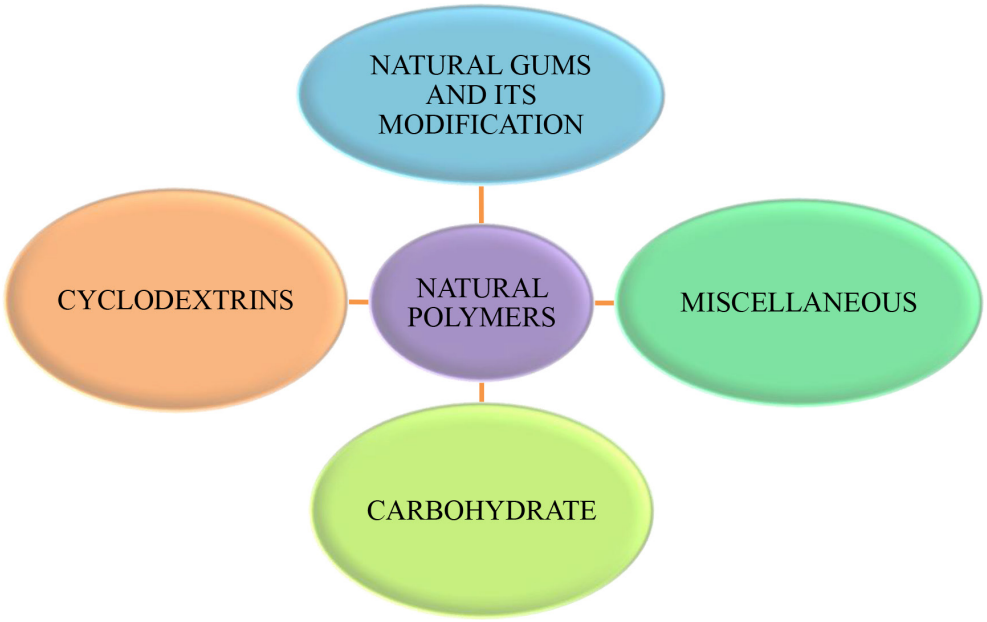


Figure 6. Classification of natural polymers.

polysaccharide extracted from the endosperm of the seed of the guar plant (*Cyamopsis tetragonoloba* L.). It primarily consists of galactomannans, which are polysaccharides composed of a β-(1,4)-linked D-mannose backbone with α-(1,6)-linked D-galactose side chains shown in Figure 7. The degree of galactose substitution influences its solubility, viscosity, and functional properties. Due to its unique properties, guar gum is widely used in the food, pharmaceutical, and industrial sectors as a thickening agent, emulsifier, stabilizer, and controlled-release polymer in drug delivery systems. Guar gum is highly hydrophilic due to its water-retention capacity, which enables it to swell in water and form a viscous gel that aids in controlling drug release. The substance lacks solubility characteristics when placed in organic chemicals including ethanol, methanol, and acetone. Pharmaceutical formulations benefit from guar gum as an excipient because its pseudoplastic behaviour shows that viscosity declines with increasing shear stress. The substance creates steady gels for managed drug release while its stabilizing and emulsifying properties protect dispersed drug particles present in liquid formulations. Within pharmaceutical drug delivery systems through oral administration the pharmaceutical industry extensively utilizes guar gum mainly for sustained release drug formulation technologies. Guar gum demonstrates high viscosity with swelling properties which results in better drug dissolution properties and extended therapeutic benefits. The substance provides valuable functionality in drug delivery through its ability to resist degradation in upper gastrointestinal regions before breaking down to release medication within the colon. The physical mixing process combined with kneading and solvent evaporation allows cefixime (an antibiotic) to improve drug dissolution through its combination with guar gum. Licofelone treatment for osteoarthritis patients relies on co-grinding 1:6 proportions of natural guar gum and heat processed guar gum to boost pharmaceutical release. The high water-retention capability of guar gum enables its use in sustained and controlled drug release systems as well as colon-targeted drug delivery systems. The drug absorption rate increases slowly because of this property which leads to better drug response rates. The pharmaceutical compounds diltiazem hydrochloride (for hypertension) along with metoprolol tartrate (cardiovascular uses) and trimetazidine dihydrochloride (angina treatment) utilize guar gum to manage drug release kinetics. Simvastatin which is a cholesterol-lowering drug utilizes guar gum together with microwave-induced solid dispersion methods to boost its solubility levels[60,61].

4.2.2 Locust Bean Gum

Locust Bean Gum (LBG), also known as carob gum, is a natural polysaccharide derived from the seed endosperm of the carob tree (*Ceratonia siliqua*),

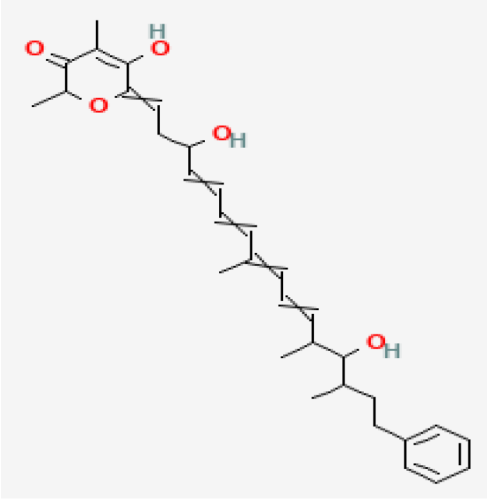


Figure 7. Guar gum.

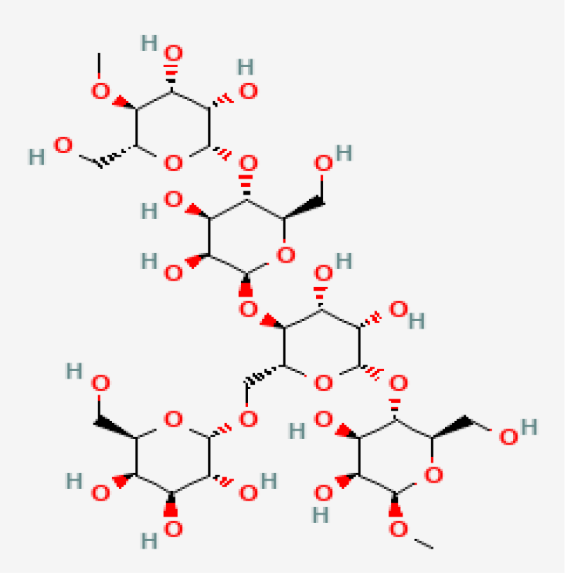


Figure 8. Structure of locust bean gum.

which belongs to the subfamily *Caesalpinioideae* of the *Leguminosae* family. Like guar gum, LBG is composed of galactomannan polymers, consisting of β-(1,4)-linked D-mannopyranosyl monomers with D-galactopyranose side chains (Figure 8). This structural similarity gives LBG comparable drug release properties to guar gum and scleroglucan, making it a valuable excipient in pharmaceutical formulations, particularly for sustained and controlled drug release. Locust bean gum becomes more soluble after heat and enzymatic treatments produce Modified Locust Bean Gum (MLBG) that exhibits better functional properties. LBG serves as a popular pharmaceutical and food additive ingredient due to its thickening and gelling properties. This material demonstrates non-Newtonian fluid characteristics when subjected to high shear forces which cause viscosity to decrease although at low shear it functions as a Newtonian fluid with constant viscosity levels. The controlled drug delivery systems benefit highly from this property because they require sustained flow consistency. The viscosity of LBG functions at stable levels when operating within pH levels extending from 4-9 which allows its use in diverse formulations with different pH conditions. LBG demonstrates widespread utility in pharmaceutical drug delivery research because of its ability to support extended drug release procedures. Researchers utilized LBG to develop delivery systems for medication control of diclofenac sodium as well as lovastatin pharmaceutical compounds. By acting as a carrier material for these drugs LBG helps to increase availability and effective drug actions. The combination of dietary fiber in LBG leads to synergistic LDL-cholesterol reduction which scientists attribute to its high dietary fiber content. People who have hyperlipidemia together with cardiovascular conditions can gain benefits from using this substance. Studies indicate that LBG demonstrates promising therapeutic effects for diabetes mellitus treatment outside its drug delivery functions. LBG functions as a gel through its properties to slow stomach emptying which creates feelings of satisfaction thereby decreasing food consumption and improving blood glucose management. The delayed stomach emptying function of LBG functions to control blood glucose which establishes it as a beneficial natural food component for diabetic patients[62-66].

4.2.3 Gum Karaya

Gum karaya is a natural polysaccharide obtained as an exudate from the stems and branches of the *Sterculia* tree, belonging to the *Sterculiaceae* family. It is a complex, partially acetylated polymer composed of rhamnose, galactose, and glucuronic acid monomers. This unique composition contributes to its hydrophilic nature, swelling capacity, and adhesive properties, making it valuable in pharmaceutical applications, particularly in drug solubility enhancement and controlled drug release systems. Compared to guar gum, gum karaya

exhibits superior mucoadhesive properties, making it particularly effective in buccal drug delivery. Additionally, it follows a zero-order drug release profile, ensuring a consistent and sustained release of the active pharmaceutical ingredient over time. The key pharmaceutical use of gum karaya involves improving drug solubility for medications that demonstrate limited water solubility. Drugs benefit from solubility and dissolution rate improvements using three modification methods which consist of co-grinding and kneading and solvent evaporation approaches. When NM is co-ground with modified karaya gum the drug properties achieve superior solubility performance through better wettability and dissolution and lower crystalline structure. The co-grinding technology increases NM distribution throughout the solution so the drug is accessible for absorption processes. Glimepiride antidiabetic drug demonstrated enhanced solubility through solvent evaporation formulation with karaya gum at the drug-to-gum ratio of 1:9. Gum karaya demonstrates extensive use within buccal drug delivery systems because it provides excellent adhesive properties which help maintain drug retention at absorption sites. Direct absorption routes along with bypassing first-pass metabolism become achievable due to this property which improves drug bioavailability. A therapeutic response needs sustaining formulations to contain at least 50% w/w gum karaya concentration for delivering sustained drug release[67-69].

4.2.4 Xanthum Gum

Xanthan gum is a natural polysaccharide produced through the fermentation of the gram-negative bacterium *Xanthomonas campestris*. Structurally, it consists of a β-D-glucose backbone, like cellulose, with a side chain composed of β-D-mannose, β-D-glucuronic acid, and α-D-mannose (Figure 9). These sugar units collectively form a pentasaccharide structure, which contributes to its unique rheological and functional properties. The widespread application of xanthan gum as a thickening agent and stabilizer together with viscosity modifier makes it vital in pharmaceutical and cosmetic and food industries. The pivotal physicochemical quality of xanthan gum appears as pseudoplastic behavior since it demonstrates decreased viscosity during higher shear stress conditions. Xanthan gum demonstrates favorable behavior by providing smooth texture enhancement and stability improved by flow stability for pharmaceutical solutions and topical pharmaceutical formulations. At all pH levels between acidic and basic ranges xanthan gum maintains its stability effectively. Xanthan gum maintains high water solubility and moisture retention thus its widespread use in cosmetics and toothpaste products and pharmaceutical development to enhance product texture. Xanthan gum often teams up with various polymer compounds inside pharmaceutical formulations to achieve controlled medication release patterns. Pharmacologists use Hydroxypropyl Methylcellulose (HPMC) together with xanthan gum to develop modified-release tablets containing diltiazem hydrochloride which functions as a calcium channel blocker for treatment of hypertension and angina. Experts found that a blend of xanthan gum and galactomannan serves as an ideal combination to control theophylline drug release pattern which functions as a bronchodilator for respiratory condition treatment. Xanthan gum acts as a vital component to improve the dissolution profile of gliclazide oral hypoglycemic agent through its incorporation with guar gum and huppu gum during co-grinding formulation. The drug combinations improve both solubility levels and drug release duration and enhance the ability of drugs to reach their target site. As a highly functional material xanthan gum demonstrates exceptional thickening properties combined with solid stabilizing effects and well-controlled release abilities. Pharmaceutical and cosmetic industries together with food industries favor xanthan gum because of its water solubility combined with pH stability and its pseudoplastic behavior. The combination of xanthan gum with other natural and synthetic polymers enhances drug dissolution properties as well as bioavailability and controlled release capabilities which positions it as vital for contemporary drug delivery platforms[70-72].

4.2.5 Aegle Marmalos Gum

Bael gum, also known as Aegle Marmelos Gum (AMG), is a natural polysaccharide obtained from the fruits of *Aegle marmelos*, belonging to the *Rutaceae* family. It is composed of various monosaccharides, including L-arabinose (12.5%), D-galactose (71%), D-galacturonic acid (7%), and L-rhamnose (6.5%), which contribute to its unique physicochemical and functional properties.

AMG demonstrates exceptional abilities to interact with water which enables its effective utilization in pharmaceutical products as binding agent and swelling agent and solubility enhancer. The main use of AMG occurs through increasing solubility of pharmaceuticals which poorly absorb water. Using AMG with Modified Aegle Marmelos Gum (MAMG) obtained through heat treatment increases drug solubility parameters along with dissolution rate performance and drug wettability characteristics. The combination of AMG and MAMG in higher concentrations leads to improved drug solubility and bioavailability of aceclofenac through co-grinding or physical mixture techniques. Aceclofenac is a Nonsteroidal Anti-Inflammatory Drug (NSAID) treated with such solubility enhancement methods. The better dissolution profile enables enhanced therapeutic effects and improves drug absorption speed in the human body. The extensive use of AMG involves its work as a hydrophilic carrier in solid dispersion formulations because of its remarkable swelling index along with its exceptional water retention and strong binding properties. As a result, this technique performs exceptionally well for boosting poor drug dissolution rates of hydrophobic pharmaceuticals. Research data demonstrates that atorvastatin as a lipid-lowering drug achieves superior dissolution speed from its lyophilized form with AMG at 1:1 ratio compared to unmodified atorvastatin. Better bioavailability occurs because atorvastatin achieves increased solubility when formulated with AMG which improves treatment effectiveness[73-75].

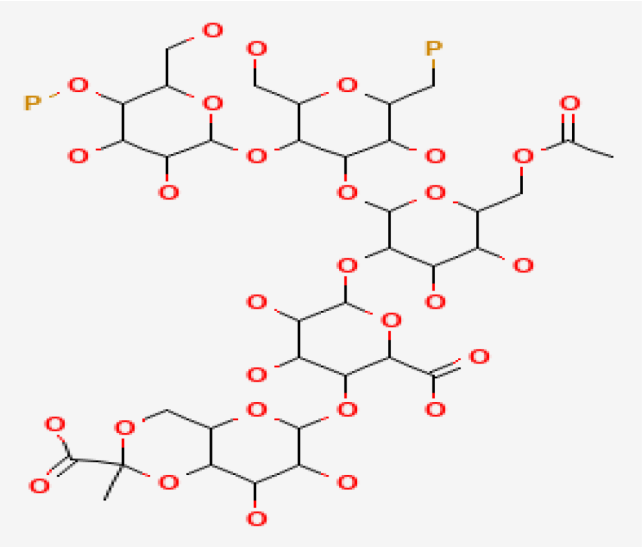


Figure 9. Structure of xanthan gum.

4.2.6 Hupu Gum

Hupu gum, also known as silk cotton gum, is a natural exudate obtained from the dried gummy secretions of *Cochlospermum religiosum*, a plant belonging to the *Cochlospermaceae* family. It is a hydrophilic polysaccharide known for its high swelling capacity, water retention ability, and biocompatibility, making it a valuable excipient in drug delivery systems. Hupu gum and its modified form have been extensively researched for their role in enhancing solubility, dissolution, and bioavailability of poorly water-soluble drugs. Hupu gum is its ability to improve the solubility and bioavailability of drugs through various formulation techniques. Studies have shown that the co-grinding method, which reduces particle size and enhances surface area, significantly improves the solubility and dissolution rate of Pioglitazone HCl, an antidiabetic drug. Similarly, Clopidogrel bisulfate, an antiplatelet medication, has demonstrated enhanced solubility when formulated using the gel entrapment method with hupu gum, ensuring better drug dispersion and controlled release. Additionally, hupu gum has been investigated as a drug carrier in combination with other natural polymers to achieve optimized drug release profiles[76,77].

4.2.7 Cyclodextrin

Cyclodextrins are cyclic oligosaccharides of 6, 7 or 8 glucose units, joined together by α 1,4 glucosidic linkage and are respectively called as α-, β- and γ- cyclodextrins shown in Figure 10, which helps to enhance solubility, stability, dissolution rate and bioavailability, reducing the volatility. β-cyclodextrins act as dissolution enhancers because it is a cone like structure. β-cyclodextrins are most commonly used carrier due to its suitable cavity diameter (7-8 Armstrong) for guest molecules, the hydroxyl groups present on the outer surface forms the hydrophilic portion while the inner portion,due to the presence of glycosidic ether oxygen at O-4 and the hydrogen attached to C-3 and C-5 and thereby provides a hydrophobic environment into which drug can enter and is included without any covalent bonding, while outer hydrophilic environment contributes to drug dissolution. It is widely used with drugs like naproxen, carbamazepine by inclusion complex formation by solvent method. Hydroxyl propyl β cyclodextrin is widely used with drugs like glipizide- inclusion complex

by kneading method and meloxicam with technique of inclusion complex by freezing method[36-38,54,55].

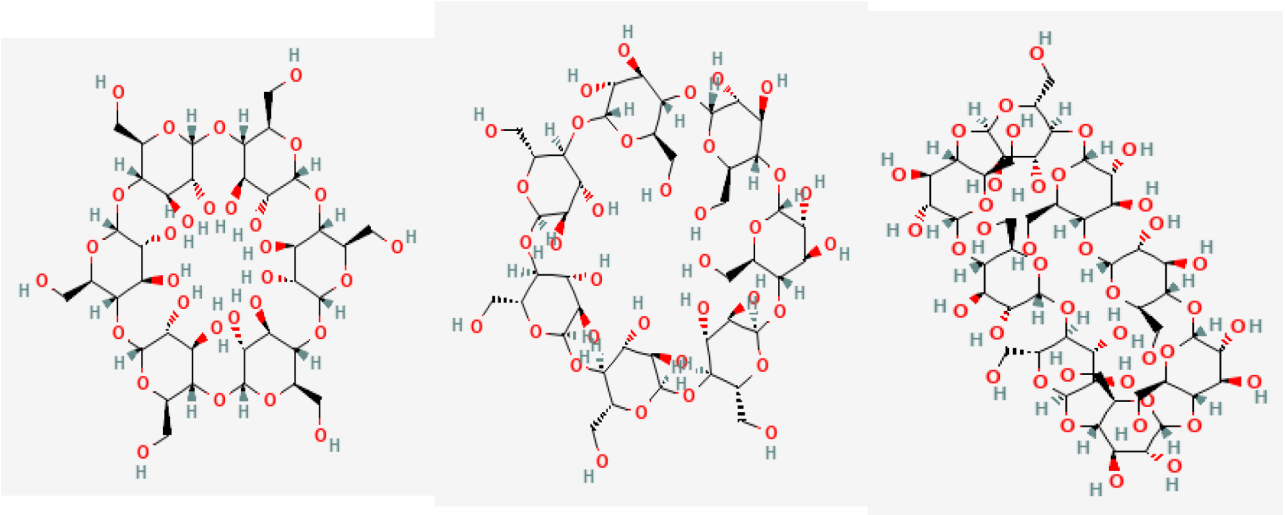
4.3 Carbohydrates

4.3.1 Pectin

Pectin is a component of plant cell wall made of D-galacturonic acid residues linked with α-1, 4 bond. Obtained widely from citrus peel of *Citrus Simon* or *Citrus Aurantium* of *Rutaceae* family and from apple pomace, *Malus domestica.* The composition of polysaccharides can vary according to source; citrus peel has a smaller number of sugar and with a smaller molecular size than that of apple pomace. Because of its high potential to show hydrophilic carrier ability, it is widely used in controlled drug delivery system, especially in colon drug delivery system and transdermal patches of chloroquine to mask its bitter taste. Also used in ophthalmic microparticulate polymer delivery of piroxicam and it showed enhanced bioavailability into the aqueous humour *in-vivo* test. A mixture of xyloglucan and pectin produced an *in-situ* gel formation showing sustained delivery of paracetamol in preclinical tests[78-81].

4.3.2 Chitosan

Chitosan exists as a natural polysaccharide originating from the deacetylation of chitin that scientists derive primarily from the crab and lobster and shrimp exoskeletons[8]. Chitosan can be in the radulas of mollusks while beaks of cephalopods and exoskeletons of insects as well as being present in fungal cell walls. Chitosan materials consist of glucosamine and N-acetylglucosamine monomers which establish β-(1,4) glycosidic bond connections (Figure 11). During the deacetylation process of chitin, the product becomes 2-amino-2-deoxy-β-D-glucan thus creating chitosan with its distinctive functional traits. The excellent pharmaceutical candidate status of chitosan stems from its excellent properties which include remarkable biodegradability together with biocompatibility and low toxicity values. The adhesive quality of chitosan improves the absorption process of oral drugs which results in better availability of poorly dissolved medications[25]. The drug delivery systems that utilize chitosan include films along with capsules, microspheres, and nanoparticles due to their hydrophilic structure and high permeability together with its swelling properties. Due to its extensive study researchers have confirmed that chitosan strengthened drugs through solubility improvement and better dissolution outcomes. Scientists discovered that combining nifedipine with chitosan through co-grinding resulted in easier solubility and reduced crystalline nature that benefits drug absorption. Abstracts or results using chitosan and abietic acid in solid dispersions have demonstrated methods to boost drug therapeutic performance. The wide range of pharmaceutical possibilities of chitosan enables



Alpha-cyclodextrin **Beta-cyclodextrin** **Gamma-cyclodextrin**

Figure 10. Structure of cyclodextrin.

its crucial use in controlled drug delivery combined with gene and protein transport and wound care and biomedical systems development. The pharmaceutical properties of chitosan function as a valuable excipient because it improves drug solubility and enhances both permeability and delivery duration[42,53-56,69,82]. Some applications of chitosan in various types of cancer treatment shown in Table 3.

4.3.3 Mannitol

The production of mannitol as a sugar alcohol starts from fructose hydrogenation that leads to its synthesis (Figure 12). People can find mannitol in saw palmetto (*Serenoa repens*) among natural plant specimens. The pharmaceutical industry depends on mannitol because of its water solubility combined with non-hygroscopicity and inertness as an excipient. The key use of mannitol as an excipient involves improving the ability of drugs that poorly dissolve in water. Stability tests revealed that rofecoxib NSAID drug demonstrates enhanced dissolution profiles after hot melt processing with mannitol and sorbitol at different percentages including 50%, 75% and 90%. Better drug dispersion along with improved wettability results from drug-carrier interactions that surpasses both drug-water and carrier-carrier interactions. Pharmaceutical researchers have established the effectiveness of mannitol to enhance the solubility characteristics of nifedipine which expresses low dissolving capabilities in water solutions. Drug dissolution properties of diazepam significantly enhance when this benzodiazepine receives mannitol treatment through spray drying for pharmaceutical use.

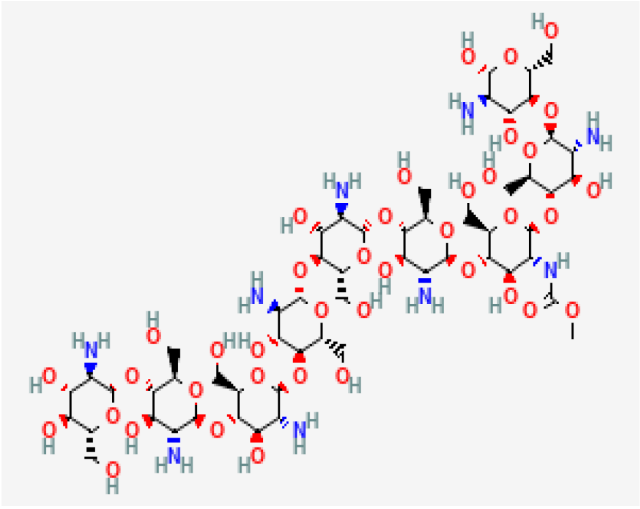


Figure 11. Structure of chitosan.

The spray drying method minimizes drug crystalline structures which boosts drug solubility alongside improving its bioavailability. Pharmaceutical solutions use mannitol as a preferred excipient because it is non-toxic and water-soluble and acts as a stabilizer throughout various solid formulations and oral medications as well as quick-dissolving systems. A drug delivery system depends on mannitol as a fundamental element because it promotes drug solubility while raising dissolution rates and delivering stable drug carriers[83-85].

4.3.4 Lactose

Lactose is a widely used as excipient in majority of solid dosage forms because of its suitable properties, such as good hydrophilicity, low hygroscopicity, and good compression. Structure of lactose shown in Figure 13. Recent research shows that, dispersion with indomethacin, with minimum particle size and to increase the number of hydrogen bonds, also the number of interactions between the carboxyl group of indomethacin and the hydroxyl groups of lactose were increased through the mechanical activation using the vibrating ball mill. The desired solubility of the solid dispersion of indomethacin and lactose has increased almost 3-fold, compared to that of pure indomethacin. Other research also showed that indomethacin in a ternary mixture of drug with fine lactose and coarse lactose or in a binary mixture of drug and fine particles have better dissolution rate and in agglomeration[86].

4.4 Miscellaneous

4.4.1 Albumin

Human Serum Albumin (HSA) exists as the predominant plasma protein while making up between 35-50 g/L of the human serum composition. The liver produces this protein compound which weighs 66.5 kDa and exists at a half-life point of about 19 days. Maintaining osmotic pressure and transporting drugs together with metal ions and all other biomolecules represents one essential physiological function of albumin. Rated protein binding sites within albumin exist for penicillins and sulfonamides as well as indole derivatives and benzodiazepines and transition metal ions including Cu^{2+} and Ni^{2+} yet albumin shows nonspecific binding properties toward Ca^{2+} and Zn^{2+}. Reversible drug interactions with albumin increase the solubility and bioavailability of drugs that are

Table 3. Applications of chitosan in various cancer treatment.

Type of Cancer	Chitosan Used in Formulation	Mechanism of Action	Drug	Examples
Breast cancer	Chitosan nanoparticles, hydrogels	pH-responsive drug release, targeted delivery	Doxorubicin, Paclitaxel, Curcumin, 5-Fluorouracil	Chitosan-Folic Acid NPs targeting folate receptors in MCF-7 cells
Lung cancer	Chitosan-PLGA NPs, microparticles	Improved cellular uptake, sustained release	Cisplatin, Gemcitabine, Berberine	Chitosan-coated lipid NPs for lung tumour accumulation
Colon cancer	Chitosan-based hydrogels, mucoadhesive NPs	Enzyme-responsive, site-specific drug release	5-Fluorouracil, Irinotecan, Resveratrol	Chitosan-gelatin hydrogel for colonic drug delivery
Prostate cancer	Chitosan conjugates, polymeric nanoparticles	Enhanced apoptosis, androgen receptor inhibition	Docetaxel, Resveratrol, Curcumin	Chitosan-PEG NPs delivering Docetaxel to PC-3 cells
Liver cancer (Hepatocellular carcinoma)	Chitosan coated liposomes, polyelectrolyte complexes	Liver-targeted therapy, controlled release	Sorafenib, Doxorubicin, Gallic Acid	Chitosan-functionalized liposomes for HCC therapy
Brain cancer (Glioblastoma)	Chitosan-gold NPs, hydrogels	Blood-brain barrier penetration, local delivery	Temozolomide, Curcumin, siRNA	Chitosan-based nanogels for glioma treatment
Pancreatic Cancer	Chitosan-lipid hybrid NPs, Microspheres	Passive targeting *via* EPR effect, sustained release	Paclitaxel, Doxorubicin, Quercetin	Chitosan-stearic acid NPs for pancreatic cancer therapy
Leukemia (Blood Cancer)	Chitosan-Dendrimer Complexes, Polymeric Micelles	Receptor-mediated targeting, DNA interaction	Imatinib, Daunorubicin, siRNA	Chitosan-DNA nanocomplex for leukemia gene therapy
Ovarian Cancer	Chitosan-Gelatin NPs, PEGylated Chitosan	Enhanced bioavailability, tumor penetration	Carboplatin, Paclitaxel, siRNA	Chitosan-folic acid NPs for ovarian cancer cell inhibition
Esophageal Cancer	Chitosan-Peptide Nanocarriers	pH-sensitive release, apoptosis induction	Cisplatin, Quercetin, 5-FU	Chitosan-Alginate NPs enhancing esophageal drug absorption
Cervical Cancer	Chitosan-Lipid Nanocapsules	Sustained drug release, cervical cell apoptosis	Curcumin, Cisplatin, Paclitaxel	Chitosan-hyaluronic acid NPs targeting HPV-infected cells
Skin Cancer (Melanoma)	Chitosan-Silver NPs, Topical Gels	Photothermal therapy, reactive oxygen species generation	Curcumin, Doxorubicin, Photodynamic agents	Chitosan-Au NPs for melanoma photothermal therapy
Bladder Cancer	Chitosan-Coated Liposomes, Nanoparticles	Intravesical drug retention, mucoadhesion	Mitomycin C, Gemcitabine	Chitosan-based hydrogels for bladder cancer drug delivery
Thyroid Cancer	Chitosan-Biopolymer Nanoparticles	Receptor-specific uptake, enhanced cytotoxicity	Doxorubicin, Sorafenib	Chitosan-Hydroxyapatite hybrid NPs targeting thyroid carcinoma

poorly soluble in water. The binding of drugs to albumin increases their water solubility which enables them to stay in circulation longer and boosts drug stability together with controlled release effects. The binding interaction produces two benefits: Enhanced solubility together with extended drug half-life which makes it suitable for use as a drug delivery carrier. Clinical evidence reveals that albumin in its HSA and BSA and egg albumin forms delivers significant *in-vitro* dissolution benefits for hydrophobic drugs. Research has shown Indomethacin (IND) complexed with BSA produces enhanced dissolution rates

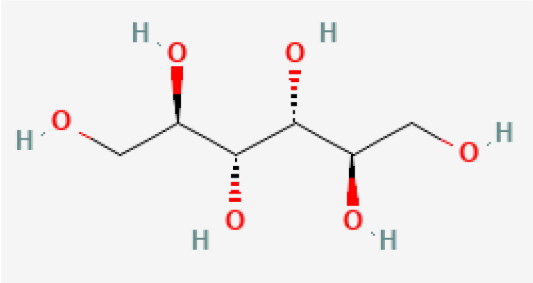


Figure 12. Structure of mannitol.

because of hydrophobic interactions and hydrophilic interactions and salt bridge formation mechanisms. The combination of nifedipine with egg albumin and water-soluble gelatin and β-cyclodextrins improved the solubility of this poorly soluble calcium channel blocker. Research indicates albumin shows promise as a molecule that enhances drug solubility while serving as a carrier during drug delivery applications for targeted and sustained release systems. Albumin demonstrates exceptional potential as a pharmaceutical formulation component because it improves hydrophobic drug bioavailability alongside its ability to enhance solubility and extend drug persistence within bloodstream circulation. Scientists actively investigate protein-based drug delivery strategies and nanoparticle formulations and sustained-release systems using albumin because of its useful drug delivery properties[58,87].

4.4.2 Skimmed Milk

Skimmed milk also called as lecithin is an alternative for milk in the formulations. due to presence of lactose in skimmed milk which provide polar effect and due to reduced crystallinity of the drug, it is used with drugs like Meloxicam by rotary vacuum evaporation technique with enhanced aqueous solubility and dissolution rate and with valsartan by solid dispersion method showing marked improvement in the solubility behaviour and increased drug release and showed no drug- carrier interaction. As the concentration of skimmed milk increases the surface area thereby increasing the dissolution of drug. Skimmed milk is used with simvastatin by lyophilization technique to enhance the solubility of pure drug up to 86.69 %[88].

4.4.3 Silica

Here we are discussing about two forms of silica

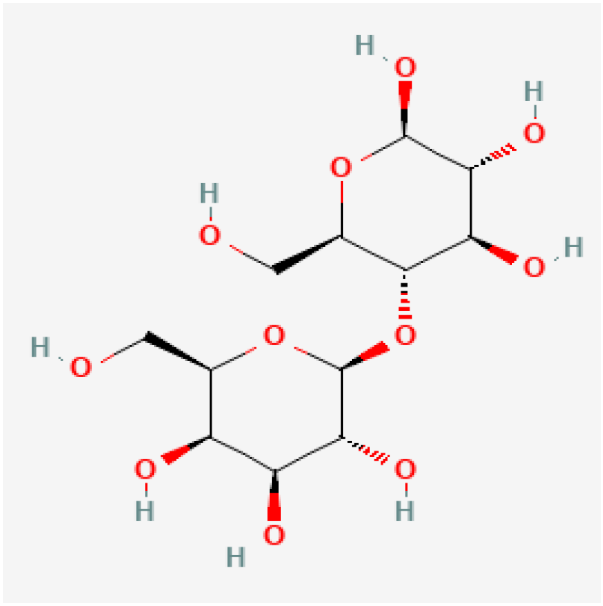


Figure 13. Structure of lactose.

4.4.3.1 Granulated Fumed Silica

In one of the types of research, it was selected carrier, which is basically a micro sized particles (about 30-40µm) of granulated colloidal silicon dioxide which is porous giving higher surface area providing an increased drug loading capacity. This characteristic has lead to variety of properties like increased absorbability, good flowability *etc* and its inert nature which has developed silica fumes as potential drug carrier. The increased solubility of drugs is due to interaction between drug and the silanol groups present in silica fumes which converts the mesoporous silica to amorphous form[89-90].

4.4.3.2 Silica Gel

Research was done using flurbiprofen drug with 5 different polymer carrier like soluble starch, MCC, silica gel, lactose and dicalcium phosphate. Even though lactose and soluble starch were used in higher ratio than others, it showed less dissolution rate of drug due to its nature to rapidly dissolve itself, leaving drug behind. While insoluble carriers like MCC, silica gel and dicalcium phosphate remains suspended and makes drug to dissolve better[90,91].

4.4.4 Urea

Water contains high solubility for organic urea due to its hydrotropic properties that improve the water absorption

of poorly dissolvable drugs. Urea forms tetragonal crystals when it crystallizes yet it can also take the hexagonal crystal structure as one of its polymorphic forms. The hexagonal crystal structure (Figure 14) has a distinctive feature which lets it absorb small molecules into its void spaces while improving drug solubility alongside dissolution speed. Urea functions as a prominent hydrophilic carrier ingredient in different pharmaceutical products including solid dispersions systems. Scientific studies proved that drugs such as flurbiprofen and rofecoxib underwent enhanced bioavailability and solubility improvement through combination with urea through fusion method processing. The drug particle dispersion becomes more efficient due to urea's high wettability and hydrotropic characteristics. Urea concentration and solubility enhancement show a direct relationship, so drug solubility increases progressively as the urea amount increases. The application of urea extends to both topical and transdermal approvals. The pharmaceutical industry relies on ascorbyl palmitate as an effective skin permeation dependent derivative of vitamin C for optimum productivity. Scientists have discovered that urea functions as an efficient carrier which enhances ascorbyl palmitate skin penetration making it better suitable for dermatological products. Pharmaceutical formulations benefit from urea because of its complete dissolubility in water and its ability to show different crystal forms along with its high tendency to absorb water. The dissolution along with enhanced bioavailability and permeation properties of drugs make urea an essential component for pharmaceutical delivery carriers to improve hydrophobic drugs[92,93].

5. Applications of Natural Polymers

The pharmaceutical industry and polymer industry utilize natural polymers for various significant applications showed in Table 4. The pharmaceutical sector expands extensively therefore new uses of pharmaceutical components deserve perpetual examination. The evaluation of natural polymer integration with pharmaceutical applications enables the polymer industry to detect additional functions that would lead to enhanced tailoring of properties for product requirements. The main pharmaceutical application of polymers exists in designating drug delivery mechanisms. This section will explain drug entry methods into the body along with natural polymer applications for drug delivery systems. In the Table 5, various natural polymers used in cancer treatment was mentioned[94-97].

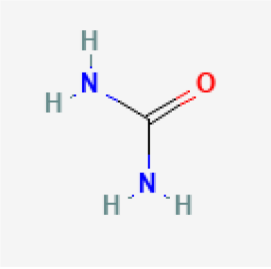


Figure 14. Structure of urea.

6. Challenges and Future Prospective of Natural Polymers in Cancer Treatment

The combination of nanomaterials possessing distinct advantageous characteristics together with improved drug delivery systems produces substantial hurdles as well as opportunities in cancer treatment. Drug delivery advancements during recent years predicted fundamental transformations for the healthcare system through nanotechnology implementation. Developing successful cancer nanotherapeutics presents a complicated procedure because few nano-formulations advance to clinical trials. Nanomedicine faces an important challenge because the physical and chemical attributes of nanomaterials determine how they interact with biological systems as well as how suitable they are for use and what level of toxicity they might cause. The development of safe nanomaterials needs controlled production techniques since uncontrolled nanocarrier interactions with biological systems could be harmful to biological structures. Medical applications using nanocarriers trigger safety concerns because research demonstrates that certain nanocarriers contain toxic properties. Nanotoxicology functions as an essential specialized area that represents a vital academic domain inside nanomedicine. The evaluation process for nanoparticle safety during therapeutic applications uses a standardized method to detect potential toxicities before nanoparticles become available for medical use. The therapeutic

Table 4. Natural polymers with their pharmaceutical applications

Natural Polymer	Source	Chemical Composition	Key Properties	Solubility Characteristics	Pharmaceutical Applications
Guar Gum	Endosperm of *Cyamopsis tetragonoloba* (Cluster bean)	Galactomannan (1,4-β-D-mannose with α-D-galactose)	High viscosity, swelling ability, bioadhesive, biocompatible	Swells in water, forms a gel-like structure	Used as binder, thickening agent, emulsifier in drug formulations, sustained drug release (*e.g.*, cefixime, licofelone)
Locust Bean Gum (LBG)	*Ceratonia siliqua* (Carob tree)	Galactomannan (1,4-β-D-mannose and D-galactose)	Non-newtonian flow, stabilizer, high fiber content	Water-insoluble but forms a gel with heating	Sustained drug release, used with diclofenac sodium, lovastatin
Gum karaya	Stem exudate of *Sterculia* species	Acetylated polysaccharide (rhamnose, galactose, glucuronic acid)	High viscosity, adhesive property, bioadhesive	Swells in water but is poorly soluble	Used in buccal drug delivery, sustained release (*e.g.*, nimodipine, glimepiride)
Xanthan gum	Fermentation of *Xanthomonas campestris*	β-D-glucose, β-D-mannose, β-D-glucuronic acid	Pseudoplastic flow, thickening agent, stabilizer	Soluble in hot and cold water, stable at different pH levels	Used in modified release formulations (*e.g.*, diltiazem HCl, gliclazide, theophylline)
Aegle marmelos gum (Bael Gum)	Fruit of *Aegle marmelos* (Bael tree)	L-arabinose, D-galactose, D-galacturonic acid, L-rhamnose	High water retention, binding ability, hydrophilic carrier	Swells in water, increases solubility of drugs	Used in solid dispersions (*e.g.*, atorvastatin, aceclofenac)
Hupu Gum	Exudate from *Cochlosper mumreligiosum*	Polysaccharide	High swelling, gel-forming ability	Hydrophilic forms a gel in water	Used in controlled release (*e.g.*, gliclazide, rofecoxib, pioglitazone HCl)
Chitosan	Derived from chitin (*Crustacean* shells, fungi)	Glucosamine and N-acetylglucosamine (β-1,4 linkage)	Biodegradable, bioadhesive, mucoadhesive	Soluble in acidic solutions	Used in gene delivery, oral absorption enhancer, microencapsulation (*e.g.*, nifedipine, abietic acid)
Albumin (HSA/BSA)	Human serum, bovine serum, egg albumin	66.5 kDa protein	Reversible binding with drugs, extends drug half-life	Soluble in water, binds hydrophobic drugs	Used in drug delivery (*e.g.*, indomethacin, nifedipine, β-cyclodextrins complexes)
Silica	Natural mineral (Quartz, Sand, Diatomaceous earth)	Silicon dioxide (SiO_2)	High surface area, adsorbent, moisture resistance	Insoluble in water but dispersible	Used as glidant, moisture barrier, drug stabilizer (*e.g.*, amorphous silica in drug delivery systems)
Urea	Organic compound (synthetically derived)	NH_2CONH_2	Hydrotropic, improves wettability, polymorphic nature	Highly soluble in water	Used as solubility enhancer (*e.g.*, flurbiprofen, rofecoxib, ascorbyl palmitate)
Sikkim Milk	Milk obtained from Himalayan cattle in Sikkim region	Proteins, fats, lactose, casein	Nutritional, stabilizer, bioavailability enhancer	Soluble in water and fat-based solutions	Used in nutraceutical formulations, protein-based drug delivery systems
Mannitol	Sugar alcohol (Hydrogenation of fructose)	$C_6H_{14}O_6$	Non-hygroscopic, stabilizer, wetting agent	Soluble in water	Used as carrier in solid dispersions (*e.g.*, nifedipine, diazepam, rofecoxib)

Table 5. Natural polymers in cancer treatment

Natural Polymer	Source	Application for Cancer Therapy	Examples of Drugs/Formulations
Chitosan	Crustacean shells	Nanocarriers, drug delivery, mucoadhesive properties	Chitosan-based nanoparticles for doxorubicin delivery
Alginate	Brown seaweed	Hydrogel formulation, sustained release	Alginate-encapsulated Paclitaxel
Hyaluronic acid	Animal connective tissue	Targeted drug delivery (CD44 receptor targeting)	HA-doxorubicin conjugates
Gelatin	Collagen (animal source)	Injectable drug carriers, hydrogel formation	Gelatin-based nanoparticles for cisplatin
Dextran	Bacteria (Leuconostoc)	Macromolecular prodrugs, nanoparticle stabilizer	Dextran-doxorubicin conjugates
Pullulan	Fungal fermentation	Nanoparticle carrier, bioadhesive film	Pullulan-paclitaxel conjugates
Pectin	Fruits (apple, citrus)	Colon-specific drug delivery	Pectin-based 5-Fluorouracil formulations
Cellulose derivatives	Plants, bacterial sources	Controlled drug release, film coating	Hydroxypropyl Methylcellulose (HPMC) in anticancer tablets
Carrageenan	Red seaweed	Bioadhesive, controlled release	Carrageenan-based nanoparticles for curcumin
Starch	Plants (corn, potato)	Nanoparticle matrix, controlled release	Starch-based drug carriers for doxorubicin

application of nanotechnology in cancer medicine continues to face challenges because drug release profiles measured in laboratory settings do not properly correspond to biological system conditions. The mismatch between laboratory testing data and medical practice conditions complicates the assessment of nanomedicine treatment effectiveness thus creating an obstacle for broad clinical use. The production of nanomedicine products at industrial quantities faces difficulties because establishing stability and quality control parameters during manufacturing processes proves challenging. Nanotherapeutics face delays in the regulatory approval process as a major critical issue. Today the U.S. Food and Drug Administration (FDA) operate without clearly established approval directives designed for medical nanomaterials. Nanoparticle characteristics remain inadequately addressed by existing bulk materials regulations through their use of guidelines written for larger-scale materials. Each nano-formulated drug receives regulatory decisions through individual case evaluations because both benefits and risks must undergo extensive assessment for approval. The customized evaluation procedure lengthens approval processes thereby prolonging the commercial availability of nanomedicine products. Regulatory challenges will likely escalate in complexity because persistent nanoplatform development results in advanced systems with integrated multiple diagnostic and therapeutic features that make assessments more challenging. Nanomaterials should only be applied in medical practice after strategically designed and developed methodology systems have been established to handle their associated challenges. Toward improved medical results from cancer treatments researchers need to understand cancer cells natural functions alongside tumour environments alongside drug absorption patterns and nanometer carrier body responses. Evaluation methods for cancer nanotherapeutics must be individualized to unlock the maximum potential of nanotechnology-based therapeutic strategies. The development of cancer nanotherapeutics demands an immediate creation of a detailed regulatory system that specifies clear protocols for evaluating testing and approving commercializing nanomaterial-based cancer treatments. Procedures to evaluate nanomedicine will enable safe and efficient transfers from research laboratories to clinical settings by protecting patients from risks and maximizing the benefits of advanced treatments. Developing nanocarrier-based therapies

encounters fundamental roadblocks because nanomaterials physical and chemical specifications determine their biological system performance levels and safety outcomes. Scientific analysis of nono-material behaviour in biological spaces requires focused investigation since these materials show distinct chemical and structural traits. The development of nanocarriers demands exact fabrication methods to avoid unwanted toxicities which harm human tissues. The inability to establish *in vitro-in vivo* correlations between drug release tests severely limits scientists ability to forecast how nanomedicines function inside living beings through laboratory methods alone. The prolonged approval period for nanomedicine products continues since organizations have yet to establish clear guidelines that facilitate regulatory procedures. The assessment process becomes more complex because of multifunctional nanoplatforms that contain multiple drug-delivery and diagnostic functions. Successful cancer treatment through nanotechnology requires dedicated scientific progress and both regulatory refinement and customized evaluation processes to tackle these existing obstacles. The advancement of research will lead to safer treatment options and enhanced effectiveness of nanomedicine-based cancer therapies available to patients worldwide[96].

7. Regulatory Aspects of Natural Polymers in Anticancer Drug Delivery

Natural polymers used in drug delivery processes for cancer therapy need to pass exact regulatory approvals established by three key global agencies: The U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) and India's Central Drugs Standard Control Organization (CDSCO). Chitosan along with alginate hyaluronic acid and gelatin represent natural polymers which have become popular because they demonstrate properties of biocompatibility and biodegradability and minimal toxicity. The validation of pharmaceutical applications for these materials depends on meeting established regulatory rules. The FDA in the United States determines how it regulates natural polymers through the specific use requirements. Pharmaceutical products containing natural polymers as excipients need to pass good manufacturing practice evaluations for GRAS designation or they must meet USP requirements for pharmaceutical excipients. Natural polymers used for drug encapsulation and controlled-release formulations need to pass through New Drug Applications (NDA) or Abbreviated New Drug Applications (ANDA) acceptance criteria under 21 CFR (Code of Federal Regulations). Natural polymer-based drugs need to fulfill examination criteria under the International Council for Harmonization (ICH) guidelines until they receive Marketing Authorization (MA) status after fulfilling comprehensive toxicological and pharmacokinetic and biocompatibility testing requirements. The CDSCO in India requires pharmaceutical companies to meet rejection criteria of Drugs and Cosmetics Act 1940 for natural polymers in drugs that verify compliance with Indian Pharmacopeia (IP) standards and require clinical trials before product authorization. Natural polymer-based nanomedicines that treat cancer need to pass through an exceptionally demanding regulatory procedure. The application of these polymers as active pharmaceutical ingredients or nanocarriers for drug delivery requires thorough preclinical evaluations alongside pharmacokinetic studies and in vivo toxicity determination. The inconsistent nature of natural polymers presents a significant challenge because these compounds come from shellfish (chitosan), seaweed (alginate), and animal tissues (hyaluronic acid, gelatin) which prevents reaching consistent batch levels. The requirement for sterility and low endotoxin content becomes crucial for cancer treatment because immunocompromised patients face elevated risks of infection. The absence of established regulatory frameworks for nanocarrier-based drug formulations delays approval timelines since each product needs individual assessments that consume significant time. Multiple drug formulations made from natural polymers have received both FDA and EMA regulatory approvals despite their production-related difficulties. Users of Abraxane® benefit from FDA together with EMA approval to receive approved albumin nanoparticle paclitaxel delivery treatment for lung cancer and breast cancer conditions. The FDA granted Oncaspar® PEGylated enzyme formulation its approval for treating patients with Acute Lymphoblastic Leukemia (ALL). Medical professionals have accepted GelFoam® **as a** gelatin-based hemostatic agent for use in surgical applications. The drug delivery potential of natural polymers becomes

increasingly clear through these regulatory clearances yet requires improved quality control practices along with toxicity assessments and compliance enforcement. The pharmaceutical industry should establish standardized international quality criteria to enable easier regulatory approval pathways for natural polymer-based therapeutic medicines. The approval process for trained regulatory entities must work with established GRAS polymers while utilizing AI-enhanced predictive modelling to evaluate biodegradability and safety and efficacy of these materials. The advancement of nanomedicine requires both manufacturing guideline improvements and standardized risk assessment and regulatory standards which will guarantee the safe implementation of natural polymers in pharmaceutical systems including cancer therapy[97-101].

8. Conclusion

This article improves our knowledge about natural polymers used as carrier in different types of solid dispersion method. Here these methods are used to enhance the solubility, dissolution rate, and to decrease crystalinity that affects the BCS Class II and IV drugs. Due to its non-toxic, biodegradable and highly water solubility, natural polymers like cyclodextrins, carbohydrates, natural gums, proteins and other carrier polymer, has been widely used in pharmaceutical industries and other research. Increased solubility of poorly water-soluble drugs with these natural polymers are mainly due to its hydrophilic nature, complex formation, hygroscopicity, binding properties *etc*. Thus, to increase water solubility of drugs, these natural polymers can be used efficiently in recent formulations.

9. Author Contribution

PD supervision wrote and edited final draft, BR collected data of regulatory aspects, AM wrote manuscript, and tables and MK wrote final editing of manuscript. All authors have read and agreed to the published version of the manuscript.

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