

凹凸棒石在生物医学领域中的应用研究进展

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摘 要: 凹凸棒石是一种具有 2:1 型链层状结构的硅酸盐黏土矿物, 针棒状的晶体长度约为 0.5~5.0 μm , 是一种不可再生的天然纳米材料。凹凸棒石特殊的结构赋予了它优异的吸附性, 胶体性等性质。凹凸棒石作为绿色的天然矿物材料, 具有良好的生物相容性, 并且储量丰富, 价格低廉, 所以在生物医药领域有着广泛的应用潜力。本文综述了凹凸棒石在生物抗菌、药物输送、骨组织工程、伤口敷料等方面的应用研究进展, 并对其未来的应用前景进行了展望。本文对于凹凸棒石的生物医学应用研究具有重要的参考价值。

关键词: 凹凸棒石; 硅酸盐矿物; 纳米材料; 生物医药; 复合材料

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黏土矿物作药用拥有悠久的历史。有资料显示, 尼安德特人曾利用水和黏土的混合物用于治愈伤口、缓解刺激; 在古希腊时期, 黏土也常被用于治疗皮肤疾病。凹凸棒石作为代表性的黏土矿物之一, 具备良好的吸附性与生物相容性, 能被应用于高附加值的生物医药领域^[1-4]。另一方面, 凹凸棒石棒晶束解离关键共性技术的突破^[5], 实现了凹凸棒石从传统应用领域到高端应用领域的拓展, 使凹凸棒石在生物医药领域具有更广阔的应用前景。同时中国为推进产业结构战略性调整和优化升级, 加快生物医药产业的发展, 全力推动医药工业在“十四五”期间跃上新台阶^[6]。可以预见, 未来凹凸棒石在生物医药领域有着巨大的应用潜力。

本文总结了凹凸棒石在生物抗菌、药物输送、组织工程、伤口敷料等生物医药领域的应用, 对相关原理、方法和优缺点进行了总结分析, 并结合目前所存在的问题与优势对凹凸棒石在生物医药领域的应用前景进行了未来展望。本综述对凹凸棒石在生物医药领域的应用研究提供参考与借鉴。

1 凹凸棒石的简介

凹凸棒石又名坡缕石, 是一种 2:1 型层链状结构的含水富镁铝硅酸盐黏土矿物^[7-8], 其晶体呈棒状、纤维状, 单根晶体纤维的直径在 20 nm 左右, 长度可达 1 μm 。目前普遍接受的凹凸棒石的晶体结构是由 Bradley^[9]提出的晶体模型。其基本构造单元是由平行于 C 轴的硅氧四面体双链组成, 链中硅氧四面体自由氧原子的指向每 4 个 1 组, 上下交替排列。顶点氧原子分别指向(010)和(100)晶面方向, 与 Mg(II)、Al(III)等八面体组成离子进行配位, 形成由连续四面体层和不连续的八面体层组成的、沿(001)方向无限延伸的 2:1 型链层单元, 其中四面体基平面之间距离约为 0.66 nm, 这与云母中四面体结构类似, 各链层单元通过 Si—O—Si 键连接, 形成截面尺寸 0.37 nm×0.64 nm 的沸石状孔道(图 1)^[10-12]。理想的凹凸棒石晶体为三八面体, 然而由于类质同晶效应, 一些三价阳离子, 如 Al^{3+} 和 Fe^{3+} , 可能会取代八面体位置的 Mg^{2+} , 从而形成二

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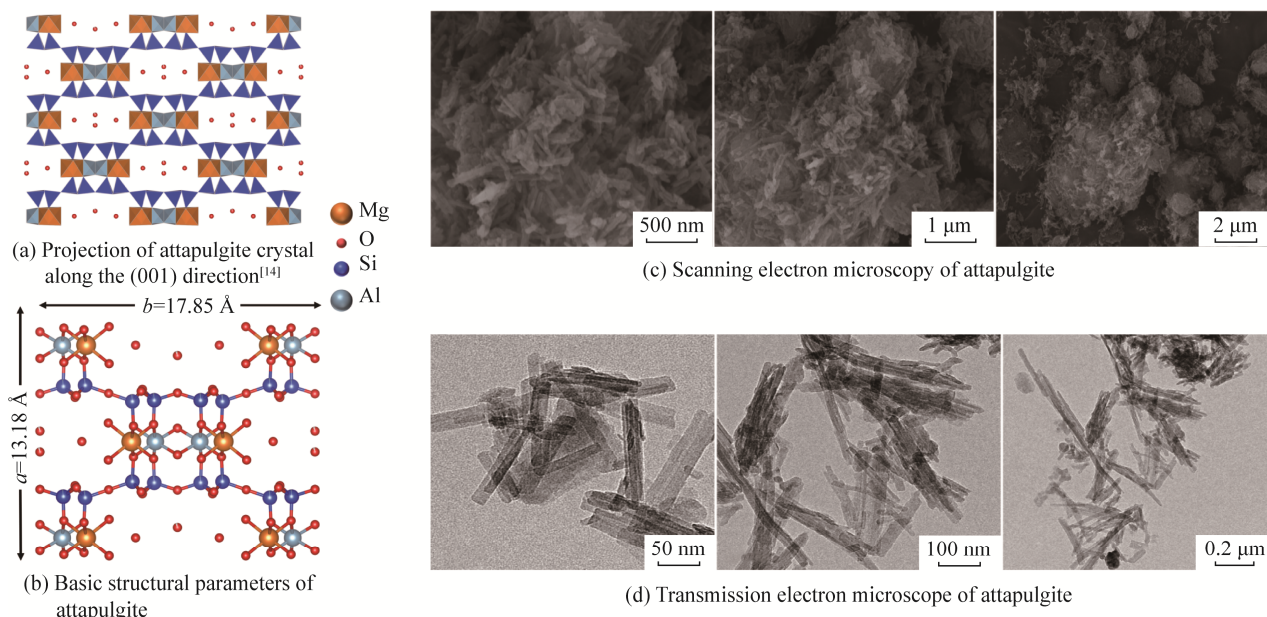


图1 凹凸棒石晶体投影图、基本结构参数及扫描电子显微镜(SEM)照片、透射电子显微镜(TEM)照片

Fig. 1 Projection diagram, basic structural parameters, SEM, and TEM of attapulgite crystals

八面体或中间结构,所以自然界中的凹凸棒石多以二八面体和三八面体的过渡态形式存在^[13]。

由于凹凸棒石的独特晶体结构,使其产生两个新奇的特性:1)该结构由三维链组成,因此它不能像具有三维层状结构的黏土(如蒙脱石)那样膨胀;2)沿着Si—O—Si键平行于(110)平面的解理将板条固定在一起,使其呈现出寻常的针棒状^[14]。凹凸棒石针棒状晶体结构,使其具备了特殊的理化性质,其主要的理化性质包括选择吸附性、胶体性、阳离子交换性等^[15-16],凭借其优异的性质凹凸棒石被广泛应用于医药、农业^[17]、环保^[18]、化工^[19]等领域。

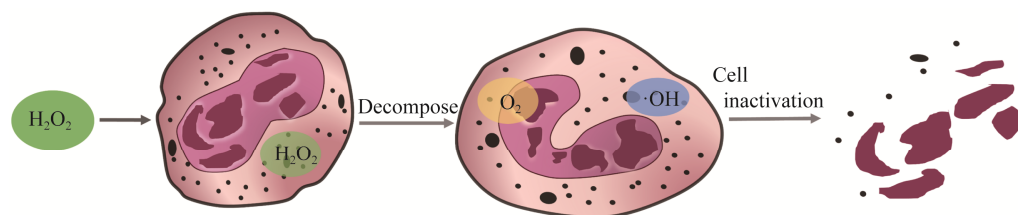
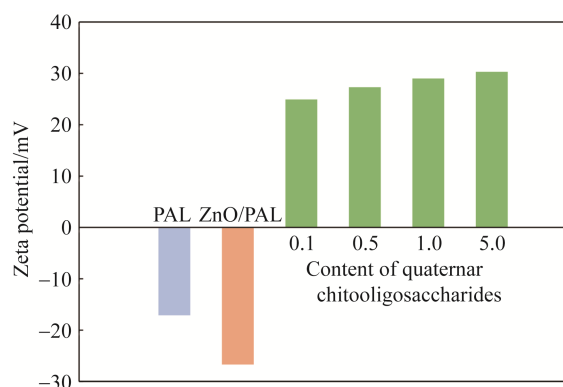
2 凹凸棒石在生物医药领域中的应用

2.1 凹凸棒石在复合抗菌材料中的应用

随着抗生素在全球范围内的滥用,使得细菌产生了耐药性,对人体和家禽产生了很大的威胁。纳米颗粒、有机酸、植物提取物以及有机抗菌剂等正逐渐成为抗生素的替代品,但他们单独使用时在安全性和稳定性方面存在一定局限性。凹凸棒石具有一定抗菌性,其可能的抗菌机理可解释为:1)类质同晶取代效应产生的负电荷表面和边缘价键断裂产生的可变电荷决定的表面电荷可能导致其通过静电黏附在细菌细胞膜表面,从而影响细胞的渗透性^[20];2)凹凸棒石纤维状晶体的针刺效应破坏细胞的细胞质膜^[21]。此外凹凸棒石晶体中存在四种形式的

水:表面吸附水、沸石水(H₂O)、结晶水(OH₂)、结构水(OH)^[22],同时其表面拥有大量的活性基团,这为其他抗菌剂的负载和组装提供了极好的条件^[20]。例如Huo^[23]利用ZnO纳米颗粒包覆于凹凸棒石(PAL)上制备出了ZnO/PAL复合抗菌材料,该复合抗菌材料与纯ZnO相比具有了更高的抗菌活性。主要原因可能在于凹凸棒石吸收水后在氧化锌表面产生了H₂O₂,抑制细胞的生长,甚至杀死细胞,从而达到抑菌的目的(图2),另一方面在于凹凸棒石独特的纤维状结构能够稳定和分散所负载的纳米颗粒^[20]。但是,制备出的复合抗菌材料并不具备靶向行为,所以其抗菌性能并不十分突出。

通过在无机抗菌材料中掺入多糖是一种提高抗菌材料靶向性的新途径。在最近一项研究中,采用静电自组装工艺将季铵甲壳低聚糖(QACOS)掺进ZnO/PAL中,改变了ZnO/PAL的负电性(图3)提高了抗菌材料对细菌的靶向行为,同时在QACOS与ZnO/PAL的协同作用下其整体抗菌能力与抗菌效率显著提高^[24]。在另一项研究中,用凹凸棒石黏土作为用腰果胶稳定的银纳米颗粒(AgNPs-CG)的载体,制备出Pal/AgNPs-CG纳米复合抗菌材料,与AgNPs-CG相比其抗菌性能大幅提升,对大肠杆菌和金黄色葡萄球菌的抑制作用分别高达70.2%和85.3%,几乎是AgNPs-CG的两倍,同时其毒性低,有利于其在生产实践中的应用^[25]。

图 2 ZnO/PAL 抗菌活性提高的可能机理^[23]Fig. 2 Possible mechanism of increased antibacterial activity of ZnO/PAL^[23]

PAL is Palygorskite. ZnO/PAL is ZnO/Palygorskite. QACOS is Quaternary ammonium chitosan oligosaccharides. QACOS/ZnO/PAL is Quaternary ammonium chitosan oligosaccharides/ZnO/Palygorskite.

图 3 PAL、ZnO/PAL、(质量分数为 0.1%、0.5%、1.0%、5.0%) QACOS 制备 QACOS/ZnO/PAL 纳米复合材料的 Zeta 电位^[24]

Fig. 3 Zeta potential diagram of QACOS/ZnO/PAL nanocomposites prepared by PAL, ZnO/PAL, (0.1%, 0.5%, 1.0%, 5.0%, in mass) QACOS^[24]

目前,金属/黏土矿物复合抗菌材料的研究重点之一是探索简单绿色的制备方法,这对于大规模生产和毒性的控制是必要的^[20]。有研究者以羊毛纤维衍生的碳点(CDs)为还原剂,采用快速简便的紫外辐射法($\lambda=254\text{ nm}$)制备了 Ag-Pal 纳米复合材料,该材料制备简单、稳定性较好且对大肠杆菌和金黄色葡萄球菌具有良好的抗菌活性^[26],该法为凹凸棒石绿色、简单的制备提供了新方法。

研究表明,许多植物提取物也对细菌表现出了强大的抗菌活性^[27],但其挥发性、水不溶性、高粘度等特点限制了它们的广泛应用^[28],以凹凸棒石为载体将植物提取物负载或封装能很好地克服其缺点。Hong 等^[29]采用离子交换工艺制备出 CEO(姜精油)/PAL 复合抗菌材料,该材料表现出了优异的抗菌活性,热稳定性、耐酸性和耐碱性也显著提高,同时凹凸棒石对细菌的吸附能力与姜精油的抗菌能力完美结合使其具备了特异性的靶向抗菌能力。最近的一项研究中,研究者采用机械研磨法制备出 EO(精油)/PAL 系列杂化材料,并通过密度泛函理论计算揭示了精油与凹凸棒石表面的作用机理,结果

表明含氧基团的 EO 更易与凹凸棒石表面作用,且主要作用位点为外表面的 Si—OH 基团与内表面的 Mg—OH₂,其通过氢键与 EO 作用,同时部分 EO 进入凹凸棒石的纳米孔道中^[30],这为凹凸棒石基纳米复合抗菌材料的改性机理提供了理论支撑,有利于后续探究更加绿色、简便的改性方法。

还有研究者报道了不同的凹凸棒石基复合抗菌材料(表 1),它们都呈现出了较好的抗菌活性。

2.2 凹凸棒石在复合饲料添加剂中的应用

自 2020 年 7 月 1 日起,中国禁止生产、使用含有促生长类药物饲料添加剂(中药类除外)的商品饲料^[31],所以具备安全性、抗菌性的凹凸棒石类复合材料成为理想的促生长类药物饲料添加剂的替代物,拥有巨大的应用潜力。一方面凹凸棒石作为家禽的饲料添加剂对家禽的生长性能是有益的。研究发现,在泌乳荷斯坦奶牛的日粮中加入 10 kg/t 的凹凸棒石可以提高牛奶的产量和质量,增加牛奶中蛋白质的含量,减少牛奶中微生物的含量^[32];在肉鸡的日粮中加入凹凸棒石可有效提高肉鸡的肠道免疫力,抗氧化状态和屏障功能^[33],同时还能够增加肉鸡胰腺的相对重量以及对养分的利用率^[34],可能的原因在于凹凸棒石增强了胰腺淀粉酶的活性^[35],同时吸附饲料中的霉菌毒素(例如:玉米赤霉烯酮、黄曲霉毒素等)^[36-37]。

另一方面,植物提取活性因子已被证明具有抗氧化性、抗菌性等生物学功能,相关产品已被评估为实践中使用的抗生素生长促进剂的安全替代品^[38-39]。但这些活性因子水溶性低,挥发性高,耐热性差的特性严重限制了它们的应用,而具有强大吸附性能的凹凸棒石已被批准用作工业和动物营养领域的载体^[40],将植物活性因子负载于凹凸棒石上不仅能够提高它们的稳定性,还可能具有更好的应用效果。例如 Cheng 等^[41]通过离子交换工艺制备的 EO(香芹酚和百里香酚)/PAL 复合饲料添加剂能够增强鸡的免疫力和抗氧化能力并能够调节蛋鸡肠黏膜的吸收和消化能力,提高蛋鸡的生长性能。但研究者并没有说明造成这种结果的主要原因,这样的结果可

表 1 凹凸棒石基复合抗菌材料对比
Table 1 Comparison of attapulgite based composite antibacterial materials

Antimicrobial material	Preparation Method	Antimicrobial properties
Monoammonium glycyrrhetic acid/zinc oxide/attapulgite antibacterial material	Precipitation method	For <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Fecal Enterococcus</i> , <i>Pseudomonas aeruginosa</i> , methicillin-resistant <i>Staphylococcus aureus</i> and extended spectrum bacteria β- The MIC of <i>lactam Escherichia coli</i> is 1.00, 0.10, 0.25, 5.00, 0.10 mg/mL and 2.50 mg/mL respectively ^[42]
Nano silver/attapulgite antibacterial material	Metal salt pyrolysis	The concentrations of the materials were 5 μg/mL, the growth of <i>Escherichia coli</i> and <i>Staphylococcus aureus</i> was almost completely inhibited ^[43]
Cobalt/zinc oxide/attapulgite antibacterial materials	Sol-gel method	The materials could inhibit <i>E. coli</i> up to 99% ^[44]
Silver sulfide/molybdenum disulfide/attapulgite antibacterial material	Hydrothermal method	MICs against <i>Escherichia coli</i> and <i>Staphylococcus aureus</i> were 0.3 mg/mL and 0.5 ^[45]
Selenium/zinc oxide/attapulgite antibacterial materials	Plant mediated (Aloe vera)	MICs against <i>S. aureus</i> and <i>E. coli</i> were 0.625 mg/mL and 2.500 mg/mL, respectively ^[46]
Plant extracts/attapulgite antibacterial coating	Situ bio reduction	It has good antibacterial activity against almost all Almost all (except the highly resistant <i>Escherichia coli</i>) ^[47]
Chlorhexidine diacetate/attapulgite antibacterial material	Cation-exchange reacion	Diameter of inhibition zone: (0.83±0.05) mm for CA/Pal 0.5, (0.88±0.08) mm for CA/Pal 1.0 and (0.92±0.05) mm for CA/Pal 2.0 ^[48]
Quaternary phosphonium salt/attapulgite antibacterial material	Intercalation modification	MIC: (0.8±0.05) mg/mL for <i>E. coli</i> and (0.15±0.02) mg/mL for <i>S. aureus</i> ^[49]
Fe/Cu/attapulgite antibacterial material	Impregnation method	The antibacterial rate against <i>Escherichia coli</i> and <i>Staphylococcus aureus</i> was 99.9% ^[50]
Zn(OH) ₂ /attapulgite antibacterial coating	Co-precipitation method	Quickly and effectively kill bacteria. This antibacterial effect can last for 5 d ^[51]
SiO ₂ -NT@Cu antibacterial material	Mixed heating method	SiO ₂ -NT@Cu nanocomposite can inhibit effectively the growth of <i>E. coli</i> and <i>S. aureus</i> , with the minimal inhibitory concentration (MIC) of 2.0 mg/mL and 0.6 mg/mL ^[52]

能是得益于 EO 的抗菌性和抗氧化性，也有可能得益于凹凸棒石对肉鸡胃肠道系统的保护^[53]。

相关报道指出益生菌可以通过调节家禽肠道菌群增强其生长性能^[54]，利用凹凸棒石和益生菌的复合物作为肉鸡的补充膳食，不仅可以增强肉鸡血浆的抗氧化能力和免疫能力，提高肉鸡的产蛋率，而且鸡蛋质量有所提高，主要的原因在于凹凸棒石提供了丰富的 Ca²⁺供肠道吸收，增加了蛋壳厚度^[55]。此外，凹凸棒石基金属复合物也是一种新型的饲料添加剂，它不仅可以提供家禽生长所必须的微量元素，而且还具有优异的抗菌、止泻功能。例如凹凸棒石基纳米氧化锌复合饲料添加剂可改善断奶仔猪的肠道形态，增加免疫球蛋白分泌，减少促炎细胞因子分泌，从而降低断奶仔猪的腹泻率，还能有效提高断奶仔猪的肠道屏障功能来提高其生长性能^[56–57]。在另一项研究中，含锌凹凸棒石被添加到肉鸡的日粮中，研究其对肉鸡的生长性能、肉质、抗氧化状态的影响，结果表明，含锌凹凸棒石不仅可以改善肠道形态以增强对 Fe 和 Mg 的积累，还能提高肉质的抗氧化能力和保水能力，这或许得益于含锌凹凸棒石对肌肉中 Zn 和 Mg 的补充^[58–59]。

凹凸棒石基植物活性因子饲料添加剂、凹凸棒石基益生菌饲料添加剂、凹凸棒石基金属复合饲料

添加剂各有优点(表 2)，目前已被应用于生产实践中，且相关生产技术已趋于成熟。

2.3 凹凸棒石在药物载体中的应用

当服用某些药物时通常需要高剂量才能达到治疗效果，然而这会诱发很多副作用，如发烧、呕吐、皮疹等^[60]，开发药物输送系统，可以使药物在病灶处保持一定的浓度^[61–62]以增强药物的靶向功能，从而减少副作用，达到最好的治疗效果。药物输送系统由药物与药物载体构成，且常以纳米颗粒、水凝胶、纳米纤维等形式呈现^[63–66]。最初有研究发现几种药物与某些黏土共同施用时会降低药物的生物利用度^[67–68]，但同时人们很快意识到这些黏土对药物的影响可能不完全是负面的^[69]，借助黏土对药物缓释的能力，可将其作为药物载体来实现药物输送、缓释的目的，凹凸棒石作为纤维黏土矿物的代表，常被用作药物输送载体。

黏土对外部条件变化的敏感性较差(如 pH、温度等)，使得其作为药物输送载体难以在目标病灶对药物进行释放^[70]，而通过调控药物载体实现药物的精准释放却是可行的。例如，研究者采用离子凝胶法制备出 pH 敏感型的瓜尔胶/凹凸棒土/海藻酸钠复合水凝胶珠，该水凝胶珠中，凹凸棒石的存在改变了药物的释放行为，同时还消除药物突释现象，而

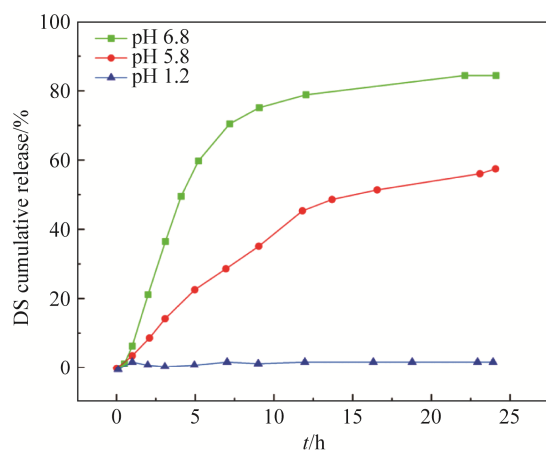
且药物的释放速率随着凹凸棒石含量的增加而减少^[71](图 4), 可能的原因在于凹凸棒石含量增加时, 导致水凝胶珠产生了更多的交联点, 增加了交联密度, 最终水凝胶珠的膨胀率降低, 从而抑制了药物通过膨胀行为进行释放。但是, 采用表面改性技术

制备出温度敏感型的 PNIPAM/ATP 复合水凝胶(图 5)却呈现出了相反的结果, 在 37 °C、pH=7.38 时, 药物的释放量和释放效率随着凹凸棒石含量的增加而增加^[72], 主要原因在于水凝胶中药物的包覆量随着凹凸棒石的含量增加而增加。

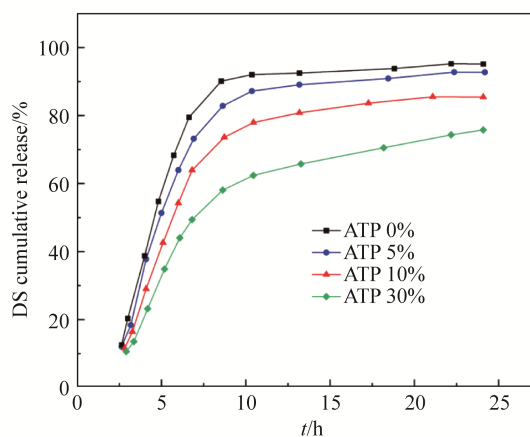
表 2 三类凹凸棒石基复合饲料添加剂对比

Table 2 Additive comparison of three categories of attapulgite based composite feeds

Types of compound feed additives	Preparation process	Action effect	Advantages
Plant essential oils attapulgite based composite feed additives	Surface modification; Ion exchange process	Enhancing immunity and antioxidant capacity in poultry; Regulates the gastrointestinal system and improves growth performance	Excellent antioxidant properties, some antibacterial properties ^[41]
Attapulgite based compound feed additives for probiotics	Surface Absorption	Improve poultry immunity and modulate the balance of intestinal flora leading to improved growth performance in poultry	Reduces the toxin effect of mycobacteria and is able to modulate the gut flora ^[73]
Attapulgite based composite feed additives of metals	Surface Absorption	Provide obligatory trace elements for poultry, improve poultry immunity, reduce diarrhea and thereby improve growth performance	Can provide essential trace elements for growth, excellent antimicrobial ^[74]



(a) Cumulative release profiles of drugs from composite hydrogel beads at different pH values

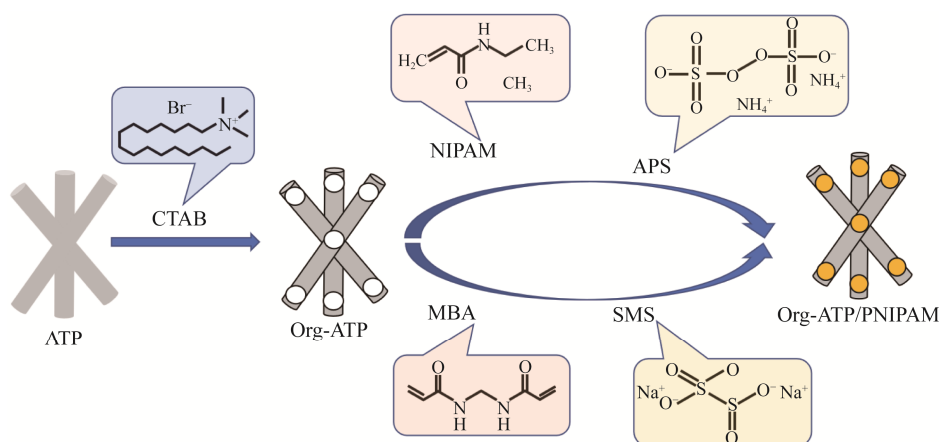


(b) Cumulative release profiles of drugs from different contents of attapulgite composite hydrogel beads at pH=6.8

DS is diclofenac sodium. ATP is attapulgite.

图 4 凹凸棒石复合水凝珠的药物累计释放曲线

Fig. 4 Cumulative drug release curve of attapulgite composite hydrogel beads

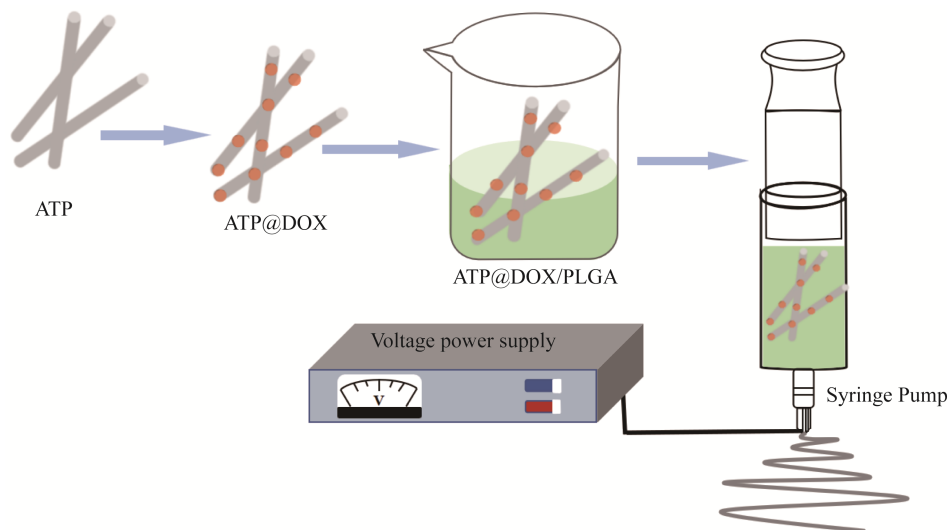


CTAB is Cetyltrimethylammonium bromide. Org-ATP is organic attapulgite. NIPAM is N-isopropylacrylamide. MBA is N, N'-methylene double acrylamide. SMS is sodium metabisulfite. Org-ATP/PNIPAM is organic attapulgite/pnipaam.

图 5 PNIPAM/ATP 复合水凝胶制备方案^[72]Fig. 5 Scheme of preparation of PNIPAM/ATP composite hydrogel^[72]

此外, 静电纺丝的纳米纤维也常被用作药物输送载体。纳米纤维相较于水凝胶具有比表面积大、孔隙率高、生物相容性好的特点, 而且还能有效地携带大量亲、疏水药物^[75]。若在纳米纤维中添加无机纳米颗粒不仅可以增强纳米纤维的强度, 还能实现药物的长期缓释, 同时在一定程度上可以消除药物突释现象^[76]。例如 Wang 等^[77]将

凹凸棒石(ATP)负载抗癌药物阿霉素(DOX)并与聚乳酸—乙醇酸(PLGA)混合, 然后通过静电纺丝技术制备出杂化纳米纤维(图 6), 该杂化纳米纤维在 ATP 和 PLGA 的双重缓释作用下能够持续释放阿霉素, 避免了药物的突释现象, 主要原因在于药物在释放过程中需先从 ATP 中释放, 再从 PLGA 基体中释放。



ATP@DOX is attapulgite/Doxorubicin. ATP@DOX/PLGA is attapulgite@Doxorubicin/Poly(lactic acid glycolic acid).

图 6 ATP/DOX/PLGA 杂化纳米纤维的制备^[77]

Fig. 6 Preparation of ATP/DOX/PLGA hybrid nanofibers^[77]

虽然水凝胶和有机杂化纳米纤维在体外都呈现出了较好的药物释放效果, 但目前少有文献报道其在体内的药物释放效果。可能的原因在于药物在体内的输送与释放机制是复杂的, 影响因素和干扰条件较多, 难以控制实验变量, 同时很多药物都是通过血液输送到病灶处, 凹凸棒石具有极好的稳定性, 难以分解, 若将其作为药物输送载体进入血液循环系统, 如何将其排出将会是一个巨大的问题, 而且其进入血液循环系统后对人体的影响仍有待考证。但凹凸棒石通过消化系统从人体排出却是可行的, 将凹凸棒石作为药物的赋形剂, 通过口服进入消化系统, 在此过程中凹凸棒石不仅能够对药物起到缓释作用, 还能通过排泄的方式将其安全排出体外^[78]。在最近的一项研究中, 研究者利用碳酸钠改性凹凸棒石(Na-ATP)作为赋形剂制备出胃肠动力调节剂—多潘立酮缓释片, 该片剂在人工模拟胃液中呈现出了更好的释放性能, 同时随着 Na-ATP 含量的增加, 细胞增殖显著, 细胞活性显著增强^[79]。在最近的一项授权专利中^[80], 研究者在酸性条件下利用酪氨酸对凹凸棒石进行改性将其作为止痛药物—盐酸吗啡的载体, 制得酪氨酸—凹凸棒石@盐酸吗啡药物。

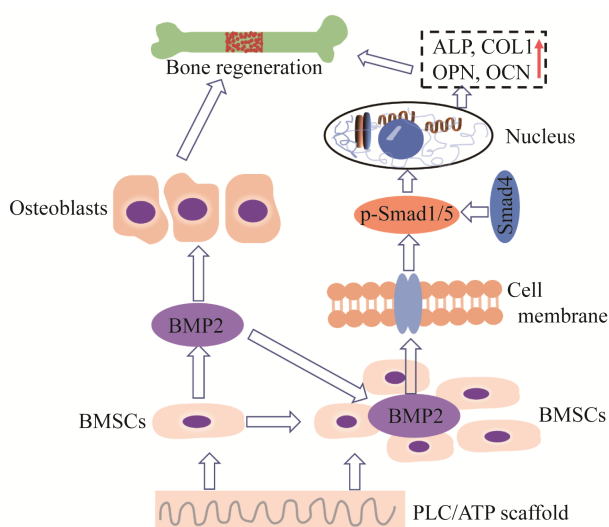
然后将含有相同盐酸吗啡剂量的该药物与某品牌盐酸吗啡止痛口服片剂(药物 1)进行临床实验比较, 临床结果表明: 酪氨酸—凹凸棒石@盐酸吗啡药物中凹凸棒石作为载体能有效延缓盐酸吗啡的释放速率, 而且该药物能够有效缓解盐酸吗啡带来的如恶心、呕吐、呼吸抑制、嗜睡、眩晕、便秘、排尿困难、胆绞痛等副作用, 其中嗜睡、呕吐和便秘症状全部消失, 同时酪氨酸—凹凸棒石@盐酸吗啡药物的止痛效果更佳。可见以凹凸棒石作为赋形剂制备药物缓释片拥有潜在的应用价值。

2.4 凹凸棒石在复合支架材料中的应用

静电纺丝的纳米纤维不仅可以用作药物输送载体, 还可运用于组织工程领域。组织工程的重要工作在于制造可以支持细胞生长增殖的三维支架^[81]。通过静电纺丝制备出的纳米纤维具备高比表面积、高表面活性和较好的生物相容性, 所以其被广泛用于组织工程中仿生三维支架的制备^[82]。单纯的静电纺丝纳米纤维孔径较小, 会抑制细胞在纳米纤维上的迁移, 并限制营养物质的供应^[83], 但是在静电纺丝纳米纤维中加入无机成分后能够提高纳米纤维的机械强度, 并促进相关细胞的增殖与分化, 有望将

其用作骨修复支架材料^[84]。

有研究者采用静电纺丝工艺制备出光滑均匀的 ATP/PLGA 杂化纳米纤维, 该无机杂化纳米纤维相较于单纯的 PLGA 纳米纤维具有了更高的亲水性和机械耐久性, 有助于间充质干细胞(hMSCs)的黏附和增殖以及亲水营养物质的渗透, 而且其在引导骨再生技术上表现出了优异的成纤维细胞屏障功能^[85], 这表明凹凸棒石对于成骨过程是有益的^[86]。但是, 凹凸棒石的掺入却降低了纳米纤维的孔隙率, 尽管一些文献的报道显示不同孔隙率的支架的成骨结果没有差异, 但高孔隙率的材料被证实可以增强骨的内向生长^[87]。例如, 有报道指出利用静电纺丝技术制备出 PCL(聚己内酯)/PEG(聚乙二醇)/ATP 复合支架, 并进行洗涤除去水溶性的 PEC 纤维后, 支架的孔隙率显著增加, 大大提高了细胞迁移、增殖、浸润和分化的能力。同时该研究结果还表明: 凹凸棒石激活了 BMP/Smad 信号通路, 以此促进间充质干细胞分化为骨细胞^[88], 这是凹凸棒石影响间充质干细胞分化可能的机制(图 7)。



BMSCs is mesenchymal stem cells. BMP2 is rabbit monoclonal bone morphogenetic protein2. p-Smad1/5 is p-Smad1/5 antibody. PLC/ATP is polycaprolactone/attapulgite. COL1 is rabbit monoclonal collagen1. OPN is rabbit monoclonal osteopontin. OCN is mouse monoclonal osteocalcin.

图 7 PCL/ATP 支架通过 BMP/Smad 信号通路刺激成骨分化和骨形成的可能机制示意图^[88]

Fig. 7 Schematic of the possible mechanisms of PCL/ATP scaffolds in stimulating osteogenic differentiation and bone formation through BMP/Smad signaling pathway^[88]

此外, 有报道指出, 以凹凸棒石为原料, 聚乙烯醇为粘结剂, 采用 3D 生物打印工艺制备出一种新型的纳米凹凸棒石支架, 其孔隙率和机械强度与

松质骨相似, 该支架不仅在体外对 hBMSCs 成骨细胞具有优异的生物相容性, 而且在大鼠体内的颅骨缺损模型中也表现出良好的骨再生性能^[89]。相较于静电纺丝的支架, 3D 打印的生物支架不仅制备更加简单, 而且还更具特征性、选择性, 这也为某些特定骨支架的制备提供了方向^[90]。

目前凹凸棒石基组织工程支架在体外的诱导成骨研究呈现出了较好的效果, 但其在体内诱导成骨的相关理论研究较少且不全面。同时凹凸棒石能诱导成骨作用的机制尚不清楚, 目前虽有报道将其成骨作用归因于凹凸棒石含有大量的 Mg 和 Si, 它们可以刺激骨干细胞的成骨分化^[91], 但仍未被充分证实。

2.5 凹凸棒石在伤口愈合材料中的应用

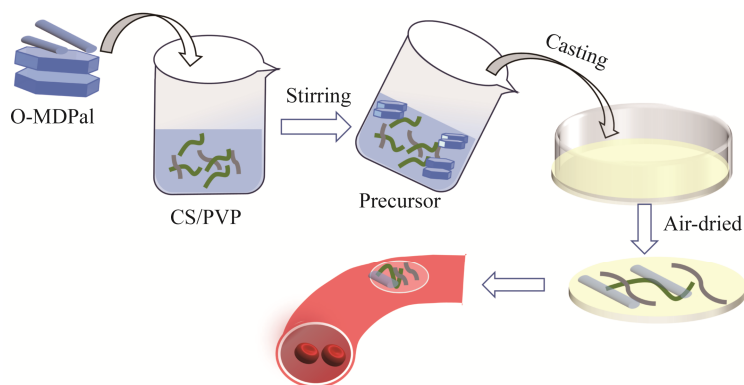
慢性伤口是常见的健康问题, 若不及时治疗会引起毁灭性的后果(截肢、甚至死亡), 因此研究开发伤口愈合材料势在必行^[92-93]。随着人们对自然疗法的兴趣日益浓厚, 黏土基材料逐渐成了伤口愈合的代替品, 凹凸棒石作为纤维状黏土的代表具有广泛的应用前景^[94-95]。早期研究者比较了天然凹凸棒石和经有机改性的凹凸棒石对大鼠伤口愈合的影响, 结果表明天然凹凸棒石具有更好的伤口愈合效果, 且伤口愈合后组织学切片显示胶原蛋白更好地重组^[96], 这或许得益于凹凸棒石可以改善组织修复, 减少局部炎症, 促进血管的生成^[97]。有趣的是, 最近的一项研究表明由泉水和凹凸棒石制成的水凝胶用作伤口敷料时, 其释放的元素量和元素比例极大的影响了治疗地最终效果。具体而言, 水凝胶中生物活性元素(Mg、Ca 等)的高释放不是获得最大治疗效果的必要条件; 水凝胶中释放元素的比例, 尤其是 Zn 和 Ca 的释放比例却极大地影响了最终的治疗效果^[98]。

随着研究的深入, 人们发现复合凹凸棒石杂化材料对伤口愈合有着更好的效果^[99]。例如研究者开发出系列香芹酚(CVR)/黏土杂化的聚合物薄膜, 并采用 DoE 方法确定了凹凸棒石为最佳的黏土成分, 采用全因子设计, 在两个水平上研究了 PVA(聚乙烯醇)、PVP(聚乙烯基吡咯烷酮)、CS(壳聚糖谷氨酸盐)的浓度, 确定出最佳配方。在该配方下, CVR 负载到凹凸棒石中可以维持 CVR 的抗氧化性, 改善其对成纤维细胞的细胞毒性并增加抗菌特性, 有望将其用作伤口愈合材料^[100]。为提高伤口敷料的抗菌性, 在材料中加上金属氧化物也是一种可行的方法。例如 Zhang 等^[101]以壳聚糖、甘草酸、氧化锌/凹凸棒石(ZnO/PAL)为原料, 以溶液浇筑法制备出复合薄

膜, 该薄膜的机械性能有所提高, 并且增强的物理性能有助于提供高湿度环境并吸收伤口渗出物, 出色的透光率有助于实时监测伤口的变化。同时其对常见的致病菌甚至耐药菌都呈现出了优异的抗菌性, 是伤口愈合的理想材料。

此外, 由图 8 可见, 在最新的一项研究中, 研究者首次将经草酸浸出后的混维凹凸棒石(O-MDPal)掺进壳聚糖/聚乙烯吡咯烷酮(CS/PVP)基质中, 采用

溶液浇筑法制备出高性能的止血纳米复合薄膜(O-MDPal/CS/PVP)。该薄膜不仅在引入 10%~20% O-MDPal 后表现出良好的物理性能、热稳定性、力学性、适当降解性和优异的生物相容性, 同时在体外也具有优异的止血性能, 其在小鼠截尾模型实验中的止血速度甚至明显快于医用纱布^[102]。可以预见, 凭借混维优异的物理性能和止血性能, 未来或许会作为止血材料广泛用于伤口愈合领域。



O-MDPal is Mixed dimensional attapulgite. CS/PVP is Chitosan/Polyvinylpyrrolidone.

图 8 纳米复合薄膜的制备及止血应用示意图^[102]

Fig. 8 Preparation and hemostatic application diagram of nanocomposite films^[102]

3 面临的问题与未来展望

我国是凹凸棒石的资源大国, 储量约占全球储量的 60%^[103], 在几十年的发展中, 尤其是棒晶解离技术的开发使得凹凸棒石已被广泛应用于各个领域。虽然目前凹凸棒石在生物医药领域的应用范围有限, 但是未来的应用潜力值得期待。

1) 凹凸棒石作为生物抗菌材料方面, 由于凹凸棒石纤维间的强氢键作用和范德华力的作用, 在一定程度上限制了它们作为纳米抗菌材料的应用^[20]。未来需加快凹凸棒石单晶深度解离和强化分散的技术研究。同时凹凸棒石基复合抗菌材料的表面改性技术仍有进步空间, 未来需要开发更加绿色、高效的改性技术, 提高生产效率, 减少对环境的污染并降低生产成本。

2) 凹凸棒石作为药物载体方面, 由于凹凸棒石稳定性强, 难以分解, 目前还尚不能作为泌尿系统、血液系统的药物载体材料。鉴于此未来应深入凹凸棒石作为药物载体在体表、消化系统中的应用研究, 同时需找到合适的途径、方法拓展凹凸棒石在泌尿系统、泌尿系统疾病治疗中的应用。

3) 目前凹凸棒石在生物医药领域的实际应用

还较少。未来需要拓宽凹凸棒石在生物医药领域的实际应用, 加快凹凸棒石基医药产品的开发, 例如: 利用凹凸棒石的高效吸附性开发快速止血纱布; 利用凹凸棒石的抗菌性和生物相容性制备骨科、牙科的替代产品^[104–105]等。

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Research Progress on Application of Attapulgite in Biomedicine

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Extended Abstract

Attapulgite is a rod like silicate clay minerals with a 2:1 type chain layered nanostructure, and the length of rod crystal is 0.5–5.0 μm . It is a non-renewable natural nanomaterial. The layered crystal structure of the attapulgite chain endows it with special physical and chemical properties, including adsorption, colloidal, and cation exchange properties. Attapulgite is widely used in agriculture, environmental protection, chemical industry, and other fields due to its superior properties. The breakthrough in key common technologies for the dissociation of crystal beams in palygorskite rods enables the expansion of palygorskite from conventional applications to high-tech applications. Attapulgite as a non-toxic natural mineral material has good biocompatibility, abundant reserves, and low price. It has an enormous application potential in the field of high value-added biopharmaceuticals. This review summarized recent research work on the application, the structure and properties of attapulgite.

The first part summarized the research progress of the application of attapulgite in the field of biological antibacterial, elaborated on the possible antibacterial mechanisms of attapulgite composite antibacterial materials, compared the preparation methods and antibacterial properties of different attapulgite based composite antibacterial materials, and gave that one of the research hotspots for attapulgite based composite antibacterial materials is to explore a simple and green preparation method.

The second part summarized the application of attapulgite in the field of feed additives, represented the preparation of three different attapulgite based feed additives and their respective advantages and disadvantages, and pointed out that the relevant products are used in production practice, and listed some typical production process diagrams of the products.

The third part represented the application of palygorskite in drug carriers. Attapulgite based drug carriers are mainly in the form of hydrogels and nanofibers. At present, there is no research on the application of attapulgite based drug carriers *in vivo*. The main reason is that the safety of palygorskite *in vivo* is unknown, and it is also stable, making it difficult to enter the blood and urinary circulation system as a drug carrier. However, the prepared attapulgite sustained-release tablets can be discharged through the digestive system and have great application prospects.

The fourth part represented the application of attapulgite in composite scaffold materials. Although attapulgite based composite scaffold materials have a good osteogenic induction *in vitro*, their osteogenic induction *in vivo* is still unclear, and the mechanism of osteogenic induction *in vitro* is still unclear.

The fifth part summarized the application of attapulgite in wound healing. Attapulgite based wound dressings have a good usability. Mixed dimensional attapulgite seems to have better usage effects and is expected to become a novel generation of hemostatic materials.

Summary and prospects 1) In the future, it is necessary to accelerate the technological research on the full dispersion of attapulgite single crystals. Also, there is still a room for progress in the surface modification technology of attapulgite based composite antibacterial materials. The more attention should be paid to green and simple physical modification technologies, which can improve the production efficiency, and reduce the environmental pollution and costs. 2) Further research should be conducted on the application of palygorskite as a drug carrier on the body surface and digestive system, and pathways and methods suitable should be found to enable palygorskite to undergo harmless degradation in the blood and urinary systems. 3) It is necessary to accelerate the research on surface modification technologies of palygorskite, and make palygorskite based wound dressings into a form similar to gauze, which can to some extent reduce the risk of its entry into the blood system. 4) The practical application of attapulgite in the field of biomedicine is still relatively limited. In the future, we should accelerate the clinical research of attapulgite in the field of biomedicine, while still expanding the research of attapulgite in the field of biomedicine practice. For instance, we could use attapulgite to adsorb the metabolite of cholesterol-bile acid to treat hypertension and hyperlipidemia. The adsorption of palygorskite is used to regulate the intestinal flora and interfere with the occurrence of type 2 diabetes. It is possible for the treatment of tumors to utilize the stability and biocompatibility of attapulgite to prepare high-performance drug loaded microspheres for embolization. The antibacterial and biocompatibility of attapulgite are also utilized to prepare alternative products for orthopedics and dentistry.

This review provided a reference for the application research of attapulgite in the field of biomedicine.

Keywords attapulgite; silicate minerals; nano materials; biopharmaceuticals; composite materials