综述 (172 ~ 188)

电雾式检测器的研究进展及在药物领域中的应用

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摘要: 液相色谱搭配紫外检测器系统是药物检测中最常使用的分析仪器之一,在大多数情况下能够应对各种分析任务. 然而在实际应用中,常会遇到待测成分没有紫外吸收的情形,这时其他响应机制的检测器往往能起到很好的检测效果. 其中,电雾式检测器(CAD)近年来倍受青睐. 简要介绍了 CAD 的机理和仪器结构,对比了 CAD 与其他类型气溶胶类检测器间的异同,汇总了近年来 CAD 在药物分析领域中的应用,最后展望了 CAD 未来的发展.

关键词: 电雾式检测器; 气溶胶类检测器; 药物检测
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Progress in Charged Aerosol Detector and Its Applications in Pharmaceutical Analysis

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Abstract: The liquid chromatograph with UV detector system is one of the most commonly used analytical instruments in pharmaceutical analysis, which can deal with most analytical tasks. However, the analytes without UV spectral absorption are often encountered in practical applications, when other detectors with different response mechanisms as supplements might achieve good results. The charged aerosol detector (CAD) have been widely used in recent years. The mechanism and instrument structure of CAD were briefly introduced. The similarities and differences between CAD and other aerosol-based detectors were compared. The applications of CAD in the field of pharmaceutical analysis in recent years were summarized and finally the future development of the detector were prospected.

Key words: charged aerosol detector; aerosol-based detector; pharmaceutical analysis

液相色谱的检测器有很多,如紫外(UV)检测器、荧光检测器(FLD)、蒸发光检测器(ELSD)、示差折光检测器(RID)等,但这些检测器常受限于样品的光学性质,质谱(MS)检测器发展虽快但价格较高,而电雾式检测器(CAD)可弥补以上检测器的缺点. 在药物研究中,对质量控制要求极为严格,从药物分子的发现、活性、药理、安全性研究到工艺和质量控制等环节都需要明确待测样品成分,这给紫外、荧光等检测器提出了较大挑战,但给 CAD 带来了机遇.

CAD 属于气溶胶类检测器,Magnusson 等曾在 2015 年综述了气溶胶类检测器的基本情况[1],随后几年 CAD 在结构和定量技术方面又做了改进,2017 年 Gamache 出版了 CAD 相关的书籍[2]. Schilling[3] 和 Haidar Ahmad[4] 分别在 2020 年和 2021 年从质量控制和早期药物研发的角度综述了 CAD

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在药物领域中的应用. 本文介绍了 CAD 的原理与结构, 对比了 CAD 与其他气溶胶类检测器的异同, 汇总了近年来 CAD 在药物领域的应用性研究并进行了展望, 期望能对广大仪器终端用户和国产仪器厂商同行有所帮助, 共同振兴我国科研仪器产业.

1　CAD 的原理与应用

1.1　CAD 设计及其原理

在仪器设计方面, CAD 的雾化装置设计经历了两代 [如图 1(a)(b)所示], 第一代中载气与色谱流分呈垂直布局式设计, 样品喷雾与碰撞器之间的距离较近. 如今第二代的设计与第一代差别显著, 首先载气与色谱流分采用同轴式设计, 其次没有专用的碰撞器(collision wall), 而是使用喷雾室(spary chamber)的后面板实现碰撞器的功能, 喷雾与碰撞部件之间的距离较长(如图 1 中虚线方框所示), 喷雾溶胶的传输效率得到增强, 而且特征残留颗粒尺寸也相对较大[2].

CAD 无需待测成分具有紫外或可见光吸收特性, 因此有较好的通用性, 唯一的要求是待测成分的挥发性需低于色谱流动相. CAD 的分析过程大致可以分为以下步骤, 即: 样品溶液的雾化、气溶胶粒径的选择、气溶胶的干燥以及气溶胶的检测. 在样品溶液的雾化过程中, CAD 使用了气溶胶制备技术中的“分散法”, 即高速气流通过喷嘴喷雾剪切液体, 形成细小的喷雾液滴, 这种雾化方式具有装置简单, 粒子浓度较高的特点, 但不足之处是易产生多分散气溶胶(几何标准偏差 1.5~2.0)[5]. 因此在样品溶液雾化过程中喷雾器的设计对气溶胶的分布影响较大[6], 而在喷雾器固定的情况下, 雾化气和色谱流分的流速, 流动相密度、粘度、表面张力等因素也会影响雾化粒径, 其平均粒径(D_0)可由式(1)计算[1, 7]:

$$D_0 = 585\frac{\sqrt{\sigma}}{v\sqrt{\rho}} + 597\left(\frac{\mu}{\sqrt{\sigma\rho}}\right)^{0.45}\cdot\left(1\,000\frac{Q_l}{Q_g}\right)^{1.5} \quad (1)$$

其中: Q_l 和 Q_g 分别为液体和气体的流速, v 是气体流和液体流之间的相对速度, ρ 为液体密度, μ为粘度, σ 为液体表面张力.

粒径的分布可以通过对数正态分布来描述, 如式(2)所列[2]:

$$\log\,\text{normal}(D,CMD,GSD) = \frac{e^{-1/2\cdot\left[\frac{\ln D/CMD}{\ln GSD}\right]^2}}{\sqrt{2\cdot\pi}\cdot D\cdot\ln GSD} \quad (2)$$

其中: D 为液滴尺寸, CMD 为计数中位直径, GSD 为几何标准偏差.

样品溶液雾化之后是碰撞和传导过程. 碰撞过程仅允许部分尺寸的气溶胶颗粒通过, 尺寸过大的溶胶会因惯性效应而碰撞、聚集、去除, 尺寸过小的溶胶则会因过强的布朗运动而无法通过. 该过程会决定气溶胶残留颗粒的大小分布以及样品的传质效率. 碰撞的效果受载气流、初始雾化液滴的大小和碰撞器设计等因素的影响(例如: 碰撞器的表面角度、粗糙程度、硬度、安装位置等)[8]. 碰撞结束后, 剩余的气溶胶会通过一个加热通道脱除溶剂. 脱除溶剂的样品颗粒尺寸可由式(3)描述[1]:

$$d_p = D_{cut}\cdot\left(\frac{C_m}{\rho}\right)^{1/3} \quad (3)$$

其中: d_p 为残留颗粒的直径, D_{cut} 为经过碰撞器选择后的溶胶直径, C_m 和 ρ 分别为溶胶内非挥发性待测成分的浓度和脱除溶剂后溶胶残留物的密度.

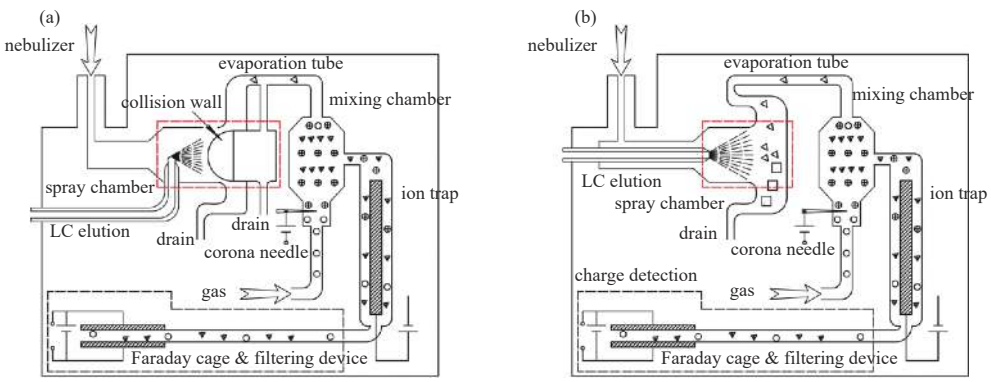

图 1　CAD 原理结构示意图(a)第一代 CAD, (b)第二代 CAD

Fig. 1　Principle and structure diagrams of CAD

在经历雾化、碰撞、传导过程之后，CAD 通过检测电荷的方式测定待测成分. 使用电晕针电离 N_2，当待测成分通过漂移管后，与经电晕针处理的 N_2 相向混合，这个过程中电荷会通过扩散作用传递. 样品颗粒的带电与溶胶残留颗粒的体积有关. 假设颗粒均为球状，则可通过半经验公式的推导结论来评估单位颗粒所带的电荷数，如式(4)所列[9]：

$$n_p\left(d_p\right)=36.78d_p^{1.16} \quad (4)$$

其中 n_p 为电荷数(C). 但 Robinson 等[10]后来发现样品表面积的影响更为直接，其相关性甚至优于上样质量.

粒子带电后，需要再通过离子阱去除混合物中电迁移率低的带电粒子(如电离的 N_2、带电荷的溶剂蒸汽等)，最后再对剩余的样品粒子进行电荷检测. 总体来说，信号响应可由式(5)描述[2]：

$$A=a\left(m_{inj}\right)^b \quad (5)$$

其中，A 为峰面积，a 和 b 为常数，常见的 b 值在 0.5 附近(0.35~0.78)，m_{inj} 为上样质量.

理论上来说，仅在 b=1 时对应的有效浓度才会获得较好的线性关系. 因此需频繁优化分析方法和上样质量，在 b 值接近 1 且浓度变化范围较小的条件下进行信号强度-上样质量的拟合，该方法通常在 2 个数量级的范围内可以获得良好的线性. 如果使用二阶函数、对数关系(log-log)拟合，则可能获得 4 个数量级范围的线性[11]. Haidar Ahmad 等[4]研究表明，通过 log-log 和二阶函数拟合的 CAD 检测结果总体准确度优于一阶线性拟合，尤其是使用外延法估计数据时. 如果使用一阶和二阶函数进行外推法估值，低浓度范围估值结果偏差很高，而高浓度偏差较低. 相比之下，使用 log-log 法进行外推时结果更准确. 然而，二阶函数和 log-log 拟合在药物筛选或研发前期还可以接受，在方法验证和转移以及 GMP 阶段(数据结果需要审核、验证和批准，而验证过程包括验证公式、执行的计算和数据测试)都会遇到诸多不便. 赛默飞(Thermofisher)在二代 CAD 的工作站软件中引入了幂函数调节功能(*PFV*, power function value)，可以对采集信号进行调整，利用倒数关系，在一定范围内使回归曲线中原本显著偏离 1 的幂指数回归至 1 附近，从而获得更好的线性和重复性. 但 Thermofisher 未公开其具体算法，类似式(6)及如下处理方法：

$$S_1=S_0^{PFV}+k \quad (6)$$

其中，S_0 是原始检测器信号，S_1 是变换后检测器信号，*PFV* 通常在 0.67~2.00 之间，k 是常数. 在试验过程中，色谱条件(如流动相组成、梯度、流速、柱温等)会影响 *PFV* 值的选择[12-13]. Soliven 等[12]以阿米卡星为例讨论了高效液相色谱-电雾式检测器(HPLC-CAD)的方法开发、验证、*PFV* 值的选择以及注意事项. *PFV* 值的确定需要基于多步严谨的试验和分析，应用赛默飞 Chromeleon™ 软件处理数据时常在 *PFV*=1.00 时获得一系列样品数据，之后重新设定 *PFV* 值对这些数据进行转换，*PFV* 的选值通常是从 0.80 到 1.40(每步增量为 0.05)，再为每个 *PFV* 数据组生成一个信号通道评估线性[14]. 然而未明确表述计算方法在 GMP 阶段的质量控制和新药申报法规中是不易被接受的，无论是从行业规则还是从市场垄断的角度来看都值得商榷. Haidar Ahmad 等[15]公开了一种幂函数值的具体算法，为此类算法在药物领域的应用提供了一种选择. Pawellek 等[14]评价了以上几种获得 *PFV* 的方法，结果表明都是有效的，但同一 *PFV* 用于同一样品中多组分的评估会有风险. 另外值得注意的是，Tam 等[16]的研究表明，对于不同 CAD，即使应用于同一分析方法和样品时也需要分别设置 *PFV* 值，这对于分析方法的验证和转移来说也是不利的.

第二代 CAD 主要调节参数有雾化温度、过滤器常数以及 *PFV*. Schiling 等[13]在脂肪酸和聚山梨酯的研究中表明，*PFV* 和蒸发温度对检测器响应的线性度和定量限影响很大. 他们应用人工网络建立了结构-性质的量化关系(quantitative structure-property relationship)，讨论了影响 CAD 响应的多个因素，结果表明：(1)促溶剂(如五氟丙酸)和丙酮有利于减小流动相体系的氢键作用和粘度，从而有利于 CAD 的响应. (2)高流速会因影响雾化质量而影响 CAD 的响应. (3)表面积较大的溶胶残留颗粒会容易带更多的电荷而增加 CAD 的响应. (4)带有更多高电负性基团或原子的分子也有更高的响应[17]. Pawellek 等[18]使用梯度提升树(gradient boosting tree)进行了结构-性质的量化关系建模，研究了不同试验条件下 CAD 对同源脂肪酸的响应因素，结果表明：*PFV* 值>流动相的流速>分子量>蒸发温度>有机试剂的种类>有机试剂的比例，其中较低的流速、

较高的分子量、低蒸发温度、低沸点、低粘度及高比例有机试剂等有利于提高检测灵敏度.

1.2　CAD 应用研究

CAD 已经广泛应用于药物控制、糖类、磷脂、脂质体、杂质分析、寡核苷酸、生物表面活性剂、氨基糖苷、单克隆抗体制剂、酶催化和反应监测[3-4]. 近 4 年的相关应用案例主要应用于 4 个方面, 即: 天然产物研究(NPS)、工艺优化(process)、质量控制(QC)和组学研究(omics). 天然产物研究中多为酚类、黄酮、脂质体、糖类、生物碱、氨基酸等[19-25]. 工艺优化方面的应用多见于发酵产物、多糖或者脂质体[26-37]. CAD 在组学研究中的应用较少[38-40], 而最主要的应用领域是药物质量控制相关研究(文献数量约占 80.65%). 其中包括中药材(CMM)中黄酮、萜类、甾体、糖类、皂苷等活性成分的检测[41-55], 中药制剂(CMP)中药效成分的检测[56-79], 化学药(CM)中激素类、大环抗生素类, 他汀类、糖类、离子类等缺乏紫外基团的主成分及有关物质检测[80-95], 生物药(BP)中氨基酸、肽、核酸、小分子杂质的检测[96-102]. 值得一提的是, 随着药物辅料(PE)质量管理的加强, CAD 也常用于辅料及其降解产物的检测[103-111]. 对于一些相对较新的给药载体的质量检测(如脂质纳米粒子), CAD 也取得了较好的应用效果[112]. 除此之外, Đajić等[113] 还利用 HPLC-CAD 法, 评估了环糊精(CD)空腔与客体分子(对利培酮、奥氮平及其结构相关杂质)结合的稳定性. 由于 CAD 对非挥发性盐有好的响应, 因此也常用于药用生理溶液的检测, Toussaint 等[114] 指出在使用亲水作用色谱(HILIC)分析生理溶液时, NaCl 中的正、负离子可分别与流动相中的反离子及固定相作用, 还可能与样品成分作用, 从而影响峰形和响应值, 因此在定量时需特别注意校正因子的选择. 如表 1 所列, 在所列应用研究中, 涉及的色谱柱有反相柱(RP)、混合模式柱(mix-model)、氨基柱(amino)、强阴离子交换柱(SAX)、体积排阻柱(SEC)、石墨化碳柱(GCB)、酰胺基柱(amide)、离子交换柱(IC)、苯基柱(Phenyl)和疏水作用柱(HIC)等多种类型. CAD 在应用中也常与其他检测器联用, 实现优势互补, 最为常见的是与紫外检测器联用.

在 HPLC-CAD 仪器校准方面, 吴晓惠等[115] 建

表 1　CAD 应用汇总表

Table 1　Summary of CAD applications

检测器	类型	固定相	成分	样品	参考文献
CAD	NPS	RP	皂苷、糖类、氨基酸	芦笋	[19]
CAD	NPS	RP	甾体生物碱	加州加藜芦	[20]
CAD	NPS	RP	酚类和非极性组分	沙棘	[21]
CAD	NPS	mix-model	生物碱	延胡索紫堇、大叶紫堇、大花紫堇、卧紫堇提取物	[22]
CAD	NPS	amino	单糖组成	灵芝多糖	[23]
CAD	NPS	amino	游离糖和甘露醇	蘑菇	[24]
UV-CAD-MS	NPS	RP	单宁、酚酸和黄酮类化合物	*Cariana estrellensis*(Raddi) Kuntze	[25]
FLD-CAD	process	SAX	聚唾液酸	K1大肠杆菌	[26]
CAD	process	RP	奥贝胆酸及有关物质	奥贝胆酸	[27]
CAD	process	RP	黄芪甲苷	黄芪甲苷	[28]
CAD	process	RP	鼠李糖脂	发酵液萃取物	[29]
CAD	process	RP	3-(3-羟基烷酰氧基)烷酸	发酵产品	[30]
CAD	process	RP	多元醇酯类化合物(liamocin)	普鲁兰霉培养物	[31]
UV-CAD	process	RP	线性聚乙烯亚胺	寡核苷酸/聚乙烯亚胺多肽的制剂	[32]
CAD	process	RP	16元大环内酯	发酵产品	[33]
UV-CAD	process	RP	天然合成脂质、磷脂、亲脂性荧光标记物及其降解产物	脂质体、磷脂、亲脂性荧光标记物	[34]
CAD	process	RP	脂质体成分	脂质纳米颗粒	[35]
CAD	process	RP	小肽	合成肽	[36]

续表 1

检测器	类型	固定相	成分	样品	参考文献
UV-CAD	process	RP, HILIC	多糖抗原	发酵产品	[37]
CAD	omics	—	低聚果糖类物质	尿和血浆	[38]
CAD	omics	RP	肝甘油三酯	肝脏提取液	[39]
CAD	omics	RP	白消安	人血浆	[40]
UV-CAD	QC-CMM	RP	黄酮类和黄芪甲苷	黄芪	[41]
CAD	QC-CMM	amide	低聚糖	太子参	[42]
CAD	QC-CMM	SEC	糖组分	茯苓	[43]
CAD	QC-CMM	RP	人参皂苷	大叶三七叶	[44]
CAD	QC-CMM	RP	黄酮类	甘草	[45]
CAD	QC-CMM	GCB	水溶性非皂苷成分和三七素	三七、人参、西洋参	[46]
CAD	QC-CMM	RP	三萜皂苷	白头翁	[47]
CAD	QC-CMM	amino	单糖和低聚糖	党参	[48]
CAD	QC-CMM	amide	糖类	甘草	[49]
UV-CAD	QC-CMM	RP	黄酮类和二芳基庚烷类化合物	铁皮石斛	[50]
UV-CAD	QC-CMM	RP	黄酮、香豆素、萜类和柠檬苦素类	川佛手	[51]
CAD	QC-CMM	RP	5种桔梗皂苷	桔梗	[52]
CAD	QC-CMM	RP	黄酮苷类成分、柠檬苦素和诺米林等	枳壳药材生品、小麦麸皮及苦荞麸皮、炒枳壳炮制品	[53]
CAD	QC-CMM	HILIC	多糖水解成分	西洋参不同部位	[54]
CAD	QC-CMM	RP	脱氧胆酸类物质	不同产地熊胆粉, 不同动物胆汁	[55]
CAD	QC-CMP	HILIC SEC	酸性糖、中性糖和氨基糖 透明质酸	聚糖	[56]
CAD	QC-CMP	RP	萜类内酯类物质	银杏叶相关制剂	[57]
CAD	QC-CMP	RP	生物碱和香豆素	元胡止痛胶囊	[58]
CAD	QC-CMP	RP	黄酮	小儿解感片	[59]
CAD	QC-CMP	RP	黄酮、生物碱、三萜类	二陈丸	[60]
CAD	QC-CMP	RP	生物碱、萜类、酚类、香豆素	风湿定片	[61]
CAD	QC-CMP	GCB, RP	水溶性非皂苷成分、三七素	三七药材, 血塞通注射剂	[62]
CAD	QC-CMP	RP	滋肾玉泰丸中多组分	滋肾玉泰丸	[63]
CAD	QC-CMP	RP	生物碱、酚酸、苯丙素、黄酮及蒽醌类	千柏鼻炎片	[64-65]
ELSD/CAD	QC-CMP	amino	单糖、二糖	注射用益气复脉冻干剂	[66]
CAD	QC-CMP	RP	7种柴胡皂苷	小柴胡颗粒	[67]
CAD	QC-CMP	RP	萜类、芳香酸	复方芪参益气滴丸	[68]
CAD	QC-CMP	RP	梓醇、葛根素、丹酚酸B 、人参皂苷Rg1、人参皂苷R1、人参皂苷	补肾活血方	[69]
CAD	QC-CMP	RP	多种皂苷	人参衍生产品	[70]
CAD	QC-CMP	RP	三七皂苷R1、人参皂苷Rg1	保心宁片	[71]
CAD	QC-CMP	RP	酚酸、萜类、苯酞、香豆素类	川芎茶调颗粒	[72]
UV-CAD	QC-CMP	RP	人参皂苷类、五味子素类等成分	生脉胶囊	[73]
CAD	QC-CMP	RP	6种胆汁酸类物质	牛黄解毒片	[74]
UV-CAD/MS	QC-CMP	RP	黄酮类物质	土茯苓标准汤剂	[75]
CAD	QC-CMP	RP	酚酸及酚酸苷	紫苏子及炒紫苏子配方颗粒	[76]

续表 1

检测器	类型	固定相	成分	样品	参考文献
CAD	QC-CMP	RP	三萜酸	山楂及其炮制品	[77]
CAD	QC-CMP	mix-model	盐酸水苏碱	复方益母草胶囊	[78]
CAD	QC-CMP	RP	酚酸、萜类	山银花配方颗粒	[79]
UV-CAD	QC-CM	RP	睾酮	睾酮	[80]
CAD	QC-CM	IC	放射性[11C]胆碱	放射性[11C]胆碱	[81]
UV-CAD	QC-CM	RP	疏水性药物和常规脂质体成分	依维莫司, 米托坦的环糊精包合物	[82]
CAD	QC-CM	RP	乔沙霉素、米卡霉素	16元大环内酯(乔沙霉素、米卡霉素)	[83]
CAD	QC-CM	RP	白霉素及其有关物质	白霉素及其片剂	[84]
CAD	QC-CM	RP	9种氨基酸类有关物质	复方氨基酸注射液	[85]
UV-CAD	QC-CM	mix-model	维伐他汀	维伐他汀	[86]
CAD	QC-CM	mix-model	阿仑膦酸钠、杂质磷酸盐、亚磷酸盐、4-氨基丁酸	阿仑膦酸钠片	[87]
CAD	QC-CM	HILIC	氨丁三醇	注射用氨丁三醇无菌溶液	[88]
CAD	QC-CM	GCB, amide	阿卡波糖及其有关物质	阿卡波糖	[89]
CAD	QC-CM	RP	尿素	尿素乳膏	[90]
CAD	QC-CM	RP	钠、钾、镁和钙离子	复方醋酸钠林格注射液	[91]
CAD	QC-CM	RP	盐酸洛美沙星有关物质	盐酸洛美沙星滴耳液	[92]
CAD	QC-CM	RP	熊去氧胆酸有关物质	熊去氧胆酸	[93]
CAD	QC-CM	RP	二氢辛伐他汀、洛伐他汀、辛伐他汀	二氢辛伐他汀、洛伐他汀、辛伐他汀	[94]
CAD	QC-CM	RP	原料药中的7 种有关物质	舒更葡糖钠	[95]
UV-CAD	QC-BP	Phenyl	siRNA和磷脂类物质	脂质纳米颗粒	[96]
DAD-CAD-MS	QC-BP	RP×RP	艾塞那肽、奥曲肽、环孢菌素a和催产素等	治疗用肽	[97]
UV-CAD	QC-BP	amide	*L*-天冬氨酸、甘氨酸	*L*-天冬氨酸、甘氨酸	[98]
CAD	QC-BP	mix-model	小分子杂质	抗体药物	[99]
CAD	QC-BP	RP	脂质体杂质	脂质纳米颗粒配制的信使核糖核酸疫苗	[100]
CAD	QC-BP	RP	脂质体成分	脂质纳米颗粒包裹的新冠肺炎mRNA疫苗	[101]
CAD	QC-BP	RP	去氧胆酸钠	甲型肝炎灭活疫苗和23 价肺炎球菌多糖疫苗原液	[102]
CAD	QC-PE	HIC-RP	聚山梨醇酯的降解产物	治疗性蛋白质制剂或安慰剂	[103]
CAD	QC-PE	RP	酶促及氧化水解产物	聚山梨醇酯20和聚山梨醇酯	[104]
CAD	QC-PE	RP	多元醇、单酯和高阶酯	聚山梨醇酯20	[105]
CAD	QC-PE	RP	稳定性研究中的有关物质	聚山梨醇酯	[106]
CAD-MS	QC-PE	IC×RP	聚山梨醇酯	单克隆抗体药物	[107]
CAD	QC-PE	RP	脂肪酸	油酸	[108]
CAD	QC-PE	mix-model	聚山梨酯	人凝血因子Ⅷ制品	[109]
CAD	QC-PE	SEC	羟乙基纤维素	氨溴特罗口服溶液	[110]
CAD	QC-PE	RP	脂肪酸	聚山梨醇酯80和硬脂酸镁	[111]

注: DAD为二极管阵列检测器

立了一套参数, CAD 模块的参数包括基线噪声、基线漂移、最小检测浓度以及定性/定量的重复性(以咖啡因溶液为标准品), 为 GMP 体系下校验和日常设备维护提供了参考.

2 气溶胶检测器的对比

2.1 ELSD 与凝结核光散射检测器(CNLSD)结构的简要介绍

CAD、ELSD 和 CNLSD 同属于气溶胶类检测器, 在结构和原理过程上有相似之处, 其分析过程都包括雾化、气溶胶粒径的选择和干燥步骤. ELSD 和 CNLSD 的结构如图 2 所示, 其中图 2(a)为 ELSD, 图 2(b)为 CNLSD 的第一代仪器, 即凝结核粒子计数仪(CPC, condensation partical counter), 图 2(c)为 CNLSD 的第二代仪器, 即水基凝结核粒子计数仪(WCPC, water based condensation partical counter), 或者称为纳克级激光计数检测器(NAQD, nano quantity analyte detector).

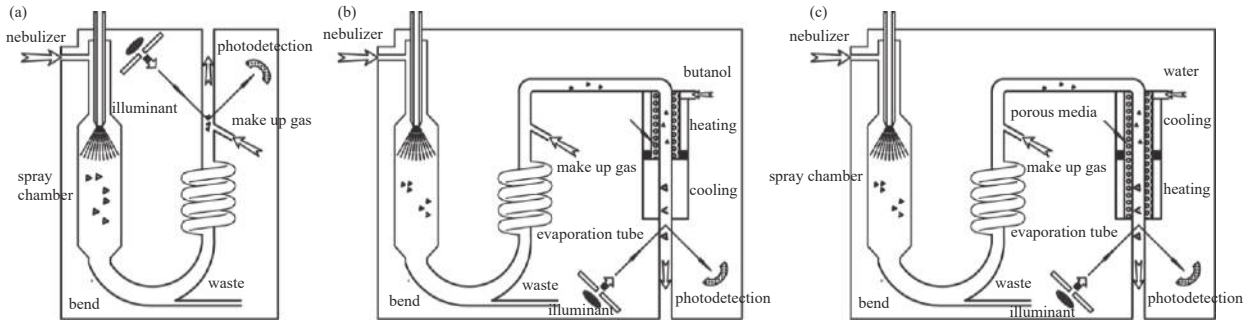

图 2 ELSD 和 CNLSD 原理结构示意图

(a) ELSD, (b) 第一代 CNLSD, (c) 第二代 CNLSD

Fig. 2 Principle and structure diagrams of ELSD and CNLSD

如图 2(a)所示, 在 ELSD 检测器的分析程序中, 雾化后的气溶胶会经过一个弯管, 这个弯管起到了碰撞器的作用. 通过弯管的气溶胶被导入漂移管(蒸发管), 通过加热去除溶剂后形成(待测成分的)残留颗粒. 这些残留的颗粒最终会进入光散射池, 进行散射光的检测.

CNLSD[图 2(b)(c)]可视为 ELSD 的改良版仪器, 始于上世纪七十年代[116], 改进点主要是在漂移管后使用了气溶胶制备技术中的凝聚法, 令饱和的溶剂蒸汽与颗粒残留物混合, 之后以颗粒残留物为核发生凝结, 这种方法可以调节颗粒残留物的尺寸, 提高溶胶残留物中小尺寸颗粒的检测能力, 进而提高灵敏度水平[117]. 但是, 表面张力会影响相关溶剂在颗粒残留物上的凝结, 即引湿性对信号强度有影响, 这在一定程度上削弱了该检测器的通用性.

CPC 与液相色谱仪的联用最早由 Allen 等人提出, 多使用正丁醇为凝结试剂, 在样品溶胶残留物表面发生异核凝结, 之后通过光散射进行检测[118-119]. Lu 等[120] 还将 CNLSD 引入到毛细管色谱和毛细电泳技术中. WCPC 由 Hering 等[121] 提出, 使用水为凝结试剂, 其商业化仪器很快与 HPLC 进行了联用[122]. CPC 中首先加热正丁醇使之达到蒸汽饱和状态, 再让其与样品的胶体残留物混合、冷却降温, 以便发生异核凝结. 与之不同的是, WCPC 先使样品颗粒与冷却的水气相遇, 之后在加热的条件下成核. 这是由于 CPC 的凝结成核过程中凝结试剂(正丁醇)的扩散速度较慢, 而 WCPC 中水蒸汽的扩散速度快, 沿流动中心线具有最大过饱和度[121].

2.2 气溶胶检测器的响应机理对比

在气溶胶检测器中, ELSD 和 CAD 的通用性较好, 其响应都可以用式(5)进行描述[123]. 前文提到, CAD 中常见的幂指数 b 值为 0.35~0.78. 相比之下, ELSD 的光散射过程会受待测物折射率、吸收系数等性质影响, 因此 b 值会随着晶粒尺寸在 0.67~1.3~2.0 之间变化(0.67~1.3 和 1.3~2.0 区间的变化趋势差别显著). 这种幂指数的变化会使气溶胶检测器的响应值和上样质量呈现出“亚线性(sublinear)”和“超线性(supralinear)”的对应关系, 如图 3 所示. 由于 ELSD 的 b 值变化更大, 因此 ELSD 回归曲线的线性范围更有限. 另外, 由于光学性质的差异, 不同种类物质即使在上样质量相同的情况下, ELSD 的响应也会有所不同, 这在一定程度

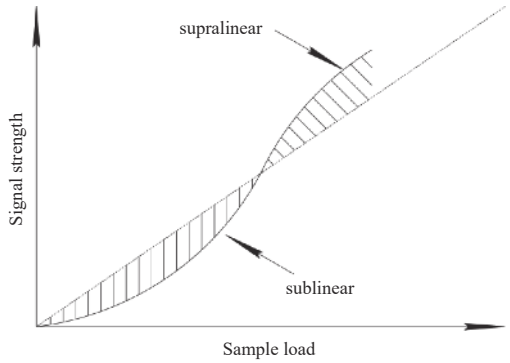

图 3　超线性与亚线性示意图

Fig. 3　Schematic diagram of supralinear and sublinear

上削弱了 ELSD 质量检测器方面的属性.

相比之下, CAD 使用了电荷检测的方式, 避免了光学性质的影响, 可以使许多非挥发性成分具有相似的影响因子, 在没有对照品的情况下评估样品中某一非挥发成分的量值, 而 ELSD 等检测器则需要明确的相对响应因子[124]. 但是 CAD 的这个特点在药物质量控制领域的应用中却需要谨慎, 一是由于许多杂质的属性(如挥发性)不明确. 二是由于杂质的量值与原料药成分差别过大, 相对响应因子很难近似为 1, 不宜直接使用峰面积百分比评估成分含量. 三是对于多分散体系的成分(如表面活性剂), 可能由于官能团数量、构象等因素影响样品溶胶残留颗粒的表面积, 进而呈现出不同的响应因子[125]. Causevic 等[126] 在脂类样品检测的应用研究中发现, CAD 的响应强烈依赖于色谱峰形状, 因此建议将混合样品中的成分按照半峰宽和响应因子值的关系进行分类, 之后再进行含量的评估.

光学检测和电荷检测会造成 *b* 值的差异, 除此之外样品气溶胶的粒径分布、传输效率和残留颗粒尺寸等因素都会显著影响曲线形状和定量分析的线性, 而这些因素主要取决于样品溶液的雾化和传质方式. 气溶胶类检测器在与液相色谱联用时都使用了相似的雾化和传质方式, 因此有相似性. 首先, 它们对非挥发性杂质的灵敏度高, 色谱流动相中不溶性颗粒、非挥发/半挥发性盐、缓冲试剂、表面活性剂等都对基线水平有显著的影响[127], Pawellek 等的研究表明, 表面活性剂的链长对 CAD 的基线影响显著[86, 128]. 固定相的流失也会严重影响信噪比, 因此一些低流失固定相(如多孔石墨化碳柱)的应用得到了人们的关注[129-130]. 另一方面, 流动相中的酸/碱成分可能与待测的挥发或半挥发性成分形成盐, 从而提高灵敏度[131]. 流动相中的有机试剂挥发性强, 且有利于降低喷雾液滴的粘度和表面张力, 从而优化雾化效果和传质效率, 提高灵敏度, 一些研究中亲水作用色谱模式灵敏度较高就与此有关[11]. 改变雾化温度是另一个调整检测灵敏度的常用方法, 降低雾化温度有利于增加半挥发性成分的灵敏度, 但同时也会提高背景噪声水平.

在常规反相色谱梯度洗脱的应用中, 基线水平会随着水比例的变化而改变, 此时可使用柱后反梯度的方法来调整流动相, 使进入检测器的流动相均一稳定. 由于气溶胶型检测器为质量型检测器, 因此这种方法不会像浓度型检测器(如示差折光检测器、紫外检测器等)一样因待测流分被稀释而降低灵敏度, 但却会因流动相中水的比例变化而影响雾化效果, 进而影响灵敏度. 相比之下疏水反相色谱的流动相中各有机溶剂挥发性差别不大, 不会对灵敏度造成显著影响[126]. 在数据处理方面, 前文提到 CAD 中采用了 *PFV* 的方法, 而 ELSD 还可以用指数倒数的参数修正方法, 获得线性[132].

2.3　气溶胶检测器的应用情况

气溶胶型检测器都属于质量型检测器, 前期已经有不少学者对比过各气溶胶检测器和其他检测器的性能[1], 总体来说气溶胶检测器的定量性能不及光学检测器, 尤其是线性范围方面差距显著. 但是气溶胶检测器无需复杂的衍生前处理, 只要样品的挥发性较低就会有高的响应, 例如 CAD 对多数成分的检测限低至 0.1~100 ng, 使用混合模式色谱分离时甚至更低[11]. 气溶胶类检测器对流动相的紫外吸收无要求, 因此丙酮等低沸点、高截止波长的试剂也可以应用于色谱技术[18, 133]. 在仪器联用方面, 由于超临界液体的粘度更低、挥发性更高, 因此更适合气溶胶类检测器发挥其优势, 获得较好的应用效果[134]. 超高效液相色谱(UHPLC)的流量低, 有利于提高雾化效率, 也很适合使用气溶胶类检测器.

在气溶胶类检测器中, CAD 质量检测器属性相对更强[135], 非挥发性样品成分有相对接近的响应因子, 在线性和重复性方面, CAD 一般也更优于 ELSD 和 CNLSD[1, 66, 136-137]. CNLSD 虽然在灵敏度方面优势明显, 但不足之处是常受到凝结液与溶胶残留颗粒间张力作用的限制.

目前在药物质量控制领域 ELSD 的应用比较普遍, 这点从中、欧、美药典应用中不难看出. 中国

药典中仅有色谱法通则部分提到 CAD, 欧洲药典中色谱法通则部分中提到 CAD, 另外仅乳布醇、维伐他汀等极少数品种使用了 CAD, 美国药典中, 仅脱氧胆酸等极少数品种中涉及 CAD[3, 86]. 尽管如此还是可以看出, CAD 的应用正在快速增加, 一些原本使用 ELSD 的方法也有向 CAD 过渡的趋势, 尤其是在中药颗粒剂方面, 多个省份的多个配方颗粒剂品种(如盐巴戟、千年健、玉竹、枸骨、青葙子)质量标准中都使用了 CAD, 而以往这些检测方法使用的都是 ELSD. 相比之下, CNLSD 的应用目前已经很少.

3 结论

总之, 气溶胶类检测器极大地方便了缺少紫外吸收官能团物质的分析, 但遗憾的是其定量能力不足. 基于电荷检测, CAD 克服了光学检测的一些不足, 在定量能力方面相对较强. 然而相比于 UV 检测器和 MS 检测器仍有不小的差距, 另外合理而透明的数据处理方法也有待进一步开发.

从仪器技术本身来说, 目前 CAD 和其他气溶胶检测器都使用了“分散法”来产生气溶胶, 这种气溶胶属于多分散体系, 在进入蒸发管前需要进行碰撞来选择溶胶尺寸, 造成了传质的损失, 也影响了仪器灵敏度, 而最终残留颗粒的不均匀也会影响定量. 因此, 雾化器和碰撞器的设计仍是气溶胶检测器进一步发展的关键技术. 遗憾地是, 能将色谱流分在动态条件下变为单分散气溶胶的技术还鲜有报道, 而蒸发管的样品处理能力也有待加强, 如果能同时处理好这两个方面, 相信气溶胶类检测技术在重复性和定量性方面上会有极大的提升.

目前, CAD 检测器的主要供应商仅有 Thermofisher, 尽管我公司也于近期推出了国产的 CAD 仪器, 但供应商数量少的现状仍未得到改变, 这对于药物行业和科研仪器市场的健康发展不利, 国产科研仪器在面临巨大挑战的同时也将获得更多机遇.

参考文献:

[1] Magnusson L E, Risley D S, Koropchak J A. Aerosol-based detectors for liquid chromatography[J]. Journal of Chromatography A, 2015, 1421: 68-81.

[2] Gamache P H. Charged aerosol detection for liquid chromatography and related separation techniques[M]. Hoboken, NJ: John Wiley & Sons, Inc., 2017.

[3] Schilling K, Holzgrabe U. Recent applications of the charged aerosol detector for liquid chromatography in drug quality control[J]. Journal of Chromatography A, 2020, 1619:460911-460924.

[4] Haidar Ahmad I A, Blasko A, Wang H, et al. Charged aerosol detection in early and late-stage pharmaceutical development: selection of regression-models at optimum power function value[J]. Journal of Chromatography A, 2021, 1641: 461997-462004.

[5] Hinds W C. Aerosol technology: properties, behavior, and measurement of airborne particles [M]. 2nd ed. New York: Wiley, 1999.

[6] 刘志军. 高效空气过滤器测试用气溶胶发生器的研制及性能评价[D]. 天津: 天津大学, 2007. [LIU Zhijun. Design and evaluation of an aerosol generator for testing high efficiency particulate air filter[D]. Tianjin: Tianjin University, 2007.]

[7] Nukiyama S, Tanasawa Y. An experiment on the atomization of liquid: 4th report, the effect of the properties of liquid on the size of drops[J]. Transactions of the Japan Society of Mechanical Engineers, 1939, 5(18): 136-143.

[8] Trujillo M F, Mathews W S, Lee C F, et al. Modelling and experiment of impingement and atomization of a liquid spray on a wall[J]. International Journal of Engine Research, 2000, 1(1): 87-105.

[9] Woo K S, Chen Daren, Pui D Y H, et al. Use of continuous measurements of integral aerosol parameters to estimate particle surface area[J]. Aerosol Science and Technology, 2001, 34(1): 57-65.

[10] Robinson M W, Hill A P, Readshaw S A, et al. Use of calculated physicochemical properties to enhance quantitative response when using charged aerosol detection[J]. Analytical Chemistry, 2017, 89(3): 1772-1777.

[11] Zhang K, Kurita K L, Venkatramani C, et al. Seeking universal detectors for analytical characterizations[J]. Journal of Pharmaceutical and Biomedical Analysis, 2019, 162: 192-204.

[12] Soliven A, Haidar Ahmad I A, Tam J, et al. A simplified guide for charged aerosol detection of non-chromophoric compounds-analytical method development and validation for the HPLC assay of aerosol particle size distribution for amikacin[J]. Journal of Pharmaceutical and Biomedical Analysis, 2017, 143: 68-76.

[13] Schilling K, Pawellek R, Lovejoy K, et al. Influence of charged aerosol detector instrument settings on the ultra-high-performance liquid chromatography analysis of fatty acids in polysorbate 80[J]. Journal of Chromatography A, 2018, 1576: 58-66.

[14] Pawellek R, Muellner T, Gamache P, et al. Power function setting in charged aerosol detection for the linearization of detector response-optimization strategies and their application[J]. Journal of Chromatography A, 2021, 1637: 461844-461854.

[15] Haidar Ahmad I A, Blasko A, Tam J, et al. Revealing the inner workings of the power function algorithm in charged aerosol detection: a simple and effective approach to optimizing power function value for quantitative analysis[J]. Journal of Chromatography A, 2019, 1603: 1-7.

[16] Tam J, Ahmad I A H, Blasko A. A four parameter optimization and troubleshooting of a RPLC-charged aerosol detection stability indicating method for determination of S-lysophosphatidylcholines in a phospholipid formulation[J]. Journal of Pharmaceutical and Biomedical Analysis, 2018, 155: 288-297.

[17] Schilling K, Krmar J, Maljurić N, et al. Quantitative structure-property relationship modeling of polar analytes lacking UV chromophores to charged aerosol detector response[J]. Analytical and Bioanalytical Chemistry, 2019, 411(13): 2945-2959.

[18] Pawellek R, Krmar J, Leistner A, et al. Charged aerosol detector response modeling for fatty acids based on experimental settings and molecular features: a machine learning approach[J]. Journal of Cheminformatics, 2021, 13(1): 53-66.

[19] Zhu G L, Wang B, Feng G, et al. Exploring the processing-related components from asparagi radix *via* diversified spectrum-effect relationship[J]. Chinese Journal of Analytical Chemistry, 2023, 51(2): 100214-100223.

[20] Turner M W, Rossi M, Campfield V, et al. Steroidal alkaloid variation in Veratrum californicum as determined by modern methods of analytical analysis[J]. Fitoterapia, 2019, 137: 104281-104287.

[21] Skalski B, Stochmal A, Żuchowski J, et al. Response of blood platelets to phenolic fraction and non-polar fraction from the leaves and twigs of *Elaeagnus rhamnoides* (L.) A Nelson *in vitro*[J]. Biomedicine & Pharmacotherapy, 2020, 124: 109897-109907.

[22] Wang R, Liu Y F, Zhou H, et al. Integration of microfractionation, high-performance liquid chromatography-ultraviolet detector-charged aerosol detector-mass spectrometry analysis and cellular dynamic mass redistribution assay to accelerate alkaloid drug discovery[J]. Journal of Chromatography A, 2020, 1616: 460779.

[23] 梁琰, 赵志国, 张敏敏, 等. 超声辅助酸解-超高效液相色谱-电雾式检测器测定灵芝多糖的单糖组成[J]. 食品工业科技, 2020, 41(23): 216-222. [LIANG Yan, ZHAO Zhiguo, ZHANG Minmin, et al. Analysis of monosaccharide compositions of ganoderma lucidum polysaccharide by ultrasonic assisted acid hydrolysis-ultra performance liquid chromatography-charged aerosol detection method[J]. Science and Technology of Food Industry, 2020, 41(23): 216-222.]

[24] Sławińska A, Jabłońska-Ryś E, Stachniuk A. High-performance liquid chromatography determination of free sugars and mannitol in mushrooms using corona charged aerosol detection[J]. Food Analytical Methods, 2021, 14(2): 209-216.

[25] Tiepo A, Coutinho I, Machado G, et al. Phenolic compounds from leaves of *Cariniana estrellensis* (raddi) Kuntze (lecythidaceae): a Brazilian Atlantic forest tree[J]. Journal of the Brazilian Chemical Society, 2022, 34: 146-152.

[26] Boßmann D, Bartling B, de Vries I, et al. Charged aerosol detector HPLC as a characterization and quantification application of biopharmaceutically relevant polysialic acid from *E. coli* K1[J]. Journal of Chromatography A, 2019, 1599: 85-94.

[27] 冯卫东. 安立生坦与奥贝胆酸的合成工艺研究[D]. 杭州: 浙江工业大学, 2020. [FENG Weidong. Process research for the synthesis of Ambrisentan and Obeticholic acid[D]. Hangzhou: Zhejiang University of Technology, 2020.]

[28] 沈建伟, 李天才, 周党卫, 等. 柱后补偿电雾式液相色谱仪测定黄芪甲苷含量[J]. 生物化工, 2019, 5(5): 89-91, 94. [SHEN Jianwei, LI Tiancai, ZHOU Dangwei, et al. Determination of Astragaloside A by post-column compensation electrospray liquid chromatography[J]. Biological Chemical Engineering, 2019, 5(5): 89-91, 94.]

[29] Demling P, von Campenhausen M, Grütering C, et al. Selection of a recyclable *in situ* liquid-liquid extraction solvent for foam-free synthesis of rhamnolipids in a two-phase fermentation[J]. Green Chemistry, 2020, 22(23): 8495-8510.

[30] Germer A, Tiso T, Müller C, et al. Exploiting the nat-

ural diversity of RhlA acyltransferases for the synthesis of the rhamnolipid precursor 3-(3-hydroxyalkanoyloxy) alkanoic acid[J]. Applied and Environmental Microbiology, 2020, 86 (6): e02317-e02319.

[31] Scholz K, Seyfried M, Brumhard O, et al. Comprehensive liamocin biosurfactants analysis by reversed phase liquid chromatography coupled to mass spectrometric and charged-aerosol detection[J]. Journal of Chromatography A, 2020, 1627 : 461404.

[32] Socia A, Liu Y, Zhao Y J, et al. Development of an ultra-high-performance liquid chromatography-charged aerosol detection/UV method for the quantitation of linear polyethylenimines in oligonucleotide polyplexes[J]. Journal of Separation Science, 2020, 43 (20): 3876-3884.

[33] Wang J, Liu G J, Zhu B Q, et al. Universal quantification method of degradation impurities in 16-membered macrolides using HPLC-CAD and study on source of the impurities[J]. Journal of Pharmaceutical and Biomedical Analysis, 2020, 184 : 113170-113179.

[34] Weber F, Rahnfeld L, Luciani P. Analytical profiling and stability evaluation of liposomal drug delivery systems: a rapid UHPLC-CAD-based approach for phospholipids in research and quality control[J]. Talanta, 2020, 220 : 121320-121327.

[35] Kinsey C, Lu T, Deiss A, et al. Determination of lipid content and stability in lipid nanoparticles using ultra high-performance liquid chromatography in combination with a corona charged aerosol detector[J]. Electrophoresis, 2022, 43 (9-10): 1091-1100.

[36] Alexopoulou F, Buch-Månson N, Pedersen S L, et al. Identification of GDF15 peptide fragments inhibiting GFRAL receptor signaling[J]. Peptides, 2023, 168 : 171063.

[37] Corrado A, De Martino M, Bordoni V, et al. A universal UHPLC-CAD platform for the quantification of polysaccharide antigens[J]. Scientific Reports, 2023, 13 (1): 10646-10657.

[38] Chi L D, Khan I, Lin Z B, et al. Fructo-oligosaccharides from *Morinda officinalis* remodeled gut microbiota and alleviated depression features in a stress rat model[J]. Phytomedicine:International Journal of Phytotherapy and Phytopharmacology, 2020, 67 : 153157.

[39] Gutierrez J A, Liu W, Perez S, et al. Pharmacologic inhibition of ketohexokinase prevents fructose-induced metabolic dysfunction[J]. Molecular Metabolism, 2021, 48 : 101196-1011211.

[40] 刘思鲁, 胡蕾, 刘博宇, 等. 用HPLC-CAD法测定人血浆中白消安的浓度[J]. 中国临床药理学杂志, 2023, 39(5): 738-741. [LIU Silu, HU Lei, LIU Boyu, et al. Determination of the concentration of busulfan in human plasma by HPLC-CAD[J]. The Chinese Journal of Clinical Pharmacology, 2023, 39 (5): 738-741.]

[41] Zhang C G, Liang L J, Yu X H, et al. Quality assessment of Astragali Radix from different production areas by simultaneous determination of thirteen major compounds using tandem UV/charged aerosol detector[J]. Journal of Pharmaceutical and Biomedical Analysis, 2019, 165 : 233-241.

[42] Hu D J, Han B X, Chen C W, et al. Determination of seven oligosaccharides and sucrose in *Pseudostellaria heterophylla* by pressurized liquid extraction and ultra-high performance liquid chromatography with charged aerosol detector and tandem mass spectrometry[J]. Journal of Chromatography A, 2020, 1609 : 460441.

[43] Zhu L X, Wang X, Li S, et al. Qualitative and quantitative characterization of carbohydrate profiles in three different parts of *Poria cocos*[J]. Journal of Pharmaceutical and Biomedical Analysis, 2020, 179 : 113009-113018.

[44] 胡瀚文, 郑振兴, 黄碧君, 等. HPLC-CAD测定大叶三七叶中人参皂苷Rb1的含量[J]. 中药与临床, 2020, 11(2): 10-12. [HU Hanwen, ZHENG Zhenxing, HUANG Bijun, et al. Determination of ginsenoside Rb1 in the leaf of Daye Sanqi by HPLC-CAD[J]. Pharmacy and Clinics of Chinese Materia Medica, 2020, 11 (2): 10-12.]

[45] 任霞, 胡冲, 张亚中. 高效液相色谱-电雾式检测法测定甘草中4种有效成分的含量[J]. 安徽医药, 2020, 24(7): 1304-1308. [REN Xia, HU Chong, ZHANG Yazhong. Determination of four active components in radix glycyrrhizae by HPLC-CAD[J]. Anhui Medical and Pharmaceutical Journal, 2020, 24 (7): 1304-1308.]

[46] 张艳海, 杨远贵, 施磊, 等. 基于高效液相色谱-电雾式检测的三七及人参、西洋参中水溶性非皂苷类部位的指纹图谱表征分析和三七素的含量测定[J]. 中国中药杂志, 2020, 45(14): 3475-3480. [ZHANG Yanhai, YANG Yuangui, SHI Lei, et al. Fingerprinting analysis of non-saponins from water-

soluble part and determination of dencichine from Panax notoginseng, P. ginseng and P. quinquefolium based on liquid chromatography coupled with charged aerosol detection[J]. China Journal of Chinese Materia Medica, 2020, 45 (14): 3475-3480.]

[47] Jiang H H, Zhang W D, Yang J X, et al. Miniaturized solid-phase extraction using a mesoporous molecular sieve SBA-15 as sorbent for the determination of triterpenoid saponins from *Pulsatilla chinensis* by ultra high-performance liquid chromatography-charged aerosol detection[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 194 : 113810-113819.

[48] Xie Q, Tian H M, Huan X H, et al. Quality evaluation of Codonopsis Radix and processed products based on the analysis of monosaccharides and oligosaccharides by liquid chromatography coupled with charged aerosol detector[J]. Phytochemical Analysis, 2022, 33 (2): 262-271.

[49] 陈蓉, 马冬阳, 郭彬, 等. HPLC-CAD法结合化学计量学同时测定甘草中多种糖类[J]. 中国药师, 2021, 24(10): 1932-1937. [CHEN Rong, MA Dongyang, GUO Bin, et al. Simultaneous quantification of saccharides in Glycyrrhizae Radix et Rhizoma by HPLC-CAD combined with chemometrics[J]. China Pharmacist, 2021, 24 (10): 1932-1937.]

[50] Wang C, Chao I C, Qin Y, et al. Comparison for quantification of eight components in *Alpinia officinarum* Hance by using high-performance liquid chromatography coupled with diode array detector and charged aerosol detector with individual and substitute reference compound[J]. Journal of Pharmaceutical and Biomedical Analysis, 2022, 210 : 114545-114550.

[51] 曾利, 李雪敏, 杨欢, 等. HPLC-DAD-CAD法同时测定川佛手中5个成分的含量[J]. 环境化学, 2022, 41(6): 2143-2145. [ZENG Li, LI Xuemin, YANG Huan, et al. Simultaneous determiation of five constituents in citri sarcodactylis fructus by HPLC-DAD-CAD[J]. Environmental Chemistry, 2022, 41 (6): 2143-2145.]

[52] 黄澜, 张金瑞. 不同产地中药桔梗中5种桔梗皂苷含量的测定[J]. 中国药物评价, 2022, 39(6): 473-477. [HUANG Lan, ZHANG Jinrui. Determination of the contents of five platycosides in platycodonis radix from different habitats[J]. Chinese Journal of Drug Evaluation, 2022, 39 (6): 473-477.]

[53] 王迪, 何悦月, 李阳倩, 等. UPLC-CAD法比较小麦麸皮与苦荞麸皮炒枳壳有效成分含量的变化[J]. 环境化学, 2022, 41(9): 3118-3120. [WANG Di, HE Yueyue, LI Yangqian, et al. Changes of effective components content of wheat bran and Tartary buckwheat bran fried Aurantii Fructus by UPLC-CAD method[J]. Environmental Chemistry, 2022, 41 (9): 3118-3120.]

[54] 赵志国, 张敏敏, 李月, 等. 基于亲水色谱-电雾式检测器-电喷雾-飞行时间质谱技术的西洋参不同部位单糖组成的对比分析[J]. 山东科学, 2022, 35(4): 1-8. [ZHAO Zhiguo, ZHANG Minmin, LI Yue, et al. Analysis of monosaccharide composition in polysaccharides from different parts of Panacis Quinquefolii Radix using HILIC-CAD-ESI-TOF/MS[J]. Shandong Science, 2022, 35 (4): 1-8.]

[55] Yuan M B, Zhou T, Lei K L, et al. Identification of the authenticity and geographical origin of bear bile powder by using high performance liquid chromatography-charged aerosol detector fingerprints combined with chemometrics[J]. Chemistry & Biodiversity, 2023, 20 (3): e202201109-e202201119.

[56] Ghosh R, Kline P. HPLC with charged aerosol detector (CAD) as a quality control platform for analysis of carbohydrate polymers[J]. BMC Research Notes, 2019, 12 (1): 268-274.

[57] 白钢钢, 袁斐, 叶慧, 等. HPLC-CAD法测定4种银杏叶制剂中萜类内酯类成分的含量[J]. 药物分析杂志, 2019, 39(6): 1102-1107. [BAI Ganggang, YUAN Fei, YE Hui, et al. Determination of ginkgolides in four kinds of Ginkgo leaf preparations by HPLC-CAD[J]. Chinese Journal of Pharmaceutical Analysis, 2019, 39 (6): 1102-1107.]

[58] 邓磊, 和明伟, 侯连兵. HPLC-CAD法同时测定元胡止痛胶囊中6种生物碱及香豆素类成分的含量[J]. 中南药学, 2019, 17(1): 88-92. [DENG Lei, HE Mingwei, HOU Lianbing. Simultaneous determination of 6 alkaloids and coumarins in Yuanhu Zhitong capsules by HPLC-DAD[J]. Central South Pharmacy, 2019, 17 (1): 88-92.]

[59] 方灵芝, 吴雪松, 张玥. 高效液相色谱-电雾式检测器法同时测定小儿解感片中7种黄酮类成分的含量[J]. 中国医院药学杂志, 2019, 39(23): 2402-2406. [FANG Lingzhi, WU Xuesong, ZHANG Yue. Simultaneous determination of seven kinds of flavonoids components in xiaoerjiegan tablets by HPLC-CAD[J]. Chinese Journal of Hospital Pharmacy, 2019, 39 (23): 2402-2406.]

[60] 侯爱荣, 邢晔忠, 吴雪松. HPLC-CAD法同时测定二陈丸中7个活性成分的含量[J]. 药物分析杂志, 2019, 39(4): 662-668. [HOU Airong, XING Yezhong, WU Xuesong. Simultaneous determination of seven active ingredients in Erchen pills by HPLC-CAD[J]. Chinese Journal of Pharmaceutical Analysis, 2019, 39 (4): 662-668.]

[61] 罗昌明, 吴雪松, 雷明珠, 等. 风湿定片中8种指标成分的HPLC-CAD含量测定研究[J]. 中南药学, 2019, 17(6): 863-867. [LUO Changming, WU Xuesong, LEI Mingzhu, et al. Simultaneous determination of 8 ingredients in Fengshiding Tablets by HPLC-CAD[J]. Central South Pharmacy, 2019, 17 (6): 863-867.]

[62] 张艳海. 三七不同药用部位及其制剂化学成分差异表征[D]. 上海: 上海中医药大学, 2019. [ZHANG Yanhai. Differential profiling of chemical constituents from different medicinal parts of panax notoginseng and its preparations[D]. Shanghai: Shanghai University of Traditional Chinese Medicine, 2019.]

[63] Cao J L, Lei T, Wu S J, et al. Development of a comprehensive method combining UHPLC-CAD fingerprint, multi-components quantitative analysis for quality evaluation of Zishen Yutai Pills: a step towards quality control of Chinese patent medicine[J]. Journal of Pharmaceutical and Biomedical Analysis, 2020, 191 : 113570.

[64] 段萍萍, 陈云辉, 辛建娟. HPLC-CAD法同时测定千柏鼻炎片中盐酸麻黄碱、绿原酸、对羟基桂皮酸、金丝桃苷及大黄素5个活性成分的含量[J]. 中国药师, 2020, 23(7): 1432-1435. [DUAN Pingping, CHEN Yunhui, XIN Jianjuan. Simultaneous determination of ephedrine hydrochloride, chlorogenic acid, P-hydroxycinnamic acid, hyperoside and Rhein in qianbai Biyan Tablets by HPLC-CAD[J]. China Pharmacist, 2020, 23 (7): 1432-1435.]

[65] 邢晔忠, 宋韶锦. HPLC-CAD法同时测定千柏鼻炎片中7个活性成分的含量[J]. 中国药师, 2020, 23(6): 1216-1219. [XING Yezhong, SONG Shaojin. Simultaneous determination of seven active constituents in qianbai Biyan Tablets by HPLC-CAD[J]. China Pharmacist, 2020, 23 (6): 1216-1219.]

[66] 王莹, 刘芫汐, 岳洪水, 等. 电喷雾式检测器与蒸发光散射检测器用于注射用益气复脉中糖成分测定比较及方法准确性探讨[J]. 中国中药杂志, 2020, 45(22): 5511-5517. [WANG Ying, LIU Yuanxi, YUE Hongshui, et al. Comparison between charged aerosol detector and evaporative light scattering detector for analysis of sugar in Zhusheyong Yiqi Fumai and study on accuracy of methods[J]. China Journal of Chinese Materia Medica, 2020, 45 (22): 5511-5517.]

[67] Liu A X, Xu T T, Yang W N, et al. Quantitative determination of 7 saikosaponins in Xiaochaihu granules using high-performance liquid chromatography with charged aerosol detection[J]. Journal of Analytical Methods in Chemistry, 2021, 2021 : 6616854-6616860.

[68] Wu L L, Zhang S N, Zhou L H, et al. Establishment and validation of the quantitative analysis of multi-components by single marker for the quality control of Qishen Yiqi dripping pills by high-performance liquid chromatography with charged aerosol detection[J]. Phytochemical Analysis, 2021, 32 (6): 942-956.

[69] Xie M J, Yu Y T, Zhu Z Y, et al. Simultaneous determination of six main components in Bushen Huoxue prescription by HPLC-CAD[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 201 : 114087-114095.

[70] Xu X Y, Wang S M, Wang H M, et al. Simultaneous quantitative assays of 15 ginsenosides from 119 batches of ginseng samples representing 12 traditional Chinese medicines by ultra-high performance liquid chromatography coupled with charged aerosol detector[J]. Journal of Chromatography A, 2021, 1655 : 462504-462515.

[71] 刘玲, 王欢, 倪恒凡, 等. HPLC-CAD同时测定保心宁片中3种皂苷含量[J]. 中药与临床, 2021, 12(3): 46-49. [LIU Ling, WANG Huan, NI Hengfan, et al. Simultaneous determination of three saponins in Baoxinning tablets by HPLC-CAD[J]. Pharmacy and Clinics of Chinese Materia Medica, 2021, 12 (3): 46-49.]

[72] 刘群, 王磊, 肖云娜. 高效液相色谱-电雾式检测器法同时测定川芎茶调颗粒中7个活性成分[J]. 中国医院药学杂志, 2021, 41(14): 1417-1422. [LIU Qun, WANG Lei, XIAO Yunna. Simultaneous determination of seven active ingredients in Chuanxiong Chatiao granules by HPLC-CAD[J]. Chinese Journal of Hospital Pharmacy, 2021, 41 (14): 1417-1422.]

[73] Wu L L, Gong X C, Pan J Y, et al. Establishing a chromatographic fingerprint using tandem UV/charged aerosol detection and similarity analysis

for Shengmai capsule: a novel method for natural product quality control[J]. Phytochemical Analysis, 2022, 33(3): 460-472.

[74] 林楚慧, 柴瑞平, 张璐, 等. 高效液相色谱-电雾式检测器测定牛黄解毒片中的6种胆汁酸[J]. 分析化学, 2022, 50(5): 764-771. [LIN Chuhui, CHAI Ruiping, ZHANG Lu, et al. Determination of six kinds of bile acids in Niuhuang Jiedu tablets using high performance liquid chromatography coupled with charged aerosol detector[J]. Chinese Journal of Analytical Chemistry, 2022, 50(5): 764-771.]

[75] Shi W Q, Wu Z H, Wu J P, et al. A comprehensive quality control evaluation for standard decoction of *Smilax glabra* Roxb based on HPLC-MS-UV/CAD methods combined with chemometrics analysis and network pharmacology[J]. Food Chemistry, 2023, 410: 135371.

[76] 邸继鹏, 赵艺晨, 彭倩, 等. 基于电雾式检测器的紫苏子及炒紫苏子配方颗粒多成分含量测定[J]. 环境化学, 2023, 42(1): 341-344. [DI Jipeng, ZHAO Yichen, PENG Qian, et al. Determination multi-components contents of Perilla Frutenscens seed and fried seed formulations based on charged aerosol detector[J]. Environmental Chemistry, 2023, 42(1): 341-344.]

[77] 杜蕾蕾, 陈雏, 冉良骥. 快速溶剂萃取-电雾式检测器同时测定山楂及其炮制品中5种三萜酸类成分的含量[J]. 环境化学, 2023, 42(6): 2132-2135. [DU Leilei, CHEN Chu, RAN Liangji. Simultaneous determination of five triterpenic acids in Crataegi Fructus by accelerated solvent extraction-charged aerosol detector[J]. Environmental Chemistry, 2023, 42(6): 2132-2135.]

[78] 劳永真, 苏江敏, 章军, 等. 高效液相色谱-电雾式检测法测定复方益母草胶囊中盐酸水苏碱[J]. 环境化学, 2023, 42(2): 675-678. [LAO Yongzhen, SU Jiangmin, ZHANG Jun, et al. Determination of stachydrine hydrochloride in compound leonurus japonicus capsules by high performance liquid chromatography-charged aerosol detector[J]. Environmental Chemistry, 2023, 42(2): 675-678.]

[79] 李火云, 刘潇潇. HPLC-CAD法测定山银花配方颗粒中绿原酸等成分含量[J]. 广东化工, 2023, 50(5): 194-196, 220. [LI Huoyun, LIU Xiaoxiao. Simultaneous determination of three active ingredients of lonicera flos dispensing granules phase by HPLC-CAD[J]. Guangdong Chemical Industry, 2023, 50(5): 194-196, 220.]

[80] Davies S R, Kankaew P, Tarrant G J, et al. Comprehensive certification of a testosterone calibration standard facilitating the investigation of charged aerosol detection for the quantification of impurities of related structure[J]. Metrologia, 2019, 56(2): 024004-024023.

[81] Hashimoto H, Furutsuka K, Kawamura K, et al. Simultaneous measurements of the molar radioactivity, radiochemical purity and chemical impurity in the [^{11}C] choline injection using radio-HPLC with a corona-charged aerosol detector[J]. Applied Radiation and Isotopes, 2020, 162: 109192-109200.

[82] Langer C, Süss R. HPLC-DAD-CAD-based approach for the simultaneous analysis of hydrophobic drugs and lipid compounds in liposomes and for cyclodextrin/drug inclusion complexes[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 201: 114120-114126.

[83] Liu G J, Zhu B Q, Ren X J, et al. Universal response method for the quantitative analysis of multi-components in josamycin and midecamycin using liquid chromatography coupled with charged aerosol detector[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 192: 113679-113689.

[84] Liu G J, Zhu B Q, Wang F, et al. Quantitative analysis of impurities in leucomycin bulk drugs and tablets: a high performance liquid chromatography-charged aerosol detection method and its conversion to ultraviolet detection method[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 202: 114148-114156.

[85] Qiu X D, Zuo L M, Sun S N, et al. Impurity profiling of compound amino acid injection (6AA) using ion-pair high performance liquid chromatography coupled with corona-charged aerosol detection and high resolution mass spectrometry[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 201: 114099-114106.

[86] Pawellek R, Holzgrabe U. Influence of the mobile phase composition on hyphenated ultraviolet and charged aerosol detection for the impurity profiling of vigabatrin[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 201: 114110-114117.

[87] 步玉如, 顾王文, 熊亮, 等. 混合模式色谱柱全水相测定阿仑膦酸钠片的含量和有关物质[J]. 中国现代应用药学, 2021, 38(8): 977-984. [BU Yuru, GU Wangwen, XIONG Liang, et al. Determination of the content and related substances of alendronate sodium

tablet using the mixed-mode chromatographic column in all aqueous system[J]. Chinese Journal of Modern Applied Pharmacy, 2021, 38 (8): 977-984.]

[88] Beck T I H, Toussaint B, Surget E, et al. Investigation of hydrophilic interaction liquid chromatography coupled with charged aerosol detector for the analysis of tromethamine[J]. Talanta, 2022, 238 (2): 123050-123062.

[89] Leistner A, Holzgrabe U. Alternative methods to assess the impurity profile of a monographed API using acarbose as an example[J]. Journal of Pharmaceutical and Biomedical Analysis, 2022, 221 : 115063-115070.

[90] 柳冬梅, 赵慧. 高效液相色谱-电雾式检测器法测定尿素乳膏含量[J]. 安徽医药, 2022, 26(10): 1929-1932. [LIU Dongmei, ZHAO Hui. Determination of the content of urea cream by HPLC-CAD[J]. Anhui Medical and Pharmaceutical Journal, 2022, 26 (10): 1929-1932.]

[91] 杨琴, 袁军, 刘峰, 等. HPLC-CAD同时测定复方醋酸钠林格注射液中钠、钾、镁、钙的含量[J]. 中国测试, 2022, 48(5): 72-76. [YANG Qin, YUAN Jun, LIU Feng, et al. Simultaneous determination of sodium, potassium, magnesium and calcium in compound sodium acetate Ringer injection by HPLC-CAD[J]. China Measurement & Test, 2022, 48 (5): 72-76.]

[92] Gao J R, Xu B Y, Li P, et al. Universal response method for the quantitative analysis of photodegradation impurities in lomefloxacin hydrochloride ear drops by liquid chromatography coupled with charged aerosol detector[J]. Journal of Pharmaceutical and Biomedical Analysis, 2023, 234 : 115552-115560.

[93] Huang Y W, Lu H, Li Z, et al. Development of HPLC-CAD method for simultaneous quantification of nine related substances in ursodeoxycholic acid and identification of two unknown impurities by HPLC-Q-TOF-MS[J]. Journal of Pharmaceutical and Biomedical Analysis, 2023, 229 : 115357-115364.

[94] Walther R, Holzgrabe U. Simplification of pharmacopoeial liquid chromatography methods for related substances of statins by hyphenated ultraviolet and charged aerosol detection[J]. Journal of Pharmaceutical and Biomedical Analysis, 2023, 225 : 115218-115326.

[95] 冯中, 朱冬青, 庞余江, 等. HPLC-CAD法测定舒更葡糖钠中的有关物质[J]. 中国医药工业杂志, 2023, 54(5): 785-790. [FENG Zhong, ZHU Dongqing, PANG Yujiang, et al. Determination of the related substances in sugammadex sodium by HPLC-CAD[J]. Chinese Journal of Pharmaceuticals, 2023, 54 (5): 785-790.]

[96] Li L, Foley J P, Helmy R. Simultaneous separation of small interfering RNA and lipids using ion-pair reversed-phase liquid chromatography[J]. Journal of Chromatography A, 2019, 1601 : 145-154.

[97] Karongo R, Ikegami T, Stoll D R, et al. A selective comprehensive reversed-phase×reversed-phase 2D-liquid chromatography approach with multiple complementary detectors as advanced generic method for the quality control of synthetic and therapeutic peptides[J]. Journal of Chromatography A, 2020, 1627 : 461430.

[98] Pawellek R, Schilling K, Holzgrabe U. Impurity profiling of L-aspartic acid and glycine using high-performance liquid chromatography coupled with charged aerosol and ultraviolet detection[J]. Journal of Pharmaceutical and Biomedical Analysis, 2020, 183 : 113149.

[99] Chin S, Lin X X, Santarra B, et al. Multiplexed small molecule impurity monitoring in antibody-based therapeutics by mixed-mode chromatography paired with charged aerosol detection[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 197 (1): 113952.

[100] Packer M, Gyawali D, Yerabolu R, et al. A novel mechanism for the loss of mRNA activity in lipid nanoparticle delivery systems[J]. Nature Communications, 2021, 12 (1): 6777-6787.

[101] Yu X J, Yu C F, Wu X H, et al. Validation of an HPLC-CAD method for determination of lipid content in LNP-encapsulated COVID-19 mRNA vaccines[J]. Vaccines, 2023, 11 (5): 937-948.

[102] 邵天舒, 李珉, 李玉立, 等. 高效液相色谱-电雾式检测器测定疫苗原液中去氧胆酸钠残留量[J]. 医药导报, 2023, 42(3): 401-404. [SHAO Tianshu, LI Min, LI Yuli, et al. Determination of residual sodium deoxycholate in vaccine bulk by HPLC-CAD[J]. Herald of Medicine, 2023, 42 (3): 401-404.]

[103] He Y, Brown P, Bailey Piatchek M R, et al. On-line coupling of hydrophobic interaction column with reverse phase column-charged aerosol detector/mass spectrometer to characterize polysorbates in therapeutic protein formulations[J]. Journal of Chromatography A, 2019, 1586 : 72-81.

[104] Kranz W, Wuchner K, Corradini E, et al. Factors influencing polysorbate's sensitivity against enzymatic hydrolysis and oxidative degradation[J]. Journal of Pharmaceutical Sciences, 2019, 108 (6): 2022-2032.

[105] Doshi N, Martin J, Tomlinson A. Improving prediction of free fatty acid particle formation in biopharmaceutical drug products: incorporating ester distribution during polysorbate 20 degradation[J]. Molecular Pharmaceutics, 2020, 17 (11): 4354-4363.

[106] Dwivedi M, Buske J, Haemmerling F, et al. Acidic and alkaline hydrolysis of polysorbates under aqueous conditions: towards understanding polysorbate degradation in biopharmaceutical formulations[J]. European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences, 2020, 144 : 105211.

[107] Zhang S S, Xiao H, Molden R, et al. Rapid polysorbate 80 degradation by liver carboxylesterase in a monoclonal antibody formulated drug substance at early stage development[J]. Journal of Pharmaceutical Sciences, 2020, 109 (11): 3300-3307.

[108] Zhao X, He Y Z, Chen J G, et al. Identification and direct determination of fatty acids profile in oleic acid by HPLC-CAD and MS-IT-TOF[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 204 : 114238-114245.

[109] 邵天舒, 丁锐, 周长明, 等. 人凝血因子Ⅷ制品中聚山梨酯80残留量高效液相色谱-电喷雾检测器检测方法的建立及验证[J]. 中国生物制品学杂志, 2021, 34(9): 1105-1110. [SHAO Tianshu, DING Rui, ZHOU Changming, et al. Development and verification of high performance liquid chromatography coupled with charged aerosol detection for residual polysorbate 80 content in human coagulation factor Ⅷ products[J]. Chinese Journal of Biologicals, 2021, 34 (9): 1105-1110.]

[110] 郑秋灵, 包瑶萍, 李燕贤, 等. 高效液相色谱-电雾式检测器测定氨溴特罗口服溶液中羟乙基纤维素含量[J]. 中国药品标准, 2023, 24(1): 104-108. [ZHENG Qiuling, BAO Yaoping, LI Yanxian, et al. Determination of hydroxyethyl cellulose in ambroxol oral solution by high-performance liquid chromatography-electrospray detector (HPLC-CAD)[J]. Drug Standards of China, 2023, 24 (1): 104-108.]

[111] Walther R, Krmar J, Leistner A, et al. Analytical quality by design: achieving robustness of an LC-CAD method for the analysis of non-volatile fatty acids[J]. Pharmaceuticals, 2023, 16 (4): 478-494.

[112] Fan Y C, Marioli M, Zhang K. Analytical characterization of liposomes and other lipid nanoparticles for drug delivery[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 192 : 113642.

[113] Đajić N, Otašević B, Malenović A, et al. Corona Charged Aerosol Detector in studying retention and β-cyclodextrin complex stability using RP-HPLC[J]. Journal of Pharmaceutical and Biomedical Analysis, 2021, 193:113711.

[114] Toussaint B, Immame Hassane Beck T, Surget E, et al. Exploration of the effects of chloride ions on the analysis of polar compounds at low concentrations by hydrophilic interaction liquid chromatography coupled to a charged aerosol detector: application to tromethamine[J]. Journal of Separation Science, 2023, 46 (6): e2200766.

[115] 吴晓惠, 黄彬磊, 吴成新, 等. 液相色谱仪–电雾式检测器的校准[J]. 化学分析计量, 2019, 28(2): 118-121. [WU Xiaohui, HUANG Binlei, WU Chengxin, et al. Calibration of liquid chromatography-charged aerosol detector[J]. Chemical Analysis and Meterage, 2019, 28 (2): 118-121.]

[116] Grundler W, Jentzsch U, Stark W. Detection of ultrafine particles by means of a continuous flux condensation nuclei counter-sciencedirect[J]. Fine Particles, 56(4): 565-580.

[117] Koropchak J A, Heenan C L, Allen L B. Direct comparison of evaporative light-scattering and condensation nucleation light-scattering detection for liquid chromatography[J]. Journal of Chromatography A, 1996, 736 (1-2): 11-19.

[118] Allen L B, Koropchak J A. Condensation nucleation light scattering: a new approach to development of high-sensitivity, universal detectors for separations[J]. Analytical Chemistry, 1993, 65 (6): 841-844.

[119] Allen L B, Koropchak J A, Szostek B. Condensation nucleation light scattering detection for conventional reversed-phase liquid chromatography[J]. Analytical Chemistry, 1995, 67 (3): 659-666.

[120] Lu Q, Koropchak J A. Corona discharge neutralizer for electrospray aerosols used with condensation nucleation light-scattering detection[J]. Analytical Chemistry, 2004, 76 (18): 5539-5546.

[121] Hering S V, Stolzenburg M R, Quant F R, et al. A laminar-flow, water-based condensation particle counter (WCPC)[J]. Aerosol Science and Technology, 2005, 39 (7): 659-672.

[122] Olsovská J, Kameník Z, Cajthaml T. Hyphenated ultra high-performance liquid chromatography-nano quantity analyte detector technique for determination of compounds with low UV absorption[J]. Journal of Chromatography A, 2009, 1216(30): 5774-5778.

[123] 王巧娥, 丁明玉. 蒸发光散射检测技术研究进展[J]. 分析测试学报, 2006, 25(6): 126-132. [WANG Qiaoe, DING Mingyu. Progress on evaporative light-scattering detection[J]. Journal of Instrumental Analysis, 2006, 25(6): 126-132.]

[124] Zhou L H, Ni H, Zhang L L, et al. Calculating relative correction factors for quantitative analysis with HILIC-HPLC-ELSD method: eight fructooligosaccharides of *Morinda officinalis* as a case study[J]. Journal of Analytical Methods in Chemistry, 2022, 2022: 8022473.

[125] Dufour A, Thiébaut D, Loriau M, et al. Corona charged aerosol detector non-uniform response factors of purified alcohol ethoxylated homologues using liquid chromatography[J]. Journal of Chromatography A, 2020, 1627: 461402.

[126] Causevic A, Olofsson K, Adlercreutz P, et al. Non-aqueous reversed phase liquid chromatography with charged aerosol detection for quantitative lipid analysis with improved accuracy[J]. Journal of Chromatography A, 2021, 1652: 462374-462384.

[127] Graceffa O, Kim E, Broweleit R, et al. Choice of buffer in mobile phase can substantially alter peak areas in quantification of lipids by HPLC-ELSD[J]. Journal of Chromatography B, Analytical Technologies in the Biomedical and Life Sciences, 2022, 1209: 123417-12323.

[128] Pawellek R, Holzgrabe U. Performance of ion pairing chromatography and hydrophilic interaction liquid chromatography coupled to charged aerosol detection for the analysis of underivatized amino acids[J]. Journal of Chromatography A, 2021, 1659: 462613.

[129] Furota S, Ogawa N O, Takano Y, et al. Quantitative analysis of underivatized amino acids in the sub- to several-nanomolar range by ion-pair HPLC using a corona-charged aerosol detector (HPLC-CAD)[J]. Journal of Chromatography B, Analytical Technologies in the Biomedical and Life Sciences, 2018, 1095: 191-197.

[130] Lie A, Pedersen L H. Resolution and signal-to-noise in analysis of carbohydrate isomers by graphitised carbon chromatography with charged aerosol detection[J]. Journal of Chromatography A, 2018, 1567: 147-154.

[131] Cohen R D, Liu Y, Gong X Y. Analysis of volatile bases by high performance liquid chromatography with aerosol-based detection[J]. Journal of Chromatography A, 2012, 1229: 172-179.

[132] Boborodea A, O'Donohue S. Linearization of evaporative light scattering detector signal[J]. International Journal of Polymer Analysis and Characterization, 2017, 22(8): 685-691.

[133] Maljurić N, Otašević B, Golubović J, et al. A new strategy for development of eco-friendly RP-HPLC method using Corona Charged Aerosol Detector and its application for simultaneous analysis of risperidone and its related impurities[J]. Microchemical Journal, 2020, 153: 104394-104402.

[134] Takeda H, Takahashi M, Hara T, et al. Improved quantitation of lipid classes using supercritical fluid chromatography with a charged aerosol detector[J]. Journal of Lipid Research, 2019, 60(8): 1465-1474.

[135] Ligor M, Studzińska S, Horna A, et al. Corona-charged aerosol detection: an analytical approach[J]. Critical Reviews in Analytical Chemistry, 2013, 43(2): 64-78.

[136] Vervoort N, Daemen D, Török G. Performance evaluation of evaporative light scattering detection and charged aerosol detection in reversed phase liquid chromatography[J]. Journal of Chromatography A, 2008, 1189(1-2): 92-100.

[137] Takahashi K, Kinugasa S, Senda M, et al. Quantitative comparison of a corona-charged aerosol detector and an evaporative light-scattering detector for the analysis of a synthetic polymer by supercritical fluid chromatography[J]. Journal of Chromatography A, 2008, 1193(1-2): 151-155.