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Review Article

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Recent Trends in the Chemistry of Polymers used in Oral Drug Delivery Systems

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Abstract Tablet is one of the utmost chosen dosage forms administered orally**.** Disintegrants are substances added to tablets and some encapsulated preparations to encourage the breaking up of both tablet and capsule "slugs" into smaller fragments in an aquatic environment. This increases the surface area that is available and speeds up the release of the drug component. They increase moisture penetration and distribution of the tablet matrix. Tablet disintegration has attracted a lot of attention as an important stage in achieving rapid drug release. The concentration on drug availability emphasizes the significance of a tablet's comparatively quick disintegration as a criterion for determining unrestricted drug-dissolving behavior. Several factors affect the disintegration replacement of tablets. The primary purpose of the disintegrants is to counteract the effectiveness of the tablet binder and the physical forces that work during compression to prepare the tablet. For the tablet to release its medication, the disintegrating agents must be more effective, and the binder must be stronger. It should ideally cause the tablet to shatter into the powder particles used for the granulation as well as the granules from which it was compressed. This review comprehensively focuses on rationalizing the recent trends in the utilization of natural or synthetic polymers, in designing oral drug delivery systems.

Key words: Tablet, Quality by Design, Polymers, Natural, Synthetic, Immediate release, Extended release, Modified release

Introduction

Disintegrants are crucial to the formulation of tablets. The capability to strongly interact with water is required for the disintegration function. The mechanisms of disintegrant action include swelling, wicking, distortion, and/or a combination of these. In granulated formulation methods, a disintegrant can be more effective if it is used both "intra-granular" and "extra-granular," breaking the tablet directly into granules and causing the granules to further disintegrate to discharge the drug component into solution [1-2]. Anyhow, the component of the disintegrant integrated intragranular in the wet granulation method is often less effective than the portion integrated extragranular because it is subjected to drying and wetting as part of the granulation process, which decreases the action of the disintegrant. The disintegrant utilized intragranular inclines to sustain good disintegration activity since the compaction procedure does not entail its interaction with drying as well as wetting. [3-6] The polymers produced by natural inchoation are much more effective and harmless. They are effortlessly accessible in natural locations throughout the world hence these polymers are chosen above synthetic polymers. The Drugs in connection with the (BCS-II) Biopharmaceutical classification system – II, which followed the issue of poor solubilization, nonetheless, high permeability has been reduced by means of methods such as solid dispersion procedures using the medication

in an amorphous state and complexation methods. The prolonged half-life of medications' bioavailability is also increased by an elevation in solubility, whereby leads drugs to accumulate and become toxic. Mesoporous silica materials (MSM), as well as other mesoporous particles, display a hexagonal structure (MCM-41) with a larger surface area employed as a drug release reservoir. For medicines with limited solubility, drug carriers MCM-41 and HMS were both used. [7,8]

Natural Polymers Used in Oral Disintegrating Tablets

1. Chitin and Chitosan. Chitin (also known as (β-(1→4)-N-acetyl-D glucosamine) is indeed an organically generated polysaccharide that can be found in the shells of both shrimp and crabs. According to the liberated amino groups of chitosan, chitin contains an amino group covalently linked to the acetyl group. Chitin is processed into chitosan for business usage. Chitin is a structural element of the exoskeleton of crustaceans (like crabs as well as shrimp) and also the cell wall of fungi. Irrespective of the drug's solubility, once chitin has been introduced into conventional tablets, in 1978 according to Bruscato and Danti, the tablets disintegrated within 5 to 10 minutes. Surface-free energy could be utilized for analysis of both the wetting and disintegration times in the oral cavity. Chitosan is the most well-known natural polysaccharide used in the pharmaceutical sector for its wide range of applications [9].

2. Guar Gum: It is generated by the endosperm from the seeds of the Cyamopsis tetragonoloba (L) Taub, a guar plant. Guar gum has been predominantly formed of large molecular weight which is 50,000 to 8,000,000 and polysaccharides that are prepared of galactomannans (Syn. Cyamopsis psoralioides). It is permissible in most countries around the world such as the EU, USA, Japan, Australia, etc., and it is utilized as an emulsifier, stabilizer, and thickener. Guar gum is the gum that occurs naturally (the marketing trade name is Jaguar). It is a neutral polymer made up of sugar units that are freely streaming, completely soluble, and proven to be safe for use in food. Guar gum is insensitive to the pH, moisture content, or dissolution of the tablet matrix. In alkaline tablets, guar gum is not usually perfectly white and occasionally ranges in color from off-white to tan. It also tends to discolor over time. [10]

3. Gum Karaya. The trees of the genus Sterculia produce an exudate called gum karaya. It is also called vegetable gum. The chemical composition of gum karaya indicates that it is an acid polysaccharide consisting of the sugars galactose, galacturonic acid, and rhamnose. Because of its high viscosity, gum cannot be employed as a disintegrant or binder in the production of conventional dosage forms. It has been noted that gum karaya has the potential to disintegrate tablets. Several studies found that altered gum karaya helps tablets to disintegrate swiftly**.** Because of its low price**,** biocompatibility**,** and easy accessibility, it could be utilized as an alternative super disintegrant to commonly obtainable synthetic and semisynthetic super disintegrants [11].

4. Agar and Treated. Agar is the dried gelatinous material derived from various different species of red algae, including 'Pterocladia' (Gelidaceae), 'Gracilaria' (Gracilariaceae), and 'Gelidium amansii' (Gelidanceae). Agar can be found as divests, flakes on a sheet, and fine powder. Agar is a yellowish gray as well as white to almost colorless, odorless, and mucilaginous taste. It contains two polysaccharides, which are agar pectin and agarose. Agarose is accountable for gel vigor and for the viscosity of agar solutions, agar pectin is responsible. Agar has a high gel vigor, making it a potential contender as a disintegrant. [12].

5. Fenugreek Seed Mucilage. Fenugreek, also known as Trigonella foenum-graceum, is a herbaceous plant in the family of leguminous plants. A significant amount of mucilage is present in fenugreek seeds (a natural gummy material present in coatings of various seeds). Albeit it doesn't disintegrate within the water, when mucilage **c**ontact with liquids, it congeals into a thick, sticky mass. Like other materials containing mucilage, fenugreek seeds swell and become slippery when exposed to liquids. The study found that fenugreek mucilage, a naturally occurring super disintegrant, has a more pronounced disintegration property than Ac-di-sol, the most often utilized synthetic super disintegrant in the formulation of fast-dissolving tablets**.** Studies revealed that the mucilage extract is effect well as a disintegrating agent and as a pharmaceutical adjuvant [13].

6. Soy Polysaccharide: Soy polysaccharide is a natural super disintegrant that doesn't consist of any starch and sugar therefore it can be used in nutrition material. Soy polysaccharide, a type of high molecular mass

polysaccharide derived from soybeans, was evaluated by Halakatti et al. in 2010, [14] for the dissolution of tablets produced through directly compressing with fillers such as Dicalcium phosphate dihydrate and lactose. Corn starch and a cross-linked sodium carboxymethyl cellulose were used as control disintegrants. In direct compression formulation, soy polysaccharide functions admirably as a disintegrating agent, with outcomes comparable to those of cross-linked CMC [15-18].

7. Locust Bean Gum: Locust bean gum is also called carob bean gum**.** It's a galactomannan vegetable gum derived from the seeds of a tree named carob (Ceratonia siliqua) available in the Mediterranean region. In the food industries, locust bean gum is used as a bioadhesive, thickening agent, and gelling as well as to increase solubility. It is a powdery, odorless white to yellow-white color. It is non-soluble within the majority of organic solutions like ethanol and others**.** It requires heating to above 850 for 10 minutes to get total solubility in water, since it is only partially soluble at room temperature and soluble in hot water [19-23].

8. Ficus Indica Fruit Mucilage. A super disintegrant is made from the mucilage of the Ficus Indica fruit, which is made from the fruit's pulp**.** The Ficus Indica is an astronomically immense tree that grows quite quickly, reaching heights of up to 3 meters, and has Arial roots and spread-out branches. The Ficus Indica tree produces cherries-sized fruits. The fruit has both therapeutic and nutritional value. Per 100 gm or 3.5 ounces of dried and uncooked Ficus Indica fruit, there is 230 kcal (963 KJ) of nutrients available. The Ficus Indica fruit is used to treat blood problems, urinary problems, wound rejuvenation, fever, pain, and inflammatory problems [24].

9. Mangifera indica Gum (MIG): Mangifera indica, also known as mango, is a member of the Anacardiaceae family. MIG is non-toxic and used in a variety of formulations as a disintegrant, binder, suspending agent, and emulsifying agent. The gum powder is white to off-white in color, and the powder was soluble in water and virtually insoluble in acetone chloroform, ether, methanol, and ethanol. It is easily accessible, the gum is non-toxic, and every part of the tree has medicinal properties, including those for urethritis, diabetes, asthma, diarrhea, scabies, and astringent [25].

10. Treated Agar and Hibiscus Rosa Sinensis Mucilage: Hibiscus rosa Sinensis is also known by the names shoe flower plant, China rose, and Chinese hibiscus and is a member of the Malvaceae family. Mucilages are used as disintegrants, thickeners, suspending agents, and water retention agents. The plant is easily accessible, and the mucilage found in its leaves also includes L-rhamnose, D-galacturonic acid, D-galactose, and D-glucuronic acid**.** Treated Agar is made into yare by being treated along with water for a day [26].

Polymers Used in Pharmaceutical Coating

Polymers are essential to the coating technique; they are occasionally employed to alter the delivery of dosage form, flavor muffling, and film-forming agent.

1. Cellulose acetate phthalate CAP

Cellulose Acetate phthalates (CAP), Cellulose Esters, and Cellacefate were widely utilized to achieve an enteric coating and sustained release of capsules or tablets. At a pH level higher than 6, CAP dissolves, resulting in a natural polymer that is utilized for enteric coating and to give delayed action regarding drug absorption. Its hygroscopic nature makes it soluble in water and susceptible to moisture infiltration into Gastrointestinal fluids [27]. Another factor that influences the polymer's characteristics is its molecular weight of CAP. The characteristics of polymers change based on variations in factors such as rheology, viscosity, surface tension, and conductivity. Beads were yielded by a polymer with a lower molecular weight, whereas large-diameter fibers were yielded by a polymer having a larger molecular weight. For electrospinning, larger molecular mass polymers are used to produce a preparation with the necessary viscosity. The chain tangling of polymer chains is immediately reflected in the viscosity of a solution. Contrastingly, the polymer's electrospinning processing chain entanglement shows a critical function. [28]

2. Cellulose Acetate Trimellitate (CAT)

The only difference between CAP and CAT is that CAT has an aromatic ring that has a carboxylic group on it. Producers provided values around 22% for acetyl as well as 29% for timely correspondence. When it dissolves at pH 5.5 in the intestine's upper portion, this polymer demonstrates its enteric coating characteristic. Degradation studies also showed that the solubility characteristics of CAP and CAT in organic solvents are similar**.** In the meantime,

research on aqueous solvents has shown that using ammoniacal solutions of CAT with water allowed for the achievement of full enteric characteristics. Diethyl phthalate, triacetin, and acetylated monoglyceride are the plasticizers that are advised for use with aqueous solvents [29].

3. Methylcellulose (MC)

Methylcellulose (MC) is one of the most widely and commercially utilized polymers. The polymer, called cellulose ether, is used in a variety of industrial processes**.** It is a derivative of cellulose that replaces the hydroxyl (OH) group at positions C-2, 3, and 6 with a structure comprising a methyl group followed by an anhydrous-D-glucose moiety. Methylcellulose is one of the most significant esters in the methyl family (MC). It is structurally composed of a methoxy group, which composes about 27.5 to 31.5% of the entire Methylcellulose (MC). Heat-related gelling characteristics were present in an aqueous solution of MC. Water can dissolve it, MC molecular weight typically ranges from 10,000 to 220,000 daltons. When temperatures rise above LCST, it becomes almost insoluble. That can be the reason why the saturated solution of the polymer copolymer possesses outstanding physicochemical and amphiphilic properties. Depending on the placement of the OH group is switched from three to zero, the polymer's solubility changes from being water-soluble to being organo-soluble. However, it was reported that the thermal behavior was singular, which cause viscosity to decrease and an aqueous solution to generate, which was seen as the polymer's temperature was raised near a critical temperature. The polymer MC's lowest critical solution temperature (LCST), which generated a thermos-reversible gel with increased viscosity, was seen when the temperature rose constantly. The polymer remains insoluble at temperatures higher than LCST, whereas MC is highly water soluble below LCST temperature. That could be the potential reason why heating caused the polymer's saturated solution to transform into a solid state**.** [31-33]

4. Ethylcellulose (EC)

Directly, Ethylcellulose is initially immiscible in water; but, after the addition of other additives, such as HPMC, it becomes both water and fluid soluble. It is a partly cellulose ether derivative (O-ethylated). Ethylcellulose exists in a number of molecular grades with different viscosities. Ethyl chloride (EC) was produced using the structural combination of alkali cellulose. Throughout this reaction, the substitution of ethoxy groups was managed. Pharmaceutical formulations choose EC as a binding agent, taste-masking, and sustained release agent. [34-36] The polymer, which is frequently used in organic solvents, is non-toxic, tasteless, and colorless. EC has a drug release resistance. EC may also be utilized to integrate ingredients through wet granulation and direct compression. EC microparticles were encapsulated using several microencapsulation methods. It is among the most used polymers for coating solids which are water-insoluble dosage forms [37]. Kumbhar et al. created colorectal capecitabine-based microspheres with the use of natural polysaccharide polymers to increase cost-effectiveness. Microspheres were created utilizing a single emulsification method using calcium chloride loaded with pectin and then coated with EC via solvent evaporation method. The microspheres were further characterized in terms of particle size, Differential Scanning Calorimetry (DSC), Surface Electron Microscopy (SEM), Fourier-Transform Infrared Spectroscopy (FTIR), drug release, and entrapment efficiency. According to drug release studies, in an acidic medium less than 20% of the medication was released. Although there was an initial burst of drug release, towards the conclusion of the 12th hour, the total drug release of 85.33% to 95.55% was seen due to Ethylcellulose coating.

5. Hydroxyethyl Cellulose (HEC)

Hydroxyethyl Cellulose is a cellulose-based polymer that is used for gelling and thickening. The chemical structure is also used in hydrophilization, which improves the drug solubility profiles in gastrointestinal fluids. HEC is a contender for drug carrier systems due to its weight of 90 kDa, enhanced water solubility, and neutral nature. In terms of demand, it is a strong choice for pharmaceutical formulations due to its great biochemical stability and remarkable thickening characteristic. Before developing a carrier system, the properties of both the medication and the carrier must be thoroughly investigated. [38] It is also chosen for cleaning solutions, household items, and cosmetics because it has abilities of water-soluble and non-ionic. HEC creates solid water phases and crystal-clear gels for cosmetic emulsions. This polymer has a significant disadvantage in that it lumps when first moistened with water. One of the grades of HEC known as R grade is utilized for solution formation because no lumps are produced when in contact with moisture, which eventually improves solubility and process time of formation. [39-42]

Paliperidone bilayer film-coated tablets were created by Chowdary et al. Let was further characterized for in-vitro drug release studies**.** Variable polyox concentrations were used when formulating the tablet. The sub-coating with HEC and the cellulose acetate coating were optimized by an enteric coating. Various impacting aspects were investigated into, such as the coating ingredients and the tablet's core composition. By comparing the results of in vitro drug release experiments, the formulations were improved. [43]

6. Hydroxypropyl Methylcellulose (HPMC)

Hydroxypropyl Methylcellulose is a synthetic modification of natural polymer**.** HPMC has no flavor or odor and is white to slightly off-white in color. It is a polymer that is soluble in water and can also be used in tablets that sustain release. Both coated and uncoated matrix tablets employ it. The polymeric chains were untangled when the matrix was hydrated with water [50]. A two-way mechanism governs how medications are released from drugs. The drug is released from the gel layer of the polymer in the first stage, whereas the swelling layer is eroded after the drug release in the second mechanism. Because cellulose ether is present, it may be utilized in the preparation of oral medications with controlled release. Hydroxypropyl Methylcellulose could also be used to coat films with solvents and aqueous solutions. It is possible to create matrix-based tablets either direct compression or wet granulation [44-48]. Another study by Ifat Katzhendler et al. examined the release of naproxen and naproxen sodium by altering the molecular weight of HPMC. Based on the results, it was concluded that naproxen sodium increased the pH of the system while naproxen sodium decreased drug solubility when taken alone, therefore increasing drug loading, therefore, the release of the drug also increases. [49]

7. Polyvinyl Pyrrolidone (PVP)

PVP is a polymer that dissolves in water, with a molecular weight range of 40,000 to 600,000 Daltons, and is distinguished in various grades. Vinyl pyrrolidone is polymerized in water and or in isopropyl alcohol to produce PVP. Polar amide is highly water-soluble because of the presence of both a hydrophobic alkyl group and a polar amide group. It is a great contender for a drug carrier system because of its high level of compatibility. PVP is a thermostable, non-toxic, and carcinogen-free polymer. PVP demonstrates a superior drug transport mechanism [50-52]. In order to increase the bioavailability of medications that are weakly water-soluble, various grades of PVP were utilized. Essentially, it serves as a binder in the production of tablets. When compared to other binders, this polymer's wet granulation results in granules with higher binding strength, lower friability, and better flowability. [54]. Paliperidone tablets were created by Tang et al. using simple production techniques, and they were subsequently coated to achieve a long-lasting effect. Tablets' in-vitro drug release behavior was analyzed and investigated. An extremely viscous HPMC K 100 M and HPC coat was used to coat the tablets. The core tablet composites, the materials used for FC, and also the preparation characteristics were taken into consideration while evaluating the in-vitro drug release parameters. The mechanism of drug release was identified using gravimetric analyses. The Peppas model was then updated with the results from drug release profiling.

8. Shellac

Shellac was considered as having distinct qualities because of its unusual structural novelty. It is mainly composed of polyhydroxy polybasic acids and an ester complex. Shellac can be used in a variety of ways, such as an insulator, adhesive, film-forming agent, and thermoplastic agent. Due to its animal origins and major differences from other polymers, shellac has special properties that are made possible by challenging-to-find resins, aromatic compounds resume phenolic compounds, oxidized polyterpenes acids, and resinotannols. [53] Shellac contains an acidic group with a highly acidic dissociation value. Because of this, it is difficult for the group to dissociate in the gastric environment, therefore resulting in a diminished dissolving action in the stomach (pH 2). The addition of sodium carbonate (an alkaline group) to the chemical structure of shellac enhanced its performance in the stomach. One study created nanofibers and nanoparticles of ketoprofen, combined them with shellac, and carried out its characterization (SEM, XRD, FTIR). [54]

9. Sodium Carboxymethylcellulose (SCMC)

SCMC has a further polynomial cross-linked form called croscarmellose sodium. SCMC has excellent hydrophilic, absorbing, and swelling properties. Commercially, Sodium Carboxymethylcellulose is offered within different (DS) degrees of substitution between the range of 0.7 to 1.2 as well as with the subsequent value of 6.5 to 12% of the sodium content of its total weight. Sodium Carboxymethylcellulose has a high hygroscopicity and can absorb more

than half of its water content. Tablets manufactured with SCMC have a tendency to become harder over time. [55] With its outstanding disintegration and dissolving properties, croscarmellose sodium increases the bioavailability of many formulations. In oral preparations, croscarmellose sodium is employed as a disintegrant. Despite being connected to the pharmaceutical sector, it is also utilized to manufacture tablets with direct compression and as an insecticide in the paper and textile sectors. It behaves as a protective colloid to prevent water loss [56]. Shinde et al. tried to develop sustained swellable matrix-release tablets using diltiazem hydrochloride as a model drug. The purpose of the dosage form was to improve the dissolution profile of the drug as the drug is more soluble in the upper part of the GI tract.

10. Zein

It is a natural polymer derived from plant origin and is more beneficial than synthetic polymers. It can be used for biomedical procedures as well as controlled drug release. Zein has a high nutritional value since it contains a variety of components, including proteins**.** According to its dry weight, it contains 6 to 12% protein and 50% corn protein. Between the bran and germ, 25% of this protein is found in around its total amount, while endosperm tissues contain 75% of the protein. Zein is additionally utilized for vaccines, tissue engineering, and gene delivery. Due to its two primary properties like biocompatibility and biocompatibility, it is utilized as a biopolymer. [58] Although zein structure has still not been clearly illustrated, several of its characteristics were identified in the 1980s using chromatographic techniques**.** The helical structure of zein was discovered (with 10 consecutive folds) using the small-angle X-ray scattering (SAXS) technique [59-61]. Based on the extraction technique as well as molecular weight, zein was obtained in the following forms: α-, β-, δ-, and γ. In addition, it was utilized in a number of industrial sectors, such as adhesives, ink, ceramics**,** chewing gums, the production of candy, and packaging of plastic products, and the food industry**.** Zein was initially employed as a protective layer over coated materials because of its increased resistance to humidity, abrasion, and heat tolerance. It was also used in an immediate-release dosage form as a flavor enhancer because of its low cost.

11. Eudragit L-100-55

Eudragit L-100-55 is a copolymer derived from both acrylic acids and esters of methacrylic, while for its physicochemical characteristics, the functional group [R] is responsible. Eudragit is in white color, anionic, and with free-flowing characteristics. It dissolves at a pH of 5.5 or above and is used for entering coating purposes [62]. Eudragit, which is soluble throughout a wide pH range, is one of the most frequently used pH-sensitive polymers in the pharmaceutical industry. The Eudragit L100-55 has controlled the discharge of the pharmacologically active ingredients at pH values greater than 5.5. The substitution of a methyl group instead of an ethyl group caused a difference to appear between Eudragit L100 and Eudragit L100-55. The dissolving profiles of both polymers eventually shift at various pH levels due to the difference in the functional groups. In order to enhance the physical and chemical characteristics of lansoprazole tablets, Alsulays et al. created enteric-coated tablets using a novel process called hot-melt extrusion. Magnesium oxide (MgO) was used as an alkalizing agent**,** and as a plasticizer, Lutrol F68 was used, as well as Kollidon 12PF was used as a polymer. When lansoprazole was extruded using Kollidon 12 and Lutrol F68, an amorphous state manifested and provided a greater drug release. Incorporating MgO also makes lansoprazole more extrudable and enhanced its release, causing more than 80% of the drug to release inside the buffer zone.

Conclusion

Natural polymers have more preponderant effects on fast-dissolving tablets than synthetic polymers. Natural polymers are used as binder super disintegrants and diluents because they increased the drug release rate from the tablet and decreased the dissolving rate and disintegration rate. Natural polymers are chosen over synthetic polymers due to their non-toxicity, ease of accessibility, inexpensive, and use at low concentrations, and are naturally extracted to provide a nutritional supplement. The disintegrating abilities of natural super disintegrants such as Plantago ovate, Lepidium sativum, gum karaya, Guar gum, mucilage from fenugreek seeds, mango peel pectin, and others have been investigated in comparison to artificial super disintegrants. Natural super disintegrants, therefore, show quicker drug disintegration and enhanced bioavailability, enabling effective therapy and better

patient compliance. Thus the natural super disintegrant can be efficaciously utilized as disintegrants in tablet formulations**.** Tablets were discovered to be the most widely used and traditional dose form. Tablets were produced by hand prior to the invention of efficient machinery for their production. Therefore, coatings were applied to cover the disagreeable taste of various active constituents as well as to protect them against atmospheric conditions, and even prevent a harsh gastrointestinal environment. The coating of the dosage form was done using a variety of coating techniques, each of which has benefits and drawbacks. FC is an important but regular procedure that creates a dosage form with various capabilities, hence satisfying various therapeutic needs. FC was determined to be the most practical and lightweight coating material. In the pharmaceutical sector, FC not only disguises the disagreeable flavor and improves patient compliance, yet it additionally shields the Active pharmaceutical ingredients from water directly, improving their stability.

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