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新型药物递送系统在兽药制剂领域的研究进展

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[摘　要]　新型药物递送系统在新药研发中的应用近年来在国内外受到了广泛的重视。兽用新型载药系统的研究,解决了兽用药物在动物体内半衰期短、靶向性差、药物利用率低以及药物溶解性特定要求等问题,可开发出新型、高效、安全的生物药物剂型。兽药新型递药系统已在兽药领域展现出广阔的前景,并成为兽药研发的新方向之一。本文就目前主要递药系统(如缓控释递药系统、纳米递药系统、靶向给药系统、透皮给药系统、生物粘附给药系统、植入控释给药系统以及自乳化给药系统等)在兽药制剂领域的研究进展进行综述,并分析和探讨了新型递药系统在兽医领域应用瓶颈、现有研究面临的挑战及未来的发展趋势,以期为新型递药系统在兽药领域的应用提供参考。

[关键词]　药物递送系统;兽药;制剂

Research Progress in Novel Drug Delivery Systems for Veterinary Pharmaceuticals

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Abstract: The application of new drug delivery systems in the research and development of new drugs has received widespread attention at home and abroad in recent years. The research of veterinary new drug carrier system solves the problems of short half - life, poor targeting, low drug utilization and specific requirements for drug solubility in animals, and can develop new, efficient and safe drug dosage forms. The new drug delivery system of veterinary drugs has shown broad prospects in the field of veterinary drugs and has become one of the new directions for the research and development of veterinary drugs. This paper reviews the research progress of major drug delivery systems (such as sustained controlled - release drug delivery system, nano - drug delivery

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system, targeted drug delivery system, transdermal drug delivery system, biological adhesion drug delivery system, implanted controlled release drug delivery system and self - emulsifying drug delivery system, etc.) in the field of veterinary drug preparations, and analyzes and discusses the application bottlenecks of new drug delivery systems in the veterinary field, the challenges faced by existing research and the future development trend, in order to provide a reference for the application of new drug delivery systems in the field of veterinary drugs.

Key words: novel drug delivery system; veterinary drug; preparation

兽药制剂研究在兽药研发中起着至关重要作用。传统兽药剂型有片剂、胶囊、粉剂、颗粒剂、溶液、混悬剂、乳膏、糊剂、软膏、凝胶等[1]。传统兽药制剂多为短效制剂,需要频繁给药,特别是需要长时间持续给药的慢性病和寄生虫病,极大地降低了患病动物的依从性,并且药物还有失效风险;部分传统兽药制剂使用后,药物吸收不完全就被排泄,不仅造成药物浪费,也会造成公共卫生安全问题,同时临床兽医也面临着诸多挑战。新型给药系统(Novel Drug Delivery System,NDDS),通常借助于材料的作用来改善传统药物的理化性质,以提高药效、减低副作用。在过去的八十年里,制药行业在药物递送系统领域取得众多里程碑。第一代药物递送系统(1950 - 1980 年)以口服缓释制剂、吸入制剂和透皮贴剂为主,发展迅猛并且转化效率高。第二代药物递送系统(1980 - 2010 年)主要集中在纳米药物和缓控释药物的开发和递送,例如脂质体、纳米粒、微球以及基因递送,但这类递送系统到目前为止,上市产品数量较少。第三代药物递送系统(2010 年以后),集中于突破生理限制,包括克服口腔黏膜屏障、增加难溶性药物溶解度、增加载药量、精准控制释药动力学、刺激敏感型给药系统、多肽和蛋白类药物的超长效制剂、精准靶向给药等。近年来在兽药制剂领域受到广泛关注。对比传统兽药制剂,NDSS 有以下优点:(1)提高药物稳定性,减少药物降解;(2)改善药物体内分布,提高靶区药物浓度,减少不良反应;(3)缓控释放药物等[2]。新型药物递送系统,涉及到多学科领域,各递药系统相互交叉,本文按照给药系统药理作用特征(缓控释给药系统、靶向给药系统)、给药系统的理化性质(纳米给药系统、生物粘附给药系统)、给药路径(透皮给药系统、植入控释给药系统、自乳化给药系统)及其临床应用和研究进展阐述,并分析和探讨新型递药系统在兽医领域应用瓶颈、现有研究面临的挑战及未来的发展趋势,以期为新型递药系统在兽药领域的应用提供参考。

1 缓控释给药系统

缓控释给药系统根据药物释放性质分为两种:缓释给药系统(Sustained Release Drug Delivery System,SRDDS)是指药物在体内从制剂中非恒速地缓慢释放,从而延长药效的给药系统;控释给药系统(Controlled Release Drug Delivery System,CRDDS)是指药物以受控形式恒速从制剂中释放至靶部位而发挥疗效的给药系统。

Deway 等[3]于 1958 年首次研制出用于反刍动物的瘤胃钴缓释重丸剂,自此缓释剂开始在兽药中使用;Robsion 于 1978 年提出控释给药系统概念[4],Prichard 等[5]报道了治疗动物胃肠道蛔虫的控释制剂开启了 CRDDS 在兽药制剂领域的应用。相对于短效剂型,缓控释剂型的药物释放能持续数天,减少给药次数,控制药物释放于靶部位[6]。

目前兽药中的缓控释制剂的剂型主要为口服和注射制剂,尤以抗寄生虫和抗生素制剂为主,部分已上市的兽药缓控释制剂见表 1。Anderson 等[7]研制出阿苯达挫缓释胶囊,缓释药量仅为单次口服的十分之一,即可祛除绵羊体内 90% 的奥斯特线虫。王建培等[8]利用阿维菌素制备复方缓释制剂防治绵羊寄生虫病,发现其药效可持续 100 日左右。Joohyeon 等[9]研发了马博沙星(Marbofloxacin,MAR)微囊微粒,利用泊洛沙姆调控 MAR 的释放,使其抗菌活性保持至 48 h。Genchi 等[10]评价了莫西菌素微球注射剂预防犬爬行丝虫感染的效果,莫

西菌素微球注射液有 100% 的预防效果,并持续至少 6 个月。

虽然兽药缓控释制剂具有长效和控释等优点,但其发展中也面临着挑战:(1)部分药物吸收不充分,生物利用度低;(2)价格昂贵;(3)因其缓释特性导致剂量调节受限。

表 1　部分已上市兽药缓控释制剂

Tab 1　Some of the listed sustained – release preparations of veterinary drugs

药物名称	商品名	主要用途	研发单位	上市时间
埃普诺菌[11] Eprinomectin	LongRange©	防治肠道蛔虫、肺虫、牛皮蝇、尘螨	勃林格殷格翰动物健康公司(美国)	2011 年 9 月
丁丙诺啡[12] Buprenorphine	Simbadol™	治疗猫术后疼痛	硕腾公司(美国)	2014 年 7 月

2　靶向给药系统

靶向给药系统(Targeted Drug Delivery System, TDDS)诞生于 20 世纪 70 年代,是一种通过载体将药物选择性运输至靶部位的给药系统,增加靶部位的药物浓度,提高药物利用率,减少全身的药物毒性。靶向给药系统的机理分为被动靶向(渗透和滞留效应,Enhanced permeability and retention effect, EPR)、主动靶向和物理化学靶向。

德国免疫学家 Paul Ehrlich 于 1906 年提出靶向制剂的概念[13];1993 年,Florence 创办的专门刊登靶向制剂论文的《Journal of Drug Targeting》促进了药学界对靶向制剂的研究[14];美国食品药物监督管理局(FDA)于 1997 年批准了第一个肿瘤靶向药物利妥昔单抗;1991 年 Tonetti 等[15]研究发现将阿霉素封装于戊二醛处理的红细胞可以使红细胞靶向至犬的肝脏。靶向给药系统也成为兽药研究领域的热点,常见的靶向制剂载体有脂质体、微球和金属纳米粒等[16]。部分已上市的靶向制剂兽药见表 2。

脂质体为材料的靶向性制剂,能够减少对其他组织的毒性。Zhao 等[17]用紫杉醇脂质体对犬进行肺靶向递送测试,紫杉醇脂质体在肺部的药物浓度远高于其他器官,2 h 肺部血药浓度为紫杉醇注射液的 15 倍;微球为材料的靶向制剂也具有缓释药物和靶向递药等特点[18]。Yang 等[19]制备了替米考星明胶微囊并在对观察其在兔体内的药代动力学特征,替米考星明胶微球在肺部的摄取率是注射替米考星的 8.48 倍,肺内半衰期长于替米考星注射剂;金纳米粒是由诸如金(Au)等贵金属组成的粒径为 1 ~ 100 nm 的颗粒[20],具有靶向送药和易于修饰的特点。Raposo 等[21]制备并测试了负载钴和锌化合物([$Zn(DION)_2$]Cl 和[$CoCl(H_2O)(DION)_2$][BF_4])的金纳米粒对犬乳腺癌细胞的作用效果,发现其容易进行表面修饰,且比游离化合物更有效的递送细胞毒性物质。

靶向兽药制剂纳米载体尤以脂质体为多,氧化纳米锌、硒纳米颗粒和微囊等多应用于饲料添加剂,其他纳米材料在靶向兽药制剂中的研究不多,需要进一步探索。

靶向递药系统的应用改善了传统兽药制剂的局限性,但也出现了新的挑战:靶向制剂制备工艺复杂、研发成本高和缺乏临床疗效证明,同时需要进一步研究纳米颗粒在靶动物体内的毒性与免疫原性。

表 2　部分已上市靶向制剂兽药

Tab 2　Some veterinary drugs have been listed for targeted formulations

药物名称	商品名	主要用途	研发单位	上市时间
托拉尼的磷酸[22] Toceranib Phosphate	Palladia©	治疗犬复发性皮肤肥大细胞肿瘤	硕腾公司	2009 年 5 月
马来酸奥拉替尼[23] Oclacitinib	Apoquel©	控制犬过敏性皮炎相关的瘙痒症和的特应性皮炎	硕腾公司	2013 年 5 月

3　纳米给药系统

纳米给药系统(Nano Drug Delivery System, NDDS)是一类利用各种类型的纳米载体携带药物运输至靶区域的给药系统,具有增强难溶药物的递送和保护药物不被降解等优点。纳米递药系统常用的纳米粒子见图 1。

美国物理学家 Richard Feynman 在 1959 年提出“纳米技术”概念。1974 年,美国国立卫生研究院(National Institutes of Health)认为纳米药物是纳米技术的一个分支,自此制药领域进入了纳米时代[24],同时纳米技术受到兽药研发领域的关注,并开始将纳米技术应用于兽药领域,部分已上市纳米给药系统制剂兽药见表 3。其中使用最多的纳米载体为脂质体、固体脂质体纳米颗粒、微囊和聚合物载体等。

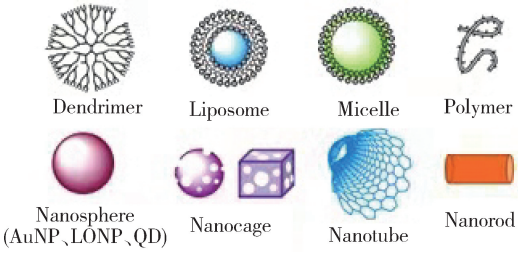

图 1　用于递药系统的不同纳米粒子[25]

Fig 1　Different nanoparticles used in drug delivery systems

脂质体是将药物包封于类脂质双分子层内而形成的微型囊泡,能够提高药物的溶解性,减少用药量,延长药物半衰期。最早由 Bangham 等于 1965 年发现并命名,随后由 Gregoriadis 等研发为药物载体[26]。Bo 等[27]对鸡饮用水中加入奎氧喹酯脂质体防治柔嫩艾美耳球虫,仅需原药的八分之一即可达到相似效果,改善了药物的溶解度。Burton[28]等比较庆大霉素脂质体和游离庆大霉素在马驹体内的药代动力学,庆大霉素脂质体延长了药物体内半衰期。

固体脂质纳米粒(Solid Lipid Nanoparticles, SLN),最早由 Muller 等提出[29],利用天然或合成脂质作为材料来吸附、包裹或分散药物,提高药物生物利用度和减少用药量。Yuzhu Sun 等[30]证明氢化蓖麻油固体脂质纳米粒(SLN)使吡喹酮在狗体内的生物利用度和平均停留时间分别提高了 5.67 倍和 4.94 倍[31]。Zhou 等[32]利用 SLN 技术与原位水凝胶技术制备替米考星纳米凝胶,并利用替米考星凝胶对奶牛金黄色葡萄球菌乳腺炎进行治疗,替米考星凝胶减少了治疗所需剂量[33]。

微囊是由聚合物或蛋白质组成的微小颗粒,通常为 5 ~ 200 μm 的颗粒,可提高药物的稳定性和生物利用度。如阿苯达唑亚砜微囊可以提高生物利用度[34];地克珠利肠溶微囊胶囊相较于地克珠利,具有高生物利用度、稳定和缓释的特点[35]。

聚合物纳米材料因其稳定的结构、优良的生物相容性[36]和黏膜粘附性,在疫苗佐剂领域应用广泛。El Naggar 等[37]通过鼻腔和喷雾给药对无特定病原体的鸡接种黏膜双价聚合物佐剂 H9N2 型禽流感灭活疫苗,由于聚合物的粘附性使得喷雾给药更有效。此外,如聚乳酸和聚乙醇酸等具有生物生物降解性和可吸收性的聚合物成为了药物递送系统的新选择[38]。

目前国内外兽药研究人员已经在纳米递药系统开展了许多研究,可见纳米递药系统在兽药制剂应用的巨大潜力,其他材料如纳米壳、巴基球、碳纳米管、铝硅酸盐纳米颗粒、纳米银、金纳米颗粒和氧化铁纳米颗粒[39]等纳米材料也是研究热点,本文不再赘述。部分基于纳米递药系统制备的兽药见表 4。纳米药物虽然很多优点,但临床使用将面临一系列挑战:(1)复杂的制备和检测过程;(2)成本高;(3)纳米材料毒性等。

表 3　部分已上市纳米给药制剂兽药

Tab 3　Some veterinary drugs that have been listed for nano – administered preparations

药物名称	商品名	主要用途	研发单位	上市时间
头孢维星钠[40] Cefovecin sodium	Convenia©	治疗多杀性巴氏杆菌引起的猫皮肤感染	硕腾公司(美国)	2008 年 4 月
替米考星(微囊)	肺立通	治疗猪传染性胸膜肺炎、猪肺疫、猪气喘病	湖北博大生物有限公司(中国)	2018 年 7 月
氟苯尼考(微囊)	万特斐灵	治疗多杀性巴氏杆菌、溶血性巴氏杆菌及嗜血杆菌等引起的牛、羊呼吸道疾病	武汉回盛生物有限公司(中国)	2021 年 12 月

表 4　部分基于纳米递药系统制备的兽药

Tab 4　Veterinary drugs prepared partly based on nanodrug delivery systems

类型	有效成分	主要用途	优势	参考文献
脂质体	头孢噻呋钠	治疗奶牛乳腺炎	血药浓度维持时间比单药使用的持续时间更长； 最低抑菌浓度是单药的 1/4	[41]
	黄体酮类化合物	含有抗癌和雄激素的化合物	缓释药物 脂质体包封药物血药浓度高于不包封药物	[42]
固体纳米脂质体	牦牛干扰素 - α	抗水泡性口炎病毒	缓释药物，16 日内持续释放抗病毒活性物质 无细胞毒性	[43]
微囊	卵黄免疫球蛋白 IgY	预防控制猪胃肠道疾病	微囊化 IgY 显著减少 24 h 内的腹泻（未微囊化药物为 72 h） 微囊化 IgY 组增重效果好	[44]
多孔阳离子纳米颗粒	氨基苯	治疗非洲锥虫病	研发出了氨基苯的 70DGNP + 胶体制剂	[45]
金属纳米粒	银纳米粒	灭蚊	对蚊子高毒性 对非目标水生虫几乎无毒	[46]

4　生物粘附给药系统

生物粘附给药系统（Bioadhesive Drug Delivery System，BDDS）是药物通过粘附性聚合物载体的生物作用，长时间粘附于黏膜，通过接触黏膜上皮细胞从而在局部或全身发挥疗效的系统[47]，于 20 世纪 80 年代被引入控制给药领域[48]。生物粘附制剂的作用部位为各种腔道表皮细胞粘膜或皮肤表层，如口腔、鼻腔、眼、阴道等。生物粘附制剂具有延长药物作用时间、避开首过效应和给药简单等特性，生物粘附制剂增加药物吸收的原理见图 2。目前国内外已在兽药领域获得许多生物粘附给药系统的研究成果，部分已上市的生物粘附制剂兽药见表 5。

国外的兽药生物粘附制剂主要为镇静剂和抗生素制剂：Reza Seddighi 等[50]对比地托咪定凝胶阴道给药（IVG 组）和盐酸地托咪定注射给药（IV 组）对母马的镇静效果，结果显示 IVG 组的镇静时间比 IV 组长，地托咪定凝胶的阴道内给药延长了作用时间，且使用方便。Baeyens 等[51]对两组结膜炎患犬分别进行内含硫酸庆大霉素的可溶性生物粘附眼科药物插入物（BODI©）插入治疗和庆大霉素滴眼剂 Tiacil©治疗，两种治疗在 3 d 和 7 d 后获得了相似的恢复结果，说明 BODI 在保证药效的同时能减少给药次数，提高患病动物的依从性。

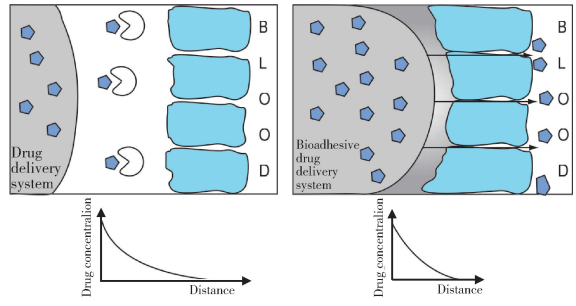

图 2　非粘合剂系统（左）与生物粘合剂制剂（右）增强药物吸收的假设原理（粘附制剂（药物为蓝色颗粒）在吸收窗口（灰色区域）的停留时间延长，增加了给药间隔；药物输送系统与吸收粘液的紧密接触会产生更陡峭的浓度梯度，从而增加吸收速率[49]）

Fig 2　The hypothetical principle of enhanced drug absorption by non - adhesive systems (left) and bioadhesive agents (right): Prolonged residence time of the adhesion agent (Drug is blue granule) in the absorption window (Gray area), increasing the interval between dosing; The close contact between the drug delivery system and the absorbing mucus creates a steeper concentration gradient, which increases the rate of absorption

国内的兽药粘附制剂主要研究方向为消炎药为主：周生银[52]研制出治疗奶牛子宫内膜炎的纯中药制剂“宫得健”的凝胶制剂，其体外组织粘附力

强于生理盐水和宫得健水剂;在体外释药长达 48 h;对子宫内膜炎模型组奶山羊进行治疗试验,宫得健凝胶和环丙沙星治疗结果相同,避免了产后努责导致的药物排出,提高药物利用率。

虽然生物粘附制剂通过粘附性延长了药物在黏膜的滞留和释放时间,并且操作简便,在兽药领域应用广泛且具有很大的发展潜力,但仍面临着许多挑战:(1)药物质量评价缺乏指标:对制剂的体外溶出、粘附强度、黏膜透过性等指标进行评价,保证药物质量;(2)需寻找更合适的粘附材料:无毒、无免疫原性,同时具有更好的粘附性、稳定性、生物相容性的粘附材料。

表 5　部分已上市生物粘附制剂兽药

Tab 5　Some veterinary drugs with marketed bioadhesion preparations

药物名称	商品名	主要用途	研发单位	上市时间
盐酸地托咪定[53] Detomidine Hydrochloride	Dormosedan Gel©	马匹镇静	奥利安集团(芬兰)	2010 年 3 月
盐酸锥双净[54] trybizine hydroch loride	盐酸锥双净鼻用凝胶喷雾剂	抗锥虫病	上海医药工业研究院(中国)	2006 年 5 月

5　透皮给药系统

透皮给药系统(Transdermal Drug Delivery System,TDDS)是指通过皮肤给药途径,达到局部或全身治疗的给药系统,是继口服和注射之后的第三大给药系统[55]。美国于 1979 年批准使用治疗晕动症的东莨菪碱贴片,证明经皮给药可以成为一种可行的新型给药方式,十年后的尼古丁贴片更是提高了透皮给药的知名度[56]。

透皮给药系统包括软膏、硬膏、贴片、膜剂、涂剂和气雾剂等剂型[57]。透皮贴剂局部应用后,溶质渗透模型见图 3。透皮给药系统为需要静脉输液、频繁给药、口服利用度差、患病动物顺从性差的药物提供了一种有效的给药途径。透皮给药系统在兽药制剂领域的应用以镇痛药为主,部分已上市的兽药透皮制剂见表 6。

国外兽用透皮制剂的研究以止痛剂和杀虫剂为主。Tokonami 等[59]对比静脉注射芬太尼和芬太尼贴剂对考拉的镇痛作用,静脉注射仅提供短期镇痛效果,贴剂则能提供 12 ~ 72 h 的镇痛效果。Jim E. Riviere 等[60]研究局部应用氟虫腈防治猫狗跳蚤感染,即使动物多次清洗,其毛囊干内的药物依然可以延长药物作用时间。

国内兽用透皮制剂研究内容主要为消炎和解热镇痛药为主。路孝兵[61]对患有乳房炎的奶牛使用中药“浦和饮”透皮贴剂治疗,奶牛乳房炎治愈率高,避免了需要多次煎服给药的困难。王洋等[62]比较柴胡挥发油透皮贴剂与柴胡注射液对感染性发热家兔的解热作用,发现透皮贴剂解热作用明显,较注射液作用时间长。

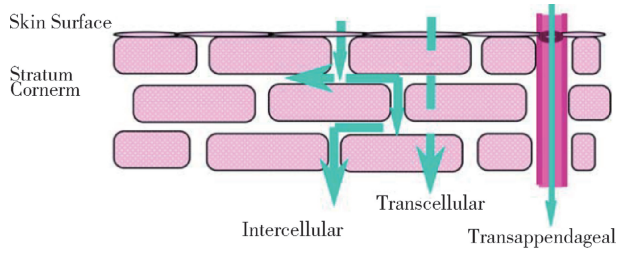

图 3　溶质通过表皮转运的可能途径:细胞间(左)、跨细胞(中)、皮肤附属器(右)通路[58]

Fig 3　Possible routes of solute transport through the epidermis: Intercellular (left), transcellular (middle), transappendageal (right) routes

透皮贴剂虽然可以透过皮肤给药、避免首过效应和使用方便,但兽药透皮制剂的设计开发也面临下列挑战:(1)物种皮肤屏障特异性致使穿透数据不通用;(2)角质层屏障影响药物吸收;(3)同一物种不同部位皮肤的透皮药代数据不同等,需要进一步研究增加透皮制剂的药物渗透率的方法。

表 6　部分已上市透皮制剂兽药

Tab 6　Some veterinary drugs with marketed transdermal preparations

药物名称	商品名	主要用途	研发单位	上市时间
氟尼辛葡甲胺[63] Flunixin Meglumine	Banamine© Paste	缓解马因肌肉骨骼疾病引起的炎症和疼痛	英特威公司(荷兰)	2011 年 11 月
芬太尼[64] Fentanyl	Recuvyra©	用于控制手术后犬的疼痛	艾兰科公司(美国)	2012 年 6 月

6　植入控释给药系统

植入控释给药系统(Inserted Controlling Release Drug Delivery System,ICRDDS)是一类经手术植入皮下或经穿刺针导入皮下的控释给药系统,其剂型有固体载药植入剂(图 4)和注射给药植入剂(图 5)等。Deansley 于 1937 年首次提出植入剂的概念:将片(丸剂)植入皮下,起到缓慢释放的效果[65]。ICRDDS 在兽医领域应用广泛,尤以抗生素、抗寄生虫药和半永久绝育植入剂为多,部分已上市的植入控释制剂兽药见表 7。ICCRDDS 具有以下优点:(1)避免间歇给药造成的血药浓度峰、谷现象,在用药部位恒速缓释药物,小剂量即可达到疗效;(2)避免药物快速代谢,延长作用时间;(3)为难以用其他途径给药的药物提供给药途径;(4)减少给药次数,减轻其他剂型引起的副作用[65]。

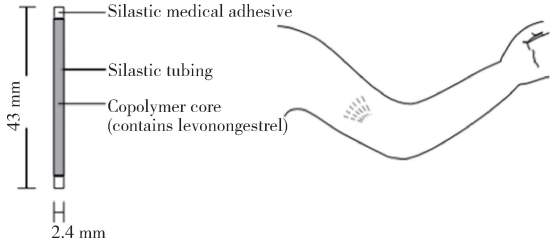

图 4　一种皮下植入剂的实际大小(左)和植入部位(右)[66]

Fig 4　Actual size of a subcutaneous implant (left) and site of implantation (right)

国外植入控释兽药制剂有控制繁殖剂和类胰岛素缓控释放剂等:Goericke - Pesch 等[68]在公猫颈部皮下植入缓释促性腺激素释放激素(GnRH)激动剂植入物,药物作用时间长达 32 周,并且没有明显的副作用。Klotsman 等[69]对健康猫皮下植入 OKV - 119 药物释放系统(皮下植入和释放 GLP - 1RA 艾塞那肽(一种胰岛素样激素)系统)评估植入物的安全性和耐受性,结果表明在植入和取出过程,猫没有植入反应,植入后维持血药浓度长达 35 d,减少了给药次数和对动物的伤害。

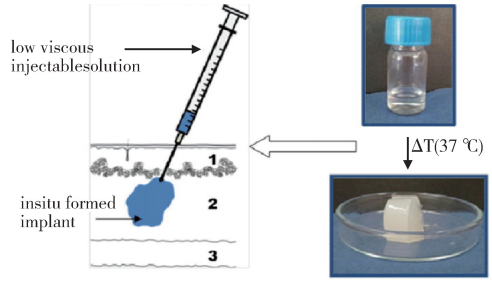

图 5　原位形式热诱导凝胶系统(1:真皮和表皮,2:皮下组织,3:肌肉)(注射前为低粘度注射剂,注射至皮下变为固体或半固体[67])

Fig 5　An in situ forming thermally - induced gelling system (1: epidermis and dermis, 2: subcutis, 3: muscle) (It is injected with low viscosity before injection and becomes solid or semi - solid under the skin)

国内植入控释兽药制剂主要为抗生育植入剂和抗寄生虫植入剂:李婷婷等[70]测试了醋酸甲羟孕酮原位凝胶植入剂(MPA - PLA)对雌性小鼠繁殖的影响,发现 MPA - PLA 组对比空白组的平均生育时间延长 10 ~ 20 d。耿智霞[71]对比了 4% 伊维菌素(IVM)注射用原位凝胶和 IVM 注射液对犬寄生虫感染的防治作用,IVM 注射用原位凝胶可以维持有效血药浓度达 110 ~ 120 d。

植入控释制剂可以有效避免因手术引起的并发症和频繁给药带来的不便,在兽医领域应用广泛,但仍面临着以下挑战:(1)材料降解性不好引起炎症和过敏反应;(2)植入物在体内位移或破碎;(3)制备时的有机溶剂带来的毒性作用等等,还需

要进一步进行寻找生物可降解材料、增强植入剂稳定性以及减少药物毒性的方法。

表 7　部分已上市植入控释制剂兽药

Tab 7　Some veterinary drugs have been marketed for implanted controlled – release formulations

药物名称	商品名	主要用途	研发单位	上市时间
乙酸地洛瑞林[72] Deslorelin Acetate	Suprelorin©	犬半永久绝育	法国维克有限公司(法国)	2007 年 11 月 2019 年 11 月[73](国内)
黄体酮[74] Progesterone	EAZI – BREED™ CIDR©Cattle Insert	使牛同期发情	硕腾公司	2002 年 5 月

7　自乳化给药系统

自乳化给药系统(Self – emulsifying Drug Delivery System,SEDDS)是由油相、表面活性剂、助表面活性剂组成的固体或液体给药系统,在水或胃肠道内温和搅拌下形成亚微米级的乳状液[75],通常形成尺寸在几纳米到几微米不等的乳状液[76],固体自乳化片剂作用机理见图 6,提高难溶性药物的溶解力,加快药物的吸收速度,从而提高生物利用度,是一种新型亲脂性药物载体[77]。

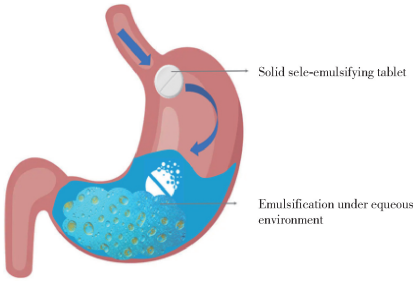

图 6　固体自乳化片剂的作用机理(SEDDS 定义为药物、合成油或天然油、固体或液体表面活性剂和助表面活性剂的各向同性或均匀混合物,它们在蠕动运动产生轻微搅动后在胃肠道中稀释时容易形成细微的水包油(o/w)乳剂[78])

Fig 6　Mechanism of action of Solid self – emulsifying tablets (SEDDS are defined as an isotropic or uniform mixture of drug, synthetic or natural oil, solid or liquid surfactant & co – surfactant which have tendency to form fine oil in water (o/w) emulsion formulation upon slight agitation produced by peristaltic movement, followed by dilution in the gastrointestinal aqueous fluid)

自乳化递药系统在人医领域已发展的相对成熟。目前国内外关于兽药自乳化制剂的研究较少。相对于其他递药系统,兽药领域对自乳化递药系统的研究还有很大的进步空间,具有非常大的发展潜力。查阅文献仅有 Boonme 等[79]成功开发了由甜罗勒油或指根油组成的 SEDDS 配方,用于鸡饮用水预防和治疗球虫病,提高了药物的生物利用度。

8　新型递药系统兽药制剂与传统兽药制剂的比较

传统兽药制剂(口服制剂和注射制剂等)在体内药物半衰期短,需多次给药;部分药物靶向性差,在体内分布广泛,到达病灶部位的药物减少,造成药物生物利用度低和全身毒性;部分药物缓控释效果差,在体内出现血药浓度“峰谷”现象等情况促使研究人员开发具有更好疗效的新型兽药制剂。

新型药物递送系统为兽药的缓控释药物、靶向给药、增强药物稳定性、获得更好的治疗效果带来了曙光,为改良传统剂型和制备新型药物提供了新思路。各递药系统制剂的优势和局限性见表 8。

9　结　语

新型兽用递药系统的研究,解决了兽用药物在体内半衰期短、靶向性差、药物利用率低以及药物溶解性特定要求等问题,可开发出新型、高效、安全的纳米生物药物剂型。目前国外新型递药系统兽药已有许多上市药物,而国内新型递药系统兽药制剂研究大多还处于试验阶段,商品化产品少,具有较大的发展空间。本技术应用前景广阔,可适用于同类药物新型制剂的开发,具有重要的经济效益、社会效益和推广应用前景,可推动我国兽药研究和生产技术的进步,增强我国兽药企业在国内外的兽药市场竞争能力。

表 8　各递药系统制剂的优势和局限性

Tab 8　Advantages and limitations of formulations of each delivery system

制剂类型	优势	局限性
口服制剂(传统)	· 成本低,无痛[80] · 对黏膜和皮肤不会造成伤害,患者顺从性好[81] · 剂量精准可控 · 易存放,使用方便[82]	· 部分药物生物利用度低[82-83] · 部分药物靶向性差 · 缓、控释效果差 · 全身代谢快,需频繁给药
注射制剂(传统)	· 高生物利用度[84] · 无需口服,避免酶和 ph 对药物的影响	· 注射引起组织增生、局部感染,污染肉制品 · 人工成本高[85] · 引发疼痛刺激 · 存储运输困难、昂贵[86]
缓控释制剂	· 剂型丰富,给药途径多 · 药物释放可控 · 高生物利用度 · 减少给药频率 · 改善患者依从性[82]	· 成本高 · 给药剂量把控受限 · 制备用材料可能存在的毒性 · 网状内皮系统的摄取降低疗效[82]
纳米递药系统制剂	· 减少用药量[87] · 增强药效,减少毒副作用[88] · 掩盖不良气味,对于拒绝口服的动物容易使用 · 高生物利用度,缓释药物,延长药物在体内的作用时间[89]	· 成本高 · 部分纳米颗粒具有毒性[89] · 合成过程复杂,可重复的合成特定纳米药物很困难[90]
靶向制剂	· 作用于靶部位,提高药效[91] · 减少全身毒性 · 减少用药量 · 提高药物稳定性	· 成本高 · 治疗效果存在个体差异[91] · 纳米颗粒的抗原性可能影响疗效[91]
透皮制剂	· 成本低、受控药物释放[92] · 避免肝脏首过效应和胃肠道效应[93] · 提高患者依从性	· 皮肤刺激性 · 大分子制剂和离子药物不能给药[94]
生物粘附制剂	· 延长药物在吸收部位停留时间,提供持续的药物释放 · 减少药物在其他部位降解[95] · 患者顺从性好	· 粘附力不足,药物滞留时间偏短[96] · 除口腔黏膜和阴道黏膜外,无法用外力促使粘附剂与病灶紧密接触[97]
植入控释制剂	· 便捷安全 · 缓释药物,减少给药频率	· 需定期更换 · 药剂位移、破碎导致效果不佳[98]
自乳化制剂	· 制备工艺简单 · 稳定性好[99] · 改善药物溶解度和口服生物利用度[100]	· 多数 SEDDS 载体组分需要特定组合才能自乳化,需要大量处方筛选 · 高浓度的表面活性剂会产生 胃肠道刺激性[101]

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