Pickering乳液给药系统的研究进展

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摘要: Pickering乳液是通过固体微粒吸附于乳滴界面起到稳定作用的一种新型乳液, 较传统的表面活性剂乳液具有更好的抗合并稳定性和安全性, 近年来在药剂学方面的应用受到越来越多的关注。除了皮肤给药之外, 最近还出现了新型口服和注射的Pickering乳液给药系统, 可以减少表面活性剂对皮肤的刺激性、促进药物经皮吸收、提高药物口服吸收和稳定性、控制药物释放和靶向给药, 以及作为新型免疫佐剂的载体等, 显示出广阔的应用前景。影响Pickering乳液给药系统构建的因素很多, 尚未见报道对这些影响因素进行系统分析。本文总结了Pickering乳液在药剂学领域的研究应用, 探讨了作为药物载体的Pickering乳液的制备和评价, 尤其是固体微粒、油相、制备工艺及各因素的交互作用对Pickering乳液给药系统构建的影响, 分析了Pickering乳液给药系统研究的主要挑战和未来方向, 以期为Pickering乳液给药系统的深入研究提供参考。

关键词: Pickering乳液; 给药系统; 固体微粒; 纳米晶; 口服; 经皮; 注射

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Research progress of Pickering emulsion drug delivery systems

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Abstract: Pickering emulsion is a new type of emulsion which is stabilized by the adsorption of solid particles on the interface of emulsion droplets. In recent years, its applications in pharmacy have attracted more and more attention because of its higher resistance to coalescence and better safety than traditional surfactant emulsions. The Pickering emulsion was first used for topical administration to reduce skin irritation of surfactants and promote transdermal absorption of drugs. Recently, new oral and injectable Pickering emulsions have also been reported, which can promote oral absorption of insoluble drugs, improve stability of drugs, control drug release, targeted-delivery drugs, and serve as the carrier for novel immunological adjuvants. All these studies show Pickering emulsion a promising drug delivery system. However, its development in pharmacy is still in its infancy. There are many factors influencing the preparation of Pickering emulsions. But there is no systematic analysis of these factors up to now. In this review, we gave an overview of Pickering emulsions from their application in pharmaceutical field, preparation and evaluation, focusing on the effects of solid particles, oil phase, preparation technology and interaction of various factors on the fabrication of Pickering emulsions. The challenges and future directions of this exciting and rapidly expanding research area were further commented on, in order to provide reference for the in-depth study of Pickering emulsion drug delivery systems.

Key words: Pickering emulsion; drug delivery system; solid particle; nanocrystal; oral; topical; injection

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近年来, 用固体微粒代替传统表面活性剂为稳定剂的乳液, 即Pickering乳液受到广泛关注。相对于表面活性剂乳液, Pickering乳液的抗合并稳定性更好、毒性小、环境友好[1-3], 已被广泛应用于化工、食品和化妆品等领域[4,5], 最近在医药领域的应用研究, 特别是作为药物载体的研究也越来越多[6]。尽管Pickering乳液已显示出良好的给药系统应用前景, 但其研究仍处于初始阶段。研究Pickering乳液给药系统首先是要能构建稳定的载药Pickering乳液。影响Pickering乳液给药系统构建的因素很多, 但目前尚未见对这些影响因素的系统分析。本文从药剂学领域的应用、制备和评价等3方面对Pickering乳液给药系统的研究进展进行了综述, 重点讨论了固体微粒、油相、制备工艺和各因素交互作用对Pickering乳液给药系统构建的影响, 分析了Pickering乳液给药系统研究面临的主要挑战和未来方向, 以期为基于Pickering乳液的新型给药系统的开发提供参考。

1 Pickering乳液在药剂学领域的应用

以Pickering乳液作为给药系统, 最早、最多的应用是皮肤给药, 可克服传统乳液中表面活性剂对皮肤的刺激, 控制药物释放速率, 促进药物渗透进入或穿透皮肤[7-18]; 后来也有用于口腔局部给药治疗口腔念珠菌感染[19]、口服给药提高难溶性药物生物利用度[20]、减缓药物释放速率[21,22]和靶向给药治疗直肠癌[23]的研究。最近还出现了新型的口服和注射Pickering乳液给药系统, 如以药物自身纳米晶为稳定剂的Pickering乳液(drug nanocrystal self-stabilized Pickering emulsions, DNSPE)[24,25]、作为免疫佐剂的皮下注射Pickering乳液[26]和长效注射W/O型Pickering乳液[27]。在新型DNSPE系统中, 药物部分溶解于水相或油相, 部分以纳米晶形式吸附于乳滴界面充当稳定剂, 可进一步减少异相固体微粒潜在的安全性问题, 提高载药能力, 并可同时负载难溶性药物和挥发油, 为解决难溶性药物的口服生物利用度问题, 特别是成分复杂的中药复方提供了新的口服给药策略。表1总结了目前已报道的代表性Pickering乳液给药系统, 这提示Pickering乳液给药系统具有不可忽视的广阔应用前景。

2 Pickering乳液给药系统的制备及影响因素

Pickering乳液常用的制备方法是将含药内相和含固体微粒的外相混合, 在机械力的作用下内相以液滴形式分散于外相, 同时外相中的固体微粒吸附于液滴表面, 阻止液滴的合并, 稳定乳液。决定Pickering乳液构建及其稳定的主要因素是固体微粒和油相的性质, 制备方法也有一定影响, 各因素之间还可能存在一定的相互作用。

2.1 固体微粒的影响

在微粒与乳滴相互接近、碰撞并吸附于乳滴表面的过程中, 微粒性质, 尤其是润湿性、粒径和微粒间的静电作用对Pickering乳液有重要影响[28]。

2.1.1 微粒的润湿性 目前较多研究认为, 固体微粒的润湿性是Pickering乳液能否形成的决定性因素[7,29]。固体微粒要有适当的润湿性才能获得足够的界面吸附率, 即微粒必须能被油水两相润湿却不能完全溶于任何一相。微粒的润湿性通常用三相接触角来描述。一般来说, 接触角越接近90º, 越易形成稳定的乳液; 当用强疏水性 (接触角接近180º) 或强亲水性 (接触角接近0º) 微粒作稳定剂时, 不能形成稳定的乳液[30]。有报道[31], 固体微粒的接触角需在30～150°之间才能形成Pickering乳液。

2.1.2 微粒的粒径 有研究认为, 固体微粒的粒径要比乳滴的粒径至少低1个数量级才能形成稳定的Pickering乳液[30]。一般而言, 减小固体微粒的粒径有利于Pickering乳液的形成与稳定, 而且形成的乳滴粒径也更小[32,33]。Elmotasem等[22]分别以氧化镁纳米粒 (平均粒径为94.6 nm) 和普通微粒 (平均粒径为541.9 nm) 为稳定剂, 制备了载咖啡因的W/O型Pickering乳液。所得乳液的乳滴平均粒径分别为665.9 nm和1 763 nm; 前者室温贮存2个月仍稳定, 后者1周后出现明显的分层和合并, 1个月后出现相分离。这可能是因为小微粒的自由能较低, 更易吸附在油水界面, 因此具有更高的吸附率, 可以在界面形成更加均匀的微粒层, 阻止液滴的合并。然而, 也有报道[34], 当固体微粒粒径太小, 如小于10 nm时, 微粒的吸附自由能远远小于本身的热能, 微粒易自身聚集在一起而难以吸附于油水界面, 或更倾向于从油水界面脱离, 反而不利于Pickering乳液的稳定。

固体微粒的粒径除了受到制备工艺条件, 如高压均质的时间和压力等[24]影响外, 也可能受到水相pH值的影响, 尤其是蛋白、纤维素和壳聚糖等带电微粒及弱酸、弱碱性药物的固体微粒。Shao等[21,35]以大豆蛋白为稳定剂构建口服缓释Pickering乳液时发现, 只有在水相pH值为3条件下才可成功制备出稳定的乳液, 因为只有在此pH值时, 大豆蛋白才可形成纳米粒。作者对DNSPE的研究[36]也观察到类似现象: 阿魏酸和葛根素在pH值为5的水相中几乎不能制得DNSPE, 样品放置不到1天就完全分层; 而增大水相pH值至11以上时, 2种药物制得的Pickering乳液均可稳定7天以上。进一步研究发现, 阿魏酸和葛根素在pH值为11的水相中可形成200～300 nm的纳米级微粒 (纳米晶), 而在pH值为5的水相中微粒粒径高达4～5 μm。

Table 1 Representative Pickering emulsion drug delivery systems

Model drug	Solid particle	Type of emulsion	Route of administration	Main characteristics
Caffeine	Hydrophobic silica HDK® H20	W/O	Topical	The pseudo-steady state flux and cumulated amount of caffeine after 24 h exposure for Pickering emulsion were 3 and 2.1 times those of classical emulsion, respectively. After 24 h exposure, caffeine in the receptor fluid, dermis and epidermis was 12.7%, 0.8% and 0.3%, respectively[9].
Retinol	Hydrophobized fumed silica HDK® HKS D	O/W	Topical	High storage of retinol inside the stratum corneum was favored by the Pickering emulsion, showing Pickering emulsion a promising drug penetration vehicle either for targeting the stratum corneum or aiming at slow release of drug from stratum corneum which could be used as a reservoir to the deeper layers of skin[10].
Methyl salicylate	Starch modified by octenyl succinic anhydride	O/W	Topical	The type of oil affected the cosmetic and rheological properties of the emulsion but did not affect the transdermal diffusion *in vitro*. The pseudo-steady state flux of methyl salicylate across pig skin from emulsions prepared with miglyol, paraffin and sheanut oil were all about 8 $g\cdot(cm^2\ h)^{-1}$, which was double that of drug solution[11].
Econazole nitrate	Cyclodextrin	O/W	Topical	The rheological behavior showed that Pickering emulsion remained compatible for topical applications. The Pickering emulsion loaded econazole nitrate was able to inhibit fungus and bacterial growth (*C. albicans* and *S. aureus*), thus being expected to be used for epidermal/dermal skin targeting[13].
Rutin	Self aggregated chitosan particles	O/W	Topical	The release of rutin from Pickering emulsion was almost 100% within 24 h. The sustained release of rutin in a solubilized form as well as the synergistic effect of other components of the prepared Pickering emulsion increased wound healing effect compared with the control group, which made the rutin-loaded Pickering emulsion be an effective pharmaceutical formulation for the cutaneous wound healing[14].
Retinol	Block copolymer nanoparticles of poly (lactide)-block-poly (ethylene glycol)	O/W	Topical	Loading drug inside both oil droplets and block copolymer nanoparticles enhanced skin absorption of drugs. More accumulation of retinol in the stratum corneum, epidermis and dermis were observed for the Pickering emulsion compared with the surfactant-based emulsion and an oil solution[15].
Bupivacaine	Cyclodextrin	O/W	Topical	Bupivacaine in Pickering emulsion was released over an extended period with a releasing ratio of 12.2% − 23.1% after 48 h. Pickering emulsion could regulate the target site of skin depending on various types of oil used. Ring-structured oil allowed the highest permeation amount through skin and linear chain oil showed the highest skin-retaining amount after 24 h of exposure[16].
Minocycline	Aluminum starch octenylsuccinate	O/W	Topical	Although Pickering emulsion could not prompt drug to permeate through the entire skin layer, it provided a prolonged minocycline release, always above its minimum inhibitory concentration against *Staphylococcus aureus*, which made it effective against superficial infections caused by *S. aureus* through topical administration[17].
Aspirin	Silica nanoparticles possessing 50% silanol groups	O/O	Topical	The special non-aqueous Pickering emulsion could be used for transdermal formulations and exhibit high drug loading capacity. In addition, the presence of silica nanoparticle layer around oil droplets could limit the *in vitro* release of the aspirin with a cumulative aspirin release of 46.8% after 8 h[18].
Amphotericin B	Starch CAPSUL®	O/W	Oral cavity	The antifungal activity of amphotericin B in Pickering emulsion was enhanced upon incubation with α-amylase, which showed that Pickering emulsion had a potential to deliver hydrophobic antifungal compounds to treat oral candidiasis[19].
Ibuprofen	$Mg(OH)_2$ nanoparticles	O/W	Oral	Pickering emulsion could not only protect patients from the side effects of acid medicines but also could contribute to the increase of the bioavailability of these drugs, because $Mg(OH)_2$ had an advantage of being solubilized in an acid medium leading to the destabilization of Pickering emulsion and the release of ibuprofen orally[20].

Continued

Model drug	Solid particle	Type of emulsion	Route of administration	Main characteristics
β-Carotene	Pea protein isolate	O/W	Oral	Gel-like Pickering emulsion could be formed at oil fractions (ϕ) of 0.6, which exhibited a low release of β-carotene, and high stability towards degradation during the digestion[21].
Caffeine	Magnesium oxide nanoparticles	W/O	Oral	Pickering emulsion afforded sustained release of caffeine within 48 h following zero order kinetics. It also showed good growth inhibition of hepatocellular carcinoma (HepG2) and elicited significant hepato-protection. So this formula could act as an economical approach to multiple therapy and afford safe effective sustained level for caffeine[22].
Curcumin	Fe_3O_4@ cellulose nanocrystals	O/W	Oral	Pickering emulsion could increase stability of curcumin by 40 folds compared with the solution and prolong release of curcumin, totally 53.30% over a 4-day period. It effectively inhibited the human colon cancer cells growth down to 18% in the presence of external magnetic field and resulted in 2-fold reduction on the volume of the 3-D multi-cellular spheroids of HCT116 as compared to the control sample, suggesting that the special Pickering emulsion could be a promising yet effective drug delivery system for magnetic-triggered release of bioactive and therapeutics[23].
Silybin	Silybin nanocrystals	O/W	Oral	Pickering emulsion of silybin could be stabilized by nanocrystals of silybin itself. The AUC of Pickering emulsion was increased by 3.8-fold and 1.4-fold compared with silybin coarse powder and nanocrystal suspension, respectively[24].
Puerarin	Puerarin nanocrystals	O/W	Oral	Puerarin nanocrystals could stabilize Pickering emulsion of Ligusticum chuanxiong essential oil without any other stabilizers. The relative bioavailability of Pickering emulsion to puerarin coarse powder suspension, nanocrystal suspension, and surfactant-based emulsion were 262.43%, 155.92%, and 223.65%, respectively[25].
Antigen	PLGA nanoparticles	O/W	Injection	Pickering emulsion enhanced the recruitment, antigen uptake and activation of antigen-presenting cells, potently stimulating both humoral and cellular adaptive responses, and thus increasing the survival of mice upon lethal challenge, which may provide an effective and safe strategy to enhance adaptive immunity against infections and diseases[26].
Oseltamivir phosphate	Molten glycerol monostearate nanoparticles	W/O	Injection	Oseltamivir phosphate encapsulated in Pickering emulsions displayed a near linear release profile over 30 days, which significantly reduced cell viability in the human PANC-1 pancreatic cancer cell line for up to 30 days[27].

由此可见, 调节水相pH值改变固体微粒的粒径可能是构建稳定的Pickering乳液的有效途径之一。

2.1.3 微粒的浓度 作者对水飞蓟宾DNSPE的研究[24]显示, 水飞蓟宾加入量对Pickering乳液的构建和乳滴粒径具有非常明显的影响。当水飞蓟宾加入量仅为100或200 mg时, 形成的药物纳米晶较少, 不能对油滴形成完全包裹, 只能覆盖油滴的部分表面, 所得乳滴粒径较大; 当药物加入量达到300 mg时, 体系中已有足够量的药物纳米晶, 可对油滴形成完全包裹, 乳滴粒径有所减小; 而继续增加药物加入量, 乳滴形态和粒径不再有显著变化。Dammak等[37]以平均粒径为38.4 nm的壳聚糖纳米粒为稳定剂制备大豆油−水的Pickering乳液, 研究显示壳聚糖纳米粒浓度是影响乳液稳定性的最主要因素。当壳聚糖纳米粒浓度从0.2%增加到1.1% (w/w) 时, 乳液稳定性增强, 原因可能在于: ① 壳聚糖有非极性和极性区域, 可以降低油水界面张力; ② 增大壳聚糖纳米粒浓度可在乳滴表面形成更厚更致密的吸附层; ③ 高浓度壳聚糖可增大水相的黏度, 降低乳滴碰撞、合并的速率。然而, 继续增大壳聚糖纳米粒浓度, 乳液稳定性反而下降。原因是界面吸附达到饱和, 多余的壳聚糖纳米粒分布在连续相中, 可能导致油滴间的吸引力增加, 且这种吸引力随着壳聚糖纳米粒浓度的增加而增大, 最终超过乳滴之间的排斥作用, 导致乳滴絮凝。

2.1.4 微粒的电荷 多数研究认为, 固体微粒的高电荷有利于乳液的形成。乳滴所带电荷与固体微粒的电

荷呈正相关, 微粒的zeta电位高, 则乳滴的zeta电位也较高, 乳滴之间的静电斥力作用强, 可阻碍乳滴合并, 有利于乳液的稳定[38]。Xia等[26]用粒径约为100 nm的不同分子质量的PLGA纳米粒为稳定剂制备载抗原的皮下注射Pickering乳液。放置2周后, 分子质量为42和72 kDa的PLGA纳米粒制备的乳液粒径均有显著变化, 但分子质量为13 kDa的PLGA纳米粒制备的乳液粒径无明显变化。原因可能在于分子质量为13 kDa的PLGA具有最高浓度的羧酸酯端基, zeta电位更高。然而, 也有研究发现, 带电微粒接近油水界面时, 会遇到“镜像电荷”引起的斥力屏障, 如果微粒电荷过高, 这种斥力可能远大于促使微粒向界面靠近的对流力, 微粒难以吸附在油水界面, 无法形成稳定的Pickering乳液[39]。而对于某些固体微粒, 如纤维素纳米晶, 当微粒的zeta电位较低时, 微粒之间出现部分絮凝, 有利于3D网状结构的形成, 可在一定程度上提高Pickering乳液的稳定性[40]。

微粒的电荷主要取决于微粒本身的结构。此外, 水相pH值对微粒的电荷可能也有重要影响。Luo等[41]以黄酮类化合物作为稳定剂制备口服Pickering乳液的研究发现, 在较高pH值的水相中, 固体颗粒的zeta电位显著增加, 从而增加Pickering乳液中乳滴的电荷, 乳液稳定性更好。在水相中加入NaCl等盐类, 增加水相离子强度, 也可以通过影响静电斥力而影响乳液的粒径及稳定性[42]。如在以芋头淀粉微粒为稳定剂的Pickering乳液中加入NaCl, 乳滴粒径减小, 进而提高了乳液稳定性。原因可能是, 水相中NaCl与淀粉颗粒表面的负电荷中和, 使淀粉颗粒的zeta电位减小, 淀粉颗粒更强烈地吸附于油水界面, 阻止乳滴的合并, 使乳滴粒径减小。但加入的NaCl浓度过高时, 乳滴之间的静电斥力减小, 反而使乳滴容易合并。因此得到最佳稳定性的NaCl浓度范围是0.04～0.06 mmol·L^{-1}。

2.2 油相的影响

2.2.1 油相性质和结构 目前用于Pickering乳液给药系统的油相有: isopropyl myristate、油酸、中链甘油三酯、橄榄油、大豆油、小麦胚芽油、棕榈油和菜油等。油相通过影响固体微粒的润湿性而对Pickering乳液的构建有重要影响。作者关于中药DNSPE的研究[43]比较了一系列油相, 发现乳液的稳定性与药物在不同油相中的三相接触角 (即固体微粒在油−水界面的接触角) 密切相关, 如葛根素在川芎油/水中的接触角为82.14°, 丹参酮ⅡA在Capmul C8/水中的接触角为99.2º, 因此分别以川芎油和Capmul C8为油相制备的乳液稳定性最好。

油相对以环糊精 (CD) 为稳定剂的Pickering乳液也有很大影响, 但机制与微粒的润湿性无关。CD与油复合, 其极性头部对应于CD, 未复合的非极性部分为疏水性尾部。这种自组装的CD/油包合物吸附于乳滴表面以稳定乳液, 因此乳液的稳定性主要取决于CD/油包合物的稳定性[13]。Hu等[16]考察了6种油对这种Pickering乳液的影响, 发现油相的体积大小必须与CD的空穴相适应, 并形成部分氢键以获得稳定的CD/油包合物, 才可能制得稳定的Pickering乳液。如同为甘油酸酯类油相, 中链甘油三酯只能与α-CD形成稳定的乳液, 而蓖麻油却能与α-CD和β-CD都形成稳定的乳液。

2.2.2 油相用量 多数研究显示, 在固体微粒浓度不变的情况下, 过量的油相不利于Pickering乳液的稳定。如Asfour等[14]以壳聚糖纳米粒为固体微粒, 将芦丁溶解于丙二醇和油酸 (1∶9, *v*/*v*) 中制备Pickering乳液, 发现在相同的壳聚糖浓度下, 随着油相体积比的增加, 乳滴粒径增大, 乳液稳定性降低。但是, Li等[44]以乳清蛋白为固体微粒, 中链脂肪酸甘油酯为油相, 在5%～50%油相体积比范围内都能得到稳定的载姜黄素Pickering乳液。原因是在不同油相体积比时乳液的稳定机制不同: 油相体积比低于30%时, 形成的乳滴粒径小, 约为220 nm, 有利于乳液的稳定; 油相体积比达到40%以上时, 乳滴粒径虽然增大, 但乳液的黏度也增大, 减慢了油滴的运动, 因此稳定性也好。

2.3 制备方法的影响

已报道的Pickering乳液的制备方法包括一步法和两步法。目前多数采用两步法: 先将固体微粒分散于连续相形成纳米分散液, 再加入非连续相乳化即得。乳化的方式主要有超声和高压均质, 其中高压均质制备的乳液粒径更小、更均匀, 应用最多。在制备过程中, 均质时间、压力和次数等都可能对Pickering乳液产生影响。作者对水飞蓟宾DNSPE的研究[24]显示, 均质压力越大, 药物纳米晶的粒径越小, 压力大于100 MPa时粒径变化较小。固体微粒首先分散的初始相也会对乳液类型产生影响, 如以强疏水性微粒姜黄素为固体微粒, 先分散于油相可制得W/O型的Pickering乳液[45], 而先将其分散于水相却可制得O/W型的Pickering乳液[46]。

Laredj-Bourezg等[15]研究了一步法制备PLA-*b*-PEG或PCL-*b*-PEG嵌段共聚物稳定的Pickering乳液。将溶有嵌段共聚物、视黄醇和油相的丙酮在搅拌下倒入水中, 油相的机械分散和嵌段共聚物胶束的自发乳化同时进行, 40℃下减压挥发除去丙酮后即可得到Pickering乳液。与两步法相比, 一步法制得的Pickering乳液的乳滴粒径及分布都无显著差异, 但制备方法影

响了模型药物视黄醇的分布, 一步法制得乳液的水相中含1%～3%视黄醇, 而两步法制得乳液的水相中没有视黄醇。

2.4 各因素的交互作用

影响Pickering乳液构建的各种因素不是独立的, 而是存在一定的相互影响。Leclercq等[13]以CD为稳定剂制备Pickering乳液, 水、油和CD三者比例只有在适当范围内, 才能形成稳定的Pickering乳液; 使用不同类型的油相 (液体石蜡、肉豆蔻酸异丙酯) 和CD (α-, β-, and γ-CD) 时, 三者比例的适当范围都不相同。这说明, 油相和稳定剂的结构与三者比例之间有相互影响。固体微粒的浓度和分散相体积是影响乳滴粒径的两个关键因素。Sy等[20]研究发现这两个因素之间有交互作用: 在油相-纳米粒的比例低于2%时, 固体微粒浓度对乳滴粒径几无影响; 超过2%后, 固体微粒的浓度增大, 可使乳滴粒径从100 nm迅速增大到250 nm。

3 Pickering乳液给药系统的评价

除了乳液类型、乳滴粒径及分布、乳滴形态 (光学显微镜、透射电镜、扫描电镜、激光共聚焦显微镜观察)、体外稳定性 (室温放置或离心, 观察乳液的分层、测定乳滴粒径和浊度变化) 等常规评价方法之外[13,16,19,22], 目前各研究还根据Pickering乳液给药系统的临床应用进行评价。

3.1 皮肤给药

关于Pickering乳液局部给药的研究相对较多, 其评价主要集中于以下几方面: ① 乳液的流变学评价, 考察乳液是否适宜局部给药; ② 释药速率评价, 多采用Franz扩散池进行, 将乳液直接铺展在释放介质表面, 乳液的高黏度能保证即使在轻度搅拌下乳液和介质也不会混合, 定时取样测定释放介质中的药物含量[9,18]; ③ 体外透皮评价, 一般也采用Franz扩散池进行, 大多采用完整猪皮作为离体皮肤; ④ 皮肤中的药物分布评价, 可取Franz扩散实验24 h后的皮肤, 分离角质层、活性表皮和真皮层, 分别测定各层中的药物含量, 计算分布率[17]; 或将乳液用尼罗红标记后进行Franz扩散实验, 采用激光共聚焦显微镜观察角质层、活性表皮、真皮和毛囊中的药物荧光[15,16]; ⑤ 安全性评价, 多在体外用MTT法检测Df细胞、HaCaT细胞等接触乳液后的细胞活性[12,17]; 也有用白兔背部皮肤给药或志愿者背部皮肤给药后评价其皮肤刺激性[12]。

3.2 口服给药

Pickering乳液口服给药的研究不多, 与口服给药相关的评价主要包括: ① 体外药物释放评价, 口服给药的Pickering乳液多为液体形态, 故多采用透析法研究其体外释药。一般是将乳液和释放介质 (如pH值为1.2的盐酸溶液或pH值为6.8的磷酸盐缓冲液) 混合后装于透析袋或透析管中, 再置于一定体积的释放介质中, 在37 ℃下振荡, 测定不同时间点的释药量[22,23]。Shao等[21]将Pickering乳液与模拟胃液 [pH 1.2 盐酸溶液, 含0.32% (*w*/*v*) 胃蛋白酶和0.2% (*w*/*v*) NaCl] 或模拟肠液 (pH值为7.5磷酸钾缓冲液, 含10 mg·mL^{-1}胆盐和2.4 mg·mL^{-1}胰酶) 直接混合, 在37 ℃下振荡孵育, 定时取样, 10 000 ×g离心30 min分离出清亮的水层, 测定水层的药物含量, 计算药物释放率。该法模拟了胃肠道的pH值和酶环境, 同时减少透析袋 (管) 对药物释放的影响, 实验结果具有更好的参考性; ② 口服吸收效果评价, 一般多通过大鼠灌胃给药的药动学实验获得C_{max}和AUC等参数, 以评价Pickering乳液改善药物口服吸收的效果[24,25]; ③ 药效学评价, 目前研究主要以体外细胞实验评价为主, 仅少数进行了模型动物实验。

3.3 注射给药

注射给药是目前Pickering乳液在药剂学的最新应用, 研究不多, 需要更多和更深入的应用和评价研究。Xia等[26]制备了载抗原的PLGA纳米粒稳定的Pickering乳液, 重点评价了该乳液的柔韧性、侧向移动性、生物安全性和抗原负载能力。Wood等[27]用甘油单硬脂酸酯纳米晶为稳定剂制备载奥司他韦的Pickering乳液, 主要采用透析法进行体外释药研究以评价其长效释药性能, 采用WST-1细胞增殖检测方法测定其对人PANC-1胰腺癌细胞活性的抑制作用, 并采用不同直径的注射针头评价Pickering乳液的可注射性。

4 展望

Pickering乳液给药系统的研究越来越受到关注, 目前主要有以下两方面问题限制其药剂学应用。

首先是关于Pickering乳液给药系统构建的基础问题需要进一步探究。固体微粒是影响Pickering乳液构建和稳定的关键因素。现有文献都是用接触角表示微粒的润湿性, 但多数测定的是微粒-水-空气的三相接触角。而空气和油相性质不同, 微粒在水-空气中的三相接触角与其在水-油中的三相接触角可能存在较大差异, 如阿魏酸在空气-水中的接触角仅为26.13°, 而在Capmul C8中的接触角却为161.05°[36]。而且, 制备Pickering乳液时大多使用纳米级固体微粒, 但测定接触角时却使用粒径较大的固体微粒。微粒变成纳米级粒径后, 很多性质会发生变化, 是否也会引起三相接触角的改变? 如何才能测定Pickering乳液中的纳米级固体微粒在油水界面的真实润湿性? 现有微粒电荷和粒径对Pickering乳液构建的影响研究结果差异很大, 是否因为忽视了固体微粒结构的影响? 另外, 微粒

的微观形态和表面粗糙度对Pickering乳液构建的影响也缺乏足够研究。

其次, 目前大部分Pickering乳液给药系统的研究仅根据研究目的进行了一定的效果评价, 而且多以体外模拟评价为主, 如体外透皮扩散、体外药物释放和体外细胞实验, Pickering乳液给药后的体内命运及机制研究严重缺乏, 如口服后胃肠道环境的影响、注射后血浆环境对乳液稳定性和乳滴结构的影响、药物从乳液中释放机制以及体内影响因素等问题, 都尚未研究。缺乏这方面的研究结果, 将限制基于Pickering乳液的新型给药系统的研发和临床应用。

最近有关新型口服和注射Pickering乳液给药系统的研究显示, Pickering乳液不仅可以外用以减少表面活性剂对皮肤的刺激性和促进药物的皮肤渗透, 而且可以提高难溶性药物的口服吸收, 实现缓释和靶向给药, 尤其适用于中药口服新剂型研究, 还可以作为新型免疫佐剂的载体, 在药剂学方面潜在应用前景广阔。系统研究Pickering乳液给药系统构建的影响因素, 解决影响构建和稳定的基础问题, 深入研究Pickering乳液给药系统的体内命运及相关机制, 建立合理的体内外评价方法, 将为开发基于Pickering乳液的新型给药系统提供坚实基础。

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