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·综 述·

刺激响应型微针的研究进展

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摘 要：传统的给药方式存在生物利用度低、操作过程复杂、不适用于针头恐惧患者等问题。透皮给药可以避免这些问题，但是由于大多数药物难以直接穿透皮肤角质层使其应用受限。微针技术作为一种新兴的局部给药方式，能够以微创方式穿透皮肤角质层并将药物直接递送到病变部位，从而提高治疗效果。刺激响应型微针也因其具有时空可控性、药物递送效率高和潜在副作用小等优点而备受关注。本文重点介绍了刺激响应型微针的常用材料、各种刺激响应触发的微针类型及药物释放机制，阐述了其作为药物递送系统的生物医学应用，并探讨了刺激响应型微针面临的挑战和潜在解决方案。

关键词：微针技术；刺激响应；药物递送；释放机制；生物传感

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Research progress in stimuli-responsive microneedles for biomedical applications

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Abstract: Conventional administration methods have problems including low bioavailability, complex operation process, and discomfort of patients with fear of needles. Transdermal delivery can avoid these problems, whereas most drugs are difficult to directly penetrate the skin cuticle and reach the diseased site. Microneedling is an emerging method of local drug delivery, enabling the drug penetration through the stratum corneum of the skin in a minimally invasive manner and delivering the drug directly to the diseased site, thereby improving the treatment effect. Stimuli-responsive microneedles have attracted much attention because of the spatiotemporal controllability, high drug delivery efficiency, and mild potential side effects. This review introduced the commonly used materials and various types of stimuli-responsive microneedles and the drug release mechanisms. In addition, this paper expounded the biomedical applications of stimuli-responsive microneedles as drug delivery systems in response to different stimuli and discusses the challenges and potential solutions for stimuli-responsive microneedles.

Keywords: microneedling; response to stimuli; drug delivery; release mechanism; biosensing

传统的药物递送系统通常具有一定的局限性，例如口服给药与首过代谢有关，会降低药物的生物利用度[1-2]；注射给药尽管避免了首过代谢，但是需要专业人员操作，并且不适用于针头恐惧患者[3]。透皮药物递送系统是将药物经皮肤给药进入体循环以达到全身或者局部治疗效果，因其安全有效而备受关注。然而，由于大多数药物难以直接穿透皮肤角质层，导致其递送效果仍较差[4-5]。因此，如何穿透皮肤屏障成为目前透皮药物递送系统亟待解决的问题。

近年来，随着材料科学与生物技术的发展，微针技术作为一种新型皮下药物递送途径显示出广阔的应用前景[6]。微针是由多个微米级针尖组成的阵列贴片，长度为 150−1 500 μm，宽度为 50−250 μm，尖端直径为 1−25 μm。通过这种特殊结构设计，微针不仅可以定向穿透角质层并形成微通道用于药物缓慢释放，而且还可以避免与皮肤中的神经末梢接触，减轻疼痛感[7]。因此，基于微针技术的药物递送系统能穿透皮肤屏障实现高效的药物递送，在生物医学应用中表现出潜在优势。

目前，根据结构和材料的不同，微针可以分为固体微针、空心微针、包被微针、溶解微针和水凝胶微针[8]。固体微针是最早出现的微针类型，通常由硅、金属和陶瓷等材料制备而成[9-11]。其递送药物主要分为 2 步：第 1 步是使用微针刺穿皮肤表面形成微通道；第 2 步是移除微针并将药物贴剂贴在微针穿刺部位以实现药物递送。由

于固体微针存在操作复杂且药物作用时间短等问题，因此其应用受限[12]。空心微针是微米级的微型注射器，其独特的中空结构可以负载药物并在浓度梯度作用下实现药物释放。尽管这种微针能够很好地控制药物递送时间，但是仍存在针头断裂和管腔堵塞等风险[13]。包被微针，又称涂层微针，是利用涂层、浸润等方式将药物负载在微针表面。这种载药方式的载药量较低，此外给药过程中也会因与皮肤摩擦而降低药物递送剂量[14-15]。溶解微针是由生物可降解的聚合物材料和药物制成的。微针刺入皮肤后材料完全溶解并释放药物，这个过程操作简单且载药能力强，但是需要考虑其在潮湿环境中能否保持机械特性[16]。水凝胶微针是最新形式的微针，其制备方法与溶解微针类似，也通常被认为是溶解微针的亚型。由于水凝胶的溶胀特性，微针插入皮肤后会迅速吸收组织液并将药物释放到体循环中[17]。这类微针能够在药物递送后完全去除，不存在针头残留问题，而且制备工艺简单，容易商业化[18]。此外，刺激响应型水凝胶微针也因其时空可控性、药物递送效率高和潜在副作用小等优点逐渐成为生物医学领域的研究热点。

本文系统介绍了刺激响应型水凝胶微针及其在生物医学领域的最新研究进展(图 1)。首先介绍了刺激响应型水凝胶微针的常用材料以及各种刺激响应型水凝胶微针的类型和药物释放机制，同时还阐述了其作为药物递送系统在生物医学中的应用，例如肿瘤治疗、组织再生和生物传感等，最后讨论了刺激响应型水凝胶微针在生物医学应用中面临的挑战和潜在解决方案。

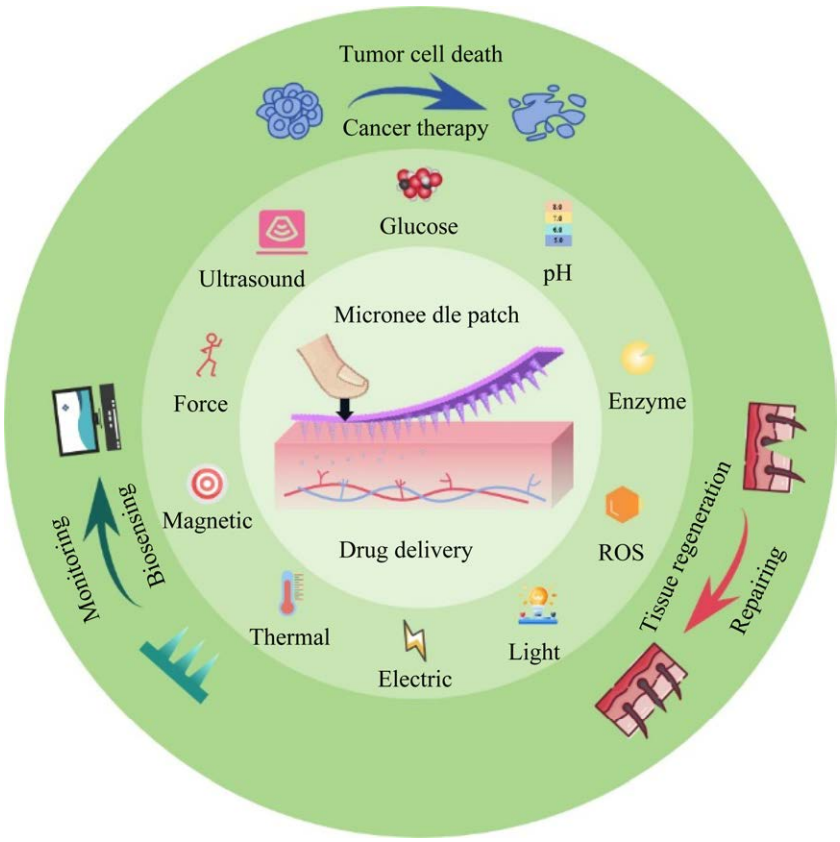

图 1　刺激响应型微针在生物医学中的应用示意图

Figure 1　Schematic diagram of the application of stimuli-responsive microneedle in biomedicine.

1 刺激响应的形式

根据药物递送机制的差异，水凝胶微针可以分为无响应型和刺激响应型两种类型。无响应型微针是通过微针的溶胀、降解等方式实现药物释放。尽管这类微针具有一定的治疗效果，但是无法满足按需给药的要求，并且可能面临治疗效果差或药物过量等风险。刺激响应型水凝胶微针可以通过靶向组织与正常组织之间的微环境差异或者外部刺激实现药物按需递送，有效提高药物的靶向性和治疗效果[19-21]。因此，与无响应型微针相比，刺激响应型微针具有时空可控性、药物递送效率高和潜在副作用小等优点。下文主要介绍由内部和外部刺激介导的水凝胶微针类型。

1.1 由内部刺激介导

在病理和正常状态下，生物体的微环境略有差异，例如葡萄糖、pH、活性氧和酶等。因此，由内部刺激介导的微针可以利用这些差异响应刺激以实现药物释放。

1.1.1 葡萄糖响应

近年来，基于葡萄糖响应的微针被广泛应用于治疗糖尿病。对糖尿病患者来说，水凝胶微针插入皮肤后不仅可以感知生物体微环境变化以实时监测血糖水平，而且可以按需递送胰岛素以维持正常血糖水平。该类微针主要通过3种方法进行响应：基于葡萄糖氧化酶催化的环境变化[22-23]、葡萄糖结合蛋白[3]和苯硼酸[24-25]。由于蛋白类的材料，如葡萄糖氧化酶、葡萄糖结合蛋白等，均存在容易变性、不宜长期储存等问题，因此，苯硼酸(phenylboronic acid, PBA)及其衍生物受到广泛关注[26-27]。其作用机制是当溶液 pH 大于 PBA 的解离常数(dissociation constant, pKa)时，PBA 带负电荷且亲水，可以与葡萄糖特异性结合形成更稳定的苯硼酸酯复合物；当溶液 pH 值低于 PBA 的 pKa 时，PBA 就会变成中性且疏水。基于这一特性，在葡萄糖存在的情况下，由于静电相互作用，PBA 基微针可以通过膨胀或者收缩来实现药物的可控释放[28]。Yu 等[29]基于苯硼酸设计的葡萄糖响应微针不仅表现出良好的生物相容性，而且可以快速响应葡萄糖水平变化，并维持正常血糖水平超过20 h。Lu 等[30]制备的新型 PBA 基葡萄糖响应水凝胶微针不仅具有微创、形态均匀、皮肤穿透能力强等优点，而且能够快速降低糖尿病大鼠的血糖水平并维持稳定，为糖尿病治疗提供了巨大的应用潜力。葡萄糖响应型微针可在人体血糖浓度升高或者降低时快速释放胰岛素，从而维持正常血糖水平。这不仅极大减少了糖尿病患者皮下注射的疼痛，而且避免了胰岛素递送过量或者不足的风险。然而目前，葡萄糖响应型微针仍然处于动物实验阶段，需要更多的临床数据支持。

1.1.2 pH 响应

人体不同器官或者组织的 pH 值通常较稳定。然而，细菌感染或者癌细胞增殖会使 pH 值升高或者降低。因此，pH 响应型微针可以通过微针的结构变化(如膨胀或降解)来响应环境 pH 的变化，从而实现药物的可控释放[31]。Li 等[32]通过逐层组装技术构建了一种 pH 响应型基因负载微针贴片，结果表明该微针插入皮肤后会迅速膨胀并促进 p35 DNA (癌细胞的抑制基因)释放，从而抑制体内皮下肿瘤生长。Lei 等[33]将 pH 响应型聚合物 2,3-二甲基马来酸酐-聚乙烯亚胺-聚乳酸羟基乙酸共聚物(DMA-PEI-PLGA, DPP)和光敏剂(chlorin e6, Ce6)偶联抗菌肽(AMP-Ce6, AC)自组装形成的胶束负载在甲基丙烯酰化透明质酸(hyaluronic acid methacryloyl, HAMA)水凝胶微针上，结果表明该微针可以响应细菌生物膜的酸性微环境并实现抗菌肽的快速释放以促进慢性伤口愈合(图 2)。pH 响应型微针可以根据

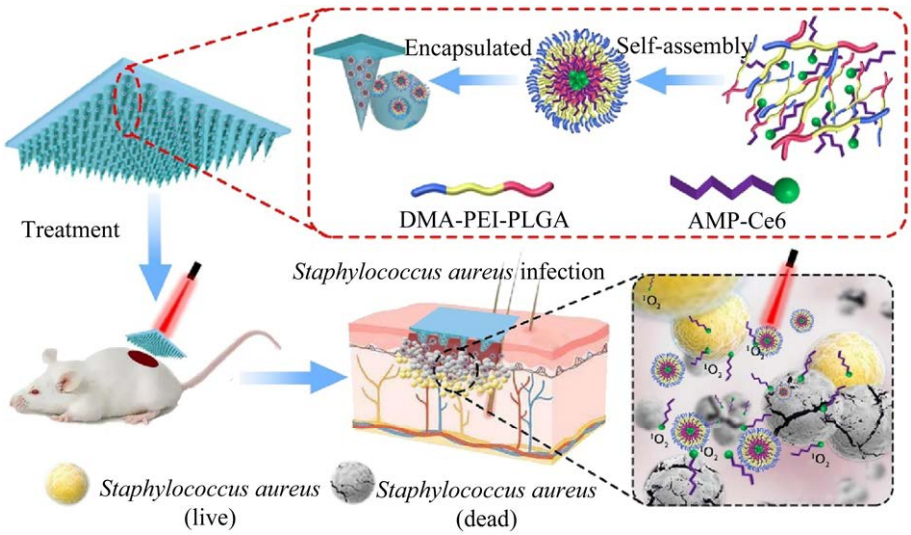

图 2　pH 响应型微针及其在细菌感染慢性伤口治疗中的应用示意图[33]

Figure 2　Schematic diagram of pH-responsive microneedle and its application in the treatment of chronic wounds with bacterial infections[33].

人体生理环境 pH 的变化实现药物的智能可控释放，有效减少药物副作用，适用于皮肤伤口患者或者癌症患者。然而，该类微针也存在载药量低、生物安全方面支撑数据不足等问题。

1.1.3　酶响应

酶是由生物体内的活细胞产生的一类生物催化剂，其化学本质是蛋白质(少数是 RNA)。生物体内的酶催化反应都可以在温和条件下高效有序地进行。此外，由于酶可以特异性识别底物，因此酶响应型水凝胶微针可以利用这一特性实现药物的靶向递送和治疗。Wu 等[34]开发了一种多功能 HAMA/羧甲基壳聚糖(carboxymethyl chitosan, CMCh)核壳微针贴片用于治疗细菌感染和糖尿病伤口愈合，结果表明 HAMA 外壳可以被金黄色葡萄球菌分泌的透明质酸酶降解，从而释放反义 RNA (antisense RNAs, asRNA)以达到抗菌效果，从 CMCS 内核释放的碱性成纤维细胞生长因子(basic fibroblast growth factor, bFGF)能够促进糖尿病伤口愈合。因此，该多功能微针贴片在加速细菌感染性糖尿病伤口愈合方面表现出巨大的应用潜力。Wang 等[35]利用谷氨酰胺氨基转移酶的特异性转氨反应构建了负载铁/单宁酸纳米粒子的明胶/聚赖氨酸水凝胶微针(gelatin/polylysine@FeTA, Gel/PL@FeTA)，结果表明该微针不仅能够在生理条件下释放一氧化氮(nitric oxide, NO)并促进血管生成，而且聚赖氨酸的内源性抗菌能力和 FeTA 纳米粒子的光热效应协同作用提高了其抗菌效果，从而加速糖尿病伤口愈合。酶响应型微针可以利用生理和病理状态下酶的差异性来实现药物的智能释放，但是通常需要与其他响应方式相结合，如 pH 响应、热响应等，才能更好地实现药物的治疗效果。

1.1.4　活性氧响应

活性氧(reactive oxygen species, ROS)作为氧代谢的产物，在机体内参与许多重要的生理和病理过程，如细胞信号传导[36]、炎症反应[37]和肿瘤发生[38]等。ROS 响应聚合物通常含有易被 ROS 氧化的元素或者易被 ROS 裂解的基团。因此，ROS 响应型水凝胶微针可以通过 ROS 诱导的聚合物亲疏水性质或者结构改变来实现药物靶向递送，从而改善治疗效果。Ding 等[39]设

计了一种负载整合素 avβ6 阻断抗体(integrin avβ6-blocking antibody, 10D5)的 ROS 响应型微针，结果表明 ROS 可以诱导微针部分溶解并释放 10D5，从而靶向转化生长因子-β1 (transforming growth factor-β1, TGF-β1)活性位点用于治疗肝纤维化。Bi 等[40]制备了一种负载甲氨蝶呤(methotrexate, MTX)和表没食子儿茶素没食子酸酯[(-)-epigallocatechin gallate, EGCG]的 ROS 响应型水凝胶微针，结果表明针尖插入牛皮癣样皮肤后会迅速吸收间质液并膨胀成多孔凝胶以释放 MTX 用于抑制角质形成细胞的增殖，随后 ROS 可以诱导针尖部分降解以持续释放 EGCG 用于清除 ROS 达到抗炎效果。因此，两种药物的联合作用模式在治疗银屑病方面具有潜在应用。活性氧响应型微针具有灵敏度高、生物相容性好、特异性好等优点，适用于肝纤维化、皮肤疾病或者肿瘤等多种疾病治疗，但是实验只在动物模型中测试了其治疗效果，后期还需要更多的临床数据进行验证。

由内部刺激介导的微针可以响应患者病理环境的生物信号，如葡萄糖、pH、酶、活性氧，以实现药物递送的时空可控性。例如，这种微针系统可以根据受伤皮肤组织与正常皮肤组织的温度或者 pH 差异实现按需释药，而且不需要其他辅助设备，具有操作简单、成本低廉等优点。此外，对于葡萄糖患者来说，葡萄糖响应型微针也可以作为闭环给药系统，实现胰岛素的长期递送。但是这种类型的微针不适用于缺乏内部刺激的疾病。

1.2 由外部刺激介导

由内部刺激介导的水凝胶微针虽然可以实现药物靶向治疗，但是不适用于某些缺乏内部刺激的疾病，例如心血管疾病、神经系统疾病等[20]。与内部刺激介导的微针相比，由外部刺激介导的微针可以通过外部刺激(例如光、电、热、磁等)精确调控药物释放，因此在疾病治疗中具有明显优势。

1.2.1 光响应

与其他响应信号相比，光信号具有明显优势，例如无创、非接触性、时空可控性等。目前，大多数光响应材料中引入的光敏基团通过光致异构化或者光化学反应实现光响应。因此，该类微针可以利用这一特性实现按需释药用于疾病治疗[41]。Xu 等[42]制备了一种基于铁(III)交联海藻酸盐的光响应微针系统(cross-linked alginate microneedle patch, ICAMP)；该微针系统不仅具有优异的生物相容性，而且能够在 405 nm 的光照下迅速降解成铁(II)和海藻酸盐并持续释放乳酸铵(ammonium lactate, AL)用于治疗皮肤干燥症。Bian 等[43]设计了一种负载低剂量光敏剂(low-dose chlorin e6, L-Ce6)的快速溶解微针贴片用于治疗黑色素瘤；结果表明，该微针不仅能够将 L-Ce6 靶向递送到肿瘤部位，而且可以在 660 nm 激光照射下促进细胞间 ROS 的产生并诱导肿瘤细胞凋亡和免疫原性细胞死亡(immunogenic cell death, ICD)，从而实现光动力疗法(photodynamic therapy, PDT)治疗黑色素瘤。光响应型聚合物微针可以通过光控制药物的精确释放，但是近红外光产生的高温也容易破坏药物结构，改变药物的理化性质，降低药物的生物活性。此外，光响应型聚合物微针在疾病治疗中还有许多方面需要探索和优化，如光源选择、药物选择、生物安全性等。

1.2.2 电响应

电响应型水凝胶微针是通过掺入导电材料制备的。导电材料主要分为两类：一类是导电聚合物，包括聚吡咯(polypyrrole, PPy)、聚呋喃(polyfuran, PFu)和聚苯胺(polyaniline, PANI)等[44]；另一类是导电纳米粒子，包括金属纳米粒子和碳基纳米粒子[45]。Yang 等[46]基于压电纳

米发电机(piezoelectric nanogenerators, PENG)和微针贴片(microneedle patch, MNP)制备了一种负载地塞米松(dexamethasone, Dex)的自供电可控透皮给药系统(self-powered controllable transdermal drug delivery system, sc-TDDS)用于治疗牛皮癣。PENG 能够将关节弯曲或者拍手产生的生物机械能转化为电能。此外，由于 PPy 的可逆氧化还原特性，MNP 可以响应电信号并将 Dex 释放到皮肤组织，从而达到抗炎效果。Qi 等[47]制备的硫醇化丝素蛋白微针(thiolated silk fibroin microneedles, TSF@MNs)在胰岛素递送方面展现出优异的电响应特性。在通电条件下，二硫键会断裂导致微针膨胀并释放胰岛素；断电后，巯基会被氧化并重新形成二硫键，从而减缓药物释放速率。电响应型微针可以通过控制电场的通电条件实现智能释药，有效减少药物的副作用，适用于糖尿病、皮肤疾病等。但是长期的外部电刺激会对皮肤造成损伤。PENG 和 MNP 形成的自供电系统减少了对外部电源的依赖，在临床医学中具有潜在应用价值。然而电响应型微针的研究数据偏少，需要更多的数据支撑其智能性和安全性。

1.2.3 热响应

热响应型聚合物是基于低临界溶液温度(lower critical solution temperature, LCST)与环境温度之间的差异，从而触发相变。当环境温度低于 LCST 时，聚合物处于溶液状态。然而，一旦环境温度高于LCST，聚合物会通过疏水相互作用或者构象变化实现凝胶化[48]。此外，这种溶胶-凝胶转变是可逆的。因此，热响应型水凝胶微针可以通过外加热源使聚合物发生相变，从而实现药物递送。Zhang 等[49]开发的可分离微针由负载二甲双胍(metformin)的聚己内酯(polycaprolactone, PCL)针尖和聚乙烯醇/聚乙烯吡咯烷酮(polyvinyl alcohol/polyvinyl pyrrolidone, PVA/PVP)基底组成。微针插入皮肤后，PCL 针尖会与 PVA/PVP 基底分离。当用电加热片处理针尖时，PCL 熔化并释放二甲双胍，用于治疗糖尿病(图 3)。热响应型水凝胶微针可以通过控制外部热源实现药物按需释放，有效减少药物的副作用。然而，局部温度过高会对皮肤造成损伤，而且热响应性聚合物材料的生物安全性和温度响应阈值的准确性需要更多数据验证。

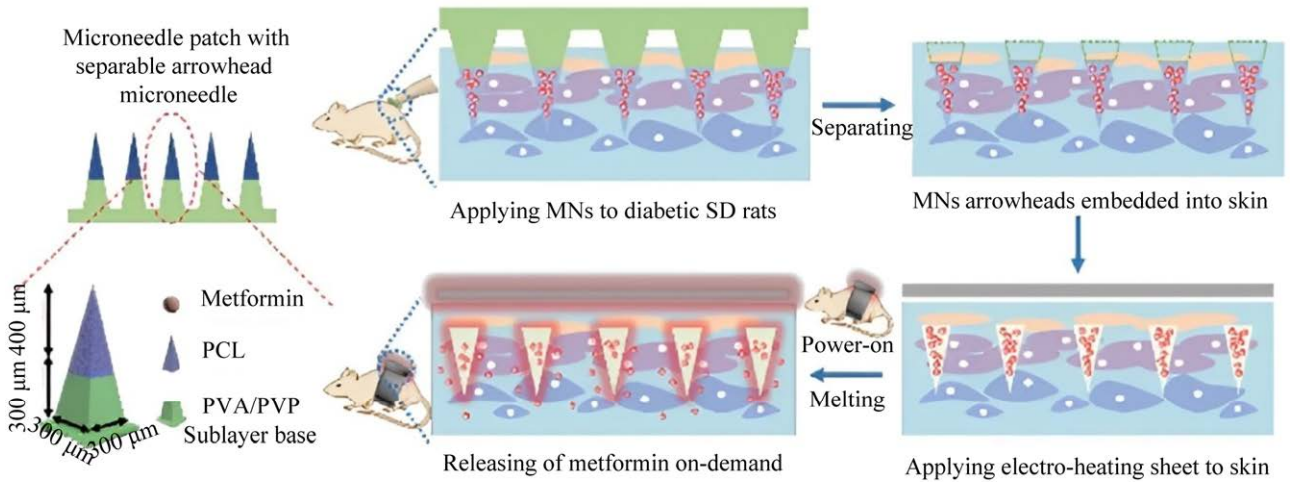

图 3 热响应型微针及其对糖尿病 SD 大鼠治疗的应用示意图[49]

Figure 3 Schematic diagram of thermal-responsive microneedle and its application in the treatment of diabetic SD rats[49].

1.2.4 磁响应

磁响应型微针贴片通过掺入磁性材料以快速响应外部磁场，从而实现药物控释[50-51]。Zhang 等[52]提出了一种磁响应微针机器人用于口服给药，该微针机器人主要包括磁性基板、可分离连接和尖端 3 个组件。首先，在商业化肠溶胶囊的辅助下，微针机器人可以口服并进入小肠；其次，磁性基板在外部磁场驱动下定向移动到小肠壁；随后，可分离连接在与消化液接触后迅速降解；最后，载药微针会刺穿小肠壁并持续释药。Lee 等[53]设计了一种内部搭载多层载药微针的磁驱动胶囊以实现药物的靶向递送。根据永磁体与胶囊体之间的相对位置，胶囊处于 2 种状态：运动状态和递送状态。在运动状态下，载药微针贴片位于胶囊体内，并且在外加磁场驱动下，胶囊会移动到病变部位。在递送状态下，微针从胶囊体内移动到边缘并释放药物。磁响应型微针系统兼具微针的穿透力强、微创、痛感低的优点和磁信号的远程调节、功能丰富、适用于复杂环境的优点，在口服给药治疗多种疾病中具有潜在优势。然而，关于磁响应型微针给药系统的研究较少，还需要大量的数据证明其有效性和安全性。

1.2.5 机械力响应

机械力响应可以分为内源性和外源性两类。内源性机械力包括关节运动产生的压力、肌肉运动产生的拉力以及血管疾病引起的高剪切力等；外源性机械力则涉及外部施加的压力或者拉力等[54]。与其他类型的外部刺激相比，该类刺激不需要辅助设备即可实现自我按需药物递送。Kim 等[55]设计了一种压力响应型透皮给药贴片用于药物递送，该贴片由 3 部分组成，储液槽、应变传感器和固体 MN。当手动按压时，药物通过微通道从一侧储液槽流向另一侧储液槽并在微针刺穿皮肤后，药物透过微针渗透到真皮层，从而实现按需给药。Di 等[56]将拉伸应变触发药物递送系统与微针贴片相结合用于治疗糖尿病，结果表明当施加拉力时，该系统的弹性体薄膜表面积增大和泊松比率诱导的压缩能够促进胰岛素释放并维持正常血糖水平。日常关节运动或者外部施加力可有效促进抗菌、抗炎或者抗癌药物的缓释，用于伤口愈合或者肿瘤治疗。但是在伤口愈合过程中，日常关节运动容易造成二次损伤。此外，对于机械力响应型微针给药系统的安全性也需要更多的实验数据进行验证。

1.2.6 超声响应

超声波是一种周期性的机械波，具有无创性、可控性和穿透性，在医学诊断和治疗中被广泛应用。超声响应材料可以利用超声引起的空化、微流、散射和声辐射力等触发 ROS 的产生，用于治疗细菌感染[57]。氧化钛(titanium dioxide, TiO_2)是一种广泛使用的声敏剂，可以有效将超声能量传递到超声产生的空化微泡，并作用于感染部位。Liang 等[58]开发了负载过氧化铜/氧化钛纳米材料(copper peroxide/titanium oxide, CuO_2/TiO_2)的微针贴片用于治疗细菌感染。这种微针结合了声化学动力学和声热抗菌疗法的优点，5 min 内病原体消除率可达 99.999 9%，能够有效促进伤口愈合。此外，纳米酶抗菌疗法也被应用于治疗细菌感染，具有广谱抗菌性和最小的细菌耐药性[59]。然而，长期处于激活状态的纳米酶可能会对正常细胞产生副作用并降低抗菌活性。Shi 等[60]设计了负载铂-钌/氮化碳纳米酶(platinum-ruthenium/carbon nitride C_3N_5, $PtRu/C_3N_5$)的透明质酸微针，超声和光的不同刺激响应可以实现抗菌和抗炎作用的灵活切换和精确控制。因此，超声响应微针有望成为一种新的抗菌治疗策略。然而，需要更多研究来确定超声时间和强度，既能减少对正常组织的损害，又能实现最好的抗菌效果。

表 1 列举了各类刺激响应型微针及其给药

表 1 刺激响应型微针给药系统

Table 1 Stimuli-responsive microneedle delivery system

Types		Materials	Size	Medicine	Disease application	Advantages	Disadvantages	References
Internal stimuli	Glucose	PLL-PBA and GG	Height was approximately 490 μm, the base width was 200 μm, and the central spacing was 500 μm between adjacent needles	Insulin	Diabetes	Glucose responsive administration of insulin with minimal invasion and pain	Only suitable for the treatment of diabetes	[30]
	pH	HAMA	Height was approximately 600 μm, the base diameter was 250 μm, and the central spacing was 550 μm between adjacent needles	DPP@AC	Bacterial infected chronic wound	Precise bacterial targeting and stimulus-responsive drug release	Low drug loading	[33]
	Enzyme	HAMA and CMCh	Conical shapes with a height of 600 μm and tip-to-tip spacing of 600 μm	GO, AS yycF and bFGF	Bacterial infected diabetic wounds	Intelligent release of drugs	The cost is high	[34]
	ROS	HA	Square pyramid shape with a height of 650 μm, a base diameter of 200 μm and a distance of 500 μm between the centers of two adjacent needle bases	MTX and EGCG	Psoriasis	High sensitivity and good specificity	The preparation progress is complicated	[40]
External stimuli	Light	AR	Conical needles with a height of 1 400 μm and a bottom diameter of 1 000 μm	AL	Xerosis	Long-term stable curative effect	High temperature is also easy to destroy the drug	[42]
	Electric	SF	Conical shape with a length of 650 μm and a bottom diameter 300 μm	Insulin	Diabetes	Good insulin release performance	High cost	[47]
	Thermal	PCL, PVA and PVP	Pyramidal shape with a height of 400 μm, the width of 300 μm, and the tip-to-tip distance of each two MNs of 600 μm	Metformin	Diabetes	On-demand control of the timing and dose of drug released	High temperature is also easy to destroy the skin	[49]
	Magnetic	Gel	The height of the MN is approximately 250 μm and the diameter of the MN patch is approximately 11 mm	Lissaminegreen B and rhodamine 6G	Gastrointestinal diseases	Targeted drug delivery is remotely regulated	Magnetic materials usually contain metal ions	[53]
	Force	PLGA	The conical MNs have a base diameter of 300 μm and height of 900 μm	Rhodamine B	Nerve disorders	Real-time dose regulation	The preparation technology is complicated	[55]
	Ultrasound	HA	Round cone construction with a distance of roughly 600 μm between two neighboring needles and a height of 600 μm	CuO_2/TiO_2	Bacterial infections in wound sites	Precise control of drug release	Ultrasoundmaterials usually contain metal ions and damage the human body	[58]

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系统。由外部刺激介导的微针可以通过外部刺激，如光、电、热、磁、机械力，实现远程精确调控药物的剂量和速率，提高药物的递送效率，降低药物过量带来的副作用。此外，这类微针也可以外接储液设备实现药物的按需释放，克服微针载药率低等问题。然而，光热产生的局部高温会损伤皮肤，而且通常需要辅助设备，存在操作复杂、成本高昂等问题。此外，关于刺激响应型微针的研究数据较少，需要更多的实验数据支持其进入临床阶段。

2 微针材料的选择

水凝胶微针材料通常分为两类：天然高分子聚合物和合成高分子聚合物。天然高分子聚合物主要包括多糖和蛋白，例如透明质酸(hyaluronic acid, HA)、硫酸软骨素(chondroitin sulfate, CS)、壳聚糖(chitosan, Ch)、明胶(gelatin, Gel)和丝素蛋白(silk fibroin, SF)等。合成聚合物主要包括聚乳酸(polylactic acid, PLA)、聚乙烯吡咯烷酮(polyvinyl pyrrolidone, PVP)、聚乙烯醇(polyvinyl alcohol, PVA)、聚乳酸羟基乙酸 [poly(lactic-co-glycolic acid), PLGA]和聚 N-异丙基丙烯酰胺[poly(n-isopropyl acrylamide), PNIPAM]等。

2.1 基于天然聚合物的微针

2.1.1 透明质酸(HA)

HA是一种线性的非硫酸化糖胺聚糖，其分子结构由 β-(1,4)-N-乙酰基-D-葡萄糖胺和β-(1,3)-D-葡萄糖醛酸的重复 2 糖单元组成[61-62]。作为细胞外基质的关键成分，HA广泛分布于人体皮肤组织、关节滑液和眼玻璃体等[63]。此外，HA 不仅参与多种细胞反应，例如细胞黏附、增殖和迁移等，而且具有多种生物学功能，例如保湿性、润滑性和抗压性等[64]。因此，基于 HA 的水凝胶微针被广泛应用于药物递送。Ge 等[65]制备了一种多功能可溶解 HA 微针用于治疗口腔溃疡，结果表明当微针刺穿口腔黏膜并迅速溶解后，尖端会释放曲安奈德(triamcinolone acetonide, TA)和表皮生长因子(epidermal growth factor, EGF)并发挥抗炎和促血管生成作用。同时，微针底部释放出的沸石咪唑盐骨架-8 (zeolitic imidazolate frameworks-8, ZIF-8)具有抑菌作用。这种多功能可溶解 HA 微针设计为治疗口腔溃疡提供了一种新的治疗策略。Zhang 等[66]首次将 I 型胶原蛋白(collagen I, COL I)负载在 HAMA 水凝胶微针用于治疗压力性尿失禁(stress urinary incontinence, SUI)；结果表明，该微针表现出良好的力学性能和生物相容性，而且可以通过持续释放 COL I 来增强小鼠 SUI 中 COL I 的表达水平。

2.1.2 硫酸软骨素(CS)

CS 是由 N-乙酰基-D-半乳糖胺和 D-葡萄糖醛酸通过 β-(1,3)和 β-(1,4)糖苷键交替连接而成的重复 2 糖单元组成[67]。CS 不仅可以作为细胞外基质的主要成分，维持细胞正常代谢活动，而且能够作为细胞信号因子，直接或者间接地影响细胞信号传递过程[68]。此外，CS 具有多种生物活性，例如抗炎、抗氧化和免疫调节等[69-71]。Yu 等[72]制备了一种负载盐酸利多卡因(lidocaine hydrochloride, LIDH)的半互穿网络基微针，结果表明该微针不仅具有优异的机械性能，而且 PVP 的快速溶解能够促进 LIDH 的快速释放，从而有效实现局部麻醉。Liu 等[73]将重组葡萄球菌肠毒素 B (recombinant staphylococcal enterotoxin B, rSEB)负载在 CS 基溶解微针中，证明了微针能在插入小鼠皮肤后快速溶解并释放 rSEM 以实现免疫治疗。

2.1.3 壳聚糖(Ch)

Ch 是一种由甲壳素经过脱乙酰化得到的线

性多糖，主要由 N-乙酰基-D-氨基葡萄糖和 D-氨基葡萄糖的重复 2 糖单元组成[74]。由于 Ch 具有抗菌、抗氧化、抗肿瘤、止血等生物活性，因此在生物医学领域中被广泛应用[75-76]。Khalid 等[77]制备了巯基壳聚糖(thiolatedchitosan, TCh)和聚醋酸乙烯酯(polyvinyl acetate, PVA)微针用于递送地屈孕酮(dydrogesterone, DYD)；体外药物释放结果显示微针中的 DYD 在 48 h 的累积释放量为(81.45±2.768)%，然而纯 DYD 在 12 h 会达到(96.7±1.75)%；此外，体外渗透试验表明微针插入皮肤后形成的微通道有助于 DYD 渗透到真皮浅层，渗透率为(81.46±2.25)%。因此，该微针在 DYD 透皮递送中表现出巨大潜力。Yang 等[78]制备了负载银纳米粒子的壳聚糖/白芨多糖复合微针(chitosan/bletilla striata polysaccharide miccroneedles, Ch/BSP MNs)用于促进细菌感染伤口的愈合，结果表明该微针不仅具有优异的抗菌效果，而且表现出独特的抗炎和抗氧化作用，从而加速伤口愈合。

2.1.4 明胶(Gel)

Gel 是由动物皮肤、骨骼、韧带和肌腱中的胶原蛋白经过水解或者热变性获得的蛋白类聚合物[79]。根据提取方法不同，Gel 分为两种类型：通过酸提取得到的 A 型 Gel 和通过碱提取得到的 B 型 Gel[80]。二者也具有不同的等电点(isoelectric point, PI)，A 型 Gel 在生理 pH 值下带正电荷，而 B 型 Gel 带负电荷[81]。由于 Gel 不仅具有良好的生物相容性、生物降解性和无免疫原性，而且含有类似胶原蛋白的精氨酸-甘氨酸-天冬氨酸基团以实现细胞黏附和增殖，因此 Gel 基微针在药物递送方面具有潜在应用[82]。Hao 等[83]使用 HA/Gel 基微针透皮递送原儿茶醛(protocatechualdehyde, PA)用于治疗增生性疤痕(hyperplastic scar, HS)，结果表明从微针中释放的 PA 可以诱导细胞凋亡、减少胶原沉积并抑制血管生成，为 HS 治疗提供了一种新的策略。Erkus 等[84]使用 3D 打印技术制备了负载阿莫西林(amoxicillin, AMX)的甲基丙烯酰化明胶微针(gelatin methacryloyl microneedles, GelMA MNs)用于透皮药物递送系统。该微针具有优异的机械性能和良好的抗菌活性，能够有效抑制金黄色葡萄球菌和大肠杆菌的生长。

2.1.5 丝素蛋白(SF)

从蚕丝中提取的 SF 由重链(390 kDa)、轻链(26 kDa)和糖蛋白(25 kDa)按 6:6:1 的比例组成。2008 年，SF 已被美国食品药品监督管理局(Food and Drug Administration, FDA)批准用于生物医学工程。与其他天然聚合物相比，SF 具有优异的机械性能、良好的生物相容性和缓慢的降解速率等优点，因此 SF 基微针备受关注[85-87]。Chen 等[88]将基质细胞衍生因子-1 (stromal cell derived factor-1, SDF-1)负载在 Gel-SF MNs 用于招募脂肪干细胞(adipose-derived stem cells, ASC)。研究表明，该微针可以实现 SDF-1 的持续释放并通过基质细胞衍生因子-1/CXC 受体 4 (stromal cell derived factor-1/CXC receptor 4, SDF-1/CXCR4)信号通路促进 ASC 迁移，为治疗缺血性伤口提供了新策略。Chong 等[89]制备了 SF/PVA MNs 用于递送黑色素细胞刺激素(α-melanocyte-stimulating hormone, α-MSH)以治疗白癜风。当微针刺入皮肤并形成微通道后，尖端释放的 α-MSH 可以促进黑色素的产生和传输来改善皮肤色素沉积，为白癜风治疗提供了新思路。

2.2 基于合成聚合物的微针

2.2.1 聚乳酸(PLA)

聚乳酸(polylactic acid, PLA)是乳酸(lactic acid, LA)经过聚合反应制备的脂肪族聚合物。LA 是手性分子，以两种异构体形式存在：L-异构体和 D-异构体。这两种异构体的比例会影响 PLA 的机械性能、降解性能和结晶类型[90]。

PLA 基微针具有优异的机械强度，刺入皮肤后不会断裂[91]。Zhang 等[92]报道了一种基于 PLA MN 的葡萄糖传感器用于实时监测血糖；体外实验显示，该传感器在磷酸缓冲盐溶液(phosphate buffer saline, PBS)中展现出良好的灵敏度和较低的检测限。因此，这种 PLA 基 MN 传感器在微创血糖监测方面具有潜在优势。Yang 等[93]设计了一种基于聚乳酸-铂-聚吡咯(polylactic acid-platinum-polypyrrole, PLA-Pt-PPy)的电响应型微针贴片用于治疗特应性皮炎(atopic dermatitis, AD)，结果表明该微针贴片能够通过电刺激实现按需释药，从而有效缓解 AD。

2.2.2 聚乙烯吡咯烷酮(PVP)

PVP 是由单体 N-乙烯基吡咯烷酮经过聚合反应得到的[94]。PVP 具有两亲性，极性内酰胺基团决定了亲水特性，非极性亚甲基部分决定了亲酯特性。由于其具有良好的生物相容性、pH 和温度稳定性，因此被广泛应用于生物医学工程[95]。Jeong 等[96]使用伽马射线制备了负载氧化石墨烯(graphene oxide, GO)的 PVP/GO MNs。这种智能药物递送系统不仅展现出优异的机械强度和韧性，而且可以通过电刺激控制药物递送效率。Zare 等[97]开发了可溶解的羧甲基纤维素/聚乙烯吡咯烷酮微针(carboxymethyl cellulose/polyvinyl pyrrolidone microneedles, CMC/PVP MNs)用于递送两性霉素 B (amphotericin B, AMB)；研究表明该微针具有金字塔形状，针尖高度为(586±10) μm；在刺入皮肤后，MNs 会迅速溶解并释放 AMB，48 h 的累计释放量高达 87%。

2.2.3 聚乙烯醇(PVA)

PVA 是由醋酸乙烯酯通过聚合、水解反应制成的。水解程度决定 PVA 的理化性质，例如熔点、黏度和溶解性等[98]。由于 PVA 具有优异的机械性能和生物相容性，因此通过物理交联、化学交联或者辐照交联制备的 PVA 基水凝胶微针被广泛应用于生物医学工程[99]。Fang 等[100]将咪唑修饰的石墨烯量子点(imidazole-modified graphene quantum dot, IMZ-GQDs)负载在 PVA/PVP 溶解微针贴片，用于治疗细菌性角膜炎(bacterial keratitis, BK)；基于 IMZ-GQDs MNs 的高抗菌活性和药物递送效率，金黄色葡萄球菌诱导的兔 BK 在第 7 天得到缓解。Hasnain 等[101]设计了精氨酸修饰的壳聚糖/聚乙烯醇水凝胶微针作为姜黄素(curcumin, CUR)递送系统用于加速伤口愈合。体外试验表明，MNs 不仅具有优异的机械性能以刺入皮肤，而且还表现出抗氧化和抗菌活性；体内实验证明 MNs 能够加速胶原沉积并抑制炎症反应，从而加速伤口愈合。

2.2.4 聚乳酸羟基乙酸(PLGA)

PLGA 是由 LA 和羟基乙酸(glycolic acid, GA) 两种单体随机聚合得到的[102]。两种单体的比例决定了 PLGA 的亲疏水性，进而影响其理化性质，例如溶解性、机械性能和降解速率等[103]。此外，PLGA 可在体内水解为 LA 和 GA 单体，随后通过三羧酸循环(tricarboxylic acid cycle, TAC)转化成二氧化碳和水[104]。因此，PLGA 基微针在药物递送方面具有潜在优势。Huang 等[105]设计了一种电刺激和药物递送联合治疗的 PLGA 基微针。研究表明，该微针不仅可以通过周期性电刺激促进细胞迁移，还能通过释放抗炎药(阿司匹林和布洛芬)减少炎症反应，从而有效治疗肌肉损伤。Wang 等[106]制备了负载氢化镁(magnesium hydride, MgH_2)的 PLGA 微针贴片用于治疗糖尿病伤口；微针释放的 MgH_2 接触体液后会持续释放 Mg^{2+}和 H_2，H_2可以减少 ROS 的产生，Mg^{2+}可以诱导 M2 巨噬细胞极化；此外，MgH_2还可以促进细胞增殖、迁移和血管生成，从而加速糖尿病伤口愈合。

2.2.5 聚 N-异丙基丙烯酰胺(PNIPAM)

PNIPAM 是由单体 N-异丙基丙烯酰胺

(N-isopropylacrylamide, NIPAM)聚合而成的。NIPAM 结构中的酰胺基和异丙基赋予了 PNIPAM 温敏特性，LCST 约为 32 ℃。当温度低于 LCST 时，PNIPAM 处于溶液状态；当温度高于 LCST 时，PNIPAM 处于凝胶状态[107-108]。因此，基于 PNIPAM 的温度响应型水凝胶微针作为药物递送系统具有广泛应用。Zhu 等[109]开发了一种具有可控药物释放能力的湿黏附微针贴片用于治疗口腔溃疡或者早期黑色素瘤；PNIPAM 的加入赋予了 MNs 温度-机械响应性，药物(抗炎药地塞米松、抗癌药 5-氟尿嘧啶)主要有两种释放行为：体温介导的短期释放和微针渗透介导的持续释放。Zhang 等[110]将共晶镓铟纳米粒子(eutectic gallium-indium, EGaIn)掺入基于螺旋蛋白的多功能微针贴片，EGaIn 可以将近红外光能转化为热能并使温度达到 PNIPAM 的 LCST，从而实现血管内皮生长因子(vascular endothelial growth factor, VEGF)的可控释放以加速伤口愈合(图 4)。表 2 总结了以上微针给药系统的材料。

3 生物医学应用

3.1 肿瘤治疗

癌症是人类死亡的主要原因之一。据统计，2020 年，癌症死亡人数约占总死亡人数的 18%，仍然是仅次于心脏病的第二大死因[111]。临床上，癌症治疗的主要方法是手术切除、化疗药物和放射疗法。然而，这些治疗方法存在局限性，例如治疗效果有限、特异性低和耐受性差等[112]。刺激响应型水凝胶微针作为一种新兴的药物递送系统，可以实现药物的按需靶向缓释，从而提高肿瘤治疗效果[113]。Wang 等[114]将光敏剂(organic molecular fluorophore, Flav7)和化疗药物阿霉素(doxorubicin, DOX)共同负载在可分离微针中，用于浅表肿瘤的光热治疗；PCL、Flav7 和 DOX 组成尖端部分，PVA/PVP 组成基底部分；位移-应力曲线显示当位移为 0.5 mm 时，微针的应力约为 0.166 N，这足够穿透皮肤，体外和体内实验表明，当 MN 刺入皮肤后，PVA/PVP 基底部分可迅速被组织液溶解，PCL 尖端留在皮肤中。在近红外光照射下，

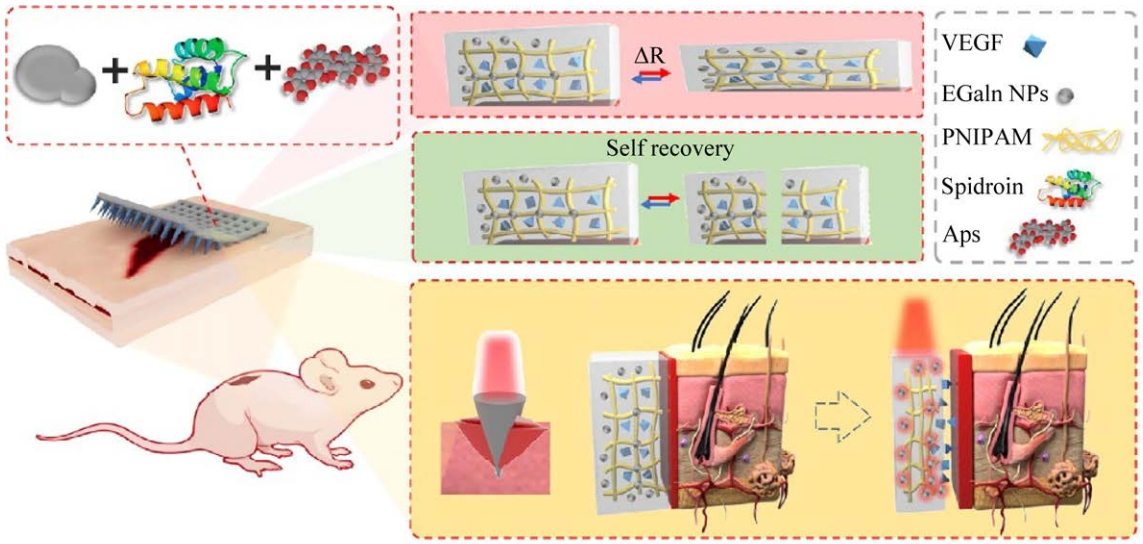

图 4 光响应型微针及其在伤口愈合中的应用示意图[110]

Figure 4 Schematic diagram of light-responsive microneedle and its application in the wound healing[110].

表 2　微针给药系统材料

Table 2　Materials for the microneedle delivery system

Materials		Size	Medicine	Disease application	Advantages	Disadvantages	References
Natural polymers	HA	The needle length was (470±5) μm and the distance between the needles was (700±5) μm	TA, EGF and ZIF-8	Oral ulcers	Unique viscoelasticity, biocompatibility, biodegradability, and non-immunogenicity	Poor mechanical properties	[65]
	CS	Quadrangular pyramid tips with a height of 600 μm	LIDH	Local anesthesia	Superior biodegradability and low toxicity	Poor mechanical properties	[72]
	Ch	The single four-pyramid microneedle was 600 μm in height, 300 μm in side length, and 550 μm in tip spacing	Ag NPs	Bacterial infected wound	Antibacterial activity	Poor mechanical properties	[78]
	Gel	Quadrangular pyramid tips with a height of 1 mm and the width of 450 μm	PA	Hypertrophic scars	Good biocompatibility	Poor mechanical properties	[83]
	SF	The height of the pyramid tip is 800 μm and the base is 200 μm	α-MSH	Vitiligo	Good biocompatibility and high mechanical strength	Few studies	[89]
Synthetic polymers	PLA	The height of MN is 500 μm and the width of MN base is 390 μm	GOx	Glucose sensor	Enough mechanical strength	The degradation cycle is difficult to control	[92]
	PVP	The length of the MNs was confirmed to be approximately 750−755 μm	GO	Smart drug delivery system	Sufficient strength and flexibility	Strong hygroscopicity	[96]
	PVA	The height of MN is 319 μm and the width of MN base is 190 μm	IMZ-GQDs	Bacterial keratitis	Excellent mechanical properties	Poor biocompatibility	[100]
	PLGA	Rectangular pyramid shape of the needle tips with a 200 μm×200 μm×500 μm (W×L×H) dimensions	MgH_2	Diabetic wound healing	Good biodegradability with controllable degradation rate	Poor biological activity	[106]
	PNIPAM	The height is 500 μm	DEX or 5-FU	Oral ulcers or early superficial tumors	Temperature-sensitive characteristics	Low mechanical strength and low biodegradability	[109]

PCL尖端随着Flav7的光热转化效应而熔化，然后释放出DOX以抑制肿瘤细胞增殖；此外，所有接受治疗的乳腺癌小鼠在50 d时均未出现肿瘤复发或者器官损伤等现象。Song等[115]将有机PSs纳米粒子(organic PSs nanoparticles, N3-4F NPs)负载在可溶性微针中，以防止术后肿瘤复发和转移；扫描电子显微镜测试结果显示，所制备的MNs尖端排列有序，长度约650 μm，这足够到达肿瘤部位。当近红外光照射后，Gel MNs可以快速溶解，并实现N3-4F NPs的靶向递送。随后，由近红外光触发N3-4F NPs产生的ROS和光热效应可以诱导残留肿瘤细胞的免疫原性死亡，并激活树突状细胞(dendritic cells, DCs)以产生系统免疫。因此，刺激响应型微针在肿瘤治疗中表现出巨大的临床转化潜力。

3.2 组织再生

组织再生是指当局部组织或者细胞受损后，机体可以利用周围健康组织或者细胞的再生能力来修复受损组织并使其恢复正常状态[116-117]。然而，对于大面积的缺损，机体无法自我愈合。近年来，组织工程作为一种新兴的生物医学技术，在组织再生方面受到越来越多的关注。刺激响应型微针载药系统可以穿透组织屏障，并以微创方式靶向递送生物活性因子，从而实现组织再生[118-119]。Sun等[120]设计了一种温度响应型富血小板血浆(platelet-rich plasma, PRP)/GelMA微针以实现生长因子(growth factors, GFs)的持续释放，用于改善头发再生；微针针尖由温度诱导PRP自组装形成的第1网络和光诱导GelMA交联形成的第2网络组成，基底由PVA组成；结果表明，MNs呈金字塔形，且排列均匀，PRP网络可以增强微针机械强度，约为1.21 N，这足够刺入皮肤(0.17 N/微针)；GFs在24 h从PRP-MNs的多孔结构快速释放，4−6 d随微针降解而缓慢释放，从而促进小鼠毛发再生。Zhang等[121]制备了负载黑鳞量子点(black phosphorous quantum dots, BP QDs)和血红蛋白(haemoglobin, Hb)的可分离微针以实现近红外光触发的氧气的可控释放，从而加速糖尿病伤口愈合；GelMA作为尖端材料，PVA作为基底材料，当刺入皮肤后，基底会在几分钟内快速溶解，GelMA尖端留在伤口内；当暴露于1.56 W近红外光下，BP QDs可以迅速将光能转化为热能，局部温度可在3 min内达到40 ℃，并且降低Hb的氧结合能力，使氧气在24 h内缓慢释放，从而促进糖尿病伤口在第9天几乎愈合。因此，该MNs在治疗1型糖尿病大鼠全层皮肤创伤方面表现出出色的伤口愈合能力。刺激响应型微针在组织再生方面具有广阔的应用前景，但是研究仍然处于动物实验和实验可行性验证阶段，还需要更多的实验数据支撑其进入临床阶段。

3.3 生物传感

皮肤间质液(interstitial fluid, ISF)含有与多种疾病相关的多种特异性生物标志物，例如蛋白质、葡萄糖和脂肪酸等[122]。因此，生物标志物的早期检测对疾病诊断和治疗具有重要意义。常规的ISF提取方法有植入式毛细管法、微移液管插入法和水泡法等[123]。随后，使用质谱、酶联免疫吸附和PCR等技术对间质液中的生物标志物进行检测。然而，角质层创伤、操作复杂和成本高昂等问题限制了其临床应用[124]。近年来，基于MN的生物传感器因其可以以微创方式连续检测代谢标志物而备受关注。Zheng等[125]首次报道了一种基于适配体探针的甲基丙烯酸化透明质酸微针生物传感器用于生物标志物[葡萄糖、三磷酸腺苷(adenosine triphosphate, ATP)、L-酪氨酸酰胺和凝血酶]的定量检测。当针头穿透皮肤并接触ISF后，荧光标记的适配体探针会与目标分子特异性结合，使淬灭基团解离并产生荧

光信号。该传感器具有很高的灵敏度和特异性，葡萄糖的检测限(limit of detection, LOD)为 1.1 mmol/L，ATP 的 LOD 为 0.1 mmol/L，L-酪氨酸酰胺的 LOD 为 3.5 μmol/L，凝血酶的 LOD 为 25 nmol/L，且检测时间仅需 2 min。Wang 等[126]开发了一种 pH 响应型水凝胶微针用于原位提取 ISF 和响应葡萄糖以实时监测血糖水平；微针针尖由 GelMA、纳米羧甲基纤维素纳-聚乙二醇二丙烯酸酯-2-羟乙基丙烯酸酯[nano(sodium carboxymethyl cellulose-poly (ethylene glycol) diacrylate-2-hydroxyethyl acrylate, nano(CMC-pHEA)]和葡萄糖氧化酶组成；由于 CMC-pHEA 的电离和质子平衡，当其插入小鼠皮肤 5 s 后，微针就会迅速膨胀来响应葡萄糖浓度变化；在血糖水平正常(8.3 mmol/L)的小鼠中，微针的高度为(730.6±17.7) μm；在血糖水平较高(25.7 mmol/L)的小鼠中，微针的高度降低到(610.6±13.5) μm。上述结果表明，该微针贴片可以实现快速、微创、精确的血糖监测，在糖尿病诊断和治疗方面具有应用潜力。因此，这种智能微针提供了一个快捷、微创的生物标志物检测平台，在疾病监测方面具有重要意义，有望进入临床阶段。

4 总结与展望

刺激响应型水凝胶微针作为一种新兴的药物递送系统，可以通过多种生理或者外部刺激来实现全身或者局部药物释放，从而促使药物精确递送到病变部位，提高治疗效果；此外，该系统还具有监测作用，为糖尿病、黑色素瘤等疾病的诊断和治疗提供了新方法。与传统的皮下注射针头相比，微针具有微创、操作简单、靶向递送等优势，因此在药物递送领域展现出巨大的应用潜力。然而，微针载药系统仍存在一些问题：(1) 微针尺寸仅有微米级，载药能力较低；(2) 刺激响应型微针在药物递送过程中可能出现脱靶现象；(3) 外源性刺激可能会对健康组织造成损伤。因此，如何高效运用微针系统以发挥疾病诊断和治疗优势已经成为研究者亟待解决的关键问题。研究者可以考虑在微针外部连接药物存储设备以提高其载药能力，或者可以设计一种能够在出现脱靶效应或者不良反应时自动拆卸的微针以降低其副作用。此外，研究者还需要通过系统的细胞、动物和临床试验来综合评估其安全性和有效性。随着科技的发展和研究的不断深入，相信刺激响应型水凝胶微针贴片将在生物医学领域发挥重要作用，为未来的医疗创新提供更多可能性。

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