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A Review on Lignin and Cellulose Blend as Pharmaceutical Excipient for Tablet Manufacturing

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ABSTRACT

Tablets are the most commonly used pharmaceutical dosage form. They are relatively simple to manufacture, show good physical stability and extensively accepted by patients. Polymers are commonly used in almost all major dosage form including tablets, films, capsule etc. Considering the time and resources required to obtain regulatory approval when a new excipient is to be utilized, polymer blend present an attractive alternative means. The goal of blending polymers from a functionality stand points is to improve, customize, or maximize material performance. In the present work the use of these biopolymer as excipient to prepare tablet was studied. For this purpose LIG was combined with MCC and used as excipients to prepare tablet. The excipient contains different concentrations of LIG: 100%, 75%, 50%, 25% and 0% (W/W). When formulations were prepared using LIG as the only excipient, tablet were formed, but they showed lower density and crushing strength than the once obtained with only MCC or LIG or MCC blends.

INTRODUCTION

Tablets (Tab) are the most commonly used pharmaceutical dosage form [1]. They are relatively simple to manufacture, show good physical stability and they are extensively accepted by patients [2]. Direct compression is the preferred method of tablet preparation. This method involves the tableting of a mixture of ingredients without preliminary agglomeration or granulation processes. This method presents advantages over other tableting methods such as wet granulation as it requires shorter processing times, fewer excipients and reduced stability risk during processing. [3]

Polymers are widely used in the formulation of pharmaceutical and healthcare products. Polymers are commonly used in almost all major dosage forms including tablets, films, capsules, semisolids, suspensions, gels, and transdermal patches as well as in specialized delivery systems such as long-acting injections and biodegradable implants. Considering the time and resources required to obtain regulatory approval when a new excipient is to be utilized, polymer blends present an attractive alternative means by which to address various formulation and drug delivery challenges. The goal of blending polymers from a functionality standpoint is to improve, customize, or maximize material performance.

PHARMACEUTICAL EXCIPIENTS

The word excipient is derived from the Latin excipere, meaning “to except” which is simply explained as “other than”. Excipients are inert substances used in drug production to assist manufacturing of dosage form. These are the ingredients which along with Active Pharmaceutical Ingredients make up the dosage forms. Excipients act as protective agents, bulking agents and can also be used to improve bioavailability of drugs in some instances. On the basis of their functions, excipients can be categorized as binders, cosolvents, fillers, disintegrates, lubricants, surfactants, emulsifying agents, suspending agents, antimicrobials, preservatives, etc.[10]

PHARMACEUTICAL EXCIPIENTS

Types of excipients	Examples
Binders	Starch, cellulose or modified cellulose such as microcrystalline cellulose, hydroxypropyl cellulose, lactose
Fillers	Lactose, cellulose, sucrose, Glucose
Disintegrants	Polyvinyl pyrrolidone, sodium starch glycolate
Lubricants	Talc and fats

MICROCRYSTALLINE CELLULOSE

Microcrystalline cellulose $(C_6H_{10}O_5)n$ is refined wood pulp. It is a white, free-flowing powder. Chemically, it is an inert substance, is not degraded during digestion and has no appreciable absorption. In large quantities it provides dietary bulk and may lead to a laxative effect. Microcrystalline cellulose is a commonly used excipient in the pharmaceutical industry. It has excellent compressibility properties and is used in solid dose forms, such as tablets. Tablets can be formed that are hard, but dissolve quickly. Microcrystalline cellulose is the same as cellulose .It is also found in many processed food products, and may be used as an anti-caking agent, stabilizer, texture modifier, or suspending agent among other uses.

DESCRIPTION OF MICROCRYSTALLINE CELLULOSE

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless tasteless, crystalline powder composed of porous particles. It is commercially available in different particle size and moisture grades.

Typical properties

- Angle of repose = 34.40-490
- Density (bulk) = 0.337g/cm3
- Density (tapped) = 0.478g/cm3

- Density (true) = 1.512-1.668g/cm
- Melting point: Chars at 260-270°C
- Moisture content: Typically, less than 5%w/w
- Particle size distribution: Mean particle size 20-200µm
- Solubility: Slightly soluble in 5%w/v NaOH solution and practically insoluble in water, dilute acid and most organic solvent

STRUCTURE OF MICROCRYSTALLINE CELLULOSE

Cellulose, a fibrous carbohydrate found in all plants and is a linear polymer of glucose. . Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose having the formula (C6H10O5)n. It is prepared by treating alpha cellulose with mineral acids. This polysaccharide polymer consists of a linear chain of several hundred to over ten thousand β(1 → 4) linked D-glucose units, consisting of linear chains of β-1,4-d anhydro glucopyranosyl units. MCC is generally considered as the diluent having the best binding properties and is recognized as one of the preferred binders. It is used as a binder/diluent in oral tablet and capsule formulations including both wet granulation and direct compression processes.

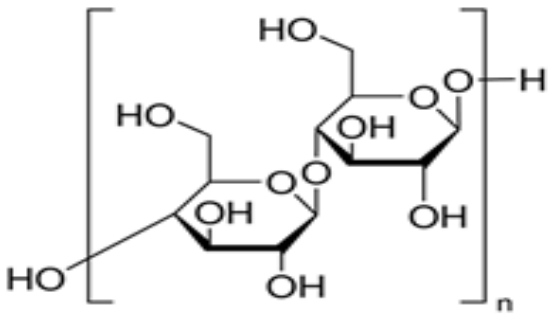

Fig no 1: Structure of Microcrystalline Cellulose

LIGNIN

Lignin is an organic substance belonging to a group of aromatic alcohols. It is naturally produced by certain plants (especially woody plants and certain algal species). It is found in the secondary cell walls of plants where it serves as a binder for cellulose fibers and provides stiffness to the cell walls. It is present in wood primarily to provide structural support and protection against degradation by microorganisms. It fills the spaces in the cell wall particularly in xylem tracheids, vessel elements and sclereid cells**.**

DESCRIPTION OF LIGNIN

Lignin is an amorphous polymer that is gradually lightened from black to brown as decrease in pH value. Typically molecular weight of lignin varies, with the nature of source softwood having 20,000 g/mol and hardwood having a lower molecular weight. The type of lignin and the way lignin is prepared can affect its molecular weight.

- **Glass transition temperature**

Lignin is an amorphous thermoplastic polymer. Glass transition temperature of a polymer (Tg) is a region in which the polymer undergoes a change from glassy to rubbery state immediately without a phase transformation. At low temperatures, the polymer is in glass state .The glass transition temperature of lignin is 90^0C.

- Melting point(MP): 170^0C

- Solubility: lignin has strong intramolecular and intermolecular forces, arising from hydroxyls and polar groups present in its structure. It is soluble in hot alkali.

STRUCTURE OF LIGNIN

LIG is a biopolymer present in the cell walls of vascular plants formed by randomly cross-linked networks of methoxylated and hydroxylated phenylpropane. This compound provides mechanical protection to the plant. Moreover, LIG protects the plants from external biological and chemical stresses as it possesses antioxidant and antimicrobial properties. LIG is one of the most abundant polymers on Earth, second after cellulose. Lignin is used as pharmaceutical excipients for tablet manufacturing. [4]

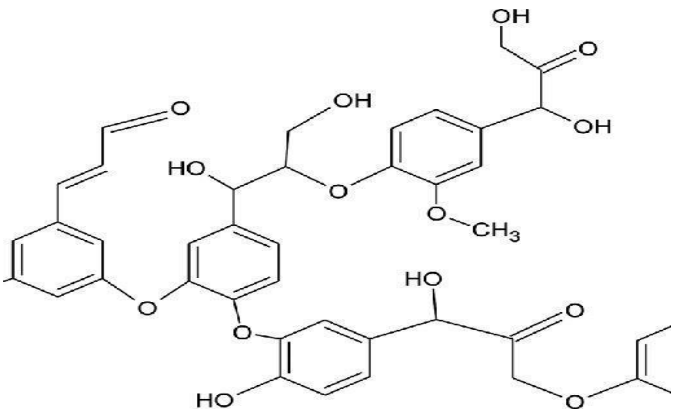

Fig no 2: Structure of Lignin

LIGNIN AND CELLULOSE BLEND

Extensive efforts are being made to find alternative uses for lignin (LIG). In the present work the use of this biopolymer as excipient to prepare tablets was studied. For this purpose, LIG was combined with microcrystalline cellulose (MCC) and used as excipients to prepare tablets. The excipients contained different concentrations of LIG: 100%, 75%, 50%, 25% and 0% (w/w). When formulations were prepared using LIG as the only excipient, tablets were formed, but they showed lower densities and crushing strength than the ones obtained with only MCC or LIG/MCC blends. The presence of LIG in the tablets modified significantly the release profile of drugs. Finally, a DPPH (2,2-diphenyl- 1-picrylhydrozyl) assay was performed to confirm that the presence of LIG provided antioxidant properties to the formulations. Accordingly, LIG has potential as a pharmaceutical excipient.

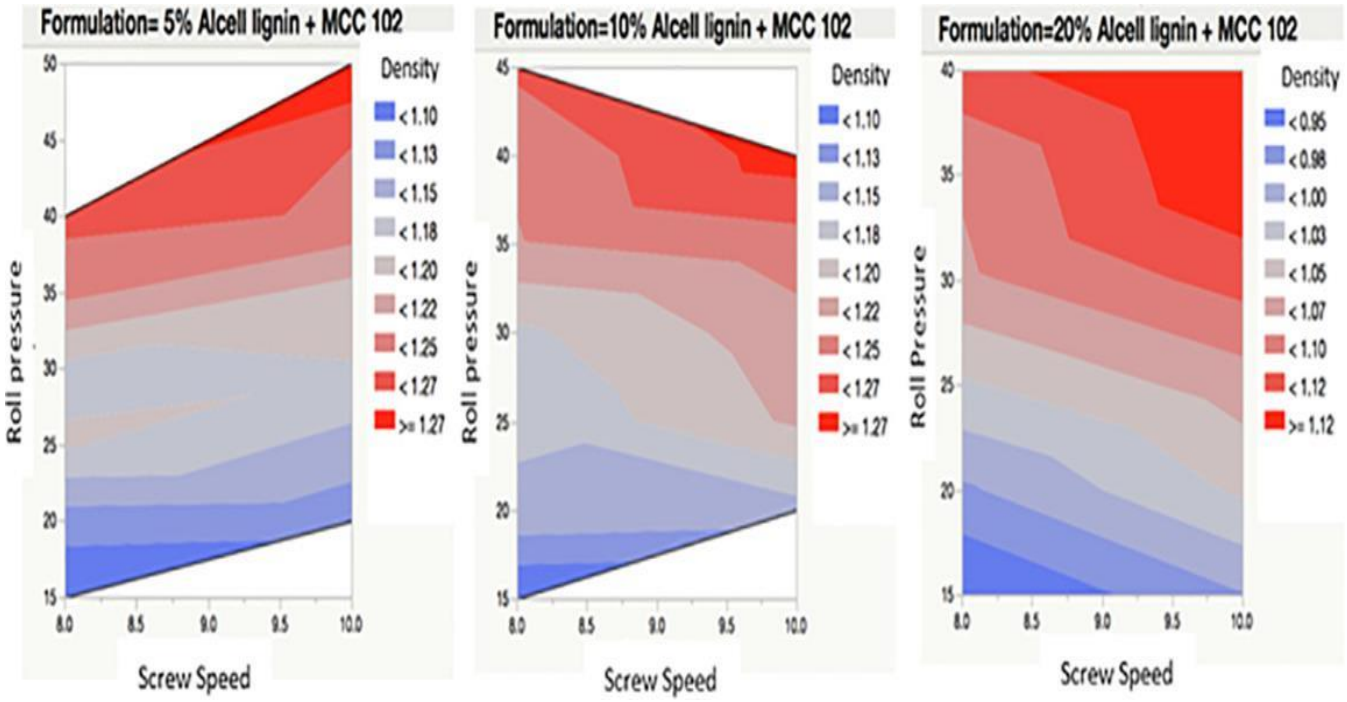

Fig no 3: Graphical representation of lignin and cellulose blend

A new excipient formulation based on natural polymers (lignin and cellulose) was utilized to improve the properties and reduce costs associated with tablets production. A variety of lignin and microcrystalline cellulose (MCC) formulations were compacted followed by milling to obtain granules. Formulations were also characterized in terms of compressibility and flowability. Densities of ribbons as well as granule size distribution were mapped versus critical process parameters. Based on this work as initial study, roll pressure was found to be a critical process parameter, higher ribbon density and larger granule size obtained with

higher roll pressure. It was also revealed that the process map is a powerful tool in understanding the dry granulation, and can be used to construct a design space for pharmaceutical manufacturing.

APPLICATIONS OF LIGNIN CELLULOSE BLEND

- **Lignin: cellulose blends as Carbon Fiber precursors Carbon fibers**

(CFs) are gaining increasing importance in lightweight composites, but their high price and reliance on fossil based raw materials stress the need for renewable and cost-efficient alternatives. Commercial CFs for composite applications are mainly produced (>96%) from the fossil-based polymer polyacrylonitrile (PAN), only minor amounts being produced from petroleum or coal-tar pitch and Rayon (regenerated cellulose). Lignin and cellulose are two interesting candidates as sources for CF because they are renewable macromolecules available in high quantities. The high carbon content of kraft lignin (60–65 wt %) suggests a high yield after conversion into CF, but its structural heterogeneity means that the CFs have inferior mechanical properties. The carbonization time during the preparation of CFs from a lignin−cellulose precursor can be reduced from70 to 24 min with no significant loss of tensile properties, which is beneficial from an economical perspective. [5]

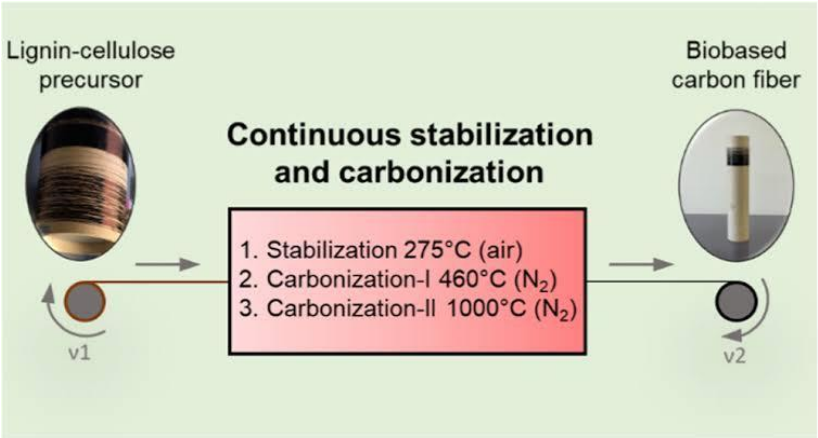

Fig no 4: Lignin cellulose blend as carbon fiber precursor

- **Formulation of Tetracycline using direct compression method**

In the present work the use of this biopolymer as excipient to prepare tablets was studied. For this purpose, LIG was combined with microcrystalline cellulose (MCC) and used as excipients to prepare directly compressed tablets containing a model drug, tetracycline (TC). Two different compression forces were used (two and five tonnes). Tablets prepared using

five tonnes of compression force showed TC releases ranging from 40% to 70% of the drug loading. On the other hand, the tablets prepared using two tonnes of compression force showed a faster and more efficient TC release, between 60% and 90%. The presence of LIG in the tablets modified significantly the release profile and the maximum amount of TC released. [6]

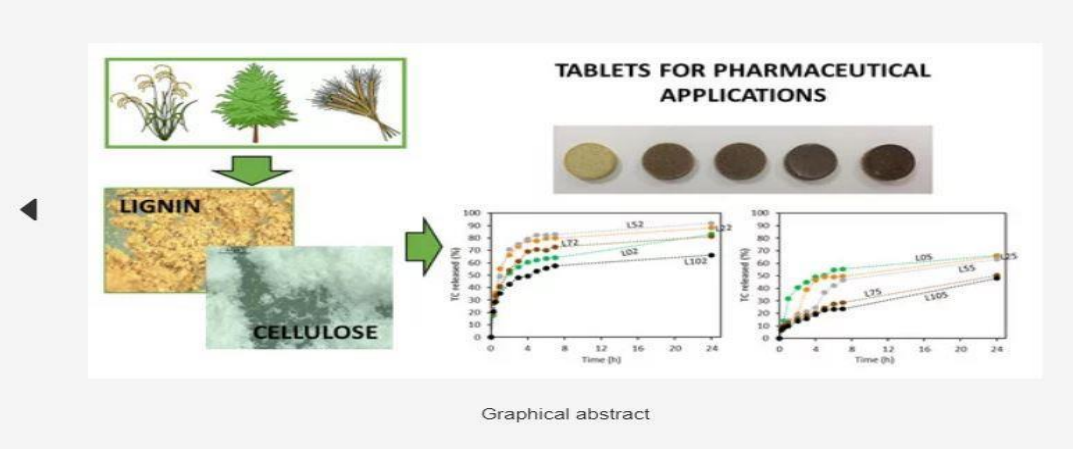

Fig no 5: Tablet manufacturing

- **Antibacterial activity**

For a long time, natural cellulose and related composites have been prepared and applied in many different fields including packaging, optics, and sensor technologies. Within the last five years, first examples of lignin/cellulose-based coatings have been reported. In the context of food preservation, few studies have been reported on the use of organic active principles against bacteria /fungi plant pathogens, while a large amount of literature is available on how these active agents can be incorporated in bio based polymerics matrix.[20]

- **Antioxidant activity**

LIG is a well-known antioxidant compound. This property could provide added value to the final product. It can be included as a protective agent that will prevent the degradation of drugs in the formulation. Formulations containing only MCC showed very low antioxidant capacity in comparison with the blends containing mcc and lignin which shows higher amount of antioxidant activity.[22]

- **As Disintegrants**

Solid oral dosage forms such as tablets undergo several steps before systemic absorption of the drug. Disintegration is the first step immediately after administration of oral dosage forms that breakup the dosage forms into the smaller fragments in an aqueous environment. Converting of solid dosage forms to smaller fragments, increase the available surface area and promote a more rapid release of the drug substances from dosage forms.

- **In bioadhesive and mucoadhesive drug delivery systems**

Bioadhesives and mucoadhesive are drug containing polymeric films with ability of adhering to biological membranes after combining with moisture or mucus compounds. Bioadhesives were developed in mid 1980s as a new idea in drug delivery and nowadays they have been accepted as a promising strategy to prolong the residence time and to improve specific localization of drug delivery systems on various biological membranes.

- **Coating agent**

Solid dosage forms such as tablets, pellets, pills, beads, spherules, granules and microcapsules are often coated for different reasons such as protection of sensitive drugs from humidity, oxygen and all of inappropriate environmental conditions, protection against acidic or enzymatic degradation of drugs, odor or taste masking or making site or time specific release characteristics in pharmaceuticals to prepare various modified release drug delivery systems such as sustained release, delayed release, extended release, immediate release, pulsatile release or step-by-step release dosage forms.

- **As gelling agents**

Gels are semisolid systems consisting of dispersions of very small particles or large molecules in an aqueous liquid vehicle rendered jelly like by the addition of a gelling agent. In recent decades, synthetic and semi-synthetic macromolecules are mostly used as gelling agents in pharmaceutical dosage forms. Some of these agents include: carbomers, cellulose derivatives and natural gums. Cellulose derivatives such as HPMC and CMC are the most popular gelling agents used in drug formulations. These polymers are less sensitive for microbial contamination than natural gelling agents such as tragacanth, acacia, sodium alginate, agar, pectin and gelatin. Cellulose derivatives generally dissolve better in hot water (except MC grade) and their mechanisms of jellification is thermal.

- **Fillers in solid dosage forms**

Cellulose and related polymers are commonly used in solid dosage forms like tablets and capsules as filler. Various forms of cellulose have been used in pharmaceutical preparations as multifunctional ingredients thus; they are concerned as precious excipients for formulation of solid dosage forms. Cellulose and its derivatives have many advantages in using as filler in solid pharmaceuticals such as their compatibility with the most of other excipients, pharmacologically inert nature and indigestibility by human gastrointestinal enzymes. These polymers do not cause any irritancy potential on stomach and esophagus protective mucosa. Various forms of pure cellulose and cellulose ether derivatives can be used as filler in these formulations.

- **As binding agent**

Binders are the essential components of solid drug formulations made by wet granulation process. In wet granulation process, drug substance is combined with other excipients and processed with the use of a solvent (aqueous or organic) with subsequent drying and milling to produce granules. Cellulose and some derivatives have excellent binding effects in wet granulation process. A number of MCC grades such as PH-101 are widely used as binder in wet granulation.

HUMAN

PREPARATIONS

ISOLATION OF LIGNIN FROM WOOD

Lignin can be isolated from various raw materials, i.e. wood and black liquor. There are several methods for lignin isolation from wood, generally, where lignin is isolated either by removing non-lignin or lignin components. Moreover, carbon dioxide or sulfuric acid is used to isolate lignin from black liquor. Lignins probably exist in wood as branched-chain polymer molecules which may comprise an almost infinite network, and this network may be integrated and chemically combined with hemicelluloses or other nonlignin components of wood. In this state, lignin will here be called protolignin. Broadly speaking, lignin may be separated from associated wood components either by preferentially dissolving lignin or by preferentially dissolving nonlignin components.

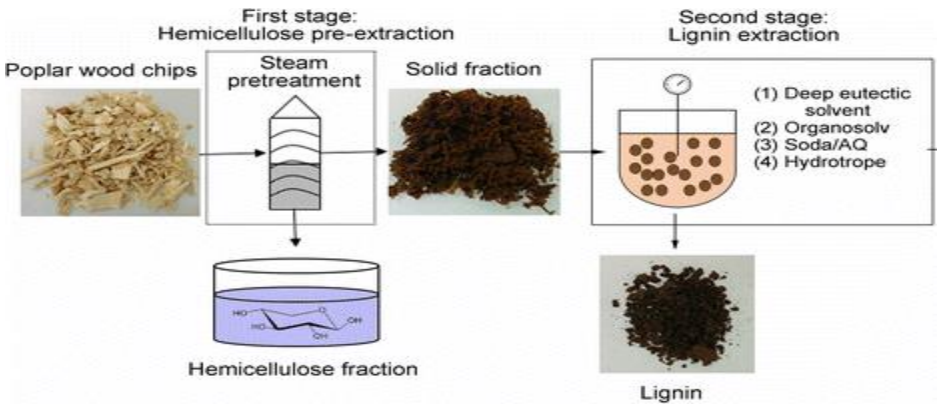

Fig no 6: Isolation of lignin

Removing of nonlignin components

➢ Klason Lignin (sulfuric acid lignin): Wood meal is extracted with alcohol benzene which is employed to remove materials, such as waxes, fats, some resins, and possibly some portions of wood gums, then stirred at room temperature and hydrolysis with 64 to 75% sulfuric acid.[19] The Klason lignin is obtained after removing the polysaccharides, and refluxed with dilute acid; then the Klason lignin or sulfuric acid lignin is filtered, dried, and weighed.

➢ Willstätter Lignin: wood meal is extracted and hydrolyzed with concentrated hydrochloric acid, and produces an insoluble lignin residue, this is so-called Willstätter lignin.

➢ Cuproxam Lignin: substantially all carbohydrate components in extracted wood meal may be dissolved with cuprammonium hydroxide with alternate dilute acid hydrolysis, and this is the basis for preparation of Freudenberg of Cuproxam lignin.

Removing of lignin components

➢ Brauns or Native Lignin (BNL): Fresh wood meal is extracted with cold water, then with ether for 48 hours, and finally with ethanol at room temperature for 8 to 10 days. The solution of lignin in ethanol is then purified by solvent precipitation until the methoxyl content is constant, resulting in a lignin which in yield is only a few per cent based on lignin content of the wood.

ISOLATION OF CELLULOSE

Cellulose is the most abundant naturally occurring polymer on Earth, being a candidate for providing such "nanoparticles as a reinforcing agent. The inherent stiffness and high degree

of crystallinity make it ideally suited for reinforcing and load bearing applications in composites. Apart from this, cellulose is a sustainable resource, biodegradable in nature, and inexpensive. cellulose isolation method from plant waists depends on the needed dimension of the fibers.

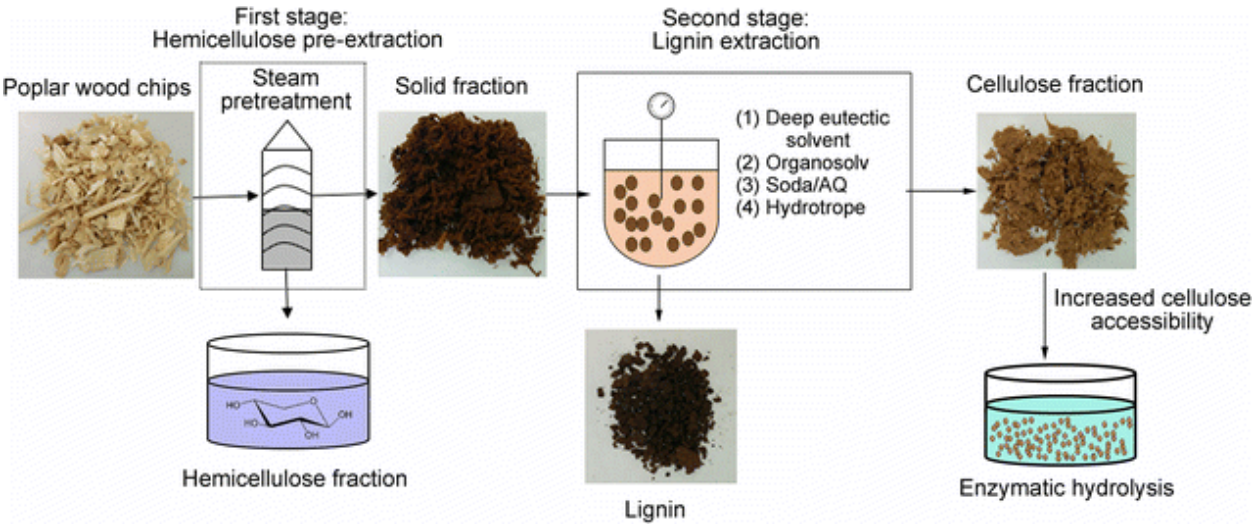

Fig no 7: Isolation of cellulose

- **Cellulose Isolation by Using Alkaline Procedure**

Initially, the dried plant tissue is digested at 80 °C in a 4% sodium hydroxide solution for 4 h. This removes the greater part of lignin and a large part of hemicellulose.[17] Because of persistent discoloration the product is subsequently bleached with a sodium chlorite/glacial acetic acid mixture to remove any residual lignin and hemi cellulose that may have been present. The bleached cellulose fibers are washed repeatedly, initially with a 5% aqueous NaOH and subsequently deionized water in order to attain a neutral pH. In procedure of bleaching and washing of the material fast Preparation system may be involved, to obtain material with higher purity.

- **Cellulose isolation by applying ultrasound treatment**

The procedure for isolation of cellulose using alkaline peroxide with ultrasonic treatment comprises sequential treatment of the plant material with water at 55 "C for 2 h. then with ultrasonic irradiation for 40 min. In subsequent steps the material is treated with 0.5 M NaOH. 0.5,9.1 .0% 1.5%, 20%, and 3.0% H2O2; in 0.5 M NaOH, and 2 M NaOH at 55 °C for 2 h. The insoluble residue is collected by filtration, washed with distilled water until the pH of the filtrate is neutral, and then dried at 60 °C .[15]

PREPARATION OF LIGNIN AND CELLULOSE BLEND

Lignin shows poor compatibility with cellulose. On the one hand, the hydrophilic groups of lignin are mostly wrapped in hydrophobic chains, making it incompatible with hydrophilic carbohydrates such as cellulose. On the other hand, due to the normal pH and no chemical additives, cellulose and lignin have negative charges, which lead to electrostatic repulsion between them.[7]Cellulose is a polyhydroxy compound that can be combined with other materials through hydroxyl hydrogen bonds, leading to the formation of a space-entangled structure; therefore, trying to use hydrogen bonds to connect polymers can effectively combine cellulose and lignin. The use of green solvents (such as ionic liquids) can aid in the formation of lignin and cellulose composite membranes. An extraction procedure with a toluene/ethanol mixture was applied to lignin cellulose (LC) in order to remove the organic-soluble extractives. In this procedure, 2.42 g of LC was treated by a mixture of toluene/ethanol (2:1v/v) in a Soxhlet extractor for 6h. The extractive-free solid-residue was air-dried for 24 h and dried to constant weight in an oven at 60 °C under vacuum. Subsequently, 1.41 g of the solid-residue was further extracted with absolute ethanol in a Soxhlet apparatus for 4 h and dried to constant weight.17 An extraction procedure with water was applied to LC in order to remove water soluble extractives. Briefly, 2.04 g of LC was treated with 100 mL of Millipore water at room temperature under intense magnetic stirring for 5 h. The sludge was filtrated on paper and washed with water. The extractive-free solid residue was dried to constant weight in an oven at 60 °C under vacuum.

EVALUATION

POWDER CHARACTERISTICS

- **Morphology of lignin and MCC**

The morphology of MCC and LIG powder was evaluated by using scanning electronic microscopy (SEM). Pictures were taken under vacuum using a Hitachi TM3030 environmental SEM.

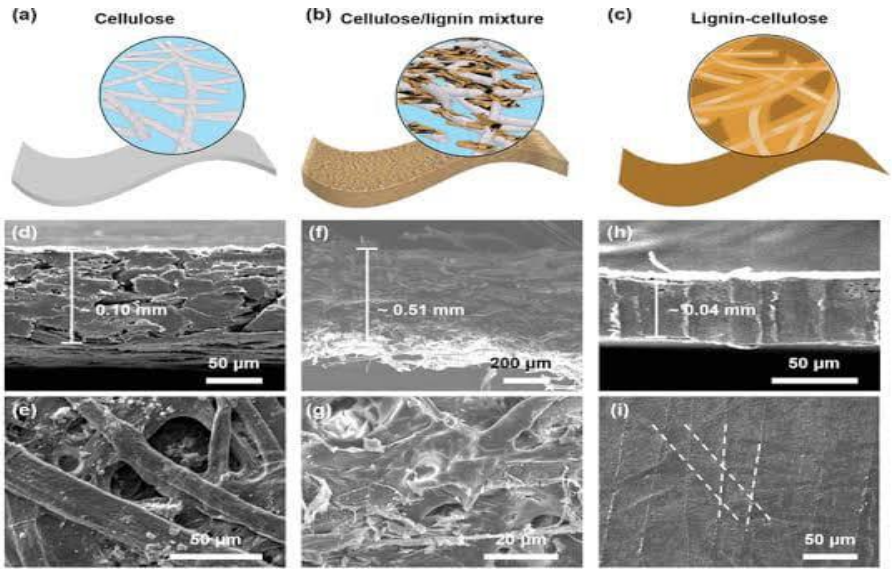

Fig no 8: Morphology of lignin and cellulose blend

- **Determination of particle size distribution**

Malvern Mastersizer 3000 instrument fitted with an Aero S dry dispersion unit was used to determine the particle size distributions of LIG and MCC. Approximately 1 g of each excipient was weighed and added to the general tray. Using an air pressure of 1 and 1.5 bar for MCC and LIG, respectively, and a feed rate of 40% to provide a reasonable flow of powder into the instrument. Three measurements were performed for each sample to give an estimate of the variability about the measurement.[11]

- **Determination of tapped and bulk density**

To determine bulk and tapped densities, approximately 50 g of each granule sample was poured into a 100 cm 3 cylinder, and the volume was measured. Immediately after, the powder mass was tapped 50 times, and the volume was measured again . Bulk and tapped densities were calculated using Equations:

Bulk density = sample mass /volume

Tapped density = sample mass / Tapped volume

Hausner ratio = Tapped density/bulk density [8]

Carr's index = Tapped density –bulk density /tapped density

- **Determination of surface area**

The Brunauer–Emmet–Teller (BET) method was applied to calculate the specific surface area (SBET) and pore size of the MCC and LIG from the desorption curve. The samples were degassed under nitrogen flow, heated to 90 °C for 3 h and then to 150 °C for 24 h until they reached constant weight. These powder properties were analysed by means the nitrogen adsorption isotherm, using a Micrometrics TriStar II porosimeter.[18]

In order to evaluate the compactability of MCC and LIG powders, the Kawakita model was used.

$$p/c = p/a + 1/b$$

EVALUATION OF TABLET

- **Uniformity of thickness:**

To determine the uniformity of thickness random selection of tablets has to be done from each and every batch and need to measure its thickness independently. If the thickness of any single tablet varies then the batch containing that batch will not be dispatched into market. [8]

- **Weight variation test**

The weight variation test would be a satisfactory method for determining drug content uniformity of drug distribution. In practice this test is performed by taking 20 tablets, from a batch. 20 tablets are weighed at a time and the average weight is taken. Then the tablet is weighed individually.

Average Weight	Percentage Difference
130 mg or less	10
More than 130 mg through	7-5
More than 324 mg	5

- **Thickness and diameter**

The thickness of individual tablets is measured with a micrometer, which gives us information about the variation between tablets. Tablet thickness should be within a ±5% variation of a standard value.

- **Hardness and friability**:

To perform this test tablets are located between two anvils and force is applied to the anvils, and the strength required to break the tablet is noted. If the tablet is too hard, the disintegration time is long and cannot meet up the dissolution specification, if it's too soft, it cannot withstand handling when dealing with processes such as coating or packaging and shipping operations. The force with which the tablet is broken is expressed in kilograms and a hardness of 4Kg is usually well thought-out to be the minimum for satisfactory tablets. Oral tablets have a hardness of 4 to 10 kg but, hypodermic and chewable tablets have a hardness of 3 kg and sustained release tablets have about 10-20 kg.

Friability is the tested for a tablet to see whether the tablet is stable to abrasion or not, it is tested by using Roche friabilator. This is made up of a plastic drum fixed with a machine which rotated at 25 rpm for 100 revolutions. And then the twenty tablets which were weighed prior to the test are taken out of the drum and cleaned with a cloth and weighed once again, the weight variation must not be less than 0.5 to 1.0% for a conventional tablet.

- **Disintegration:**

The disintegration apparatus consists of 6 glass tubes with a 10 number mesh at the bottom, each tube is 3 inch long. This arrangement of 6 tubes is placed in a medium simulated to the disintegration environment. Which is maintained at 37℃ +/- 2℃, in 1 liter vessel. This system is made to move up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. The disintegration time of the tablet is compared with the values in the monograph.[12]

- **Dissolution:**

Tablet dissolution: Disintegration time determination is a useful tool for production control, but disintegration of a tablet does not imply that the drug has dissolved. A tablet can have a rapid disintegration time yet be biologically unavailable. The dissolution rate of the drug from the primary particles of the tablet is the important factor in drug absorption and for many formulations is the rate-limiting step. Therefore, a dissolution time is more indicative of the availability of a drug from a tablet than the disintegration test. The rate and extent of drug release form the tablet is estimated by dissolution test. Different types of apparatus are used to study the dissolution test of the tablet. As per IP apparatus I (paddle) and apparatus II (basket) are used called basket dissolution apparatus and paddle dissolution apparatus.

CONCLUSION

Excipients play a significant role in the final product of pharmaceutical solid dosage form. In the last decade, lignin based polymer has been widely explored in different applications such as drug and gene delivery, tissue engineering, food science, water purification, biofuels, environmental, pharmaceuticals, nutraceutical, catalysis, and other interesting low-value-added energy applications[23,24]. Tremendous progress has been made in drug delivery and tissue engineering in recent years. Lignin based polymer has an excellent physicochemical property, along with other important properties such as biocompatibility, biodegradability, renewable nature, feasibility to form nanoparticles, and encapsulation of drugs, which makes it a promising candidate in drug delivery and tissue engineering applications. Lignin can be utilized in ROS responsive carriers to deliver drugs against inflammatory bowel diseases. There is a great scope for researchers to explore lignin-based polymers use in other control and targeted drug delivery, tissue engineering, and other biomedical application.[25]

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