中药制剂前物料的性质体系及其表征技术研究

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摘要: 中药制剂现代化进程中面临诸多挑战, 中药粉末、中药提取物和中药组分作为中药制剂前最具有代表性的3类物料, 其性质是指导中药制剂剂型设计的核心基础。本团队在长期研究中药制剂物料性质的基础上, 根据中药制剂物料在一定条件所处的状态及物质之间相互作用特点, 构建了中药制剂物料的性质体系, 由物质构成、空间构造、体性质、面性质及理化性质5大类18小类构成, 并进一步建立了相应的指标体系, 包含61项指标及表征技术, 为中药制剂的现代化奠定基础。

关键词: 中药剂型设计; 中药粉末; 中药提取物; 中药组分; 中药物料性质; 表征技术

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The overview of the property system and characterization techniques of Chinese medicine materials before the pharmaceutical

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Abstract: At present, the modernization of Chinese medicine preparations (CMPs) is still a challenging task. The 3 typical Chinese medicine materials (CMMs) used for preparing CMPs are the powders, extracts, and components of Chinese medicine and their properties of CMMs are important for designing CMPs. Basing on our long term research, we have established a property system for CMMs according to the state of CMMs under an exactly condition and according to the interaction characteristics between substances. The property system could be divided into 5 categories: material composition, spatial structure, body property, surface property, physicochemical properties, and they could also be divided into 18 subcategories. Furthermore, we also established the corresponding index and characterization system, where the 61 indexes and characterization techniques were systematically summarized. At last, we hope that the article will promote the modernization of CMPs.

Key words: dosage form design; Chinese medicine powder; Chinese medicine extract; Chinese medicine component; Chinese medicine material property; characterization technique

中药制剂从传统剂型到现代剂型的创新发展历程中形成了较为完整的制剂理论体系, 而中药剂型设计技术也在不断地创新发展之中。目前, 中药制剂除物质基础不明、生产效率低、顺应性差等问题[1]外, 还存在许多难题亟待解决, 例如如何根据中药的剂量及自身特点选择适合的剂型、在复杂的制剂工艺中成型性是否能准确预判、以何为依据设计中药制剂递释特性等。中药制剂无论何种剂型, 其制剂前的物料, 由临床处方中的饮片经过提取浓缩或提取分离精制等前处理过程所得。因此, 对中药制剂 (前) 物料的性质研究是

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解决以上问题的关键。

根据2020版《中国药典》一部中1 634首单方制剂及成方制剂的统计[2], 中药制剂物料 (Chinese medicine materials, CMMs) 主要呈现2类形式: 中药粉末和中药提取物。中药粉末由中药饮片直接粉碎而得, 剂型主要聚焦在散剂及丸剂, 分别占比3.4%和24.8%, 该类中药物料以全成分入药, 但压缩性差; 中药提取物由饮片提取浓缩或提取分离精制后所得, 包括流浸膏、干浸膏和油脂类, 剂型主要聚焦在片剂、胶囊剂与颗粒剂, 分别占比19.7%、19.2%和14.9%, 中药提取物主要有流动性与压缩性差、黏附性及吸湿性强等问题。中药经过提取、精制并进一步纯化、达到同一类化学物质占到90%以上或接近90%的含量, 如人参茎叶总皂苷等, 可作为中药制剂的第3类物料: 中药组分提取物, 可简称为中药组分。虽然目前以中药组分为制剂原料的品种较少, 但中药组分是未来中药制剂发展的基础和方向[3], 有大量事实表明, 中药组分在体内外所呈现的结构及物理性质是组分装载、释放、转运和起效的重要因素[4]。随着第3类CMMs中有效物质的纯度不断提高, 其物性可能发生质的转变, 以CMMs性质为核心依据, 选择剂型及设计递释特性, 将是发展具有中药自身特点的制剂理论的有效突破口。

目前, 对CMMs性质的表征缺乏系统性, 关键性质及指标的筛选仍主要凭借试错法[5], 物料性质之间的相关性研究还有待进一步深化。本研究根据中药物料的特点, 系统地总结了CMMs的性质5大类18小类、物性指标及表征技术61项, 构建具有普遍适用性的CMMs性质及表征技术体系, 为中药制剂及剂型设计理论奠定基础。

1 CMMs的分类及特点

根据CMMs的前处理过程及性质特点, 将其分为中药粉末、中药提取物和中药组分3类。中药提取物与中药组分的区分是: 如果提取物中2种及以上的物质含量之和≥90%定义为中药组分[6], 含量不到90%定义为中药提取物; 其中若1种物质的含量即已达到≥90%时为组分的特例, 按“中药单体物质”的名称定义。由于中药制剂对中药粉末承载能力的限制, 中药提取物成为了目前CMMs的主流[3]。随着工业化生产中精制、纯化等新技术的应用, 少数CMMs已达到中药组分的要求。中药组分最大程度地保留了有效成分[7], 而组分单元制剂技术为发展多组分递释系统提供了技术支撑[8]。现行《中国药典》一部收载的中药制剂品种中, CMMs常常不是单一的物料形态, 可能是多种CMMs形态的共存 (图1)。对CMMs进行合理的分类将有利于其物性进一步系统化、深入化。

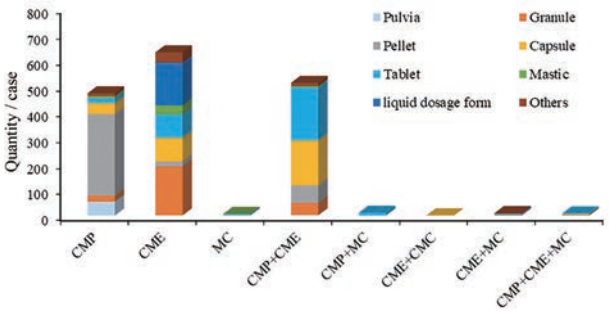

Figure 1 Different types of Chinese medicine materials (CMMs) used for preparing prescribed preparations in Chinese Pharmacopoeia (2020 Edition). CMP: Chinese medicine powder; CME: Chinese medicine extract; MC: Monomer compound; CMC: Chinese medicine component

2 CMMs性质体系的构建

中药制剂的剂型选择及设计需要一个完整的、具有普遍适用性的CMMs性质体系作为理论指导依据。在制剂过程中, 仅仅依据某方面的性质难以从整体上把握CMMs的成型性, 建立多方面且相互之间关联的性质体系是指导中药制剂设计的最佳方案。由于3类CMMs的存在状态及性质差异较大, 提取三者的共性建立具有普遍适用性的物料性质体系, 对CMMs具体的物性表征及物性之间相关性研究能起到纲领性指导作用。

CMMs具有物质属性, 而在一定的时间、空间及热力学条件下, 任何客观存在的物质均具有一定的物质构成特征, 必然存之以“形”而表现为不同的空间构造, 通过物质之间各种力的作用而在物质的外表面及内部显现出内在特性。因此, 本课题组在物质的共性特征基础上, 建立了适用于3类CMMs且相互之间关联的物料性质体系 (图2)。CMMs性质应包含物质构成、空间构造、面性质[9]、体性质及理化性质, 该体系中各性质之间存在的关联性是目前研究的热点, 如中药作用力提取物的粉末直压特性与核壳粒子结构的相关性[10]可归属于体性质与空间构造的相关性问题。此外, 还可拓展研究粉末直压性与粒子的物质构成、表面性质等相关性, 其相关性可以启发研究的创新性。

2.1 CMMs的物质构成性质 CMMs的物质构成性质包括构成要素、物质的量及排列分布, 其中构成要素及物质的量是中药剂型设计的基础, 而构成要素在空间中的排列及分布亦是造成中药制剂设计难、成型难和质量控制难的重要因素。首先, 物质构成性质与服用剂量直接相关, 是所有中药剂型设计所面临的共同问题[11], 准确地表征构成要素及量比关系是剂型选择的关键; 其次, 物质构成性质是其他一切性质的“根由”

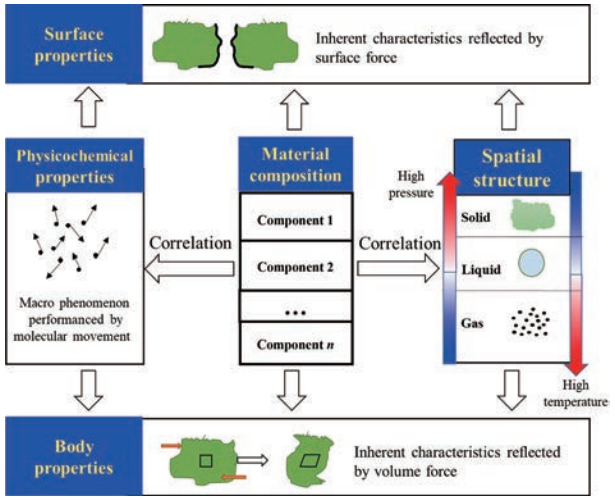

Figure 2 The property system of CMMs

所在, 中药饮片的炮制方法、前处理工艺及生产批次等因素会造成物质构成变化[12], 减小其波动范围可使制剂前物料的性质保持相对的稳定。3类CMMs的物质构成特点鲜明, 准确地表征物质构成性质才能更好地发挥其指导剂型设计的作用。此外, 另一类不依靠力的作用而反映的内在特性为空间构造性质, 该性质亦为中药制剂设计的重要依据之一。

2.2 CMMs的空间构造性质 CMMs的空间构造性质极易随制剂环境的变化而变化, 是中药制剂过程控制难及成型质量预测难的主要原因之一, 但同时又使得CMMs具有极强的被设计和被改造空间。CMMs的空间构造性质包括形貌、尺度及密集程度, 常规的粉体学性质, 如粒径及其分布、比表面积、孔隙和密度等[13]归属于空间构造性质的范畴。在物质构成性质明确的情况下, CMMs的空间构造存在多样性, 尤其固体物料常与液体接触而导致粒径及形貌的改变[14]并难以控制, 而稳定的尺度及形貌特征往往是制剂单元功能稳定的前提。大量事实证明, 空间构造性质的改变可能引起性质向极端转变, 如尺度效应所引起疏水与亲水性之间的转变[15,16], 尺度效应愈来愈成为中药制剂所关注的焦点而被运用于中药剂型设计。朱砂和羚羊角等致密性较高的矿物类、动物类中药粉末易发生离析及腥臭味等问题均可通过核壳粒子结构设计而被有效解决[17]。此外, 空间构造性质不局限于固体制剂, 在一定条件下液体制剂中的组分可能形成稳定的胶粒[18], 对其尺度、形貌及密集性与中药组分的递释规律密切相关[19], 是中药口服液体制剂或中药注射剂设计的核心依据。然而, 由于制剂过程中CMMs的空间构造容易变化, 因此对形貌等性质进行准确表征将有利于相关性的规律研究, 继而用于指导中药的剂型设计。

2.3 CMMs的面性质 外表面是CMMs区别于其他物质的分界, 是制剂环境对其直接作用的场所。在对物质的表面性质研究基础上[20-22], 根据CMMs的相态及表面作用方式的不同, 可将其面性质分为吸附性、润湿性及黏附性 (图3)。

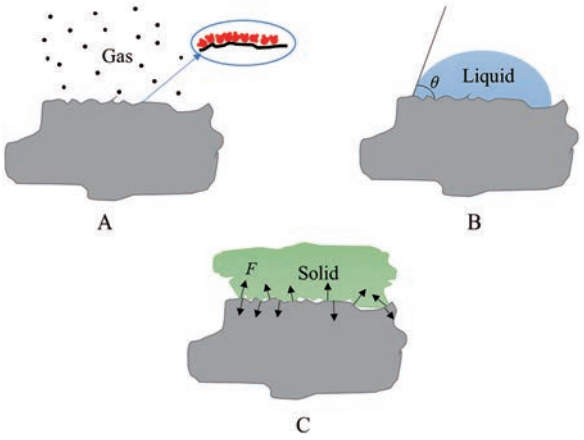

Figure 3 The surface properties of CMMs. A: Absorbability; B: Wettability; C: Adhesivity

在CMMs的表面上存在范德华力、线性张力、弹性力、表面张力和电场力等跨越7个量级的力相互竞争[23], 是产生复杂表面性质的原因。表面吸附性主要由电场力、范德华力等作用下对物质小分子的吸引, 如微量元素和水分子等[24], 其中对水分子的吸附则表现为吸湿性, 控制吸湿性对制剂生产过程中的物料转移、粉末的流动和制剂成型后的防潮具有重要意义[25]。表面润湿性主要由弹性力、表面张力等中量级的力作用, 用于表征液体对固态物料的铺展能力, 溶剂的润湿能力及润湿速率对颗粒剂、片剂等工艺产生重大影响, 实际生产过程中往往不能给予充分润湿时间[26], 而有效成分从已成型的制剂中溶出的首要阶段是润湿, 因此探究不同pH值和温度下液体对CMMs的润湿性影响, 对制剂工艺参数的选择及释药速率的控制具有重要指导意义。表面黏附性是表面各种量级力的综合反映[27], 该性质在中药递释系统的设计中具有不可忽视的作用, 如在体外选择合适的黏合剂及用量对颗粒的成型及得率具有决定性作用, 而在体内则对生物膜黏附的靶向递释系统的设计具有指导作用[28]。由此可见, CMMs的表面性质广泛渗透于中药制剂的成型设计、功能设计及质量评价等各阶段。

探究表面性质及其改性规律是中药制剂设计的创新源泉之一, 表面性质与表面的物质构成及空间构造的相关性是表面改性技术所依据的核心规律。中药固体物料的表面性质与固态物料粒子的形貌、粒径、表面粗糙度、孔隙度和曲率半径等因素相关[29], 控制粒度是

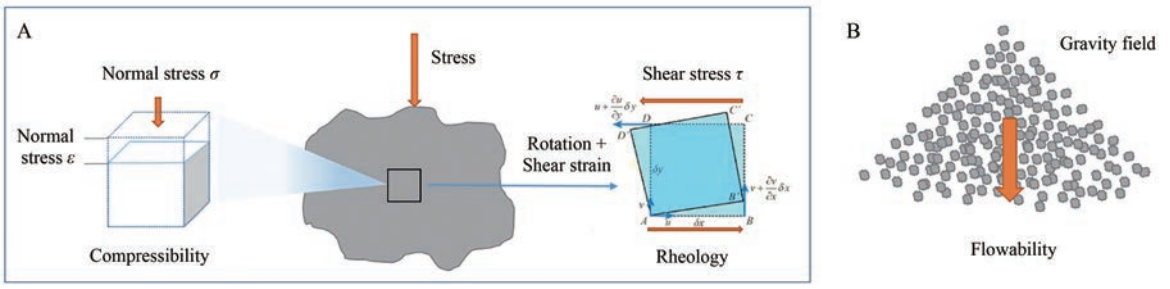

Figure 4 The body properties of CMMs. A: Deformation of continuous mass point; B: Deformation of discontinuous mass point

改变表面性质的常用方法, 而粒子表面包覆技术等是表面改性的常用技术手段[30]。CMMs的粒子达到微纳米尺度时, 表面性质的作用及影响占据主要地位, 掌握其表面改性规律及技术有利于向许多高科技前沿延伸[31]。然而, 表面改性技术需结合面性质的评价指标才能展开更深入的相关性研究。

2.4 CMMs的体性质 以一定凝聚态存在的CMMs受力时必然发生形变, 而每种物料都有其独特的形变特性, 与中药制剂的成型性密切相关, 该特性定义为体性质。根据物料内部质点的相对位移的特点, CMMs的体性质分为压缩性、流变性及流动性 (图4)。

不同相态的CMMs表现出的体性质不同。固态物质在正应力下内部质点发生正应变而表现为压缩性质, 该性质对制剂压缩工艺过程的影响较大。压缩性差的物料可能造成压片机压力过载、裂片等问题[32]; 用干法制粒时可能使颗粒的得率降低而需多次碾压。半固体或液态CMMs在切应力作用下发生切应变而表现为流变性质, 以“轻按即散”的标准制备软材、物料的孔挤出过程[33]、调节药液的黏度而防止成分析晶[18], 都是CMMs流变性质的具体应用。此外, CMMs的最小单元如果为粉或粒的形式, 此时每个粒子视为非连续性的质点, 而在重力等力场的作用下表现为流动性。该性质对CMMs的填充行为有较大影响, 如硬胶囊的填充、粉末直压时在模具中填充, 是影响中药成型质量的重要因素。

CMMs的压缩性与物料粉体粒子的空间构造、物质构成因素密切相关, 探究CMMs的压缩性规律对提升中药制剂品质有重要意义。例如, 通过设计粒子的核壳等空间构造可提高CMMs的直压性能, 该方法成为目前的研究热点[10], 以及采用粒子包覆技术等可改善CMMs的流动性。CMMs的体性质在中药制剂领域涉及面广, 在中药制剂现代化剂型设计中占有十分重要的地位, 科学合理地表征CMMs的体性质是中药剂型设计及改性技术的基础。

2.5 CMMs的理化性质体系 一定热力学条件下, 根据分子的运动形式及在宏观上的表现, CMMs的理化性质包含溶解性及渗透性、热学性及电磁性、解离性及结构化学性 (图5)。

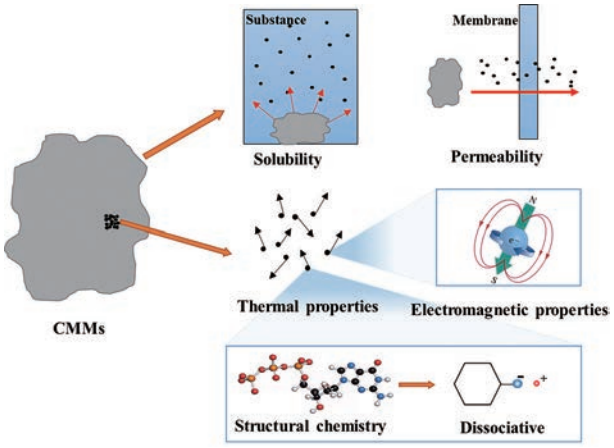

Figure 5 The physicochemical properties of CMMs

CMMs的理化性质是由特定结构的物质分子及其永无休止的运动在宏观上的表现。物质分子向介质中或穿透介质的扩散运动, 分别表现为溶解性及渗透性, 二者是中药组分生物药剂学分类系统的核心性质[34], 在以往口服液体制剂中CMMs的溶解性及渗透性容易被忽视。由于溶解性及渗透性差而导致生物利用度低, 使用增溶剂、助溶剂等是制剂常用的增溶方法, 多组分的协同提高溶解性及渗透性是中药制剂的特色之一[35]。微观粒子的运动形式包括线运动、自旋和振动等, 物质的热学性实质是由微观粒子的运动在宏观整体的表现, 如根据物理学定律可知, 温度就是由分子的平均动能所引起, 而电磁场实质由静电荷及带电粒子的运动所激发。中药制剂在一定热力学条件下成型, 热学性对CMMs的挥发性[36]、玻璃态转化和熔化等过程的控制具有重要指导意义, 电磁性是中药组分的“特征基团”(印记模板) 在体内形成稳定的超分子的驱动力[37,38], 如控制胶粒的ζ电位可防止出现絮凝作用, 提高液体制剂的稳定性。解离性是对物料分子在介质中发生解离程度的表征, H^+的解离是其中一种特殊情况,

宏观上表现为酸碱性[39], 解离性由CMMs分子的结构化学性质所决定[40]。

CMMs的理化性质特点在于多组分性质的整体表现, 该特点决定了其理化性质表征不同于单一成分。中药饮片批次、前处理工艺等对CMMs的物质构成影响较大, 致使总体理化性质的波动, 如果探究各种复杂成分与总体理化性质的相关性, 则有利于提升对理化性质的可预测性。

3 CMMs性质的指标体系及其表征技术

对CMMs性质的评价应以客观的指标进行表达, 确证科学的指标须依据一定的科学理论及科学方法。现代科学的发展为CMMs性质的指标及其表征技术体系的建立提供了技术支撑。

3.1 物质构成评价指标及表征技术 中药粉末及中药提取物的构成要素较为复杂, 但现代成分检测技术对物质构成性质的表征奠定了坚实基础 (表1)[41,42]。物质构成性质与中药饮片或处方的剂量密切相关, 其中构成要素的量与量的关系是剂型选择的依据, 然而临床处方随病证不断变化导致问题的复杂化。因此, 本课题组首次提出精制系数指标, 用于从理论上指导CMMs的剂型选择与设计。

精制系数指标, 系指中药饮片或处方经过加工处理所得CMMs的质量与投料饮片总质量之比的倒数, 见公式 (1); 在明确的中药饮片来源及稳定的前处理工艺条件下, 每种CMMs的精制系数较为稳定, 该指标是表达中药处方质量与载药量之间关系的纽带, 见公式 (2)。

$$Ex = 1/m \quad (1)$$

$$D = W/Ex \quad (2)$$

其中, Ex为精制系数; m为单位中药饮片所得的制剂前物料质量; W为中药饮片的日服用剂量; D为中药制剂前物料的日服用剂量。

精制系数用于表征CMMs的物质构成性质, 实际制剂工艺存在配方与合方2种基本的制剂方式, 与制剂的载药量密切相关 (图6), 如配方颗粒的CMMs日服用剂量是各种饮片日服用剂量的线性加和, 而合方制剂的则可能为非线性叠加, 需通过实验数据寻找相关规律。

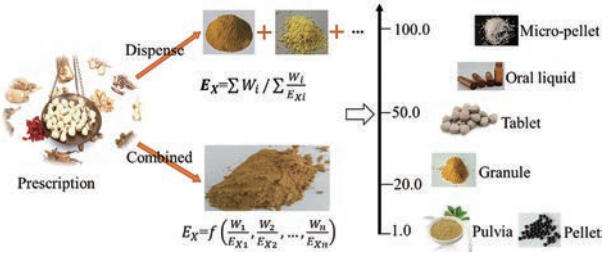

Figure 6 Relationships between the selection of dosage form and the refining coefficient of CMMs

3.2 空间构造评价指标及表征技术 一定热力学条件下, 粉体粒子或液体中微粒的空间构造性质相对稳定, 对尺度的表征方法及原理可归纳为直观法、等效转换法及标准参照法 (表2)[43-49]。直观法利用显微技术直接获取微纳米尺度粒子的形貌特征, 如使用X射线图像结合计算机技术处理CMMs表面及内部的三维结构[50]; 等效转化法则是将物料粒子分散后, 通常利用光波或超声波的透射、散射及反射强度等效转化进行定量表征; 标准参照法的原理是使用具有标准参数的设备与CMMs比较, 如用已知孔径的药典筛表征药物粉末的粒径及分布等。

3.3 面性质评价指标及表征技术 CMMs的表面作用力十分复杂, 目前还缺乏直接、准确的测定方法 (表3)[51-54]。CMMs的表面性质随物质构成、空间构造、温度、pH等因素变化[55], 尤其对黏附性的产生机制尚不十分明确, 表征该性质的指标有待考证。此外, 通常的表征技术不能全面描绘性质变化过程信息, 为进一步完善CMMs的面性质表征技术体系, 本课题组以吸湿性及润湿性为例创新性地提出动态多维表征技术及衍生的新指标。

在各种吸湿动力学模型中[56], 一级动力学方程及双指数模型符合大多数中药粉末及中药提取物的吸湿性过程, 考虑到双指数模型的参数较多, 因而选择一级动力学模型进行泰勒展开, 见公式 (3) 和 (4), 可以导出达坪吸湿量F^{∞}、半吸湿时间$t_{1/2}$、初始吸湿速率K_0及

Table 1 The material composition properties and its characterization techniques of CMMs

Material composition	Index	Characterization technique
Constituents	Macromolecular substances	Phenol sulfuric acid method (polysaccharide), Coomassie brilliant blue method (protein), orange red staining method (lipid), ultraviolet-visible absorption spectrophotometry (UV-vis), nuclear magnetic resonance (NMR)
	Small molecule substance	Chromatography, mass spectrometry, UV-vis
	Trace element	X-ray fluorescence spectrometry, microwave digestion HG-ICP-AES[41]
Quantity and mole ratio	Refining coefficient	/
	Mass fraction	Chromatography, UV-vis, atomic absorption spectrophotometry
Matter distribution	Uniformity	Online near infrared (NIR) detection[42]

Table 2 The spatial properties and its characterization techniques of CMMs

Spatial property	Index	Characterization technique
Scale	Imaging particle size	Optical microscope, electron microscope, transmission electron microscope, atomic force microscope (AFM)[43]
	Sieving particle size	Screening machine, aerosizer, capillary method, optical screening method[44]
	Spherical equivalent particle size	Coulter counter, photoresist particle counter, dynamic light scattering particle sizer[45], laser particle sizer/light scattering particle sizer, ectroacoustic spectrometer, X-ray gravity settler
	Specific surface area	N_2 adsorption method[46]
Morphology	Roundness/sphericity	Macro description method
	Space filling factor (looseness, firmness, irregularity index)	Mesoscopic description[47]
	Concavoconvex degree	Mesoscopic description
	Roughness	Mesoscopic description
	Fractal dimension	Micro description method[48]
Density	Bulk density, tap density	Powder physical property tester (PPPT), measuring cylinder
	True density	Pycnometer method, suspension method, true density tester[49]
	Porosity	N_2 adsorption method, mercury intrusion porosimetry

Table 3 The surface properties and its characterization techniques of CMMs

Surface property	Index	Characterization technique
Adsorptivity	Equilibrium moisture absorption rate (F^{∞})/half moisture absorption time ($t_{1/2}$)	Dynamic vapor sorption resolution (DVS resolution)[51], weighing method
	Critical relative humidity	DVS resolution, weighing method
Wettability	Contact angle (static/dynamic)	Contact angle measurement[52]
	Surface energy	Surface energy analyzer
	Wetting tension[53]	Meansofaluminium foil
Adhesivity	Adhesion strength	Minimum peeling force method, adhesion tester, AFM[54]
	Adhesion work	Minimum peeling force method and adhesion force, adhesion tester

一级动力学常数k等衍生指标, 各指标之间的关系见公式 (5) 和 (6)。一般情况下, 12 h内的吸湿时间时$kt\rightarrow 0$, 此时可省略高阶无穷小项, 吸湿呈线性增长且K_0为常数 (图7A)。吸湿速率曲线的二次拟合模型是一级动力学模型省略2阶以上的高阶无穷小项的特殊情况, 因此吸湿时间较短时该模型较为准确。

$$F = F^{\infty}\cdot(1 - e^{-kt}) \tag{3}$$

$$F = F^{\infty}\cdot[\,kt - \frac{1}{2!}(kt)^2 - \cdots - \frac{1}{n!}(-kt)^n] \tag{4}$$

$$K_0 = F^{\infty}\cdot k \tag{5}$$

$$t_{1/2} = \ln 2/k \tag{6}$$

动态表征技术与多维表征技术联合可增加二者的应用范围。首先, 吸湿性速率曲线是以时间 (t) 为参变量的动态表征方法, 参变量还可选择位移 (x)、温度 (T)、压力 (p)、物质的量 (n), 这5类基本参变量适用于描述任何性质指标的动态过程, 如润湿性[57]等动态表征 (图7B) 的参变量可选择时间、润湿剂的pH值等; 其次, 多维表征技术是选择多种指标从不同角度对CMMs进行描述, 所选择的衍生指标应具有普适性, 如F^{∞}及$t_{1/2}$由特殊曲线所推导, 却适用于任何类型的吸湿速率曲线的表征。具体地, 对于吸湿性及润湿性可形成按强弱、快慢的分类体系 (图7C、D)。在动态表征技术的基础上, 结合多个衍生指标即可构成多维表征技术, 从不同角度描述却能形成统一整体。

3.4 体性质评价指标及表征技术 CMMs的体性质是在力的作用下而反映的内在特性, 因此相应的表征技术以应力-应变关系, 即本构关系为核心依据, 相关的指标亦由本构关系所衍生 (表4)[58-62]。

目前, 主要运用传感技术获取本构关系, 如Gao等[60]运用质构仪对软材进行多次压缩获取本构关系, 根据导出的指标将软材分为5类; 多功能压片机等可获取CMMs的压缩曲线等属于本构关系范畴。由于CMMs的物质构成及空间构造复杂, 增加了对其体性质的表征难度, 而目前的表征技术不能满足复杂的物质构成及空间构造与体性质相关性研究的大样本需求。因此, 本课题组对目前利用应力及位移传感技术获取本构关系的方法进行了改进, 使之适用于粉末、软材等多种状态的CMMs体性质研究 (图8)。所改进的装置可根据需要更换适合的量程及精密度的位移传感器及压力传感器, 并灵活设置符合CMMs特点的压缩程序, 以获取其本构关系, 再结合开尔文体、马克斯威尔体等理论模型[63], 导出相应固体及半固体的压缩性、流变性的表征指标。

3.5 理化性质指标及表征技术 目前, 对CMMs理化性质的表征指标及表征技术研究相对成熟。CMMs理化性质的关键指标的确定依据了物理化学的基本原

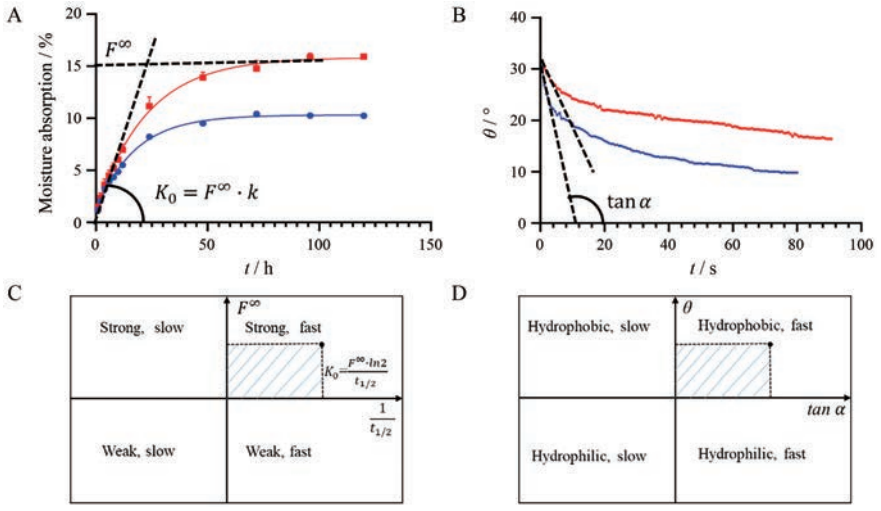

Figure 7 The multi-dimensional dynamic characterizing technique used for describing the surface properties of CMMs. A: Dynamic moisture absorption rate with time; B: Dynamic wetting contact angle with time; C: Two dimensional characterization of hygroscopicity; D: Two dimensional characterization of wettability

Table 4 The body properties and its characterization techniques of CMMs

Body property	Index	Characterization technique
Flowability	Angle of repose	PPPT, standard funnel method
	Carr index, Hausen ratio[58]	PPPT
	Velocity of flow	PPPT
	Cohesion	Jenike shear box, box flow factor meter
	Internal friction angle	Jenike shear box
	Apparent viscosity (powder)	Powder rheometer[59]
Compressibility	Elastic modulus, shear modulus	Texture analyzer (TA)[60], multifunctional tablet press, elastic modulus tester
	Yield pressure	TA, multifunctional tablet press
	Elastic coefficient of restitution	Collision method[61]
Rheology	Viscosity	Rheometer, capillary viscometer, falling ball viscometer, rotary viscometer
	Loss modulus	Dynamic mechanical property spectrometer
	Consistency	Consistency detector
	Chewiness	TA
	Plastic potential	Stress component partial derivative method [62]

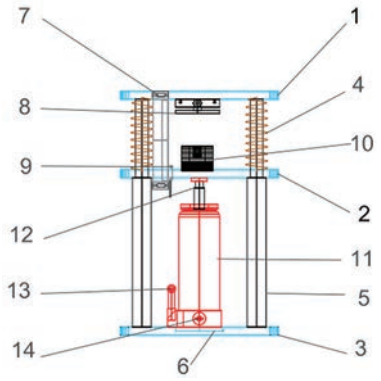

Figure 8 A testing device for getting constitutive relation of CMMs. 1: Top plate of compression support; 2: Middle plate of compression support; 3: Bottom plate of compression support; 4: Compression spring; 5: Pillar; 6: Groove; 7: End caps of grating ruler; 8: Pressure sensor; 9: Reading head of grating ruler; 10: Pressing die; 11: Electro hydraulic system; 12: Loading bar; 13: Pressure bar; 14: Pressure relief valve

理, 其中以多组分的化学热力学原理最为普遍, 在准确表征了CMMs物质构成的基础上, 可由其广度变量导出相关理化性质的指标, 见公式 (7)。

$$dX = \left(\frac{\partial X}{\partial T}\right)_{p,n} dT + \left(\frac{\partial X}{\partial p}\right)_{T,n} dp + \sum\left(\frac{\partial X}{\partial n_i}\right)_{T,p,n_j \neq i} dn_i \quad (7)$$

其中, X为任意广度变量, T、p分别为系统的温度及压力, n_i为任意成分的物质的量。

如果选择吉布斯自由能G为该广度变量, 则对n_i的偏导数为化学势μ_B, μ_B又是T、p、n_i的函数。总之, 不同CMMs具有不同的溶解性、渗透性、解离性和热学性, 是由于物质转移程度及平衡点不同而造成的差异[64], 相应的表征指标所依据的方法及原理为化学平衡、相平衡和电化学等规律, 目前对理化性质的表征技术也大多基于化学热力学或化学动力学方法 (表5)[65-70]。

Table 5 The physicochemical properties and its characterization techniques of CMMs

Physicochemical property	Index	Characterization technique
Solubility	Intrinsic solubility	Constant temperature stirring method, clarity detector[65]
	Equilibrium solubility	HPLC, UV spectrophotometry
	Solubility parameter	Swelling method, chemical group contribution calculation method
Permeability	Oil water partition coefficient	Shake flask UV spectrophotometry[66]
	Apparent permeability coefficient	Caco-2 cell model
Thermal properties	Glass transition temperature[67]	Differential scanning calorimetry(DSC), laser pulse instrument, thermometer
	Specific heat capacity	DSC, thermometer
	Thermal conductivity	Thermal conductivity tester
	Boiling point	Thermometer
Electromagnetic properties	ζ potential	Zeta potentiometry[68]
	Conductivity	Conductometer
Dissociative	pH	pH meter, acid-base titration, TLC pH method
	Dissociation constant[69]	Capillary electrophoresis, UV spectrophotometry, potentiometric titration
Structural chemistry	Molecular weight	High performance gel permeation chromatography, static light scattering, osmotic pressure method
	Molecular structure	Computer aided
	Crystalline form[70]	X-ray diffraction, infrared absorption spectroscopy, laser micro Raman spectroscopy, polarizing microscopy, melting point and microscopy method, differential thermal analysis, thermogravimetry, scanning tunneling microscopy, NMR, DSC

4 CMMs性质体系的应用及发展

CMMs的性质、指标及表征技术体系对中药剂型设计具有重要应用价值。首先根据CMMs的精制系数预测中药的载药剂量, 从而选择适合的剂型。根据CMMs物性体系中各性质之间的相关性可进行成型性设计, 如根据中药干浸膏粉末粒子的粒径、孔隙、形貌等空间构造性质与吸湿性、压缩性等体性质和面性质的相关性, 结合辅料改性技术及工艺改性技术制备具有一定空间构造性质的粒子, 可以解决CMMs的成型性问题[10]。此外, 中药制剂的功能设计也需要依据CMMs物性体系中各性质之间的相关性规律, 在确保成型性的前提下使中药制剂具备某种特殊的递释特性。通过原子包覆技术可改变CMMs表面性质以设计中药时控递释系统[71]; 再如通过微流控技术设计制备粒径、表面电荷及硬度不同的纳米粒, 具有不同的靶向性及生物效应等[72]。然而, CMMs的物性较为复杂, 相应的指标及表征技术仍在不断地发展, 新指标的产生需有理论依据, 其科学性还需实践考证。目前, 对CMMs性质的表示方法存在创新的空间, 如能将指标无量纲化、高维化、非线性化和概率化等可能会更合理地描述CMMs的性质, 再如应力状态的表征可采用二阶张量法以确定物料中某质点任何方向的应力状态等。因此, 掌握指标所依据的核心原理及方法才能在更高层次把握CMMs性质指标体系的扩充与发展。

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