

纤维素纳米纤丝复合材料在药物缓释中的应用



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摘要：纳米纤维素具有可再生、环境友好、可生物降解、比表面积大、弹性模量高、生物相容性好等优异特性。利用纤维素纳米纤丝开发药物载体材料，有助于促进农林生物质资源的高值化应用。本文系统地综述纤维素纳米纤丝复合水凝胶材料、复合气凝胶材料、复合膜材料在药物缓释领域的研究现状，阐述其药物缓释机理，并展望纳米纤维素在药物缓释领域的发展方向。

关键词：纤维素；纤维素纳米纤丝；药物缓释

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Application of Cellulose Nanofibrils Composite Materials in Drug Release System

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Abstract: Nanocellulose has many excellent characteristics such as renewable, environmentally friendly, biodegradable, large specific surface area, high elastic modulus and good biocompatibility. Using nanocellulose to develop drug carrier materials is helpful to promote the high-value application of agricultural and forestry biomass resources. The recent advances of cellulose nanofibrils composite hydrogels, composite aerogels, and composite films in drug release system were reviewed in this paper. The mechanism of drug release was explained in detail. The development trend of nanocellulose in the field of drug release was envisioned.

Key words: cellulose; cellulose nanofibrils; drug release

由于化石资源的过度开发及人们对环境问题的日益关注，利用可再生的生物基材料替代传统的石油基材料已经引起人们的高度重视^[1]。纤维素作为世界上储量最丰富的生物基材料，具有可再生、环境友好、可生物降解、廉价等优点，在制浆造纸及食品领域得到了广泛应用^[2-3]。随着纳米技术在生物质精炼方向的迅速发展，研究人员发现利用纤维素制备得到的纳米纤维素，除具有纤维素的优良特性外，还具有质轻、弹性模量高、比表面积大、生物相容性好等优异特性^[4-7]。纳米纤维素基材料因其具有较好的生物相容性、可生物降解性、优异的力学

稳定性，成为了生物医学领域（例如药物缓释载体、促伤口愈合敷料、组织工程支架等）的重要材料^[8-10]。

纳米纤维素主要包括纤维素纳米纤丝（cellulose

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nanofibril, CNF)、纳米纤维素晶体 (cellulose nanocrystal, CNC) 和细菌纤维素 (bacterial cellulose, BC) 等^[11]。目前, CNF 复合药物载体有多种形式, 包括水凝胶、气凝胶、膜材料等 (图 1)^[12-14]。受材料内部结构的影响, 不同药物缓释体系的释药过程和释药机理存在差异。将 CNF 应用于药物缓释领域通常采用以下 2 种方式: ①直接添加 CNF 到高分子材料的三维网络结构中, 制备不同形式的复合材料, 该方法具有简单、易操作的优点; ②通过接枝改性的方式, 将其他高分子聚合物接枝到 CNF 上, 可以赋予 CNF 环境敏感特性, 比如温度和 pH 敏感释药特性等^[15]。本文主要综述了 CNF 复合水凝胶材料、复合气凝胶材料和复合膜材料在药物缓释领域的研究进展。

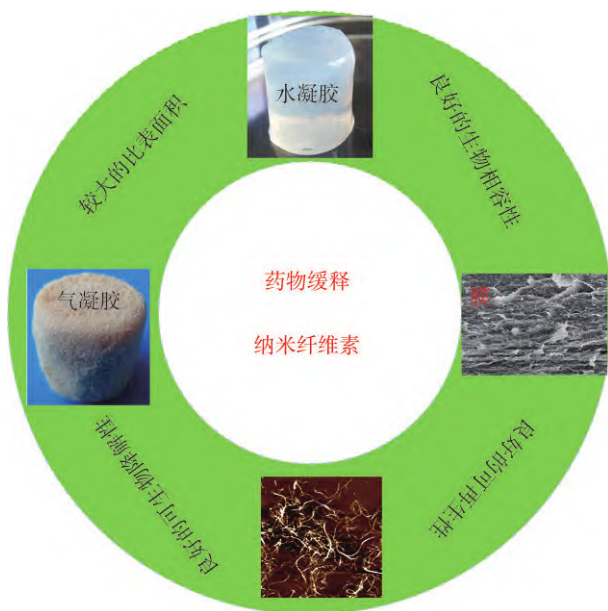


图 1 CNF 基药物缓释材料^[12-14]

Fig. 1 CNF-based materials for drug release^[12-14]

1 CNF 复合材料的性能特点

CNF 复合材料应用到药物缓释领域, 需要具备良好的强度性能、表面化学性能、较好的生物相容性和可生物降解性等^[16-17]。

1.1 强度性能

CNF 复合材料应用到药物缓释领域需要较好的杨氏模量、拉伸强度和韧性等^[18]。CNF 结晶结构中无序的无定形区和有序的结晶区赋予其良好的强度性能^[19-20], 其中无定形区有助于材料可塑性和柔韧性的提升, 结晶区决定了材料的弹性和硬度^[20-22]。

1.2 表面化学性能

CNF 的表面性质决定了其对不同药物的负载能力^[23-24]。CNF 表面的羟基和羧基等基团为其表面改性提供了反应平台。表面改性的主要目的是在 CNF 的表面引入新的官能团来负载药物, 而不改变 CNF 基材料的形态、化学结构和结晶性能等^[25]。另外, 还可以通过静电结合等方式实现对药物的负载。

1.3 生物相容性

CNF 复合材料应用到药物缓释领域需要较好的生物相容性^[26]。据报道, 采用酶法制备得到的 CNF 在 10~1000 $\mu\text{g/mL}$ 的浓度范围内无细胞毒性^[27]。CNF 较好的生物相容性可能来源于其独特的三维纳米纤维网络结构, 能够促进细胞的增殖^[28]。

1.4 可生物降解性

纤维素是一种具有可生物降解性的天然高分子, 随着外界温度的升高, 会发生降解, 其主要挥发性分解产物之一是左旋葡聚糖^[29]。纳米尺寸的 CNF 并没有失去可生物降解的性质^[30], 但由于动物和人体细胞不能合成纤维素酶, CNF 在动物和人体组织中的可生物降解性并不清楚。

2 CNF 复合载药材料

2.1 CNF 复合水凝胶

水凝胶是由亲水性聚合物通过非共价键或共价键交联而成, 具有三维网络结构^[31-32]。由于水凝胶具有与软组织相似的物理性质, 使其已广泛应用于药物缓释系统^[33-34]。此外, 水凝胶能够在水中发生溶胀^[35], 当药物负载到水凝胶的三维网络结构中时, 水凝胶能够保护药物, 免受外界环境破坏。另外, 具有环境敏感性的智能水凝胶材料 (例如 pH 敏感型、温度敏感型、场/磁敏感型、光敏感型等) 能够随着外界环境的变化而变化, 从而达到可控释药的目的^[36-37]。复合水凝胶的制备方法有很多种, 通常可以分为物理方法和化学方法 2 类^[38]。物理方法是指通过物理共混或分子链缠结^[39]。化学方法一般利用电离辐射、紫外线照射引发聚合或化学交联^[40-41]。

生物质基水凝胶材料通常具有较好的生物相容、可生物降解性等优点^[42-43]。近期关于 CNF 复合水凝胶材料的制备及其在药物缓释方面的应用引起了广泛关注^[44-46]。CNF 复合水凝胶材料的制备一般是将 CNF 以共混的方式, 直接添加到一些高分子水凝胶的三维网络结构中。一方面, 利用 CNF 较大的比表面积延长药物释放时间; 另一方面, 利用 CNF 较好的机械性能提高复合水凝胶的物理强度^[47-48]。例如, Masruchin

等人^[49]制备了CNF/聚丙烯酰胺复合的pH和温度双响应型复合水凝胶材料,该复合水凝胶的pH响应性可以根据CNF的羧基含量进行控制,同时复合水凝胶的润胀性能也可以通过温度变化控制。Li等人^[50]采用化学交联双醛淀粉的方法,构建了具有可控孔隙度、可逆网络结构的CNF/明胶复合水凝胶材料,该水凝胶可用于药物模型物氟二氧嘧啶的缓释(图2)。结果表明,随着CNF用量和交联程度的增加,药物负载率随之增加。复合水凝胶材料的孔隙结构可以通过CNF和明胶的比例、交联度进行调节。由于双醛淀粉的可逆水解作用,复合水凝胶可以实现氟二氧嘧啶的可控释放,其最长缓释时间为12 h。

另外,离子交联法也是制备CNF药物缓释材料的常用方法^[51]。CNF含有丰富的羧基基团,可以与其他带正电的离子产生非共价键相互作用,在水凝胶中引入静电吸引和离子键。该方法相比于其他化学方法,具有简单、绿色、毒性小的优点。Zhang等人^[37]采用钙离子对海藻酸钠和CNF进行交联制备得到pH敏感型复合水凝胶材料(图3(a)和3(b))。实验结果表明,该复合水凝胶在酸性环境中具有很好的稳定性,继而确保了负载的益生菌在胃液环境中的稳定性。此外,该复合水凝胶能够在人工配置的肠液中润胀,实现益生菌的有效释放。Yang等人^[52]通过两步法制备复合水凝胶,首先进行原位聚合,然后利用CNF表面的羧基进行第二步金属离子交联(图3(c)),制备了CNF增强的聚丙烯酰胺复合水凝胶。结果发现,该复合水凝胶具有很高的强度并且具有一定的弹性,可应

用于医药领域。Xu等人^[53]通过改变CNF阴离子和甲壳素纳米纤维阳离子的比例,自组装合成了具有可调节力学性能和膨胀性能的复合水凝胶(图4)。结果表明,药物的释放行为和复合水凝胶的润胀性能有关。当甲壳素纳米纤维阳离子的比例为40%时,复合水凝胶具有最大的药物负载率和缓释量;当甲壳素纳米纤维阳离子的比例为60%时,复合水凝胶具有较好的强度性能和润胀性能。

本研究组采用钙离子交联的方式制备得到CNF/聚多巴胺复合水凝胶材料,并以盐酸四环素作为药物模型物,研究了其释药性能(图5(a)和图5(b))^[54]。结果表明,该复合水凝胶的药物缓释时间为24 h,是纯CNF水凝胶材料的2.4倍。另外,该复合水凝胶对大肠杆菌和金黄葡萄糖球菌等具有较好的抗菌性能。通过体外小鼠实验发现,该复合水凝胶材料具有较好的促伤口愈合能力。此外,本研究组进一步设计了具有包封结构的CNF复合水凝胶材料(图5(c))^[55]。首先,将药物(盐酸四环素)负载到制备的多孔聚多巴胺上,负载率为35%。然后,利用氧化石墨烯包裹多孔聚多巴胺,用来延长药物释放时间和减少前期的突释现象。最后,采用离子交联的方式得到复合水凝胶材料。研究发现,该复合水凝胶材料具有较好的pH敏感释药特性和近红外光敏感释药特性,并且具有较好的强度性能。此外,该复合水凝胶材料具有较好的长时间释药性能,其缓释时间为72 h,这可能主要来源于氧化石墨烯的包裹作用。其他的CNF复合水凝胶材料在药物缓释领域的应用情况如表1所示。

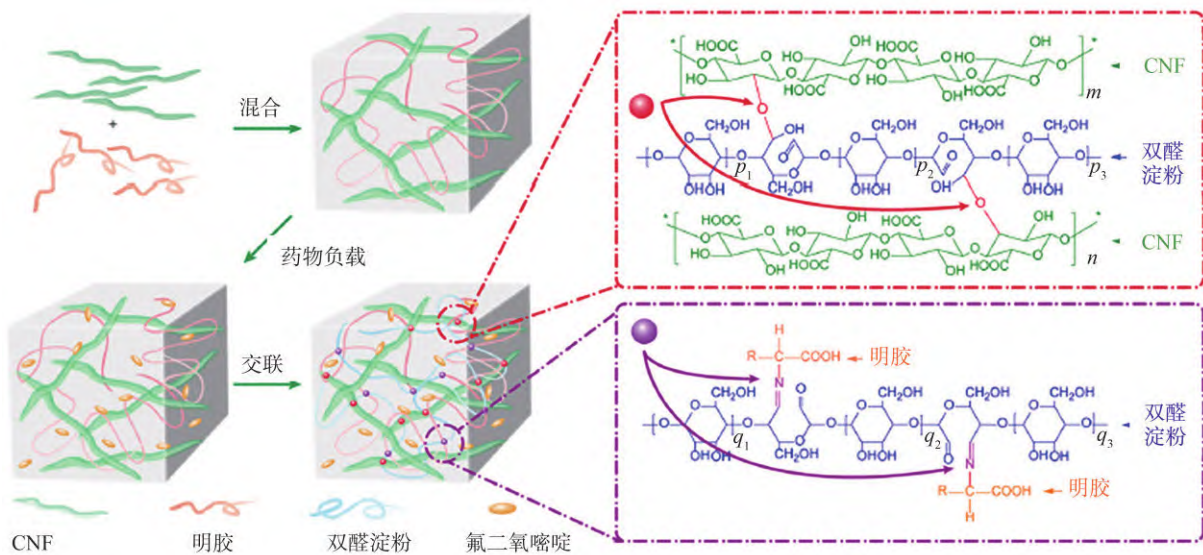


图2 CNF/明胶复合水凝胶材料的制备^[50]

Fig. 2 Synthesis of CNF/gelatin composite hydrogels^[50]

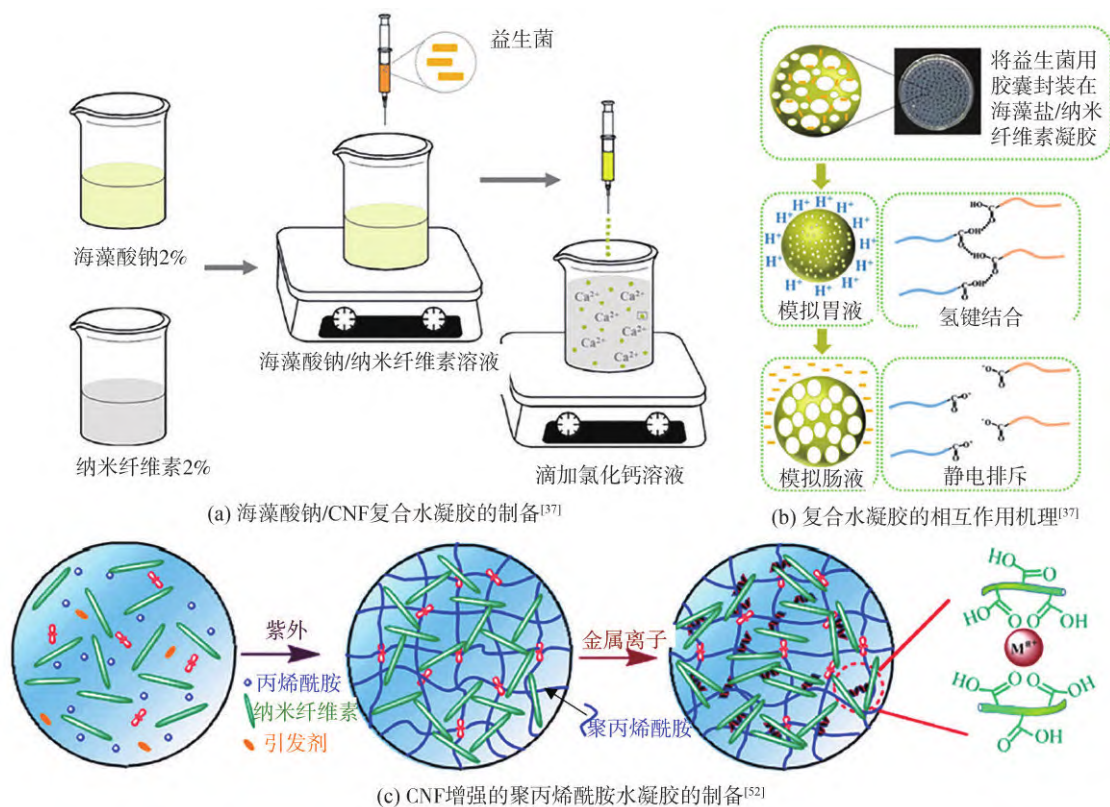


图3 离子交联法制备CNF基复合水凝胶

Fig. 3 Schematic illustration of the preparation of CNF-based composite hydrogels via ion crosslinking method

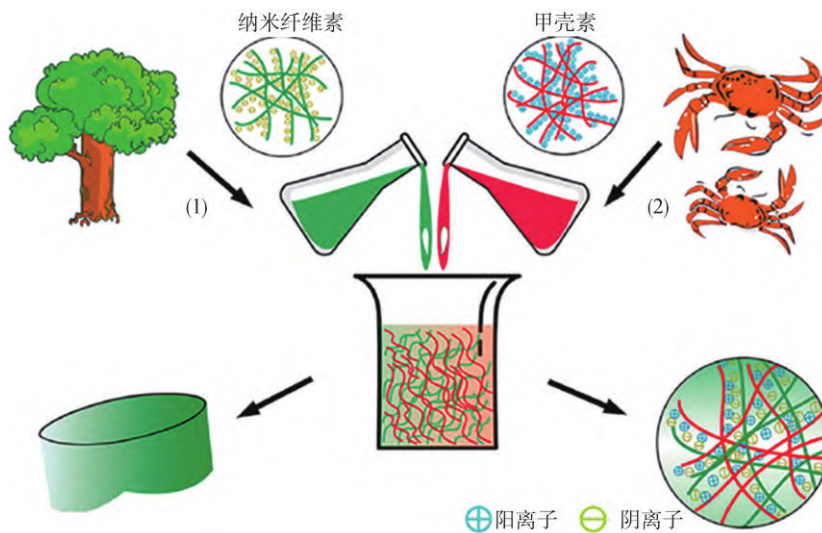


Fig. 4 Schematic illustration of the formation of α -chitin nanofibers/CNF hybrid hydrogel^[53]

2.2 CNF复合气凝胶

CNF复合气凝胶具有较高的比表面积、高孔隙率、可调节的孔隙结构等优点,使其成为优良的药物缓释载体^[62-63]。CNF气凝胶材料通常是由CNF水凝胶材料冷冻干燥得到^[64]。CNF复合气凝胶材料的药物释

放行为可以通过调整CNF和纳米颗粒之间的化学作用进行控制,且不同来源的CNF复合气凝胶材料具有不同的药物释放能力^[65]。CNF复合气凝胶材料的参数主要包括形貌表征、不同pH环境中的润胀行为/释药行为、强度等^[66]。CNF复合气凝胶材料通常是采用

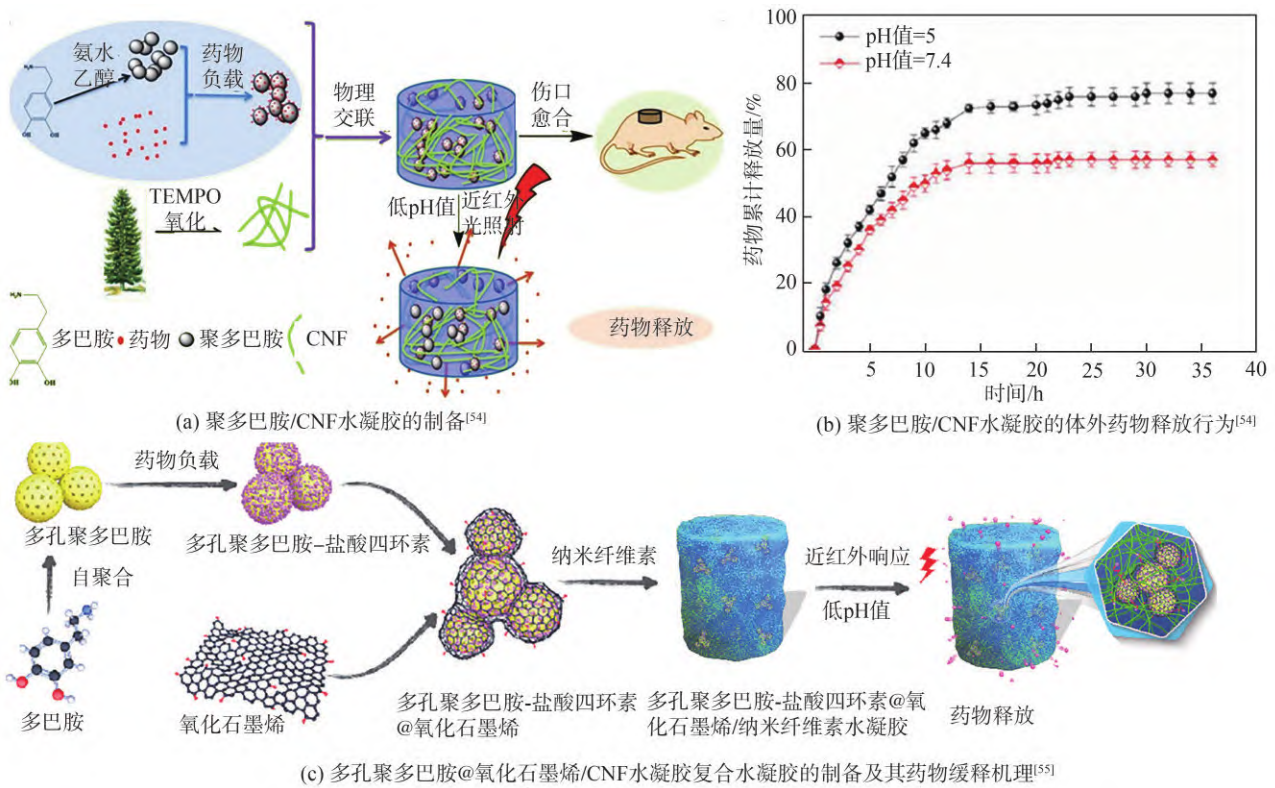


图5 聚多巴胺/CNF水凝胶的制备及其释药机理

Fig. 5 Schematic illustration of the preparation of the PDA/CNF composite hydrogel and its drug release mechanism

表1 CNF复合水凝胶材料药物释放行为的对比

Table 1 Comparison of drug release behaviors of different CNF composite hydrogels

药物载体	药物模型	释放行为	参考文献
海藻酸钠/CNF复合水凝胶	异硫氰酸荧光素葡聚糖	在中性条件下,最大药物释放量为80%	[56]
改性CNF/甲基纤维素水凝胶	丝裂霉素	药物成功地负载到凝胶中,药物缓释时间为14天	[57]
CNF/纳米甲壳素基水凝胶	苦杏仁苷	在60 h时,药物最大释放量为80%。此外,该复合水凝胶呈现出一定的pH敏感释药性	[58]
淀粉/CNF微粒	邻苯二甲酸二甲酯	用CNF强化淀粉可显著降低突释现象,并可提高药物释放量	[59]
化学改性的CNF复合物水凝胶	阿霉素	在pH值为7.4时,最大药物释放量约为65%	[60]
聚多巴胺@聚乙炔亚胺修饰的CNC/CNF复合水凝胶	四环素	复合水凝胶在中性介质中的药物释放时间为30 h	[61]

吸附的方式进行载药,载药量主要取决于CNF上基团的含量。Zhao等人^[67]将聚乙烯亚胺接枝到CNF上,得到复合气凝胶材料,实验中以亲水性的水杨酸作为药物模型物(图6)。实验结果发现,该复合气凝胶材料可以实现药物的缓慢释放,并且具有一定的温度和pH敏感性能。唐爱民等人^[68]采用冷冻干燥的方式制备出CNF气凝胶材料,以庆大霉素作为药物模型物。研究表明,该气凝胶的最大药物释放时间为7 h,体外释药以扩散控释为主,并且气凝胶材料体现出较好的抗菌特性。

2.3 CNF复合膜

CNF复合膜材料通常是采用抽滤、静电纺丝、喷涂、分层组装等方法制备得到^[12]。CNF复合膜材料与水凝胶和气凝胶相比有以下优点:制造成本较低、通常采用非注射给药、方便快捷、制备过程比较简单、运输较容易等。另外,CNF复合膜材料可以负载疏水性药物(如二丙酸倍氯米松、消炎痛、伊曲康唑等),并实现有效释放。表2列举了几种CNF复合膜材料载药及释药情况。

理想的CNF复合膜材料应具有载药量大、给药部位停留时间长等优点^[74]。例如,将CNF与疏水性药

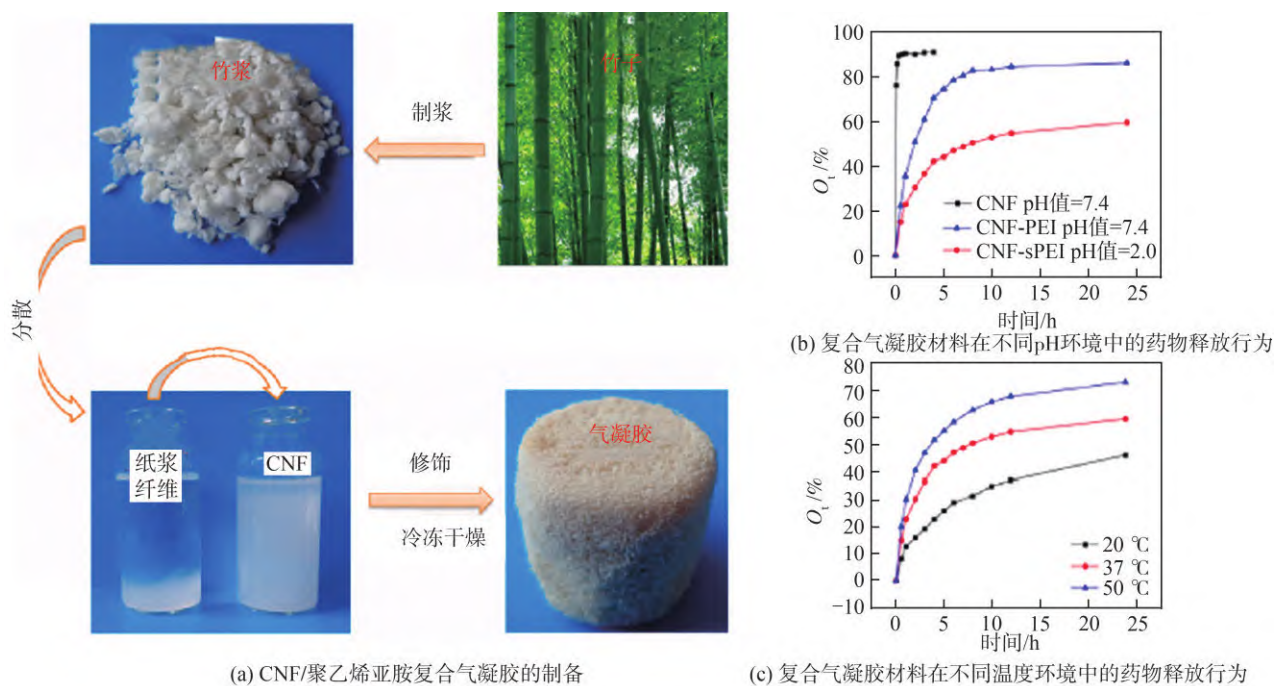


图6 CNF/聚乙烯亚胺复合气凝胶的制备及其释药行为^[67]

Fig. 6 Schematic illustration of the preparation of the CNF/polyethyleneimine composite aerogels and its drug release curves^[67]

表2 CNF复合膜材料药物释放行为的对比

Table 2 Comparison of drug release behaviors of different CNF composite films

药物载体	药物模型	释药行为	参考文献
海藻酸盐/纳米纤维素复合膜	氨苄西林	海藻酸盐/纳米纤维素膜的释药量高于纯海藻酸钠膜	[69]
CNF/聚异丙基丙烯酸酯复合膜	盐酸地尔硫卓	复合膜在5 h和20 h时的释药量分别为7.78%和22.9%	[70]
高岭土/海泡石/CNF复合膜	布洛芬	在60 min时,释药量为60%	[71]
聚乙烯醇/CNF复合膜	醋氨酚	复合膜的释药时间长达144 h	[72]
卡拉胶/聚乙烯醇/CNF复合膜	姜黄素	在50%的乙醇环境中,药物呈现出先快速释药后缓慢释药的行为	[73]

物共混,然后抽滤,得到载药膜材料,疏水性药物即可镶嵌在CNF膜中。与喷雾干燥方法相比,该方法赋予膜材料较高的药物负载率和包封率。Meneguín等人^[75]制备了CNF增强的淀粉/果胶纳米复合膜,结果发现,随着CNF用量的增加,复合膜的热稳定性随之增加。体外药物实验表明,该复合膜增加了难溶药物甲氨蝶呤的溶出速率,也可以作为难溶药物的载体。Kolakovíc等人^[76]采用抽滤的方式得到CNF复合膜材料,该膜具有较好的强度性能,药物负载率在20%~40%之间,药物缓释时间长达3个月。Laurén等人^[77]采用阴离子型CNF作为成膜材料,黏蛋白、果胶和壳聚糖作为功能生物黏附增强剂,制备复合膜材料。实验结果表明,膜的厚度在40~240 μm之间,这主要取决于组成成分。此外,药物释放过程有明显的突释现象,在30 min内药物释药量高达60~80%。

Löbmann等人^[78]采用平铺的方式得到CNF载药膜材料。研究表明,复合膜对药物吡哆美辛的最大负载率为21%,但是存在明显的药物突释现象。本研究组采用抽滤的方式得到聚多巴胺/CNF复合膜材料(图7)^[79]。当CNF羧基含量为1.2 mmol/g时,CNF膜材料和聚多巴胺/CNF复合膜材料的药物包封率分别为32%和41%。在中性pH环境中,聚多巴胺/CNF复合膜材料的药物缓释时间为28 h,体现出较好的缓释效果。

3 药物缓释机理

药物缓释一般是指高分子载体与药物结合,通过扩散、渗透等作用力,最终将药物释放到周围环境的过程^[80],受药物分子运动的影响,并且受渗透压产生的化学势梯度和对流的影响。药物的持续释放主要通

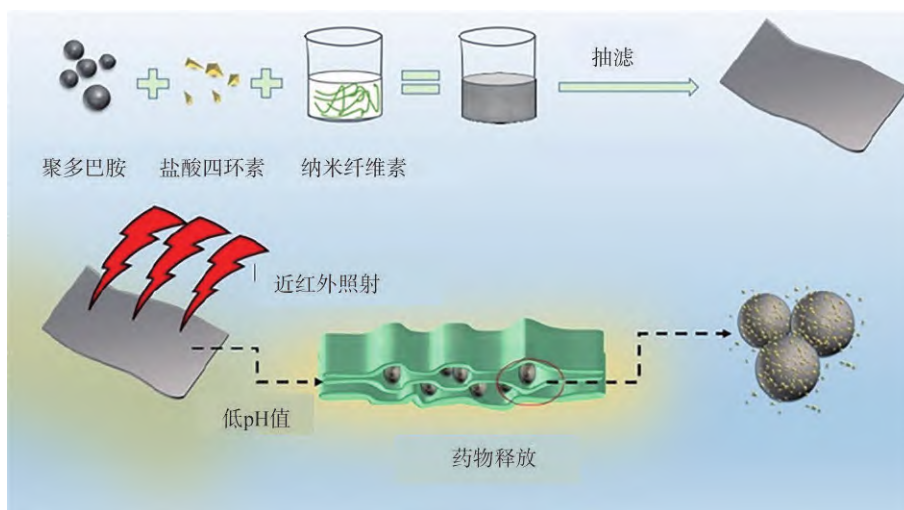


图7 聚多巴胺/CNF复合膜材料的制备^[79]

Fig. 7 Schematic diagram of the fabrication of the PDA/CNF composite films^[79]

过扩散作用及溶蚀作用实现。扩散作用是指由于药物浓度差的存在，载体内药物初始浓度比较高时，药物的扩散速率比较大；随着机体与载体内药物浓度差的不断减小，药物的释放速度也逐渐变慢。溶蚀作用是指由于载体材料的降解，载体材料在进入机体时，在体内环境及药物的影响下，发生溶蚀生成了孔隙，使药物从载体中释放出来。因此，对于具有可降解性的药物载体，其药物释放速率主要由载体孔隙结构控制。对于不可降解的药物载体，扩散是药物释放的主要驱动力。而对于纳米纤维素基载体，药物释放可通过载体的扩散速率和降解速率来预测^[81]。此外，药物与纳米纤维素骨架之间的相互作用及药物在溶出介质中的溶解度是影响药物释放的主要原因。

药物释放的数学模型可以预测药物释放速率和药物的扩散行为^[82]。将实验数据与数学模型进行比较，有助于优化药物释放动力学，确定药物释放机制。数学模型可以将药物释放过程中涉及的扩散行为通过实验数据来表示，从而预测药物的释放情况，显著减少产品开发过程中所需的实验次数，节省时间和降低成本。目前，研究者已经提出了一系列数学模型来预测药物的释放行为，如Zero-order模型（式(1)）、First-order模型（式(2)）、Higuchi模型（式(3)）、Korsmeyer-Peppas模型（式(4)）等^[83]。然而，这些模型没有限制不同药物载体的形状、性质和结构，导致药物释放行为的模拟存在一定的误差^[84]。因此，纤维素纳米纤维药物载体的药物释放机理还需要进一步的深入研究。

$$\frac{M_t}{M_\infty} = K_0 t \quad (1)$$

$$\ln \left(1 - \frac{M_t}{M_\infty} \right) = -K_1 t \quad (2)$$

$$\frac{M_t}{M_\infty} = K_2 t^{\frac{1}{2}} \quad (3)$$

$$\frac{M_t}{M_\infty} = K_3 t^n \quad (4)$$

式中， M_t 是在时间 t 时药物累积释放量，%； M_∞ 为平衡状态时药物累积释放量，%； $\frac{M_t}{M_\infty}$ 是指药物在时间 t 的累计释放百分数； n 为扩散指数，代表不同药物缓释机理对应的指数（表3）； K_0 、 K_1 、 K_2 和 K_3 代表式(1)~式(4)的释药系统的特性常数。

表3 不同几何形态的药物载体的释药机理及其扩散指数^[82-84]
Table 3 Exponent n and drug release mechanism of different drug carriers with different geometry^[82-84]

药物缓释机理	n		
	膜	圆柱体	球体
Fickian 扩散	≤ 0.5	≤ 0.45	≤ 0.43
非常规运输	$0.5 < n < 1$	$0.45 < n < 0.89$	$0.43 < n < 0.85$
Case-II 运输	1	0.89	0.85

4 结语及展望

目前，纤维素纳米纤维复合水凝胶材料、复合气凝胶材料和复合膜材料已经广泛应用于化疗药物、消炎药和抗（杀）菌药物等负载和缓释，并取得了一定的效果，但是还存在药物负载率低、缓释时间短、突

释现象明显等问题,需要研究人员投入更多的时间和精力克服。因此,未来需要进一步加强以下几个方面的研究。

4.1 纳米纤维素在生物医学领域还处于科学研究阶段,未来需要重点进行动物体内药物释放的研究。

4.2 由于纳米纤维素复合材料在人体降解难度较大,纳米纤维素与细胞的相互作用机制尚不清楚,还需要更多的研究来分析和评估纳米纤维素对人类的潜在影响,探索纳米纤维素的引入是否会对人体产生潜在的伤害等。纳米纤维素复合载药材料在体内循环效率、免疫调节、生物降解和生物毒性等方面还需要进一步深入的研究和探讨。

4.3 尽管纳米纤维素复合材料在生物医学领域已经显示出巨大的前景,但纳米纤维素复合材料的大规模商业化应用与材料的结构和性能密切相关。研究者们需要设计出结构更好、功能性(如磁响应、pH响应、光响应等)更多的纳米纤维素复合材料。故研究人员仍需致力于解决当前的困难和挑战,使纳米纤维素在生产、改性、产业化、商业化等方面不断优化,为纳米纤维素应用于医学领域提供理论基础和技术支持。

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