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CURRENT PROGRESS IN HOT-MELT EXTRUSION OF NATURAL POLYMERS FOR DRUG DELIVERY

Aanchal P. Singhania[a,1], Yashvi S. Agarwal[a,1], Srushti M. Tambe[a,1], Divya D. Jain[a,1] and Purnima D. Amin[a]*

[a]Institute of Chemical Technology, Department of Pharmaceutical Science and Technology, Mumbai 400019, India.
[a1]All author contributed equally to this work as first authors.

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***Corresponding Author**
Purnima D. Amin
Institute of Chemical Technology, Department of Pharmaceutical Science and Technology, Mumbai 400019, India.
pd.amin@ictmumbai.edu.in,

ABSTRACT

Natural polymers or biopolymers have gained immense popularity in biomedical applications, distinctly in the pharmaceutical industry owing to their advantages over synthetic polymers. Over the years, hot-melt extrusion (HME) has also emerged as a promising technology for producing a myriad of pharmaceutical dosage forms. An essential requirement of materials used in HME is their ability to exhibit thermoplastic characteristics, drug-polymer miscibility as well as thermal stability in an allowable extrusion temperature range. Since natural polymers like starch, celluloses are rigid, high molecular weight polymers that do not soften or melt below their decomposition temperatures, exhibit difficultly in extrusion via HME. The fundamental objective of this review is to bridge the current manufacturing gap in the pharmaceutical sphere that exists owing to the poor extrudability of natural polymers via HME. The critical polymer parameters including melt viscosity, T_g, T_m, solubilization capacity, mechanical properties, plasticizer effects as well as characterization techniques with regards to natural polymers are discussed. In light of the current paradigm of drug development, this review summarizes various reports on natural polymers-based formulations developed using HME technology. This review discusses technical and scientific specificities of extrusion of natural polymers to encourage systematic screening and selection of natural polymers for the HME process to minimize the number of trials and improve study design to achieve target formulation.

KEYWORDS: Hot-melt extrusion, Natural polymers, Melt viscosity, Solubilization capacity, Drug-Polymer miscibility, Polysaccharides.

INTRODUCTION

Polymers form the chief constituent of drug delivery systems. Polymers are used in drug delivery systems to impart adequate weight to the formulation, consistency, and volume for accurate dosing while also playing an important role in drug targeting, bioavailability enhancement, as well as improving patient acceptability.[1] Naturapolyceutics is a new science and technology framework for designing and developing drug delivery systems that combine natural polymers and pharmaceutics. Natural polymers are promising in this field because of their biological properties, sustainability, chemical versatility, and human and ecological friendliness.[2] Owing to their potential benefits such as biodegradability, non-toxic and abundant in nature, chemically inert, and less expensive as compared to synthetic polymers. They can also be modified in a variety of ways to create custom materials for drug delivery systems, making them a viable alternative to synthetic excipients.[3] Natural polymers are a subcategory of polymers that are derived from natural sources (plants or animals). They primarily consist of carbohydrates and proteins, which are found in both plants and animals and provide structural support. Moreover, natural polymers are readily tolerated by the body and have high bioactivity and biocompatibility because they mimic the components found in biological extracellular matrices. In terms of their origin, polymers found in nature can be divided into six categories: Proteins, polysaccharides, polynucleotides, polyisoprenes, polyesters, and lignin.[4] Natural polymers are used in both the polymer and pharmaceutical industries and have a diverse range of applications. Figure 1. represents various natural polymers from different sources. Natural polymers have been used in drug delivery for a variety of purposes, including emulsification,[5] suspension,[6] controlled release,[7] film coating,[8] disintegration,[9] solubilization, bioadhesion, thickening, viscosity modulation, gelling, bulking agent,[10] microspheres,[11] nanoparticles,[12] drug devices,[13] encapsulation[14] and mechanical strengthening.[3,15,16] Moreover, in order to achieve targeted drug delivery in chronic and site-specific diseases, researchers are now gradually utilizing natural polysaccharides.[17,18] Hot-melt extrusion (HME) has gained a foothold in the pharmaceutical industry over the last three decades, and its tremendous potential to develop various novel pharmaceutical products is driving

its massive progress.[19] Continuous production, cost-effectiveness, solventless process, industrial feasibility, automation potentiality, high reproducibility, and real-time monitoring are some of the notable advantages of HME technology. The use of HME in the production of novel products has been reported in the literature e.g., pharmaceutical cocrystals,[20,21] coextrusion for developing fixed-dose drug combinations,[22] chronotherapeutic drug delivery systems,[23] self-emulsifying drug delivery systems,[24] twin-screw granulation,[25] semisolid drug delivery systems,[26,27] abuse-deterrent systems,[28] three-dimensional (3D) printed drug delivery systems,[29] etc. Concisely, HME is a one-step, continuous, or semi-continuous manufacturing technology where materials are melted, mixed, homogenized, and pumped out.[19] This literature review focuses on the processing of natural polymers via HME with brief emphasis on the critical polymer properties including melt viscosity, glass transition temperature (T_g), melting temperature (T_m), solubilization capacity, mechanical properties, plasticizer effects as well as characterization techniques with regards to natural polymers. It appraises the role of HME in pharmaceutical systems and provides technical and scientific specificities of the widely used natural polymers. This paradigm-changing technology is steadily expanding its feasibility to develop various natural polymer-based drug delivery systems with the aim of making them a clinical success. Table 1. lists the present market status of HME products with drug, route of administration, and natural polymers used.

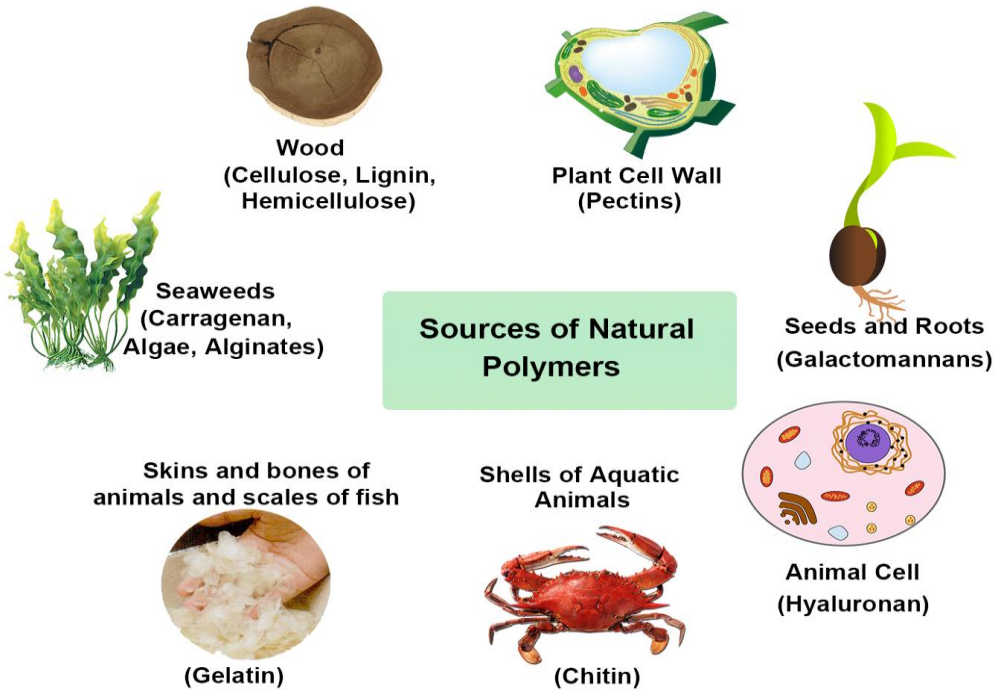

Fig. 1: Various sources of natural polymers.

Table 1: The present market status of HME products with drug, route of administration, and natural polymers used.[30-34]

Brand name/Drug	Indication and route of administration	Natural Polymer	Product shape and dimensions
Lacrisert®, Valeant (no drug)	Dry eye syndrome	Hydroxypropyl cellulose	Rod-shaped implant 1.27 mm × 3.5 mm
Onmel®, Merz (itraconazole)	Onychomycosis, Oral tablet	Hydroxypropyl methylcellulose	Oval tablet
Covera-HS®, Pfizer (Verapamil HCl)	Angina pectoris and hypertension, Oral tablet	Hydroxypropyl cellulose	Round tablet
Nurofen (Meltlets lemon®) Reckitt Benckiser Healthcare (ibuprofen)	Analgesic, Oral tablet	Hydroxypropyl methylcellulose	Round tablet
Eucreas®, Novartis (vildagliptin/ metformin HCl)	Type II diabetes Oral tablet	Hydroxypropyl cellulose	Oval coated tablet
Zithromax®, Pfizer (azithromycin enteric-coated Multiparticulate prepared by HME and melt congealing)	Bacterial infection, Oral tablet	Pregelatinized Starch	Oval tablet

Critical Polymer Properties for HME Processing

For developing an effective pharmaceutical preparation and manufacturing process, the choice of polymer carrier system is critical. Polymer and drug material physicochemical and mechanical properties must be carefully assessed. The schematic representation of HME equipment along with critical polymer properties and their methods of determination is shown in Figure 2.

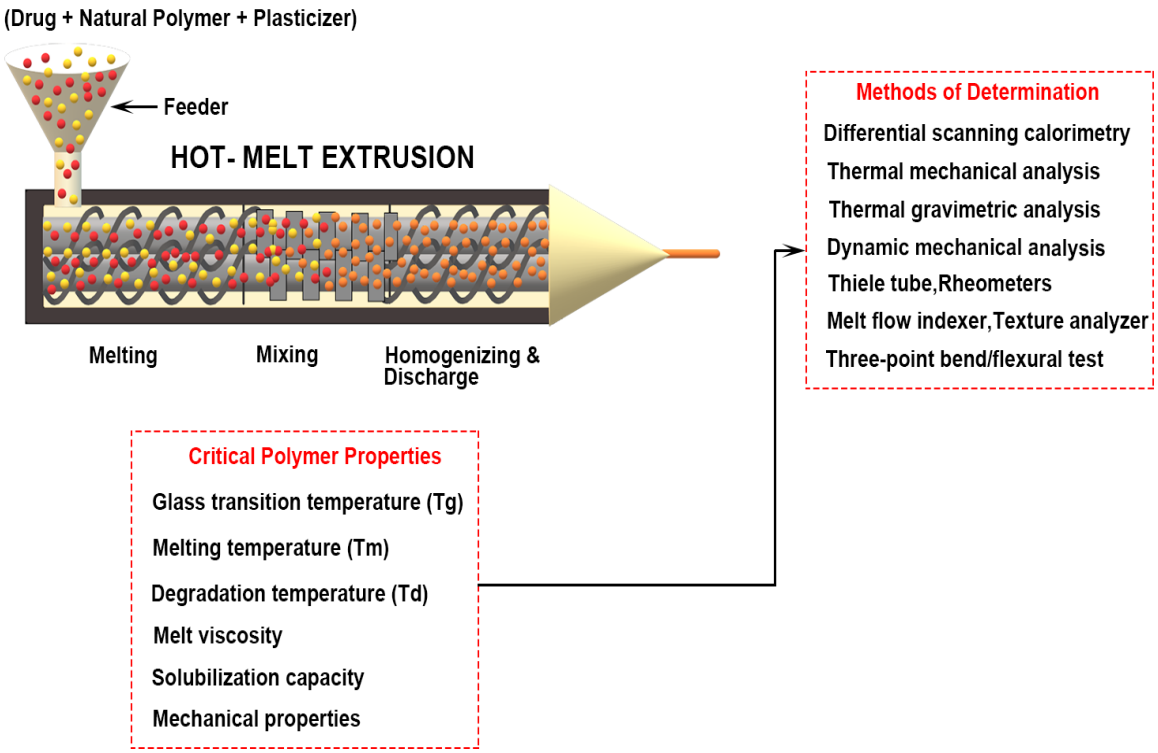

Fig. 2: Schematic representation of HME equipment along with critical polymer properties and their methods of determination.

Polymer chemical properties

Thermal stability, described as a material's ability to withstand high temperatures, is an important requirement that must be met before any excipient can be used in HME because, during extrusion, a significant amount of shear stresses and heat are applied to the materials. Any alternation with regards to the stability of the formulation and its chemical properties must be monitored in order to avoid any degradation issues as the excipients may undergo chemical reactions.[35, 36] Lui et al.[37] studied the degradation of various types of starches (varied amylose content) due to shear produced during HME processing. The extruded samples were characterized using size exclusion chromatography. According to the reports, amylopectin, a highly branched portion of the starch, is more prone to degradation than low molecular weight and short branched amylose. Because of the variations in chemical structures, amylopectin is, therefore, more vulnerable to mechanical degradation during the HME process due to its lack of flexibility. A class of polymers that experience a major lowering in molecular weight during the HME process are cellulose derivatives, like few grades of hydroxypropyl methylcellulose (HPMC) and starch, due to chain scission reactions during the heating process. According to Zaccaron et al.[38] sometimes unsaturated products are produced owing to cleavage of the glucose ring in HPMC at a higher temperature. The formation of alcohol structures due to the scission of ether groups along the polymer backbone was also stated by the authors. In another study, Hughey et al.[39] based on the Cross Polarization–Magic Angle Spinning C NMR spectra demonstrated a chemical shift suggesting the existence of a double-bonded carbon, implying a substance resulting from the dehydration or demethoxylation of Hypromellose's cellulosic backbone (i.e., Methocel E50) that induced a reduction in the molecular weight during the HME process. The authors also theorized that the E50LV system's high melt viscosity induced excessive stress inside the extruder barrel, essentially removing metal from the barrel or screws during processing, resulting in the coloration of the extrudates. This hypothesis was confirmed by Proton Induced X-ray Emission analysis that showed 449.6 ppm iron content in the HME extrudates. In the HME processed extrudates, detectable amounts of chromium, nickel, copper, and zinc were also identified. This result demonstrated the difficulty in processing a polymer with a high melt viscosity, such as E50LV, by HME. Dong et al.[40] studied the hydroxypropyl methylcellulose acetate succinate (HPMCAS)-related side chain removal and possible drug–polymer incompatibility. It was observed that HPMCAS is hydrolyzed to produce acetic and succinic acids during the extrusion process. These acidic side chain removal by-products appear to react with

hydroxyl groups on drug substances through an esterification reaction, resulting in process-related impurities.

Thermal Properties of the Polymers

The T_g, T_m, or a combination of both can be used to determine the extrusion conditions of a polymer, so it's necessary to have an understanding of these parameters.[41] A discontinuous leap of the first derivatives dF/dT and dF/dP is correlated with the glass transition, which is caused by a rise in density fluctuation, where F, P, and T stand for thermodynamic quantity, pressure, and temperature, respectively. The glass transition temperature, T_g, is the temperature at which the transition occurs. T_g is affected by kinetic factors such as scanning rate sample preparation, additives (plasticizers and fillers), strain, frequency, molecular parameters (molecular weight, branching, tacticity,), crystallinity, and so on.[42] Another very critical parameter is the equilibrium melting temperature, T_m, of a crystalline polymer, which is the melting temperature of a perfect crystal of infinite molecular weight. It not only represents a chain's molecular and conformational features but also yields the interfacial free energy for nucleation when used to analyze crystallization kinetics. T_m differences of just a few degrees can have a big impact on basic crystallization mechanisms.[43] Based on the thermal properties, some key factors are important to consider while choosing a polymer such as stability of the polymer at the extrusion temperature, polymer's thermoplastic properties, and T_g and T_m of the polymer as high T_g and T_m may degrade thermosensitive drugs.[41] To overcome the issue of high T_g and T_m, plasticizers can be incorporated in the formulation that can effectively reduce the T_g and viscosity of the polymer. The plasticizing effect is attributable to an increase in free volume, reduced friction among polymer chains, and thus improved polymer chain mobility. Some APIs also function as a plasticizer for T_g such as ibuprofen,[44] methylparaben,[45] guaifenesin,[46] ketoprofen,[47] chlorpheniramine maleate,[48] etc. In a study, since the T_g of the itraconazole–HPMC system decreased with increasing drug loading, Six et al.[49] recognized itraconazole can effectively function as a plasticizer for HPMC. High temperature diffuse reflectance infrared transform spectroscopy confirmed the weak interactions between drug and HPMC as hydrogen bonds, resulting in a negative deviation from the theoretical T_g.

Melt viscosity

Melt viscosity is another critical parameter that determines the possibility of a smooth HME process. The rate of movement of polymer chains relative to each other is defined as the melt viscosity of a polymer, and it is primarily regulated by the entanglement degree and flexibility of the chain.[50] If the melt viscosity of the polymer is elevated, torque within the extruder will increase drastically, overloading the motor and screw.[51,52] The ideal melt viscosity range for melt extrusion of a polymer is between 1000 and 10,000 Pas to allow the smooth processing of polymers in HME.[36] Polymers like celluloses have high melt viscosity values and therefore produce high torque within the extruder which makes them a highly unsuitable choice for HME processing.[36,53] In contrast, polymers possessing low melt viscosity significantly prevent the formation of extrudates through the extrusion die. The polymer's molecular weight also has a crucial role to play in determining polymers' flow behavior at temperatures higher than their Tg or Tm (semi-crystalline polymer or an amorphous polymer).[51] The melt viscosity of the polymer is directly proportional to the molecular weight of the polymer.[54,55] The melt viscosity of the polymers can be effectively reduced by the addition of plasticizers to smoothly extrude high molecular weight polymers. In a study, polyethylene oxide (PEO) in the concentration range of 15-55% was used to decrease the melt viscosity of HPC. In a recent study, Benzine et al.[56] studied triethyl citrate, dibutyl stearate, or polyethylene glycol (PEG) 1500 as plasticizers to improve the extrudability of a variety of blends of ethyl cellulose with guar gum (80:20). It was observed that PEG 1500 did not reduce the T_g of the polymer blend whereas the other two plasticizers effectively reduced the T_g from 170 °C to 100 °C. It's also worth noting that the length of polymer chains affects melt viscosity because polymers have different molecular weights depending on chain length. Also, the higher the degree of entanglement in the polymer chain, the higher the melt viscosity. Higher temperatures are thought to cause the disentanglement of polymer chains as well as their linear arrangement, lowering the melt viscosity of polymers.[57] The relationship between molecular weight and melt viscosity can be given by the following equation when the chain length is below the critical entanglement chain length and the weight-average molecular weight of a polymer is below the threshold (equation 1):[58]

$$\eta = K_L \, X \, M_w \quad \ldots\ldots\ldots\ldots\ldots (1)$$

where K_L is a constant, η is the zero-shear melt viscosity, and Mw is the weight-average molecular weight intermolecular entanglement occurs when the chain length exceeds the critical entanglement chain length, and the melt viscosity is given by the equation below (equation 2):

$$\eta = K_H \, X \, M_w^{3.4} \quad \ldots\ldots\ldots\ldots\ldots (2)$$

where K_H is a constant, η is the zero-shear melt viscosity, and Mw is the weight average molecular weight.

Solubilization Capacity

The polymer's solubilization capacity has a big impact on the HME process. It determines the ability of the polymer to dissolve the drug in an aqueous solution.[59] Noyes-Whitney suggests that processing above the T_g of the carrier phase can increase the dissolution of the

crystalline drug in the matrix carrier which is in a molten state. In the molten carrier phase, this would lead to an improved equilibrium solubility and diffusivity of the drug.[60, 61] In addition, enhanced solubility can also be attained by incorporating a suitable plasticizer and a co-solvent or by micronizing the API.[62, 63] The solubility capacity of polymers also plays an important role in releasing the API and increasing its resorption and bioavailability. While PEG-based surfactants are the most widely used solubilizers for liquid formulations, other polymers such as cyclodextrins and povidone have also been used, although they have comparatively less solubilization ability for APIs with poor solubility.[64-66] Since the drug can occupy the hydrophobic part inside the micelle, amphiphilic polymers have a high solubilization potential for the drug, while polymers that are non-amphiphilic in nature tend to solubilize the drug via a complexing effect with the polymer chains.[59] In addition, successful solubilization with HME is also subject to the following, apart from polymeric properties: Properties of the API, extrusion processing temperature, operating conditions, screw configuration, and shear imparted by the screws.[60]

Mechanical strength

The mechanical properties of the polymers such as strength, ultimate elongation, young's modulus, and viscoelasticity also play an important role during HME processing.[67] The impact of Vitamin E TPGS on the mechanical properties of HPC/PEO based films produced via the HME process were investigated.[68] It was observed that the tensile strength decreased with increasing TPGS concentrations. Compared with the HPC/PEO films without TPGS, the percentage elongation of HPC/PEO films with TPGS increased threefold. TPGS was found to support HPC/PEO film processing by minimizing barrel pressure and extruders torque.

Processing of natural polymers via HME

Polymers obtained from natural and animal kingdoms are being extensively studied as biomaterials for a broad range of biomedical applications including regenerative medicine and drug delivery. These polymers are biochemically identical to human extracellular matrix elements and therefore readily absorbed by the body. These include several polysaccharides (carbohydrates) and animal-derived proteins. The chemical structures of widely used natural polymers that are successfully used to develop various drug delivery systems via HME technology are shown in Figure 3. Table 2. summarizes various drug delivery systems developed using natural polymers via HME technology.

Table 2: represents theoretical properties and thermal properties of the natural/semi-synthetic polymers used in HME.

Polymer name	Trade name	T_g (°C)	T_m (°C)	Degradation Temp (°C)	(MPa 1/2)	Ref
Methyl Cellulose 15 cps (MW 14000)	Methocel™A	200	-	247	30.0	[41,69,70]
Ethyl Cellulose 4 cps	Ethocel® 4P	128	168	200	-	[35,41,69]
Ethyl Cellulose 7 cps	Ethocel® 7P	128	168	200	-	[35,41]
Ethyl Cellulose 10 cps	Ethocel® 10P	132	172	205	20.90	[41,71,72]
Hydroxypropyl cellulose (MW 95000)	Klucel® LF	111	-	227	21.27	[41,71,73]
Hydroxypropyl methyl cellulose, 100 cps, (MW 25000)	Methocel™ K100LV	147	168	259	-	[41]
Hydroxypropyl methyl cellulose, 100000 cps, (MW 150000)	Methocel™ K100M	96	173	259	21.10	[41,71,73]
Hydroxypropyl methyl cellulose acetate succinate 3cps (MW – 18000)	AFFINISOL™ HPMC HME	~115	-	>250	29.10	[63,69,74]
Hydroxypropyl methylcellulose phthalate, 40cps (MW – 45600)	HP-55	147	-	194	-	[36]
Hydroxypropyl methylcellulose phthalate, 55cps (MW – 37900)	HP-50	143	-	199	-	[36]
Corn starch	-	58	85	>200	-	[75]
Shellac		~58	-	-	-	[76]
Chitosan		203				[77]

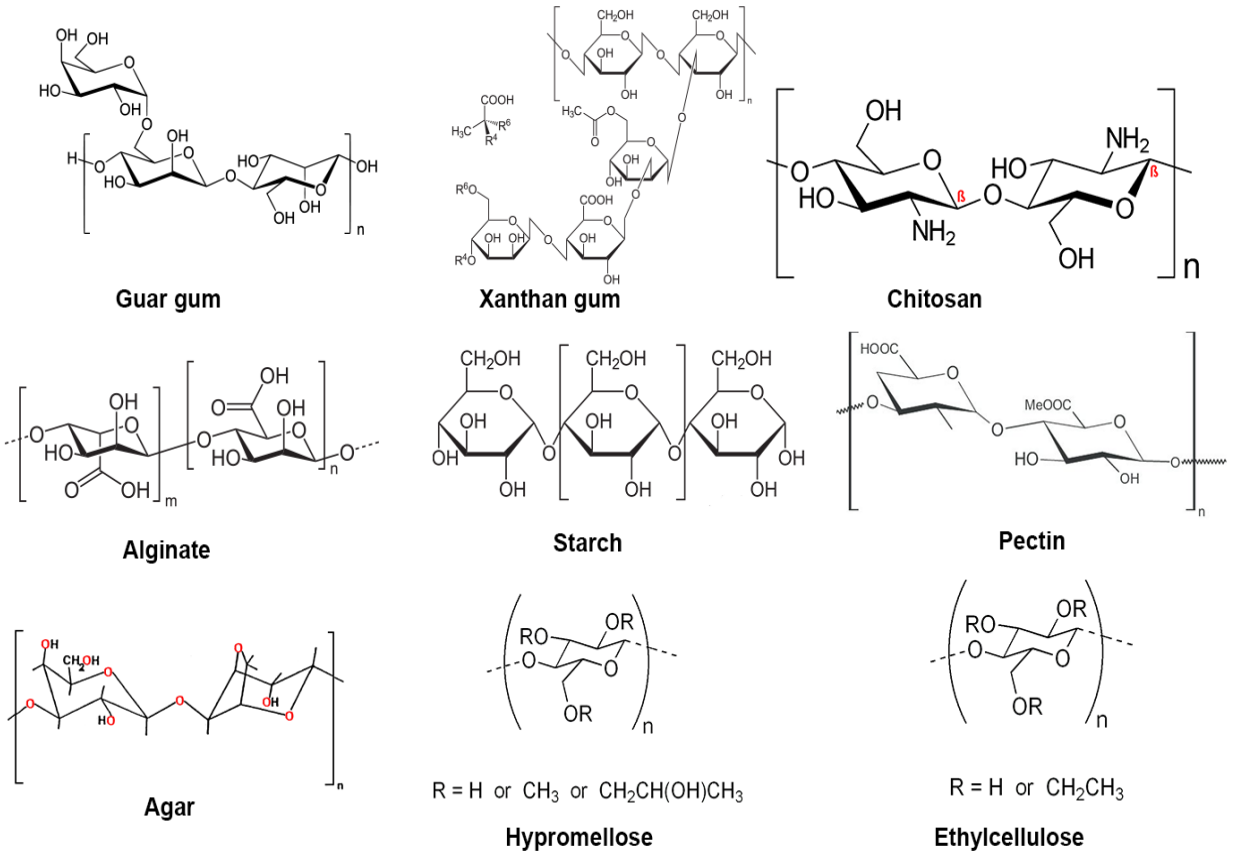

Fig. 3: Chemical structures of natural polymers used to develop various drug delivery systems via HME technology.

Guar gum

Guar gum is acquired from an annual, drought-resistant, pod-bearing plant which is called Guar or cluster bean (*Cyamopsis tetragonolobus* or *Cyamopsis psoraloides*) and belongs to Leguminosae family. The main backbone is made up of a chain of β-(1,4)-D-mannopyranosyl units connected by single α-(1–6)-D-galactopyranosyl units. The ratio of mannose to galactose is 1.2–1.8, but it varies depending on the temperature of the solution.[78] Guar gum's average molecular weight ranges from 440000 to 650000 Da, depending on the polysaccharide chain duration.[78] It is a non-ionic hydrophilic polysaccharide and usually insoluble in hydrocarbons, alcohols, fats, esters, and ketones whereas it is highly soluble in water. A 1% dispersion of good quality guar gum in water will increase viscosity to 10,000 cP. Its non-toxic nature over a broad pH spectrum, which stems from its stable and uncharged nature, is a noteworthy feature. Guar gum has a higher overall viscosity at higher temperatures than at lower temperatures.[79,80] About 95% of pure guar gum degrades at 1073.15 K.[81] The drug release mechanism is by gelatinization, water penetration, and diffusion.[82] In pharmaceuticals, it is used for a wide range of operations such as emulsifying, suspending, stabilising agent, and binding agent employed for conventional dosage forms.

Xanthan gum

Since its invention in the 1960s in the United States, xanthan gum has been a popular ingredient in food formulations.[83] Xanthan gum is an anionic polymer extracellularly obtained from the microorganism Xanthomonas campestris. It is soluble in cold water.[84] The applications of xanthan gum are in the food, pharmaceutical, cosmetics, and technical industries as a stabilizer, thickener, and binder.[85] Xanthan gum has a pH of 7 in an aqueous solution. The melt temperature of xanthan gum is approximately 55-60 °C.[86] Xanthan gum has been reported to act as a matrix retardant in several formulations, despite its primary use as a suspending agent. The drug release mechanism of xanthan gum is via matrix swelling and diffusion.[87] At low pH, xanthan gum is primarily unionized, whereas it is ionized in dilute acidic and alkaline environments.[87] Because of its inert nature, biocompatibility, and relative thermostability, xanthan gum is well known for sustained drug release preparations.[88] Xanthan gum's high molecular weight and viscous nature make it a viable candidate for use in the formulation of sustained-release dosage types.[89]

Chitosan

Chitosan which is soluble in aqueous acidic media is derived from chitin by 50% deacetylation which is in turn obtained from crustaceans.[90] It is a polymer of

glucosamine and *N*-acetyl glucosamine. Chitosan consists of polycationic chains in acid aqueous solutions. Chitinases, chitobiases, and others are capable of degrading chitosan into amino sugars. The degradation temperature of chitosan is 292.79 °C.[91] Uses of chitosan are in the agricultural, food, and environmental engineering industry as a plant stimulant, antimicrobial.[92] T_g of chitosan is between 140-150 °C.[93] The pK of chitosan is pH 6.5.[94] The drug release mechanism can be swelling, erosion, diffusion, or degradation.[95]

Alginate

Alginates are anionic polysaccharides found as a structural component in cell walls of brown algae, Ascophyllum nodosum, Macrocystis pyrifera, and Laminaria hyperborean. They also occur in bacterial strains like *Azotobacter* and *Pseudomonas*.[96] It is insoluble in water and organic solvents. Alginic acid is used as an emulsifier, thickener, formulation aid, and stabilizer. In physiological conditions, alginate degrades due to partial oxidation of alginate chains. Alginate is oxidized with sodium ions in an aqueous medium, which aids in hydrolysis.[97] T_g of alginate is 110 °C.[98] As the temperature of the alginate solution increases, viscosity decreases. For every 5.5 °C rise in temperature, the viscosity of the alginate solution decreases by approximately 12% over a limited range. Thermal depolymerization occurs when sodium alginate solutions are heated, and the amount of depolymerization depends on time, temperature, and pH. At high temperatures and lower pH values, the degradation rate is higher. It is observed in an alginate solution, lowering the temperature increases the viscosity but does not result in the formation of a gel. The appearance and viscosity of a sodium alginate solution that has been frozen and then thawed will not change.[99]

Starch

Starch is a biodegradable polymer, hydrophilic in nature, obtained from various agricultural resources like rice, corn, potato, etc. It is composed of two polymers-crystalline and linear amylose (poly-α-1,4-D-glucopyranoside) and amorphous and branched amylopectin (poly-α-1,4-Dglucopyranoside and α-1,6-D-glucopyranoside).[100] The mechanical and biodegradable properties of the various types of starch depend on the amount of amylose and amylopectin in it. An increase in amylose content leads to an increase in strength and elongation.[101] The advantages of starch include its low cost and abundance of availability. The disadvantages of starch-based products include brittleness, water sensibility, and low mechanical properties which can all be overcome by blending with synthetic biodegradable polymers or by chemical modifications like acetylation.[80] Biodegradation of starch occurs via hydrolysis of bonds in the presence of enzymes leading to the formation of non-toxic degradation products. Amylase enzyme attacks on the α-1,4 linkages while glucosidases break the α-1,6 linkages.[102]

Pectin

Pectin obtained naturally from apple pomace, citrus peel, etc. is a methylated α-(1→4)-D-galacturonic acid, containing homopolymer with some residues of rhamnose.[103] The applications of pectin include use as thickener, gelling agent, stabilizer, and water binder. It can be classified as high methoxyl or low methoxyl pectin depending on the methoxylation/esterification. It is soluble in pure water, forming an anion after dissolving. Degradation of pectin occurs by depolymerization (hydrolysis at low pH and beta elimination at high pH) and de-esterification.[104]

Agar

Agar, also called agar-agar, is a polysaccharide range obtained from Rhodophyceae family (red seaweeds), mainly Gelidium and Gracilaria species.[105] Its applications include use in the food industry, microbiology, pharmaceuticals, medicine, laboratory, etc. Highly pure agar is in soluble in water, soluble in formamide, and slightly soluble in ethanolamine, at a temperature of 25 ºC. The melting temperature of agar and agaroid gels (1.5% solids) is in the range of 60- 97 ºC.[105]

Cellulose derivatives: hydroxypropyl cellulose and hydroxypropyl methylcellulose

Cellulose is insoluble in water and organic compounds due to its supramolecular composition and extensive hydrogen-bonded chemical structure.[106] Cellulose derivatives such as cellulose esters, cellulose ethers, etc. have been developed to overcome these drawbacks. One such cellulose ether derivative namely, hydroxypropyl cellulose has been widely used in various drug delivery systems.[107] It is a pH-sensitive, non-ionic polymer and has found its applicability in the pharmaceutical industry as a tablet binder,[108] modified release carrier[108], viscosity builder,[108] film-former,[109] etc. For HME processing of HPC, the molecular weight plays a crucial role. HPC is smoothly processed via HME at a processing temperature range of 120 - 200 °C Another such widely used cellulose derivative is HPMC which is also a nonionic water-soluble polymer and has been widely used in the pharmaceutical industry.

Table 3: Various drug delivery systems developed using natural polymers via HME technology.

Model drugs, indication, route of administration	Description	Carrier	Temp (°C)	% drug release	Dosage form	Ref
Theophylline or Diprophylline (Chronic asthma, chronic bronchitis and bronchospasm, Oral)	The prepared hot-melt extrudate provided broad spectra of dissolution pattern (preferably constant drug release rates) and are also stable for long term. The ethyl cellulose has the ability to prevent the guar gum against enzymatic degradation.	Ethyl cellulose, Guar gum, pectin, maize starch, inulin, maltodextrin, HPMC, and chitosan	100	70% release in 18 h	HME extrudate's	[56]
Ibuprofen (NSAIDS, Oral)	Researchers observed a slow drug release nearly 20% from the ibuprofen–ethyl cellulose matrices (60:40 w/w) in 24 h. Due to the absence of the initial burst release, higher drug release reproducibility, and the probability of zero-order, xanthan gum matrices give some significant advantages over HPMC.	Ethyl cellulose, HPMC, and xanthan gum	60, 82	Nearly 100% release in 24 h	Mini matrices	[110]
Ibuprofen (NSAIDS, Oral)	A significant enhancement in drug release was observed when 30% w/w xanthan gum was used in the formulation owing to the presence of coarser particles leading to erosion mechanism.	Ethyl cellulose, xanthan gum	50	Nearly 100% release over 24 h.	Mini-matrices	[111]
-	In the presence of xanthan gum, the films were reinforced, an increase in solubility in water and decreased moisture content was observed.	Tapioca starch, glycerol, xanthan gum, potassium sorbate	115-130	-	Films	[112]
-	This study exhibit that PEO acted as a plasticiser and reduced the melt viscosity of xanthan gum/PEO blends. Melt flow rate and torque values were decreased with increasing % compositions of PEO in the blend.	Polyethylene oxide (PEO), xanthan gum	90-155	-	-	[86]
-	Starch-based extrudate are fragile in nature hence addition of chitosan and improves the processability and mechanical properties when extruded using HME.	Corn starch, chitosan, glycerol, and citric and stearic acid	108-140	Nearly 20% release of CBZ within 24 h	Films	[113]
-	The developed HME system exhibited good melt flow because the carboxylic groups of polyacrylic acid had a link with the amine groups of chitosan during the extrusion process. The PAA:chitosan melt blend showed a decrease of more than 10 °C in the glass transition and onset of melt transition temperature compared to that of PAA homopolymers.	Chitosan/polyacrylic acid (PAA)	160	-	-	[114]
Chlorpheniramine maleate (Antihistamine, Oral)	It was observed that the drug release from the developed HME tablets showed pH independent sustained release owing to synergistic property of chitosan and xanthan gum leading to less media penetration into a tablet. This is due to the melt state of PEO and intra-molecular hydrogelation properties in a HME tablet as compared to the powder state of PEO in the direct compression tablets.	Chitosan, xanthan gum, polyethylene oxide (PEO)	90-110	Nearly 100% in 24 h	Tablet	[77]
Ibuprofen, Acetaminophen and	The major disadvantage of developing alginate hydrogel using	Sodium alginate D-glucono-δ-lactone (GDL)	25	Nearly 70%	Hydrogel	[115]

Methylthionine chloride	convectional technique is gelation rate which is difficult to control. Authors explored HME to develop alginate hydrogels with uniform structure, screw rotation aids in higher concentration and viscosity of alginate solution. This method allows the production of alginate hydrogels in a single step using extrusion and that is cheaper contrary to the conventional lab-scale formulation for mass production.	$CaCO_3$ and $CaCl_2$		release in 12 h		
-	Authors blended approximately 40% w/w starch with biodegradable polyester like PCL to form tough nanocomposite which had elongation properties equivalent to 100% PCL, by developing a reactive extrusion process that enhanced interfacial adhesion between PCL and starch. The modulus and strength were found to be equivalent to the composites having no crosslinking.	Wheat starch, polycaprolactone (PCL)	120	-	Nanocomposite blend	[116]
-	Authors performed a study to extrude glycerol and pectin films using different combinations of starch and orange albedo and determine their microstructural and mechanical properties. Enhanced mechanical properties were observed in extruded pectin/albedo/starch/glycerol films than in pectin/albedo/glycerol films while they were comparable to extruded pectin/starch/glycerol films.	Pectin, Amylogel 03003, orange albedo, glycerol	100	-	Films	[117]
Diclofenac sodium (NSAID, Oral)	Investigators studied varying ratios of microcrystalline cellulose and agar as a filler material. The results suggested that slow release rate of the drug was observed in filler included matrix, in comparison with the matrix alone.	Agar, microcrystalline cellulose, Eudragit L 100, polyethylene oxide	70-140	-	Extrudate	[118]
Carbamazepine (Anticonvulsant, Oral)	A zero-order sustained release tablets was developed utilizing a 2:1 ratio of EC to HPC ratio for a low dose drug over 24 h.	Ethyl cellulose (EC) and hydroxypropyl cellulose (HPC), triethyl citrate (TEC)	105-125	Nearly 20% release of CBZ within 24 h	Tablet	[119]
Soybean (Bioactive compound, Oral)	Due to high shear forces of HME, a nanocomposite of soybean was yielded giving increased phenolic content and antioxidant property.	Food grade hydroxypropyl methyl cellulose	80-130	-	Nanocomposite	[120]

CONCLUSION

In pharmaceutical technology, a wide range of polymeric materials have been used for decades. Polymeric material research is primarily centered in the pharmaceutical industry, with an aim to improving bioavailability, controlling the release of active molecules, developing new ways, routes of administration, and novel pharmacological agents with clinical applications. In the last few years, the application of HME technology in the development of a myriad of drug delivery systems expanded rapidly in the pharmaceutical industry owing to its advantages like continuous manufacturing of dosage forms, solventless process, and most importantly due to its ability to process a wide range of polymers. Combining the benefits of HME technology along with polymers obtained from renewable sources can contribute immensely towards economic development. Indeed, research is continuing to progress the extrusion of natural polymers by achieving deeper insights on critical polymer properties such as melt viscosity, T_g, T_m, mechanical properties, etc. as well as extrusion of thermosensitive drugs, which would shift the paradigm even further. However, due to the high shear forces and temperatures that occur during the process, formulating thermolabile molecules via HME still remains challenging. Hence, forthcoming research should focus on overcoming the disadvantages of the high-energy input needed during the extrusion process by incorporating process engineering into the equipment

design and manufacturing. In addition, advancements in formulation science and polymer chemistry, as well as improvements in PAT tools and equipment, would ensure that HME occupies a prominent position in the pharmaceutical industry.

Conflict of interest
The authors declare no conflict of interest.

Author contributions
All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

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Abbreviations
HME: Hot-melt extrusion
T_g: Glass transition temperature
T_m: Melting temperature
EC: Ethyl cellulose
HPMC: Hydroxypropyl methylcellulose
HPMCAS: Hydroxypropyl methyl cellulose acetate succinate
HPC: Hydroxypropyl cellulose
PEG: Polyethylene glycol
PEO: Polyethylene oxide
DSC: Differential scanning calorimetry

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