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Green Alternatives in Drug Delivery: Harnessing the Potential of Natural Superdisintegrants for Enhanced Pharmaceutical Performance

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Abstract

Superdisintegrants play a pivotal role in pharmaceutical formulations, especially in orally disintegrating dosage forms, facilitating rapid disintegration and dissolution of tablets or capsules thereby enhancing drug delivery and bioavailability. Traditional synthetic superdisintegrants have been widely utilized in pharmaceutical formulations; however, there is an increasing trend towards exploring natural alternatives. Natural super disintegrants, such as starch from various sources, Plantago ovata (psyllium husk), guar gum, locust bean gum, gellan gum, and xanthan gum, offer several advantages, including biodegradability, compatibility with biological systems, and sustainable production processes. This review aims to shedding light on the characteristics and performance of natural superdisintegrants compared to synthetic counterparts, which highlights the biodegradability of natural materials, their compatibility with biological systems, and the sustainable sourcing and production processes involved. This review article explores the potential of natural superdisintegrants in improving pharmaceutical performance while minimizing environmental impact. By harnessing the unique properties of plant-based materials such as psyllium husk, guar gum, locust bean gum, gellan gum, and xanthan gum, significant advancements have been achieved in the formulation of solid dosage forms. Furthermore, the potential challenges and future prospects of incorporating natural superdisintegrants into pharmaceutical formulations are discussed. Overall, this review underscores the importance of embracing green alternatives in drug delivery and emphasizes the pivotal role of natural superdisintegrants in achieving enhanced pharmaceutical performance with environmental sustainability. This review emphasizes the critical role of natural super disintegrants in achieving enhanced pharmaceutical performance with environmental sustainability.

Keywords: *Superdisintegrants, Natural alternatives, Synthetic superdisintegrants, Drug delivery, Biodegradability, Biocompatibility, Sustainability, Eco-friendly*

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1. Introduction

In recent years, there has been a growing emphasis on incorporating green and sustainable practices in various industries, including pharmaceuticals. One area where this shift towards sustainability is particularly noteworthy is in drug delivery systems. As the pharmaceutical industry continues to explore environmentally friendly alternatives, natural superdisintegrants have emerged as promising candidates for enhancing the performance of solid dosage forms. The disintegration of solid dosage forms, such as tablets and capsules, is a crucial step in drug delivery, influencing the drug's bioavailability, onset of action, and patient compliance (Rathi *et al.*, 2019). Superdisintegrants play a crucial role in facilitating the rapid disintegration of tablets and capsules, thereby promoting efficient drug release and absorption Traditional synthetic superdisintegrants have long been employed to facilitate rapid disintegration; however, concerns regarding the environmental impact and sustainability of synthetic excipients have led researchers to explore natural alternatives.Among these alternatives, natural superdisintegrants have emerged as promising candidates for enhancing pharmaceutical performance while reducing environmental impact. The ability of superdisintegrants to facilitate rapid disintegration of solid dosage forms is crucial for improving drug dissolution and bioavailability superdisintegrants, derived from various plant and microbial sources, offer promising advantages over synthetic counterparts in terms of biodegradability, biocompatibility, and sustainability (Prajapati *et al.*, 2021). Examples of natural superdisintegrants such as starch, *Plantago ovata* (psyllium husk), guar gum, locust bean gum, gellan gum, and xanthan gum, have demonstrated promising disintegration properties in pharmaceutical formulations. These materials, not only facilitate rapid disintegration of tablets or capsules but also align with the principles of green pharmacy. This review, aimed to explore the concept of "Green Alternatives in Drug Delivery" by focusing on the harnessing of natural superdisintegrants for enhanced pharmaceutical performance. By examining the properties and applications of natural superdisintegrants, along with their comparative analysis against synthetic counterparts, seek to elucidate their potential in contributing to sustainable drug delivery systems. Through a comprehensive review of current research and development efforts, we aim to shed light on the promising avenues for incorporating natural superdisintegrants into pharmaceutical formulations, thereby advancing the paradigm of environmentally conscious drug delivery.

2. Disintegrant and Superdisintegrant

2.1. Role of Disintegrant in Drug Absorption

Disintegrants play a crucial role in drug absorption, particularly in oral solid dosage forms like tablets and capsules. Their primary function is to facilitate the breakup or disintegration of the dosage form into smaller

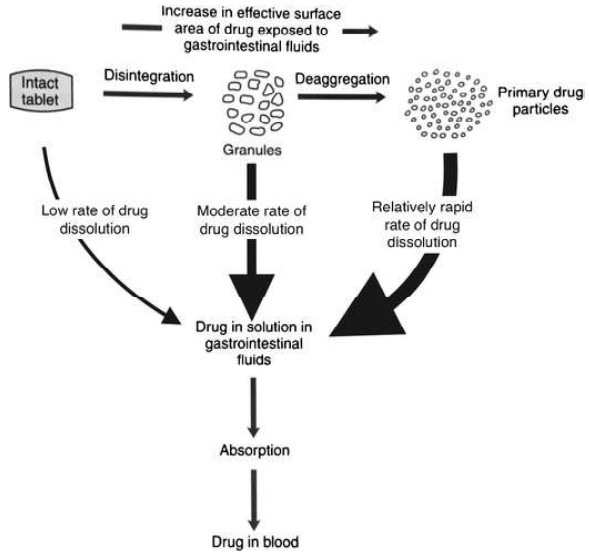


Figure 1: Sequence of Steps in the Absorption of Drugs from Orally Administered Solid Dosage Form

particles or granules upon contact with physiological fluids, thus enhancing dissolution and subsequent absorption of the drug substance (Figure 1). Key roles of disintegrants in drug absorption may include enhanced dissolution, rapid onset on action, improved bioavailability, consistent drug release and improved patient compliance.

Plasma concentration versus rate of absorption curves are essential in pharmacokinetics to understand how drugs are absorbed and distributed in the body.

The inclusion of disintegrants in pharmaceutical formulations profoundly influences the plasma concentration versus rate of absorption profiles of drugs. Disintegrants play a crucial role in promoting the disintegration of solid dosage forms, facilitating the release of the active pharmaceutical ingredient (API) and subsequent absorption into systemic circulation (Aulton, 2013). When comparing the plasma concentration versus rate of absorption curves of formulations with and without disintegrants, distinct differences emerge.

In formulations without disintegrants, the dissolution and subsequent absorption of the drug may be slower and less efficient. Consequently, the plasma concentration versus time curve exhibits a slower rise to peak concentration, reflecting delayed absorption kinetics (Banker and Anderson, 2013). On the contrary, formulations containing disintegrants demonstrate enhanced dissolution and rapid disintegration, leading to expedited drug release and absorption. As a result, the plasma concentration curve typically exhibits a steeper slope, reaching peak concentration more rapidly compared to formulations lacking disintegrants (Lachman *et al.*, 2012), which results in Flip-flop Kinetics (Figure 2) (Flip-flop kinetics refers to a situation when the rate of absorption of a compound is significantly slower than its rate of elimination from the body).

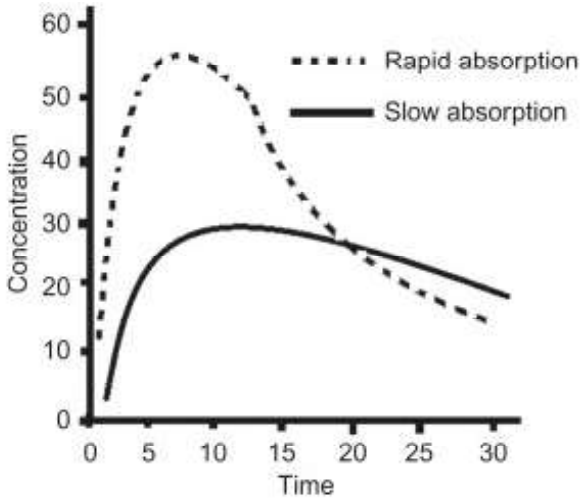


Figure 2: Concentrations of Drug Comparing a Slow Rate of Absorption to a Rapid Rate of Absorption, Demonstrating a "Flip-Flop" Kinetics, in Presence of Disintegrant (Rapid Rate of Absorption) and Absence of Disintegrant (Slow Rate of Absorption)

Moreover, the presence of disintegrants can also affect the extent of drug absorption and overall bioavailability. By promoting rapid disintegration and dissolution, disintegrants contribute to more uniform drug absorption across different gastrointestinal regions, thereby minimizing potential variability in plasma drug concentrations (Rathbone *et al.*, 2010). Consequently, formulations containing disintegrants may exhibit higher and more consistent bioavailability compared to those without disintegrants.

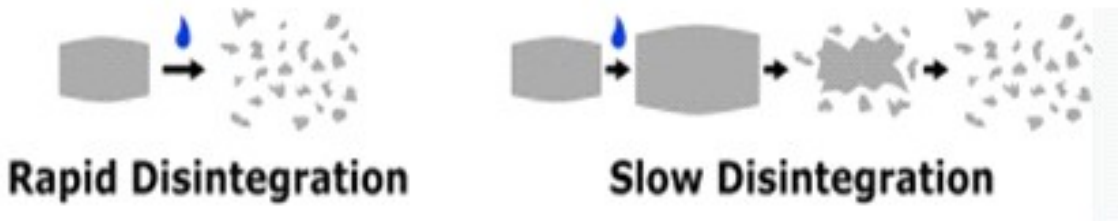
The incorporation of disintegrants in pharmaceutical formulations significantly influences the plasma concentration versus rate of absorption profiles of drugs, leading to enhanced dissolution, rapid absorption, and improved bioavailability.

2.2. Disintegrant and Superdisintegrant Regarding their Roles in Enhancing Drug Absorption

Disintegrants are excipients added to solid dosage forms like tablets and capsules to facilitate their breakup into smaller particles upon exposure to physiological fluids, thereby increasing the surface area available for

dissolution and improving drug absorption in the gastrointestinal tract (GI) (Figure 3) (Gupta *et al.*, 2018). Commonly used disintegrants include substances like croscarmellose sodium, crospovidone, sodium starch glycolate, and microcrystalline cellulose. These disintegrants function through mechanisms such as swelling, capillary action, and wicking, which aid in breaking apart the dosage form and facilitating drug release and absorption in the GI tract.

- **Croscarmellose Sodium (e.g., Ac-Di-Sol):** This is a commonly used disintegrant that functions by swelling rapidly when exposed to water, thereby promoting tablet disintegration.
- **Crospovidone (e.g., Polyplasdone):** Another widely used disintegrant, crospovidone, works by absorbing water into its internal structure, causing rapid swelling and disintegration of tablets.
- **Sodium Starch Glycolate (e.g., Explotab):** This disintegrant works by absorbing water and swelling, leading to the disruption of tablet structure and facilitating dissolution.
- **Microcrystalline Cellulose (e.g., Avicel):** While primarily used as a binder and filler, microcrystalline cellulose can also aid in tablet disintegration due to its ability to absorb water and swell slightly.



(a) (b)

Figure 3: (a) Rate of Disintegration of Disintegrant and (b) Superdisintegrant

Superdisintegrants, on the other hand, are highly efficient disintegrants that promote even faster disintegration and dissolution of solid dosage forms. They are particularly useful in formulations containing poorly soluble drugs or for drugs requiring rapid onset of action. Superdisintegrants like crospovidone and croscarmellose sodium exhibit excellent disintegrating properties due to their ability to rapidly absorb water and swell, leading to the breakup of the dosage form into smaller particles and facilitating drug release and absorption in the GI tract (Ashok *et al.*, 2017).

- **Crospovidone (e.g., Polyplasdone XL):** As a superdisintegrant, crospovidone exhibits enhanced water uptake and rapid swelling, leading to exceptionally fast tablet disintegration.
- **Croscarmellose Sodium (e.g., Ac-Di-Sol PH):** Similar to crospovidone, this variant of croscarmellose sodium is designed to provide even faster disintegration, ensuring rapid drug release.
- **Sodium Starch Glycolate (e.g., Primogel, Explotab):** Some variations of sodium starch glycolate are formulated to be superdisintegrants, displaying improved water uptake and swelling properties for rapid tablet disintegration.
- **Cross-linked Povidone (e.g., Polyplasdone XL-10):** This superdisintegrant, derived from povidone, is cross-linked to enhance its water absorption and swelling capabilities, resulting in accelerated tablet disintegration.

Both disintegrants and superdisintegrants serve to promote tablet disintegration and drug release, superdisintegrants are specifically exhibit faster and more efficient disintegration properties compared to conventional disintegrants. Chemically modified termed as superdisintegrants have been developed to improve the disintegration processes. Superdisintegrants are used at a low level (1%-10%) by weight basis as compared to a conventional disintegrant in the solid dosage form.

Traditional disintegrants, such as starches, cellulose derivatives, and cross-linked polymers, have been extensively utilized in pharmaceutical formulations for decades (Rowe *et al.*, 2009). These materials function

by absorbing water, swelling, and generating mechanical forces that disrupt the integrity of the dosage form, leading to rapid disintegration. While effective, traditional disintegrants may have limitations in terms of disintegration efficiency and speed, particularly in formulations containing poorly water-soluble drugs or those intended for fast-dissolving formulations. The demand for faster disintegration and improved drug release kinetics has led to the development of superdisintegrants, which offer superior performance even at lower concentrations (Caraballo *et al.*, 2013). Superdisintegrants exhibit enhanced swelling and water absorption properties, enabling them to achieve rapid disintegration of dosage forms within seconds or minutes, thus promoting faster drug release.

3. Types of Superdisintegrants

Superdisintegrants are primarily classified as follows (Figure 4):

a) **Natural Superdisintegrants:** A natural superdisintegrant refers to a substance of natural origin that possesses the ability to promote the rapid breakup or disintegration of pharmaceutical dosage forms such as tablets and capsules.

b) **Synthetic Superdisintegrants:** A synthetic superdisintegrant refers to a substance synthesized through chemical processes that possesses the ability to rapidly disintegrate pharmaceutical dosage forms such as tablets and capsules upon ingestion. These synthetic compounds are designed to facilitate the quick release of the active pharmaceutical ingredient (API) from the dosage form, thereby promoting its dissolution and subsequent absorption in the gastrointestinal tract (Table 1).

Table 1: Examples of Synthetic and Natural Superdisintegrants

Synthetic Superdisintegrants	Natural Superdisintegrants
Cross-linked Polyvinylpyrrolidone (crospovidone)	Croscarmellose Sodium
Cross-linked Sodium Carboxymethylcellulose	Sodium Starch Glycolate
Sodium Alginate	Locust Bean Gum
Polyplasdone XL	Guar Gum
Cross-linked Polyacrylic Acid (carbomer)	Oat Gum
Polyvinyl Alcohol	Gellan Gum
Polacrilin Potassium	Xanthan Gum
Crospovidone	Arabinoxylan
Copovidone	Pectin
Polyethylene Oxide	Agar
	Microcrystalline Cellulose
	Corn Starch
	Potato Starch
	Cassava Starch
	Maltodextrin
	Soy Polysaccharides
	Gum Karaya
	Gum Tragacanth
	Chitosan

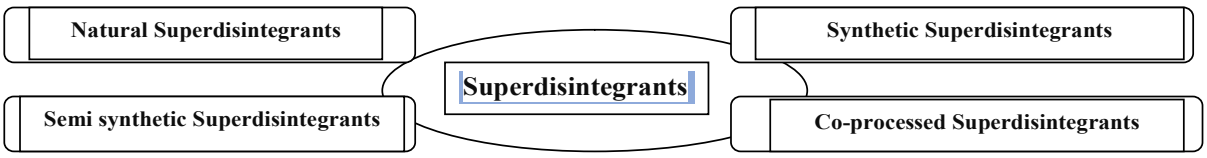


Figure 4: Classification of Superdisintegrants

c) **Semi Synthetic Superdisintegrants:** A semisynthetic superdisintegrant refers to a substance that is partially synthesized from natural materials and partially modified through chemical processes to enhance its disintegration properties in pharmaceutical formulations. These compounds combine the advantages of natural materials with the tailored characteristics obtained through chemical modification, making them suitable for various dosage forms where rapid disintegration and dissolution are essential.

d) **Co-processed Superdisintegrants:** A co-processed superdisintegrant refers to a specialized type of excipient used in pharmaceutical formulations, particularly in solid oral dosage forms like tablets and capsules. Unlike single-component superdisintegrants, co-processed superdisintegrants are created by combining two or more individual excipients through a specific manufacturing process to enhance their functionality and performance as disintegrants. Co-processed excipients exhibits synergistic effects, resulting in enhanced tablet disintegration and dissolution rates, thereby improving drug bioavailability and patient compliance (Wlodarski *et al.*, 2015).

4. Synthetic Superdisintegrant vs Natural Superdisintegrant

Synthetic superdisintegrants are pharmaceutical excipients that are synthesized artificially and added to solid dosage forms such as tablets and capsules to promote rapid disintegration when they come into contact with water or saliva. These substances are designed to swell rapidly, create pores, or undergo other physical changes to break down the tablet or capsule into smaller particles, thereby facilitating drug dissolution and absorption in the gastrointestinal tract. One of the most commonly used synthetic superdisintegrants is crospovidone, which is a crosslinked form of polyvinylpyrrolidone (PVP). Crospovidone exhibits excellent water absorption capacity and swelling properties, leading to rapid disintegration of tablets (Singh *et al.*, 2017). Other examples of synthetic superdisintegrants include Sodium starch glycolate (SSG) and Cross-linked sodium carboxymethyl cellulose (croscarmellose sodium).

A natural superdisintegrant is a substance derived from natural sources that is added to pharmaceutical formulations to promote the rapid disintegration of tablets or capsules in the gastrointestinal tract, facilitating drug dissolution and absorption (Kumar *et al.*, 2013). One example of a natural superdisintegrant is guar gum, starch, banana powder. Natural superdisintegrants are often preferred for their perceived safety profile and compatibility with natural or organic product formulations.

5. Selection Criteria for Superdisintegrants in the Formulation

Selection criteria for superdisintegrants in the formulation of solid dosage forms aiding in rapid disintegration and dissolution of tablets and capsules are crucial for ensuring the efficacy and performance of pharmaceutical products. The selection of an appropriate superdisintegrant is pivotal for ensuring the efficacy, bioavailability, and patient compliance of pharmaceutical formulations. These selection criteria encompass various aspects including disintegration efficiency, compatibility with other excipients, manufacturing processes, regulatory considerations, and cost-effectiveness.

a) **Disintegration Efficiency:** One of the primary criteria for selecting a superdisintegrant is its disintegration efficiency. The chosen superdisintegrant should have the ability to rapidly disintegrate the dosage form upon contact with aqueous fluids. This ensures quick drug release and dissolution, enhancing the bioavailability of the active pharmaceutical ingredient (API).

b) **Compatibility with Other Excipients:** The compatibility of the superdisintegrant with other excipients used in the formulation is essential. It should be compatible with binders, fillers, lubricants, and coatings

to ensure uniform distribution throughout the dosage form. Compatibility issues can lead to formulation inconsistencies and affect the performance of the final product (Gupta *et al.*, 2013).

c) Manufacturing Processes: Another crucial aspect is the compatibility of the superdisintegrant with the manufacturing processes involved. Whether the formulation utilizes wet granulation, direct compression, or other techniques, the superdisintegrant should be suitable for the chosen manufacturing method. Compatibility with manufacturing processes ensures ease of formulation and reproducibility of the final dosage form on a commercial scale. The selection of a superdisintegrant also depends on the specific characteristics of the drug formulation, including the dosage form (e.g., tablets, capsules, orodispersible tablets) and the physicochemical properties of the drug substance. Different superdisintegrants may exhibit varying performance depending on factors such as particle size, solubility, and drug release profile (Shah and Patel, 2020).

d) Regulatory Considerations: Regulatory compliance is a key factor in superdisintegrant selection. The chosen superdisintegrant should comply with regulatory guidelines and standards set forth by regulatory authorities such as the FDA (Food and Drug Administration) or EMA (European Medicines Agency). Compliance ensures the safety, quality, and efficacy of the pharmaceutical product.

e) Cost-Effectiveness: Cost-effectiveness is also an important consideration in superdisintegrant selection. The chosen superdisintegrant should provide the desired disintegration efficiency at a reasonable cost. Cost-effective formulations ensure economic viability without compromising quality or performance.

The selection of superdisintegrants for the formulation of solid dosage forms involves a comprehensive evaluation based on disintegration efficiency, compatibility with other excipients, manufacturing processes, regulatory compliance, and cost-effectiveness. A thorough understanding of these selection criteria is essential for developing efficient and high-quality pharmaceutical formulations.

6. Selection Criteria of Natural Super Disintegrants over Synthetic Super Disintegrants in the Formulation

Natural super disintegrants have gained significant attention in pharmaceutical formulation due to their potential advantages over synthetic counterparts.

a) **Biodegradability and Environmental Impact:** Natural super disintegrants offer the advantage of biodegradability, contributing to reduced environmental impact. Materials sourced from renewable plant or microbial sources degrade more readily compared to synthetic alternatives, minimizing ecological footprint (Saeed *et al.*, 2022).

b) **Biocompatibility and Safety:** Superdisintegrants derived from natural sources typically exhibit higher biocompatibility with biological systems, ensuring patient safety. This characteristic reduces the risk of adverse reactions and enhances the overall safety profile of the formulation (Jani *et al.*, 2021).

c) **Sustainability and Renewable Sources:** Utilizing natural super disintegrants promotes sustainability in pharmaceutical manufacturing. These materials are sourced from renewable sources such as plant starches or gums, reducing dependence on finite resources and supporting eco-friendly practices (Shende and Chavan, 2019).

d) Performance and Efficacy: Despite their natural origin, natural super disintegrants demonstrate comparable or superior performance to synthetic counterparts in terms of disintegration efficiency. They facilitate rapid disintegration of solid dosage forms, ensuring optimal drug release and bioavailability (Puri *et al.*, 2022).

Cost-Effectiveness: While natural super disintegrants may initially have a higher cost compared to synthetic ones, their long-term cost-effectiveness should be considered. Factors such as biodegradability, biocompatibility, and sustainability contribute to overall savings in terms of regulatory compliance and environmental impact (Sailaja *et al.*, 2022).

The choice of superdisintegrant should be based on its ability to rapidly break down the tablet matrix and promote dispersion of the active pharmaceutical ingredient (API) upon contact with aqueous media. Additionally, factors such as the mechanism of action, dosage form requirements, and cost-effectiveness

should be taken into account. Similarly, emphasize the importance of considering the physicochemical properties of the superdisintegrant, including its swelling capacity, water uptake, and interaction with other excipients (Maskare *et al.*, 2021). Natural superdisintegrants like *Plantago ovata* (psyllium husk), guar gum, and locust bean gum are favored due to their biodegradability, biocompatibility, and sustainability. In contrast, synthetic superdisintegrants such as croscarmellose sodium and sodium starch glycolate offer advantages in terms of uniformity, reproducibility, and cost-effectiveness. However, natural superdisintegrants biodegradability and environmental impact should be carefully considered in the context of sustainable formulation development (Tbale 2). Overall, the selection of superdisintegrants involves a comprehensive evaluation of their disintegration performance, compatibility with other formulation components, and

Table 2: Comparative Analysis of Natural and Synthetic Superdisintegrants

Superdisintegrant	Source	Biodegradability	Biocompatibility	Sustainability
Starch	Various sources	High	High	High
Plantago ovate	Psyllium husk	High	High	High
Guar gum	Guar bean	High	High	High
Locust bean gum	Carob tree seeds	High	High	High
Gellan gum	Bacterial fermentation	High	High	High
Xanthan gum	Bacterial fermentation	High	High	High
Croscarmellose sodium	Synthetic	Medium to high	Less	Medium to high
Sodium starch glycolate	Synthetic	Medium to high	Less	Medium to high
Cross-linked PVP	Synthetic	Low to medium	Less	Medium to high

Table 3: Natural Polymers Used in Solid Dosage Forms

S. No.	Natural Polymer	Marketed Drug	Disintegration Time	Concentration (% w/w)
1	Chitin and chitosan	Cinnarizine	60 sec	3
2	Guar gum	Glipizide	30 sec	1
3	Gum karaya	Amlodipine, granisetron hydrochloride	17.10 sec	4
4	Agar and treated agar	Theophylline	20 sec	1-2
5	Fenugreek seed mucilage	Metformin hydrochloride	15.6 sec	4
6	Soy polysaccharide	Lornoxicam	12 sec	8
7	Gellan gum	Metronidazole	155 sec	4
8	Mango peel pectin	Aceclofenac	11.59 sec	0.1–4
9	*Lepidium sativum* mucilage	Nimesulide	17 sec	5–15
10	*Plantago ovata* seed mucilage	Granisetron HCl	17.10 sec	5
11	Aegle marmelos gum	Aceclofenac	8–18 min	6
12	Locust bean gum	Nimesulide	13 sec	10
13	*Lepidium sativum*	Nimesulide	17 sec	10
14	*Mangifera indica* gum	Metformin HCL, paracetamol	3–8 min	6
15	*Hibiscus rosa-sinensis* mucilage	Aceclofenac	20 sec	6
16	Dehydrated banana powder	Ondansetron HCl/propranolol, gabapentin	15–36 sec	6

environmental sustainability, with consideration given to both natural and synthetic options based on specific formulation requirements.

The utilization of natural polymers is valuable predicated on proven biocompatibility and safety. Natural gums are among the most popular hydrophilic polymers because of their cost-efficacy and regulatory acceptance. Polymers are generally employed in floating drug distribution systems so as to target the distribution of drug to a concrete region in the gastrointestinal tract, that is, stomach. Various natural polymers can be used in variety of formulations with suitable concentration shows appropriate disintegration time (Table 3). Moreover, these polymers are safe, nontoxic, and capable of chemical modification and gel formation (Beneke *et al.*, 2009).

7. Method of Incorporation Disintegrant/Superdisintegrant in a Formulation

Super disintegrants play a crucial role in promoting the rapid disintegration of solid dosage forms, ensuring

Table 4: Method of Incorporation of Superdisintegrant in a Formulation

Method of Incorporation	Description	Importance
Direct Compression	Superdisintegrants are mixed with other excipients and the active ingredient, followed by compression into tablets.	- Simplifies the manufacturing process, reducing production time and costs. - Prevents potential degradation or alteration of superdisintegrants during processing, ensuring their efficacy in promoting rapid disintegration
Wet Granulation	Superdisintegrants are granulated with other excipients using a liquid binder before drying and milling into granules, which are then compressed into tablets.	- Enhances uniform distribution of superdisintegrants within the formulation, ensuring consistent disintegration across tablets - Improves flow properties of the powder blend, facilitating uniform tablet compression and reducing tablet weight variability.
Dry Granulation	Superdisintegrants are mixed with other excipients and compressed into compacts without the use of liquid binders, followed by milling and compression into tablets.	- Minimizes the risk of moisture-induced degradation of superdisintegrants, ensuring stability during storage - Offers an alternative for moisture-sensitive APIs, maintaining formulation integrity and efficacy
Intra-granulation	Super disintegrants are added during the granulation process, where they become part of the granules forming the tablet core.	- Ensures uniform distribution of the disintegrant within the granules, leading to consistent disintegration across all tablets. -Facilitates direct compression by improving the flow properties of the granules, reducing processing time and cost.
Extra-granulation	Super disintegrants are added as a separate ingredient during the final blend or compression stage, typically as a part of the tablet formulation blend.	- Provides flexibility in formulation development, allowing adjustment of disintegrant concentration without affecting granulation process parameters. - Enables the use of sensitive or heat-labile disintegrants that may not withstand the high temperatures involved in granulation.

optimal drug release and absorption. Each method has its advantages and limitations, and the selection depends on factors such as the properties of the active ingredient, the desired characteristics of the final dosage form, and the equipment available for manufacturing. The method of incorporation of super disintegrants, whether as intra-granulating or extra-granulating agents, significantly impacts the formulation process and the performance of the final dosage form. Both intra-granulation and extra-granulation methods play vital roles in incorporating super disintegrants into solid dosage forms. The choice of method depends on various factors, including formulation requirements, processing conditions, and the characteristics of the disintegrant used (Table 4).

8. Mechanism of Disintegration by Super Disintegrants

The mechanisms of disintegration by super disintegrants are differentiated in their own aspects (Table 5) which can be explained as follows:

Table 5: Mechanism of Disintegration by Super Disintegrants

Mechanism of Disintegration	Description	Significance	Example
Swelling	Superdisintegrants rapidly absorb water upon exposure, leading to swelling and subsequent volume increase. This swelling generates internal pressure within the tablet, facilitating mechanical rupture and fragmentation of the tablet matrix.	Ensures rapid disintegration of tablets, promoting quick drug release and dissolution, thereby enhancing bioavailability and therapeutic efficacy of the drug Crospovidone swells rapidly, leading to efficient tablet disintegration and enhanced drug release (Jani *et al.*, 2021).	Crospovidone (crosslinked polyvinylpyrrolidone)
Wicking	Superdisintegrants create channels or capillaries within the tablet matrix, allowing penetration of aqueous fluids. These channels facilitate rapid ingress of water into the tablet, resulting in internal dissolution and erosion of the tablet matrix, promoting disintegration.	Enhances the rate and extent of drug release from the tablet, ensuring efficient drug delivery and absorption within the body, leading to improved patient compliance and therapeutic outcomes Sodium starch glycolate forms channels upon hydration, facilitating rapid disintegration and dissolution of tablets (Reddy and Begum, 2020).	Sodium starch glycolate
Heat of Wetting	Superdisintegrants absorb water and release heat, which increases the temperature of the tablet. This increase in temperature accelerates the disintegration process by promoting the dissolution of excipients and drug particles.	Accelerates the disintegration process, ensuring rapid drug release and dissolution. Croscarmellose sodium releases heat upon hydration, enhancing tablet disintegration and drug dissolution (Puri *et al.*, 2022).	Croscarmellose sodium

Table 5 (Cont.)			
Deformation Recovery	Superdisintegrants deform upon hydration and recover their original shape, exerting mechanical forces that disrupt the tablet matrix. This deformation recovery process enhances tablet disintegration and drug release.	Facilitates the breakdown of tablets into smaller particles, ensuring rapid drug release and absorption. Croscarmellose sodium deforms and recovers its shape upon hydration, promoting efficient tablet disintegration and drug dissolution (Maskare *et al.*, 2021).	Croscarmellose sodium

9. Mechanism of Disintegration by Natural and Synthetic Super Disintegrants

The differences in mechanisms of disintegration between natural and synthetic superdisintegrants influence their performance and suitability (Table 6) for various pharmaceutical formulations and are tabulated as follows:

Table 6: Mechanism of Disintegration by Natural and Synthetic Super Disintegrants

Mechanism of Disintegration	Natural Superdisintegrants	Synthetic Superdisintegrants
Swelling	Natural superdisintegrants, such as guar gum and locust bean gum, exhibit swelling behavior upon hydration due to their hydrophilic nature. This swelling leads to the disruption of tablet structure and enhanced disintegration.	Synthetic superdisintegrants like crospovidone and croscarmellose sodium also demonstrate swelling upon contact with water, often more rapid and pronounced compared to natural alternatives, leading to faster disintegration.
Wicking	Natural superdisintegrants, such as Plantago ovata (psyllium husk) and gellan gum, create channels or capillaries within the tablet matrix, facilitating the ingress of aqueous fluids. These channels promote rapid penetration of water into the tablet, accelerating internal dissolution and erosion.	Synthetic superdisintegrants, including sodium starch glycolate and cross-linked sodium carboxymethyl cellulose, also create channels within the tablet matrix upon hydration, resulting in faster and more consistent tablet disintegration.
Heat of Wetting	Natural superdisintegrants typically do not generate significant heat upon hydration, as their mechanism of disintegration relies primarily on swelling and wicking.	Synthetic superdisintegrants may generate some heat upon hydration due to their rapid swelling and dissolution properties. However, the heat generated is generally minimal and does not significantly contribute to the disintegration process.
Chemical Reaction	Natural superdisintegrants generally do not undergo chemical reactions upon hydration, primarily involving physical swelling and erosion of the tablet matrix.	Synthetic superdisintegrants, such as sodium bicarbonate, may undergo chemical reactions upon hydration, releasing gases or solutes that further disrupt the tablet matrix and promote disintegration.
Particle Separation	Natural superdisintegrants facilitate particle separation upon hydration, promoting tablet disintegration.	Synthetic superdisintegrants also promote particle separation upon hydration, ensuring uniform tablet disintegration and dissolution.

Table 6 (Cont.)		
Particle Repulsive Forces	Natural superdisintegrants exert repulsive forces between particles upon hydration, facilitating particle dispersion and tablet disintegration.	Synthetic superdisintegrants exert particle repulsive forces upon hydration, enhancing tablet disintegration efficiency.
Deformation Recovery	Natural superdisintegrants may exhibit some degree of deformation and recovery upon hydration, contributing to tablet disintegration.	Synthetic superdisintegrants, such as croscarmellose sodium, are known for significant deformation and recovery properties upon hydration, promoting rapid tablet disintegration and dissolution.
Enzymatic Reaction	Natural superdisintegrants do not typically undergo enzymatic reactions upon exposure to digestive enzymes.	Synthetic superdisintegrants may undergo enzymatic reactions in the gastrointestinal tract, contributing to tablet disintegration and drug release.
Ion Exchange	Natural superdisintegrants do not participate in ion exchange reactions upon hydration.	Synthetic superdisintegrants may undergo ion exchange upon hydration, leading to repulsion of

10. Novel Techniques Used in the Processing of Natural Superdisintegrants

In recent years, novel processing techniques have been developed to improve the functionality and applicability of natural superdisintegrants in pharmaceutical formulations (Table 7). These innovative methods aim to enhance disintegration efficiency, optimize drug release kinetics, and offer versatility in formulation design.

These techniques represent innovative approaches to process natural superdisintegrants, resulting in improved functionality and versatility for various pharmaceutical applications.

Table 7: Novel Techniques Used in the Processing of Natural Superdisintegrants

Processing Technique	Natural Superdisintegrant	Example	Applications	References
Nano structuring	Chitosan	Chitosan nanoparticles	Sublingual tablets for rapid onset of action	(Patil *et al.*, 2019)
Co-crystallization	Tamarind Gum	Tamarind Gum co-crystals	Orodispersible films for pediatric and geriatric patients	(Jain *et al.*, 2018)
Electro spinning	Pectin	Electro spun Pectin fibers	Buccal patches for localized drug delivery	(Pillay *et al.*, 2017)
Supercritical Fluid Technology	Guar Gum	Supercritical CO_2 processed Guar Gum	Immediate-release tablets for enhanced dissolution	(Barzegar-Jalali *et al.*, 2018)
Freeze-Thaw Cycling	Locust Bean Gum	Freeze-thaw treated Locust Bean Gum	Fast-disintegrating capsules for elderly patients	(Lu *et al.*, 2017)

11. Types of Natural Super Disintegrating Agents and its Significance

Natural superdisintegrants play a crucial role in enhancing the disintegration and dissolution rates of pharmaceutical dosage forms, leading to improved drug delivery and bioavailability. They are derived from natural sources such as plants, seeds, gums, and marine products. This comprehensive note explores various natural superdisintegrants, their extraction methods, significance, and pharmaceutical applications.

11.1. Plant-Based Superdisintegrants

11.1.1. Psyllium Husk

Extraction Method: Psyllium husk, derived from the seeds of *Plantago ovata*, is commonly extracted by milling and sieving processes to obtain the fibrous husk (Ahmed *et al.*, 2019).

Significance: Psyllium husk is rich in soluble dietary fiber and exhibits excellent water-absorbing properties, making it an effective superdisintegrant for oral dosage forms. Its significant swelling capacity aids in rapid tablet disintegration and drug release.

Pharmaceutical Applications: It is widely used in the formulation of fast-dissolving tablets, oral disintegrating films, and granules for controlled-release formulations.

11.1.2. Guar Gum

Extraction Method: Guar gum is extracted from the endosperm of guar beans (Cyamopsis tetragonoloba) through a mechanical milling process followed by sieving to obtain the gum powder.

Significance: Guar gum is a polysaccharide with high water-holding capacity and swelling properties. It acts as an effective superdisintegrant by rapidly hydrating and promoting tablet disintegration.

Pharmaceutical Applications: Guar gum finds applications in immediate-release tablets, chewable tablets, and orally disintegrating tablets due to its efficient disintegration properties.

11.2. Seeds and Gums as Superdisintegrants

11.2.1. Locust Bean Gum

Extraction Method: Locust bean gum is extracted from the seeds of the carob tree (Ceratonia siliqua) through a series of mechanical milling, sieving, and purification processes (Mistry and Sheth, 2016).

Significance: Locust bean gum contains galactomannans, which swell rapidly upon hydration, aiding in tablet disintegration and dissolution.

Pharmaceutical Applications: It is commonly used in the formulation of fast-disintegrating tablets, chewable tablets, and controlled-release formulations.

11.2.2. Tamarind Gum

Extraction Method: Tamarind gum is extracted from the seeds of the tamarind tree (*Tamarindus indica*) using water extraction followed by purification and drying processes (Paulino *et al.*, 2019).

Significance: Tamarind gum is rich in polysaccharides and exhibits excellent swelling properties, making it an effective superdisintegrant in pharmaceutical formulations.

Pharmaceutical Applications: Tamarind gum is used in the formulation of orodispersible films, mouth dissolving tablets, and pediatric formulations due to its rapid disintegration properties.

11.3. Marine-Derived Superdisintegrants

11.3.1. Alginate

Extraction Method: Alginate is extracted from brown seaweeds such as *Laminaria spp*. and *Macrocystis spp*. through alkaline treatment, filtration, and purification processes.

Significance: Alginate forms a gel-like matrix upon hydration, which rapidly disintegrates, making it suitable for fast-dissolving formulations.

Pharmaceutical Applications: Alginate is utilized in the formulation of orally disintegrating tablets, buccal patches, and wound dressings due to its excellent water-holding and disintegration properties.

Natural superdisintegrants derived from plant sources, seeds, gums, and marine products offer promising alternatives to synthetic counterparts in pharmaceutical formulations. Their efficient extraction methods and significant properties such as water absorption, swelling, and rapid disintegration make them valuable

components in the development of various dosage forms. By harnessing the potential of natural superdisintegrants, pharmaceutical scientists can enhance drug delivery systems and improve patient compliance and therapeutic outcomes.

12. Advancements in the Field of Natural Superdisintegrants

In recent years, there have been significant advancements in the field of natural superdisintegrants, driven by the ongoing efforts to innovate and optimize these materials for improved performance and versatility in pharmaceutical formulations. This comprehensive note explores the recent developments in natural superdisintegrants, highlighting their significance and potential impact on drug delivery systems.

12.1. Exploration of Novel Sources

Researchers have been actively exploring novel natural sources for superdisintegrants to broaden the spectrum of available options. These efforts aim to identify alternative materials with unique properties that can enhance disintegration and dissolution rates in pharmaceutical formulations. For example, studies have investigated lesser-known plant species, marine-derived polysaccharides, and microbial products as potential sources of natural superdisintegrants (Babu *et al.*, 2018).

12.2. Optimization of Extraction Methods

In addition to exploring new sources, researchers are focusing on optimizing extraction methods to obtain superdisintegrants with improved properties. Advanced extraction techniques such as ultrasound-assisted extraction, microwave-assisted extraction, and enzymatic hydrolysis have been employed to enhance the yield, purity, and functionality of natural superdisintegrants. These optimized extraction methods ensure efficient utilization of raw materials while minimizing environmental impact (Gupta *et al.*, 2019).

12.3. Engineering Superdisintegrant-Based Formulations

Recent developments in formulation engineering have led to the design of innovative dosage forms utilizing natural superdisintegrants. Nanotechnology-based approaches, such as nanoparticle formulations and nanostructured materials, have been explored to improve the dispersibility, solubility, and bioavailability of superdisintegrants. Furthermore, the combination of natural superdisintegrants with other excipients and technologies, such as co-processing and co-crystallization, has been investigated to enhance their functionality and compatibility in various drug delivery systems (Kumar *et al.*, 2021).

12.4. Integration of Natural Superdisintegrants in Advanced Drug Delivery Systems

Natural superdisintegrants are increasingly being integrated into advanced drug delivery systems to address specific challenges in drug delivery. These include targeted drug delivery systems, mucoadhesive formulations, and stimuli-responsive carriers. By incorporating natural superdisintegrants into these advanced systems, researchers aim to achieve site-specific delivery, prolonged release, and enhanced therapeutic efficacy of drugs (Singh *et al.*, 2020).

The recent developments in natural superdisintegrants signify a paradigm shift towards sustainable and efficient drug delivery systems. Through ongoing research and innovation, scientists are continually striving to optimize the performance and versatility of these materials in pharmaceutical formulations. By harnessing the potential of natural sources, optimizing extraction methods, and integrating advanced technologies, the future of natural superdisintegrants holds great promise for enhancing drug delivery and improving patient outcomes.

13. Regulatory Status of Super Disintegrants

Natural superdisintegrants, derived from various natural sources such as plants, seeds, gums, and marine products, are subject to regulatory oversight to ensure their safety and efficacy in pharmaceutical formulations. The regulatory landscape for these natural excipients involves multiple regulatory authorities and standards.

13.1. Food and Drug Administration (FDA) - United States

In the United States, the regulatory status of natural superdisintegrants falls under the purview of the Food and Drug Administration (FDA). The FDA regulates these excipients as inactive ingredients used in pharmaceutical formulations. They are subject to the regulations outlined in the Code of Federal Regulations (CFR) Title 21, which governs the use of food and drugs. Natural superdisintegrants must comply with the requirements for Generally Recognized as Safe (GRAS) substances or obtain approval as food additives if they are intended for use in food products. For pharmaceutical applications, manufacturers must ensure that natural superdisintegrants meet the standards outlined in the FDA's Inactive Ingredient Database and are used in accordance with current Good Manufacturing Practices (cGMP) (Food and Drug Administration (FDA), 2020).

13.2. European Medicines Agency (EMA) - European Union

In the European Union (EU), natural superdisintegrants are regulated by the European Medicines Agency (EMA) as excipients. The EMA establishes standards and guidelines for the use of excipients in pharmaceutical formulations through the European Pharmacopoeia (Ph. Eur.). The Ph. Eur. provides monographs and specifications for natural superdisintegrants, ensuring their quality, safety, and compatibility with other ingredients in medicinal products. Excipients that comply with Ph. Eur. standards are eligible for use in pharmaceutical formulations approved for marketing within the EU (European Medicines Agency (EMA), 2020).

13.3. European Food Safety Authority (EFSA) - European Union

In the European Union, the safety of natural superdisintegrants intended for use in food products is evaluated by the European Food Safety Authority (EFSA). EFSA assesses the safety of food additives, including natural ingredients derived from plants, seeds, gums, and marine products, based on scientific evidence and risk assessment principles. Superdisintegrants intended for use in food products must meet the safety criteria established by EFSA and be authorized for use as food additives before they can be marketed in the EU (European Medicines Agency (EMA), 2020).

13.4. International Harmonization

Efforts have been made to harmonize regulatory requirements for pharmaceutical excipients, including superdisintegrants, on an international level. Organizations such as the International Pharmaceutical Excipients Council (IPEC) work towards developing guidelines and standards to ensure the quality, safety, and functionality of excipients worldwide. These initiatives aim to streamline the regulatory approval process for pharmaceutical formulations across different regions and promote global harmonization (International Pharmaceutical Excipients Council (IPEC), 2020).

The regulatory status of natural superdisintegrants involves compliance with regulations established by regulatory authorities such as the FDA in the United States and the EMA in the European Union. These regulatory frameworks ensure the safety, quality, and efficacy of natural excipients used in pharmaceutical and food products, contributing to the protection of public health and the promotion of innovation in the pharmaceutical industry. Regulatory authorities such as the FDA, CFR, GRAS, EMA, and EFSA play crucial roles in overseeing the regulatory status of natural superdisintegrants. Compliance with regulatory requirements ensures the safety, quality, and efficacy of these excipients in pharmaceutical and food products, promoting public health and consumer confidence.

14. Review of Recent Literature Reports

With the ever-increasing demand for faster-acting and more efficient drug products, there has been a surge of interest in superdisintegrants over the years. Consequently, numerous studies have been conducted on the characterization, optimization, and application of these excipients. A literature review of superdisintegrants is, therefore, essential in understanding the current state of knowledge, identifying research gaps, and providing insights for future research. This review article aims to provide a comprehensive overview of the literature on superdisintegrants, including their types, mechanisms of action, formulation strategies, and regulatory status.

By critically evaluating the existing literature, this review article will provide a valuable resource for researchers and pharmaceutical professionals in the development of efficient and safe drug products.

Dungarwal and Mundada (2023) created herbal orodispersible granules with citrus limon (lemon peel) extract. The ultrasound-assisted extraction method was used to isolate the lemon peel extract. A preliminary organoleptic assessment of the extract was done to determine its yield percentage, solubility, odor, and color. On lemon peel extract, phytochemical screening was done for the quantitative and qualitative characterization of phenolic compounds, flavonoids, etc. In order to produce distinct batches of orodispersible granules that act as superdisintegrants, banana flour was employed in a range of concentrations (1-3%). DSC and FTIR were used to conduct a compatibility analysis for lemon peel extract and excipients. By using the extrusion and spheronization method, herbal granules were produced, and their properties were assessed in terms of *in vitro* release characteristics, *in vitro* disintegration time, Hausner's ratio, Carr's index, tapped density, bulk density, and angle of repose. The amount of total phenolics in lemon peel extract was determined to be 185 mg of gallic acid equivalent/gm. However, it was shown that the total flavonoid content was 170 g of quercetin equivalent/gm of extract. We created orodispersible granules of lemon peel extract. All batches displayed improved flow characteristics. The granules dispersed out quickly in 39 to 87 seconds. Using banana flour, lemon peel extract was effectively created and tested as herbal granules. According to the study's findings, created formulations might be used to create herbal products that are higher-quality, more reliable, and more stable (Dungarwal and Mundada, 2023).

Babu *et al.* (2022), used the approach of direct compression to formulate orodispersible Clozapine tablets with different natural superdisintegrants at different concentrations (2, 4, 6, and 8%), along with a control formulation. Mannitol and microcrystalline cellulose were used to enhance the mouthfeel. All of the produced formulations had appropriate flow qualities according to the precompression properties that were identified. The tablets' dissolving studies, *in vitro* dispersion time, water absorption ratio, wetting time, homogeneity of drug content, friability, and hardness were all evaluated after compression. *In vitro* drug release rate (99%) in 30 min, wetting time (10 sec), disintegration time (13 sec), and dispersion time (9 sec) were all much faster for Clozapine that included 8% *plantago ovata* mucilage. No significant changes in drug content or *in vitro* dispersion time were found by stability investigations performed on the potential formulations. IR spectroscopy has shown that there are no interactions between excipients and drug (Babu *et al.*, 2022).

Puri and Gokhale (2022) isolated, characterized, formulated, and estimated the disintegration properties of banana starch in the formulation of Lornoxicam dispersible tablets. Sodium hydroxide was employed as a lye solution in the alkaline extraction technique to separate the starch from unripe banana fruit. Starch was characterized for its physicochemical characteristics, flow and viscosity characteristics, XRD, DSC, SEM, and FTIR studies. The standard method was used to determine the flow characteristics of starch. Starch was used as a disintegrant in the wet granulation process to create tablets, and the in-vitro release characteristics of the final products were examined. In comparison to corn starch, the disintegration qualities of various quantities of isolated starch were investigated. According to studies, obtained starch is quantitatively and qualitatively equivalent to corn starch. Data from XRD, DSC, SEM, and FTIR indicated that the starch is a polysaccharide. The starch's physicochemical characteristics passed the required tablet assessment tests. These tablets also confirmed the I.P. dissolution and disintegration criteria (Puri and Gokhale, 2022).

Saeed *et al.* (2022) employed HPMC and SCMC as two distinct filmmaking polymers to create oral rapid-dissolving films of ZLK (Zafirlukast). To create 10 formulae, various concentrations of the 2 polymers were employed. To create 10 alternative formulations, additional excipients were added in a variety of ratios. They included banana powder, polyvinylpyrrolidone (PVP), crosspivodone, and maltodextrin. The formulations' *in vitro* evaluation revealed that HPMC-based formulations exhibited enhanced dissolution rates and noticeably shorter disintegration times ($p < 0.05$). The disintegration of the films was not noticeably accelerated by the addition of maltodextrin, PVP, and crosspovidone as disintegrants to the film-forming polymers. Banana powder, however, considerably prolonged the film's disintegration. In other formulations, compatibility tests utilizing FTIR did not reveal an interaction between ZLK and excipients (Saeed *et al.*, 2022).

Sailaja *et al.* (2022) Using semi-artificial (Croscarmellose), artificial (sodium starch glycolate), and natural (hibiscus mucilage, dehydrated banana powder) super disintegrants, created and tested buccal films containing

domperidone. The pure drug and various excipients were the subject of preliminary research. According to the FTIR tests, there was no interaction between the medication and the excipients. Domperidone by complexing with hydroxypropyl beta cyclodextrin by kneading, its solubility is increased. By using the solvent casting procedure, these compounds were employed to produce buccal films. The prepared buccal films underwent testing for folding endurance, disintegration time, and weight variation. The phosphate buffer at pH 6.8 was used for the dispersion investigations. Domperidone buccal films were created utilizing a variety of polymers and super disintegrants. The films have strong mechanical qualities, as seen by the folding endurance assessments. The crosscarmellose-containing formulations (DBF4 containing Eudragit as a film former and PEG6000 as a plasticizer) among the six formulations disintegrated after 20 seconds. The Hibiscus mucilage (DBF6) formulation demonstrated a 98.81% drug release after 30 minutes (Sailaja *et al.,* 2022).

Super disintegrants were used to prepare 9 different Meclofenamate Sodium FDT (fast dissolving tablet) formulations by Agrawal *et al.* (2021). Each formulation was tested to ensure that it satisfied the required standards. Four distinct super disintegrants, including the natural super disintegrant banana powder, sodium starch glycolate, and crosscarmellose sodium, were used to create a variety of formulations utilizing the direct compression method. The blend was assessed for pre-compression factors such as tapped density, bulk density, and angle of repose. The tablet was then assessed for post-compression factors such as drug release studies, disintegration time, friability, wetting time, weight variation, hardness, drug content, and thickness. According to in-vitro dissolution trials, formulation F2 had the shortest disintegration time and, after three minutes, had a 98.55% drug release rate. As per the ICH guidelines, stability tests were conducted on the best formulations, and they were discovered to be stable (Agrawal *et al.,* 2021).

Chandini and Anu (2021) created and assessed Bupropion HCl orodispersible tablets utilizing raw banana powder as a natural superdisintegrant and sodium starch glycolate as a synthetic superdisintegrant. Sublimation was used to prepare orodispersible tablets. Superdisintegrants' impact on dissolution, disintegration, and wetting, parameters was investigated. FTIR spectroscopy was used to characterize orodispersible tablets. Preformulation studies were determined as per literature limits. Superdisintegrants and the drug were compatible. *In vitro* drug release, drug content, *in vitro* disintegration time, wetting time, friability, hardness, thickness, and weight variation were assessed for the developed tablets. With an increase in concentration of all superdisintegrants the *in vitro* disintegration time reduces. Out of all the formulations, BSG6 from sodium starch glycolate and BRB5 from raw banana demonstrated 100% drug release over the span of an hour. Nevertheless, compared to BSG6 with a greater concentration of polymer, BRB5 with a lower concentration of polymer demonstrated efficient drug release (Chandini and Anu, 2021).

15. Conclusion

The comparative exploration between natural and synthetic superdisintegrants underscores the potential advantages of natural alternatives in terms of biodegradability, biocompatibility, and sustainability. While synthetic superdisintegrants continue to play a vital role in pharmaceutical formulations, the shift towards natural alternatives reflects a broader commitment to sustainable and eco-friendly drug development practices.

The escalating demand for sustainable and eco-friendly practices in pharmaceutical development has led to a resurgence of interest in natural superdisintegrants as green alternatives for enhancing drug delivery systems, aligning with eco-friendly principles. Continued research and development in this area hold the potential to further optimize the utilization of natural superdisintegrants, paving the way for eco-conscious drug delivery systems.

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