Review Article

Cellulosic Porous Materials For Pharmaceutical Applications

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10.18579/jpcrkc/2017/16/4/118896

ABSTRACT
In recent year's cellulosic porous materials are widely used in drug delivery. It consists of numerous micro-fibrils containing crystalline and amorphous regions, which represents high tensile strength and provide flexibility. Striking advantages like the cost effective, low density, highly porous, high drug loading, safety, good potential for chemical modification and biocompatibility, made it an interesting polymer for applications in the field of biotechnology and nanomedicine in future. This review summarise the sources, isolation, properties, chemistry, characteristics, methods for size reduction and applications of cellulosic porous materials for pharmaceutical applications. Cellulose fibers have huge potential as a carrier for drug delivery in terms of patentability, scalability, and industrial application because of several characteristics properties and currently most of the researchers only focus on application in the field of material science and electronics. Outcomes of this review help to understand the concept of porous material used in drug delivery, explore natural cellulose fibers as a promising carrier and also needful for the researcher working in the field of pharmaceutical sciences.

Keywords: *Porous material, carrier, characteristic properties, drug delivery.*

Received on: 13/10/2017
Revised on: 14/11/2017
Accepted on: 22/12/2017

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INTRODUCTION

Recently, natural fibers have gained a lot of attention due to popularity as food ingredients, health benefits and most important for the socio-economic growth of rural areas in many developing and underdeveloped countries [1,2]. The natural fiber restrains crystalline and amorphous region; the crystalline region represents high tensile strength whereas amorphous regions provide flexibility [3]. The natural fiber having striking advantages such as cost effective, low density per unit volume, ease of separate, biodegradable nature, highly porous and high specific strength [4]. Natural cellulose fibers contain numerous microfibrils, which provide strength. Structurally, microfibrils have a high surface area and the capillary space between these fibrils works like a "sponge" and can trap water and oil[5], which enhanced the solubility and dissolution rate of poorly water-soluble drug[6].

SOURCES OF CELLULOSE

Cellulose is an important structural component of the primary cell wall of green plants, many forms of algae and the oomycetes [7]. Bacterial cellulose is a biopolymer synthesized in large quantity by *Gluconacetobacter xylinus* in a pure form, which requires no more intensive dispensation to remove unwanted impurities and contaminants such as lignin, pectin, and hemicellulose. [8,9].

HISTORY AND ISOLATION OF CELLULOSE FIBERS

In 1838, the French chemist Anselme Payen, isolated cellulose by subjecting various plant tissues to acid and ammonia treatments followed by water extraction [10]. Cellulose is one of the most abundant biopolymers on earth, occurring in higher plants, certain types of bacteria, algae, fungi, tunicates and such organisms[11]. The equatorial orientation of the hydroxyl group together with the linear structure of cellulose results in both intermolecular and Intramolecular hydrogen bond showing the sheet-like structure and crystalline form [12]. Microfibrils formed by the cellulose molecules stack together and make up the fibrils, which gives the cellulose fibers. Hydrophilic property of the polymer is a result of hydroxyl groups which makes it readily absorb water[13]. Owing to multiple properties such as hydrophilicity, high mechanical strength, good potential for chemical modification and biocompatibility, this materials is used for applications in biotechnology and biomedicine [9]. Method for isolation of cellulose fibers in (fig.1) involves the primary treatment grinding, chemical treatment and vigorous processing to obtain the fibrous product[14].

CHEMISTRY OF CELLULOSE

Cellulose is a carbohydrate homopolymer containing β-D-glucopyranose units joined together by β-1,4-glycosidic linkages. Cellulose has long and unbranched chains caused by -CH2OH groups alternating overhead and below the plane of rings. The absence of side chains cellulose molecules forms organized structures [15,16]. The porous material consists of atoms linked by chemical bonds and voids space between them. Atoms linked together by bonds that are stronger than van der Waals bonds (i.e. covalent, partially array ionic/covalent, metallic and hydrogen bonds), is considered to constitute the host. The voids space between the linked atoms are in three directions which are, at least approximately, orthogonal, they have a free diameter of more than 2.5 A0 [17].

Properties of cellulose

Properties of cellulose which are used for pharmaceutical applications are

High adsorption capacity:

High adsorption capacity of material having porous nature and its fundamental properties that affect this parameter are a specific surface area, surface chemical nature, and pore size. These parameters determine how much adsorbates can be accumulated per unit mass of absorbents[18].

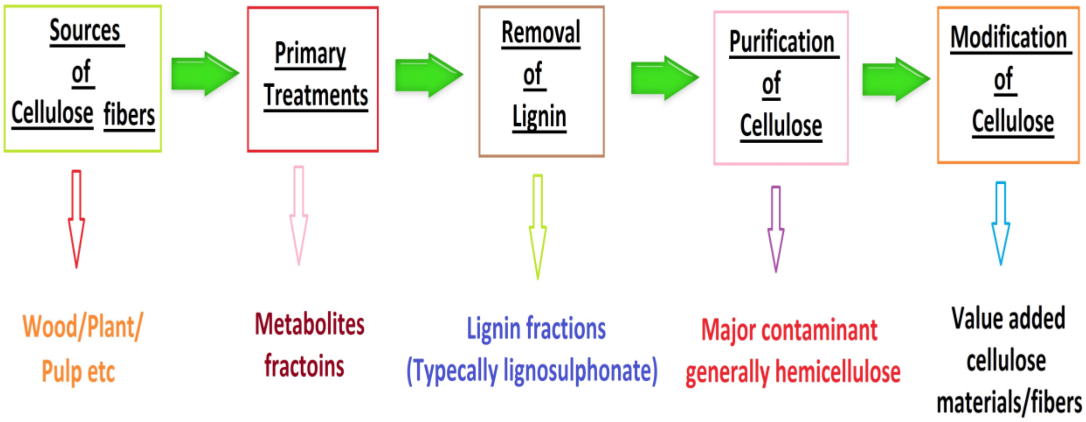
High selectivity

Selectivity is highly desired for separation in the multicomponent mixture. The selectivity of an adsorbent will depend on the pore size, shape and pore size distribution as well as the nature of the adsorbate components[18].

Favorable adsorption kinetics

Adsorption kinetics is determined by the particle (crystallite) size, the macro, meso and microporosity of the adsorbent. Favorable adsorption kinetics means that the adsorption rate is fast or controllable depending on the requirement of a particular application[18,19].

Figure 1.General method for isolation of cellulose fibers



Excellent mechanical properties

Adsorbents need to be mechanically strong and robust enough to stand attrition, erosion and crushing in adsorption columns or vessels. High bulk density, crushing strength, and attrition resistance are desirable[18].

Good stability and durability in use

Adsorbents are often subjected to harsh chemical, pressure and thermal environments. Good stability in these environments is essential in ensuring long life or durable utilization[18]. As synthesized nanoporous materials may or may not have all these desirable properties depending on the synthesis systems, methods and processing conditions[20].

2. CELLULOSE BASED NANOMATERIALS

In this era of nanotechnology, nano-cellulose has plenty applications. Nanomaterials consist of cellulose fibrils or crystallites with at least one dimension on a nanoscale. It combines the distinctive cellulose properties with the high specific surface area and high aspect ratio. Cellulose nanofibers (CNF) also referred to as nano-cellulose, nano-fibrillar cellulose nanocrystalline cellulose, cellulose nanowhiskers [21] have been used in recent times to engineer as novel materials. The current regulatory efforts and standardization for this nano cellulose is a witness of rapidly evolving activity in the field of biomedicine. Marchessault and co-workers in 1959 demonstrated that colloidal suspensions of cellulose nanocrystals exhibited nematic liquid crystalline alignment[22], while the discovery of spectacular improvements in the mechanical properties of nanocomposites with cellulose nanocrystals. Substantial research has been aimed to cellulose nanocrystal composites because of the growing interest in fabricating materials from renewable resources [23,24]. Crystalline nanoparticles of cellulose exhibit attractive properties as nanoscale carriers for bioactive molecules in nanobiotechnology and nanomedicine. For applications in imaging and drug delivery, the surface charge is one of the most important factors affecting the performance of nanocarriers. However, current methods of preparation offer little flexibility for controlling the surface charge of cellulose nanocrystals, leading to compromised colloidal stability under physiological conditions [25]. As the cleaving on cellulose chains occurred randomly during the acid hydrolysis process, the dimensions of NCC are not uniform[26]. Nanocellulose is also called as micro-fibrillated cellulose (MFC), is a material, which is composed of nanosized cellulose fibrils that have got the high length to width ratio, known as Aspect ratio. Most typical dimensions range from 5–20 nanometres width and length can range up to several nanometers. It shows pseudo-plastic behavior and poses the property of certain gels that are viscous under normal circumstances. When the shearing forces are impassive the gel regains greatly and affects its original state.

Advantages of nano-cellulose

Renewable resource and broad availability.

No impact of environmental pollution due to biodegradability.

No toxic by-products after combustion.

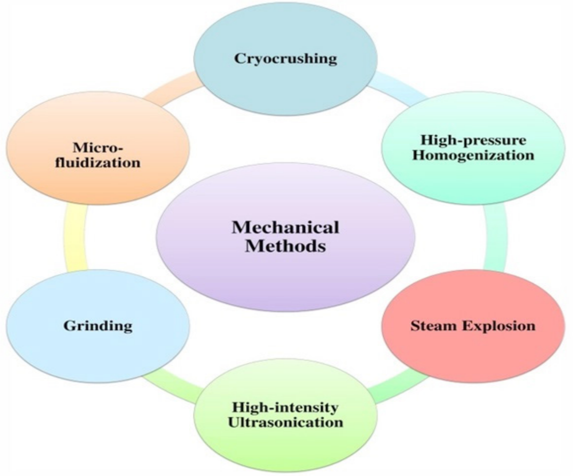
Low machine wears in processing.

Low density and high strength compared with cellulosic fillers.

METHODS OF PREPARATION OF NANO-CELLULOSE FIBERS

Cellulose consist of rich hydroxyl groups on the surface of molecules hence the major challenges in the preparation of nano-cellulose are agglomeration, absorption of atmospheric moisture, poor compatibility among polar cellulose nanofibrils and a polar polymer matrix[27]. In vascular plants, cellulose is synthesized at the plasma membrane by Rosette Terminal Complexes (RTCs). The RTCs are hexameric protein structures, approximately 25 nm in diameter, that contain the cellulose synthase enzymes which synthesized the individual cellulose chains [28]. Depending on the source and processing techniques used to attain the material, nano-cellulose properties such as fiber dimensions and surface charge can vary greatly. Cellulose is composed of aggregated micron-sized microfibrils within the fiber while cellulose fibers were rapidly expanded in the surface area and grew into their sub-structural microfibrils by mechanical action and heat[29]. The most common source of nano-cellulose includes wood-based fibers[22]. Nanocellulose obtained from native fibers by an acid hydrolysis, results to highly crystalline and rigid nanoparticles and they are shorter from 100 to 1000 nanometers than the nanofibrils obtained through the homogenization route. The length-to-diameter (*L*/*d*), is a major factor that controls the mechanical properties of nanocomposites and determines the percolation threshold value called *Geometrical Aspect Ratio,* this factor is related to the original cellulose fibers. Fillers with a high aspect ratio give the best reinforcing effect[30]. Nanocrystalline cellulose derived from acid hydrolysis of native cellulose possesses different morphologies depending on the origin and hydrolysis conditions. NCCs are rigid rod-like crystals with diameter in the range of 10–20nm and lengths of a few hundred micrometers e.g. crystallites from tunicates and green algae have lengths in the range of a few micrometers and crystallites from wood and cotton have lengths of the order of a few hundred nanometers, while some spherical shape NCCs were also produced during the acid treatment [21,31]. There are various approaches to extraction to obtain CNF. It can be performed by mechanical techniques depicted in Fig. 2. also, different acid, alkali and enzymatic hydrolysis can be utilized before mechanical processes in order to promote the accessibility of hydroxyl groups, increase the inner surface, alter crystallinity and break cellulose hydrogen bonds.

Figure 2. Methods of nano-cellulose fibres



Mechanical treatments

Inter-fibrillar hydrogen bonds break in cellulose fibers by mechanical force. However, the mechanical methods exhibit high production costs, they are also less efficient and require greater energy than the chemical methods [32].

Microfluidization

Microfluidization in z-shaped chambers (geometrically fixed microchannels) under a high pressure up to (~30,000 psi). Microfluidizer generates CNFs with several micrometers in length and less than 100 nm in diameter [33].

High-pressure homogenization (HPH)

Nanocellulose fibers were prepared at high pressure and low velocity and exposed to a pressure drop to atmospheric condition while the valve opens and closes in a cyclic motion at a temperature of 70–80°C [34].

Grinding

The breakdown of cell wall structure in cellulose by shear forces and due to generated heat in ultrafine grinder where the upper stone is fixed and the lower stone is rotating at 1400–1500 rpm [35].

Cryocrushing

Nanocellulosic fibers were prepared in liquid nitrogen under high shear and impact forces. As a result, ice crystals exert pressure on the cell walls, causing them to rupture [36]

High-intensity ultrasonication

The hydrodynamic forces of ultrasound developed high intensive waves leads to generate microscopic gas bubbles expand and implode breaking down cellulose fibers [31,37].

Steam explosion (hydrothermal process)

The generation of shear forces rapid explosion under high pressure of steam for short periods of time, which hydrolyze the glycosidic and hydrogen bonds between the glucose chains [38].

3.8. Enzymatic hydrolysis

An enzyme (*Trichoderma reesei* and *A. Xylinum*) is used to modify or degrade the lignin and hemicelluloses, reduce the size of microcrystalline cellulose. Enzymatic hydrolysis is very costly and time-consuming process[38].
3.9. Acid hydrolysis

Acid hydrolysis of microcrystalline cellulose with a mixture of sulphuric acid and hydrochloric acid under ultrasonic treatment. [21].

APPLICATIONS

The cellulosic porous materials have undergone prompt development in recent years as auspicious biomedical materials because of their excellent physical and biological properties, like biocompatibility, biodegradability and low cytotoxicity. Recently, a significant amount of research has been concentrating toward the fabrication of advanced cellulose nanofibers with different morphologies and functional properties.

Drug delivery

The cellulose was used as the carrier for fast release, controlling the release of drug in sustained and achieves the right drug concentration. Hydrothermally treated dietary fiber used as a promising carrier for solubility and dissolution rate enhancement of Repaglinide[39]. This natural polymer can also be crosslinked into hydrogels because of its affinity toward the water. Furthermore, cellulose and cellulose derivatives pass through the human body safely, some of the derivatives can be broken down by digestive enzymes into natural metabolites in the gastrointestinal tract [40]. Recently, hydrogen peroxide (H2O2) and oxygen (O2) releasing micro-fibrillated cellulose (MFC) based nano-composited were prepared that modulate the growth of mammalian cells [41].

Nanocomposites

Nanocomposites should be well dispersed in the matrix without the formation of large aggregates that may compromise the final properties and should as much as possible exhibit a small narrow size distribution. A number of approaches have been developed to attach metal NPs onto cellulose fibers [42]. Composites were prepared from swede root MFC and different resins including four types of acrylic and two types of epoxy resins. All the composites were significantly stiffer and stronger than the unmodified resins. The main merit of the study was that it demonstrated the potential for fabricating nanocomposites with good mechanical properties from vegetable pulp in combination with the arrangement of resins [43].

Wound healing

Bio-nanocomposites were reported as a superior candidate for conventional wound-dressing materials in wound healing treatment and already commercialized in the market for topical application[44].

Tissue engineering

There has been an increasing amount of attention in the progress of nano cellulose-based biomaterials for soft tissue replacement and reinforcement[45]. Biomedical constituents for soft-tissue replacement and reconstruction applications is an important aspect of the development of medical transplants that not only have similar mechanical characteristics as the tissue it substitutes but also show improved biocompatibility, nonthrombogenic, stabilizability, durability, lifespan, lesser degrees of calcification and good processability for ease of manufacturing [46]. Although various cellulose species have been used to fabricate bio-nanocomposites containing hydroxyapatite (HA), it seems that BNC is the most promising material for potential tissue engineering, mostly because of its low cytotoxicity and high porosity. the preponderance of recent studies for tissue engineering applications has used BNC, a cellulosic material with distinctive properties among other biomaterials that are used in tissue engineering scaffolds [47].

FUTURE PERSPECTIVE

In recent year's utilization of cellulosic porous materials were used in order to improve solubility, dissolution and enhance the oral bioavailability of poorly water-soluble drugs[48]. However, highly porous natural fiber have several noticeable advantages, which makes it attractive and promising carrier in liquisolid compact for oral drug delivery research.

CONCLUSION

Cellulose fibers have huge potential as the carrier for drug delivery in terms of patentability, scalability and industrial application because of several noticeable properties. There should not be any obstacles for commercialization of the technology and have GRAS status represent safety for administration with reported nutritional values used in disease conditions like diabetics, obesity etc. The cellulosic porous material can be fabricated with tailor-made properties and an available external surface can be modified for several applications not only in field pharmaceutical sciences but also in biomedical, nanomedicine, material science, electronics etc.

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