质量源于设计理念在脂质立方液晶开发中的应用

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摘要: 以质量源于设计 (quality by design, QbD) 理念作为药物研发设计基本原则已成为行业共识。本文在回顾制药QbD设计步骤的基础上, 深入探讨QbD在脂质立方液晶开发中的应用, 详细分析了脂质立方液晶设计中目标产品质量概况、关键质量属性、关键物料属性、关键工艺参数、风险评估及因素筛选、实验设计、设计空间及控制策略等QbD要素, 旨在深入挖掘QbD理念融合运用, 为脂质立方液晶制剂的开发提供参考。

关键词: 质量源于设计; 脂质立方液晶; 产品开发; 控制策略; 临床转化

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Application of the quality by design concept in the development of lipid-based cubic liquid crystalline

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Abstract: It has become an industry consensus to take the concept of quality by design (QbD) as the basic principle of drug development design. On the basis of reviewing the design steps of pharmaceutical QbD, this paper deeply discusses the application of QbD in the development of lipid-based cubic liquid crystalline, and analyzes in detail the QbD elements in the design of lipid-based cubic liquid crystalline, such as quality target product profile, critical material attributes, risk assessment and factor screening, critical material attributes, critical process parameters, experimental design, design space and control strategy, *etc.* The purpose of this study is to deeply explore the integration and application of QbD concepts and provides a reference for the development of lipid-based cubic liquid crystalline preparations.

Key words: quality by design; lipid-based cubic liquid crystalline; product development; control strategy; clinical translation

脂质立方液晶 (lipid-based cubic liquid crystalline, cubosome) 由两亲性脂质分散在水中自组装形成, 含双连续水区和脂质区的闭合脂质双层“蜂窝状”结构, 兼具各向同性液体 (如流动性) 和固体 (如分子排列位置顺序和取向) 的中间性质[1,2]。两亲性分子在三维空间无限循环, 堆叠形成晶胞并继续堆叠形成曲面度极

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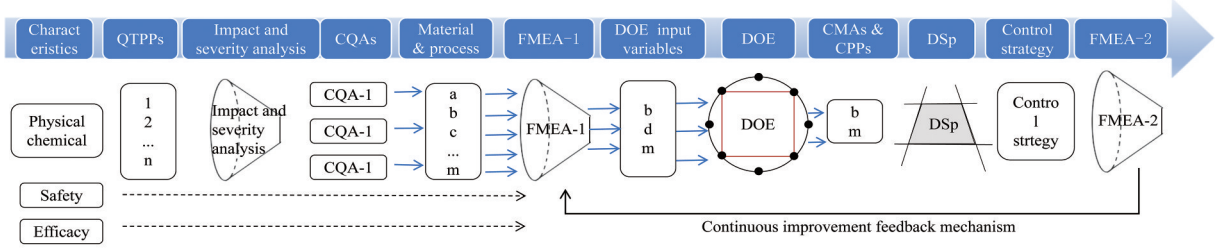
小的紧密结构, 含有两条微小且互不相通的水道, 一条与外水道相连, 另一条则是封闭的[3]。Cubosome 独特的结构性质赋予了其较强的载药适应性、较低的流动性、较大的生物黏附性以及可调节的释药速度[4]。自 1990 年 Engsrtoem 提出将其作为药物载体设想之后, cubosome 作为一种新型纳米载药体系逐渐受到国内外广大学者的关注, 已有多种给药途径应用研究报道, 如口服给药、注射给药、黏膜给药、经皮给药等[5,6]。目前的研究主要集中在制剂处方筛选、体内外药物释放等方面, 产业化的较少, 仅有 Dumex 公司的 Elyzol (液晶凝胶用于牙科治疗) 和 Camurus Technologies 公司的 Buvidal (皮下注射治疗阿片类药物依赖) 上市[7,8]。Camurus Technologies 公司研发的 CAM 2028 (生物黏附液晶薄膜用于减轻疼痛)、CAM 2029 (液晶储库技术用于治疗肢端肥大) 和 CAM 2032 (皮下注射治疗前列腺癌) 仍处于临床研究阶段[9,10]。Cubosome 具有复杂的物质组成结构和过程相态特征, 增加了其生产规模放大过程中的难度, 工艺研究大多依赖经验[11,12], 缺乏系统的理论指导。质量源于设计 (quality by design, QbD) 理念的提出旨在将管理学原则与药品研发制造规律相融合, 以提高药品质量, 是所有药物研发设计的基本原则, 设计过程对药品质量的决定性作用已成为行业共识[13-15]。本文尝试在理解 QbD 核心思想的基础上, 分析 QbD 指导 cubosome 研究的概况, 总结 QbD 指导 cubosome 研究的模式, 为 QbD 在 cubosome 研究及相关产品开发中的应用提供参考。

1 QbD 实施步骤及工具

QbD 一般遵循通用的、系统的设计步骤, 基本内容为: 以预先设定的目标产品质量概况 (quality target product profile, QTPP) 作为研发起点, 在确定产品关键质量属性 (critical quality attributes, CQAs) 的基础上, 基于风险评估和实验研究, 确定关键物料属性 (critical material attributes, CMAs) 和关键工艺参数 (critical process parameters, CPPs), 系统描述二者的定量关系, 优化并确定设计空间 (design space, DSp), 进而建立满足产品性能且工艺稳健的控制策略, 最终完成设计、完善整体战略方案, 实施产品和工艺的生命周期管理 (包括持续改进过程)[16-18]。实施步骤及常用工具如图 1 所示。

2 目标产品质量概况

QbD 框架下, 药物制剂产品开发的首要任务是明确 QTPP。人用药品技术要求国际协调理事会 (the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICH) 在 Q8 (2009 年) 中将 QTPP 定义为“兼顾药品安全性和有效性的同时, 对药品质量特性的全面、前瞻性描述, 以确保产品预期质量”[19]。安全、有效、质量可控是药物研发和评价所遵循的基本原则[20]。这一阶段, 需通



Quality target product profile (QTPP)	Critical quality attributes (CQAs)	Risk assessment	Critical material attributes (CMAs) Critical process parameters (CPPs)	Design of experiments (DOE) Design space (DSp)	Control strategy
Predetermined summary of drug product	Determine potential critical quality attributes, derived from QTPP	Analyzes the impact of a single variable and identifies key CMAs and CPPs of the drug product	CMAs and CPPs can potentially cause variations in the CQAs	To carry out experiments involving multiple variables	Continuous improvement and drug lifecycle.
Dosage form, route of administration, drug release, pharmacokinetics, restricitive period, physical attributes (color,appearance,odor), impurities and packaging	Impact and severity analysis	Failure mode effects analysis(FMEA) Relative risk-based matrix assessment (RRMA)	Process mapping Ishikawa diagram & fishbone diagram	Factorial design Box-Behnken design Plackett-Burman design D-optimal design Central composite design Artificial Neural Network	Input material controls Control for maintaining product specifications Control for CPPs Real-time release testing (RTRT)

Figure 1 Implementation process and common tools of quality by design (QbD). QTPP: Quality target product profile; CQAs: Critical quality attributes; DOE: Design of experiments; CMAs: Critical material attributes; CPPs: Critical process parameters; DSp: Design space; RRMA: Relative risk-based matrix assessment; RTRT: Real-time release testing

过文献调研以及生产经验评估, 尽可能搜集可能影响产品质量的各种因素, 对目标产品进行分析, 清楚剖析研发目标产品相关信息 (如给药途径、剂型选择、适应症、处方组成、有效期、药动学、包装系统等)[19]。给药途径作为QTPPs中的一个常见因素, 通常在早期就会被明确。此时除确定一些基本的目标外, 还会涉及一些细节内容, 如黏度、pH值的适宜范围或药物释放特性, 但往往是概括性的范围。表1[10,19,21-56]讨论了脂质立方液晶的QTPPs, 除去常规因素外, 针对凝胶状态, 还考虑了外观、黏度、接触角、流变特性等。

Table 1 Lipid-based cubic liquid crystalline quality target product profiles (QTPPs). *For topical gels of lipid-based cubic liquid crystalline. PDI: Polydispersity index; iv: Intravenous

QTPP element	Target	Justification	Ref.
Dosage form/ delivery system	Liquid crystal nanoparticles/cubosome dispersion loaded gel/lipid crystalline nanoparticles-based dry powder	Enhance the bioavailability/therapeutic efficacy/stability/ permeability/release profile of the therapeutic agent (depends on the active pharmaceutical ingredient and the route of administration)	[21-40]
Route of administration	Oral/non-gastrointestinal administration (ocular, nasal, pulmonary, periodontal, vaginal, injection, topical)	Easy to use/local action/prevent adverse effects (based on the active pharmaceutical ingredient, and therapeutic target)	[22-42]
Dose strength	X% (*w*/*w*)	The dose should be within the therapeutic range and below the maximum safe concentration to avoid any side effects	[19]
Crystalline shape	Lamellar/cubic/hexagonal	Cubosome and hexagonal phases: Highly ordered structure, slow release matrix; lamellar phase: Enhance spread ability of topical formulations	[10]
Appearance*	Smooth textured gel/colloid/emulsion	Promote patient compliance	[32,35,38]
Odor	No unpleasant odor	Promote patient compliance	[32,43]
Method of administration	Once or twice daily application	Achieve the expected therapeutic effect	[43]
Dosage design/drug release	Controlled-release formulations provide sustained drug delivery in comparison to the immediate release of free non-encapsulated	Rate of dissolution affects the drug release, absorption and permeation of the drug; reducing the frequency of application	[44]
Method of preparation	Top-down method/bottom-up method	Affects the particle size	[45]
Particle size	Uniform/≤ 300 nm	Substantially influences absorption and permeation	[46]
PDI	Uniform/≤ 0.3	Affects the homogeneity of the formulation uneven drug loading can cause fluctuation and irregularity of drug release	[47]
Zeta potential	Absolute ≥ 20 mV	Affect the physical stability and prevents formation of aggregates	[47]
Entrapment/ encapsulation efficiency	Maximum/high	Affects the retention, permeation flux, therapeutic efficacy and the drug release	[48,49]
Viscosity*	Optimum (1 000−50 000 mPa·s)	Directly influence drug diffusion rate at the microstructure level	[35,50]
Contact angle*	0°	Affects spread ability of the gel	[35,50]
Rheological properties*	Yield stress (optimum)	Affects performance of the product	[50]
Log*P* of drug	Optimum	Consideration should be given when preparing topical formulations	[51]
pH	Well-matched with formulation (for iv: 3−8, topical: 4.2−5.6)	Affects stability of the formulation, drug release, drug loading, and permeation	[10,52]
Pharmacokinetics	Improved absorption, bioavailability, and pharmacokinetic parameters compared to the free drug and/or targeting	Necessary to achieve the desired therapeutic effect	[10,53]
Water content	Optimum	Affects stability of the formulation	[54]
Impurities	Comply with the requirements of the Chinese Pharmacopoeia	Affects stability of the formulation	[54]
Microbial content	Comply with the requirements of the Chinese Pharmacopoeia	Affects stability of the formulation	[54]
Ease of storage and distribution	Store at temperature below 25 ℃/do not freeze	Depends on the excipients and the form of formulation (powder or gel) to maintain stability and integrity during storage and distribution	[27,28]
Stability (physical, chemical, biological)/ shelf life	No visible sign of instability at the time of preparation and over the restrictive period	Stability issues, like changes in pH, viscosity, appearance, aggregation, and change of crystal phase can affect the release and therapeutic effect of the formulation	[22,27,43]
Container closure system/packaging	Airtight glass bottle/collapsible tube	Prevents drug and lipid degradation to achieve target shelf life	[55,56]

3 关键质量属性

药物开发过程中, 从目标产品质量概况出发, 基于风险评估的药物质量控制研究需要确定其CQAs。纳米药物CQAs易受到制剂处方或制备工艺变化的影响, 其限度范围的确定须全面考虑所有直接和潜在因素[57]。2021年国家药品监督管理局药品审评中心发布的《纳米药物质量控制研究技术指导原则 (试行) 》, 强调了对纳米药物和体内行为相关质量指标的关注 (如粒径、表面电荷、药物释放度等), 以及与其特性相关的性能指标 (如结构形态、包封率、载药量等)[54]。粒径是药物设计与评估的一个重要质控指标, 直接关系到活性成分的载药量及释放行为, 与药代动力学、生物分布和清除途径等密切相关[58]。粒径大小分布的准确控制是保证纳米药物质量稳定性的必要条件[59]。表面电荷则影响药物的聚集状态、稳定性及生物分布, 一般基于zeta电位测量进行评估[57]。对于载体类纳米药物, 包封率和载药量与处方组成和制备工艺等密切相关, 作为评价其疗效及安全性的关键指标, 应结合具体药物特点、给药途径以及治疗剂量等进行标准化制定[60]。药物的溶出或释放则在一定程度上反应了药物的体内行为[61]。根据表1及先验经验, 基于影响分析和严重性分析, 从QTPP中筛选出脂质立方液晶的CQAs。以下两个问题构成脂质立方液晶CQAs的筛选基础: ① 处方和/或生产工艺的改变是否影响产品质量属性 (影响分析)? ② 不符合质量属性是否严重影响产品的疗效及安全性 (严重性分析)?

对于特定的QTPP要素, 若上述问题都回答“是”, 则该要素是CQAs; 否则不是。表2展示了基于影响分析和严重性分析的脂质立方液晶CQAs。

4 风险评估和因素筛选

药物质量源于设计的整体思路是基于药物评价的风险管理策略, 重点关注药物质量属性对安全性和有效性的影响, 鼓励采用科学的方法和风险管理的原则以增强对制药过程的理解, 深入剖析关键物料属性、关键工艺参数和关键质量属性之间的内在联系[62]。风险评估是识别、分析潜在风险的第一步, 其目的在于量化物料和工艺参数对产品质量的影响, 从而确定生产过程中的关键物料属性和关键工艺参数[63]。常用工具包括鱼骨图、失效模式影响分析 (failure mode and effects analysis, FMEA) 及基于相对风险矩阵分析等, 有助于

Table 2 Lipid-based cubic liquid crystalline critical quality attributes (CQAs). [a]Whether changes in the formulation and/or manufacturing process affect the quality attributes of the product? [b]Whether the non-compliance with the quality attribute seriously affects the efficacy and safety of the product?

QTPP element/quality attribute	Target	Impact analysis[a]	Severity analysis[b]	CQAs
Dosage form/delivery system	Liquid crystal nanoparticles/cubosome dispersion loaded gel/ lipid crystalline nanoparticles-based dry powder	NO	NO (dosage form is decided)	NO
Dosage design/drug release	Sustained-release compared to free drugs	NO	NO (dosage design is decided)	NO
Route of administration	Oral/non-gastrointestinal administration (ocular, nasal, pulmonary, periodontal, vaginal, injection, topical)	NO	NO (route of administration is decided)	NO
Dose strength	X% (*w*/*w*)	Yes	Yes	Yes
Crystalline shape	Lamellar/cubic/hexagonal	Yes	Yes	Yes
Appearance	Smooth transparent gel/colloid/emulsion	Yes	Yes	Yes
Method of preparation	Top-down method/bottom-up method	Yes	Yes	Yes
Particle size	Uniform/≤ 300 nm	Yes	Yes	Yes
PDI	Uniform/≤ 0.3	Yes	Yes	Yes
Zeta potential	Absolute ≥ 20 mV	Yes	Yes	Yes
Entrapment/encapsulation efficiency	Maximum/high	Yes	Yes	Yes
Dissolution	Suitable drug release profile (sustained release)	Yes	Yes	Yes
Viscosity	Optimum (1 000−50 000 mPa·s)	Yes	Yes	Yes
Rheological properties	Yield stress (optimum)	Yes	Yes	Yes
Contact angle	0°	Yes	Yes	Yes
Log*P* of drug	Optimum	Yes	Yes	Yes
pH	Well-matched with formulation (for iv: 3−8, topical: 4.2−5.6)	Yes	Yes	Yes
Water content	Optimum	Yes	Yes	Yes
Stability	Improved absorption, bioavailability, and pharmacokinetic parameters compared to the free drug and/or targeting	Yes	Yes	Yes
Microbial content	Comply with the requirements of the Chinese Pharmacopoeia	NO	Yes	Yes
Impurities	Comply with the requirements of the Chinese Pharmacopoeia	NO	Yes	NO
Ease of storage and distribution	Store at temperature below 25 ℃/do not freeze	NO	Yes	NO
Container closure system/packaging	Airtight glass bottle/collapsible tube	NO	Yes	NO

深入识别风险, 并为后续的风险控制和审查提供科学依据。

鱼骨图作为QbD理念实施及全面筛选影响因素的有效工具, 鱼头代表研究主题, 鱼刺代表风险因素。图2所示总结了脂质立方液晶制备过程, 主要关注点在于人 (men)、设备 (machines)、物料 (materials)、测量 (measurement)、方法 (methods)、环境 (milieu) 等“6 M”在制备过程中的风险[64]。风险矩阵分析作为定性手段, 确定影响过程特性主要变量并进行高、中、低分级[65]。FMEA则从失效影响、潜在原因、控制方法等角度综合分析, 结合风险指数 (risk priority number, RPN), 即失效频率 (probability of occurrence, P)、危害度 (severity, S)、可检测性 (detectability, D) 3个指标乘积对影响药品CQAs的物料属性和工艺属性进行评级, 进一步筛选关键变量[66]。基于前期研究及文献[10,44,66,67]调研工作, 制定P、S、D评判标准, 参考美国食品药品监督管理局 (Food and Drug Administration, FDA) 脂质体生产指南[68]和ICH药品研发指南Q9[69], 从1 (影响最低)～5 (影响最高) 进行评分, 根据公式 (1) 计算结合风险指数RPN:

$$RPN = P \times S \times D \quad (1)$$

其中, P为失效频率, S为危害度; D为可检测性。

评判标准: RPN > 24或S = 5时为高风险, 不可接受的风险需进一步研究以降低; 24 ≥ RPN ≥ 18时为中风险, 可能需要进一步研究; RPN < 18时为低风险, 广泛的风险无需进一步研究。

表3是材料属性FMEA分析, RPN评分对比分析发现活性药物成分 (active pharmaceutical ingredient, API) 的相对分子质量、pKa、Log$P$值、结晶形态及粒径分布等物理特性是需要重点考量的属性; 脂质辅料的种类、亲疏水特性、药物溶解性以及临界胶束浓度 (critical micelle concentration, CMC) 和稳定剂浓度等属性的评分较高, 这表明它们是相关赋形剂的关键物料属性。表4以自上而下法为例, 对关键工艺参数进行了FMEA分析, 分析结果显示混合时的温度以及高能分散操作的时间和效能是需要重点关注的方面。

5 关键物料属性和关键工艺参数

制剂工艺设计中, 关键物料属性、关键工艺参数和关键质量属性是QbD理念的关键组成部分, CMAs和CPPs代表了工艺输入, 二者的波动或变化会导致作为工艺输出部分的CQAs的显著影响[70]。表5[21,44,67,71-77]展示了QbD指导下的脂质立方液晶递药系统的应用情况, 提示采用QbD原则的脂质立方液晶递药系统研究主要集中于口服和经皮给药途径, 这类制剂中CQAs通常包括粒径及其粒径分布、包封率、zeta、药物释放等, 而影响这些CQAs的一些CMAs则包含脂质类型、脂质浓度, 表面活性剂浓度、稳定剂浓度等, 其中常见的CPPs包括温度、搅拌时间与速度、超声时间和均质压力等因素。绝大多数变量的考察通常停留在研究初期, 并未进入风险评估阶段, 如Abdel-Bar等[21]探究脂质液晶作为靶向HepG2肝细胞药物递送系统可行性时, 在未列出输入因素 (CMAs、CPPs) 并进行筛选的情况下, 依据先验经验直接选择了lipid/F127、投药量、均质压力作为影响产品最终质量的关键变量。类似的研究较多, 选定药物、给药途径及产品应用形式后, 多数停留在了脂质立方液晶的制备、处方优化、表

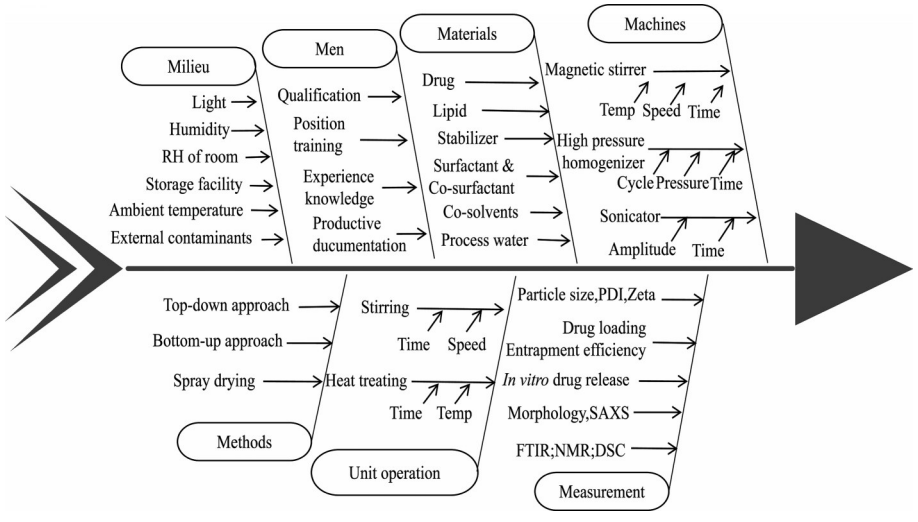


Figure 2 Causal analysis of Ishikawa diagram for lipid-based cubic liquid crystalline preparation. RH: Relative humidity; SAXS: Small-angle X-ray scattering; FTIR: Fourier transform infrared spectroscopy; NMR: Nuclear magnetic resonance; DSC: Differential scanning calorimetry

Table 3 Failure mode and effects analysis (FMEA) of the material attributes. API: Active pharmaceutical ingredient; CMC: Critical micelle concentration; P: Probability of occurrence; S: Severity; D: Detectability; RPN: Risk priority number

	Property	Material attribute	Failure mode	Effect on in-process/final product CQAs	P	S	D	RPN
API	Physical property	Molecular weight	High	Drug loading-drug release-efficacy	4	4	2	32
		Dose	High	Drug loading-drug release-efficacy/safety	3	4	2	24
		p*K*a	< 7	Parcel location-encapsulation efficiency-effectiveness	4	4	2	32
		Log*P*	Negative	Parcel location-encapsulation efficiency effectiveness	4	4	2	32
		Polymorphic form	Different	Dissolution-bioavailability-efficacy	3	4	4	48
		Particle sizeand distribution	High	Dissolution-bioavailability-efficacy	4	4	3	48
		Moisture content	High	Degradation-impurities-safety/efficiency	2	3	2	12
	Chemical property	Residual solvent	High	Degradation-impurities-safety	2	3	2	12
		Impurities	Present	Impurities limit-safety/efficacy	2	3	3	18
		Chemical stability	Unstable	Impurities limit-safety/efficacy	3	3	3	27
Excipients	Lipid	Amount	High	Drug loading-free drug-safety/efficacy	4	4	1	16
		Hydrophobicity	Low	Solubility-content uniformity-safety/efficacy	3	4	3	36
		Type	Unsuitable	Phase structure-safety/efficacy	3	5	2	30
		Melting point	High	Sensitive drug degradation-safety/efficacy	3	4	2	24
		Solubility of drug	Low	Encapsulation efficiency- safety/efficacy	3	4	3	36
		CMC	High	Critical concentration-phase structure-effectiveness	2	4	4	32
	Surfactant/ co-surfactant/stabilizer	Type	Unsuitable	Agglomeration-content	3	3	2	18
	Co-solvents	Concentration	Low	Agglomeration-content-safety/efficacy	3	4	3	36
		Suitable	Unsuitable	Drug release-bioavailability-efficacy	2	4	2	16

Table 4 FMEA of the process parameters involved in the manufacture of lipid-based cubic liquid crystalline by top-down approach. RPM: Revolutions per minute

Unit operation	Process parameter	Failure mode	Effect on in-process/final product CQAs	P	S	D	RPN
Mixing	Temperature	High	Phase changes-efficacy; drug degradation-safety/efficacy	4	4	3	48
	Time	Low	Uniformity of dispersion-content-safety/efficacy	4	3	2	24
	RPM	Low	Uniformity of dispersion-content-safety/efficacy	3	3	2	18
	Stir bar	Improper	Uniformity of dispersion- content-safety/efficacy	3	3	2	18
Size reduction technique	Type	Inadequate	Particle size distribution-efficacy	3	4	2	24
	Time	Low	Particle size distribution-efficacy	3	4	3	36
	Amplitude/pressure/speed	Improper	Particle size distribution- efficacy; practical application	3	4	3	36

征及体内外释放阶段。

6 实验设计、设计空间及控制策略

实验设计 (design of experiments, DOE), 1935年由Ronald Fisher首次提出, 强调在药品研发的早期阶段识别并消除潜在的质量缺陷[78]。以概率论和数理统计为基础, 多因素及其相互关系并探索其中统计学规律, 是常见的数据分析方法, 采用较小的试验规模 (试验次数)、较短的试验周期和较低的试验成本, 以确保对实验全程设计、全面控制和全局优化的把控[79]。具体实施包括以下步骤, 即系统或过程输入因素的选择(如种类、范围、水平)、输出或性能指标等响应变量的选择、分析方法的选择、结果分析、优化算法以得到优化结果, 一般分为筛选阶段和优化阶段[80]。表6[21,44,67,71,76,77,81,82]汇总了近年来DOE在脂质立方液晶制备过程中的应用情况, Box-Behnken设计因其具有精度高和预测性强的优势而受到广泛关注, 人工神经网络则在处理复杂的多维、非线性问题时具有显著优势, 算法收敛速度快、计算时间短、统计分析能力强, 在相关实验设计领域偶有应用。

药品研究与开发的核心目的在于设计出符合质量要求的产品, 以及能够持续生产且符合预期性能的制药工艺。设计空间在保证产品质量的前提下, 原辅料、处方、生产工艺参数, 一定范围内变化的多维组合, 这在一定程度上避免了工艺批准后的变更审查, 并利于持续的质量改进[83]。而设计空间内运行的控制策略能够最大限度上保证制剂产品所需的CQAs[84]。控制策略作为一套计划性的控制手段, 基于现行产品和工艺理解的基础上, 保证工艺稳健和产品质量可控[85]。依据国际制药工程协会 (International Society for Pharmaceutical Engineering, ISPE) 推出的产品质量生命周期应用指南 (Product Quality Lifecycle Implementation, PQLI), PQLI工作组[86]根据患者需求和商业需求的不

Table 5 Application analysis of lipid-based cubic liquid crystalline drug delivery system based on QbD. F127: Poloxamer 407; GMO: Glycerol monooleate; PEG200: Polyethylene glycol 200; CQA: Critical quality attribute; CMA: Critical material attribute; CPP: Critical process parameter

API and delivery system	Route of administration	CQA	CMA	CPP	Ref
Tofacitinib loaded crystal nanoparticles	Topical	Particle size, PDI, entrapment efficiency, permeation flux ciscosity, skin penetration	Amount of lipid, type of liquid oil, amount of liquid oil, surfactant concentration	Temperature, stirring speed, sonication amplitude, sonication time	[71]
Fluoxetine hydrochloride loaded hexosomes	Topical	Particle size, zeta potential, entrapment efficiency	/	Lipid/F127, drugs, homogenization speed	[21]
Ketoconazole loaded cubosomes	Topical	Particle size, PDI, entrapment efficiency, drug release	Amount of surfactant, amount of stabilizer, organic solven	Stirring speed and time, temperature	[44]
Tenofovir disoproxil fumarate loaded liquid crystal powder	Oral	Drug content, particle size	Lactose monohydrate, F127	/	[72]
Inhalable spray-dried erlotinib procubosomal	Inhale	Particle size, drug content, aerosolization efficiency	GMO/F127, PEG200, mannitol/ leucine	Stirring time and speed, temperature, inlet temperature, atomization pressure	[73]
Luliconazole loaded lyotropic liquid crystalline nanoparticles	Topical	Particle size, PDI, entrapment efficiency, percent drug release, retention in skin layer	Type of drug, amount of lipid, surfactant type, cosurfactant type	Heating temperature, stirring speed/time	[74]
Raloxifene loaded cubosome	Oral	Particle size, zeta potential, entrapment efficiency	Raloxifene amount, GMO/F127	/	[75]
Apigenin loaded lyotropic liquid crystalline nanoparticles	Topical	Particle size, PDI, entrapment efficiency	Amount of GMO/F127	Sonication time, temperature	[76]
Temozolomide loaded PEGylated lyotropic liquid crystals	Injection	Product pH, particle size, PDI, zeta potential, drug release, entrapment efficiency, loading efficiency, stability	Type of lipid, lipid concentration, type of surfctration/cosurfactant/ stabilizer and concentraton	Temperature, time, RPM, amplitude/pressure/speed	[67]
Curcumin loaded liquid crystalline nanoparticles	Topical	Particle size, PDI, zeta potential, entrapment efficiency	Lipid content, surfactant/ cosurfactant concentration	/	[77]

同, 将控制策略分为3个等级, 见表7, 这些控制策略同样适用于脂质立方液晶递药系统的生产过程。

7 工艺放大研究

工艺放大是药物研发中的关键环节, 确保产品从实验室到商业化生产的平稳过渡, 是技术转移和工艺验证的基石[87]。尽管许多药物在实验室阶段展现出了积极的疗效和潜力, 但能够真正跨越研发阶段最终以商品形式进入市场的却相对较少。许多脂质液晶药物的研究仍停留在实验室阶段, 放大生产面临诸多挑战。Waghule等[10]在实验室中对替莫唑胺载药液晶纳米粒子进行了优化, 并确定最佳的处方比例, 为验证这些实验室结果在大规模生产中的适用性进行了放大, 认为所制备的制剂放大至50 mL, 稀释至1 000倍时仍能保持稳定。Mahmood等[74]在卢立康唑液晶凝胶的研究中也进行了类似的放大研究, 制剂规模扩大至50 mL, 结果与实验室结果相一致。而在另一项研究中, Mahmood等[88]通过调整脂质含量、表面活性剂浓度和超声时间等变量优化处方, 放大至100 mL规模时也得到了类似结果。Gorantla等[71]研究局部递送托法替尼液晶凝胶时工艺放大至25 g, 为能适应工业生产对其放大批次的制备工艺做出了修改, 去除有机溶剂的情况下其粒径、PDI和包封率方面并无显著性差异, 4和25 ℃条件下可稳定储存45天。

8 总结与展望

脂质立方液晶因其独特的结构特点在药物载体领域有着其无可比拟的优势, 但由于制备工艺重复性差、重现性低等原因在生产中难以大规模复制, 导致工业化生产和临床应用受到限制, QbD理念可为解决这类问题提供新的视角。本文以QbD为理论核心, 以第3代纳米药物递送系统cubosome为研究对象, 通过风险评估和因素筛选, 详细分析cubosome药物递送系统制备过程中的关键质量属性、关键物料属性和关键工艺参数的设计要点, 阐述各要点之间的交互关系, 并探讨实验设计在脂质立方液晶药物递送系统中的应用情况及可靠性优化设计的关键输入、输出变量, 以及在工艺设计空间验证优化阶段的相关工艺放大研究情况, 为QbD指导下的脂质立方液晶制剂开发提供参考。

质量管理的过程, 每一个环节都是相互影响、相互制约的。生产全过程作为一个有机整体, 对影响产品质量的各类因素应从宏观、微观、人员、设备、物料、方

Table 6 Application of DOEs in lipid-based cubic liquid crystalline drug delivery systems. S/N: Signal to noise ration; T-80: Polysorbate 80; RSM: Response surface methodology; RMSE: Root mean square error; SEP: Standard error of prediction; AARD: Absolute average relative deviation; PEG: Polyethylene glycol

API and delivery system	Model	Independent	Dependent	Finding	Ref
Ketoconazole loaded cubosomes	3-Level factorial design	Lactose monohydrate, F127	Particle size, entrapment efficiency	For both the responses, the adequate precision was 19.437, and S/N was 7.806, which were both very high	[44]
Fluoxetine hydrochloride loaded hexosomes	Box-Behnken	Lipid/F127, fluoxetine hydrochloride, homogenization speed	Particle size, zeta potential, entrapment efficiency	The composition of the optimized fluoxetine hydrochloride hexosome was composed of 3.1, 1.4, 0.5, 0.2, and 94.8% for glyceryl monooleate, oleic acid, F127, fluoxetine hydrochloride, and deionized water	[21]
Tofacitinib loaded crystal nanoparticles	Box-Behnken	Amount of lipid, surfactant concentration, sonication time	Particle size, zeta potential, entrapment efficiency	The optimized lyotropic liquid crystals system was constructed with the glyceryl monooleate, myristol, polyethylene glycol and water system	[71]
Apigenin loaded lyotropic liquid crystalline nanoparticles	Box-Behnken	Amount of GMO, F127, sonication time	Particle size, zeta potential, entrapment efficiency	The optimized formula obtained using Box-Behnken design comprised of 4% GMO, 1% F127 and 3.3 min of sonication time	[76]
Temozolomide loaded PEGylated lyotropic liquid crystals	Box-Behnken	Amount of GMO, F127, PEG200	Particle size, PDI, zeta potential, entrapment efficiency	The optimized formulation used 300 mg GMO, 150 mg F127, and 1 mL PEG 200, achieving high entrapment efficiency and a small particle size with low lipid concentration	[67]
Curcumin loaded liquid crystalline nanoparticles	Box-Behnken	Amount of GMO, F127, PEG200	Particle size, PDI, zeta potential, entrapment efficiency	The amount of curcumin (5 mg was fixed for 10 mL formulation), lipid content (172.3 mg), surfactant (1.5%), and co-surfactant (122.78 mg), which was a completely different batch from all the 17, QbD batches	[77]
Carvedilol cubosomes	D-optimal design	F127, secondary stabilizer, type of the secondary stabilizer	Particle size, PDI, zeta potential, amount of carvedilol	The S/N were 15.83, 11.86, 9.98 and 11.81, the model had good predictability and discrimination; cremophor 40 is a suitable secondary stabilizer in preparing cubosomes	[81]
Selegiline lidocaine hydrochloride loaded cubosomal thermoreversible mucoadhesive gel	Experimental design/artificial neural network	GMO, F127, T-80	Particle size, entrapment efficiency, drug release (*in vitro*)	The RSM model is preferable to the artificial neural network model because it has lower RMSE, SEP, and AARD values	[82]

Table 7 Quality control strategy grading details. GMP: Good manufacturing practice of medical products

Control level	Control strategy
1	Patient need: Physicochemical and biological properties: Safety, efficacy, stability, ease of use; business need: cost-effectiveness attributes: Process feasibility, cost controllable, production safety, environmental friendliness, and strong maintainability
2	Production control indicators, monitoring the operation of production facilities, process parameters, material attributes, composition, *etc*. control CQAs meet the requirements of level 1
3	On-line quality monitoring, engineering or other advanced analytical testing technologies to achieve level 2 control, *in-situ*, in-line, near-line or off-line control methods, process models or automated control procedures to achieve production under GMP conditions

法和环境等方面进行全面控制, 建立从生产源头到成品的质量控制体系。QbD 理念作为兼容性系统的需要, 框架的搭建及发展依靠的是对规律性知识的发现、表达、组织和应用, 进而形成整体化的认识以实施有效的设计过程。

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