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polymers Review

2**Nanocelluloses: Sources, Pretreatment, Isolations, Modification, and Its Application as the Drug Carriers**

2**Valentino Bervia Lunardi** 1 , **Felycia Edi Soetaredjo** 1,2, **Jindrayani Nyoo Putro** 1, **Shella Permatasari Santoso** 1,2, **Maria Yuliana** 1, **Jaka Sunarso** 3, **Yi-Hsu Ju** 4,5 and **Suryadi Ismadji**

1,* ?????????? ??????? Citation:

16**Lunardi, V.B.; Soetaredjo, F.E.; Putro, J.N.; Santoso, S.P.; Yuliana, M.; Sunarso, J.; Ju, Y.-H.; Ismadji, S. Nanocelluloses: Sources, Pretreatment, Isolations, Modification, and Its Application as**

the Drug Carriers. Polymers 2021, 13, 2052. https://doi.org/10.3390/ polym13132052

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/). 1 Department of Chemical Engineering, Widya Mandala Surabaya Catholic University, Kalijudan 37, Surabaya 60114, Indonesia; valentinolunardi70@gmail.com (V.B.L.); felyciae@yahoo.com (F.E.S.); jindranyoo@yahoo.com (J.N.P.); shella_p5@yahoo.com (S.P.S.); mariayuliana@ukwms.ac.id (M.Y.) 2 Department of Chemical Engineering, National Taiwan University of Science and Technology, No. 43, Section 4, Keelung Rd, Da'an District, Taipei City 10607, Taiwan 3 Research Centre for Sustainable Technologies, Faculty of Engineering, Computing and Science, Swinburne University of Technology, Kuching 93350, Sarawak, Malaysia; jsunarso@swinburne.edu.my 4 Graduate Institute of Applied Science, National Taiwan University of Science and Technology, No. 43, Section 4, Keelung Rd, Da'an District, Taipei City 10607, Taiwan; yhju@mail.ntust.edu.tw 5 Taiwan Building Technology Center, National Taiwan University of Science and Technology, No. 43, Section 4, Keelung Rd, Da'an District, Taipei City 10607, Taiwan * Correspondence: suryadiismadji@yahoo.com; Tel.: +62-31-389-1264 Abstract: The 'Back-to-nature' concept has currently been adopted intensively in various industries, especially the pharmaceutical industry. In the past few decades, the overuse of synthetic chemicals has caused severe damage to the environment and ecosystem. One class of natural materials developed to substitute artificial chemicals in the pharmaceutical industries is the natural polymers, including cellulose and its derivatives. The development of nanocelluloses as nanocarriers in drug delivery systems has reached an advanced stage. Cellulose nanofiber (CNF), nanocrystal cellulose (NCC), and bacterial nanocellulose (BC) are the most common nanocellulose used as nanocarriers in drug delivery systems. Modification and functionalization using various processes and chemicals have been carried out to increase the adsorption and drug delivery performance of nanocellulose. Nanocellulose may be attached to the drug by physical interaction or chemical functionalization for covalent drug binding. Current development of nanocarrier formulations such as surfactant nanocellulose, ultra-lightweight porous materials, hydrogel, polyelectrolytes, and inorganic hybridizations has advanced to enable the construction of stimuli-responsive and specific recognition characteristics. Thus, an opportunity has emerged to develop a new generation of nanocellulose-based carriers that can modulate the drug conveyance for diverse drug characteristics. This review provides insights into selecting appropriate nanocellulose-based hybrid materials and the available modification routes to achieve satisfactory carrier performance and briefly discusses the essential criteria to achieve high-quality nanocellulose. Keywords: drug delivery; drug release; functionalization; nanocellulose 1. Introduction Drug delivery technology (DDT) is a cutting-edge applied science for delivering drugs to specific targets. This technology regulates the absorption and release of therapeutic drugs via various drug carriers

to the desired organs, including subcellular organs, tis- sues, and cells, to improve human health [1]. DDT has advanced rapidly in the past few decades, enabled by various discoveries in various fields, including pharmaceutical, materials, and biomedical sciences. DDT development aims to improve therapeutic drugs' pharmacological activity and overcome various disadvantages of conventional therapeutic drugs such as drug agglomeration, biodistribution deficiency, low bioavailability, limited solubility, and insufficient selectivity to prevent the concurrent effects of therapeutic drugs. Polymers 2021, 13, 2052. https://doi.org/10.3390/polym13132052 https://www.mdpi.com/journal/polymers The majority of research studies on drug delivery technology revolve around de- veloping materials suitable for drug delivery with desirable characteristics such as high drug adsorption capacity, targeted drug administration, controlled release, biocompati- bility, and non-immunogenic and non-toxic effects that optimize therapeutic efficacy and eliminates side effects [2]. Many engineered nanomaterials have been studied for drug delivery applications [3]. Some nanomaterials have recently been undergoing development and clinical investigation; however, each nanomaterial has its various characteristics and limitations, challenging the researcher in creating a suitable drug delivery system. Natural-based polymers have drawn considerable attention as suitable biomateri- als for numerous applications in drug delivery systems. Various nature-based

4**polymers such as** polysaccharides (**cellulose**, chitosan, **hyaluronic acid**

, pectins, alginate, cellulose ethers), proteins (silk fibroin and collagen), and peptides have been identified as promis- ing biomaterials for drug delivery systems given their biocompatibility, processability, and characteristics (e.g., nanoparticles, hydrogels, aerogels, tablets, and so on) that can be regulated by modifying various polymer functional groups such as amino groups, carboxyl groups, and hydroxyl groups [4]. The current development of these mentioned various polysaccharides, proteins, and peptides for

4**drug delivery systems have been** well-**reviewed**

elsewhere [4–7]. Several natural polymers have been shown to have a higher affinity for cell re- ceptors and modulate cellular processes such as adhesion, migration, and proliferation. These advantages make these natural polymers attractive for effective and high-efficiency drug delivery systems [8]. They can also be degraded in the presence of in vivo en- zymes, which ensures their ability to create responsive local delivery systems. However, only polysaccharides and proteins have been extensively studied in drug delivery systems (DDS). These natural polymers have unique characteristics in each tissue and have identical characteristics in the extracellular skeleton. These characteristics support these natural polymers' utilization as drug carriers with insignificant invasive features [9–11]. Cellulose is the most abundant and commonly found natural polymer [12]. Its an- nual production is estimated at more than 7.5·1010 tons [13]. As a promising fuel and chemical precursor, cellulose has been widely utilized in various industries such as textile, pulp, paper, composite, and pharmaceutical excipients [2]. However, the development of cellulose-based materials as a direct molecule controller for drug adsorption and release had not been evaluated until the discovery of nanocellulose, which became a turning point for using carbohydrate-based nanomaterials in the field of drug delivery [14,15]. As illustrated in Figure 1, the publication on nanocellulose for biomedical engineering applications increases every year, especially for drug delivery applications. The increase in the number of publications on the utilization of nanocellulose for drug delivery systems is a strong indication of the potential application of this material in the future. The rapid development of nanotechnology and materials science has brought about nanocellulose as a potential drug carrier because of its extraordinary physicochemical and biological characteristics. Nanocellulose has a large surface-area-to-volume ratio, thus enabling more significant adsorption and therapeutic drug-binding capacity than other materials. With these properties, nanocellulose can facilitate drug release mechanisms and allocate drug delivery precisely to the target to drastically reduce drug consumption, leading to improved drug delivery system effectiveness [16,17]. Nanocellulose additionally exhibits other attractive characteristics

15**such as** stiffness, **high mechanical strength**, biocompatibility, **low**

toxicity, lightweight, tunable surface chemistry, and renewability [11,18],

15**which are** desirable **for the design of advanced drug delivery**

system. Polymers 2021, 13, x 3 of 49 (a) (b)
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engineering, drug delivery, tissue engineering, wound healing, implants, Antibacterial/antimicrobial, and
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intratumoral administration, transdermalddrruugg delivery, topical administration, and local drug delivery.
This review

> 7**provides a comprehensive overview** ooff **the** preparation procedures ooff **nanocellulose and the**

various effects on drug formulation and delivery. Three types ooff nanocelluloses and a brief description of
their synthesis processes are discussed aattthe beginning of this review.
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various agricultural wastes with high cellulose content were explored as a
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> 26**hydroxyl groups** in **the repeating** chemical **structure of** the **β-D-glucopyranose**

unit. In the same chain, these

> 4**hydroxyl groups can make hydrogen** bonds with **the**

adjacent β-D-glucopyranose units. At different Each cellulose monomer contains three reactive

> 26**hydroxyl groups** in **the repeating** chemical **structure of** the **β-D-glucopyranose**

unit. In the same chain, these

> 4**hydroxyl groups can make hydrogen** bonds with **the**

adjacent β-D-glucopyranose units. At differ- ent chain locations, the bonds present are intramolecular and intermolecular hydrogen bonds responsible for the crystal arrangement, determining the cellulose's physical char- acteristics. Based on molecular orientation and hydrogen network between molecules and intramolecular, cellulose is classified into different types, i.e., I, II, III, IIII, IIIII, IVI, and IVII. For details about the classification of cellulose, the reader can refer to the work of Moon et al. [34]. Some of the cellulose characteristics are mainly represented by hydrogen linkage coordination [35,36]. Structurally, the

> 4**cellulose is a linear** chain **polymer with a** rod-**like**

configuration, aided by the glucose residues' equatorial conformation that is intensely aggregated together with the lateral size 3–5 nm [36]. Primary chains of cellulose, especially polysaccharide chains, are found on the secondary walls of plants arranged in a parallel configuration. The cellulose's basic fibers have a cross-sectional diameter between 10–450 nm with a length of several micrometers that depend on the diversity of material sources [37]. Moreover, the elementary fibrils were arranged into large pack units called microfibrils, further foregathered into fibrils [13]. There are regions within the cellulose fibrils where the cellulose chains are organized into a highly crystalline structure with a length of 50–150 nm and disordered amorphous regions with 25–50 nm [34]. The cellulose chains construct the crystalline regions through Van der Waals forces, strong intra- and intermolecular hydrogen linkage, and

> 22**β-1,4-glycosidic bonds. In**

contrast, amorphous regions are built up through the deficiency of hydrogen bonds in the crystalline region. The crystalline and amorphous regions in cellulose may vary depending on various sources. The crystalline constituent within cellulose fibers can be refined through various chemical treatments by destructing and removing the disordered amorphous or para- crystalline regions. The purified crystal fragments with particle sizes on the nanometer scale are called nanocrystalline cellulose (NCC) (Figure 3). Different shapes of NCC are present such as needle and elongated rod-like shape or spindle-like shape with high stiffness of crystalline fragments [38], which are reported as cellulose whisker [39], nanowhisker [40], nanorod [41], and spherical nanocrystal [42]. Polymers 2021, 13, x 6 of 49 Figure 3. Schematic representation nanocrystalline cellulose fabrication by chemical treatment ((a) transmission electron
mFiigcurorsec3o.pSych(TeEmMat)icimreapgreesseonftarotido-
nlikneancoeclIruylsotsaellinnaencoeclrluylsotaselsf[a3b8r]i,caretiporninbtyedchweimthicpaelrtmreiastsmioenn;tt(r(aan)stmrainsssmioinsseiloencterloenctrm

> 15**microscopy (TEM) images of rod-like** cellulose **nanocrystals** [38], **reprinted with permission**

; transmission electron micros- ccroopscyo(pTyE(MTE)Mim)aimgeasgoefs
coeflcluelllousleosneannaonwohwishkisekrerreprerpinritnedtedwwithithpepremrmisisisisoinonfrfforomm[2[255].].CCooppyyrirgighhtt
©22001199EEllsseevviieerr BB..VV..;; ((bb)) transmission electron microscopy (TEM) images ooff spherical
cellulose nanocrystal reprinted with permission from [43]. Copyright © 2018 Elsevier B.V.). Attoopp--
ddoowwnnpprroocceessssshhaassbbeeeennaapppplliieeddffoorrNNCCCCpprroodduucctiioonniinnwwhhiicchhallaarrggeeuunniittooff
cceelllluulloosseefifibbeerrss((ccmm))iissddiissiinnteeggrraatteeddtthhrroouugghhcchheemmiiccaalloorrmmeecchhaanniiccaallttrreeaattmmeennttiinnttoos
uunniittssooffnnaannooccceellllluulloossee((nnmm))
[[4444]]..NNCCCC"sscchheemmiiccaallssttrruucctuurreeiisscconnssttrruucctteeddbbyyiinnttrraa--aanndd
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sloosuercseosu,wrcietsh,twheithdiathmeedteiramanedtelrenagntdhlteynpgictahlltyypvaicraylilnygvbaertywinegenb5etawnede3n05nmandan3d0bnemtweae
1b0e0twaneedn510000namnd,r5e0s0pencmti,vreelsyp[e4c6t]iv.eTlyhu[4s,6]N.TChCussh,NavCeCbsehcoavmeebaencoamtteraacntivaettrcaacntidviedaca
drug carriers, given their outstanding physical and chemical properties [21,47,48]. date as drug carriers,
given their outstanding physical and chemical properties [21,47,48].

> 11**Cellulose nanofiber (CNF), also known as cellulose**

nanofibril, micro-fibrillated cellu-

11**Cellulose nanofiber (CNF), also known as cellulose**

nanofibril, micro-fibrillated cel- lose,

4**nano-fibrillar cellulose, nano-fibrillated cellulose**

, or cellulose microfibril, has a similar lulose,

4**nano-fibrillar cellulose, nano-fibrillated cellulose**

, or cellulose microfibril, has a molecule structure to NCCs with nano-size particles. Similar to NCC, CNF can also be pro- similar molecule structure to NCCs with nano-size particles. Similar to NCC, CNF can Polymers 2021, 13, x 7 of 49 also be produced from various cellulose sources. However, the morphology and crystal- linity of NCC and CNF are the unique features that differentiate these two cellulose-based cdoumcpedoufrnodms. vCaNrioFusshcaevlelulloonseg,sofluerxciebsl.e Hceolwluelovseer, cthheaimnsoropfhaomloogryphaonudscraynsdtaclIriynsittaylloifnNeCreC- gainodnsCiNsoFlaatered tfhroemuncieqlulуelofesaetufirbersiltshtahtrdouifgfehremneticahteanthiceasletrtweaotmceelnlutl(oFsieg- ubraese4d)[c4o6m].pTohuenddi-s. aCmNetFesr hoafvCeNloFnsgv,aflreiexsibflreomcel1lutloo1se00chnamin,swohfialemthorepirhloeunsgtahndvacrriyesstbaelltiwneeerneg5i0o0nsanisdol2a0t0e0d nvfmraor.mieTscheferloldumilmo1seetnofis1bio0rn0ilsnomtfh,CrowNuhFgislhemmthoeeclierhclauennliegcsathlistvrsaetarritoemnsgebnleyttw(iFneifeglnuue aonfdCdNeFfisbrmilolaleticounle[s49is].strongly influenced by mechanical treatment and defibrillation [49]. FFigiguurree44.. SSchchemematitcicrerepprereresesnentattaitoionnooffcceelllululolosesennaannoofifibbeerrssfafabbrricicaatitoionnbbyy mmeecchhaannicicaall ttrreeaattmmeenntt (scanning electron microscopy (SEM) images ooffmmicircorofibfirbilrlialltaetdedcecIleullluosloesreepreripnrtiendtewditwhitpherpmerismsiiosn- sfiroonmfrroemf.[5re0f].; [C5o0p];yCriogphytr©ig2h0t0©7E2l0s0ev7iEerlsLetvdi.e;rscLatndn.;inscgaenlencintrgonelmecitcrroonscmopicyr(oSsEcMop)yim(SaEgMes)oifmcaelgluesl cneallnuolofisbeenrsanreopfirbinetresdrewpirtihntpeedrmwiitshsiopnerfmroimssiroenf.f[r5o1m]. rCeof.p[y5r1i]g.hCto©py2r0i0g6hEt©lse2v0i0e6r LEtldse.)v.ier Ltd.). NCC has high crystalline cellulose purity, resultingiinn a rigid structure, whereas the CNF structure consistsooff irregular amorphous parts, with some parts exhibiting a high degreeooff crystallinity.ThTehe amorphoursegreiogniosnisn iCnNCFNcFonctornotlrtohlethsterustcrtuucrteufrleexflibeixliibtyiliotfy of nanocellulose [52]. Figure 4 presents an illustration of CNF extracted from cellulose fragments via mechanical defibrillation. The exerted force fractures the cellulose fibrils Polymers 2021, 13, x 8 of 49 nanocellulose [52]. Figure 4 presents an illustration of CNF extracted from cellulose frag- ments via mechanical defibrillation. The exerted force fractures the cellulose fibrils along ailtosnlognigtsitluodnigniatluadxinisa[l3a4x].isC[o3m4]p.aCroedmwpaitrhedNwCiCth,CNNCFCe,xChNibFitesxuhniibqiutseupnrioqpueertpiersopsuercthieas seuxcthenadseedxtleenndgethdwleinthgtehxwceiltlhenetxacesplleecnttparsoppecotrtpioronp(olerntigotnh(tloendgitahmteotedri)a,msuepteerr)l,astuivpeesrl saurrefaa,cheyadrerao,phhyidlicroitpyh,ibliiocictoy,mbpioactoibmilpitayt,ibainlidtya,dajnudstaadbjluescthabalreaccthearrisatcitcetrhisrtoicutghhrosuugrfhacs modificat[io53n].[53]. Microbial cellulose (MC), bacterial nanocellulose (BC), and bio-cellulose (BC) have been used as the other terms fofrobrabcatectreiaricaelcleulllousleos(eBC(B).CIn).clonnctoransttrtaostNtCoCNaCnCd aCnNdFC,BNCF',s BsCtr'uscstturruectcuormepcorimsepsrsiusegsasrusgwairtshwloitwh mlowolemcuollaercuwlaerigwhte.igMhatn.Mybaancytebraiactsetrriaainstsrahianvsehbaeveen bueseendutsoedgetnoergaetneeBraCteaBsCanasexatnraecxetlrlualcaerllumlaertamboeltiacbporliocdpurcot,dsuucct,hsauschGlauscoGnlaucceotnobaacce bSaacrtceirn,aS,aArceirnoab,acAteerrioab,aEctsecrhiear,iaE,sAchcehrrioam,Aobcahcrtoemr,oRbhaicztoebr,iuRmh,izRohboiudmob,acRthero,dAobzaoctto arnodbaActgerroiubmact[e5r4iu,5m5] [.5H4,5o5w].eHveorw,oenvleyr,GonlulycoGnalucectoonbaaccetteorbaxcytleirnxuyslihnaussbheaesnbeceonmcmomermciaelrlcyiaulltyi- utilizetdo tporopdroudceucBeCBoCnoann ainndiunsdtruisatlrsiaclalseca[2le7][.2T7h].e Tbhacetebraicatestrriaainstsraairnescaormemcoomnlmyoinncluy- waiirth)aasira)naesxaonpoexlyospaocclyhsaarcidche.aIrnidteh.isIncatshei,stchaesβe,-Dth-geluβc-Dop- gylruacnoopsyeruanniotssearueniintsitiaarlelyinpirteiaslelnyt incubatedniuntrnieuntrt-ierincth- raicqhueaoquuseomuesdmiaeadniad apnrdodpurcoedBuCceoBnCthoenuthpepeurplpaeyrerla(yinetre(rifnatceerfwaciteh pdruesreinngt dthuerignrgowthtehgorfocwetlhluolofsceelmluololesceumleoslweciuthleins wthiethbianctttheeriablaccetellr.iaTlhceeelll.eTmheenetalermyefinbtrairlyis firberleilaissedrealecarsoesds tahceropsosrtehseopfothreescoefIltuhleosceelsluurlofascees,uwrfhaicceh,wwahsicfhurwthaesrfaurrrtahnegreadrraanndgecdryasntadl- clrizyesdtalilniztoedmiincrtoofmibircirlsofiwbirthilstwwiistthintgwrisibtibnognrsibshbaopnes fsohlalopweefodllboywpeedllbicylepfeolrlimclaetifoonrm(Faitgiounre (5F)ig[u56re]. 5T)h[e56f]a.bTrihceatfeadbrBicCatceodmBpCricsoesmaprniasensofaibnearnsoffirabmereswfroarmkewwitohrka wdiiathmaetdeiraomfe2t0e–r1o0f0 2n0m– 10w0inthmawleitnhgathleonfgtshevoefrsaelvmeriaclrommicertoemrseatenrds aanldaraglearsguerfsaucrefaacreeaarecaomcopmopseodsemdaminaliynlyof owfawtearte(r99(9%9)% [)5[75]7.]. Figure 5. Schematic production of bacteria cellulose through extracellular secretion (scanning electron microscopy (SEM) Figure 5. Schematic production of bacteria cellulose through extracellular secretion (scanning electron microscopy (SEM) images of 3-D dimensional network of bacteria cellulose [58], reprinted with permission; (c) scanning electron microscopy images of 3-D dimensional network of bacteria cellulose [58], reprinted with permission; (c) scanning electron microscopy (T(TEEMM))imimaaggeessbbaaccteteriaiacceellllululolosseeppeellliciclele,,rerepprirnintetdedwwitihthppeermrmisisisoionnfrforommrerfe.f[.5[95]9.]C.Coo In terms of chemical composition, BC is indistinguishable from plant-based nanocel- In terms of chemical composition, BC is indistinguishable from plant-based nanocel- lulose (e.g., NCC and CNF). However, BC has higher crystallinity (up to 84–89%) with lulose (e.g., NCC and CNF). However, BC has higher crystallinity (up to 84–89%) with fewer amorphous regions than NCC and CNF. Moreover, BC contains fewer

impurities and contaminants such as hemicellulose, lignin, and pectin, mainly found in plant-based nanocellulose. BC is a biocompatible material with non-cytotoxicity and non-genotoxicity for biomedical applications, especially drug delivery [60]. BC synthesis does not involve a complicated process such as mechanical and chemical treatment to cleave the hemicellulose or lignin within the lignocellulosic biomass, thereby allowing high cellulose purity. BC's properties can be modulated by various techniques such as substrate manipula- tion, culture condition and operation parameter, and proper bacterial strain selection [17,54]. In contrast to NCC and CNF, BC provides unique characteristics such as high crystallinity of nanocellulose (84–88%) and polymerization grade, high water uptake capacity (exceed- ing

19**100 times of its weight**), large surface area (**high**

aspect proportion of fiber), outstanding

19**tensile strength (Young modulus of 15–18 GPa**

), flexibility, foldability, moldability, mechan- ical stability, and high porosity [60]. A summary of the characteristics of various types of nanocellulose is listed in Table 1. Table 1. Summary of the characteristics of various types of nanocelluloses. Types Parameter Nanocrystalline Cellulose (NCC) Cellulose Nanofibers (CNF) Bacterial Cellulose Cellulose whisker, cellulose Common names nanowhisker, cellulose nanowire, and cellulose nanorod or spherical cellulose nanocrystals Cellulose nanofibril, micro fibrillated cellulose, Nanofibrillar cellulose, Nanofibrillated cellulose, and cellulose microfibril Microbial cellulose (MC), bacterial nanocellulose (BC), and bio-cellulose (BC) Morphological structure Needles like shape, elongated rod-like shape, and spindle shape Smooth, extended, and flexible chain Twisted ribbons like shape Structure of Nanocellulose Crystalline domains amorphous and crystalline domains Crystalline domains Chain Length ≥500 500–15,000 4000–10,000 Crystallinity (%) 54–88 - 84–88 Other Impurities and contaminant Possible to contain hemicellulose, lignin, and pectin Possible to contain hemicellulose, lignin, and pectin Contain no hemicellulose, lignin, and pectin Size (Length and Diameter) Diameter:

31**5–30 nm and** Length: **100–500 nm Diameter**

: 1–100 nm and Length: 500–2000 nm Diameter 20–100 nm and several micrometric lengths Process System Top-down system Top-down system Bottom-up system Tensile strength (Gpa) 7.5–7.7 [34] 13 0.2–0.3 Modulus Young (Gpa) 110–220 [45] Approximately 15 18–20 [60] Density (gr/cm3) 1.6 [61] 1.42 1.1 Characteristics Homogenous nanorod form, exceptional aspect ratio (length to diameter), appreciable specific surface area (SSA), biocompatibility, liquid crystalline attribute, inferior breaking expansion, high young's modulus, hydrophilicity, outstanding mechanical stiffness, tunable surface characteristic due to the reactive hydroxyl group and low density Extended length with excellent aspect proportion (length to diameter), superlative surface area, hydrophilicity, biocompatibility and adjustable characteristic through surface modification afforded by high extensive of hydroxyl groups in CNF. High crystallinity of nanocellulose (84–88%) and polymerization grade,

19**high water** uptake **capacity** (exceeding **100 times of its weight**), remarkable surface area (**high**

aspect proportion of fiber), outstanding tensile strength (young modulus 15–18 Gpa), and flexibility, foldability, moldability, mechanical stability, highly biocompatible material, non-cytotoxic, un-genotoxic and high porosity Based on the previous discussion, cellulose can be subjected to a mechanical, biologi- cal, and chemical treatment to produce three different NCs, i.e., nanocrystalline cellulose, cellulose nanofibrils, and biological cellulose. They are classified based on various aspects such as morphology, particle size, crystallinity, nanocellulose structure, extraction tech- niques, and cellulose sources [56]. Moreover, other important factors such as interfibrillar arrangement, microfibril inclination, chemical constituent, cell dimension, and defects can also vary depending on the cellulose sources [62]. Among all the mentioned character- istics, mechanical strength is essential in the drug delivery field [63]. As summarized in Table 1, NCC possesses a high modulus young, up to 220 GPa, which is higher than glass (86 GPa) [61] and kevlar KM2 fiber (88 GPa) [45]. Furthermore, the mechanical stiffness of NCC can reach up to 7.7 GPa, which is higher than 302 stainless steel (3.88 GPa) [45] and kevlar KM2 fiber (1.28 GPa) [45]. 3. Sources and Pretreatment of Raw Materials for Nanocellulose Productions In general, the production of nanocellulose (NC) consists of three steps: (1) Finding the suitable sources, (2) raw material pretreatment, and (3) NC extraction. The raw material's source and type influence the physical and chemical properties and the NC product's yield. Currently, most nanocellulose sources utilize high-quality biomass such as cotton, wood pulp, and dissolving pulp, which comprises the high cellulose content. However, in response to recent essential issues, such as the

5**depletion of non-renewable energy and** increasing global temperature, **the** researchers realized **the**

development of waste-based biomass as a feedstock for the production of nanocellulose. Various types of biomass waste, including forest residues, algae, agricultural, and industrial by-products, appear as potential

18**raw materials for nanocellulose production**. In terms **of**

chemical composition, each category of biomass waste

22**is primarily composed of cellulose**, lignin, **hemicellulose**, pectin, **and**

other minor substances with different physical and chemical characteristics [64]. Agricultural and forest residues have similarities in their chemical composition, but lignin composition in agricultural waste is significantly high, while the cellulose content in forest residues is higher than in agricultural waste [64,65]. Among all of the waste-based cellulose sources, the nanocellulose extraction from industrial waste seems more complex since the chemical and structural composition of feedstock is variable and crucially depends on the residue types. The various impurities (e.g., hemicellulose, lignin, wax, and pectin) act as a structural barrier that hinders the accessibility to the cellulose material for the extraction process [22]. Therefore, pretreatment is necessary to remove the cellulose framework's impurities, permitting the aperture of the material framework to expedite cellulose microstructure access. Moreover, removing impurities is also beneficial to reduce the consumption energy of mechanical treatment for cellulose disintegration [66]. Another objective of raw material pretreatment is to regulate the biomass structure and size and overcome the plant cell wall recalcitrance. The pretreatment is generally divided into four categories such as physical (milling, grinding, microwave, ultrasound, etc.), chemical (dilute acid, mild alkali, TEMPO medi- ated oxidation, organosolv, and ionic liquid), biological (fungi, bacterial, and archaeal), and physicochemical (steam explosion, liquid hot water, wet oxidation, etc.) [67]. The effec- tiveness of the biomass pretreatment process depends on pH, temperature, type of catalyst, and pretreatment time. Selecting the appropriate pretreatment would allow avoiding the structure disintegration or loss of cellulose, ensuring low cost, and minimizing energy use to reduce toxic and hazardous waste [68]. The chemical pretreatment process is considered the most efficient and economically feasible for the disintegration of biomass with low pretreatment severity. However, chem- ical pretreatment is non-environmentally friendly and requires a wastewater treatment process [69]. Physical pretreatment is environmentally friendly and scarcely generates hazardous or toxic substances, but the major disadvantage lies in its high energy con- sumption, which is generally higher than chemical treatment [70]. Biological treatment is widely known as an eco-friendly process, operates under mild conditions, and con- sumes a lower energy amount. However, long pretreatment duration, low conversion, and carbohydrate loss tendency throughout pretreatment remain the main challenges of biological pretreatment by the microorganism [71]. Physicochemical pretreatment using a combination of chemicals and high temperature or pressure in extreme conditions can ef- fectively escalate biomass degradation. Nevertheless, high energy input is required, which translates to high operation costs for this method. Proper pretreatment of cellulosic fibers can improve the hydroxyl group's accessibility, inner surface enhancement, crystallinity alteration, and fracture of the

4**intra and** inter **hydrogen bonds of cellulose**, leading **to** the **increased**

fibers reactivity [72]. Detailed pretreatment of cellulose-based raw materials has been thoroughly discussed elsewhere [73]. The integrated pretreatment strategy of lignocellulosic waste biomass comprising two or more pretreatment stages increases the pretreatment process's effectiveness, prod- uct characteristics, and versatility of composition in extracted cellulose. An additional process that adds more steps to cellulose purification is highly undesirable [74]. For in- stance, de Carvalho Benini [75] performed alkaline treatment coupled with multiple stages of bleaching pretreatment followed by sequential dilute acid hydrolysis to increase the efficiency of impurities removal (e.g.,

10**starch, hemicellulose, and lignin/pectins**) from **the cellulose** framework. Similarly, Wijaya **et al**. [29] combined **alkaline and bleaching**

treat- ment to obtain higher purified cellulose from passion fruit peel. In a different study, Maciel et al. [76] obtained the

10**soluble and insoluble lignin after alkaline**

treatment reached 60 and 75%, respectively. The summary of the pre-treatment strategy of waste-based nanocellulose sources is presented in Table 2. Table 2. Summary of waste-based sources for nanocellulose production and its characteristic. Waste Residue Nanocellulose Isolation Technique Sources Pretreatment Treatment Nanocellulose Characteristics References WASTE BASED FOREST RESIDUE Birch and Spruce sawdust Hot water treatment and subsequent delignification; Mechanical defibrillation TEMPO oxidation σ = 171,6 MPa; E = 6.4 Gpa; CNF [77] Medium-density fiberboard Soxhlet extraction (Ethanol NCC and toluene), NaOH, and L:164.7 nm; W: 6.7 nm; CrI (%): [78] recurrent bleaching Acid hydrolysis (H_2SO_4) 71 Eucalyptus sawdust Hot water treatment, alkaline delignification, O_2 residual delignification, High pressure TEMPO-mediated homogenization Oxidation Davg: 41.0 nm; SSA: 60 m2/g; Y CNF (%) = 60 [79] Pinecone biomass Alkali treatment followed with acidification ($NaClO_2$:CH_3COOH) Mechanical grinding. σ: 273 MPa; E: 17 GPa; CNF CrI (%): 70%; D: 5–20 nm. [80] Logging residues Alkaline and bleaching pretreatment Acid hydrolysis (H_2SO_4) NCC L/D > 10; CrI (%): 86–93; TS (◦C): 208.4–211 [81] Bamboo log chips Pretreatment with glycerol; and screw extrusion Mechanical refining/Milling treatment assisted by H_2SO_4 (0.15%) as a catalyst CNF D: 20–80 nm; CrI (%): 52.7%; Y [82] (%): 77.2 WASTE BASED ALGAE RESIDUE Cladophorales - TEMPO Oxidation; CNF W: 80 nm; SSA: 77 m2/g CrI (%): 93%; D: 80 nm; Excellent mechanical and rheological characteristics [83] NCC Red algae - Acid hydrolysis (H_2SO_4) L: 432 nm; W = 28.6 nm; L/D: 15.1; CrI (%): 69.5; Yield: 20.5%; [84] TS (◦C): 220 ◦C Green Seaweed Ulva lactuca Methanol pretreatment (Soxhlet extraction) followed by bleaching, alkaline pretreatment, and neutralization Acid

hydrolysis (H2SO4) CrI (%): 83; TS (◦C): 225 ◦C NCC [85] Industrial kelp (Laminaria japonica) waste Two stages of bleaching NCC pretreatment (Chlorine L: 100–500 nm; D = 20–50 nm; dioxide followed with Acid hydrolysis (H2SO4) L/W: 5–20; Yield: 52.3%; TS [86] hydrogen peroxide) (◦C): 240 ◦C Table 2. Cont. Waste Residue Nanocellulose Isolation Technique Sources Pretreatment Treatment Nanocellulose Characteristics References Dealginate kelp residue From Giant Kelp (Calrose variety) Na2CO3 (2% wt) treatment, residual sodium alginate extraction by NaOH (2% wt); Ultrasonic irradiation; NaClO2 (

5**0.7% wt) buffer solution bleaching treatment** and **delignification** NCC **Acid hydrolysis**

(H2SO4) L: 100–500 nm; D = 20–50 nm; (◦C): 120–180 ◦C; l = 120–480 nm L/W: 30–70; CrI (%): 74.5; TS [87] Chaetomorpha Acid hydrolysis (HCl) antennina Bleaching method followed with Ultrasonic irradiation CNF E = 0.9 Gpa; CrI (%): 85.02; Y = 34.09%; TS (◦C) = 200–370 ◦C [88] Soxhlet Extraction (Ethanol: Gelidium sesquipedale Toluene) Bleaching treatment, delignification (5% KOH solution) Acid hydrolysis (H2SO4) followed with neutralization (NaOH) NCC L: 467–1650 nm; D = 18–29 nm; [89] L/W: ~40; CrI (%): ~70%; Gelidium elegansred Alkali and bleaching pretreatment Acid hydrolysis (H2SO4) NCC L: 547.3 nm; D = 21.8 nm; L/W: [90] 25; CrI (%): 73%; TS (◦C): 334 ◦C WASTE BASED AGRICULTURAL RESIDUE Waste sugarcane bagasse NCC Acidification and alkaline Acid hydrolysis (H2SO4) L: 170 nm; D = 35 nm; h = 70–90 pretreatment nm; CrI (%): 93%; TS (◦C): [91] 249–345 ◦C

5**Jute dried stalks Alkali treatment followed by steam explosion; sodium chlorite bleaching** Acid hydrolysis (**oxalic acid) followed by steam explosion**

. CNF L: few micrometers D = 50 nm; CrI (%): 82.2%; E: 138 Gpa; TS (◦C): 250–400 ◦C [92] Coconut husk Ultrasonic-aided solvent submersion. Delignification and Bleaching Pretreatment, followed by TEMPO-mediated Oxidation (TEMPO/NaClO/NaClO2; pH = 4.8) Ultrasonication CNF (%): 56.3%; TS (◦C): 190–380 ◦C L: 150–350; D = 2–10 nm; CrI [93] Citrus waste Alkaline and Bleaching Enzymatic hydrolysis and Pretreatment ultrasonication CNF L: 458 nm; W: 10.3 nm; Davg = 10 nm; L/W: 47; CrI (%): 55%; [94] TS (◦C): 190–380 ◦C Raw rice husk Size Reduction, Soxhlet extraction (toluene and ethanol); Acidification (NaClO2 and CH3COOH); and delignification (5% KOH) High pressure

5**homogenization and high-intensity ultrasonication processes (500 W**

,40 min). CNF 77.5%; L/D > 180; TS (◦C): 323 L: 1800 nm; W: 10 nm; CrI (%): [95] ◦C One pot synthesis via Corn cobs - mechanochemical esterification σ = 110–125 MPa; E = 5.5 Gpa; CNF [96] D: 1.5–2.8 nm Delignification and three Kenaf bast fiber stage of bleaching Mechanical grinder CNF D: 1.2–34 nm; CrI (%): 82.52%; Y [97] pre-treatments (%) 60.25; TS (◦C): 200–400 Passion Fruit Peels Alkaline and bleaching Acid hydrolysis (H2SO4) pretreatment followed with ultrasonication NCC L: 103–173.5 nm; CrI (%): 77.96%; TS (◦C): 303.4; Y (%): [29] 58.1 WASTE BASED INDUSTRIAL BY PRODUCT

5**Olive industry solid waste** Pretreatment including **pulping** and **bleaching Acid hydrolysis**

(H2SO4) NCC [98]

5**Lime residues Autoclaving** pretreatment **High shear and high-pressure** CNF D: **5–28 nm**; CrI (%): **44–46**

homogenization [99] Table 2. Cont. Waste Residue Nanocellulose Isolation Technique Sources Pretreatment Treatment Nanocellulose Characteristics References

5**Recycled Tetra Pak Food Packaging Wastes** Delignification **and**

Acid hydrolysis (H2SO4) bleaching pretreatment followed with ultrasonication NCC L/D: 10; CrI (%): 94.8%; TS (◦C): L: 127–258 nm; D: 11.4–14 nm; [100] 204 Waste paper Deinking method and Acid hydrolysis (H2SO4) alkaline pretreatment followed with NCC [101] ultrasonication L: 271 nm Discarded cigarette Ethanol extraction, alkaline Acid hydrolysis (H2SO4) filters pretreatment, and bleaching pretreatment, followed with ultrasonication NCC L: 143 nm; W: 8 nm; CrI (%): [102] 96.77%; Y (%): 29.4 Recycled Paper Mill Sludge Ozonation pretreatment Acid hydrolysis (Maleic acid) NCC L: 2431 nm; W: 165 nm; L/D: 16.7 CrI (%): 77%; Y (%): 0.8 [103] Citrus Pulp of Floater (CPF) Alkaline and bleaching pretreatment with autoclave Enzymatic hydrolysis n.d CrI (%):60 [104] Sweet lime pulp waste Blending and acid hydrolysis (H2SO4)

5**Komagataeibacter europaeus SGP37** incubated in **static intermittent fed-batch cultivation**

BNC Y(g/L): CrI (%):89.6; TS (◦C): [105] 348 Abbreviation: D: Diameter; L: Length; W: Width; TS: Thermal Stability; Y: Yield; L/D: Aspect Ratio; CrI: Crystallinity Index; l: Lateral size; σ: Tensile strength; E: Young Modulus. 4. Isolation of Nanocellulose 4.1. Isolation of Nano-Fibrillated Cellulose (NFC) Regardless of its

cellulose sources, NFC is mainly fabricated from cellulose pulp through mechanical treatment by breaking down the linkage of interfibrillar hydrogen [106]. The exerted mechanical force triggers the cracking phenomenon to

> 10**form a critical tension center in fibrous** substances. **The**

development of NFC from fibrous material requires intense mechanical treatment with or without pretreatment. However, fibrous material's mechanical disintegration may cause pulp clogging, causing the fiber to agglomerate and require high energy to break it down. Thus, another pretreatment is required to overcome this problem. Several pretreatments have been introduced before the primary mechanical treatment to diminish the polymerization degree and debilitate the hydrogen linkage. These pre- treatments include mechanical refining, alkaline hydrolysis, solvent-assisted pretreatment, organic acid hydrolysis, 2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-mediated oxidation, enzymatic disintegration, periodate-chlorite oxidation, oxidative sulfonation, cationization, ionic liquid, carboxymethylation, deep eutectic solvents, and acetylation [17]. The earliest production of NFC was reported by Turbak et al. [107] and Herrick et al. [108]. They isolated NFC from wood via high-pressure homogenization (HPH). HPH exerted a mechanical force on cellulose fibrils driven by crushing, shear, and cavitational forces

> 10**in which cellulose** pulp **is** transferred **into** the chamber **through a small nozzle**

to enable particle size reduction to the nanoscale of the cellulose fibrils [72]. Currently, the HPH is the most commonly utilized method for NFC production on an industrial and laboratory scale, given its simplicity, high efficiency, and lack of organic solvent requirements [109]. Furthermore, HPH enables high conversion of cellulose material toward CNF. High energy, high pressure, and long duration of the HPH process may also escalate the fibrillation degree. However, the difficulty of cleaning the equipment due to the blockage in the homogenizer valve is the major drawback of the HPH method [110]. Different processes have also been developed to produce CNF, such as micro-fluidization, micro-grinding, cryo-crushing, ultrasonication, mechanical refining, radiation, ball milling, blending, extrusion, steam explosion, and aqueous counter collision [111]. 4.2. Isolation of Cellulose Nanocrystal (NCC) According to the previous discussion, the main

> 15**difference between** NCC **and CNF lies in their** structure, in which **CNF** comprises amorphous **and**

crystalline regions while NCC has high crystalline purity in cellulose regions. Therefore, the primary step in isolating NCC is to break down the disordered amorphous or paracrystalline regions that integrate the crystalline regions within cellulose fibrils. Initially, an NCC suspension was produced in 1949 from lignocellulosic biomass through an integrated alkaline and bleaching pretreatment and acid hydrolysis [13]. Acid hydrolysis remains the paramount process for NCC extraction. The crystalline part in cellulose fibers is not hydrolyzed because it has a high resistance to acids, although acids can easily hydrolyze the amorphous regions [112]. In this method,

> 34**sulfuric acid (H2SO4), hydrochloric acid (HCl), hydrobromic acid (HBr), and phosphoric acid (H3PO4) have been**

extensively employed as the acid component to breakdown the amorphous region of cellulose. Following acid hydrolysis, the remaining free acid molecules and other impurities should be removed by diluting and washing with water using centrifugation and dialysis processes. Moreover, specific mechanical treatment like sonication may be needed to stabi- lize the NCC particles in uniform suspensions. However, the high tendency of corrosion, low recuperation rate, and high acid wastewater produced due to the high amount of water for the washing process for nanocellulose suspension neutralization become the significant drawbacks of the acid hydrolysis process [46]. To avoid excessive equipment corrosion and environmental issue, various nanocellulose isolation processes have been developed, such as extraction using ionic liquids, TEMPO oxidation, enzymatic, and others. Various researchers have carried out the combination and integration of various isolation processes to increase the isolation process's efficiency, such as enzymatic hydrolysis with TEMPO oxidation and enzymatic hydrolysis with ultrasonication [113]. Chemical treatment is crucial for NCC isolation, while mechanical treatment is the vital stage for CNF production. 4.3. Isolation of Bacteria Cellulose (BC) The selection of strains of microorganisms is a very crucial factor in the synthesis of BC. There are currently two main methods that have been used for BC production, i.e., static fermentation and submerged fermentation [54]. Static fermentation has been widely employed as an extracellular-based production route. In the static fermentation, a 3D network of gelatinous pellicles with high water content formed during the interspersing and intertwining of the ribbons structure form of BC, reaching a particular thickness corresponding to longer incubation time and causing the entrapment of bacteria cells and its further inactivity. The static fermentation produces BC with excellent crystallinity and mechanical strength, although prolonged cultivation and low productivity limit their industrial utilization. Furthermore, the BC layer 's uneven thickness is produced due to the exposure of bacteria to uncertain conditions (nutrient, oxygen level, and cell distribution) throughout the growth cycle. Fed-batch strategies and submerged fermentation involving aeration and agitation fermentation have been introduced to overcome static fermentation's sig- nificant drawbacks. Submerged fermentation leads to higher BC productivity than static fermentation, which has been extensively utilized commercially. The cultivated bacteria are adequately exposed to oxygen, thereby generating a high yield of BC in the shape of small granules or pellets during aerated fermentation [114]. Moreover, agitation in the fermentation would result in a more homogeneous BC and oxygen evenly distributed to bacterial cells. However, the produced BC has lower crystallinity and mechanical strength than

static fermentation [115]. Several submerged fermentation issues such as the advancement of cellulose non- production strains [116], irregular shapes of BC granules or pellets, and physical character- istic modification of BC remain challenging for the researcher to overcome. In addition, excessive-high rotation speed and hydrostatic stresses may promote gluconic acid pro- duction by bacteria due to the accumulation of self-protection metabolism [117]. Several factors such as bacterial strains, fermentation medium carbon sources, growth condition, and its characteristic and yield should be evaluated carefully to choose the most suitable BC synthesis process selection approach. The summary of the recent studies of BC production is given in Table 3. Table 3. Recent study of bacteria cellulose production. Bacteria Cultivation Source of Carbon and Its Concentration Culture Medium Fermentation Conditions Yield (g/L) References Komagataeib acter xylinus K2G30 (UMCC 2756) Glucose 6.17 ± 0.02 Mannitol GY Broth Static; 28 ◦C; 9 days 8.77 ± 0.04 [118] Xylitol 1.36 ± 0.05 Komagataeibacter rhaeticus PG 2 Glycerol Glucose Sorbitol and Mannitol Hestrin–Schramm (HS) liquid media Static; 28 ◦C; 15 days ~6.9 ~4.05 ~1.65–3.41 [119] Komagataeibacter xylinus B12068 Glucose Sucrose Galactose Maltose and Mannitol Hestrin–Schramm (HS) liquid media Static; 30 ◦C; 7 days ~2.2 ~1.6 ~1.4 ~0.1–0.2 [120] Komagataeibacter Glucose medellinensis Sucrose Fructose Standard 2.80 Hestrin–Schramm (HS) Medium Static; 28 ◦C; 8 days 1.68 [121] 0.38 Date syrup ~1.15 glucose ~0.85 mannitol, Yamanaka ~1.4 sucrose ~1.45 food-grade

> 23**sucrose ~0**.7 **Date syrup ~0**.65 **glucose**

~0.7 Gluconacetobacter xylinus (PTCC 1734) mannitol, Hestrin–Schramm 150 rpm; 28 ◦C; 7 days, ~1.05 [122] sucrose ~1.5

> 23**food-grade sucrose ~1**.1 Date syrup ~**0.9** glucose ~**1**

mannitol, Zhou ~

> 23**1.85** sucrose ~**1**.65 **food-grade sucrose ~1**

.15 5. Surface Chemistry of Nanocellulose for Drug Delivery Biocompatibility, biodegradability, and drug carrier capability to confine, control, and localize the drug release towards the target sites are desirable for nano-drug carrier formulation. The ability of nano-drug carriers to transport the drug and specify the sites for targeted drug release is influenced by the particle size, the surface charge, modification, and hydrophobicity. These aspects govern the nano-drug carrier interface with the plasma membrane and its diffusion across the physiological drug barrier [123]. Most NCs exhibit high specific surface area and negative interface charges as potential drug carriers, making them suitable as hydrophilic drug carriers. Therefore, the NCs' surface can be attached to the desired drug [124]. However, pristine NC cannot be used effectively as a drug carrier given its limited water solubility, moisture sensitivity, thermal instability, and lack of stability in various buffer solutions. Even though the pH adjustment of the environment can enhance the dispersibility of NCs, the scattering examination divulged the aggregation tendency of NCs, which translates to the colloidal instability of NCs. The size reduction obtained by converting cellulose into NC provides an exponential improvement of hydro- gen bonding that triggers the NC aggregation. This limitation can be made worse by the drug coordination, which is exposed on the NC exterior, consequently altering the dis- persibility and solubility [125]. Therefore, various surface modification and pretreatment fiber methodologies have been developed to overcome limitations and advance specific characteristics [126]. From a structural perspective, the three hydroxyl groups in each cellulose monomer are the most prominent characteristic that makes the NC surface reactive. The reactivity

> 20**of hydroxyl groups** influences **the surface** modification **of**

anhydroglucose units. It was reported that in the molecular framework of

> 20**cellulose, the hydroxyl group at the** sixth **position** behaves **as primary alcohol**

with a

> 29**reactivity ten times** larger **than the other hydroxyl** groups, while **the** hydroxyl group at **the**

second position has two-fold higher reactivity than that in the third position, both of which serve as secondary alcohols. This phenomenon manifests from the steric hindrance of each hydroxyl group, in which the hydroxyl group at the sixth position attached to the carbon atom that is connected to only one alkyl groups while the carbon atom that carries the hydroxyl groups in the second and third positions bonded to two alkyl groups [127]. Regarding the surface receptiveness of NC's hydroxyl groups, the addition of solvent and reactant may alter the group's receptiveness in diverse positions. De la Motte et al. [128] modified NCC through cationic epoxide 2,3-epoxypropyltrimethyl ammonium chloride (EPTMAC) by spray technique. It was revealed that the hydroxyl bunch receptiveness of cationic modified NC follows the order of OH-C6 = OH-C2 > OH-C3, which was validated through nuclear magnetic resonance (NMR). Nanocellulose surface modification for drug delivery was developed by modulating the NC hydroxyl groups. In general, the main

objective of nanocellulose surface modifica- tion is to incorporate new functional groups or drug components into the nanocellulose framework to escalate the

35**degree of substitution and** the **efficacy of** material **grafting** with- out altering **the**

structure, morphology, and crystallinity of nanocellulose [129]. Several processes have been developed for the surface modification of NC, either by physical or chemical processes, presented in more detail in the following sections. 5.1. Functionalization of Nanocellulose through Physical Technique Several physical techniques such as surface defibrillation, irradiation, electric current, and electric discharge have been developed to modify and functionalize nanocellulose surfaces for diverse applications [130]. Surface defibrillation disintegrates cellulose into elementary fibrils by exerting mechanical force using various devices such as ultra-refining, a high-pressure homogenizer, a grinder, a microfluidizer, and spray-drying. In nanocellu- lose functionalization, the combination of nanocellulose and drug entities can be subjected to surface defibrillation to modify the morphology of nanocellulose and construct a new matrix system with a tight fiber network. Microparticles from BC with fibrillar structure morphology have been prepared by spray-drying technique. An ultra-refining-assisted method was also conducted to construct bacteria cellulose nanofiber (BCNF) with various sizes and shapes. The coating of BCNF with mannitol (MN), maltodextrin (MF), and hydroxypropylmethylcellulose (HPCM) were also carried out at various ratios to study the drug release characteristics. The addition of such coating matrices exhibits benefits towards the spray-drying process and drug carrier ability, i.e., superior protection of drug confinement, decreased droplet adhesion on the drying chamber, and improved powder performance. As a result, the BC-microparticles can successfully enhance the drug uptake capacity and sustain the drug release of diclofenac sodium (hydrophilic) and caffeine (lipophilic) [131]. As a recent advanced method, irradiation exerted high energy, which modifies the cellulose exterior. For example, the radiated gamma energy can generate reactive in- termediates comprising ions and free radicals that provoke reaction pathways such as cross-linking, scission degradation, oxidation, and polymer and molecule grafting. The presence of irradiation beams, such as microwave and electron, accelerates the polymer As a recent advanced method, irradiation exerted high energy, which modifies the cellulose exterior. For example, the radiated gamma energy can generate reactive inter- mediates comprising ions and free radicals that provoke reaction pathways such as cross-linking, scission degradation, oxidation, and polymer and molecule grafting. The pr1e7so-f 47 ence of irradiation beams, such as microwave and electron, accelerates the polymer growth. UV-irradiation has also been developed to improve the reaction rate to allow pre- synthesized grafted polymer formation on the nanocellulose surface [132]. Recently, this megthroowdthha.s UbeVe-
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greroacwtitohnornanteantoocaelll-ow lulopsree-ssuyrnfathceess.ized grafted polymer formation on the nanocellulose surface [132]. Recently,
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ncoelleitnatel.ra[1c3ti3o]nm,inotdriofdieudciCnNgtFhebysuurtfailcizeionfgNdCiewlecitthrich-ybdarsoepdho-
plabsmiciatydoisrchhyardgreoptrheialitcmiteyncth,laeraadctinergisttoictsh,eanfodrminactoiropnooraftminagncyhcitaorsbaonxytolwgraorudpssc,eclalurbloos
grosutrpast,esa.nFdoroxinysgteann-
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peothlluetwinegtt,ifnagsta-nd
moodxiifdicaattiioonno,afnthdesnimanpolfiebcehresmcoicaatilntgre.aPtlmasemntas
tcroeamtmpaernetdistoanthaettcroanctvivenetrioountael fmorosduifrifcaacteiofunnc- mettihoonda.lization of nanocellulose given its benefits such as non-polluting, fast-modification, and simple chemical treatments compared to the conventional modification method.
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armegoiorpnhsothuastreagctioanssstthruacttaucrtaalsdsetfreuccttsuirnalthdeefceecltlsuilnostihcefrcaemlluelwosoirckf,rafamcielwitaotrink,gfancainliotaptair
nanporopdarutcictiloenp.rOodthuecrticohne.mOicthalerprcohceemssiecsa,lspurcohceasssTeEs,MsuPcOh-
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of cmhoemdiificcaaltmioondoiffincaatnioonceollfunloanseociseltlaubluoslaeteisdtainbuTlaabtleed4i.n Table 4. (a) Figure 6. Cont. Polymers 2021, 13, x Monocarboxylic Acid H3PO4 Hydrolisis Hydrolisis O

11**O OH O O** HO P **O O O OH** O P **OH HO** P **O O OH** O P **O OH** 3 1 2 **O OH** 1 **O**

2 3 Dicarboxylic Acid OH OH of Phospated Nanocellulose of Phospated Nanocellulose Dibasic Form 1

4**O OH O O O OH O O**

(H3PO4/water); (H3PO4/Urea)

17**O O OH O** HO 2 1 **O O O** 1 **OH O** 2 **OH O OH OH OH O O O** S **O OH O** S **O** HO 1 2 **O** 3 4 O **OH O OH O O**

4 3 2 1 OH OH O H2SO4 Hydrolisis (H2SO4; ClSO3H; H2SO4/HCl) HO 1 O O 2 4 O O 4 O 1 2 OH 3 O 1 O 1

7**OH O** 3 **O OH O HO O** O **O O O O** 3 **OH** 1 1 **OH** 3 **HO**

4 2 2

7**O OH O** 4 **OH** 2 **HO** 1 3 **O OH O**

3 1 OH 2 2 Tricarboxylic Acid Hydrolisis (Citric acid) (b) FFiigguurree 66..SiSmimplpifliiefidedmemchecahnaisnmissmosf cohfecmhiecmalicsaylnsthyenstihsensaisnoncaenlloucleolslue;lo(as)ea;c(iad)-baacsided-bcahseedmicchaelmmiocdal-imficoadtiifiocna;t(ibo)no;x(bid)aotxioidnabtiaosnedbacsheedmcihceamlmicoadlimfiocadtiifiocna.tion. Table 4. The influence of chemical functionalization on morphological nanocellulose. Table 4. The influence of chemical functionalization on morphological nanocellulose. Surface Methods Reagents AAidiedded Reagents OPaprearmateitoenr SCoeulrlucSClelooseulsorluecfelossoef MTeecchhnaMinTqieecuccahhelnainqiYucaeileld (%Y(i)%eMl)dor(pnhmMo)loor(pgnhmyo)loCgyI%) CZI%et)aPPo(ZotmeetnVteatn)iatlial (SDCmuehmrnafrsoagiclte/eyg) H2 SO4 - 5603%°CH;26S0O4m50in◦C; PMeieclrsocrystalline Ultrasonication - −46.1 H2SO4 - 63 Hm2SinO4 MicrocrCyesIltuallo-se 30%L: 1N03C–L1C:7253N0.;5CWC: 16 - −46.1 - 58.1 NCC - NCLC:103–1737.57.96 552%2%H62H0SmO2Si4nO504 ◦ CP;assioPnasFsPiroeuneilFstrUuitltrasoUnlitcraastoionnication58.1 77.96 −25 −25 CsluSlOfHo3nH2aSt(OiPoon4s/)tH-Cl - - 2COlS(O33:1H:6in);5U0lm-LMicroScurlyfastteadl-NCC Mineral trDaMsoFn;RicT;520h line Cellulose Ultrasonication - 79.31(D:10L–:115820;W: 22.7-; 88% −-66.1 h: 5.0 Acids nm) H2SO4/HCl - - H2SO4-:HCl:H2OFilteMriPcraopcreyrstalline - - - W: 22S-CNC 85 - (3:1:6); Ultrasonic Cellulose Ultrasonication (D:10–180 nm) - - H2S5O0h4:ZH;1C0l:hH S-CNCNCC - 50 °C; 9-0 min line CeFlillutelroPsaepUerltrasonication 30% - - L:250; W:WN1C:62C2 85 - NCC C73l.Sh9◦%OZC3;H;H19300PimOnhi4n5;0100 - Filter Paper Blending 76–80 NCC (15 min) NCLC:316; W: 31; 81 - ClSO3H H3(PPOo4st-sul- - - L:152; WN:CC 88% 83 −6−62.17 fonation) m11L00.0D7◦MMC;HF3;03PRmOTi4n;;Sulfated NCC Ultrasonication 79.31 2 h 22.7; h: 5.0 - 731.090%◦CH;33P0Omi4n; 10.7 M H3PO4; Cellulose CNF L: 2500 nm 81 −23 Mineral Acids - - 100 °C; 90 FilterBPiRoatepesteihdrauneol BlendHio(n1mg0otgimeneisz)e7r6–80 H3PO4 in 1105.07m◦MCi;nH303PmOi4n; (15 min) L:31N6;CWCL:: N3611C0;Cnm 81 83 −-34 molten Urea - 10.7 M CNF L: 330–480 nm 86 −24 2.5 MH3HPCOl;41;05 ◦C; HCHl3PO4 -- Blending 1004°0Cm;i3n0 Filter Paper (40 min) - NCC NCC 83 W: 20 79% −2-7 (mmol/g) - - - -SO3 H - (0.0985) -SO3H (0.0-985) -0S.O403-9H - PO3 (0.0108) --SPOO33H (0.04.345029) -PO3 (0.018) -PO3 ((01-P..00O31380)8) -PO3 (1.173) -PO3 (0.4-352) Ref. [29] [29] [134] [134] [135] [135] [136] [[113376]] [135] [137] [138] [135] [135] H2 SO4 Acetic Acid HC-l 6M HCl FormHic3APcOid4 in 0.015 M - molten FeCl3 Organic Acids Lactic Acid HCl Urea - min 1800.◦7CM;3 h H3PO4; 101005°◦C; 390h 8m0◦iCn; 4 h 10.7 M H903P◦CO;46; h 150 °C; 30 15m0◦inC; 3 h Bleached eucalyptus - kraft pulp CteethllaunloosleCRBoetistooi-n- Ho(1m0otgimenBe(2ilsez0)nemdriinng) Mduicerocrystalline Cellulose Bleached eucalyptus kraft pulp Cotton 81 NCC L: 264; W: 16 30 L: 2C5N0L0F:n26Nm9C;WC: 4581 - - NCC NCLC:236; W: 25 Blending (20 min) - nLm:200; W = 20 L: 610 nmNCC 83 - 75 CNF L:594 L: 330–48N0CC 86 80 −33 - −23- 88 −1.7 −34 75 −6.53 80 −24 - -SO3 H (0.015) -PO3 [139] (0.-018) [[114308]] Formate (-0P.4O)3 [141] (1.038) Formate [142] -PO3 L(a1c.t1a7te3) [143] Table 4. Cont. Methods Reagents Aided Operation Sources of Reagents Parameter Cellulose Mechanical Technique

1**Yield Morphology (%) (nm**) Zeta **Cl%) Potential (mV) Surface Charge Density (mmol/g) Ref**

.

1**Butyric Acid 0.027 M** NCC **HCl 105 ◦C; 9 h Cotton Blending (20 min) 20 L: 226; W = 34 - - Butyrate**

[140] -

1**70% MA; 100 ◦C; 45 min** Bleached eucalyptus - **12**% NCC - **-33 -COOH**

[144] kraft pulp (0.29) Maleic Acid (MA) - 60% MA; 120 ◦C; Bleached Microfluidizer 3%

1**L: 329.9; h = 15.9 - −46.9 -COOH**

eucalyptus (0.368) 2 h kraft pulp (120 mPa; 5 -COOH [145] passes) 84% CNF h: 13.4 - −45.2 (0.059)

1**Oxalic Acid (OA) 8.75% OA; 110 ◦C**; NCC - 15 **min Filter paper Sonication (60 min) 93.77 L: 150–200**; - −36 -COOH, [146] **W: 5–20**

0.29 - 70%

1**OA; 100 ◦C; 1 h** Bleached eucalyptus - **24.7** NCC **80 −42.5 -COOH**

[144] kraft pulp -

1**30% OA; 100◦ C**; Sonication 30 **min Celery**

(

1**18 min) 76.8 CNF h: 5.5 49 −32.9 -COOH**

[147] - 5% - - -COOH Malonic Acid 80% wt of 0.025 M Malonic Acid; 140 HCl ◦C; 3 h

1**19.8% 75 - -COOH** - 3.4% - - **Malic acid**

A80c%id;w14t0of◦MC;a3lihc Ramie Blending NCC -COOH, (1.617) 0.05 M Cellulose (5 min) L: ~220; W: ~12 [148] HCl 20% 78 - -COOH - 5.1 - - -COOH 0.05 M 80% wt of Citric HCl Acid; 140 ◦C; 3 h 20.5

1**78 - -COOH, (1**.884) **Citric Acid** - NCC, **-COOH**

, 80% wt of Citric Bleached 32 L: 251; W: 21 78 −122.9 0.65 - Acid;

1**100 ◦C; 4 h** Baggase **Pulp Ultrasonication**

-

1**CNF, L: 654; W: 32 69 190.3 -COOH**

, [149] 0.3 TEMPO (0.094 mmol)-NaBr (1.57 - mmol)- NaClO (1.24 M); 10 ◦C; 45 min Nanocrystalline NCC, Cellulose Ultrasonication - L: 100; W: 5–20 80% - - [150] TEMPO/NaCl TEMPO (0.1 /NaBr mmol mmol)- NaBr (1 mmol)- NaClO (5 -COOH; - HBKP mmol/g Ultrasonication - CNF 85% - -CHO cellulose); (1.191) [151] Oxidation Ambient Treat- condition; 1.5 h ment 50 mM TEMPO, 5 -COOH; TEMPO/O2 /Laccase U mL–1 laccase; HBKP Ultrasonication - CNF, L: > 100; W: 4–8 - - -CHO 96 h (0.837) Sequential Periodate-Chlorite Oxidation (1). 46 mmol 1 M NaIO4; 50 ◦C;4.5 Acetic h followed by (2). Acid (2) 12 g NaClO2l 50 ◦C; 40 h Hardwood Pulp Homogenizer (5 passes; 80 MPa) - CNF, L: 95.8; W: 2.72 - −128 -COOH (2.0) [152] - COOH APS Oxidation - 1 M APS; 75 ◦C; Cotton Linters - 34.4 CNF, (0.16); 16 h L: 95.8; W: 2.72 63.8 - -SO3 [153] (0.98) In general, NCC isolation comprises exposing pure cellulose material under strong acid hydrolysis with strictly controlled operating parameters such as temperature, agita- tion, time, and concentration of chemical species. As mentioned earlier, various chemical reagents such as H2SO4, HCl, HBr, and H3PO4 have been utilized as cellulosic disinte- grators. The selection of acid reagents has the most crucial role in determining drug carrier characteristics and synthesis pathways for incorporation or grafting through chemi- cal/physical modification for particular functional groups. The amorphous decomposition using HCl and HBr is not widely adopted because they provide low dispersion stabil- ity of NCC and increase the agglomeration tendency of NCC in an aqueous suspension. H2SO4 and H3PO4, on the other hand, exhibit better performance as a hydrolyzing agent because the chemical moieties can be attached to the hydroxyl group of NCC during the reaction to isolate charged surface of NCC for subsequent incorporation of phosphate or sulfate functional groups. The new functional group incorporation causes the spontaneous dispersibility of NCCs in an aqueous environment due to the colloidal stability restora- tion through electrostatic repulsion refinement, which is the preferred characteristic of drug carriers. A subsequent treatment of H2SO4 followed by HCl synthesis

30**has been** utilized **to control** the **sulfate moieties on** the NC **surfaces**

. The as-synthesized particle had a simi- lar

7**particle size** to **those** particles **directly** acquired **from acid hydrolysis**. Nevertheless, **the surface charge density** can **be**

adjusted on the hydroxyl groups exploited by sulfate groups [49]. Lin and Dufresne [137] proposed a strategy of inaugurating progressive sulfate group content on NCCs surface through the modulation ratio of reactants and post-sulfonation (chlorosulfonic acid) and desulfonation conditions. They also evaluated the impact of sulfonation degree on the morphology, dimension, physical characteristic, and surface chemistry of modified NCCs. Diverse zeta potential ranged from −7 mV to −66 mV and approximately 0.0563 mmol/g–1.554 mol/g of sulfonation degree was ac- quired. Therefore, it is indicated that the zeta potential of nanocellulose is mainly controlled by the sulfonation degree of nanocellulose itself [137]. Wijaya et al. [29] successfully isolated NCC through sulfuric acid hydrolysis of bleached passionfruit peels waste fiber by adjusting the acid concentration, hydrolysis time, and reaction temperature. The NCC was used for tetracycline hydrochloride ad- sorption through electrostatic and Van der Waals interaction. The adsorption isotherm was correlated using Langmuir and Freundlich isotherm models. With pH environment adjustment, the adsorption affinity of the drug can be altered to control the uptake and sustained release of drugs [29]. (2,

14**2,6,6-tetramethylpiperidine-1-oxyl)-mediated (or TEMPO-mediated) oxidation of** nanocellulose **has**

arisen as an alternative NC isolation route to replace the conventional acid hydrolysis method due to its environmentally friendly and facile synthesis nature. The synthesis starts by using TEMPO/NaBr/NaClO or TEMPO/NaClO2/NaClO as a reagent. TEMPO (stable nitroxyl radical) forms as the catalyst for NC synthesis, which further transforms into N-oxoammonium salt (R1R2N+=O) under certain conditions while the NaClO acts as a primary oxidant [46]. Both NaClO and NaBr can reversibly transform the N-oxoammonium salt into TEMPO form. The hydroxymethyl groups of NC (primary hydroxyl groups located on C6) are selectively transformed into carboxylated groups while the secondary hydroxyl groups remain unchanged (secondary hydroxy groups located on C2 and C3) [66]. The incorporated carboxyl groups imparted negative surface charges from the change in the environment pH, which leads to improved colloidal stability. As reported by Montanari et al. [154], TEMPO-mediated oxidation with the degree of oxidation 0.24 has imparted negative charges on the crystalline regions of nanocellu- lose, which provide dispersibility and individualization improvement time decreasing the crystallite size [154]. Meanwhile, Habibi et al. [150] underlined that the TEMPO- mediated oxidation did not affect the morphological and crystallinity of NCCs. Further- more, they highlighted that the ratio of primary oxidizing agents affected the negative charge of NCCs [150]. A novel oxidation system of TEMPO/laccase/O2 has been utilized to modify NC. The TEMPO/laccase/O2 system with sufficient catalytic amounts of laccase and TEMPO reagent produced

12**reactive TEMPO+, which** subsequently transformed **primary hydroxyl** moieties into **aldehyde**

moieties through oxidation. After the oxidation, the reactive TEMPO+ was reduced into N-hydroxyl TEMPO. However, no-cycle regeneration occurred between

12**TEMPO+ and N-hydroxyl TEMPO** due **to the**

breakdown of the

12**primary hydroxyl groups of polysaccharides and laccase molecules**

. Furthermore, the

12**N-hydroxyl-TEMPO** was accumulated **in the reaction**

environment due to the absence of active laccase in the system. Therefore, a large amount of TEMPO and laccase and prolonged reaction time are required to oxidize the primary hydroxyl groups, which are considered major disadvantages of this process [151]. TEMPO-mediated oxidation was mainly used to modify NFCs before mechanical defibrillation to promote the fiber's individualization.

35**TEMPO-mediated oxidation leads to** the breakage **of the**

strong intra-fiber hydrogen coordination to facilitate the softening and impairing of its rigid structure, which is beneficial in converting TEMPO-oxidized cellulose fiber into highly crystalline individual nanofibers through mechanical treatment. The NaClO concentration and mechanical treatment strength were considered crucial

factors in determining the polymerization degree, carboxylate group numbers, and CNFs yield. Carlsson et al. [155] emphasized the influence of surface charges in nanocellulose formulation as a drug carrier by introducing TEMPO-mediated oxidation in mesoporous claodophora cellulose for aspirin degradation. The surface charge negativity (

> 27**carboxylate content 0.44 ± 0.01 mmol g**−1) significantly accelerated **the**

degradation of aspirin compared to the native source of CNFs, which had a deficient

> 27**surface charge (0.06 ± 0.01 mmol g**−1). **This**

phenomenon is caused by the strong interaction of opposite charge entities between aspirin and TEMPO-oxidized cellulose nanofibers (TOCNFs), leading to increased partial amorphization ability inside the mesoporous TOCNFs [155]. Without a chlorine-containing oxidant, 1.1 mmol g−1 of carboxyl groups were incor- porated onto wood cellulose. High in carboxylate content, wood cellulose underwent tremendous depolymerization during oxidation. In addition, a long reaction duration of up to 15 h was required to achieve

> 12**0.6 mmol g−1 carboxylate content**, while **1.1 mmol g−1**

was achieved by increasing the reaction time up to 20 h. Prolonged reaction time is considered the major disadvantage of this process. This method has been utilized for nanocellu- lose modification in drug delivery applications [156]. The sequential periodate-chlorine oxidation selectively and simultaneously incorporates two carboxyl groups through the oxidative transformation of two vicinal secondary hydroxyl groups (located in C2 and C3 instead of C6 position), enabling higher surface charge density introduction. The increase of surface charge density is essential in retaining the colloidal stability of drug carrier and improving the electrostatic interaction between drug and carrier, which increase the loading uptake of drugs. Plappert et al. [152] investigated the pretreatment effect of sequential chlorite pe- riodic oxidation on open-porous anisotropic CNF hydrogel membrane assembly. Hy- drogel membranes were used for transdermal drug delivery systems for nonsteroidal anti-inflammatory drugs (NSAIDs) and piroxicam (PRX). By tuning the surface charge den- sity and the amount of carboxylated groups (0.74–2.00 mmol g−1) by varying the reagent concentration, the drug carrier uptake capacity can be increased to within the range of

> 28**30–60 mg g−1 with** the **surface charge**

−66 mV to −128 mV. The electrostatic interaction

> 28**between the cationic drug** (PCX) **and the anionic** characterized **surface of** CNF membranes is **the**

main driving factor behind the loading of drugs in the membrane [152]. 5.3. Functionalization through Post Chemical Modification via Covalent and Physical Bonding Strategy Maintaining the structural integrity of nanocellulose to prevent the polymorphic trans- formation and maintaining the crystalline area while modifying its surface are considered the main challenges. Therefore, several post-chemical

> 11**modifications have been** studied **for** surface modification **and functionalization of nanocellulose** surfaces before **the**

drug upload. Sulfonation treatment is the most common strategy to introduce sulfate groups into hydroxyl moieties of nanocellulose, which produces a highly negatively charged surface. Nevertheless, the degree of sulfonation was highly determined by several factors such as temperature, acid concentration, and hydrolysis time. Treatment of NC with sulfuric acid or sulfonation followed by acid hydrolysis [137,157] can improve the characteristics of NCs. However, these improvements may lead to lowering the colloidal stability of NC due to the reduction in the sulfonate degree. Since the primary goal of the drug delivery system is to achieve higher colloidal stability and strong electronegativity for further electrostatic drug adsorption or modification, straight H_2SO_4 hydrolysis remains the primary treatment for NC modification. On account of the simple and straightforward treatment,

> 7**modification of hydroxyl groups at the** NC **surface** by Fischer **esterification is**

another common approach. Several reactants have been used to acetylate the surface of nanocellulose, such as acetic, citric, malonic, and malic acid with the combination of HCl or H_2SO_4. The utilization of H_3PO_4 provides NC modification with higher thermal stability than sulfonated NC. Camarero Espinosa et al. [135] suggested that only one hydroxyl group was incorporated by one ester bond of phosphoric groups. Another study by Kokol et al. [138] revealed the possibility of phosphate-modified nanocellulose (P-NC) originating from two structural isomers, either of which can behave as monobasic acid or dibasic groups. Acetylation of hydroxyl groups of NC can also be performed using enzymatic modification. In an environmentally friendly approach, enzymatic modification serves as a favorable modification route without the need for any addition of chemicals and has low energy requirements, improving biocompatibility and

lowering the cytotoxicity of NC for drug delivery. The acid hydrolysis and oxidation treatments are mainly considered as a primary synthesis of nanocellulose. Indeed, during acid-based hydrolysis or TEMPO-oxidation, hydroxyl groups of nanocellulose grafted by anionic sulfate ester groups (-OSO3−) and carboxylate groups (-COOH) produce the negative electrostatic layer of nanocellulose. Consequently, high stability of nanocellulose occurs in the aqueous solution resulting in electrostatic repulsion between individual particles. Maintaining the structural integrity of nanocellulose to prevent the polymorphic transformation and maintaining the crystalline area while modifying its surface are considered the main challenges. Several post-chemical modifications have been studied for surface modification and functionalization of nanocel- lulose surfaces before the drug upload. Silylation is another approach to modify the surface nanocellulose by conjugating small molecules.

> 7**A series of alkyl** dimethyl-dimethylchlorosilane (**alkyl-DMSiCl) with** various **alkyl** groups such as **isopropyl, N-butyl, N-octyl, and N-dodecyl can be** grafted **on the surface of** NCC **in the** presence **of**

toluene. However, the high price and high toxicity of the reagents limit the progress of silylation modification in the drug delivery field. Recently, Li et al. [158] developed an NC template for mesoporous hollow silica material (R-nCHMSNs) for ibuprofen and lysozyme drug delivery. The presence of NC as a template increases the content of geminal silanols on the R-nCHMSNs surface. Nanoparticles with high content of geminal silanols present outstanding delivery characteristics for various drugs [158]. The amine derivatives can covalently bond the surface of NC through a carbodiimide amidation reaction. The majority of

> 14**amidation-mediated couplings were** incorporated **on** the **carboxylic groups of pre-oxidized**

NC without re-molding the morphology and crys- talline native structure. N-ethyl-N-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC) has been widely used for the amidation among carbodiimide derivatives. The addition of

> 20**n-hydroxysuccinimide (NHS) is** required **to avoid**

unstable intermediate O-acyl urea formation and to achieve the direct formation of the stable N-acyl urea. The amidation approach was presented by Akhlagi et al. [159] to create a drug delivery system based on chitosan oligosaccharides (CSOS) and TEMPO-oxidized NCC. The carboxylic moieties on the oxidized NCC were coordinated into the primary alcohol and amino moieties of CSOS. Several limiting factors such as medium reaction, time reaction, pH, and the molar ratio of reagent and cross-linker reaction can be altered, translating to the modified grafting behavior and degree of substitution of CSOS into oxidized NCC. Electrostatic interactions were performed to achieve 21.5% of binding efficiency loading and 14% w/w of procaine hydrochloride (PrHy) loading. The rapid release profile observed in this study is suitable for local drug delivery by the oral system [159]. Direct covalent drug attachment towards the NC crystal backbone via a novel spacer arm through amine-mediated couplings is another potential strategy [160]. Tortorella et al. [160] modified NCC via periodate-oxidation-generated NCC-DAC (dialdehyde cellu- lose) and inserted them into molecules of g-aminobutyric acid (GABA) via the Schiff base condensation reaction. Subsequently, the nucleophilic substitution of 4-hydroxy benzyl al- cohol (HBA) occurred and was followed by an acylation reaction with 4-nitrophenylchloroformiat that exerted a carbonate group for nucleophilic substitution of amino contained doxorubicin as model drug nucleophilic. Carbamate linkage adjacent to the linker presents highly stable conditions in an aqueous environment with harsh Polymers 2021, 13, x conditions, either basic or acidic. The drug release of active drugs was achieved o2n4lyofb4y9 hydrolysis in cells utilizing suitable enzymes to cleave a carbamate linkage (Figure 7). Figure 77..IlluIlsltursattriavteivreeprreepserensteantitoantioonfcoofnjucognajtuedgadteodxodruobxiocriunboincitno NonCtCosNthCroCusghthcrohuemghicaclhbeomnidcainlgb(otnhidsinpgict(uthreisispriec-- tdurraewins frreo-mdrTaworntofrreollmaeTtoarl.to[1r6el0l]a. Ceotpayl.ri[g1h6t0]©. SCporipnygreirgFhatc©hmSepdriienngeWriFesabchadmeendGiemnbWHi)e.sAbbabdreenviGatmiobnHs:)N.CACbbsr=ecveilaltuiolonsse: NnaCnCocsr=ysctealllsu,lDosAeCna=ncoecllruylsotsaelsd,iDalAdeChy=dcee,lGluAloBsAed=ica-ladmehinyodeb,uGtyAriBcAac=idc,-HamBAin=o 4b-uhtyydrricoxaycibde,nHzyBlAal=co4h-ohly,EdDroCxyHbCeln=zy1-l aeptlychroyihdl-oi3nl-,e(3,E-NDdPiCmCHe=tCh4yl-nl=aimt1r-oienpthohpyerln-o3yp-l(yc3lh-)dlcoiamrrobefoothdrmyiilmaamtied,ienDohIpPyrEdoArpoyc=hl)Nloc,Nraidr-dbeoi,iNdsoiHipmrSoi=dpeNyl-h-hNyyd-dertrohocyxhlylaosmruiicdnceei,n,aiNmnHhid.SeD,=MDNMF-=AhayPnd=hry4od-xdyriomusuestcdhciyimnlaiemmthiidynelo-,DfoMrmAaPm=id4e-,dDimOeXthOyNlaHm2in=odpoyxroirduinbiec,iNn,P*Cis=re4p-netiittriovpehmenoynlocmhelorrmofoolremcualtees,.DIPEA = N,N-diisopropyl-N-ethylamine, anh. DMF = anhydrous dimethylformamide, DOXONH2 = doxorubicin, * is repetitive monomer molecules. 5.4. Polymer Grafting Modified Nanocellulose 5.4. PPoolylymmereGr-rgarfatifntegdMNoCdifiheadsNbeanenocienllturloodseuced as the sought-after functionalization strat- egy toPorleyfmineert-hgeradftreudgNdCelihvaesrybepeenrfionrtrmodanuccee.dDaisfftehreesnotutegchht-naifqteurefsuhnacvtieobneaelinzadteiovnelsotrpaetdegtyo itnotrroedfiunceethfuendctriuognadleglirvoeurpyspoenrtfoorNmCanccoev.alDeniftfleyr,ein.et.t,e(ci)hTnhiqiouleesnhearveeacbtieoenn;(diie)vOelxoipmeedrteo- aincttiroond;u(cieii)fuMnicchioanelaladgdroituiopns;oanntdo (NivC) icmovinaeleanntldy, hiy.ed.,ra(iz)oTnheiosylenntheerseias.ctTiohne;se(iir)eaOcxtiiomnes hreaavcetiboene;n(iwii)eMll-idcehvaeelloapdedditfioornp;oalnydm(eivr)fuimncintieonaanldizhatyiodnrafzoorndersuygndtheelisviesr.yThsyessteemreas.ctions haveIbneteegnrwateinllg-dpeovleylmopeerdofnotropthoelyNmCersfuurnfacctieoncaanlizbaetipoenrformdreudgbdyetlhivee‘rgyrsayftsitnegmosn.to’

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eonndtog’rteocuhpnsiqounetoreeqituhierresmporde-isfiyendthoersnizoend-mpooldyimfieedr hydroxyl groups of the NC surface. The adherence of polymer onto the NC surface’s spe- cific moieties can be performed via physical or chemical attachment. The ‘grafting onto’ approach offers the possibility of characterizing polymer before grafting and modulating the resultant carriers’ characteristics. attachment that can bear the

> 14**reactive end groups onto** either **modified** or non-modified **hydroxyl groups of the** NC surface. **The** adherence of **polymer**

onto the NC surface’s specific moieties can be performed via physical or chemical attachment. The ‘grafting onto’ ers 2021, 13, x approach offers the possibility of characterizing polymer before graftin25goafn4d9modulating the resultant carriers’ characteristics. Strong electrostatic interaction can be used to initiate the polymer grafting onto NC. in PDA,
suchThaesraemisinaep,oimssiibniel,itaynodfcinacteocrhpoolragtrinougppso,lcyadnopsearmveinaes(PthDeAa)nicnhtoortshfeoNrCC
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dπralinsttearbailcittiyo.nT,haendprheysednrcoegeolfbfuonncdt-ional groups ing [161]. in PDA, such as amine, imine, and catechol groups, can serve as the anchors for NC Wang eatnadl.
t[h1e62d]rausgsetmhrboluegdhptohley(VeathnydleerthWylaeanlse ipnhteorsapchtiaoten),
(thPEeEπP–)πthinattebreaactrisopnr,oa-nd hydrogel pargyl functbioonnadliintygo[1n6to1].azide modified nanocrystalline cellulose (NCC) Cu via Cu(I)- catalyzed azide-
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ehteroxnanidoaizcoalceidcotnotianintriondgumceatlheiemeisdtee.r Tfuhnucst,iotnhebetween the drug and the maleimide ring. Finally, the Diels–Alder reaction occurs between the furan novel system of carrier provides the ester function on the linking chain for innovative functionalized CNF-t (CNF-fur) and metronidazole containing maleimide. Thus, the novel drug carrier formulation, which induces the release in the presence of esterases enzyme [163]. system of carrier provides the ester function on the linking chain for innovative drug carrier formulation, which induces the release in the presence of esterases enzyme [163]. (a) Figure 8. Cont. Polymers 2021, 13, x 26 of 49 (b)
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SoCciheetymoisftrCyh);e(mb)isptroyl)y;m(be)r-pgoralyftmederc-eglrlaufltoesde
cfiebllruillso(speNfilbPrAilms(-pgN-TIOPACNms-)g-vTiaOPCaNssse)rviniai oPnaes-speoritnrieoacnteio-n
pot reaction (this figure is redrawn from Khine et al. [164]. Copyright © 2018 American Chemical So(ctiheitsyfi).gure is redrawn from Khine et al. [164]. Copyright © 2018 American Chemical Society). A versatile grafting strategy for numerous functional groups is the Passerini reac- tionA.
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icahlilbyitgtrhafetremdainltroesTpEoMnsPivOe-noexsids,izwehdiCchNiFssp.Arosmaisriensgulfto,trhuessee
minastteirmiaulslie-rxehsipboitntshiveremcaalrrriee-rs sp(oFnigsuivreen8ebs)s[,1w64h]i.ch is promising for use in stimuli-responsive carriers (Figure 8b) [164].
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graftedUNnCde[s1i3ra2b].le reduction in surface grafting density is nonetheless observed as the
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Abnorothmeoriaspobpurotyarcyhlbroamtoimdetr(aBnIBsfBe)r
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approaches for drug delivery have been well-reviewed elsewhere [132]. 5.5. Surfactant Modified Nanocellulose 5.5. Surfactant Modified Nanocellulose The adsorption of surfactants represents a promising alternative for the chemical modification of NC. Surfactants are classified into cationic, anionic, zwitterionic, and non- ionic. The distinct properties of the surfactant manifest through its micelle formulation in the aqueous solution, which is highly beneficial in the drug delivery system. The lack of a strong covalent bond is considered the significant drawback towards enabling molecule release. Therefore, it is necessary to study several factors affecting the interaction of surfactant and NC and their impact on drug uptake and release. Tardy et al. [165] reviewed several factors that influence the affinity of NC and the surfactant. This study provides some additional information on the affinity of NC and the surfactant on the drug delivery system. The opposite charge between the NCC surface and CTAB drove the electrostatic interaction and physical adsorption for the NCC surface modified with the surfactant. NCC’s negative charge creates a non-covalent interaction towards the cationic charge of CTAB, resulting in a strong electrostatic interaction. Zainuddin et al. [166] pointed out several factors that mainly involve the interaction between NCC and the surfactant, i.e., pH and ionic strength, the CTAB concentration, and the ratio of CTAB to NCC. They highlighted that the CTAB concentration and mass ratio of NCC: CTAB affects the interaction of surfactant-modified NCC with curcumin as a hydrophobic drug model. Increasing the CTAB concentration intensifies the hydrophobic character of the carrier, which is intensely coordinated with curcumin. However, at a high concentration of CTAB, the amount of curcumin attached tends to decrease [166]. Low surfactant concentration favors the electrostatic interaction between the monomer CTAB head with the negative charge of NCC surface, giving hydrophobic properties. While the CTAB concentration increases progressively, the adsorbed monomer of the surfactant tends to restructure and initiate surfactant cluster formation induced by hydrophobic coordination between surfactant alkyl chains. The CTAB cluster molecules can be absorbed through the NCC surface by hydrophobic interaction. However, the hydrophobic coordina- tion of the surfactant and NCC manifested as a weak electrostatic interaction, which easily releases CTAB from NCC surfaces through the washing. Moreover, an excessive amount of CTAB concentration over the boundary of the surfactant critical micelles concentration (0.93 mM CTAB) might provoke the surfactant micelles formation on the NCC surface, which degrades the hydrophobic characters. Only ionic interaction between the cationic head of CTAB and anionic sulfate ester groups remains unaffected, which acts as available active sites for hydrophobic drug loading (Figure 9). Raghav and Sharma [167] reported the coordination of the hydrophobic tail of CTAB in phosphate NCC. They also observed that the surfactant types (CTAB and TBAB) influence the capability of modified NCC to bind and release the drug. By observing the structure configuration, stearic near the central nitrogen in TBAB-NCC causes the insufficiency of drug binding, which exacerbates the coordination and controlled release of the carrier [168]. Putro et al. [25] modified the NCC with various

18**types of surfactants such as cationic** (CTAB), **anionic** (sodium dodecyl sulfate), **and non-ionic**

surfactant (Tween 20). Differ- ent types of surfactants exhibit distinct interactions towards NCC, which influenced the electronegativity of modified NCC itself and the drug adsorption–desorption behavior. The presence of salt in the system had a significant influence on the uptake of paclitaxel. Different behavior of surfactants due to the salt effect significantly influences the interaction of NCC and drugs. They concluded that (1) electrostatic and Van der Waals interactions are the primary mechanism of paclitaxel adsorption towards surfactant-modified NCC, which can be enhanced through salt addition; and (2) pH played a significant role in the drug adsorption and release of paclitaxel by altering the surface charge of surfactant-modified NCC and the electrostatic interaction of hydroxyl ions and paclitaxel in solution. Polymers 2021, 13, x 28 of 49 FiguFriegu9r.eS9c.hematic representation of othfethseurfactant anadndnanocrystalline cellulose mechanism and its effect on drug ad- adsorption (t(htihsisfigfiugruereisirse-drawn frofrmomBundjaja eteatla.l[.2[62]6.]C.opyright ©©2022002E0lEselsveiverieBr.BV..V)..).
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of a multilayer carrie,r through electrostatically assembling layer-by-layer (LbL) the nanocel- CNF. A carrier s
physical and chemical characteristics can be refined by adding a surfac- lulose (either negative or positive
surface) with an oppositely charged polyelectrolyte. tant (CNF film and foams-based CNF). Currently, the
development of drug delivery carriers through LbL assembly has drawn The synthetic surfactant can induce
membrane cell lysis based on biocompatibility, considerable

> 4**attention due to their unique properties**. Various physical interactions **such**
> whichisconsideredatoxicmaterialforcells.Therefore,thenaturallyavailablesurfactants **as**

hydrogen bonding, hydrophobic interaction, and Van der Waals interaction are present in functional polyelectrolyte carriers. Those interactions act as the driving force in drug binding and maintain the stability of the multilayer [169]. LbL hybridization assembly of nanocellulose with other organic and inorganic materials usually instigates an outstanding performance improvement for the entire LbL system to stimuli-responsive and localized drug delivery. Early development of the LbL approaches was demonstrated on the flat substrates and is currently extended to spherical particles. Coating LbL film on a spherical sacrificial template becomes another layer-by-layer assembly approach for hollow polyelectrolytes capsule formation to encapsulate and re- lease the drug. Melamine formaldehyde (MF) is a popular template for microcapsules preparation via LbL assembly due to narrow-sized distribution and optimized disso- lution conditions [170]. The physicochemical characteristics of templates such as size, shape, porosity, colloidal stability, and template solubility modulate the characteristic of as-synthesized hollow capsules. For instance, the capsule size can be adjusted depending on the size of the template, which is common in the range of 150 nm to a few microme- ters [171]. Nanocellulose has been used to construct the interior of multilayer thin film and hollow microcapsules for various types of therapeutic molecules loading such as DNA, RNA, protein, and drugs. Several aspects should be considered to assemble suitable polyelectrolyte complexes through the LbL system, i.e., charge stoichiometry, charge density, molecular weight, poly- electrolytes concentration, pH, ionic strength, order of addition, mixing ratio, and mode of mixing the polyelectrolyte solution. These factors greatly influence the drug carrier thickness, the surface charge, and the morphological structure, such as the size, shape, and porous structure of the drug delivery system. Reviews on some crucial aspects that influence the stability of polyelectrolyte complexes for drug delivery systems are available elsewhere [172]. Mohanta et al. [173] produced an NCC multilayer thin film with counterionic poly- electrolytes (chitosan) on a quartz crystal microbalance (QCM) plate through LbL growth assembly. They also developed hollow microcapsules using MF as a template. By varying the concentration of the polyelectrolyte (either NCC and chitosan) and the number of depositions, a homogeneous multilayer thickness with a porous structure can be obtained. The thin film and microcapsule were utilized as carriers for hydrophilic drugs (doxorubicin) and hydrophobic drugs (curcumin). The protonation of amine groups in acidic conditions becomes the driving force for doxorubicin release, while the concentration difference be- tween the medium and carrier is considered the primary factor affecting curcumin release. The stimulus-responsive pH in LbL system-based nanocellulose may apply to local drug transport and tumor therapy [173]. Other types of layer-by-layer assembly approaches were also used to construct PEC-based nanocellulose by incorporating various types of polyelectrolytes. For in- stance, Li et al. [174] proposed the buildup technique of LbL for opposite-charge building blocks (e.g., cellulose nanocrystal (NCC), polyethyleneimine (PEI), cis-aconityl-doxorubicin (CAD), and building blocks of folate (FA)). The highly negative charge of NCC serves as an anchor to carry the positive-charge PEI through electrostatic interaction as an intermediary layer. The coordination of NCC-PEI resulted in positive-charge material for electrostatic adsorption of the negative charge of FA and CAD to construct the outermost layer, which took place sequentially (denoted as FA/CAD@PEI@NCC). The presence of FA on the surface carrier increased the active targeting ability

towards folate receptors in the tumor cell. Cis-aconityl amide linkage in doxorubicin (CAD) can specifically release DOX at the lysosomal pH due to the pH labile characteristic and hydrolysis cis-aconityl amide linkage by β-carboxylic acid under low pH. The integration of each layer can increase the uptake to 20 times larger than its counterpart due to the strong electrostatic charge. Besides the surface chemistry carrier, the carrier 's morphological structure also helps the carrier delivery reach tumor cells [174]. Another potential form of polyelectrolytes, in- cluding hydrogel, aerogel, lightweight porous materials, and integrated inorganic–organic composites, are thoroughly discussed in the following sections. 6. Hydrogel Based Nanocellulose for Drug Delivery

4**Hydrogels are three-dimensional** (3D) **cross-linked polymeric networks that**

carry absorbed water and store a large quantity of water in the swelling state. The hydrogels can be cross-linked through physical (non-covalent interaction), chemical (covalent co- ordination), or an integration of both physical and chemical cross-links [175]. Given its biocompatibility and stimulus-responsive swelling behavior, the hydrogel has gained atten- tion for drug delivery application. As a drug carrier the physically cross-linked hydrogel is preferable to the chemically cross-linked hydrogel. The covalently cross-linked hydrogel generates a permanent structure that limits the swelling ability, and therefore, most chemi- cally cross-linked hydrogels are used as implantables. Furthermore, the incorporation of the drug via adsorption towards chemically cross-linked hydrogel restrains the loading efficacy. Although the cross-linked reaction may perform drug conjugation on the hydrogel, it sacrifices the chemical integrity of the drugs. Therefore, it is more desirable to construct a hydrogel delivery system where simultaneous gel formation and drug adsorption can occur in an aqueous environment without covalent cross-linking. Due to the presence of sol-gel transition characteristics (such as swelling behavior, me- chanical strength, and network structure), which are affected by the external stimulus such as pH, thermal, light wavelength, ultrasonic waves, pressure, magnetic field, and electrical field; the smart hydrogel-based nanocellulose has been well-developed for various drug delivery formulation. Diverse types of polyelectrolytes can modify the substantial charge of nanocellulose (either positive and negative) to form a variety of intelligent hydrogels such as injectable hydrogel [161], stimuli-responsive hydrogel [176], double-membrane hydrogel [177], supramolecular hydrogel [178], microsphere hydrogels, bacteria cellulose hydrogel [179], shape memory-based bacteria cellulose [180], and aerogel/cryogel [174]. All those hydrogels have desirable physical and chemical characteristics to be adapted to various drug delivery systems. Liu et al. [161] reviewed the current development of nanocellulose-based hydrogel and its modification for drug delivery systems. How- ever, double-membrane hydrogel and supramolecular hydrogel are excluded from their review [161]. Different types of hydrogels have diverse morphological structures, network coor- dination, and functional groups, affecting the drug's diffusional path during adsorption and release. Double-membrane hydrogel was developed by Lin et al. [177], consisting of an external membrane composed of alginate and consolidation of cationic NCC (CNCC). Two different drugs were introduced on different layers of the membrane with contrasting types of release behavior. The outer hydrogel releases the drug rapidly, while sustained drug release occurs in the inner membrane hydrogel. This phenomenon occurred due

6**to the 'nano-obstruction effect' and** 'nano-locking **effect' induced by** CNCC components in **the**

hydrogels. The 'nano-obstruction effect' offers sustained drug release throughout fragmentary disintegration, and the 'Nano-locking effect' is responsible for restricting the burst of drug release through progressive hydrogel disintegration (Figure 10). The different compositions and properties of external and internal hydrogels affect the drug's behavior and diffusional path [177]. sustained drug release occurs in the inner membrane hydrogel. This phenomenon oc- curred due

6**to the 'nano-obstruction effect' and** 'nano-locking **effect' induced by** CNCC components in **the**

hydrogels. The 'nano-obstruction effect' offers sustained drug release throughout fragmentary disintegration, and the 'Nano-locking effect' is responsible for restricting the burst of drug release through progressive hydrogel disintegration (Figure Polymers 2021, 13, 205120). The different compositions and properties of external and internal hydrogels affect the drug's behavior and diffusional path [177]. (A) (B) Figure 10. (AF)igTuhree r1o0u.t(eAf)aTbhreicraotiuotne foafbsriincagtlieonmoefmsibnrgalneemaenmdbdroaunbelaen-mdedmoubbrlaen-mememicbrroasnpehmeriecrhoysdprhoegreelhwyditrhoi-ts optical (this figure isdoreupbrlien-mtedemwbirtahnpeemrmicirsossiopnhefrreomhyrderfo.g[1e7l7(]t.hiCsofipgyurrieghist r©ep2r0i1n6teAdmweitrhicpanerCmhisesmioincaflroSmocireetfy.)[;1(7B7)].schematic microscope ogfeslinwgiltehmitesmopbrtiacnael mSAic/rCosNcoCpCemoficsrionsgplehemreemhybdrarongeeSlAan/CdNSACC/CmNicCrCosdpohuebreleh-mydemrobgrealnaenmdSicAro/CspNhCerCe hydrogel Copyright © 2016 American Chemical Society); (B) schematic illustration of dual drug release mech- illustration ofandiusaml dfrroumg raeldeaosuebmle-elcahyaenrimsmemfrbormanae dhoyudbrloeg-lealyceornmstermucbteradnferohmydCroagtieolnciocnNstCruCctaenddfrAolmginCaatteio(nthicisNCC and Alginate (thisfifigguurereisisrereddrarawwnnfrforommLLinineettaal.l.[1[17777].].CCooppyyrirgighhtt ©22001166AAmmeerircicaannCChheemmicicaallSociety). SupramoleculSaurphryamdroolgeeculslahrahvyedbreoegnelcshhaarvaectbeerieznedchaasrathcteer3i-zDedsoalsidthnee3t-wDosroklihdyndertow-ork hydrogel dination, andtcioanti,oann-dπ caantdioπn--ππrainndteπra-πctiionntesr.aIcnticoonnst.rlanstcotonttrhaestchtoemthieccahlleymcircoaslsly-licnrkoessd-lhinyk-ed hydrogels, gel organizedobrgyannoizne-dcobvyalneonnt-icnotveraalecntitoninstesruacchtiaosnshysudcrhogaesnhlyindkroaggeen,hlyindkraogpeh,ohbyidcrcoopohr-

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includ- ing host–guest complexation, biomimetic interaction, hydrogen bonding, stereo-complex including
host–guest complexation, biomimetic interaction, hydrogen bonding, stereo- formation, and ionic and metal-
ligand. Hydrogel-based supramolecular self-assembly through host–guest complexation is the most widely
explored method for supramolecular hydrogel formation. Specifically, supramolecular hydrogels constructed
by host–guest inclusion between polymer and cyclodextrin demonstrated the thixotropic reversibility, which
is advantageous for syringe drug delivery. Lin and Dufresne et al. [178] produced supramolecular hydrogel
DDS by self-assembly of a covalently grafted α-cyclodextrin (α-CD) NCC surface with epichlorohydrin as a
cou- pling agent through a one-step process. Furthermore, pluronic composed of triblock copoly- mers

> 2**with different molecular weights (Pluronic F68 or F108), both bearing hydrophobic**

> 2**host–guest inclusion between polymer and** cyclodextrin demonstrated **the**

thixotropic re- versibility, which is advantageous for syringe drug delivery. Lin and Dufresne et al. [178]
produced supramolecular hydrogel DDS by self-assem- bly of a covalently grafted α-cyclodextrin (α-CD)
NCC surface with epichlorohydrin as a

> 2**coupling agent through a one-step**

process. Furthermore, pluronic composed of trib3l1oocfk47

> 2**copolymers with different molecular weights (Pluronic F68 or F108), both bearing** hydro- phobic **poly-(propylene glycol) (PPG) and hydrophilic poly(ethylene glycol) (PEG**) seg- ments (**PEG-b-PPG-b-PEG**

), were immobilized on NCCs via the inclusion interaction be- twp(PoeEelynG--(tbph-rePohPpyGydl-erbno-
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amount of NCC loaded in supramolecular hydrogels [178]. FFigiguurere1111.. Construction pathwayooff(I(I))

> 2**cellulose nanocrystal (β)CD-g**-CNggraraftfetedd **β**

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> 2**inclusion between (β)CD-g-CN**/Pluroniacnadnd **α-CD(a**()a) **hydrogel CN-CD/F68**

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> 2**b) hydrogel CN- CD/F108-2** andits morphological evidence, (**c**(c))**water, (d**()dd)rug-**loaded** hydhryodgreolgCeNl-**CD/F108-2-Dox**

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A©m20e1ri3caAnmCehriecmanicCalhSeomciiectayl.Society. Kopac et al. [181] pointed out that the main

parameter for controlling the drug deliv- ery rate in an anionic hydrogel-based nanocellulose is the average pore size (mesh size), controlled by selecting cross-linked and biopolymer concentration along with the adjust- ment of pH and temperature. The changes in the ionic strength and hydrogen bonding of functional groups in the internal hydrogel structure are responsible for altering the polymeric hydrogel network, which affected the average pore size of hydrogel (Figure 13). Due to the smaller hydrodynamic size of the drug relative to the mesh size, the drug can rapidly diffuse through the hydrogel network and vice versa without a steric barrier. However, both drugs can have a similar

> 32**drug release** rate **by modulating the** mesh **size** through cross-linking **density and**

biopolymer ratio variation [181]. s 2021, 13, x 33 of 49 Figure 12. ScFhigemuraeti1c2i.llSucshtreamtioanticofilpluosstsriabtlieonlocokfipnogsesfifbelcet loofctkhiengdreuffgevctiaohfothste–gduruesgt viniacluhsoisotn–ginuessutpirnacmluoslieocnulianr hydrogel Polymecrso2n0s2t1r,u1c3t,exd sfurpomramcyoclelocduleaxrtrhinydarnodgeclhceomnsictraullcytemdofrdoimfiedcynclaondoecxrtyrisntaallnindeccheelmluilcoaslely(tmhiosdpifiicetdurneani [17348].of 49 Copyright ©c2e0ll1u3loAsem(ethriicsapnicCthueremiiscareldSroacwienty.f)rom [178]. Copyright © 2013 American Chemical Society.) Kopac et al. [181] pointed out that the main parameter for controlling the drug deliv- ery rate in an anionic hydrogel-based nanocellulose is the average pore size (mesh size), controlled by selecting cross-linked and biopolymer concentration along with the adjust- ment of pH and temperature. The changes in the ionic strength and hydrogen bonding of functional groups in the internal hydrogel structure are responsible for altering the poly- meric hydrogel network, which affected the average pore size of hydrogel (Figure 13). Due to the smaller hydrodynamic size of the drug relative to the mesh size, the drug can rapidly diffuse through the hydrogel network and vice versa without a steric barrier. However, both drugs can have a similar

> 32**drug release** rate **by modulating the** mesh **size** through cross-linking **density and**

biopolymer ratio variation [181]. Figure 13. Schematic illustrationoffthe swelling mechanismooff hydrogel fabricated from TEMPO-mediated CNFs and alginate towards drug release (this figure is redrawn from [181]. Copyright © 2020 Elsevier B.V.). 7. Lightweight Porous Based Nanocellulose for Drug Delivery Lightweight porous materials have been classified as a 3-D solid class of material with several features

> 33**such as high specific surface area**, very **low density**

(<50%), and di- verse pore structure with

> 3**various pore** sizes **ranging from nanometer to micron**

. Sponge, foam, and aerogels

> 3**are the three** major categories **of lightweight porous materials**

. The 7. Lightweight Porous Based Nanocellulose for Drug Delivery Lightweight porous materials have been classified as a 3-D solid class of material with several features

> 33**such as high specific surface area**, very **low density**

(<50%), and diverse pore structure with

> 3**various pore** sizes **ranging from nanometer to micron**

. Sponge, foam, and aerogels

> 3**are the three** major categories **of lightweight porous materials**. The sponge **is** constructed **by**

gas dispersion in the solid matrix, commonly present as an open cell structure of low density porous elastic polymer. The sponge has a macroporous structure full of gaps and channels, permitting easy access to water or molecules flow [182]. Similarly, foam can be made through the steady gas dispersion into a hydrogel or solid matrix and even liquid. Foam is commonly characterized as having a bubble diameter (pore diameter) greater than 50 nm [183]. Aerogel is a three-dimensional (3D) porous material constructed by self-assembly of the colloidal component or polymeric chains, creating nano-porous networks that can be filled up with a gaseous dispersion medium. Aerogel is prepared through the wet-gel drying process by removing the liquid component in the hydrogel, which is replaced by a gas constituent while still preserving the gel network [184]. The specific surface area of aerogel can reach up to 1000 m2 g−1 with a porosity

range between 80 and 99.8%. On the other hand, other aerogels, namely xerogel and cryogel, have been prepared by evaporation and freeze-drying. Detailed preparation of light-weight porous material-based nanocellulose has been reviewed elsewhere [185]. For the drug delivery field, carrier morphology, especially the porosity structure, controls the drug adsorption and release since the drug will pass through the internal pore to be retained inside and release outside regardless of the chemistry interaction. Sun et al. [186] underlined that the critical factor in controlling and modulating the pore structure of ultralightweight porous materials is selecting a drying method [186]. Initially,

3**freeze-drying, supercritical drying, and evaporation drying**

have been utilized in fabricat- ing ultralightweight porous materials. Evaporation drying has emerged as a conventional technique of synthesizing

3**nanocellulose-based porous materials**. However, **there are**

sev- eral major drawbacks, such as

3**internal network structure** collapse **due to** the **capillary** forces **of the solid matrix** and the difficulty **to**

prevent the shrinkage. Therefore,

18**freeze- drying and supercritical drying have been** used **as** drying **methods**

to overcome these drawbacks. Freeze

3**drying can retain the** porous **structure** through **the** sublimation **of**

liquid into gas.

3**It is** also **possible to cross the solid–gas**

interface bypassing the liquid critical point through adjusting the temperature and pressure (supercritical drying). Both methods

3**effectively retain the pore structure** and refine **the**

porosity and specific surface area of nanocellulose-based porous materials. Aerogel-, xerogel-, and cryogel-based nanocelluloses are promising materials as the vehicle for a drug delivery system. Before the drying process,

4**physical and chemical cross- linking are** vital in controlling **the**

3D network formation and porous material performance. Physical cross-linking is commonly established by weaker

25**interactions such as Van der Waals, hydrogen bonding**, and **electrostatic interaction**. In contrast, **covalent**

cross-linking can create a 3-D robust mechanical framework through the action of covalent coordina- tion and polymerization. Chemical cross-linking exhibits better mechanical stiffness and structural stability compared to physical cross-linking. Muller et al. [180] synthesized water-responsive xerogel to retain its original shape by submerging it in water through moisture utilization as the stimulus. The post-modification of BNC with the different supplementary hydrophilic substances was performed to achieve the re-swelling behavior. Rapid re-swelling behavior can be acquired by supplementary magnesium chloride, glucose, sucrose, and sorbitol with up to 88% maximum rehydration. Their findings of re-swelling modified BNC showed the possibility of developing a carrier with controlled release properties for hydrophilic drug model azorubine in the drug delivery system. Li et al. [174] synthesized two types of nanocellulose/gelatin composite cryogels through

6**hydrogen bonding and chemical cross-linking with** dialdehyde starch (**DAS**

) for controlled drug delivery of 5-fluorouracil (5-FU).

6**DAS subsequently** reacted **with both** gelatin **and** CNF **to form** the **chemically cross-linked network**. The reaction of **aldehyde groups with the hydroxyl groups of** CNFs led **to** the formation of **hemiacetal/acetal** types **of** structures. Furthermore, **the aldehyde**

group presence effectively integrates

6**with the ε-amino groups of gelatin to** generate **a Schiff base**

coordination. They found

6**that the chemical cross-linking of**

Schiff bases and hemiacetal/acetate is crucial to regulate the structural porosity of cryogel composite. Since the porosity and cross-linking degree mainly control drug loading, selecting the chemical cross-linking method is crucial. Moreover, the presence of gelatin hydration capability and reversible hydrolysis characteristic of hemiacetal/acetate, along with its morphological structure, is also respon- sible for achieving

6**controllable and sustained release of 5-FU in**

a simulated intestinal environment. In addition, the

4**cross-linking degree and** the porosity **can be** tuned **by**

the composition and ratio of CNF, gelatin, and dialdehyde starch. The addition of CNF in- creases the drug loading and the cross-linking degree [174]. Figure 14A shows that the improvement of surface roughness and cross-section morphology reduces the pore size of cryogel, leading to an increase in the cryogel resistance against ice crystal growth during freeze-drying, resulting in the smaller pore size, higher specific surface area, and lower ers 2021, 13, x density. The smaller pore size leads to better drug loading and releases 3e6ffiocfie49ncy since the smaller pore structure limits the drug looseness (Figure 14B). (A) (B) Figure 14.
(AF)iSgyunreth1e4s.is(Apa)tShywnathyeasinsdpmathowrpahyolaongdicmalosrtpruhcotluorgeicoafl sdtirfufecrtuenret roaftidoifofefreNnFtCr/atGioeloaftinNFRCN/FGCe/lGaetliantin: (a,b) NGDC1/9; (c,dR)NNFCG/GDelaCtin3:/(a7,;b(e),Nf)GNDGCD1C/95;/(c5,.dS)uNrfGacDeC(a3–/7c;);(ecr,fo)sNs-GseDctCio5n/5(.bS,du,rff)a;c(eB()at–hce);incrflousesn-sceecotifomno(brp,dh,of)l;o(gBic)athlsetructure of NFC/GelatiinnfClureynocgeelotfomwoarrpdhsodlrouggiclaolasdtrinugct(ulreeftosfidNeF)Can/GderlealteinasCereyffiogcieeIntcoyw(arrigdhstdsriudge)lo(Tah sisidree)parinndted with permission frormele[1a7s4e]e.fCfiocpieynrciygh(rti©gh2t0s1id9eA)m(TehriiscafinguCrheeimsriceaplrSinotceidetwy)i.th

30**permission from** [174]. **Copyright** © 2019 **American Chemical Society**). Zhao **et al**

. [187] prepared polyethyleneimine (PEI) grafted to amine-modified CNF Zhao etaanld. [c1r8o7s]sp-lrinepkeadreduspinoglyegtlhuytalernaledimehinyede(PtEoI)fogrrmaftaend atoeraomgeinle(C-mNoFdsi-fPieEdI)C.TNhFe success of and cross-linthkeedauersoinggelgflourtmaraatlidoenhyddeepetondfosromnatnheaeprooglyeml(eCrNizaFtsi-oPnEIo)f. Tmheethsuyclcmesesthoafcthryelate (MMA) aerogel formation depends on

3**the polymerization of methyl methacrylate (MMA**) on **the** surface **of**

CNFs, which induced the

3**formation of** the **network between PEI and CNF**

. Pol- yethyleneimine (PEI) carries some

3**primary and secondary amine** functional **groups, which**

increase the loading of sodium salicylate (NaSA) to 20 times higher than its coun- terpart (CNFs-based aerogel). The sustained and controlled release was achieved by the

31**on the surface of** CNFs, which induced **the formation of** the **network**

between PEI and CNF. Polyethyleneimine (PEI) carries some

3**primary and secondary amine** functional **groups, which**

increase the loading of sodium salicylate (NaSA) to 20 times higher than its counterpart (CNFs-based aerogel). The sustained and controlled release was achieved by the CNFs-PEI aerogel, which is highly responsive to pH because of the protonation and deprotonation of amine groups in PEI [187]. Chemically cross-linked PEI with TEMPO-mediated BC CNF (abbreviated as PEI- BC) for aspirin, gentamicin, and bovine serum albumin (BSA) carrier has been studied by Chen et al. [156]. The PEI cross-linking induced the morphological changes of BC by increasing the density of interconnected structures and thickening the pore walls, which provide the CNF interpenetrated network with improved mechanical strength [156]. Liang et al. [188] proposed a well-balanced dual responsive polymer (temperature and pH) by modifying branched PEI with N-isopropyl acrylamide (NIPAM), which was further grafted onto CNF through the condensation reaction (abbreviated as CNF-PEI-NIPAM). Re- markably, the pH and temperature of the carrier can alter the hydrophobic and hydrophilic characteristics of CNF-PEI-NIPAM [188]. CNF has been combined with the non-edible surfactant to make air bubble confine- ment by the Pickering technique, generating stable air bubbles encapsulated in wet-stable foams. Using the unique drying technique, the dry-foams with closed holes (cellular solid material-CSM) were made. Although the three-dimensional closed-hole structure presents a fascinating drug delivery system for the prolonged release of the drug because of con- fined stable air in the internal foam's structure, such structure may induce an elongated diffusional path of medicine to modify the characteristic drug release. CNFs foam as a drug carrier with the positive buoyancy characteristic was synthesized by Svagan et al. [189]. Positive buoyancy characteristics resulting from the presence of air are retained in the closed cells. These primary characteristics highlight the practicability of CNFs foam as a floating agent for

9**gastro retentive drug delivery** systems **for site-specific drug release**

such as intestinal and stomach systems. CNF foams were synthesized by combining the cationic suspension of CNF

9**with the** consumable **surfactant (lauric acid sodium salt) as a foaming**

reagent. Subsequently, hydrophilic drug riboflavin was confined in the wet-stable CNFs foam structure and was further dried to acquire dry foam with a close hole structure with up to 50% drug loading (Figure 15A). The CNFs foam offers structural flexibility with different porosity and tortuosity, which can be modified in terms of shape and thickness and can be sliced into different pieces. An increase in the foam thickness leads to a decrease in the riboflavin release rate. In addition, the morphological foam structure showed

9**a long and tortuous diffusion path**

, prolonging drug diffusion (Figure 15B). Therefore, the

9**diffusion coefficient of** the **drug through the** porous **foam** structure **was** lower **than** the diffusivity **of**

the drug in the film structure [189]. The addition of surfactant is required to synthesize stable dry-foam-based cellulose nanofibers. Lobmann et al. [190] proposed an innovative way to synthesize stable foams by combining cationic CNF and hydrophobic drug indomethacin. Hydrophobic drugs provided a positive molecular interaction by partially covering the hydrophobic side of CNFs, which further changes the surface energy of CNFs. However, the indomethacin loading in the foams was limited to up to 21% of the loaded drug. An excessive amount of drug loading would destabilize and collapse the foam's structure since a higher fraction of free indomethacin and solvent in the solution was present in the air–water interface, which limited the surface-modified CNF aggregation [190]. (Figure 15A). The CNFs foam offers structural flexibility with different porosity and tor- tuosity, which can be modified in terms of shape and thickness and can be sliced into different pieces. An increase in the foam thickness leads to a decrease in the riboflavin release rate. In addition, the morphological foam structure showed

9**a long and tortuous diffusion path**

, prolonging drug diffusion (Figure 15B). Therefore, the

9**diffusion coefficient of** the **drug through the** porous **foam** structure **was** lower **than** the diffusivity **of**

the drug in the film structure [189]. (A) (B) Figure 15. (A). Preparation route of CNF-based foams and its morphological, structural characteristic: (a): CNF-based foams cross-section morphological image; (b) cell structure image of CNF/LA loaded with riboflavin (the arrow points to riboflavin). (B) elongated diffusional pathways of the drug in foam-based CNFs (this figure is redrawn from Svagan et al. [189]. Copyright © 2016

Elsevier B.V.). Svagan et al. [191] performed similar assembling of controlled-release CNFs foam with buoyance characteristics utilizing the poorly soluble drug furosemide as a foaming agent. They highlighted several factors such as the amount of drug loading, the foam piece dimension,

> 10**and the** solid-**state of the** incorporated **drug** that influenced **the** kinetic **release**

of the drugs. Regarding the solid-state of the drug within the closed cell of foam, at 21% furosemide loading in foam, furosemide mainly exists in an amorphous state of furosemide salt, which leads to rapid release with the increase of the drug loading. In addition, the mass of incorporated drugs inside the foam structure can provide different foam dimensions, which alter the drug release kinetics. Bannow et al. [192] investigated

> 9**the influence of processing parameters on the** foaming characteristic **and structure of**

nanofoam CNF/indomethacin. They found that the nanofoam density and the number of entrapped air bubbles depend on the pH, the mass of confined drugs, and the preparation route (pre- or post-adjustment of pH) [192]. The development of sponge-based nanocellulose for the drug delivery system by adding citric acid (CA) as a co-cross-linker between branched polyethyleneimine (bPEI) and TOCNFs was conducted by Fiorati and coworkers [193]. CA was added as an auxiliary carboxyl moieties source to improve the cross-linking process to bPEI. They investigated the as-synthesized sponge capability as a drug vehicle for amoxicillin and ibuprofen. The confined drug in the sponge structure with non-contained citric acid moieties exhibited a higher drug release percentage than that with the cross-linker. The presence of citric acid progressively increased the ibuprofen adsorption, while no significant effect was observed for amoxicillin adsorption. The presence of citric acid provided an additional carboxylic group, which was actively involved in the particular interaction with the ibupro- Polymers 2021, 13, x fen molecules. In addition, the existence of CA also refined the mechanical strength and chemical stability of the material through the occurrence of amide bond format3i9onof b4e9tween the primary amines of bPEI and with carboxylic groups of TOCNFs and CA (Figure 16). FigureFi1g6u.rePr1e6p.aPrreaptiaornatiroonurtoeuotef sopfonge-based TOCNFs via crosslinkingofobfPbEPIEanIdanTdOCTONFCsNwFitshwCiAthaCsAacarossaslcinrkoesrs;linker; arrowa(rar)oiws c(aro)siss-linking procpesrso,caesnsd,aanrdroawrro(bw) i(sb)aiusxiliary carboxyl addition (this figure isisreprinted with permission from ref. [19fr3o]m.Creofp.y[1r9i3g]h.tC©op2y0ri1g7hWt©il2e0y1-7VWCHileyV-eVrClaHg VGemrlabgHG&mbCHo.&KCGoa.AK,GWaAei,nWheeiinmh.e)i.m.). 8. 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The targeted delivery of antitumor agents towards canceroNuCsCtismsuaeysaclsaon beuctailrirzieeddatshraonuagnhopthaertiacdlevcaonacteindghfyobrrciodllmoidaatelrsitaalbwiliittyhismtipmrouvlei-or spe-cifimcernect,obginoidtieognracdhaabrilaictyte,rbiisotcicosmtpoaptiabsilsittyh,raonudghchtehmeitcaarlgfeutnecdtisointealsizsaetlieocnt.ivRealhy.imNiaentoa wit[h19t5h]efusnticmtiounlaileizffeedctNrCesCpwonitdh ttroist(h2e-aemxitneorentahlyls)taimmiunleu(sA(Me.FgC.,)pfHor,Fteem3Op4emraagtunereti,cmnaa-gnetic, andnouplatrrtaiscoleusncdoa)tainngd(fAurMthFeCr-NalPtesr).tlhneitiirapllyh,ytshioelnoagnicoaclecllhualorsaectuenridsetricwteonrtetloesayslecthhleortihdeerapeu-tictargeaetnmtewnitthfoar stpries(c2ifi-acmcionnoceethnytlr)aatmioinnetofwunacrtdiosntahleizaaftfioencte(dAMtisFsCuews.aTshcehroesfeonret,othbeetares-atment sysstiegmneadntdotheadmruingosmpeocieifiticeistyancdancabtieoinmicpcrhoavreadct,ecroisntitcrsi)b.uTthinegprteosleenscseeonfinagmsinyostgermouicp NoinneAthMelFeCss-N,tPhsewdarsuglinckaerdrietor bthieocmomethpoattriebxialittey, (MimTmX,uannoagnetniciacnitcye,rtoimximciutyn,orseusppornessisviveeness to madgrnuegt)iccagrrbaodxiyelngtsro,uapnsd. pThroispmeredthroudgwtraasnsepmoprltoaybeidlittyosstuilrlpnaessedthmeuMcThXimlimpriotavtieomnebnyt. kcaeceNypCionfCgamndtoiacwyannaclteshroedborefuf-ugtatdirlegilzeivetedsridya.esT-aihmnepadanrcoutpgtoacwrotnaicfrildnesecmhoeeaantlittnhegyffficcoearlclcsyowrlelhoaicildheeaodlps9tti1am.b2i%izliintwygiittmhhe3p0er.o4ff%vi-ement, bioedffeigcireandcyaboiflidtyr,ubgiolocaodminpgatiinbitlhietyA,aMnFdCc-hNePms.icTahlefuMnTcXti-oAnMalFizCa-tMioNnP.sRasyhsitmemieetxahli.b[i1te9d5] func-tiopnHalirzeesdpoNnsCivCitywiinthwthriisch(2,-aatmaninaoceidthicycl)oanmdiitnioen(A(pMHFoCf5).f4o),ruFpe3toO749m%aogfntehteicdnruagnowpaasrticles coarteilneagse(Ad,MwFhCile-NovPesr)f.ivIneidtiaayllsy,,itthexehnibainteodceulplutolo2s9e%undrduegrwreelenatsetobsyytlhcehplororitodneattrioenatbme-

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target sid(eF-igimurpea1c7t)t[o1w95a].rds healthy cells while optimizing the efficacy of anticancer drug deliv-
ery. The drug confinement efficacy reached 91.2% with 30.4% efficiency of drug loading in the AMFC-NPs.
The MTX-AMFC-MNPs system exhibited pH responsivity in which, at an acidic condition (pH of 5.4), up to
79% of the drug was released, while over five days, it exhibited up to 29% drug release by the protonation
behavior of MTX carboxylic groups. In addition, the nanoparticles containing MTX exhibit a higher uptake of
cellular Polymers 2021, 13, x compared to the AMFC-MNPs, which were contributed to by the chem40icoafl
4s9imilarity of MTX with folic acid (FA), which assists the internalization of receptor-mediated cellulose. This
enhances the potential of MTX for cancer cell targeting (Figure 17) [195]. (a) (b) Figure17.17(a.)
M(aa)gnMetiacgNneCtCic-bNaseCdCn-banaosceadrrineranwoitcharprHie-rreswpiotnhsivpeHc-
arpeasbpiolitnysicvoenstcraupctaiobnil.itTyheconstruction.
nnTaonhetoehcyenll)lauanmlooisnceeel(wlAuaMlsoFsuCen)dwfeurnagscotiinougnnadltioezsraygtilooantiin,oginn,ctoworsphyoiclrhaattiinroegna,actmewdin
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interac- (MtioTnX@imApMrFoCv@emMNenPts,)w;ahnidch(bc)osnchneemctaetdic
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rceidspaonndsMivTeXa,nwdhlicohcaalsiszisattsion of cancer treatment that benefited from the structural
similarity between folic acid and MTX, which assists the folate-receptor-mediated cell internalization (this
figure is redrawn from [195]. Copyright 1987 Royal Society Of Chemistry). Recently, Supramaniam et al.
[196] introduced magnetic characteristics towards nanocellulos-based hydrogels, which were further utilized
for controlling drug deliv- ery. The co-precipitation with Fe (II) and Fe (III) ions was incorporated into the
NCCs, followed by the insertion of the magnetic characteristic, and subsequently, morphologically modified
into beads with sodium alginate. It was observed that the magnetic nanocellu- lose existence refines the
physical and mechanical characteristics of hydrogel beads and swelling degree improvement and limits the
drug release due to the formation of physical entanglement inside the hydrogel. Jeddi and Mahkam [197]
developed magnetic hydro- gel beads composite-based carboxymethyl nanocellulose to deliver
dexamethasone. The composite can control the dexamethasone delivery up to 12 h. Carbon nanotubes
have outstanding characteristics such as high thermal stability, homogenous pore arrangement, high specific
area, and excellent electrical features. This advanced material has also been employed as a vehicle

> 25**in the drug delivery system** in recent years. **The** combination **of**

this material with the NC material provides some advantages. The incorporation of nanocellulose in the
composite increased biocompatibility and biodegradability while the CNTs provided good stability, magnetic
and electromagnetic behavior, and high cellular uptake [198]. Although the cytotoxicity of material still
became an issue, CNTs were widely exploited in drug delivery systems, particularly cancer therapy
applications [199]. Integration of nanocellulose into graphene-based materials through the layer-by- layer
assembly as a drug carrier was carried out by Anirudhan et al. [200]. Chemically modified GO was used as a
template for the

> 22**layer-by-layer assembly of** aminated nano- dextran (**AND**) and carboxylic **acid**

functionalized nanocellulose (NCCs) to form a MGO- AND/NCCs nanocomposite. Curcumin can be loaded
into the carrier through π–π stacking and hydrogen bonding interactions due to the phenolic and aromatic
rings of curcumin. Based on the release study, the acidic environment promotes COO- groups' protonation
and amino in aminated in nano-dextran to form NH3+. This phenomenon decreased the static interaction
between MGO-AND/NCC, resulting in the electrostatic repulsion of each component, consequently
provoking the drug release. In addition, a cytotoxicity assay on HCT116 cells exhibited high efficacy of
curcumin-loaded MGO-AND/NCC. The electrochemical activity of the carbon nanotube was utilized

> 4**to modulate the drug release. The** release **of**

ibuprofen from

> 24**a novel hybrid hydrogel composed of sodium alginate (SA), bacterial cellulose (BC), and multi-walled carbon nanotubes (MWCNTs) was**

studied by Shi et al. [176]. The release of ibuprofen can be provoked by electrostatic repul- sion. Thereby,
the on–off release mechanism can be attained by introducing electrochemical potential [176]. 9. Conclusions
Modified and functionalized nanocelluloses with low toxicity and high biocompatibil- ity render them
promising materials as advanced drug carriers. Various hydroxyl groups on the surface of the nanocellulose
serve as attachment sites of drugs through covalent and/or physical interactions. In addition, nanocellulose
modification results in a different morphological structure for the carrier, which contributes to an increase in
the diffusion pathway of the drug within the carrier. Therefore, surface chemistry is a crucial factor that
should be considered in the design

29of nanocellulose as a drug carrier for effective drug delivery

. High-purity nanocelluloses are also required to obtain drug carriers with the well-constructed framework, thus facilitating drug adsorption and release control. Considering all these factors, carrier-based nanocellulose is a promising candidate for developing novel sustained drug delivery systems. Author Contributions: Conceptualization V.B.L., F.E.S. and S.I.; redraw the figures V.B.L. and M.Y.; drafting the manuscript V.B.L., J.N.P., S.P.S. and S.I.; Supervision S.I. and F.E.S.; review and editing, J.S, and Y.H.J.; proof reading J.S. and Y.H.J.

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13Directorate of Research and Community Service, Deputy for Strengthening Research and Development, Ministry of Research and Technology/National Research and Innovation Agency, Number: 150J/WM01.5/N/2021. Institutional Review Board Statement: Not applicable. Informed Consent Statement: Not applicable

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