Patient Preference and Adherence

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REVIEW

Patient Acceptability and Preferences for Solid Oral Dosage Form Drug Product Attributes: A Scoping Review

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Background: There is no consistent framework for patient-centric drug product design, despite the common understanding that drug product acceptability and preferences influence adherence and, therefore, drug product effectiveness. The aim of this review was to assess current understanding of patient acceptability and preferences for solid oral dosage form (SODF) drug product attributes, and the potential impact of these attributes on patient behaviors and outcomes.

Patients and Methods: A scoping review was conducted. Embase, Ovid MEDLINE®, and PubMed® were searched for full-text articles published between January 2013 and May 2023. Following screening and assessment against predefined inclusion criteria, data were analyzed thematically.

Results: Nineteen studies were included. Four overarching domains of drug product attributes were identified and summarized in a framework: appearance, swallowability, palatability, and handling. Each domain was informed by specific drug product attributes: texture, form, size, shape, color, marking, taste, mouthfeel, and smell. The most frequently studied domains were swallowability and appearance, while the most studied attributes were size, shape, and texture. Smell, marking, and mouthfeel were the least studied attributes. Texture intersected all domains, while form, shape, and size intersected appearance, swallowability, and handling. Swallowability and size appeared to be the key domain and attribute, respectively, to consider when designing drug products. Few studies explored the impact of drug product attributes on behaviors and outcomes.

Conclusion: While existing studies of drug product attributes have focused on appearance and swallowability, this review highlighted the importance of two less well-understood domains—palatability and handling—in understanding patients' acceptability and preferences for SODF drug products. The framework provides a tool to facilitate patient-centric design of drug products, organizing and categorizing physical drug product attributes into four overarching domains (appearance, swallowability, palatability, and handling), encouraging researchers to comprehensively assess the impact of drug product attributes on patient acceptability, preferences, and outcomes.

Plain Language Summary: Medicines come in a variety of types and forms. These include tablets and capsules. Factors, such as the size and shape of tablets, can affect how people take medicines. However, patients are rarely involved in designing the medicines that they take. In this study, researchers summarized 19 studies published between 2013 and 2023. They wanted to understand how different factors, like size and shape, affect patients' preferences, ability, and willingness to take medicines. Researchers focused on the "physical" aspects of medicines and found 4 common themes: 1) what they look like (appearance), 2) how easy they are to swallow (swallowability), 3) how they taste and feel in the mouth (palatability), and 4) how easy they are to handle (handling). Eight factors were also found: color, markings, shape, size, smell, taste, texture, and how a medicine feels in the mouth (mouthfeel). Most studies focused on what medicines look like and how easy they are to swallow. The factors that researchers mostly looked at were the size, shape, and texture of medicines. The design of medicines can impact patients of different ages, though there may be specific needs for certain groups of patients, including children, older adults, and people with certain diseases. Patient input should become a part of future medicines design to ensure their acceptability.

Keywords: preference, acceptability, formulation, drug product attributes, drug product design

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Introduction

There is increasing recognition and desire to shift from drug-centric to patient-centric design models,[1,2] whereby the comprehensive needs of patients are identified and inform drug product design.[3–6] This has been exemplified by the Innovative Medicines Initiative-PREFER project, which has focused on integrating patient preferences throughout the medical product lifecycle.[7] Patient acceptability and preferences are often explored during the peri- and postlaunch periods; however, they are seldom studied during early and preclinical drug development, and few examples are reported in the literature.[8] Moreover, there is increasing recognition that nonadherence, medication errors, and unsafe actions (eg, crushing or scoring) could be minimized or avoided by patient-centric drug product design.[4,9,10]

In the context of patient-centered design of drug products, patient acceptability describes the ability and willingness of patients to administer a drug product as intended or authorized by a prescribing health care professional (HCP).[11–14] Patient preference is defined as

> qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ from alternative health interventions accounting for patients' "willingness and unwillingness to accept the identified risks" (p. 6)[15]

associated with the use of specific health interventions. Patient preference and acceptability are two related but distinct concepts that can inform decision-making concerning the design of drug products.[14]

While the 2009 European Medicines Agency (EMA) regulatory guidance for pharmaceutical development did not explicitly refer to acceptability, the guidance did recommend

> a summary should be provided describing the development of the formulation, including identification of those attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration. (p. 5)[16]

In the US Food and Drug Administration (FDA)'s safety considerations for product design guidance document, the importance of drug product attributes, such as size and shape, were highlighted as factors influencing patient experience and adherence to prescribed medicines.[17,18] In the 2013 EMA guideline on pharmaceutical development of drug products for pediatric use, it was noted that

> patient acceptability is likely to have a significant impact on patient adherence and, consequently, on the safety and efficacy of a medicinal product. (p. 19).[11]

Acceptability can indeed have a substantial impact on adherence, as indicated by the National Institute for Health and Care Excellence in their guideline for drug product adherence for patients aged 18 years and older. The guideline recommended supporting and involving patients in making informed decisions about their prescribed drug products.[19]

The oral route of administration remains the most common method of delivering drug products to patients.[10,20] Solid oral dosage forms (SODF), commonly referred to as oral solid dosage forms, represent the final drug product composed of the active pharmaceutical ingredient, excipients, coatings, and/or capsule shells, and are ingested by patients in solid form, most commonly tablets and capsules.[10,11,16,20,21] Acceptability of and preference for drug products depends on several physical attributes that should be considered throughout the design process.[20] Physical characteristics of drug products, such as color, shape, and size, are notable determinants of patients' acceptance and preferences.[22] Physical attributes can help patients to discern particular drug products, which can be important for those who are prescribed multiple drug products.[23] Certain physical attributes, such as color, can also influence patients' beliefs about the perceived efficacy of drug products, triggering specific emotional responses that may impact adherence and other outcomes, including drug product effectiveness.[24–27] However, previous research has highlighted limited documentation of the relationship between drug product attributes and patient acceptability and preferences, with most information recorded anecdotally.[28]

There are differing perspectives about the influence of demographic characteristics on patients' acceptability and preferences for drug product attributes. While some authors recognize similarities between different age groups (eg, pediatric and older adult patients),[9] others have highlighted potential differences by age and sex, cultural characteristics, and disease.[24] However, drug product acceptability and preferences have been studied in only a limited number of

diseases, and less is known about country- and cultural-specific preferences owing to a wide range of formulation and prescribing possibilities.[29] Furthermore, multimorbidity and age-related differences, such as changes in cognition, motor function, and sensory functions of patients, also need to be considered when developing drug products.[28,30–33]

Despite an increasing focus on patient-centric design during drug product development,[5] there remains no harmonized approach to integrating the voice of patients into determining acceptability and preference in the development, design, or evaluation of drug products.[12,14,28] Similarly, there is no consensus on how patient acceptability and preference inform regulatory approval; applicants currently need to determine and justify their choices, but there is little clarity on how these data impact decision-making.[30] Moreover, no standardized methods for assessing drug product acceptability and preference have been established, despite recognizing the impact of medication adherence on successful treatment outcomes for patients, and understanding that changes in drug product attributes may impact acceptability[11,22] and, thus, adherence. The type, number, and focus of studies exploring drug product acceptability and preference are also limited and warrant further investigation.

Therefore, a consistent framework of what to consider when assessing drug product acceptability and preference is required. While it is important to understand differences and considerations for certain populations (ie, pediatric [<18 years] and older patients [~≥50 years]) who may have additional needs, acceptability and preference are concepts that should be applied by the pharmaceutical industry in the design of drug products for all patients across the life course. The aims of this scoping review were to (1) assess current understanding about the drug product attributes that impact acceptability, (2) explore the relationship between patient preferences and acceptability, and (3) assess the likely impact of drug product attributes on patient behaviors and outcomes, including adherence.

Materials and Methods

A scoping review was undertaken, guided by the Joanna Briggs Institute Scoping Review Protocol[34] and reported in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.[35] Although a protocol was developed by the study authors, this was not published. Given the relatively limited literature on acceptability, heterogenous methods used in available studies, and lack of a harmonized approach in the field,[11] the methodological quality of included studies was not assessed. To broadly align with the included studies, the age groups of pediatric, adult, and older adult patients were defined as <18 years, 18–49 years, and ≥50 years, respectively.

Search Strategy

Embase, Ovid MEDLINE®, and PubMed® were searched in May 2023 using a strategy developed and modified for each database (Supplementary Table 1) informed by keywords and search terms specified in Supplementary Table 2. The search was limited to peer-reviewed articles published in English between January 2013 and May 2023; articles were not restricted by country.

Eligibility

The scoping review inclusion and exclusion criteria were outlined a priori of the review being conducted and are listed in Table 1, defined using the population/concept/context framework.[36]

Study Selection

Records were de-duplicated in EndNote 20.5 Windows (Clarivate, London, England, UK) and reviewed against the eligibility criteria. One author (JZ) initially screened titles and abstracts and excluded articles that were not published in English and did not fit the full inclusion criteria. Two authors (BH, SJW) and one reviewer (WM) then independently screened abstracts and applied the eligibility criteria. One author (JZ) and one reviewer (WM) independently screened full-text records using the same criteria. Included articles mentioned drug product or formulation or attributes and patient preference or acceptability. For instances of uncertainty or disagreement, articles were discussed (BH, WM, JZ, SJW) until consensus was reached.

Table 1 Inclusion and Exclusion Criteria

Criterion	Inclusion criteria	Exclusion criteria
Population	Pediatric and adult patients with any disease	
Concept	Preferences and acceptability for drug product attributes of SODF. Drug product attributes including physical and sensory attributes (eg, color, odor, palatability, roughness, size, shape, swallowing, and taste). Outcomes including acceptability, adherence, and compliance. Study designs included non-experimental, discrete-choice experiments, and reviews.	Non-SODF
Context	Not applicable	
Literature	Published peer-reviewed research	Abstract only
Date	2013 to 2023	2012 and earlier
Language	English or with English translation provided	

Abbreviation: SODF, solid oral dosage form.

Data Extraction and Synthesis

Data were extracted by one author (JZ) and one reviewer (WM) using a template data extraction spreadsheet. Data extracted included title, first author, year of publication, country, study objective, study design, study population, sample size, domain (ie, appearance, swallowability, palatability, and handling), attribute definitions, attributes (ie, color, form, marking, mouthfeel, shape, size, taste, and texture), disease, modality, outcomes, theme, and concluding remarks. Bubble plots identified the number of included studies by country and publication year. Given the heterogeneity of included study designs, data were analyzed thematically using a six-stage iterative process,[37] guided by domains previously outlined as components of acceptability.[38] The author/reviewer (JZ, WM) familiarized themselves with the data before coding the data by attributes and populations. Data were then grouped by theme, including domain, before themes were reviewed, refined, and reported. The iterative process enabled the authors and reviewer to move from a set of initial, hypothesis-driven overarching domains (ie, appearance, swallowability, palatability, and packaging) to a refined, cohesive framework of overarching domains reflective of the literature, focused on physical drug product attributes (ie, appearance, swallowability, palatability, and handling) described in ≥3 included studies.[39]

Results

Study Selection

The study selection process is presented in Figure 1. A total of 472 unique records were identified through electronic searches of bibliographic databases. After de-duplication, 301 records proceeded for title and abstract screening. Following title and abstract screening, 41 articles were eligible by full-text screening, of which 19 articles met the inclusion criteria and were included in the review.

Characteristics of Included Studies

A summary of included studies is shown in Table 2. Studies were published between 2013 and 2023 and conducted in the United Kingdom (UK; n=9, 47%),[30,32,40–46] United States of America (USA; n=2, 11%),[47,48] and Denmark,[49] France,[50] Germany,[14] Japan,[51] Poland,[29] Saudi Arabia,[52] and Switzerland[53] (n=1, 5% each; Figure 2). One study was a multinational survey of patients from France, Germany, Spain, and the UK.[54] As shown by the distribution of studies by country and year of publication in Figure 2, most studies (n=14, 74%) were published in 2019 or later.[14,29,30,40,41,43,44,47–53] Most studies focused on acceptability (n=14, 74%),[14,30,32,40–46,49,50,52,53] while less than half explored preferences (n=8, 42%);[29,46–49,51,52,54] few studies examined both patient acceptability and preferences (n=3, 16%).[46,49,52] Most studies included adult (n=10, 53%)[29,42–44,48,49,51,52,54] or older adult (n=9, 47%)[14,29,30,44,45,47,49–51] patients; fewer included pediatric (n=6, 32%) patients.[32,40,41,43,46,53] Among the included drug product acceptability studies, acceptability was assessed more consistently across pediatric,[32,40,41,43,46,53] adult,[14,42–44,49,52] and older adult patients;[14,30,44,45,49,50] fewer patient preference studies appeared to focus on pediatric[46] and older adult[29,47,51]

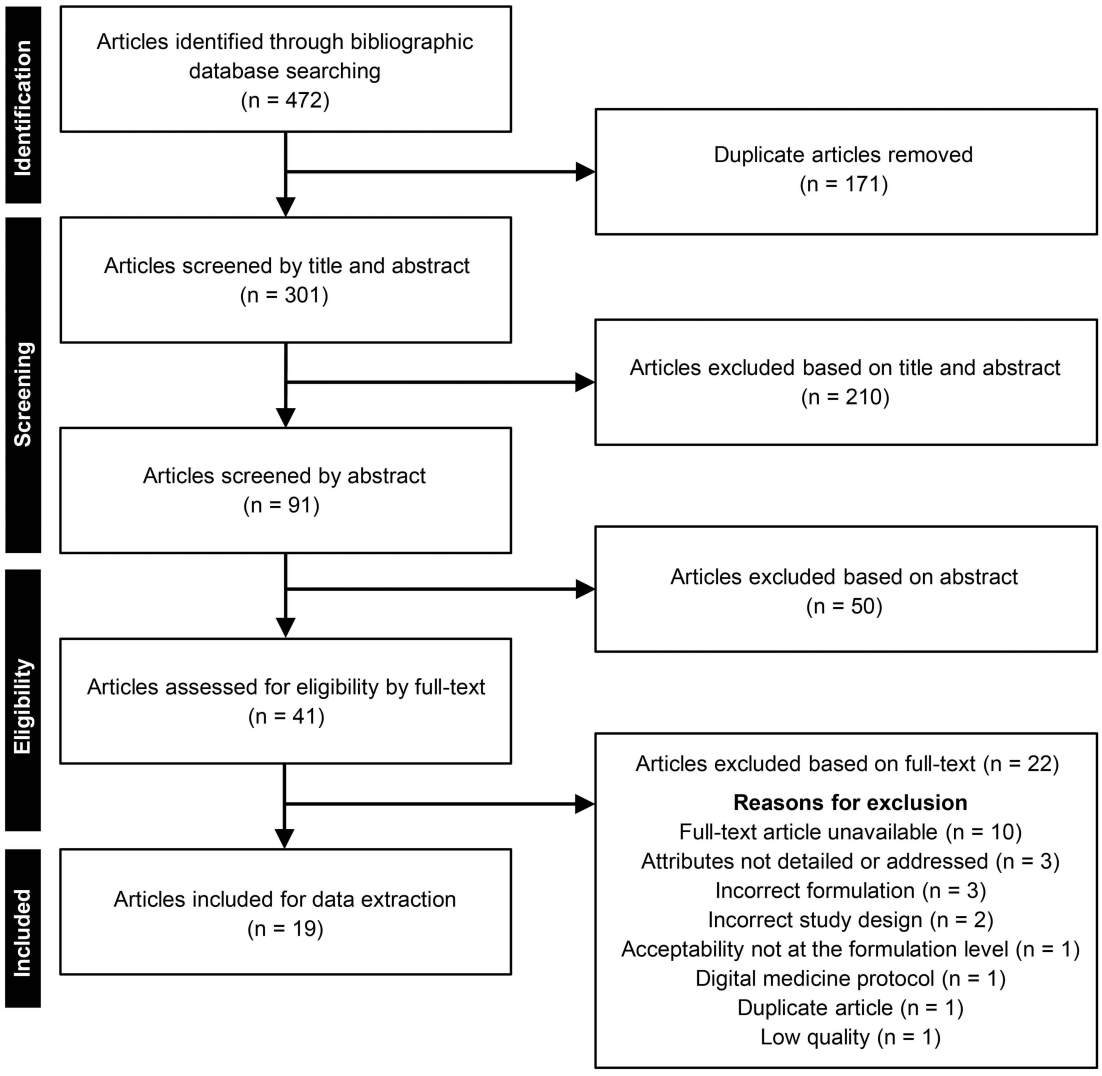

Figure 1 PRISMA Flow Chart of the Article Selection Process.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta Analyses.

versus adult[29,48,49,51,52,54] patients. Studies included healthy individuals (n=13, 68%),[14,29,30,40–44,46,50–53] symptomatic patients with life-threatening diseases (n=9, 47%),[32,40,41,45–49,51] symptomatic patients with non-life-threatening diseases (n=10, 53%),[32,40,41,45–47,49–51,54] and asymptomatic patients with non-life-threatening diseases (n=2, 11%);[47,51] Supplementary Table 3. Life-threatening diseases included cancer, cardiac disorders, and human immunodeficiency virus. Non-life-threatening diseases (though treatment may be deemed medically necessary) included cystic fibrosis, diabetes, endocrine disorders, epilepsy, glaucoma, hyperlipidemia, hypertension, Parkinson's disease, renal disorders, rheumatic and musculoskeletal diseases, tuberculosis, and ulcerative colitis. Most studies were cross-sectional (n=8, 42%),[29,30,45,47,49,50,52,54] while others included prospective placebo-controlled (n=5, 26%),[14,42–44,48] mixed method (n=4, 21%),[40,41,46,53] pragmatic (n=1, 5%),[32] and cross-over (n=1, 5%)[51] designs. Where findings are specific to pediatric or older adult patients, this is noted; otherwise, findings on the relative importance of drug attributes are likely to apply to all adult patients.

Drug Product Domains and Attributes

Four overarching drug product domains of acceptability (themes) were identified: appearance, swallowability, palatability, and handling. Domains were informed by nine specific drug product attributes identified as being related to acceptability (subthemes): texture, form, size, shape, color, marking, taste, mouthfeel, and smell. Domains and attributes

Table 2 Summary of Included Studies

First author (year study published)	Study design	Country of study	Study population	Sample size	Type of intervention	Tool
Almukainzi (2021)[52]	Cross-sectional	Saudi Arabia	Adults	250	Non-interventional	Survey
Barenie (2020)[47]	Cross-sectional	USA	Older adults	1000	Non-interventional	Survey
Bracken (2020)[40]	Mixed methods	UK	Pediatrics	55	Interventional	Survey, hedonic scale
Bracken (2022)[41]	Mixed methods	UK	Pediatrics	30	Interventional	Survey, hedonic scale
Fastø (2019)[49]	Cross-sectional	Denmark	Adults, older adults	8	Interventional	Semi-structured interview
Goyanes (2017)[42]	Prospective, placebo-controlled	UK	Adults	50	Interventional	PRO, RRO
Hofmanová (2019)[44]	Prospective, placebo-controlled	UK	Adults, older adults	84	Interventional	Preference, acceptability
Hofmanová (2020)[43]	Prospective, placebo-controlled	UK	Pediatrics, adults	101 (pediatrics) 52 (adults)	Interventional	PRO, RRO
Hummler (2023)[14]	Prospective, placebo-controlled	Germany	Adults, older adults	52	Interventional	Survey
Kabeya (2021)[51]	Cross-over	Japan	Adults, older adults	40	Interventional	Survey
Kurczewska-Michalak (2020)[29]	Cross-sectional	Poland	Adults, older adults	200	Non-interventional	Semi-structured interview, survey
Liu (2016)[45]	Cross-sectional observational	UK	Older adults	156	Interventional	Survey (SSQ)[a]
MacKenzie-Smith (2018)[54]	Cross-sectional	Online survey of patients in France, Germany, Spain, and the UK	Adults	380	Non-interventional	Survey
Osborn (2019)[48]	Prospective, placebo-controlled	USA	Adults	50	Interventional	Preference
Ranmal (2013)[46]	Mixed methods	UK	Pediatrics, caregivers	>200 (pediatrics) >150 (caregivers)	Non-interventional	Survey
Shariff (2020)[30]	Cross-sectional	UK	Older adults	52	Non-interventional	Preference
Vallet (2020)[50]	Cross-sectional	France	Older adults	938	Non-interventional	Observation, survey, hedonic scale
Venables (2015)[32]	Pragmatic	UK	Pediatrics	221	Non-interventional	Semi-structured interview
Wargenau (2022)[53]	Mixed methods	Switzerland	Pediatrics	141	Interventional	Observation, visual analog scale, video documentation

Notes: N=19. [a]The SSQ is a validated 17-question, self-report inventory, developed to measure symptomatic severity of oral-pharyngeal dysphagia as reported by the patient. The SSQ uses a 100 mm long visual analogue scale for all but one question (question 12).[55]

Abbreviations: PRO, patient-reported outcome; RRO, research-reported outcome; SSQ, Sydney Swallow Questionnaire; UK, United Kingdom; USA, United States of America.

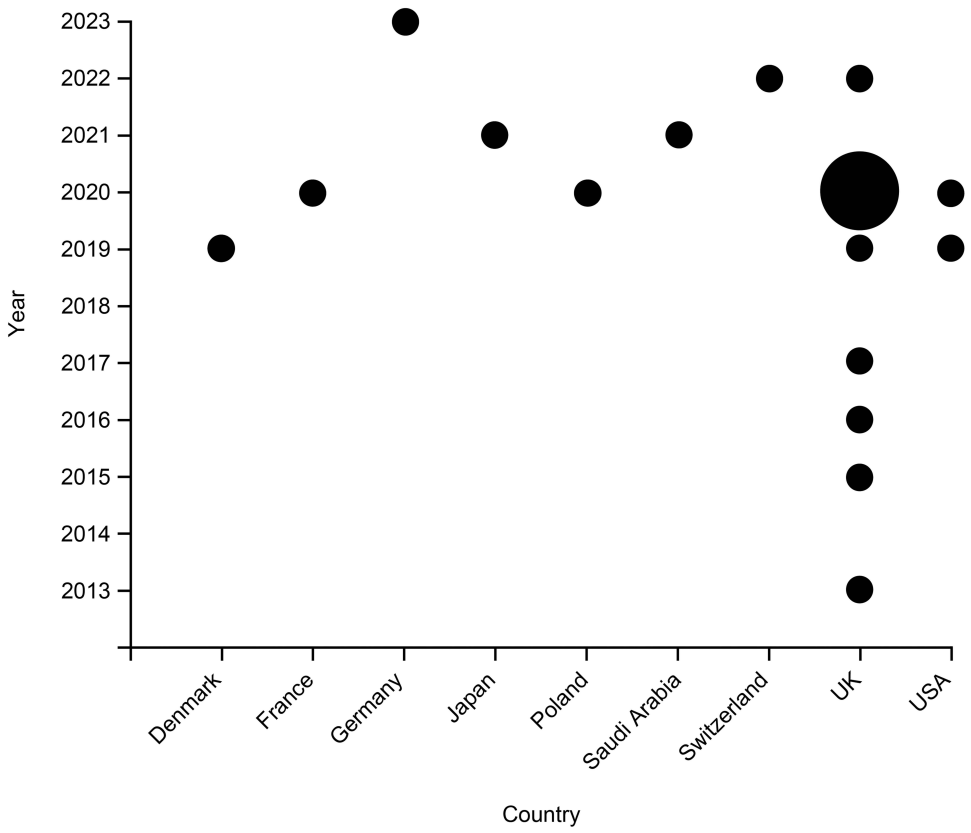

Figure 2 Studies by Country and Year of Publication.
Notes: N=18. One study published in 2018 is not shown since it was a multinational survey of patients from France, Germany, Spain, and the UK.[54]
Abbreviations: UK, United Kingdom; USA, United States of America.

are defined in Table 3. Certain drug product attributes—especially texture, form, size, and shape—were relevant to multiple domains (Table 4).

The most frequently studied domains were swallowability (n=18, 95%)[14,29,30,32,40–46,48–54] and appearance (n=11, 58%).[29,32,42,43,46–49,51,52,54] The three most studied attributes were size (n=19, 100%),[14,29,30,32,40–54] shape (n=13, 68%),[14,29,30,42,45,47–54] and texture (n=10, 53%).[14,30,32,40,41,43,44,46,48,54] Among all attributes, the size of SODF drug products appeared to be the most important attribute to patient acceptability across all patient populations and disease classifications (Table 4). On the whole, there was minor variation between patient population and disease classifications for the rate of identified attributes reported within the included studies. However, smell appeared to be more important[32,41] and shape less important[53] for pediatric patients compared with adults. Markings also appeared to be more important to older adults,[30,47,49] while mouthfeel appeared to be more important for healthy individuals compared to patients with diagnosed diseases.[30,41,43,44]

Domain 1: Appearance

Relevant Attributes: Color, Form, Marking, Shape, Size, and Texture

Appearance was considered more important to patients compared with HCPs; the most important attribute impacting patient preference was appearance (44%), compared with other aspects such as units per administration and number of administrations per day, which ranked more highly for prescribing HCPs.[54] Overall, the importance of physical characteristics in both short- and long-term treatment scenarios was the same—color, form, and size.[29]

The color of a drug product is a critical attribute as it is used for several reasons, including brand recognition, helping individuals to differentiate between prescribed drug products, and potentially affecting drug product efficacy.[24–28] White was the most represented color in drug products[49] and tended to be the most common and preferred color for SODF.[52] In

Table 3 Domain and Attribute Definitions

Domain	Definition
Appearance	Aesthetic factors of a drug product, such as color, markings, form, shape, size, and texture[33]
Swallowability	Ability to ingest a drug product without gagging or choking[56]
Palatability	Physical expressions, gestures, or opinions in response to a drug product by organoleptic properties, such as appearance, smell, taste, texture, and mouthfeel, that make it pleasant to ingest[13,30,53,56]
Handling	Ability to pick up and handle a drug product prior to ingestion[42]
Attribute	**Definition**
Texture	Surface attributes of a drug product perceptible by means of mechanical, tactile, visual, and auditory receptors[44]
Form	The way in which a drug product is presented, such as a tablet or capsule[57]
Size	Overall dimensions or magnitude of a drug product
Shape	External form, contours, or outline of a drug product
Color	Properties possessed by a drug product of producing different sensations on the eye as a consequence of the way it reflects light
Marking	Imprint of coded alphanumeric characters, symbols, and/or shapes on a drug product[58]
Mouthfeel	Tactile properties perceived from the point a drug product is placed in the mouth to when it is swallowed[44]
Smell	Perceived or detected odor or scent of a drug product via the nose
Taste	Perceived or experienced flavor of a drug product in the mouth

one study, white drug products were preferred by the majority of individuals (69%) owing to the perception that they did not contain additives and/or were a safer formulation.[52] White drug products were also preferred by pediatric patients who took drug products regularly.[46] However, one study found there was no consensus on the importance of color, with some patients considering color irrelevant.[49] Beyond white, there was little consensus on other preferred colors, with a wide range of reactions observed.[42] Preference for specific colors appeared to be based on individual preferences and color influences on perceptions,[49] such as red being considered stimulating.[28] Having too many drug products of the same color, shape, or size can make it more difficult for patients to differentiate between drug products; different colors were seen as prompts by some patients to identify drug products and remember when, how, and in what quantities to take them (eg, three green, one yellow).[49]

The formulation of SODF had a considerable impact on patients' ability to identify, handle, and swallow drug products. Tablets were the preferred solid form to take drug products. In one study, 84% of patients preferred tablets;[48] while in another study, tablets were preferred over capsules by the majority of individuals (79%).[52] Among tablets, coated tablets were preferred; almost all individuals assessed in a double-blind study found coated tablets acceptable (~95%) versus two-thirds (66%) who found noncoated tablets acceptable.[44]

Markings, such as those used to indicate administration schedules (eg, day or time), were only valuable if they were relevant to the patient's disease or dosage regimen. Generally, patients felt markings were irrelevant because prescribing information was either provided on the pharmacy label or drug products were organized into dosette boxes and pill organizers. Patients felt that markings (eg, sun and moon markings to indicate morning and evening administration schedules, drug product name, and strength) could act as visual cues for older adults and patients who are less likely to adhere to their prescribed medicines; however, the studies highlighted the need for markings to be simple and legible.[30,49]

Shapes similar to conventional SODF were most preferred for both familiarity and functional reasons. Round shapes were highly rated and preferred by individuals,[42,52] while another study found that patients were most familiar with, and preferred, round or oval shapes.[49] Similar to color, common shapes increased the difficulty for patients to differentiate drug products of the same size; unique shapes (eg, heart shape in the case of Hjertemagnyl®) appeared to aid identification,[49] particularly for patients requiring polypharmacy.

Smaller-size drug products were generally preferred, though some differences in preference were observed between pediatric and adult patients. In one study, more patients preferred to take a greater number of smaller drug products (42%) over a fewer number of larger drug products (36%) if offered a choice.[48] Nearly all patients (96%) agreed that the ideal drug product size was 4–9 mm,[48] though small, round drug products (<7 mm) were least accepted among older

Table 4 Summary of Domains and Attributes

First author (year study published)	Domain				Attribute								
	Appearance[a]	Swallowability[b]	Palatability[c]	Handling[d]	Color	Form	Marking	Mouthfeel	Shape	Size	Smell	Taste	Texture
N (%)	11 (58)	18 (95)	4 (21)	4 (21)	9 (47)	9 (47)	3 (16)	4 (21)	13 (68)	19 (100)	2 (11)	8 (42)	10 (53)
Almukainzi (2021)[52]	✓	✓			✓	✓			✓	✓			
Barenie (2020)[47]	✓				✓		✓		✓	✓			
Bracken (2020)[40]		✓								✓		✓	✓
Bracken (2022)[41]		✓						✓		✓	✓	✓	✓
Fastø (2019)[49]	✓	✓		✓	✓		✓		✓	✓			
Goyanes (2017)[42]	✓	✓		✓	✓				✓	✓			
Hofmanová (2019)[44]		✓	✓		✓			✓		✓		✓	✓
Hofmanová (2020)[43]	✓	✓						✓		✓		✓	✓
Hummler (2023)[14]		✓							✓	✓			✓
Kabeya (2021)[51]	✓	✓		✓		✓			✓	✓			
Kurczewska-Michalak (2020)[29]	✓	✓				✓			✓	✓			
Liu (2016)[45]		✓				✓			✓	✓			
MacKenzie-Smith (2018)[54]	✓	✓			✓	✓			✓	✓		✓	✓
Osborn (2019)[48]	✓	✓				✓			✓	✓			✓
Ranmal (2013)[46]	✓	✓	✓		✓	✓				✓		✓	✓
Shariff (2020)[30]		✓	✓	✓	✓		✓	✓	✓	✓		✓	✓
Vallet (2020)[50]		✓							✓	✓			
Venables (2015)[32]	✓	✓			✓	✓				✓	✓	✓	✓
Wargenau (2022)[53]		✓	✓			✓			✓	✓			

Notes: N=19. [a] Relevant attributes: color, *form*, marking, *shape*, *size*, and *texture*. [b]Relevant attributes: *form*, *shape*, *size*, and *texture*. [c]Relevant attributes: mouthfeel, smell, taste, and *texture*. [d]Relevant attributes: *form*, *shape*, *size*, and *texture*. Attributes that are relevant to multiple domains are shown in *italic*.

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individuals.[30] Pediatric patients appeared more sensitive to size. The ability to swallow a 7.5-mm drug product was much lower in children than in adults (62% vs 98%);[43] though the authors of one study reported that older pediatric patients (80% of children aged ≥12 years) found ≥10 mm acceptable.[46] Major axis + minor axis + thickness (ie, length + width + depth) was identified as an effective way to evaluate patient preference regarding size, with drug products with a length + width + depth ≥21 mm considered by patients to be too large to ingest.[51]

Texture appeared to be a lesser component of appearance, discussed in a small number of studies. In a study exploring preferences towards three-dimensional printed drug products, individuals felt that they

> looked cool but the texture was bad (p. 8).[41]

Another study showed that more than one-third of patients (40%) preferred drug products with a smooth coating,[48] while another highlighted a preference for the plastic texture of capsules over uncoated tablets.[30] Venables et al stated texture was a significant predictor of nonadherence, affecting 8% of prescribed oral drug products.[32] Interestingly, use of the phrase "texture" caused some confusion in another study, with the authors recommending alternative wording for future acceptability and preference studies.[40]

Domain 2: Swallowability

Relevant Attributes: Form, Shape, Size, and Texture

Size seemed to be most important for swallowability, with the authors of one study concluding that moderate swallowability may be acceptable for short-term treatments; however, good swallowability was necessary to encourage adherence to long-term treatment, particularly for older adult patients.[14] Notably, issues with swallowability appeared age-related, with younger adult patients (<55 years) reporting more issues than older patients (≥55 years).[44] In one particular study, size was considered one of the most important attributes to acceptability in pediatric patients.[46] Smaller size drug products were rated as easier to swallow among pediatric patients; all patients were able to swallow 6-mm tablets versus 90% for 8-mm tablets and 75% for 10-mm tablets.[41] Tablets can also be too small to see and may cause unintentional non-adherence, as remarked by informal (family) carers, who reported difficulties in visually confirming whether or not small tablets were administered by patients in their care,[30] though tablets <7.5 mm were positively accepted by individuals.[50] One study reported tablets or capsules should be ≤22 mm in size (length + width + depth/thickness), and between 2 and 6 mm in thickness.[51] Swallowing tablets and capsules of large sizes (>11 mm, >13 mm, and >size #00 capsules) were more difficult for patients with dysphagia than without.[45] Tablets >8 mm in size were more likely to be related to swallowability issues. Increasing the size of tablets or capsules was associated with an increase in the number of complaints related to swallowing difficulties.[30] Atypical shapes, such as heart, diamond, pentagon, triangle, and cube shapes, were rated as least acceptable in terms of swallowability.[42]

Round drug products were preferred for a SODF because the shape requires less effort to swallow;[52] tablets were also preferred over capsules by the majority of patients (79%), primarily owing to a perception of easier swallowability.[52] Capsules were seen as more likely to be trapped in the throat, causing dysphagia or a bad taste.[52] Fastø et al identified swallowability as an important physiological factor for patients, with particular shapes preferred for drug products, namely heart, almond, and oval shapes, with oval or almond shapes associated with easier swallowability.[49]

Texture appeared to have less of an impact on acceptability compared with size or shape. Texture was primarily influenced by the presence of a coating, which made drug products easier to swallow and more palatable. One study identified the most important attributes for swallowability as size (40%) and smoothness (38%).[48] Another study found that size, taste, and texture were barriers to swallowability.[54] Reasons for drug products being difficult to swallow included the texture being hard or rough; film coating made a smoother surface that was easier to swallow.[40] Indeed, smoother, more slippery drug products attributed to a coating correlated with liking and acceptability,[43] and improved swallowability. Uncoated tablets appeared to stick in a patient's throat and esophagus more frequently, requiring more time and greater volumes of liquid to successfully swallow.[30,44] Texture or surface roughness may have more impact on younger adult patients (18–55 years) than older adults (>55 years); younger patients were able to discern differences in smoothness between different drug product coatings, while older patients only discerned differences in smoothness in coated versus noncoated drug products.[44] Roughness was stated more by older patients (≥65 years) than younger patients

(19–36 years) as a factor for swallowing impairment.[14] Women also appeared more sensitive to texture and were more able to assess smoothness of drug products, but not slipperiness.[43] In one study, older people in general highlighted the texture of coated preparations, often described as "shiny" and "slippery", which people found easier to swallow.[30]

Domain 3: Palatability

Relevant Attributes: Mouthfeel, Smell, Taste, and Texture

Palatability can be important for improving swallowability.[30,53] Taste was the most important driver of palatability across pediatric and adult patients, with size and texture as secondary attributes linked to palatability. Taste was the strongest determinant of liking and acceptability.[43] In another study, taste was considered one of the most important attributes to acceptability in pediatric patients.[46] Bitter taste and unpleasant aftertaste both correlated with lower acceptability in all individuals, regardless of age.[43] Bitter-tasting drug products were described as being more difficult to take, with one study indicating taste may lead to nonadherence that may not be identified until patients have a medical review.[30] In one study, taste was the most important barrier to drug product administration for pediatric patients, affecting 35% of all prescribed oral drug products and associated with 64% of formulations that were refused.[32] Some differences by age were also observed. Pediatric patients appeared more sensitive to taste; adults provided higher overall ratings and responded to the same drug products as less bitter, while children had stronger negative reactions, especially to taste (eg, very bitter or disgusting).[43] In one study, women were also more sensitive to bitterness than men.[43]

Texture was the second most significant predictor of drug product refusal.[32] In one study, older people in general highlighted the superior texture, mouthfeel, and taste of coated preparations, in particular those with sugar coatings. In addition, people appeared more likely to accept coated versus uncoated preparations.[30] Women also appeared more sensitive to mouthfeel and were more able to assess stickiness and smoothness of tablets, but not slipperiness and aftertaste.[43] The most preferred drug products appeared to be smooth, slippery, and less bitter, highlighting the impact of mouthfeel on palatability and thus acceptance, and not just as a function of taste alone.[43,44]

Interestingly, smell was considered less important to patients as an attribute of their drug products for palatability relative to taste, texture, and size,[41] and was not seen to impact nonadherence.[32]

Domain 4: Handling

Relevant Attributes: Form, Shape, Size, and Texture

Easier handling was related to improved patient acceptability and adherence.[42] Kabeya et al noted women had less difficulty handling drug products compared with men.[51] Capsule formulations received worse evaluations than tablets for ease of being picked up.[51]

Most shapes had little impact on patients' ability to pick up drug products; atypical shapes, such as a pentagon or tilted diamond, were slightly more difficult to pick up.[42] Rounded shapes were slightly preferred for handling, as were oval or almond shapes because they were, in part, more practical and easier to pick up.[30,49]

There appeared to be trade-off between handling and swallowability for size.[30] Larger drug products (eg, ≥6 mm) were easier to pick up but more difficult to swallow; drug products ≤2 mm thick were harder to pick up.[51] Shariff et al identified small, round tablets (≤6 mm) as being difficult for individuals to remove from blister packs, dosette boxes, and pill organizers, particularly for older patients and those with poor eyesight and manual dexterity.[30] One consequence of poor handling of small drug products included dropping them on the floor, which could lead to nonadherence if patients ran out of their drug product earlier than prescribed and did not report these difficulties to HCPs.[30]

Impact on Behaviors and Outcomes, Including Adherence

Only three out of 19 studies (16%) went beyond measuring acceptability or preference to consider the impact of drug product attributes on behaviors and outcomes.[47,48,54] In one study, one-third of patients (32%) said larger size would make them not want to take a tablet daily; 16% said shape would make them not want to take a tablet daily, though the particular shapes disliked were not detailed.[48] In the same study, larger-sized tablets impacted adherence for 16% of patients; other factors impacting adherence included taking multiple daily doses (38%) and multiple tablets per dose (14%).[48] Although

Mackenzie et al did not investigate the impact of drug product size on adherence, they did report adherence and overall disease management may improve when drug products are prescribed according to patient preferences.[54]

Among patients who reported experiencing a change in appearance of a generic drug product between prescription refills, 12% reported stopping their drug products or using it less frequently, with Black and Hispanic patients more likely than White patients to be nonadherent following a drug product change in appearance.[47] Other behavioral impacts or actions indicated confusion or the need for confirmation as to whether tablets were received in error—nearly one-third (29%) of patients thought they received the wrong tablet, with some patients taking action by asking their pharmacist (35%) or HCP (9%) about the change.[47]

Discussion

This scoping review has provided a current understanding about drug product attributes that impact acceptability and has highlighted the relationship between preferences and acceptability for drug product attributes among pediatric, adult, and older adult patients. To assist in standardizing the assessment of drug product acceptability and preference, a new framework is proposed as a tool to facilitate patient-centric drug product design; this framework organizes and categorizes physical drug product attributes into four overarching domains (Figure 3).

Most studies included in this review were cross-sectional by design and conducted in the UK. Many were published in 2019 or later, reflecting the contemporary nature of this field. Fewer studies explored patient preferences compared with acceptability, with only three studies investigating both acceptability and preferences. The majority of studies within this review focused on healthy individuals. Over three-quarters of the studies included either pediatric or older patients; however, one-half exclusively focused on or compared these specific patient populations against average adult patients. Moreover, preference studies tended not to focus on pediatric and older adult patients. Previous research in the field of drug product design has focused on pediatric and older patients given their specific needs;[10,13] however, this review has confirmed preference and acceptability of drug products are relevant to all patient groups, though specific considerations may be necessary for particular groups, such as pediatric and older adult patients.

Swallowability and appearance were the most commonly studied domains, which is consistent with previous research suggesting swallowability is the key domain to be considered when designing drug products.[9] While most published studies of drug product attributes evaluate appearance and swallowability,[5] this review has also highlighted the importance of considering palatability and handling. Considered together, these four domains provide a more complete understanding about acceptability and preferences for drug products that may enhance their design in the future by encouraging a more patient-centric approach during the drug product design process.

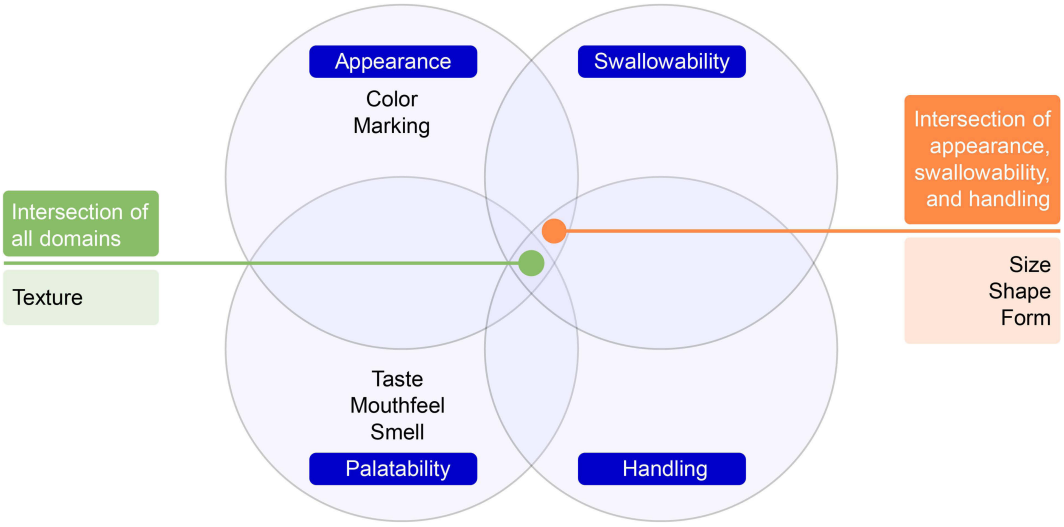

Figure 3 Drug Product Domain/Attributes Framework.

Among all attributes, the size, shape, and texture of SODF drug products appeared to be the most important for patient acceptability across all patient populations and diseases. Meanwhile, smell, markings, and mouthfeel were the least studied attributes among included studies across all patient populations and diseases, highlighting the need for further investigation of these attributes and their effects on acceptability and subsequent outcomes, including adherence. As demonstrated in Figure 3, certain attributes were related to multiple domains; texture intersected all domains, while form, shape, and size intersected appearance, swallowability, and handling domains. However, some variations were observed within the literature: smell was more important and shape less important for pediatric compared with adult patients, while markings appeared more important for older adults, and mouthfeel seemed more important for healthy individuals compared with patients living with a disease. Certain drug product attributes (eg, size) were found to have both a positive and negative effect on patient acceptability; a "middle ground" for these attributes is therefore required, particularly for pediatric and older adult patients. This was exemplified by the trade-off required between handling and swallowability over the size of drug products. For drug products used as short-term treatment (eg, anti-infectives), this may be less of an issue compared with those used as long-term treatment (eg, for chronic, long-term diseases).

Smaller-size drug products seemed to ease swallowability, especially for pediatric patients, and were of greater importance than shape. However, drug products that were too small could also be problematic for patients in terms of swallowing and handling, such as removing them from blister packs, picking them up, and organizing them in dosette boxes or pill organizers—especially for older patients. With regard to shape, patients preferred conventional round and oval drug products that were familiar, required less effort to swallow, and were easier to handle. However, there was also a point of tension for patients between preference for most common drug attributes (eg, round and white coated tablets) and the ability to differentiate between multiple drug products, particularly for patients requiring polypharmacy. Unique shapes were seen to aid identification but were often regarded as more difficult to handle; therefore, addressing these issues could help to avoid potential drug product errors and drug product-related harm. In addition, markings were seen to only be valuable if they were relevant to a patient's disease or treatment regimen.

While swallowability and palatability were recognized as key domain attributes to patient acceptability, there is limited understanding of the relative importance of physical and sensory parameters that comprise these domains (eg, size, shape, and texture). Moreover, while swallowability and palatability are distinct yet overlapping domains, they are inconsistently defined and differentiated in the literature, in part owing to poor definitions for palatability, which is linked to and important for improving swallowability. The framework and definitions provided in this review should help to address the way in which researchers consider these two domains during drug product design. Similarly, other gaps in the literature were identified, including the impact of taste on acceptability, which may be due, in part, to the complex multisensory inputs that determine taste. This review has highlighted that taste may increase nonadherence, particularly for pediatric patients, with bitter and unpleasant aftertaste decreasing the acceptability of drug products. Mouthfeel was also seen to impact palatability and thus acceptability of particular drug products, highlighting that mouthfeel is not just a function of taste alone. Interestingly, the perceived taste can also be influenced by appearance; one systematic literature review of drug product preferences found an apparent relationship between the color of a drug product and the expected taste,[28] in particular among pediatric patients,[28] though color sensitivity can vary by demographic characteristics, such as age and sex, and cultural characteristics.[24] The variability of findings related to drug product color preference underlines the need for more patient-centered studies that better evaluate the effects of appearance on the acceptability of drug products.[28] With regard to the texture, smooth, slippery, and less bitter drug products (ie, those with a coating) were easier to swallow and preferred by patients, though as a lesser priority than size and shape.

Less than one-quarter of studies considered the impact of drug product attributes on behaviors and outcomes beyond measuring acceptability and preferences, despite recognition that such attributes can impact patients' adherence, disease outcomes, and quality of life.[59] While the likely impact of certain drug attributes on patient behaviors and outcomes was inferred from the included studies, future studies need to examine the relationship between acceptability, preferences, and outcomes for patients, especially adherence. Among the studies that explored this area, adherence and overall disease management were believed to be improved when drug products were prescribed according to patient preferences. Unfortunately, nonadherence to proper usage of SODF can lead to poor disease management and increased side

effects.[52] The impact of nonadherence can also be more serious and concerning for patient populations with life-threatening diseases, such as cancer, or long-term, chronic diseases requiring pharmacological treatment to manage.[60,61]

While it was difficult to draw conclusions from the included studies on geographic differences in assessment of acceptability and preferences, some differences according to sex were identified, including females being more sensitive to mouthfeel, taste, and texture, as well as reporting fewer difficulties with handing SODF. In this review, it was unclear if changes in drug product attributes differed by disease; for example, whether changes may be less of an issue for patients with cancer because of the life-threatening component of the disease that overrides patients' preferences when faced with the prospect of premature mortality. Clearly, optimizing the administration manner of SODF, bearing in mind patients' perceptions of palatability, is a demanding factor that needs to be considered by pharmaceutical manufacturers, regulatory agencies, and HCPs.[52]

This review has highlighted the need for greater attention to, and exploration of, the relationship between acceptability, preferences, and adherence for different patient groups, diseases, and disease severities, consistent with other recent reviews.[62] It is reassuring that regulators already emphasize the importance of acceptability testing of drug products among different patient populations. The EMA recently published a letter of support[63] for testing oral drug product acceptability in children <12 years using the ClinSearch Acceptability Score Test®, which was developed following publication of the EMA guideline on pharmaceutical development of drug products for pediatric use.[11]

Future drug product development is likely to customize existing approaches and make use of a contemporary SODF, such as pellets and minitablets,[64] to improve acceptability and thus adherence for all individuals, while also addressing the specific needs of particular patient populations, such as pediatrics, older adults, those with dysphagia, and those with cognitive impairment.[6] To deliver a truly patient-centered approach to drug product design, patients need to be more actively involved in designing drug products so as to directly determine their priorities and what is important to them.[65,66] This will require multistakeholder collaboration between scientific, regulatory, provider, and patient communities to ensure that all drug products are developed using patient-centric approaches that consider acceptability, preferences, and the impact of drug product attributes on adherence and other outcomes.[2]

Strengths and Limitations

A strength of this review is its broad focus on acceptability of drug product attributes across different diseases and patient populations (ie, age), and the novel approach to structuring the review of drug product attributes. Owing to the volume of records identified, only articles that detailed information within the abstract addressing all of the inclusion criteria were included. Additionally, the inter-rater reliability[67] of articles that were screened and subsequently retrieved for data extraction was not evaluated, and a critical appraisal of included studies (including for methodological quality) was not performed. Unlike systematic reviews, scoping reviews do not consistently appraise the methodological quality of included evidence.[68] While this may impact the overall strength of evidence and conclusions that can be drawn from the review, the aim of this scoping review was not to grade the level of evidence but, rather, to identify and map the evidence related to the acceptability and preferences of drug product attributes.[69]

Conclusion

While most existing studies of drug product attributes tend to focus on appearance and swallowability, this review has highlighted the importance of less well-understood domains of palatability and handling, in addition to appearance and swallowability, in understanding patients' acceptability and preferences for SODF drug products. Among all drug product attributes, the size, shape, and texture of SODF appeared to be the most important for patient acceptability, while smell, markings, and mouthfeel were the least studied attributes and require further and more consistent investigation. Drug product design decisions impact patients of all ages, though acceptability can vary by population or disease, and further studies are required among more diverse populations to understand whether any variations exist. The proposed framework presented in this review provides a tool to facilitate patient-centric design of drug products. The framework organizes and categorizes physical drug product attributes into four overarching domains of appearance, swallowability, palatability, and handling, encouraging researchers to comprehensively assess the impact of drug product attributes on patient acceptability, preferences, and outcomes, including adherence, particularly as modalities evolve.

Abbreviations

EMA, European Medicines Agency; FDA, Food and Drug Administration; HCP, health care professional; PRISMA-ScR, Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews; PRO, patient-reported outcome; RRO, research-reported outcome; SODF, solid oral dosage form; SSQ, Sydney Swallow Questionnaire; UK, United Kingdom; USA, United States of America.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Brett Hauber, Mark V Hand, Bruno C Hancock, Joseph Zarrella, Ljiljana Harding, Michaela Ogden-Barker, Amy S Antipas, and Stephen J Watt are employees of, and own stock in, Pfizer. The authors report no other conflicts of interest in this work.

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