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Review Article

Topic - Controlled Drug Release by Excipient Modification: A Review

Prithvijeet Singh Kharnal*
Independent Researcher, USA

***Corresponding author:** **Prithvijeet Singh Kharnal**
Independent Researcher, USA.
Email: prithvijeet.kharnal2@gmail.com

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Abstract

Excipients play an essential role in the physical and chemical characteristics of the oral dosage form. The excipient modification can alter the parameters like dissolution and disintegration. Oral dosage form passes through the varying pH of the human gastrointestinal tract and delivers the drug at a specific site. For providing pH-responsive dosage form, novel techniques are used, which include hydrogels, nanoparticles, and microspheres. The article also reviews problems related to drug excipient interactions and questions related to delivering the drug to specific targets by showing pH-responsive drug release. The addition of excipients like lignin can achieve a better pH modified version and controlled release of the active pharmaceutical excipient. The biopolymer lignin can be altered due to many functional groups in its chemical structure. The use of lignin can help to release the drug in specific targets within the gastrointestinal tract. The use of natural polymers should be increased to manufacture eco-friendly and economical dosage forms.

Introduction

Excipients are considered as inert components of a dosage form but affect the dosage form in different ways [1]. The final product is affected by the excipients, and any changes in the excipient material attribute can cause an impact on tablet dosage form performance, which includes hardness, disintegration, bioavailability, and processability [1]. A through understanding of excipient interactions with the gastrointestinal tract must be taken into consideration [1]. Biodegradable polymeric nanoparticles have shown an excellent therapeutic effect in controlled release drug delivery systems [2]. The polymeric nanoparticles have sustained drug release behavior, good bioavailability, and tissue permeability [3]. The use of natural biopolymers has increased due to their excellent biocompatibility and biodegradability [3]. Natural biopolymers can be used as excipients to cause little to no damage to the environment. Lignin is an abundant biopolymer material, which can be extracted from the cell wall of higher vascular plants and has an antioxidant capacity [5]. Lignin has excellent biodegradability and biocompatibility [5]. In carbon fiber manufacturing use of lignin reduces the manufacturing cost and is also suitable for the environment [4].

Lignin use is being extended in other areas, which includes biofuels, bioplastics, and controlled release carriers [5]. Lignin protects against various biochemical stresses and inhibits the enzymatic degradation of different components of the cell [5]. A lot of chemical modification is also possible in the lignin due to available highly functional character, which includes phenolic and aliphatic hydroxyl groups [5]. Lignin is a versatile biopolymer with many potential uses and produced as a by-product of many industrial processes. Lignin provides strength to the woody plants and giving structure to their cell walls [5].

Lignin is a highly branched polymer with various functional groups [5]. The groups are aliphatic, phenolic hydroxyls, carbonyl, carboxylic, and methoxy groups [5]. Lignin is an amorphous polymer and is thermoplastic in nature with a glass transition temperature [5]. The degradation of lignin is a complex process, which includes a lot of aggressive steps or reactions due to its hindered structure [5]. Lignin seems to be a promising renewable source and an environmentally friendly source [5]. The biopolymer lignin has beneficial properties like resistance to decay and has high stiffness and antioxidant properties [5]. Lignin can be used as an excipient for controlled release dosage form due to various possible modifications in its chemical structure, and its vast supply from nature. Lignin is also produced from the pulping process, which includes the paper and biorefinery industries [5].

Lignin modified capsules and tablets have a great application in controlled release drugs [7]. The oral dosage form is preferred dosage form than the parenteral dosage forms due to its convenience in administration to the patient, and tablets increased compliance [11]. Lignin is a biopolymer present in the cell walls of vascular plants formed by the cross linked networks of methoxylated hydroxylated phenylpropane [10]. Lignin is the most abundant polymer after cellulose. The most advantage of

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using lignin is that it is a renewable and less exploited source [10]. Lignin is used in direct compression in the preparations of drugs containing tablets [10].

The tablet dosage form is compliant to the patient if the dose must be administered frequently [11]. Tablet dosage form faces numerous challenges in drug delivery, such as enzyme degradation, hydrolysis of drugs [11]. The intestinal membrane also serves as a barrier to the hydrophilic macromolecules, which includes the peptides, proteins, and nucleic acids [11]. Hydrophilic macromolecules face difficulty in crossing the lipid bilayer of the intestine and get the drug absorbed in the specific site [11]. The pH-responsive drug delivery system helps to increase the stability of the Active Pharmaceutical Ingredient (API) in the stomach and delivering the API successfully in the intestine [11]. The tablet dosage form faces challenges due to chemical instabilities in the GI pH, which can be overcome by the addition of a pH-responsive drug delivery concept.

Some drugs are unstable in the stomach acidic pH, which can alter their stability and cause toxicity to the patient. The pH-responsive system aids for targeted release drugs in the small intestine to increase the stability in the acidic pH of the stomach [11]. Natural polymers like alginate, hyaluronic acid, and chitosan serve as functional matrices for solid oral dosage form [11]. The natural polymers have excellent biocompatibility and physicochemical properties [11]. Alginate shrinks in the low pH condition and forms an insoluble alginic acid skin, and in high pH, it again forms a soluble film to deliver the drug in the intestinal tract [11].

For delivering the drug, medicament technologies such as hydrogels can be used [20]. Hydrogels show dynamic pH-responsive behavior by which the drug can be released in the small intestine [20]. Hydrogels show high swelling properties at pH around 7.4 and match the pH of the intestine [20]. The swelling of hydrogels in the small intestine pH helps to show functional drug release kinetics [20]. Hydrogels can be employed for controlled release, biomaterials, and agricultural applications [20]. Hydrogels require pH as an external stimulus by which hydrogels can show sol-gel transition and fluorescent behavior [20]. The swelling property of hydrogels is inversely proportional to the crosslinking [20]. Hydrogels can also be used for delivering the drug in specific areas with controlled- release other than the small intestine.

Other than hydrogels, microspheres can also be used as a controlled and specific drug release delivery system. Microspheres are spherical and exhibit swelling properties [21]. The microspheres are known to show excellent efficiency to help prolong the half-life of the drug [21]. The bioavailability of the drug is also known to increase by administering the medication through microspheres [21]. By including bio adhesives in the microspheres, drug delivery, a controlled release profile, and persistent contact of the drug can be maintained with mucosa [21]. Due to the mucosa adhesion, specific drug target delivery can be achieved [21]. The small size of the microspheres aids them in getting trapped in the folds of the small intestine and stay for a longer time in the target area of drug release [21]. Diseases such as peptic ulcers can be treated using microspheres by achieving the target and prolong the release of medicament [21]. The use of microspheres has also been extended to the gastro retentive drug delivery system [21].

Main Analysis

Gastrointestinal Tract in Humans

The digestive tract also called the Gastrointestinal tract (GI) [15]. The GI tract in humans is 10-12m in length, which starts from the mouth and ends in anus [15]. The GI tract consists of mouth, esophagus, stomach, small intestine, and the large intestine [15]. Besides these, the GI also consists of salivary glands, liver, pancreas, which secrete various enzymes for digestion [15]. The nutrient absorption occurs in the GI tract and then is spread to all parts of the body.

The GI tract is composed of four concentric layers namely (from innermost to outermost) [15] – Mucous layer – Releases mucus and Hydrochloric acid [15]

Submucosal layer – Forms the connective tissue [15] the outer layer and serous layer [15].

The mouth is the starting of the alimentary canal, which is being followed by the esophagus [15]. Oesophagus is a 15 – 20cm long tube-like structure that carries the food to the stomach [15]. The stomach is the muscular organ that is in the J shape [15]. The stomach is the fullest part of the gastrointestinal tract [15]. The mixing of food in the stomach is carried by the presence of muscles that contract and mix the diet [15]. Nutrients like proteins, starch, and triglycerides are being digested in the stomach [15]. Water can also be absorbed with some other substances that can be digested in the stomach [15]. The most amounts of the nutrients are incorporated in the small intestine, which has a length of 6-7 meters [15]. The small intestine is distinguished into three parts, namely, duodenum, jejunum, and ileum [15]. The small intestine has some finger-like projections on the surface, which helps to increase the surface area of the mucosa [15]. The villi may further have microvilli, which can further increase the absorption of nutrients [15]. The villi have lymphatic, and blood vessels through which the absorbed food and nutrients can be transported to the lymphatic system and rest parts of the body through blood [15] after small intestine comes the large intestine which has a length of 1.5–1.8 meters and is the final portion of the GI [15]. The large intestine consists of three parts which are caecum, colon, and rectum [15]. The primary function of the large intestine is to remove the waste product from the digestion [15].

The physiological pH varies along the Gi tract, from very acidic in the stomach to neutral in the large intestine [15]. The upper intestine has a pH of 5.5; the ileocolonic has a pH of 7.5, and the rectum has a pH of 6.7 [15]. The absorption of drugs in the Gi tract is through passive mechanisms [15]. Following the pH partition theory, only the unionized fraction of the drug substance can pass through the lipid membrane of the GI tract [15]. The amount of unionized fraction of drugs depends upon the relation between the medium in which the drug is and the pKa [15]. The pH of the stomach acid and favors the absorption of the weak acidic drug, and the small bowel supports the incorporation of the soft base's drugs [15]. The intestine has carrier-mediated transport, which is carried by hydrophilic molecules and transport proteins [15]. The gastric enzymes released by the stomach can cause instabilities in the drugs [15].

Types of Instability

The excipients are affected by various chemical, physical,

and microbiological properties [9]. Physically their uncertainty due to phase transformation [9]. Phase transformation may occur due to polymorphic changes, hydration, and dehydration, and it might also be affected by the precipitation or changes in the amorphous or crystalline nature [9]. Phase transformation may occur via coagulation, melting, or solvent-mediated mechanisms [9]. Due to changes in the physical or chemical modifications of excipient during manufacturing or storage will reduce its acceptance in the market [9]. Chemical instability includes thermolytic oxidation or degradation due to photolytic degradation [9]. Microbiological instability occurs due to the failure of the preservative action of formulation due to its interaction in the formulation [9].

Excipients are divided Into Classes Given by IPEC. Excipients Have Four Main Types which are as Follows

1. New chemical excipients – Excipients belonging to this category have no historical evidence. These excipients have not been used in existing drug products [9]. For these excipients, the pre- clinical safety tests must be performed before using in humans [9].

2. Existing chemical excipients – These chemical excipients have animal safety data available [9]. But the tests on the healthy human volunteers must be performed before using in drug products [9].

3. Existing chemical excipients – These chemical excipients are used in humans before but with variations in dosage routes of administration [9]. The exceptions are also in the dosage strengths of the dose [9]. Additional safety tests must be performed on human volunteers [9].

4. New modification or combination of existing excipients – These are also known as co- processed excipients [9]. There are some modifications performed, and so no safety data is required before using it in humans [9]. Also, no safety evaluations are performed [9].

Role of varying pH in the Gastrointestinal Tract and pH-Responsive Carriers

Achieving a constant and adequate bioavailability through solid dosage form has become a challenge [11]. Various formulation approaches for the pH-responsive oral dosage forms have developed, which include hydrogels, nanoparticles, microspheres, and mini tablets [11]. The research of new excipients is required to obtain excellent safety and stability profile of the drug product [9]. The pharmaceutical market requires improved physicochemical and stability properties of the drug product [9]. So, there is increasing pressure on the search of new excipients, which would help to enhance the security and properties of the formulation [9].

The specific peptides and proteins present in the tablet dosage form can be degraded by various enzymes present in the stomach [11]. The varying pH in the stomach and small intestine can cause deamidation or oxidation of the protein present in the tablet [11]. The human body has different pH in the gastrointestinal tract, which varies from pH 1.5 in stomach and pH 8 in the small intestine [12]. The varying pH in the GI affects the weak acid and weak base drugs [12]. The ineffective base drug is not highly ionized at pH eight as compared to the weak acid [12]. The ineffective base drug dissolves more in the lipid membrane of the intestine and gets absorbed [12].

pH-Responsive Formulations for Oral Dosage Forms

The oral route of the dosage form increases the bioavailability of the solid dosage form [11]. The solid dosage form is exposed to various stressful low pH conditions of the stomach, which can cause alteration in the absorption of the drug in the system [11]. To overcome the stressful situations faced by the reliable dosage drug should be delivered using the pH-responsive carriers. The pH-responsive drug carriers can provide the drug in the intestine by various mechanisms. Some dosage form which comes under the category of pH-responsive drug delivery can contain the drug in the colon without degradation from the low stomach pH [11]. The various formulations developed for the pH-responsive oral delivery system are hydrogels, nanoparticles, and microspheres [11]. A novel system composed of hydroxyethyl acryl chitosan and sodium alginate can be used for improving the drug delivery of oral dosage forms [8]

Hydrogels

Hydrogels have ample features of the bulk structure that can be changed to obtain several therapeutic effects [11]. The crosslinked hydrogels have many cross-linkages which help to protect the drug from the low pH environment of the stomach [11]. The cross-linkages also protect the drug content from their degradation from the enzymes present in the stomach [11]. The different drugs get released from the pH-responsive hydrogels after the material gets swelled at different pH [11]. The two strategies used for delivering the dose at the required pH are (1) the addition of the ionizable groups that have a solubility in the pH environment or show conformational changes in the different physiological pH [11]. The (2) way is to incorporate acid-sensitive bonds that can release a molecule in response to the acid environment [11]. The intestinal delivery of the dosage form protects the acidic environment and enzymatic degradation and ensures the release of drug in the specific parts of the small intestine [11]. The hydrogel pH-responsive technique offers a highly controlled and protective release of the dosage form in the ending parts of the small intestine.

Nanoparticles

Experiments on the delivery of oral dosage form are extensively performed using nanoparticles that have been delivered [11]. Nanoparticles can prevent the solid dosage form from the drug efflux pump, enzymatic degradation, and low pH environment [11]. The nanoparticles that have pH-responsive release property can be used to deliver organ-specific drug release [11]. The nanoparticles that contain surface-functionalized ligands, which include vitamins, can small peptides can be used to make retention in the release of the drug in the stomach [11].

Microspheres

Microspheres are derived from the natural and synthetic polymers, which are used to study the therapeutics of oral delivery systems [11]. The major disadvantage faced by the microspheres is the hydrophilic nature of the enteric-coated dosage form [11]. The hydrophilic nature of these enteric- coated materials causes microspheres to show low drug-carrying capacity [11]. The microspheres can deliver drug selectively in the intestine with functional reconstitution and proves to increase the bioavailability of the therapeutic agents [11].

Control Drug Release Systems

Controlled drug release drugs are those drugs that deliver

the medicament in the dosage form in a predetermined way for a specific period. Controlled drug release of the dosage form can be utilized to optimize the pharmacotherapy of the dosage form [13]. The drug should be released in a controlled way following the purpose of drug delivery and pharmacological properties [13]. The release profile of the drug can determine the therapeutic efficacy from the dosage form [13]. Based on the time-release patterns of the dosage form, they can be divided into four types, which are immediate release, prolonged release, modified release, delayed-release, and sustained release [13]. The immediate-release aims to increase the dissolution and the absorption of poorly water-soluble drugs from the dosage form [13]. Prolonged-release seeks to sustain the release of water-soluble drugs in the dosage form [13]. The modified release aims to balance the drug bioavailability according to the delayed-release rate of the drug [13]. The delayed-release seeks to provide a pH-dependent release and site targeted release [13].

Immediate Release

Immediate-release dosage form finds vast application in the situation where there is an emergency case, and the release of medicament is expected to be fast [13] amongst all the dosage forms for immediate release oral dosage form it the most preferred [24]. The tablet dosage form for immediate release has small solid granules in the tablets and helps to modify the surface area to volume ratio of the dosage form [24]. For obtaining an immediate release, various hydrophilic materials are being used for attaining immediate release [13]. All the available drugs do not suit the constant release profile in the market; some require repeated administration [25]. Reasons due to which immediate release of dosage is preferred are high metabolism of the active pharmaceutical ingredient, the short half-life of the medicament, and limited absorption window of the drug-like levodopa [25]. The release of such drugs by sustained release pattern might decrease the bioavailability [25]. The improvements in the release profile are observed due to the increased solubility and wettability properties of the drugs [13]. Formulations that are required for antipyretics, vasodilation, and analgesics require an immediate release of the medicament [13]. The direct release dosage form can increase the bioavailability of the poorly soluble drug in the GI tract. The direct release dosage shows a fast onset of action in the patient to relieve the patient from any severe condition. Dosage form ranging from implantable gels to nanoparticle suspensions oral immediate-release capsules and capsules are the most used dosage form [24]. Excipients like polyethylene glycol 8000 are used in the immediate release tablets [24]. The release time for the drug in the GI medium is from three to thirty minutes [24].

Delayed-Release

The delayed dosage form is classified as a time-controlled dosage form [13]. The drug is being released in the intestinal medium and protected from the acidic pH of the stomach [13]. The hydrophobic excipients are being used for the delayed release of the dosage form, which has a weak acidic group [13]. The vulnerable acidic group does no solubilize in the highly acidic pH of the stomach and therefore making the release of the drug delayed in the stomach [13]. The dosage form when it reaches the ingestion where the pH is towards high essential character there is ionization of the acidic group, which releases the drug [13]. Due to the pH-dependent release behavior of the dosage form, it will release the medicine at the starting of the small intestine [13].

Prolonged-Release

The slow-release dosage forms try achieving zero-order or pH-independent release of drugs [13]. The zero-order release provides a constant blood level release of medication for a more extended period [13]. The advantage with the zero-order release is that it can reduce the frequency of the dosage, the efficacy of the drug can be prolonged, which in turn decreases the toxicity associated with the administration of solid dosage form [13]. The prolonged-release dosage form can increase the life span of drug staying in the body. The therapeutic efficiency can be increased by using the mechanism of prolonged-release.

The controlled release model includes various other dosage forms that can release the drug at a controlled rate.

Sustained Release

Amongst all the dosage forms available to patient's oral dosage form remain the most administered dosage form due to the most straightforward route of dosage [22]. The controlled release dosage form is developed for patients to comply with medication and get effectively cured [22]. The conventional dosage form developed was made to release the medicament immediately [22]. By releasing the medicine, a quickly repeated dosage was required to be administered [22]. The sustained release dosage form ensures that the patient has not skipped the dosage form in the patient's routine, thereby increasing patient compliance to medication [22]. Sustained release dosage form ensures a steady plasma concentration of the drug without any fluctuation as compared to the conventional dosage form [22]. The dosage form which delivers the drug immediately is required to provide dose frequently for Active Pharmaceutical Ingredient (API) with short half-life [22]. The efficiency of the drug is limited until the residence of the medicament in the blood plasma, where sustained release dosage form comes into play [23]. The sustained release dosage form is a modified dosage form with hydrophilic matrices [23]. The polymers used to provide hydrophilic property are polysaccharides, xanthan gum, and chitosan [23]. Xanthan gum offers high thickness property and suitable water-absorbing property to the dosage form [23]. The xanthan gum absorbs water and prevents the immediate release of the medicament from the dosage form by entrapping the medicine in the thick gelled layer [23].

Enteric-Coated Dosage Forms

Enteric coating dosage forms are prepared over the past 100 years [14]. Still, there is less research and evaluation conducted on the biopharmaceutical evaluation [14]. The enteric coating mechanism needs more in vitro release tests to be performed, and new data generated [14]. Enteric-coated dosage forms delay the drug release process from the coated dosage form [14]. The dosage form is not released until the gastric emptying occurs [14]. The main aim of performing the enteric coating is to protect the drug from its degradation from the gastric juices and any irritation caused to the gastric mucosa by the drugs [14]. The enteric film formers are generally weakly acidic, and the film formers do not ionize or solubilize in the highly acidic pH of the stomach [14]. The weakly acidic film formers ionize or get solubilized in the high basic pH of the intestine [14]. By this mechanism, the drug release is delayed, or the onset of action of the drug is delayed [14]. The dose is not released until after the dosage form is emptied from the pylorus [14]. After forming the enteric coating film, there are specific tests that must be performed to evaluate the dissolution of the dosage in the

intestine. Dissolution and disintegration tests are performed to check-in vivo release profiles [14]. The two tests are performed first in the acidic medium for at least one to two hours to check if there is any release of drug in the acidic medium [14]. After the tests are performed in the acidic medium, the test is then conducted in the essential medium to check the current release of drug in the intestine [14]. The iron enteric coated preparations are low bioavailable due to their tendency to start disintegrating after passing the iron preferential site in the duodenum and jejunum [14].

The enteric coating of the tablets can solve the drugs and the coated polymers which face the problem of instability in the gastric pH. The most common dosage form used to deliver enteric coating drugs is tablets [19]. The gastric emptying of the tablets from the stomach occurs when the stomach muscles apply a strong contraction force by the muscles in the abdomen or by gastric motor activity [19]. The contraction is called as 'house-keeper' wave [19].

Functions of Enteric Coating

Enteric coating is an outer coating usually performed for the oral dosage form [15]. The enteric coating material is generally formed by natural or synthetic polymers [15]. The polymers include cellulose acetate phthalate and hydroxypropyl methylcellulose phthalate [15]. Enteric coating is used to alter the odour or taste of the drug product [15]. Enteric coating also protects the drug against the environmental conditions present in the stomach (pH) [15]. Due to enteric coating, the release of drug is prevented in the stomach and released in the small intestine [15]. For enteric coating, the technical procedures used are film coating and sugar coating [15]. The amount of the polymers added is two to three times as compared to standard coating [15].

Extended-Release OROS Method

OROS stands for the osmotic controlled-release oral delivery system (OROS) [17]. The formulation is in the form of a tablet with an outer semipermeable membrane and one or more laser-drilled holes for the delivery of drugs [17]. OROS drug delivery system can be used to deliver a controlled release of medicated drugs through tablet dosage form. The OROS drug delivery system is used to optimize the extended-release of medicated medicines [17]. The oral dosage form, including tablets and capsules, can be used to obtain predetermined drug release in the patient's body, and pulsed discharge can also be obtained [17]. The OROS drug release uses the osmotic controlled release of the medicated drug through the semipermeable membrane [17]. The OROS drug delivery can benefit the patients who require a whole day controlled release drug. The OROS drug delivery helps to expand the range of patients and is also available in over the counter products for nasal/ sinus congestion medications [17]. The novel OROS controlled-release tablets have an efficient structure to deliver the medicated drug, which I will be observed in figure 3 [17]. Figure 3 [17] shows the controlled expulsion of the medicated drug through the orifice. The OROS drug delivery system can deliver a variety of medicated medications in a controlled release fashion, which led to an increase in the range of patients covered.

The OROS has many advantages, which include patterned delivery to the patient, meets specifications of the medicated drugs, reduces the drug level fluctuations in the patient's body, and beneficial for the drugs with short half-lives to extend the release of the medicament [17]. The extended-release behavior of OROS technology can reduce the frequency of taking the medicament and benefit the patient. However, OROS technology has one disadvantage that the release of the drug cannot be stopped after the administration of the drug [17].

The drug delivery through OROS technology follows the zero-order kinetics [17]. A semi-permeable membrane covers the OROS tablet, and the semi-permeable membrane is permeable only to water and impermeable to ions present in the GI and the drug in the medicament [17]. The mechanism of action of OROS drug delivery includes the first development of the osmotic gradient by the core drug components by pulling in water [17]. The pulling in of water depends upon the composition and thickness of the semi-permeable membrane [17]. After the entering of water, the core medicament starts to suspend in the water, and the solution might be suspension or solution [17]. The flow of drugs from the orifice depends on the rate at which the water is entering the core [17]. The delivery of the drug medicament is not affected by the pH of the GI tract and is an added advantage to the OROS delivery system [17].

For patients suffering from chronic diseases like cancer, the pain is unbearable for the patient, and the pain remains for a long time. The OROS drug delivery system can be used to deliver a once a daily pill or tablet to work for 24 hours and deliver an analgesic effect at a controlled rate [18].

The Outcome of Lignin Modification on Tablet Disintegration

Tablet disintegration is the time the tablets take to break apart upon exposure to water and a little agitation [16]. The tablets disintegrate into aggregates of primary particles which disintegrate into fundamental drug particles [16]. The tablet breaking force ensures the robustness of the tablet batch during the manufacturing of the same coating and in handling and shipping [16]. Tablet breaking force can be measured by observing the maximum stress, which may be compressive or tensile can be sustained by the tablet [16]. Both tablet disintegration and tablet hardness force have a damaging effect on the tablet structure to analyze the behavior of tablet in the GI [16]. The tablet disintegration time, and tablet hardness depend on factors like tablet density, tablet size, shape, thickness, and manufacturing process of tablets [16].

The disintegration time taken by the tablet will affect the dissolution of the tablet [6]. The more is the hardness of the tablet, the more time the tablet will take to disintegrate into the GI tract [6]. The incorporation of the carboxylated lignin in the tablet can cause the faster disintegration of the oral dosage form and reduce the hardness of the oral dosage form, which can be referred from the figure 1 and figure 2 [6]. By the incorporation of carboxylated lignin in the dosage form can increase the porosity of the oral dosage form, which can reduce the hardness of the oral dosage form, which will lead to lower disintegration time [6].

The figure 2 [6] describes the decrease in the hardness of the carboxylated lignin tablet, the decreased hardness of the table will lead to the fast disintegration of tablets and quicker release of the medicament from the dosage form [6]. The disintegration of the tablet relates to the drug dissolution and the drug release from the dosage form. The faster the disintegration of the tablet dosage form, the faster will be the release of the medicament. The modified lignin tablets have the fastest disintegration

time, and which will show the quickest drug release rate [6].

Controlled Release Profile from Lignin Carboxylation

Including lignin as an excipient in the tablet dosage form has shown an increased drug release rate due to the amorphous structure of lignin [6]. The increase in the carboxyl groups in lignin helps to increase the drug release at intestinal pH (7.2 pH) as compared to the stomach pH (1.2 pH) [6]. The controlled release at the intestine is observed due to the decreased electrostatic repulsion force present between lignin carboxyl groups due to the protonation of carboxyl groups in the stomach pH [6]. The swelling effect is observed in the small intestine pH due to the ionization of carboxyl groups and higher the release rate of drug components in the intestine as compared to the stomach [6]. The carboxyl groups being ionized produce negative charges which tend to repel each other and show swelling properties and release the medicament [6]. The ionization of the modified lignin is the leading cause of the release of the active pharmaceutical ingredient in the small intestine. Weak acids get ionized in the high pH value found the small intestine leading to a delayed release of the medicament. For testing the release of the API in the small intestine, tests such as dissolution and disintegration can be performed. Due to the controlled release of the medicament, slower and steady delivery of the drug can be expected.

The use of lignin as an excipient shows excellent controlled release properties and helps to increase the solubility of the medicament in the gastrointestinal tract [6]. The use of synthetic and non-bio degradable excipients for controlled release is causing harm to both patients and the environment. The use of biopolymers should be enhanced for a better environment.

Conclusion

Excipients are inert materials added to the dosage form but affect the physical, chemical, and release profile of the dosage form. The focus of the dosage manufacturing market should increase from synthetic excipients to more natural and biodegradable excipients. Lignin is chosen as an excipient as lignin is a natural polymer and has many functional groups attached to it for possible modifications. The human gastrointestinal environment offers a varying pH to the oral dosage form. The pH- responsive dosage form and controlled release are used to avoid the harmful effects of unstable medicament in the gastric environment. Nanoparticles, microspheres, and hydrogels are used to deliver dosage form through the pH modified-release technique. Added excipients to the dosage form face instabilities due to the various digestive enzymes and low pH of the gastric environment. The active pharmaceutical ingredients are unstable in the gastric pH environment and can cause toxicity to the patient. Based on time-release profiles, different dosage forms available in the market. Modification in the lignin structure gives a controlled release of the oral dosage form and affects the tablet hardness. The drug release is enhanced by the incorporation of modified lignin in the dosage form. Lignin is a suitable excipient for delivering targeted controlled release of the medicament.

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