•综述•

口溶膜制剂开发策略及质量评价

丛 容[1,2], 刘 浩[2*], 王 俊[2]

(1. 复旦大学药学院, 上海 201203; 2. 上海市食品药品检验研究院, 上海 201203)

摘要: 2025版《中华人民共和国药典》将膜剂定义为原料药物与适宜的成膜材料经加工制成的膜状制剂, 供口服或黏膜使用。其中, 口溶膜系指口溶膜即指在口腔中快速溶化起全身或局部作用的膜剂。口溶膜规避了口崩片所具有的易破碎、可能引发窒息等缺陷, 该剂型因剂量准确、方便携带、适用于老人、儿童或具有吞咽困难症状的患者, 目前受到了学术界与医药产业界的广泛关注。本文综述了口溶膜的优势及局限性、目前上市情况、适用药物活性成分、常用辅料、制备工艺和新兴的纳米颗粒技术, 同时针对剂型特点, 对其在溶出度、溶化时限、机械性能等方面的质量评价要求进行了重点阐述, 旨在帮助读者和研究人员对口溶膜的开发与评价建立起较为全面的认知。

关键词: 口溶膜; 口腔速溶膜; 新型口服给药; 处方工艺; 质量评价

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Development strategies and quality evaluation of orodispersible films

CONG Rong[1,2], LIU Hao[2*], WANG Jun[2]

(*1. College of Pharmacy, Fudan University, Shanghai 201203, China; 2. Shanghai Institute for Food and Drug Control, Shanghai 201203, China*)

Abstract: The 2025 edition of the Chinese Pharmacopoeia defines films as film-like preparations made by processing active pharmaceutical ingredients with suitable polymers, intended for oral or mucosal use. Among these, orodispersible films (ODFs) are specifically defined as films that rapidly dissolve in the oral cavity to exert systemic or local effects. ODFs circumvent the drawbacks associated with orally disintegrating tablets, such as fragility and the potential risk of choking. This dosage form has aroused significant interest among both academic world and the pharmaceutical industry due to its accurate dosing, portability, and suitability for elderly and pediatric patients or those with swallowing difficulties. This review summarizes the advantages and limitations of ODFs, their listing status, suitable active pharmaceutical ingredients, commonly used excipients, preparation techniques, and emerging nanoparticle technologies. Additionally, it emphasizes quality evaluation requirements—such as dissolution, disintegration time, and mechanical properties—tailored to the characteristics of this dosage form. The aim is to provide readers and researchers with a comprehensive understanding of the development and evaluation of ODFs.

Key words: orodispersible film; orally dissolving film; new oral drug delivery; formulation process; quality evaluation

吞咽是一个由三阶段 (口腔、咽部和食道) 组成的几乎同步摄取固体和/或液体食物的物理过程。虽然口服药物因其易于给药、便于长期使用、无创、高患者依从性而成为首选和广泛接受的给药方法, 但在进食前和吞咽困难等情况下, 患者经常面临吞咽药物的困难。例如有呕吐倾向、双相情感障碍、口腔癌和帕金森氏病的患者很难服用需吞咽的固体口服剂型[1]。

在我国老年人吞咽障碍总体患病率为38.7%, 其中养护机构的老年人占26.4%～32.5%。针对吞咽障碍患

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*通讯作者 Tel: 86-21-50798180, E-mail: liuhao1968@hotmail.com
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者的口服用药问题, 口腔崩解片发展成为传统片剂和胶囊制剂的替代品。尽管如此, 口崩片仍有其固有的缺点, 例如易吸湿、易破碎、类似“奶片”的咀嚼口感导致滥用, 运输取用时易破碎, 以及可能落入气管引发窒息[2]。

故需要一种可规避上述缺陷的药物剂型, 以减轻患者的服药困难。口溶膜 (orodispersible films, ODFs) 是一种轻薄、柔韧、邮票大小的聚合物薄膜。它不像传统固体剂型 (片剂或胶囊) 那样需要使用者咀嚼或喝水。当给药于舌头时可以立即水化, 迅速分散在口腔中, 与唾液一起自然吞咽通过胃肠道被吸收进入体循环, 或经黏膜吸收[3]。

本文拟从定义、特点、应用、制备方法、质量评价等方面对口溶膜这种剂型进行综述。

1　口溶膜剂型的定义和特点

《中华人民共和国药典》2025年版 (四部) 通则中膜剂系指原料药物与适宜的成膜材料经加工制成的膜状制剂, 供口服或黏膜用[4]。膜剂按使用部位不同可分为口用膜、阴道膜、眼用膜等。其中口用膜分为口溶膜、口颊膜、舌下膜和口腔贴膜4类, 表1中列举了4种口用膜的定义、代表药物和质量要求。在《欧洲药典》中, 口溶膜被定义为由适宜材料组成单层或多层在口腔中快速溶解的薄片[5]。而《美国药典》将口溶膜定义为在口腔内放置的薄片, 包含一个或多个含药或不含药层[6]。

口溶膜最初由Frederick Deadman于60年代初构思, 首次出现始于非医药产品, 即辉瑞公司推出的作为口腔清新膜的李斯德林 (Listerine)。目前全球已有多种口溶膜产品上市, 详见表2。

由表2可看出, 目前口溶膜制剂的用途多集中在精神分裂和神经系统紊乱疾病治疗领域, 在止吐、性功能障碍、过敏、降糖等领域的应用也较为广泛。

口溶膜的优点包括: ① 体积小、质量轻、便于携

Table 1　Definitions, quality requirements, and representative drugs of four types of oral films

Type	Definition	Quality requirement	Representative drug
Orodispersible films	Refers to a film that rapidly dissolves in the oral cavity	Disintegration time testing should be performed, for orodispersible films made from poorly soluble drugs, dissolution testing should be conducted	Ondansetron; olanzapine; montelukast
Sublingual films	Refers to a film that is placed under the tongue, rapidly dissolves, and allows the drug to be absorbed through the sublingual mucosa to produce systemic effects	The active pharmaceutical ingredient in sublingual films should be readily absorbable directly, and sublingual films should undergo dissolution testing	Dexmedetomidine hydrochloride; apomorphine hydrochloride
Buccal films	Refers to a film that is attached to the oral cavity and exerts systemic effects after being absorbed through the mucosa	Buccal films should possess adequate adhesiveness and undergo dissolution or release testing	Buprenorphine hydrochloride; naloxone hydrochloride
Oral patch	Refers to a film that adheres to the oral cavity and exerts local effects	Oral patches should possess adequate adhesiveness	Dexamethasone; ornidazole

Table 2　Global marketed orodispersible film products. USA: United States of America; JP: Japan; EU: European Union; OD: Oral dispersible

Aera	Drug name	Specification/mg	Indication	Time
USA	Ketoprofen oral soluble film	12.5	Rheumatism, arthritis, *etc*.	2009
	Clobazam oral film	5, 10, 20	Pediatric epilepsy	2018
	Ondansetron oral soluble film	4, 8	Chemotherapy and postoperative vomiting	2010
	Riluzole oral film	50	Amyotrophic lateral sclerosis	2019
JP	Voglibose OD film	0.2, 0.3	Postprandial hyperglycemia in diabetes	2006
	Loratadine OD film	10	Allergies	2011
	Donepezil hydrochloride OD film	3, 5, 10	Alzheimer's disease	2011
	Olopatadine hydrochloride OD film	2.5, 5	Allergic rhinitis, urticaria	2012
	Amlodipine OD film	2.5, 5	Hypertension	2013
	Zolpidem tartrate OD film	5, 10	Insomnia, sleep disorders	2012
	Viagra OD film	20, 25, 30	Erectile dysfunction	2016
	Nalfurafine hydrochloride OD film	0.002 5	Chronic kidney disease-associated pruritus	2018
EU	Ondansetron orodispersible film	4, 8	Chemotherapy and postoperative vomiting	2011
	Olanzapine Renantos orodispersible film	5, 10, 15, 20	Schizophrenia	2010
	Risperidone SandozSchmelz film	0.5, 1, 2, 3	Schizophrenia	2013
	Rizatriptan benzoate film	5, 10	Migraine	2015
	Donepezil hydrochloride SandozSchmelz film	5, 10	Alzheimer's disease	2015
China	Olanzapine oral soluble film	5, 10	Schizophrenia	2020
	Montelukast sodium oral soluble film	4, 5	Asthma, allergic rhinitis	2021
	Ondansetron oral soluble pellicles	4, 8	Chemotherapy and postoperative vomiting	2022
	Memantine hydrochloride oral soluble film	5, 10	Alzheimer's disease	2022
	Tedalafil oral soluble film	5, 10	Erectile dysfunction	2022

带; ② 在口腔中快速分散, 无需用水吞服, 无窒息风险; ③ 可以改善患者依从性, 适用于老人、儿童[7]和精神病患者, 能有效解决患者吐药、藏药等情况; ④ 口腔黏膜血管丰富, 酶活性低, 药物可通过口腔黏膜快速渗透、绕过胃中的酸水解和肝脏首过效应, 提高生物利用度[8]; ⑤ 口溶膜可以通过负载活性成分纳米颗粒或者微晶的形式提高药物的生物利用度[9]。然而, 口溶膜同时也具有自身的局限性和缺点: ① 药物负载量低[10], 只适用于活性强的低剂量药物; ② 表面积大, 易受水分、光照的影响, 影响药物稳定性; ③ 口感差, 需要进行掩味处理; ④ 制成改性释放制剂如缓控释制剂的能力有限。

2 口溶膜的开发策略

2.1 药物活性成分的选择

在口溶膜制剂中, 原料药通常以1%～30% (*w*/*w*)的比例加入成膜材料和其他辅料中。已上市口溶膜的药物包括抗过敏药和抗组胺药 (如氯雷他定、孟鲁司特等)、抗炎药和镇痛药 (如苯甲酸利扎曲普坦)、止吐药 (如昂丹司琼)、抗精神病药 (如利培酮、奥氮平、阿立哌唑)、生殖系统用药 (如他达拉非、西地那非等)、心血管药物 (如氨氯地平)、神经系统药物 (如盐酸纳呋拉啡、盐酸多奈哌齐、酒石酸唑吡坦)、维生素、营养补充剂等 (表2)[11]。

由于口腔内空间有限, 为不影响患者依从性, 口溶膜的尺寸一般不超过2 cm × 2 cm, 厚度约为50～500 μm[12]。因膜片尺寸限制了原料药的负载量, 口溶膜主要由强效低剂量的BCS I类药物制成[13,14]。增加药物载量可能会导致药物在溶剂蒸发后和/或储存期间在口溶膜中结晶, 从而影响药品的机械强度和溶解速度。如果添加的药物超过其溶解度, 则该药物将以微粒形式存在, 导致口溶膜的表面具有沙砾感[15]。目前许多研究致力于通过纳米悬浮液、微粉、纳米晶体等技术提高口溶膜的药物载量, 扩大其应用范围。

2.2 口溶膜的处方组成

口溶膜配方中的常见成分包括药物活性成分 (active pharmaceutical ingredient, API)、成膜材料、增塑剂, 以及必要时添加的矫味剂、着色剂、唾液刺激剂、稳定剂、表面活性剂和溶剂。表3[13,16]列举了常用的口溶膜辅料、处方比例及它们的作用。

在口溶膜的组成中, 成膜材料是其骨架部分, 目前用于生产口溶膜的成膜材料多为亲水性聚合物, 包含天然和人工合成等不同来源, 例如天然来源的淀粉、壳聚糖、明胶、果胶、透明质酸等, 以及人工合成的羟丙基甲基纤维素 (hydroxypropyl methyl cellulose, HPMC)、羧甲基纤维素 (carboxymethyl cellulose, CMC)、聚乙烯醇 (polyvinyl alcohol, PVA) 等。不同的聚合物具有不同的特性, 例如淀粉成本低、来源广泛, 但天然淀粉结晶度较高, 需通过化学/物理改性降低其结晶度, 改善薄膜均匀性[17]; 壳聚糖具有良好的生物黏附性和生物相容性, 仅溶于弱酸性溶液, 低分子质量下可快速崩解[18]; 聚乙烯醇化学稳定性好、机械强度高、耐高温, 但较易吸湿[19]。正确选择成膜材料对口溶膜的性能至关重要, 需根据目标产品在释放率、黏着性、机械性能、稳定性等方面的要求进行选择[20,21]。有时单一的载体材料不足以满足需求, 可使用两种成膜材料混合或改性后使用[22]。明胶具有良好的生物相容性和成膜能力, 但单一的明胶亲水性较差, Garcia等[23]在制备针叶粉

Table 3 Excipients and their roles in ODFs formulation. ODFs: Orodispersible films

Excipient	Concentration	Role	Example
Polymers	40%−60%	Providing film-forming properties and structural integrity to the film, while also improving its elasticity, dissolution behavior, and mechanical strength	Modified starches, hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose, gelatin, hydroxypropyl cellulose, hydroxyethyl cellulose, pullulan, locust bean gum, xanthan gum, guar gum, polyvinyl pyrrolidone, crosslinked polyvinylpyrrolidone, polyvinyl alcohol, polyethylene oxide, maltodextrins
Plasticizers	0%−20%	Providing elongation, tensile strength and plasticity; improve absorption and solubility, preventing crushing, and reducing brittleness and glass transition temperature	Glycerine, mannitol, propylene glycol, sorbitol, polyethylene glycol, sucrose, oleic acid, citric acid, phthalic acid
Taste maskers	0%−10%	Masking nauseating and bitter tastes to improve patient compliance	Glucose, fructose, sucrose, sucralose, maltose, sorbitol, stevioside sodium, ribose, cyclamate salts, aspartame, sylose, ribose, maltodextrin, cyclamate, hydroxypropyl-*β*-cyclodextrin
Coloring agents	0%−5%	Enhancing their appearance, differentiating between different ODFs	Titanium dioxide, indigo carmine, brilliant blue dyes, fast green, tartrazine dyes
Stabilizing agents	0%−5%	Maintaining structural integrity, preventing degradation, and ensuring the desired properties of the films	Hydroxypropyl cellulose, polyvinyl pyrrolidone, xanthan gum, sodium alginate, carrageenan, gelatin, sorbitol
Surfactants	0%−5%	Shortening the disintegration time of ODFs, enhancing wettability	Poloxamer, sodium lauryl sulfate, polysorbate, laureth-A, sucrose esters, dodecyl maltoside, cetyl trimethylammonium bromide
Saliva stimulants	0%−5%	Increasing saliva production in the mouth	Ascorbic acid, citric acid, tartaric acid, malic acid, lactic acid

口溶膜时, 在明胶中加入了预胶化淀粉, 增加了膜的亲水性, 缩短了膜的崩解时间。HPMC作为半合成纤维素醚, 通过醚化修饰改善了溶解性、成膜性和稳定性, 有多种黏度、取代度可供选择, 具有多功能性, 是药物递送的常用辅料之一。Joshone等[24]使用阿拉伯胶、瓜尔胶、罗望子胶等天然胶对HPMC进行改性以提升其机械性能和药物递送特性, 替代增塑剂的使用, 结果显示, 0.2%阿拉伯胶改性的HPMC膜具有最优的机械性能和崩解时间。

增塑剂是添加到成膜材料溶液中以提高口溶膜塑性和柔韧性的低分子质量辅料, 增塑剂的加入可降低聚合物从玻璃态向橡胶态的玻璃化转变温度, 在应用于非水溶剂系统时将聚合物的玻璃化转变温度降低到40～60 ℃, 用于水溶剂系统时则低于75 ℃。增塑剂的选择需重点考察以下3个方面: 相容性、有效性、耐用性。以亲水性纤维素基聚合物作为成膜材料可以有效地与含有极性羟基的增塑剂 (如聚乙二醇、丙二醇、甘油、多元醇等) 结合, 相反, 亲水性较差的纤维素聚合物可以用柠檬酸三乙酯和邻苯二甲酸酯塑化。甘油是最常用的增塑剂, 与淀粉、明胶、HPMC、PVA等成膜材料相容性良好, 可降低膜片脆性, 增加其延展性和柔韧性[25]。另外, 也有研究指出增塑剂的用量与成膜材料的比例对口溶膜的机械性能等关键质量属性具有显著的影响[26]。一般而言, 在聚合物干重的16%～20% (*w*/*w*) 之间的增塑剂用量不会使薄膜出现不期望的物理、机械和热性能。

其他在配方中占比较少的辅料也对口溶膜的性能有所影响。例如, 表面活性剂 (泊洛沙姆、聚山梨酯、十二烷基硫酸钠等) 一般用于增强口溶膜的溶解度和润湿性, 使活性成分可以更快释放。矫味剂 (蔗糖、麦芽糖、甘露醇等) 用于掩盖原料药的难闻气味和苦味, 提升口感和患者依从性。唾液刺激剂 (苹果酸、柠檬酸等) 可以通过刺激口腔唾液的产生促进口腔膜的分解, 对于那些患有口干症或难以产生足够唾液的人有益。

2.3　口溶膜的制备方法

目前用于制备口溶膜的主要方法包括溶剂铸造技术、静电纺丝、热熔挤压和可用于个性化给药的新兴打印技术, 表4中列举了部分常用的制备方法及其各自的工艺流程和优缺点。

溶剂铸造法是商业化生产口溶膜时应用最普遍的方法[27], 具有工艺成熟、成本低、适用性广等优势。然而, 膜片的厚度通过浇铸液的用量控制, 局部的厚薄差异难以避免[28], 在更大尺寸上 (单批生产超20 cm × 30 cm) 控制膜片的完整性和厚度均匀性对生产设备的要求较高[29], 扩大生产规模需对现有涂布设备和干燥装置进

Table 4　Processses and characteristics of the preparation methods of ODFs. API (s): Active pharmaceutical ingredient (s)

Method	Process	Advantage	Disadvantage
Solvent casting method	Excipients and the API are dissolved in an aqueous solvent. The solution may be stirred and/or heated to complete solubilization. Once a homogeneous solution is obtained, it is cast onto a substrate. After the solvent evaporates in a drying process, the resulting solid film is cut to the desired size	It features low cost and simplicity and is suitable for heat-sensitive and light-sensitive active pharmaceutical ingredients	Local variations of thickness are generally unavoidable, and there are difficulties in scaling up along with the possible presence of residual solvents
Hot melt extrusion	The API-excipient blend is fed into an extruder, where it is heated and subjected to shear forces, forming a homogeneous melt. This melt is then forced through a shaping die. The resulting extrudate is cooled and cut to yield the final product	The process is solvent-free, continuous, and scalable, and it can improve the water solubility of hydrophobic drugs through the formation of solid dispersions	Not suitable for heat-sensitive drugs
Electrospinning technology	A high voltage is applied to create an electric field, which acts on the polymer solution at the capillary tip to form a Taylor cone. As a jet is ejected from the cone and elongates, the solvent evaporates. The resulting fibers are deposited onto a grounded collector, forming a thin film	The process can produce films with a high surface area and fast dissolution, and it allows for flexible adjustment of fiber diameter, morphology, and alignment, thus enabling the development of personalized medicine approaches	The process is complicated and costly, and there are material limitations. Moreover, the films produced have poor extensibility and low mechanical strength
Printing technology	2D printing: A drug-containing ink is printed in a controlled manner onto a suitable, edible substrate. The printed substrate subsequently undergoes drying and packaging processes 3D printing: A design is developed using computer-aided design software, or a direct three-dimensional scan of the product is obtained. The digital model is then used to guide the print head along the required axes to fabricate the product layer by layer	It ensures an even distribution of APIs, which enhances the consistency and efficacy of the product. It has precise control over drug dosage, as well as film size and shape, allowing for the development of personalized medicine	It has a high initial cost, shows limited material compatibility, and is slower in the printing process when compared to traditional methods

行升级, 提高了生产成本, 对低附加值产品而言回报率较低。热熔挤出法允许难溶性药物以无定型分散在成膜材料中, 提高难溶性载药量, 且可在一个步骤中获得挤出物, 减少了操作步骤实现连续性生产, 且无残留溶剂影响, 适合工业化扩大生产[30]。但热敏性材料和药物易在熔融过程中降解, 限制了该方法的应用范围。静电纺丝技术和打印技术可实现个性化给药和精准医疗, 契合“患者为中心”的理念, 其中, 静电纺丝技术通过制备极高比表面积的纳米纤维膜, 加速了药物溶出, 提高了难溶性药物的生物利用度[31]。而打印技术具有显著的灵活性, 通过设计可精确控制药物剂量和膜片内部结构[32]。但由于两种方法的生产设备复杂、设计参数众多且对材料要求较高[33], 目前仍局限于实验室小规模制备, 扩大生产需对生产设备进行革新, 开发出多喷头协同控制技术和高速打印技术。

将水溶性差的原料药制成口溶膜是口溶膜药物开发的一个挑战。将自微乳化系统引入口溶膜中是为应对这一挑战开发的创新技术[34], 然而, 制备过程中需引入大量的油相, 影响了膜片的长期稳定性。

目前, 在上述制备方法中引入纳米颗粒是将难溶或低溶解度药物开发成口溶膜的有效策略, 具有多方面优势, 包括增强药物的溶解性和渗透性、制成缓控释剂型、靶向给药、掩盖不良气味、提高储存和运输过程中的稳定性[35]。纳米颗粒可通过不同技术制备, 包括自上而下的干湿研磨和高压匀质及自下而上的抗溶剂沉淀法、乳化法和声波沉淀法等[36]。Nguyen 等[37]通过单因素设计优化了纳米颗粒的制备条件, 最终选择了0.6%羟丙甲纤维素 E6、0.1%十二烷基硫酸钠、药物质量浓度为 60 mg·mL^{-1}、溶剂/反溶剂体积比为 1/100 的条件, 将 BCS II 类药物氯雷他定制成纳米颗粒载入口溶膜。Abdelhameed 等[38]使用甲醇和含聚乙烯吡咯烷酮 K25 的蒸馏水作为溶剂和反溶剂采用反溶剂沉淀法制成盐酸非索非那定纳米混悬液, 再将其通过溶剂铸造法制成口溶膜, 与市售 Telfast 药片相比, 优化后的盐酸非索非那定口溶膜在家兔体内的生物利用度提升了4.15 倍。在另一项研究中, 研究人员选择了两种难溶性药物非诺贝特和萘普生[39], 采用 5 种不同的策略将其嵌入口溶膜中——无定型固体分散体、脂质纳米混悬液、脂质纳米乳、药物纳米颗粒和微粉化药物。经检测, 无定型固体分散体和载药脂质纳米乳所制得的薄膜具有较快的溶出速度。

尽管负载纳米颗粒在提升口溶膜的性能上表现出很大潜力, 但仍存在纳米颗粒毒性、扩大规模生产和质量控制等方面的障碍, 在开发立项时必须慎重考虑配方选择, 以确保用药的安全性和有效性。

2.4 口溶膜的质量控制

口溶膜在提高患者依从性、增强药物疗效, 实现个体化治疗等方面具有巨大的潜力, 同时, 不同的制备方法相继涌现, 口溶膜的性能也获得了极大的改善。然而目前各国现行药典均未收载针对口溶膜制剂的质量评价标准,《中华人民共和国药典》2025 版膜剂通则 1025[4]中规定膜剂应进行重量差异 (进行含量均匀度检查的膜剂, 一般不再进行重量差异的检查) 和微生物限度检查 (照非无菌产品微生物限度检查: 微生物计数法、控制菌检查法和非无菌药品微生物限度标准检查)。对比 2020 版《中华人民共和国药典》, 2025 版《中华人民共和国药典》中对膜剂在生产与贮藏期间的要求进行了修订, 新增了口感、口腔黏膜刺激性、机械性能、溶出度、水分、含量均匀度及残留溶剂方面的要求, 同时口溶膜定义中还要求检查溶化时限。针对口溶膜剂型的特点, 除常规质量属性外, 应对以下几种项目进行重点论述。

2.4.1 外观 《中华人民共和国药典》2025 版膜剂通则中规定, 膜剂外观应完整光洁、厚度一致、色泽均匀、无明显气泡。药物在生产和贮藏期间结晶、药物与成膜材料之间的相互作用可能导致薄膜表面粗糙、易破碎和透明度降低[40], 同时影响机械性能和溶出。建议在贮藏前后分别观察膜片内晶体形态和分布, 以评价其稳定性。形态评价可以通过以下几种技术进行: 显微镜、光学偏振、近红外光谱、透射电子显微镜、X 射线衍射或扫描电子显微镜。

膜片的厚度对膜片的机械性能和适口性也具有一定影响, 口溶膜厚度可使用微米螺旋规进行测定, 即将膜片放置于螺旋规的中心轴, 并在中心和四角共计 5 个测量点处测量厚度, 标准差越小提示膜片厚度均一性越好。

2.4.2 水分 口溶膜中适量的水分可以保证口溶膜的柔韧性并减弱膜剂脆性[41], 但同时, 过量的水分会改变原料药的机械性能, 增加其黏性、微生物负荷和物理化学稳定性[42,43], 应根据研究确定适宜的上下限范围, 一般而言, 小于处方量 15% 的水分含量不会对口溶膜的生产、包装、使用造成困扰[44]。水分测定通常使用热重法、红外光天平或卡尔费休氏滴定法来获得。在某些情况下, 热重分析有助于确定基质中含有的水分类型, 重量差异易于量化, 并与薄膜脱水、低沸点化合物蒸发或热降解成分[45]进行相关。

2.4.3 口感 2025 版《中华人民共和国药典》要求口用膜应口感良好, 对口腔黏膜无刺激性。口溶膜直接在口腔中分解, 较好的适口性可以提升患者依从性。考虑到薄膜重量小, 配方空间有限, 所以多选择掩味策

略减弱苦味和不良气味, 例如, 使用HP-β-CD形成包合物[46]、味觉掩蔽微颗粒[47]、介孔二氧化硅纳米颗粒[48]、离子交换树脂络合[49]等技术掩盖原料药的苦味、提升口感。味觉掩蔽技术的有效性可通过体外电子舌或体内试验进行评价。前者使用带有多通道阵列的味觉传感器来模拟人类舌头味蕾, 这些传感器通常被称为电子舌 (e-tongue, ET)[50]。与人体模型相比, 由于快速、简单、相对较低的成本和风险, 电子舌系统在制药和食品领域越来越普及[51,52]。然而对于复杂的混合物, 电子舌难以区分不同的化学味道。因此, 适口性评价一般采用健康成年人作为受试者的人群口尝试验[53]。然而, 儿童的味觉偏好与成人不同, 因此在生产儿科用药时, 这种方式也存在局限性。

除味觉外, 口溶膜表面的酸碱度也影响其适口性, 口腔的pH值在5.5～7.4内, 过酸或过碱的口溶膜会对口腔黏膜产生刺激性, 适宜的pH值为6.0～7.5。由于不能直接测定干膜的pH值, 所以首先将膜溶解在2 mL蒸馏水中, 再将pH计的电极置于溶液表面, 10 min后记录读数, 以使测得值稳定[54]。

2.4.4　机械性能　口溶膜应具有适宜的机械性能, 以避免在生产、包装、运输、使用过程中发生损坏。评价口溶膜机械性能的指标包括拉伸性能、耐折度、黏性等, 建议根据实际应用途径和口溶膜特点建立评价方法。

口溶膜的拉伸性能可使用拉力测试仪或质构分析仪, 通过绘制应力–应变曲线进行计算并推断出以下参数, 用于评价口溶膜的机械性能: ① 抗拉强度是口溶膜在断裂前对施加力的反作用力, 或者是口溶膜试样断裂时施加的最大应力, 由断裂时最大力 (F_{max}) 除以口溶膜初始截面积计算, 单位MPa[55]; ② 杨氏模量 (Young's modulus) 是对口溶膜刚度的度量。它由应力–应变曲线线性部分的斜率进行计算, 杨氏模量 = 应力σ/应变ε, 硬脆的膜片一般具有较高的抗拉强度和较高的杨氏模量[56]; ③ 断裂伸长率: 也称为断裂伸长率或断裂应变, 它是一种测量材料在断裂或断裂之前所经历的变形量的方法。断裂伸长率 = $[(L - L_0)/L_0] \times 100\%$[57], 其中, L为口溶膜断裂时长度, L_0为初始长度, $(L - L_0)$为变形量。

耐折度又称柔韧性, 表征的是工业生产中薄膜卷筒成形或展开过程中及在患者使用过程中承受弯曲而不断裂的性能。ODFs耐折度是通过将薄膜在同一位置以180°角度反复折叠直至薄膜出现裂纹来确定的, 将薄膜折叠不断裂的次数计为耐折度值。一般而言, ≥ 300次折叠表示薄膜具有极佳的耐折度[58]。

黏性是指在低接触压力下试样与另一种材料表面黏结的牢固性。太黏稠的口溶膜在给药过程中可能难以脱离包装材料并在放入口腔前粘在患者的手指上。口溶膜的黏性可分别通过拇指黏性试验和探针黏性试验进行定性和定量评价。前者通过多次改变拇指与膜片接触的压力和时间, 记录不同条件下拇指与ODFs分离难度, 分析薄膜与拇指黏合的容易程度、速度和强度以评价口溶膜的黏性[59]。后者通过测定探针尖端与设定尺寸的膜片分离所需的力, 除以探针表面积求得最大剥离应力对黏性进行表征[43]。

2.4.5　溶化时限　现行《中华人民共和国药典》的膜剂通则项下仅要求口溶膜进行溶化时限检查, 但并未对溶化时限试验的相关要求进行规定,《欧洲药典》中也仅要求ODF“快速分散”, 但没有明确体内外的最长可接受时间。口溶膜若在较长时间内无法完全溶化, 未溶解部分可能产生窒息风险[60], 理想的溶化时限应限制在30 s之内。溶化时限测定常用崩解仪法, 采用合适的方法固定膜剂样品, 记录膜片完全溶化并通过筛网的时间。经改良的方法包括悬挂重物法、框架法、滴法和培养皿法等[61], 但仍存在终点模糊、操作复杂、无法模拟药物真实使用环境等问题。部分企业参考了口崩片的检查方法和限度, 如采用900 mL水或磷酸缓冲液作为介质, 但与口腔内的实际使用环境相差较大。建议建立检查方法时应模拟口腔实际环境, 考虑唾液体积、舌头机械力, 使用人工唾液作为介质。例如, 在一项研究中, Ouda等[62]将制得的口溶膜放置于装有10 mL模拟唾液液 (pH 6.4) 烧杯中, 以10 r·min^{-1}的速度进行搅拌温度保持在37 ± 0.5 ℃, 以膜片破碎为终点。

2.4.6　溶出度　口溶膜最主要的特性即在口腔中迅速释放药物, 而溶出度是评估这一特性的重要工具。同时, 溶出度也在预测口溶膜体内性能、适口性评价、生物等效性豁免申请等方面具有突出作用[63]。Koland等[64]评价了不同聚乙烯吡咯烷酮K30用量的盐酸昂丹司琼口溶膜的体外释放谱和体内吸收谱, 建立了良好的体内外相关性, 显示了体外溶出/释放试验在预测薄膜剂型在活体内的性能方面的潜在应用。美国上市了两种规格的盐酸昂丹司琼口溶膜, 仅8 mg规格与参比制剂口崩片进行了生物等效性试验, 4 mg规格仅与8 mg规格进行了溶出度的比较, FDA认为, 溶出度数据足以证明这两种产品剂量成比例, 并批准了生物豁免[65]。

在片剂、胶囊剂等传统固体制剂的药物溶出试验中, 因为药物经吞咽服用, 与口腔接触时间短暂, 一般不会将口腔作为药物溶出的部位。而口溶膜需要与口腔充分接触, 为得到准确的溶出数据, 用于口溶膜的溶出试验方法需要模拟口腔生理条件, 因此, 在溶出试验装置、溶出介质、介质体积、介质流速、搅拌速度等方面有别于常规溶出方法。目前口溶膜的溶出度缺乏统一

Table 5 Apparatus and method of dissolution testing for oral soluble films marketed in the USA and JP. HCl: Hydrogen chloride

Aera	Drug name	Apparatus	Speed/r·min^{-1}	Medium	Ref
USA	Ketoprofen	Paddle	50	pH 7.2 (phosphate buffer)	[69]
	Ondansetron	Paddle over disk	50	0.1 mol·L^{-1} HCl	[65]
	Clobazam	Paddle over disk	75	0.1 mol·L^{-1} HCl	[70]
	Riluzole	Basket	50	0.1 mol·L^{-1} HCl	[71]
JP	Olopatadine hydrochloride	Paddle	50	pH 6.8 (2nd fluid for disintegration test)	[72]
	Ondansetron hydrochloride	Paddle (using sinking assembly)	50	H_2O	[73]
	Donepezil hydrochloride	Paddle	50	pH 6.8 (2nd fluid for disintegration test)	[74]
	Loratadine	Paddle	50	pH 1.2 (1st fluid for dissolution test)	[75]

的质量评价方法,《中华人民共和国药典》2025版中相关的技术指导原则尚为空白。根据CDE于2025年7月的《化学药品口溶膜剂药学研究技术指导原则 (试行)》[66], 溶出行为及溶出度应基于药物的理化性质及制剂的特性, 参考《普通口服固体制剂溶出度试验技术指导原则》[67]等建立考察方法, 必要时可选用流通池法、桨碟法等, 并对方法的区分力进行考察, 选择一种方法订入质量标准。

Zhang等[68]对国外口溶膜溶出度考察方法进行了总结, 美国对上市口溶膜的溶出度评价多采用篮法、桨法、桨碟法, 而日本上市的4种口溶膜都采用桨法测定溶出度, 具体汇总于表5[65,69-75]。这些药典标准装置即便进行了调整, 仍存在滞留体积大, 滞留时间短, 因膜片漂浮或黏附于溶出装置导致试验方法重现性差及预测药物体内生物利用度较差等缺陷。

近年来, 针对口溶膜的溶出度提出了许多改良方法, 主要关注以下两点: ① 试验条件模拟口腔生理环境; ② 使用合适的方式防止膜片漂浮。Speer等[76]使用3D打印技术开发了一种膜片支架, 以无水茶碱为原料药制备了不同释放特性的口溶膜, 使用人工唾液、胃液、肠液作为溶出介质, 考察方法的区分力。Krampe等[77]在桨碟法中引入了压盖过滤装置, 模拟舌头机械力、小液体体积、唾液流速等口腔生理条件, 对酮洛芬口溶膜进行了溶出度评价。Xia等[78]引入了垂直样品池设计和合适的筛网作为膜支架, 与小杯法进行对比, 该方法具有更小的死体积、可以灵活调节介质流速、无对流搅拌等优势。He等[79]采用Franz扩散池装置和UV/Vis成像方法研究沙奎那韦口腔膜的释放, 两种方法的结合为药物释放研究提供了有益的信息。McCarthy等[80]比较了3种不同的方法 (桨叶法、流通池法和转移模型), 并发现使用流通池结合生物相关介质 (模拟胃液和禁食状态模拟肠液) 的转移模型方法适合预测体内生物利用度。Li等[81]基于流通池原理开发了膜剂用漏槽式溶出装置对盐酸格拉司琼口溶膜、他达拉非口溶膜、马来酸阿塞那平舌下膜、甲磺酸雷沙吉兰舌下膜的溶出度进行测定, 结果表明, 将溶出介质以滤芯分散, 将膜剂用滤网固定并增强密封性的溶出池设计可实现具有普适性的溶出检测功能。

此外, 由于口溶膜快速溶解的特性, 在线紫外光谱光纤传感器系统[82]也受到广泛关注, 以提供可靠的溶出曲线, 克服了传统采样程序滞后的缺陷。

3 总结与展望

综上所述, 口溶膜是个体化给药领域中一种便携且以患者为中心的药物剂型。在有特殊需要的人群 (例如吞咽困难、精神疾病、老年或儿童患者) 中, 它们在获得患者依从性方面的巨大优势。该剂型是施用于治疗心血管系统、中枢神经系统疾病等少量强效药物的重要选择。截至目前, 国内已有6个口溶膜品种上市, 4家药物生产企业共获17个批准文号。口溶膜开发策略的不断进展, 例如引入纳米颗粒改善药物释放特性、扩大适用于该剂型的原料药范围、提高贮藏运输稳定性, 为口溶膜剂的应用开辟了更广阔的赛道。除化学药以外, 在国内外的研究中, 作者也可以查阅到口溶膜被用于负载中草药提取物[83]、益生菌[84]、疫苗[85]等成分的例子, 提示为该剂型新的开发方向。但同时也需注意到研发过程中尚存在的难点, 例如掩味技术优化、成膜材料和增塑剂的筛选、规模化扩大生产、合理质量控制等方面的挑战仍需要研究人员的不断探索寻求解决方案。

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