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Seeds as Drug Delivery Systems: Mechanisms, Formulation Strategies, and Recent Advances (2020–2026)

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Abstract:

Background: Seed derived excipients, including mucilages, polysaccharides, fixed oils, and proteins, have garnered significant attention as sustainable, biocompatible, and functional components in pharmaceutical drug delivery systems. Their unique physicochemical properties including swellability, mucoadhesion, biodegradability, and stimuli responsiveness make them versatile platforms for controlled, targeted, and site-specific drug delivery.

Objectives: This review comprehensively examines the classification, extraction, characterization, and pharmaceutical applications of seed derived materials as drug delivery excipients, with a focused analysis of advances published between 2020 and 2026.

Methods: A systematic literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar using keywords: 'seed drug delivery', 'seed mucilage formulation', 'natural polysaccharide nanoparticles', and related terms. Over 120 peer-reviewed publications from 2020–2026 were screened; 70 were included based on relevance and quality.

Results and Conclusion: Seed based systems demonstrated remarkable versatility across oral, topical, ocular, and parenteral routes. Recent innovations include stimuli responsive hydrogels, nanostructured lipid carriers, 3D/4D-printed devices, and AI-guided formulation optimization. These systems significantly enhanced drug bioavailability, reduced systemic toxicity, and enabled precision targeting. Despite promising results, challenges such as regulatory standardization, batch to batch variability, and scale-up remain. Future directions include machine learning assisted formulation design and exosome mimetic seed nanovesicles.

Keywords: Seed Drug Delivery, Seed Mucilage, Natural Polysaccharide, Controlled Release, Nanoparticles, Bioadhesion, Colon Targeting, Green Excipients, Sustained Release.

1. INTRODUCTION

The global pharmaceutical industry is increasingly shifting toward sustainable, naturally derived excipients that offer not only biocompatibility and biodegradability but also inherent pharmacological activity. Seeds represent one of nature's most concentrated repositories of bioactive molecules, including polysaccharides, proteins, fixed oils, alkaloids, and phenolic compounds. Historically, seed derived materials such as guar gum, psyllium husk, and locust bean gum have been used in food and pharmaceutical applications. However, recent decades particularly post 2020 have witnessed a renaissance in seed-based drug delivery research driven by advances in nanotechnology, green chemistry, precision medicine, and computational formulation design. Drug delivery systems (DDS) derived from seeds encompass a broad spectrum of platforms: hydrogels, nanoparticles, microparticles, matrix tablets, lipid-based systems, and novel 3D-printed devices. These systems exploit specific

seed material properties to achieve therapeutic goals such as controlled release kinetics, site-specific targeting, mucoadhesion, and improved pharmacokinetics.[1][2][3]

The unique advantages of seed-based excipients over synthetic polymers include: (i) Global availability and low cost (ii) Generally Recognized as Safe (GRAS) status for many materials (iii) Inherent bioactivity offering therapeutic synergy (iv) Renewability and environmental sustainability (v) Structural versatility enabling extensive chemical modification.[4][5] This review systematically examines the classification of seeds used in drug delivery, their physicochemical properties, formulation mechanisms, and critically evaluates recent literature from 2020–2026 representing the current frontier of this field. Special attention is given to emerging technologies including stimuli responsive systems, machine learning assisted formulation, and gene delivery using seed derived nanovesicles.

2. CLASSIFICATION OF SEEDS USED IN DRUG DELIVERY

2.1. Based on Primary Active Component

Seeds utilized in pharmaceutical drug delivery can be categorized based on their primary bioactive component: [6] [7]

(a) Mucilage yielding seeds: Psyllium (Plantago ovata), flaxseed (Linum usitatissimum), chia (Salvia hispanica), and basil (Ocimum basilicum) produce hydrophilic polysaccharide mucilages upon contact with water, forming viscous gels useful in sustained release and mucoadhesive formulations.

(b) Galactomannan rich seeds: Fenugreek (Trigonella foenum graecum), guar (Cyamopsis tetragonoloba), and locust bean (Ceratonia siliqua) contain galactomannans non-ionic polysaccharides with excellent gelling, thickening, and colonic targeting properties.

(c) Fixed oil rich seeds: Sesame (Sesamum indicum), flaxseed, hemp (Cannabis sativa), and nigella (Nigella sativa) provide fixed oils forming the basis of lipid based drug delivery systems (LBDDS), nanostructured lipid carriers (NLC), and solid lipid nanoparticles (SLN).

(d) Protein rich seeds: Quinoa (Chenopodium quinoa), hemp, and sunflower (Helianthus annuus) provide amphiphilic proteins useful in nano-emulsification, colloidal stabilization, and bioadhesive formulations.

(e) Saponin containing seeds: Quinoa and horse chestnut (Aesculus hippocastanum) yield saponins that act as natural surfactants, penetration enhancers, and vaccine adjuvants.

2.2. Based on Route of Administration

Seed derived systems have been formulated for virtually all routes of drug administration: oral (most common, utilizing mucilage based matrices and galactomannan hydrogels), topical (NLC and microemulsions using sesame and flaxseed oils), ocular (viscosity enhancing mucilages for eye drops), rectal/vaginal (suppositories and pessaries using cocoa butter and seed waxes), and parenteral (lipid nanoemulsions from sesame and soybean oils). [8][9]

3. PHYSICOCHEMICAL PROPERTIES OF SEED DERIVED EXCIPIENTS

3.1. Swelling and Hydration

The swelling behavior of seed mucilages and galactomannans is fundamental to their pharmaceutical utility. Upon hydration, these polymers form three dimensional networks that entrap drug molecules, controlling their diffusion. Psyllium husk demonstrates a swelling index of 40–60 mL/g, while fenugreek galactomannan exhibits swelling ratios of 15–30 g/g depending on pH and ionic strength. [10][11]

3.2. Mucoadhesive Properties

Seed mucilages rich in acidic polysaccharides (uronic acids, sulfate groups) exhibit strong mucoadhesive properties through electrostatic interactions, hydrogen bonding, and interpenetration with mucin glycoproteins. Flaxseed mucilage demonstrates mucoadhesive force of 12–18 N/cm2, making it superior to synthetic HPMC K4M in certain formulations. [12][13]

3.3. Rheological Characteristics

The rheological behavior of seed polymer solutions pseudoplastic (shear-thinning) for most mucilages makes them ideal for bioadhesive formulations, suspensions, and injectable gels. Viscosity, storage modulus (G'), and loss modulus (G") are key parameters governing sustained release performance and injectability. [14]

3.4. Thermal and Chemical Stability

Most seed polysaccharides exhibit good thermal stability up to 200–250°C (TGA), broad pH stability (3–9), and resistance to autoclaving. However, fixed oils (flaxseed, sesame) are susceptible to oxidative degradation requiring antioxidant stabilization. Chemical modification (acetylation, carboxymethylation, grafting) significantly enhances stability and drug loading capacity. [15][16]

4. CLINICAL BENEFITS AND OUTCOMES

Table 1 summarizes the principal mechanisms and corresponding formulation parameters exploited in seed based drug delivery systems.

Table 1: *Mechanisms and formulation parameters of seed based drug delivery systems*

Mechanism	Seed Excipient Used	Formulation Parameter	Advantages
Matrix diffusion	Fenugreek galactomannan	Viscosity, MW of polymer	Controlled release, simple process
Mucoadhesion	Psyllium husk, flaxseed mucilage	Mucoadhesive force, contact angle	Prolonged GI residence time
pH-dependent swelling	Guar gum, ispaghula husk	Degree of cross-linking, swelling index	Site-specific delivery (colon)
Enzymatic degradation	Guar gum, locust bean gum	Enzyme sensitivity, particle size	Targeted colonic release
Lipid encapsulation	Sesame oil, flaxseed oil	Zeta potential, PDI, EE%	Enhanced lipophilic drug absorption
Stimuli-responsive	Chia mucilage hydrogels	Temperature/pH trigger threshold	Smart, on-demand release
Nano-encapsulation	Quinoa saponins, chia mucilage	Nano size 100-400 nm, surface charge	Improved solubility, cellular uptake

4.1. Matrix Tablet Systems

Seed galactomannans (fenugreek, guar) function as hydrophilic matrix formers in oral sustained release tablets. Drug release follows Higuchi diffusion kinetics or anomalous (non-Fickian) transport depending on the degree of polymer cross linking. Fenugreek galactomannan matrices showed T50% (time for 50% drug release) of 6–8 hours for glipizide, demonstrating superior glycemic control in diabetic animal models.[17][18][19]

4.2. Nanoparticle Systems

Chia seed mucilage nanoparticles (100–300 nm) prepared by ionic gelation or nanoprecipitation significantly enhanced the oral bioavailability of BCS Class IV drugs. Surface functionalization with targeting ligands (folic acid, RGD peptides) enabled tumor targeted delivery, exploiting the enhanced permeability and retention (EPR) effect.[20][21]

4.3. Lipid-Based Systems

Sesame oil and flaxseed oil serve as lipid phases in self emulsifying drug delivery systems (SEDDS), nanostructured lipid carriers (NLC), and solid lipid nanoparticles (SLN). These systems markedly improved oral absorption of lipophilic drugs (paclitaxel, tamoxifen) by promoting lymphatic uptake, bypassing first pass metabolism, and forming mixed micelles in the GI tract.[22][23][24]

4.4. Hydrogel and IPN Systems

Interpenetrating polymer network (IPN) hydrogels combining seed polymers with synthetic polymers (chitosan, polyacrylic acid) demonstrated pH responsive swelling ideal for colon targeted delivery. Psyllium-chitosan IPNs exhibited minimal drug release at pH 1.2 (<5%) and complete release at pH 7.4 (>90%) simulating colonic microenvironment. [25][26]

4.5. Mucoadhesive Systems

Flaxseed and psyllium mucilages have been extensively employed in mucoadhesive buccal films, nasal inserts, ocular gels, and vaginal tablets. The prolonged mucosal residence time achieved by these systems translates to sustained drug plasma levels and reduced dosing frequency. [27]

5. SEED TYPES AND THEIR DRUG DELIVERY POTENTIAL

Table 2 provides a comparative overview of major seed sources employed in drug delivery research, along with their botanical classification, key components, and primary pharmaceutical applications. [1-31]

Table 2: *Seed types, key components, and drug delivery applications*

Seed Type	Botanical Name	Key Components	Drug Delivery Application	References
Flaxseed	*Linum usitatissimum*	Mucilage, lignans, omega-3 FA	Colon targeting, sustained release	[1,5,12]
Psyllium	*Plantago ovata*	Arabinoxylan, mucilage	Oral controlled release, GI targeting	[2,8,14]
Fenugreek	*Trigonella foenum-graecum*	Galactomannan, alkaloids	Matrix tablets, bioadhesion	[3,9,21]

Ispaghula husk	*Plantago ispaghula*	Glucomannan, fiber	Hydrogel, mucoadhesive systems	[4,16]
Chia	*Salvia hispanica*	Mucilage, polyphenols, omega-3	Nanoparticles, encapsulation	[6,18,28]
Quinoa	*Chenopodium quinoa*	Saponins, proteins	Nano-emulsions, amphiphilic systems	[7,22]
Guar gum seed	*Cyamopsis tetragonoloba*	Galactomannan polysaccharide	Colon targeting, matrix systems	[10,19,30]
Sesame	*Sesamum indicum*	Sesamin, sesamolin, oil	Lipid nanoparticles, topical	[11,25]

6. RECENT ADVANCES IN SEED BASED DRUG DELIVERY SYSTEMS (2020–2026)

The period 2020–2026 represents a transformational era in seed based drug delivery, characterized by convergence of nanotechnology, digital health tools, synthetic biology, and advanced manufacturing. Table 3 presents a chronological summary of key findings from landmark studies during this period.

Table 3: *Recent advances in seed-based drug delivery systems (2020–2026)*

Year	Seed Source	Formulation Type	Drug Loaded	Key Finding	References
2020	Flaxseed	Mucoadhesive microparticles	Metformin	Enhanced GI retention and hypoglycemic effect	[12]
2020	Psyllium husk	Interpenetrating polymer network hydrogel	Losartan potassium	pH-responsive release, improved bioavailability	[13]
2021	Chia seed mucilage	Nanoparticles	Curcumin	6-fold increase in oral bioavailability	[18]
2021	Fenugreek	Bioadhesive tablets	Glipizide	Prolonged release >12 h, improved diabetic control	[21]
2022	Guar gum	Colon-targeted nanoparticles	5-Fluorouracil	Colon-specific delivery, tumor suppression in vivo	[19]
2022	Quinoa saponins	Self-nano emulsifying system	Paclitaxel	Enhanced lymphatic absorption, reduced toxicity	[22]
2023	Flaxseed lignans	Solid lipid nanoparticles	Doxorubicin	Synergistic anticancer effect, tumor targeting	[24]
2023	Sesame oil	Nanostructured lipid carriers	Tamoxifen	Sustained release 72 h, improved tumor uptake	[25]
2024	Psyllium-Chitosan	3D-printed scaffolds	Ciprofloxacin	Programmable release profile, antimicrobial activity	[26]
2024	Chia mucilage	Stimuli-responsive hydrogel	Insulin	Glucose-responsive release, glycemic control in rats	[27]
2025	Hemp seed	Exosome-mimetic nanovesicles	siRNA	Gene silencing in hepatic cells, 85% knockdown	[29]
2025	Flaxseed mucilage	AI-optimized microemulsion	Repaglinide	ML-guided formulation, 3× bioavailability	[30]
2026*	Chia/Quinoa blend	4D-printed thermoresponsive device	GLP-1 agonist peptide	Shape-morphing, temperature-triggered release	[31]

** Emerging/anticipated research direction (2026).*

6.1. Stimuli-Responsive Hydrogel Systems

A landmark development was the engineering of glucose responsive chia seed mucilage hydrogels for closed loop insulin delivery (2024). [27] The system incorporated glucose oxidase enzyme within the mucilage matrix; elevated glucose concentrations triggered pH reduction via gluconic acid production, inducing gel-to-sol transition and insulin release. In Sprague-Dawley diabetic rats, single administration maintained normoglycemia for 10 hours, outperforming free insulin injection controls.

6.2. Nanoparticulate and Lipid Carrier Advances

Flaxseed lignin loaded solid lipid nanoparticles (SLN) demonstrated synergistic anticancer activity with doxorubicin in MCF-7 breast cancer cells (2023). [24] The sesamin component of the SLN inhibited P-glycoprotein efflux, reversing multidrug resistance, while the nanoparticle architecture enhanced intratumoral

accumulation via EPR effect. Tumor volume reduction was 62% versus 41% for free doxorubicin in xenograft mouse models. Sesame oil based nanostructured lipid carriers (NLC) for tamoxifen demonstrated a sustained 72 hour release profile with zero-order kinetics and significantly improved uptake in estrogen receptor positive cancer cells.[25] Pharmacokinetic studies showed 2.8 fold increase in AUC compared to oral tamoxifen tablets.

6.3. Colon Targeted Delivery Systems

Guar gum nanoparticles cross-linked with glutaraldehyde were engineered for 5-fluorouracil (5-FU) colon delivery.[19] Exploiting guar gum's susceptibility to colonic bacterial enzymes (galactomannanases), these particles remained intact in the upper GI tract (<2% release at pH 1.2 and 6.8) but released >85% of 5-FU within 8 hours in simulated colonic fluid containing rat cecal contents. In vitro cytotoxicity against HT-29 colon cancer cells was markedly enhanced.

6.4. 3D and 4D Printing Technologies

The integration of psyllium chitosan composites with pharmaceutical 3D printing represented a paradigm shift in personalized medicine (2024).[26] Fused deposition modeling (FDM) 3D printing enabled fabrication of patient-specific tablet geometries with programmable release profiles delayed, pulsatile, or sequential release of ciprofloxacin for urinary tract infections. Antimicrobial efficacy against E. coli and K. pneumoniae was maintained with improved patient adherence metrics. Anticipating 2026 publications, 4D-printed thermoresponsive devices using chia/quinoa biopolymer blends are being investigated for GLP-1 agonist peptide delivery.[31] These shape-morphing constructs respond to colonic temperature gradients (37°C → 39°C in inflamed tissue), releasing peptide therapeutics selectively at inflammatory sites an emerging approach for inflammatory bowel disease management.

6.5. Artificial Intelligence and Machine Learning in Formulation

A pioneering 2025 study applied machine learning algorithms (Random Forest, Artificial Neural Networks) to optimize flaxseed mucilage microemulsion formulations for repaglinide.[30] Using 47 experimental data points, the ML model predicted optimal oil-to-surfactant ratios, globule size, and drug loading with 94% accuracy. The AI-optimized microemulsion demonstrated 3-fold enhancement in oral bioavailability compared to conventional tablet formulations highlighting the transformative potential of data-driven pharmaceutical development.

6.6. Gene and Nucleic Acid Delivery

Perhaps the most groundbreaking recent advance involves hemp seed-derived exosome-mimetic nanovesicles (EMNVs) for siRNA delivery (2025).[29] These plant-derived vesicles (150–200 nm) exhibited natural cellular uptake pathways, evaded lysosomal degradation, and achieved 85% gene knockdown in HepG2 hepatic cells comparable to lipid nanoparticle (LNP) benchmarks but with superior safety profiles and no immunogenicity. This positions seed-derived vesicles as a compelling alternative to synthetic delivery vectors for RNA therapeutics.

6.7. Quinoa Saponin-Based Self-Emulsifying Systems

Quinoa saponins, recognized as natural non-ionic surfactants with HLB values of 12–15, were formulated into self-nano emulsifying drug delivery systems (SNEDDS) for paclitaxel. [22] The quinoa saponin SNEDDS demonstrated enhanced lymphatic absorption (2.4-fold), reduced systemic toxicity (improved therapeutic index by 38%), and superior stability over 12 months at 25°C/60% RH compared to conventional Cremophor EL-based paclitaxel formulations.

7. SAFETY PROFILE AND REGULATORY CONSIDERATIONS

The regulatory landscape for seed derived pharmaceutical excipients presents both opportunities and challenges. Table 4 summarizes the regulatory status, safety profiles, and key challenges for major seed excipients. [32][33]

Table 4: *Regulatory Status and Safety Profile of Seed-Derived Excipients.*

Excipient	Regulatory Status	Safety Profile	Challenges
Psyllium husk	GRAS (FDA), Ph. Eur.	Well-tolerated, non-toxic	Batch-to-batch variability, moisture sensitivity
Guar gum	GRAS (FDA), USP/NF listed	Minimal toxicity, biodegradable	Microbial contamination risk, viscosity inconsistency
Fenugreek galactomannan	Food-grade, limited pharma monographs	Generally safe, mild GI effects at high doses	Lack of standardized pharmaceutical grade
Flaxseed mucilage	Food GRAS, no USP monograph	Non-toxic, antioxidant properties	Oxidative instability of omega-3, extraction yield
Chia seed mucilage	Novel food (EU), GRAS (US)	Safe, anti-inflammatory	Standardization gap, gelation variability

Sesame oil	USP listed excipient	Allergen potential in sensitive individuals	Allergenicity, oxidative rancidity

Critical regulatory gaps include: (i) Absence of pharmaceutical-grade monographs for chia seed mucilage and fenugreek galactomannan in major pharmacopeias (ii) Lack of standardized extraction protocols leading to inter-batch variability (iii) Limited long-term safety data for modified seed derivatives (iv) Insufficient guidance from regulatory agencies on novel 3D-printed seed based dosage forms.[34] The International Pharmaceutical Excipients Council (IPEC) has initiated collaborative efforts with academic institutions to develop seed excipient specifications, including identity, purity, viscosity, and microbial limits. ICH Q8/Q9/Q10 guidelines on pharmaceutical development, risk management, and pharmaceutical quality systems provide applicable frameworks that manufacturers can adopt for seed excipient development programs. [35]

8. CHALLENGES AND LIMITATIONS

Despite remarkable progress, seed based drug delivery systems face several persistent challenges:[36][37][38]

(1) Compositional Variability: Seed composition varies with climate, geography, agricultural practices, and post-harvest processing. This translates to batch-to-batch inconsistency in key pharmaceutical parameters such as viscosity, swelling index, and mucoadhesive strength.

(2) Extraction and Purification: Isolation of seed polysaccharides, proteins, and oils requires energy-intensive extraction processes. Purification challenges include co-extraction of impurities (proteins with polysaccharides, phospholipids with oils) that can affect formulation performance.

(3) Stability Issues: Fixed oils from seeds (flaxseed, hemp) are highly susceptible to oxidative rancidity, limiting shelf-life. Mucilages may undergo microbial degradation unless adequate preservatives are included, raising compatibility concerns.

(4) Scale-up and Manufacturing: Translation from laboratory-scale to commercial-scale production of seed-based nanoparticles and 3D-printed dosage forms faces significant engineering and cost challenges.

(5) Regulatory Hurdles: Absence of comprehensive pharmacopeial standards for most seed excipients creates uncertainty in regulatory submissions. Novel delivery systems (3D-printed, gene delivery vesicles) using seed materials require extensive toxicological characterization.

(6) Allergenicity: Seed-derived materials (sesame, tree nuts) may cause hypersensitivity reactions in sensitive populations, necessitating rigorous allergen testing and labeling requirements.

9. FUTURE PERSPECTIVES

The future trajectory of seed-based drug delivery is convergent with several transformative technological trends: [39] [40]

- Precision Formulation via AI/ML: Machine learning models integrating multi-omics seed compositional data with formulation response surfaces will enable in silico prediction of optimal seed excipient combinations, drastically reducing formulation development timelines and costs.
- Seed Exosomes and Vesicles: Plant-derived exosome-like nanoparticles from seeds represent a frontier in drug and gene delivery, offering innate biocompatibility, cross-kingdom biological communication, and scalable production from agricultural waste streams.[29][41]
- Responsive and Adaptive Systems: Integration of seed biopolymers with sensors, enzymes, or stimuli-responsive synthetic polymers will yield 'intelligent' DDS capable of real-time therapeutic adaptation based on disease biomarkers (glucose, pH, enzymes, and reactive oxygen species). [27][28]
- Circular Economy Applications: Seed processing byproducts (hulls, presscake, and defatted meal) represent underutilized sources of pharmaceutical Excipients aligning drug delivery innovation with zero-waste agricultural processing and bioeconomy goals. [42]
- Personalized Medicine and 3D/4D Printing: Seed biopolymers are ideally suited as 'inks' in pharmaceutical 3D printing for personalized dosage form fabrication based on individual pharmacogenomic profiles.[26][31]

10. CONCLUSION

Seed-derived materials have emerged as a compelling and multifunctional platform for next-generation drug delivery systems. Their unique physicochemical properties swellability, mucoadhesion, biodegradability, biocompatibility, and inherent bioactivity provide unmatched versatility across formulation types and administration routes. The period 2020–2026 has witnessed transformational advances: from glucose-responsive insulin hydrogels and colon-targeted nanoparticles to AI-optimized microemulsions and plant-derived siRNA nanovesicles. This review demonstrates that seed-based systems are transitioning from simple natural excipients to sophisticated, intelligent drug delivery platforms capable of competing with and complementing synthetic polymer technologies. Key successes include 3–6-fold bioavailability enhancements, >85% site-specific drug release efficiency, and clinically relevant gene silencing efficiencies comparable to synthetic lipid nanoparticles.

However, translation of these promising laboratory findings to clinical application requires concerted effort in: establishing robust pharmacopeial standards for seed excipients; developing scalable manufacturing protocols; generating comprehensive long-term safety data; and engaging regulatory agencies for expedited pathways for seed-based novel drug delivery systems. The intersection of seed biotechnology, nanotechnology, artificial intelligence, and sustainable manufacturing presents an extraordinary opportunity to develop affordable, effective, and environmentally responsible drug delivery solutions—particularly valuable for emerging economies where seed-derived materials are abundantly available. Future research should prioritize clinical translation, regulatory harmonization, and systematic exploration of underutilized seed sources to fully realize this potential.

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