

磷脂种类对吲哚菁绿脂质体制剂学性质的影响

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摘要:目的 探究磷脂种类对吲哚菁绿(ICG)脂质体制剂学性质的影响。方法 采用薄膜水化挤出法分别制备以氢化大豆卵磷脂(HSPC)、蛋黄卵磷脂为脂质成分的脂质体(ICG-H-Lipo、ICG-E-Lipo)。采用Zetasizer3000HS粒径仪测定脂质体的粒径、聚合物分散性指数(PDI)和Zeta电位;透射电子显微镜观察脂质体形态;超滤离心法分别测定ICG-H-Lipo和ICG-E-Lipo的封装率。用紫外分光光度计分别测定ICG-E-Lipo、ICG-H-Lipo及游离ICG在400~1 000 nm的紫外吸收光谱。以粒径变化为指标,考察脂质体用纯水稀释10倍、4℃条件下储存1个月的长期稳定性,考察脂质体在模拟血浆(pH 7.4大鼠血浆)中的稳定性,考察脂质体用纯水稀释10倍后给予808 nm激光辐照(1 W·cm⁻²、5 min)7 d内稳定性;将ICG-H-Lipo、ICG-E-Lipo和游离ICG 4℃避光保存,分别于0、1、3、5、7 d检测ICG在780 nm处的吸光度(A)值。将ICG-E-Lipo、ICG-H-Lipo和游离ICG配制成ICG质量浓度为25 μg·mL⁻¹的溶液,给予1 W·cm⁻²、808 nm激光辐照5 min,用红外热像仪记录温度变化;给予5个808 nm激光开-关辐照(1 W·cm⁻²,开5 min,关15 min),用红外热成像仪记录温度变化;采用1 W·cm⁻²、808 nm激光分别辐照0、1、2、3、4 min,用紫外分光光度计检测A值变化;以评价不同制剂的光热效率。结果 成功制备了ICG-H-Lipo和ICG-E-Lipo,粒径分布均匀,ICG的封装率分别为77.97%和70.67%。ICG-E-Lipo、ICG-H-Lipo均在895 nm处出现了强吸收峰,相比于游离ICG,ICG-E-Lipo、ICG-H-Lipo均发生了明显红移。稳定性结果表明,ICG-H-Lipo和ICG-E-Lipo在去离子水、血浆溶液中及激光照射后粒径没有明显变化;储存7 d后的紫外吸收光谱图显示,ICG-E-Lipo和ICG-H-Lipo具有比游离ICG更好的稳定性($P<0.05, 0.001$),且ICG-H-Lipo中的ICG稳定性最好。经过808 nm激光辐照5 min后,ICG-E-Lipo、ICG-H-Lipo、游离ICG的温度均能达到肿瘤细胞的死亡温度;在5次激光开-关循环照射后,ICG-H-Lipo的产热效率相对稳定,而ICG-E-Lipo略有下降,游离ICG的产热效率下降了64%;激光照射4 min后的紫外吸收光谱图表明,游离ICG发生严重的光漂白现象,ICG脂质体吸收峰下降较缓慢。结论 脂质体能显著改善ICG的稳定性;ICG脂质体的制剂学性质与磷脂种类密切相关;相同处方下,与蛋黄卵磷脂相比,HSPC制备的ICG脂质体具有更好的稳定性和光热性能。

关键词: 吲哚菁绿;脂质体;氢化大豆卵磷脂;蛋黄卵磷脂;稳定性;光热效率

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Impact of phospholipid type on pharmaceutical characteristics of indocyanine green liposomes

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Abstract: Objective To investigate the impact of phospholipid type on the pharmacological properties of indocyanine green (ICG) liposomes. **Methods** Liposomes (ICG-H-Lipo, ICG-E-Lipo) with hydrogenated soybean lecithin (HSPC) and egg yolk lecithin as lipid components were prepared by thin film hydration extrusion method. The particle size, polymer dispersion index (PDI) and Zeta potential of liposomes were measured by Zetasizer3000HS particle size analyzer. The morphology of liposomes was observed by transmission electron microscopy. The encapsulation efficiency of ICG-H-Lipo and ICG-E-Lipo were determined by ultrafiltration centrifugation. The ultraviolet absorption spectra of ICG-E-Lipo, ICG-H-Lipo and free ICG in the range of 400—1000 nm were determined by ultraviolet spectrophotometer. With the change of particle size as an index, the long-term stability of liposomes diluted with 10 times pure water and stored at 4 °C for 1 month was investigated, the stability of liposomes in simulated plasma (pH 7.4 rat plasma) was investigated, and the stability of liposomes diluted with 10 times pure water and irradiated with 808 nm laser ($1 \text{ W} \cdot \text{cm}^{-2}$, 5 min) within seven days was investigated. ICG-H-Lipo, ICG-E-Lipo and free ICG were stored in dark at 4 °C, and the absorbance (A) value of ICG at 780 nm was measured at 0, 1, 3, 5 and 7 days respectively. In order to evaluate the photothermal efficiency of different preparations, ICG-E-Lipo, ICG-H-Lipo and free ICG were prepared into ICG with a mass concentration of $25 \mu\text{g} \cdot \text{mL}^{-1}$ solution, irradiated with $1 \text{ W} \cdot \text{cm}^{-2}$, 808 nm laser for 5 min, and recorded the temperature change with infrared thermal imager. Give five 808 nm laser on-off irradiation ($1 \text{ W} \cdot \text{cm}^{-2}$, on 5 min, off 15 min), and record the temperature change with infrared thermal imager. Irradiate $1 \text{ W} \cdot \text{cm}^{-2}$ and 808 nm laser for 0, 1, 2, 3 and 4 min respectively, and detect the change of A value with ultraviolet spectrophotometer. **Results** ICG-H-Lipo and ICG-E-Lipo liposomes were successfully prepared by the thin film hydration and extrusion method, the ICG encapsulation of which were 77.97% and 70.67%, respectively. Both ICG-E-Lipo and ICG-H-Lipo have strong absorption peaks at 895 nm. Compared with free ICG, ICG-E-Lipo and ICG-H-Lipo have significant redshift. The stability results demonstrated that both ICG-H-Lipo and ICG-E-Lipo possess desirable colloid stability in deionized water, plasma solution and after laser irradiation. Changes of UV absorption profiles after seven days storage revealed that ICG-H-Lipo and ICG-E-Lipo generated better ICG stability than free ICG ($P < 0.05$ and 0.001), and ICG-H-Lipo possessed the best ICG stability. After irradiation of five on-off cycles, the heat production efficiency of ICG-H-Lipo was relatively stable, while ICG-E-Lipo decreased slightly, and the free ICG generate a 64% decrease, indicating that the photothermal stability of ICG-H-Lipo was better than ICG-E-Lipo and free ICG. Furthermore, the UV absorption spectrum after 4 min laser irradiation exhibited that the free ICG underwent a severe photobleaching performance, while the absorption peak of ICG liposomes decreased slowly. **Conclusion** Liposome is able to significantly improve the stability and pharmaceutical properties of the encapsulated ICG, and these improved characteristics were highly related with phospholipid type. ICG liposome consisting of hydrogenated soy lecithin displayed a better storage stability and photothermal performance than the counterpart egg yolk lecithin-constructed liposome.

Key words: indocyanine green; liposomes; hydrogenated soy lecithin; egg yolk lecithin; stability; photothermal efficiency

肿瘤的光热治疗是利用光敏剂在近红外激光辐照下将光能转化为热能来杀死肿瘤细胞,光热治疗由于其具有非侵入性、低全身毒性、不易产生耐药等优点,近年来受到研究者们广泛关注^[1-2]。吲哚菁绿(ICG)可以发射波长为820 nm的近红外光,是美国食品药品监督管理局(FDA)唯一批准用于临床的近红外荧光染料,已广泛应用于疾病的荧光成像、诊断治疗等多个方面^[3]。同时,ICG也是一种优良的光敏剂,它能有效地将吸收的光能转化为热能引起肿瘤细胞热消融^[4]。与传统光敏剂相比,ICG的光疗深度更深,具有较好的肿瘤光热治疗应用前景^[5-6]。但游离ICG在水中的稳定性差、激光照射下易发生分解、血液循环半衰期极短($<5 \text{ min}$),这些弊端严重限制了其在临床上的应用^[7-8]。寻找合适的纳米传递系统来提高ICG的稳定性和血液滞留时间成为ICG在临床应用中的关键问题。

脂质体是一种类生物膜结构的双分子层囊泡,

它具有提高药物溶解度和生物利用度、将药物靶向递送至发病位置及控制药物释放的优点^[9-11],近年来将其作为各类药物载体的研究得到了长足的发展。ICG分子中含有2个亲水性硫酸基团和2个疏水性吲哚骨架,两亲性的结构使其能够成功包裹于脂质体中^[9,12]。以往的研究表明,脂质体的磷脂组成对脂质体性质有一定的影响^[13]。因此,本课题选择ICG为模型药物,氢化大豆卵磷脂(HSPC)和蛋黄卵磷脂为脂质成分,采用薄膜水化挤出法制备ICG脂质体,通过比较其制剂学性质来研究磷脂种类对脂质体质量的影响。

1 材料

1.1 主要仪器

红外热成像仪,美国FLUKE公司;808 nm激光器,长春新产业光电科技有限公司;Zetasizer3000HS马尔文粒径仪,英国Malvern公司;EX125ZH十万分之一电子天平,常州奥豪斯仪器有限公司;LF-1脂

质体挤出器,加拿大AVESTIN公司;ZPX-150恒温振荡培养箱,厦门科析仪器有限公司;SpecordS600紫外-可见分光光度计,德国耶拿分析仪器股份公司。

1.2 主要试剂

吲哚菁绿(ICG),批号P1847104,阿达玛斯试剂,质量分数>95%;蛋黄卵磷脂,批号AL21002,上海艾伟拓医药科技有限公司;HSPC,批号C10695,上海艾伟拓医药科技有限公司;胆固醇,批号C10285475,上海麦克林生物科技有限公司,质量分数>95%;二硬脂酰基磷脂酰乙醇胺-聚乙二醇(DSPE-mPEG_{2K}),批号RM0210626,西安瑞喜生物科技有限公司。

2 方法与结果

2.1 脂质体的制备

2.1.1 ICG HSPC 脂质体(ICG-H-Lipo)的制备 采用薄膜水化挤出法制备脂质体,称取HSPC 108 mg、胆固醇 27 mg、DSPE-mPEG_{2K} 27 mg,与ICG 3 mg共同加入甲醇中超声溶解,减压除去有机溶剂,形成均匀薄膜。向薄膜中加入6 mL去离子水,在60 °C条件下水化1 h,得到粗制脂质体,再使用LF-1脂质体挤出器将粗制的脂质体依次通过200、100 nm的聚碳酸酯膜11次,得到ICG-H-Lipo,置于4 °C冰箱保存备用。

2.1.2 ICG 蛋黄卵磷脂脂质体(ICG-E-Lipo)的制备 与ICG-H-Lipo的制备方法相同,只需将HSPC换成蛋黄卵磷脂,水化温度变成40 °C。

2.2 脂质体的制剂学评价

2.2.1 粒径、聚合物分散性指数(PDI)与Zeta电位测定 将ICG-H-Lipo、ICG-E-Lipo分别用去离子水稀释10倍,采用Zetasizer3000HS粒径仪测定脂质体的粒径、PDI和Zeta电位。

ICG-H-Lipo、ICG-E-Lipo的平均粒径分别为(141.43±1.55)、(158.80±5.51) nm, PDI分别为0.11±0.01、0.18±0.01,脂质体粒径均匀,分散性较好,该粒径范围应用于肿瘤治疗时,具有较好的高渗透滞留效应(EPR),有利于肿瘤细胞对脂质体的摄取^[15]; Zeta电位分别为(-33.23±1.56)、(-41.03±0.74) mV,脂质体粒径分布范围较窄(图1),电位绝对值较大,脂质粒子之间的强静电排斥作用使脂质体保持较好的稳定性。

2.2.2 脂质体的形态 将ICG-H-Lipo和ICG-E-Lipo分别用去离子水稀释200倍后,滴到碳膜覆盖的铜网上,静置1 min后用滤纸吸去多余液体,自然

干燥后用磷钨酸染液负染2 min,滤纸吸去多余液体,自然干燥,观察脂质体在透射电子显微镜下的形态。

ICG-H-Lipo和ICG-E-Lipo均形态完整,为规则球形(图2),与Zetasizer3000HS粒径仪测定结果相比偏小,推测这可能是由于透射电镜测量过程中的真空环境导致脂质体破裂或脂质体表面水化层丢失导致^[16]。

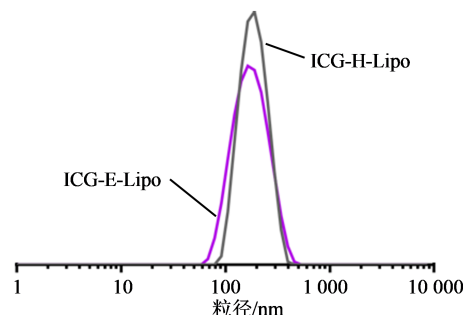


图1 ICG-H-Lipo和ICG-E-Lipo的粒径分布

Fig. 1 Particle size distribution of ICG-H-Lipo and ICG-E-Lipo

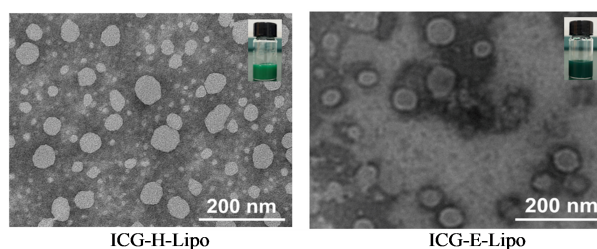


图2 ICG-H-Lipo和ICG-E-Lipo的透射电镜图

Fig. 2 TEM images of ICG-H-Lipo and ICG-E-Lipo

2.2.3 包封率与载药量 采用超滤离心法分别测定ICG-H-Lipo和ICG-E-Lipo的包封率。取2 mL脂质体于超滤离心管中,4 000 r·min⁻¹离心20 min,将上层滤液加入甲醇破乳,定容,用于测定包封的药物质量($W_{\text{包封}}$)。另取2 mL脂质体加入甲醇破乳,定容,用于测定药物总质量($W_{\text{总}}$)。参考文献报道中的紫外分光光度计法测定ICG的浓度^[14],实验平行3组。ICG的包封率与载药量按以下公式计算。

$$\text{包封率} = W_{\text{包封}} / W_{\text{总}}$$

$$\text{载药量} = W_{\text{包封}} / W_{\text{脂质体}}$$

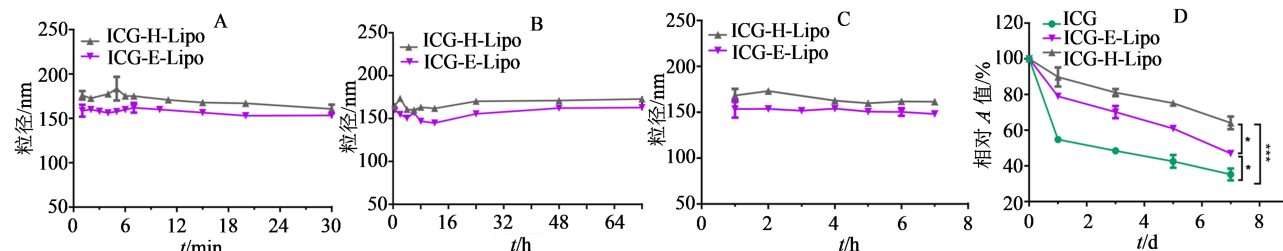
$W_{\text{脂质体}}$ 为脂质体总质量

ICG-H-Lipo、ICG-E-Lipo中ICG的包封率分别为(77.97±1.35)%、(70.67±1.29)%,载药量分别为(0.86±0.02)%、(0.80±0.02)%。结果表明,在相同处方条件下,HSPC制备的ICG-H-Lipo对ICG具有更好的包载效果。

2.2.4 稳定性 将脂质体用纯水稀释10倍,4 °C条件下储存1个月,以粒径变化为指标,考察其长期稳定性。将1 mL的脂质体溶液与9 mL 10%大鼠血浆

pH 7.4 PBS(大鼠血浆和pH 7.4的PBS以1:9的体积比混合)混合均匀,置于37℃、100 r·min⁻¹的恒温摇床中,分别于0.5、2、4、6、8、12、24、48、72 h的时间点测定脂质体的粒径,通过粒径的变化考察ICG-E-Lipo、ICG-H-Lipo在模拟血浆中的稳定性。将ICG-E-Lipo、ICG-H-Lipo用纯水稀释10倍后给予808 nm激光辐照(1 W·cm⁻²、5 min),测定激光辐照后7 d内脂质体的粒径变化,考察激光照射后脂质体的稳定性。将ICG-H-Lipo、ICG-E-Lipo和游离ICG配制成相同ICG浓度的溶液,4℃避光保存,分别于0、1、3、5、7 d检测不同溶液中ICG在780 nm处的吸光度(*A*)值,以此来比较磷脂种类对脂质体中ICG稳定性的影响。

脂质体在4℃条件下储存1个月的长期稳定性和72 h血浆稳定性如图3-A、B所示,在考察期间,



A-长期;B-pH 7.4大鼠血浆;C-激光照射后(808 nm, 1 W·cm⁻²);D-4℃储存; **P* < 0.05 ****P* < 0.001

A-long term; B-pH 7.4 rat plasma; C-after laser irradiation (808 nm, 1 W·cm⁻²); D-store at 4℃; **P* < 0.05 ****P* < 0.001

图3 ICG-E-Lipo、ICG-H-Lipo的稳定性($\bar{x} \pm s, n=3$)

Fig. 3 Stability of ICG-E-Lipo and ICG-H-Lipo ($\bar{x} \pm s, n=3$)

2.2.5 紫外吸收光谱 配制适宜浓度的ICG-E-Lipo、ICG-H-Lipo及游离ICG,用紫外分光光度计分别测定它们在400~1 000 nm的紫外吸收光谱。

ICG-E-Lipo、ICG-H-Lipo均在895 nm处出现了强吸收峰,相比于游离ICG,ICG-E-Lipo、ICG-H-Lipo均发生了明显红移。将ICG包裹入脂质体中后会发生明显吸收峰横移,这与文献报道一致^[18-19],见图4。

2.3 脂质体的体外光热性能考察

为了评价不同制剂的光热效率,将ICG-E-Lipo、ICG-H-Lipo和游离ICG配制成ICG质量浓度为25 μg·mL⁻¹的溶液,给予1 W·cm⁻²、808 nm激光辐照5 min,用红外热像仪记录温度变化;给予5个808 nm激光开-关辐照(1 W·cm⁻²,开5 min,关15 min),用红外热成像仪记录温度变化;采用1 W·cm⁻²、808 nm激光分别辐照0、1、2、3、4 min,用紫外分光光度计检测照射不同时间后的紫外吸收变化。

经过808 nm激光辐照5 min后,ICG-E-Lipo、ICG-H-Lipo、游离ICG的温度均能达到肿瘤细胞的

死亡温度,而纯水在照射5 min后温度几乎没有发生变化,表明ICG分子具有优秀的光热转化能力,见图5。对游离ICG、ICG-E-Lipo、ICG-H-Lipo光热稳定性进行考察,如图6-A所示,经过5个激光开关循环之后,ICG-E-Lipo的产热峰值略有降低,游离ICG产热能力严重下降,而ICG-H-Lipo的产热峰值

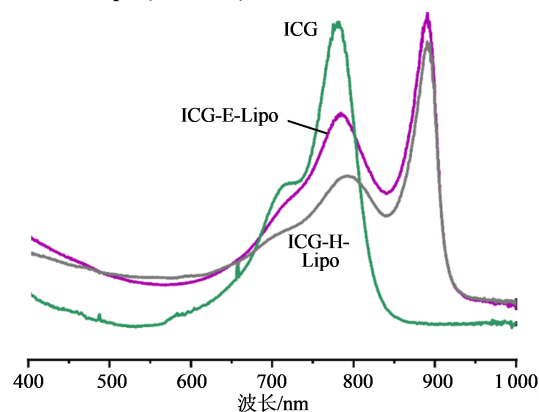


图4 游离ICG、ICG-E-Lipo、ICG-H-Lipo的紫外吸收光谱
Fig. 4 UV absorption spectra of ICG solution, ICG-E-Lipo and ICG-H-Lipo

死亡温度,而纯水在照射5 min后温度几乎没有发生变化,表明ICG分子具有优秀的光热转化能力,见图5。对游离ICG、ICG-E-Lipo、ICG-H-Lipo光热稳定性进行考察,如图6-A所示,经过5个激光开关循环之后,ICG-E-Lipo的产热峰值略有降低,游离ICG产热能力严重下降,而ICG-H-Lipo的产热峰值

几乎没有变化。图6-B为不同制剂每个循环结束后的产热峰值变化, ICG-E-Lipo和ICG-H-Lipo具有比游离ICG更好的光热稳定性, 均差异显著($P < 0.05$ 、 0.01); ICG-H-Lipo的光热稳定性优于ICG-E-Lipo($P < 0.05$)。紫外光谱图(图7)显示, 游离ICG在激光照射4 min后发生严重光漂白, 而ICG-E-Lipo、ICG-H-Lipo吸收度仅发生小幅度下降。总体而言, 脂质体能显著提高ICG的光热稳定性, 且HSPC制备的脂质体比蛋黄卵磷脂制备的脂质体对

ICG具有更好的光热稳定性。

2.4 数据分析

数据应用 GraphPad Prism 7.00、Origin 2021 处理分析并绘图, 结果用 $\bar{x} \pm s$ 表示, 经过单因素方差分析判断是否具有显著性差异。

3 讨论

ICG 是一种批准用于临床的近红外荧光染料, 可以作为光声成像和荧光成像等非侵入性成像方式的增敏剂, 广泛应用于眼科血管造影、肿瘤的光

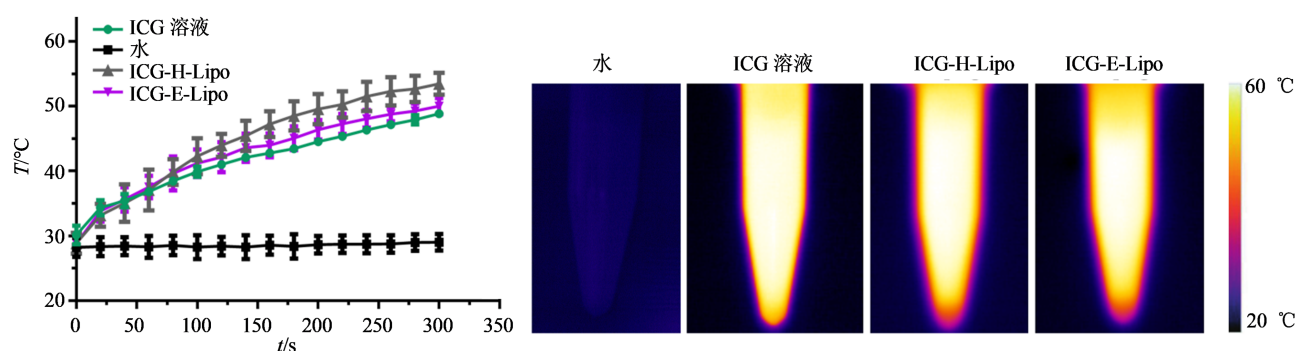


图5 不同ICG制剂激光(808 nm, $1 \text{ W} \cdot \text{cm}^{-2}$)照射5 min的体外升温评价($\bar{x} \pm s, n=3$)

Fig. 5 Evaluation of *in vitro* warming of different ICG preparations under laser irradiation (808 nm, $1 \text{ W} \cdot \text{cm}^{-2}$) for 5 min ($\bar{x} \pm s, n=3$)

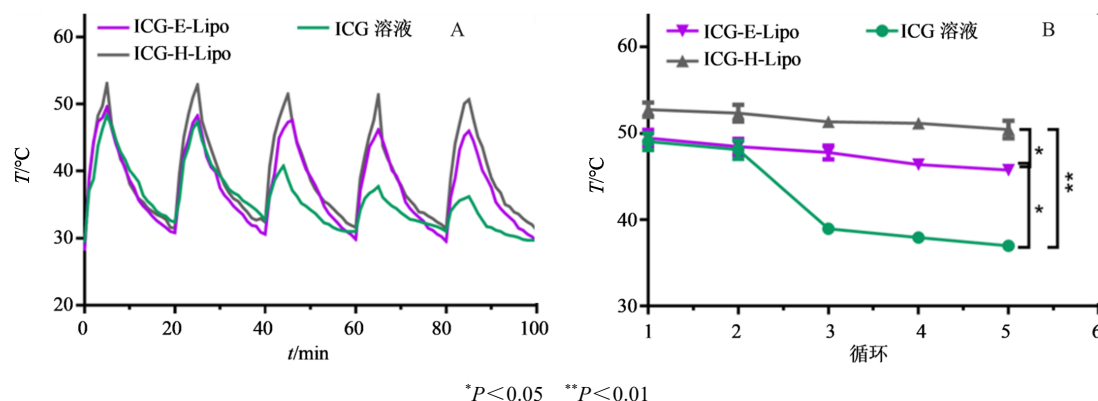


图6 游离ICG、ICG-E-Lipo、ICG-H-Lipo的5个反复激光辐照下的光稳定性(A)和5个开关循环产热峰值变化(B)($\bar{x} \pm s, n=3$)

Fig. 6 Photostability of free ICG solution, ICG-E-Lipo, and ICG-H-Lipo under five repeated laser irradiations (A) and five switching cycles of peak heat production changes (B) ($\bar{x} \pm s, n=3$)

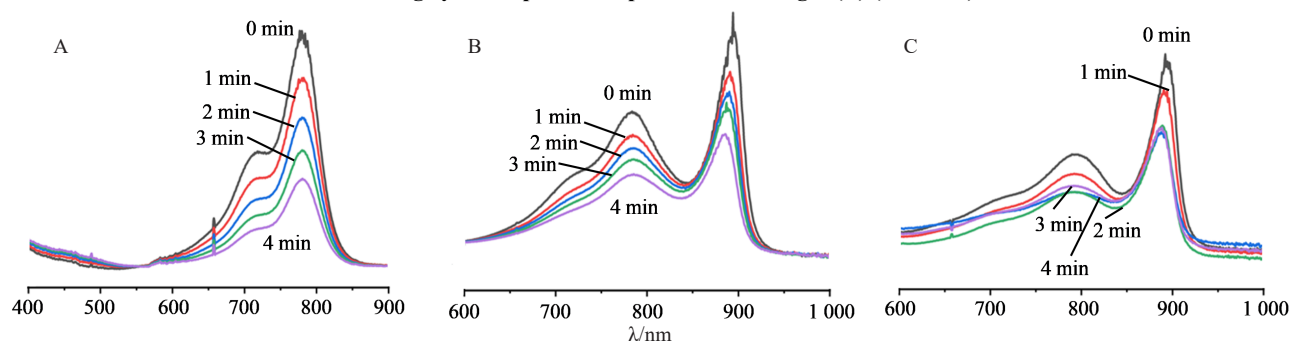


图7 经过不同时间(0、1、2、3、4 min)辐照后游离ICG(A)、ICG-H-Lipo(B)、ICG-E-Lipo(C)的紫外吸收光谱变化

Fig. 7 Changes in UV absorption spectra of ICG solution agent (A), ICG-H-Lipo (B), ICG-E-Lipo (C) after different times of irradiation (0, 1, 2, 3, 4 min)

治疗、心血管及肝功能评估等^[20]。然而,ICG由于自淬灭和自聚集在水溶液中不稳定,且在体内通过肝脏和胆管能被迅速清除^[4,19]。近年来的研究表明将ICG包载于各类纳米药物递送系统可显著改善上述问题。

脂质体具有出色的生物相容性和药物包载能力,是目前唯一被FDA批准用于临床的纳米递送系统^[21-22]。因此,本研究选用了脂质体作为药物载体,研究磷脂种类对ICG脂质体制剂学性质的影响。实验结果显示,不同磷脂制得的ICG脂质体的长期稳定性、血浆稳定性及光照后的稳定性均表现良好,粒径分布均匀,呈现较强负电位,负电位的优势使其在体内安全性大大提高^[23]。紫外吸收光谱显示,脂质体中ICG较游离ICG均发生明显红移,发生红移可能是由于包裹在脂质体膜中排列紧密的ICG分子或形成的多聚体能吸收和发射更长的波长,因此出现ICG特征峰向更大波长处移动^[24]。肿瘤的光热治疗是利用光敏剂的光热转换能力,使肿瘤部位局部高热($>42\text{ }^{\circ}\text{C}$),杀死肿瘤细胞^[25],因此光敏剂的产热稳定性及产热效率是评价光热型纳米制剂性能的重要指标。ICG-E-Lipo、ICG-H-Lipo和游离ICG在相同条件下激光辐照5 min后均升温明显,验证了ICG优良的光热转化效率。此外,HSPC制备的ICG脂质体比蛋黄卵磷脂制备的ICG脂质体具有更好的升温效果及光稳定性。在5个激光(808 nm 、 $1\text{ W}\cdot\text{cm}^{-2}$)开-关循环后,ICG-H-Lipo产热峰值保持稳定,ICG-E-Lipo产热峰值略有降低,而游离ICG被严重光漂白,这是由于ICG分子在水溶液中会发生结构改变,丧失光热转化性能,而脂质体能够将ICG与水环境隔开,增加其稳定性^[24,26]。不同磷脂制备的ICG脂质体之间光热性能的差异可能与磷脂的相变温度不同有关。蛋黄卵磷脂的相变温度为 $-18\text{ }^{\circ}\text{C}$,而HSPC的相变温度为 $50\text{ }^{\circ}\text{C}$ 。在激光照射下,随着脂质体温度的升高,蛋黄卵磷脂由于相变温度较低导致膜的流动性增加,ICG与外界水环境接触增多,引发聚集淬灭。而HSPC的相变温度较高,在激光照射下即使脂质体达到较高温度仍能维持脂质体膜的稳定性,因此包载到HSPC中的ICG表现出较好的储存稳定性和光热性能。此外,蛋黄卵磷脂中含有大量不饱和键,极易被空气氧化,而HSPC中的双键全部饱和,稳定性得到大幅度提升,即便暴露于空气及室温,短时间内对其性质产生影响也较小^[27],这可能是除相变温度外,HSPC制备的脂质体比蛋黄卵磷脂制备脂质体具有更好的ICG储存稳定性和包载效率的另一原因。

磷脂作为脂质体制备的重要载体材料,其不同的头基和脂肪酰链均能对脂质体的理化性质产生影响^[28]。不饱和度过高的磷脂极易发生氧化降解,导致脂膜的流动性变低、脂质体发生聚集沉淀、加重药物的泄漏,同时会使构建的脂质分子层结构中的磷脂分子排列疏松,使脂质体结构易发生变形引起药物泄露,进而影响药物的包载效率^[17,29]。此外,磷脂的相变温度对脂质体的制剂学性质也有很大的影响。不同磷脂的相变温度差异很大,当温度超过磷脂的相变温度时,脂质体的磷脂双分子层结构变得紊乱,脂质体膜的通透性提高,从而使包封的药物泄露增多,药物释放加快,对脂质体的稳定性、载药性能、药物释放速度等产生影响^[30]。脂质体的制剂学性质与磷脂的种类关系密切,开展磷脂种类对脂质体制剂学性质影响的工作十分必要。

本研究结果表明,脂质体能显著改善ICG的稳定性,相变温度高的HSPC制备的脂质体在包封率、ICG的储存稳定性及体外光热性能方面展示出比蛋黄卵磷脂制备的脂质体更佳的实验效果。本研究揭示了磷脂相变温度对脂质体光热治疗的影响,为光热型脂质体制剂的研发奠定理论基础。

利益冲突 所有作者均声明不存在利益冲突

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