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Review Article

Does the Formulation of Oral Solid Dosage Forms Affect Acceptance and Adherence in Older Patients? A Mixed Methods Systematic Review

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A B S T R A C T

Objectives: Age-related changes mean that the older population can encounter barriers toward taking medication orally. Further work is needed to identify the characteristics of oral solid dosage forms that will improve patient acceptance and adherence. The aim of this systematic review was to identify if and how formulation aspects of oral solid dosage forms affect acceptance and adherence in older people.
Design: Mixed methods systematic review using a data-based convergent synthesis design.
Setting and Participants: Articles were selected if they included participants aged 60 years and older, or included health care professionals, social care professionals, and informal carers of patients aged 60 years and older.
Methods: A systematic search of the following databases was undertaken: Web of Science, MEDLINE, Scopus, and The Cochrane Databases. The search of databases was supplemented by a search of gray literature, and reference lists of included papers were manually searched.
Results: A total of 16 studies were included in the final synthesis. Three themes were generated from the thematic analysis: (1) dimensions, (2) palatability, and (3) appearance. The dimensions and palatability are often modified to improve swallowability by breaking tablets in half or taste masking with food. Polypharmacy can lead to patients using the appearance to identify tablets; however, this can lead to confusion when products appear similar. No study was identified that explored formulation characteristics across all 3 categories directly in the older population.
Conclusion and Implications: Manufacturers should take into account practical problems older people may encounter when considering the dimensions, palatability, and appearance of the final drug product. These characteristics should be optimized to aid visual identification and swallowability. Medical providers and pharmacists have an important role in ensuring that these patient-centric drug products are prescribed and dispensed appropriately so that patients receive the most suitable formulation.

Optimizing the use of medication requires a patient-centered approach to provide the best possible outcomes.[1] Comorbidities, in addition to changes in cognitive, motor, and sensory functions, must be considered to prevent practical medication difficulties in older people.[2] These comorbidities include conditions that predispose older adults toward dysphagia, such as neurologic disorders and gastroesophageal disease.[3] Complications arising from gastroesophageal disease, including esophageal stricture and cancer, are more common in older people and can lead to further problems administering medication orally.[4] Although most causes of dysphagia are due to a structural cause or organic disease, many patients without a clinical diagnosis of dysphagia also report difficulties due to an aversion to swallowing medication.[5]

European Medicines Agency and US Food and Drug Administration guidance suggest the use of a wider range of colors, sizes, and shapes to help patients recognize their medication, reduce the potential for medication errors, and aid swallowability.[6,7] However, a primary focus is often placed on the safety, efficacy, and quality of a new drug product that can lead to practical issues being commonly overlooked.[8]

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Dosage forms are routinely modified,[9] and this can result in patient harm, especially when crushing and opening capsules are contraindicated for some preparations.[10] Taking into account age-related changes in the design and development of medication will help to ensure that the end product can be used by a patient group in a safe and efficacious manner.[11]

This mixed methods systematic review, therefore, aims to identify both quantitative and qualitative studies that investigate if and how the formulation of oral solid dosage forms affects acceptance and adherence in older people. Formulation has been defined as "a dosage form with a particular composition and with specific product characteristics, eg, tablet size, shape, colour, embossing, and break mark."[2]

Methods

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1), and the protocol was registered on PROSPERO (registration no. CRD42018088969).

A systematic search of the following databases from inception to May 2019 was undertaken: Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), MEDLINE, Scopus, and Web of Science. No language or time restrictions were placed on the initial search. Search terms included a combination of Medical Subject Heading terms and a comprehensive list of synonyms relating to (1) formulation factors, (2) oral solid dosage forms, (3) patient adherence, and (4) older patients (Supplementary Table 2).

The database search was supplemented by a gray literature search. The reference lists of included studies and reviews were manually checked, and reviews were then excluded from the final list of included studies. The gray literature search was further supplemented by checking a minimum of the first 100 hits on Google Scholar and continuing until 10 or more consecutive irrelevant hits were retrieved.

Included studies met the following criteria: (1) included older people aged 60 years and older (studies including patients aged <60 years were included and relevant data extracted) or included health care professionals, social care professionals, and informal carers of patients aged 60 years and older; (2) investigated the formulation of oral solid dosage forms (as defined by the European Medicines Agency[2]); (3) measured patient adherence or acceptance, either directly or indirectly; and (4) the full text was available in English.

An initial title screen identified titles that were clearly not relevant (Z.S.). Titles and abstracts were then screened independently by the reviewers (Z.S., D.D.), after which the full texts of potentially eligible studies were retrieved and also independently assessed. Disagreements were resolved by consulting a further team member (I.M.).

Study quality was independently assessed by 2 reviewers (Z.S., D.D.) using the Mixed Methods Appraisal Tool (MMAT), version 2018.[12] Studies were categorized into study design and assessed based on methodology used. The tool was adapted to include a column stating whether studies were sponsored by the pharmaceutical industry.

Data were entered onto a standardized spreadsheet. Two review authors (Z.S., D.D.) extracted data independently, and any discrepancies were identified and resolved through discussion with a third author (I.M.). Using the European Medicines Agency definition of formulation,[2] data relating to the formulation characteristic(s) explored in each study were also extracted and tabulated.

Findings from both qualitative and quantitative studies were integrated using a data-based convergent synthesis design.[13] This approach involves data transformation so that all studies are analyzed using the same synthesis method.[13] The thematic synthesis approach, as discussed by Thomas and Harden,[14] was then used to synthesize all findings.

Results

Review Process

Supplementary Figure 1 summarizes the review process; 77 articles were included at full text, of which 14 met the inclusion criteria (see Supplementary Table 3 for reasons for exclusion). Two additional articles were identified from reference searching.

Characteristics of Included Studies

The characteristics of the included studies are summarized in Table 1. Eight studies were conducted in patients older than 60 years exclusively.[15–22] Relevant data were extracted from the remainder. One study involved physicians as well as patients.[23] The formulation of oral solid dosage forms, as defined for the review, was explored directly by 10 of the 16 studies.[16,19–22,24–28] The remaining 6 studies investigated formulation indirectly, with a primary focus on generic substitution, general medication-taking practices, and swallowing difficulties.[15,17,18,23,29,30] The formulation characteristic(s) explored can be found in Table 2.

Quality Appraisal

The results from the quality appraisal are shown in Supplementary Table 4. All studies were included in the final synthesis with greater emphasis placed on higher quality studies.

Analytical Themes

Three themes were generated from the thematic analysis of data: (1) dimensions, (2) palatability, and (3) appearance.

Dimensions

Studies that investigated formulation indirectly in older people illustrated the importance of size, with 29.6% of use difficulties (situations where the participant can only complete a task with difficulty) attributed to the dosage form being too large or small.[18] In general, there was a preference for smaller dosage forms; "tablet size was too big" was the most common cause of ongoing and past swallowing difficulties in patients with dysphagia.[30] However, tablets that were too small led to difficulties handling the tablet and locating the product in the mouth.[18] Preferences for size were also often dependent on shape, because of the ease of swallowing dosage forms with a minimum cross-sectional area.[23] Little more than 40% of older people with dysphagia selected the 11-mm arched round tablet as having the potential to cause difficulties, compared with approximately 35% selecting the 13-mm oblong tablet.[16]

The presence of dysphagia influenced the findings: 40% of older people without dysphagia reported having no difficulties swallowing any of the capsule sizes presented, compared with only 6% with dysphagia.[16] Specifically, sizes of 11 and 13 mm were found to start causing difficulties in older people with dysphagia.[16] Patients with swallowing difficulties therefore modified dosage forms more often;[22] that is, 80% of patients with swallowing difficulties modified the dosage form compared with 19% of patients without.[22]

The presence of dysphagia was also found to influence preferences for shape. Two studies found that the older population reported fewer swallowing difficulties than younger people,[23,25] and one of these went on to state that of patients who were not affected by swallowing difficulties, 69.7% did not care about tablet shape.[23] This is supported by a further study conducted exclusively in older people, which found that older people without dysphagia had fewer preferences for a

Table 1
Characteristics of Included Studies (Listed Alphabetically According to First Author)

Reference	Country	Aim	Study Design	Sample Size and Age	Data Collection Methods	Data Analysis Methods
den Uyl et al[24]	Netherlands	To compare the preference and acceptability of 2 calcium plus vitamin D-3 formulations	Quantitative randomized, open, cross-over clinical trial	102 patients visiting an outpatient clinic aged between 34 and 83 y. Mean age 66 y	Acceptability questionnaire and overall preference assessment	A logistic regression model was used to analyze the difference between the 2 formulations and provide an estimate of the sequence effect. A linear mixed model was used to analyze the secondary efficacy end points
Heikkilä et al[29]	Finland	To explore the factors that influence the choice of medication following the introduction of generic substitution (GS)	Population-based survey	1844 people divided among 18-59-y-olds (61%) and 60-94-y-olds (39%)	Questionnaire consisting of structured and open-ended questions	SPSS 17.0.1 statistical software using frequencies and cross-tabulations for descriptive analysis
Hofmanová et al[25]	United Kingdom	To investigate the oral sensory properties and swallowability of coated placebo tablets	Quantitative randomized double-blind study	Nonsmoking healthy adults aged 18-75 y; those aged >55 y were targeted and made up 50.6% of the overall population	Background questionnaire and tablet sample assessment using visual analog scales	A number of statistical analyses conducted using SPSS, version 24, to explore the differences between each of the tablet samples and to explore the impact of patient demographics on responses
Jones et al[26]	United States	To compare the preference of softgel capsules vs conventional solid dosage forms	Quantitative descriptive study	300 consumers evenly divided among the age groups of 25-39 y (31%), 40-59 y (33%), and 60+ y (36%)	Consumer preference survey	Exact analysis methods not stated
Kelly et al[15]	England	To explore the experiences of taking medication for older people with dysphagia	Qualitative study with semistructured face-to-face interviews	11 patients who had different degrees of dysphagia over the age of 60 y	Semistructured interviews	Content analysis to generate themes that were then integrated so that they could be related back to the research question
Liu et al[16]	England	To assess the acceptability of a range of oral solid dosage forms (OSDFs) in older ambulatory patients	Quantitative descriptive study	156 patients taking at least 1 oral solid medicine older than 65 y	Sydney Swallow Questionnaire (assessing swallowing function); pilot of the Medicines Acceptability Questionnaire; patients shown samples of OSDFs	Data analysis was performed using the Statistical Package of the Social Sciences (SPSS) version 22.0
Marquis et al[30]	Two Swiss regions: Basel and Lausanne	To determine the prevalence of swallowing difficulties, the strategies to overcome these and health professionals' awareness of these problems	Quantitative descriptive study	410 enrolled patients aged ≥18 y (mean age 66.5 y) taking at least 3 different oral solid dosage forms	Interview combining closed-ended, open-ended, and Likert-scale items	Data analysis was performed using the Statistical Package of the Social Sciences (SPSS) version 15.0
Notenboom et al[17]	Netherlands	To identify the practical problems that older people experience with the daily use of their medicines	Qualitative study with semistructured face-to-face interviews	59 community-dwelling people aged ≥70 y (mean age 78.4 y)	Semistructured interviews	Transcribed data were coded independently. Each practical problem/management strategy was classified on a 3-point scale according to the level of discomfort and clinical deterioration likely to result
Notenboom et al[18]	Netherlands	To identify design features of oral medicines that cause use problems among older patients	Qualitative study with semistructured interviews	59 community-dwelling people aged ≥70 y (mean age 78.4 y)	Semistructured interviews	Transcribed data were coded independently. Each practical problem and management strategy was categorized as a "use difficulty" or a "use error"

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Table 1 (*continued*)

Reference	Country	Aim	Study Design	Sample Size and Age	Data Collection Methods	Data Analysis Methods
Phillips et al[19]	United Kingdom	To compare the ease of swallowing a single oral dose of a standard tablet of acyclovir vs a film-coated tablet	Quantitative randomized crossover study	104 volunteers from the department of medicine for older adults at Orpington Hospital aged 71-94 y (mean age 82 y)	Patients asked to swallow 1 formulation and then 24 hours later received a second formulation; preference assessed	Tabulation detailing the number and percentage of patients who preferred the standard formulation, the coated formulation and who expressed no preference
Rees and Howe[20]	United Kingdom	To compare the acceptability and preference of 2 chewable preparations of calcium and vitamin D: Calcichew D_3 Forte (CDF) and Ad Cal D_3 (ACD)	Quantitative randomized, investigator-blind, crossover, multicenter study	94 patients aged ≥60 y (mean age 72.6 y)	Visual analog scales (VASs) used to assess acceptability; overall preference assessment	The distribution of the VAS scores were tested using the Shapiro- Wilk test and univariate summary statistics. Data were log transformed before applying an analysis of variance for a 2-period crossover design.
Reginster et al[27]	Belgium	To compare the preference for and acceptability of 2 formulations containing calcium and vitamin D	Quantitative randomized, open-label crossover trial	199 patients were included in the intent-to-treat analysis; preference data were available for 178 patients—all aged ≥18 y (mean age 66 y)	Acceptability questionnaire and overall preference assessment	A logistic regression model was used to analyze the difference between the 2 formulations and provide an estimate of the sequence effect. A linear mixed model was used to analyze the secondary efficacy end points. SAS, version 8.2, was used in all statistical analyses.
Rodenhuis et al[28]	Netherlands	To measure patient satisfaction with score lines on tablets	Quantitative descriptive study	140 patients with prescriptions for scored tablets that had to be broken (50% of prescriptions broken by ≥60-y-olds)	Survey conducted by pharmacies to explore patient experiences with the functioning of the score line	Tabulation analyzing the prescriptions for scored tablets by age of breaker, negative evaluation, and type of negative evaluation. Data were also analyzed to explore negative evaluations of specific drugs and actions taken by the patient on negative evaluation.
Schiele et al[23]	Germany	To assess the prevalence of difficulties in swallowing oral solid dosage forms in a general practice population and to explore the reasons, nature, and characteristics of tablets and capsules causing these difficulties	Quantitative descriptive study	1051 patients taking at least 1 oral solid dosage form aged ≥18 y (mean age of those completing the medication list 62.7 y); 16 general practitioners (GPs)	Two structured questionnaires; GPs completed a separate questionnaire to predict swallowing difficulties	For the main questionnaire, a statistical analysis was conducted using the SAS statistical software package. Data from the medication lists were matched to a drug database. Medication characteristics such as the width, height, and diameter were analyzed in relation to any associations with swallowing difficulties.

Scott et al[21]	United Kingdom	To explore the relationship between alendronic acid formulations and patient acceptance and adherence	Quantitative descriptive study	33 inpatients from an Older People's Medicine ward completed the tablet questionnaire (median age 84.0 y), of whom 25 completed the liquid questionnaire	Following questionnaire testing, the Medication Acceptability Questionnaire and Medication Adherence Report Scale were used to assess acceptance and adherence of tablet and liquid formulations	Mean and 95% confidence intervals or median and interquartile range were calculated and used to describe global acceptability of the 2 formulations. The correlation between acceptability and each domain was calculated and a multiple linear regression model was estimated. This was used to identify which of the MAQ domains predict global formulation acceptability.
Vallet et al[22]	France	To confirm the validity of a multivariate approach toward assessing medicine acceptability and to develop a decision support tool for this multidimensional concept	Multicenter, cross-sectional observational study	1079 older patients in hospitals and nursing homes (mean age 86.4 y)	The health care professionals observed medicine use and filled out a standardized questionnaire consisting of measures describing acceptability	The observational procedures were explored using mapping and clustering to summarize the information into a reference framework. This involved using a multivariate data analysis procedure, using the R packages "FactorMineR" and "MissMDA." Resampling statistics were also used to validate the model's reliability.

particular shape.[16] In contrast, older people with dysphagia had a preference for "torpedo"-shaped tablets or capsules.[15]

Break marks are sometimes used to provide a means of overcoming challenges associated with larger tablets by allowing them to be broken into 2 halves that are swallowed separately. More often, a break mark enables dose flexibility by allowing half doses to be prescribed. However, neither purpose currently works well for older people who experience difficulties when the break mark does not function well, leading to use errors.[18] These include tablets breaking into unequal portions or crumbling and unintended breaking of the tablet.[18] Management techniques, including taking unequal halves, had the potential to cause severe discomfort or clinical deterioration.[17] These findings were supported by a further study investigating patient experiences with the performance of tablet score lines:[28] a total of 24 of 51 negative evaluations of the score line were reported in patients aged 60 years and older.[28]

Palatability

Texture, mouthfeel, and coating

Surface texture was the second most commonly reported cause (relating to the dosage form) of swallowing difficulties in people with dysphagia, with 70.5% of participants identifying a problem with this feature.[23] Surface characteristics further contributed to 18.5% of use difficulties in older people.[18] Participants used the term "chalky" to describe the texture of tablets that were difficult to take.[15] "Chalkiness" was also a variable that was directly measured to assess the acceptability of chewable formulations using the visual analog scale, and the results indicate an overall preference toward "not chalky at all" chewable formulations.[20]

The coating of the formulation is also important in determining the texture and mouthfeel, and further affects swallowability. In 1 study, 11 of 16 occasions when the medication became stuck in the mouth or throat occurred with uncoated tablets.[18] Of those who expressed a preference, 79% of older people preferred the coated tablet over the uncoated tablet.[19] Furthermore, patients taking uncoated tablets were found to require more water to swallow the tablet, took longer to swallow, and reported a higher incidence of the tablet being lodged within the esophagus.[25]

The nature of the coating, in addition to the presence of a coating, is important in determining acceptability and is evaluated on smoothness, stickiness, slipperiness, and palatability.[25] Paracetamol formulations that often have a "rugged coating" were most commonly reported as being the most difficult to swallow.[30] Furthermore, a "sticky coating" was reported to be the second most common cause of ongoing and past swallowing difficulties.[30]

Taste

Taste was significant in predicting the acceptability of an alendronic acid tablet formulation using the Medicine Acceptability Questionnaire.[21] Some active pharmaceutical ingredients, such as ferrous fumarate, have an inherently bitter taste and require taste masking with food.[17] The need for taste masking increased when medications were crushed; various substances such as milk, apple juice, bread, tea, and fruit smoothies were used to mask the "horrible" taste.[15] Further studies found that in 19% (205) of 1079 evaluations, older people used food or drink just before or after administration to mask the taste or to improve ease of swallowing.[22]

Chewable tablets and granules are commonly used for people with swallowing difficulties; however, the taste is significantly more important for these formulations, as they spend longer in the oral cavity. Taste was, therefore, consistently measured as a variable that would impact overall acceptability.[20,24,27] Although the taste of the chewable tablet was preferred to that of granules, comparing scores for all 5 acceptability variables (including taking the dose, time spent

Table 2
Findings in Relation to Formulation Characteristics

Author	Oral Solid Dosage Form	Formulation Characteristic	Key Findings	% Patients Aged ≥65 y	% Patients Aged ≥60 y	Mean Age, y
den Uyl et al[24]	Chewable tablets and sachets	Taste	The mean acceptability score for taste was higher for the tablet than for the powder. There was an overall significant preference for the chewable tablet.	59.4		66
Heikkilä et al[29]	Tablets and capsules	Shape Color "Splittability"	External characteristics including the shape and color were less significant than the familiarity of a medication, especially for older people.		39	54
Hofmanová et al[25]	Tablets	Coating Roughness Stickiness Slipperiness Palatability	Older people were able to distinguish between a coated and uncoated tablet. Coated tablets were more acceptable, and stickiness and roughness were most strongly linked to tablet acceptance. Palatability was not found to be associated with acceptability.	38.6		N/A
Jones et al[26]	Softgels, compressed tablets, gelatin-coated tablets, hard-shell capsules	Shape	The clear oval softgel was preferred most often, followed by the clear oblong softgel. The round compressed tablet was the least preferred.		36	N/A
Kelly et al[15]	Tablets and capsules	Shape Size Coating Texture Taste	Torpedo-shaped tablets or capsules were preferred. Small tablets were generally easier to swallow; however, small round tablets were also troublesome. A smooth coating was preferred. A "chalky" texture was described as troublesome. Taste was not a major issue unless tablets were crushed.		100	N/A
Liu et al[16]	Tablets, hard gelatin capsules, minitablets, granules, dispersible tablets, ODTs, chewable tablets	Size Shape Taste Appearance	Sizes of 11 mm and 13 mm started to cause difficulties swallowing. Mini tablets (4-mm) were considered easier to swallow; however, concerns were raised in relation to seeing and handling. Oval and oblong shapes were considered slightly easier to swallow than flat, round, and arched. There were concerns on taste for all dosage forms (apart from tablets and capsules). There were concerns on the appearance of granules.	100		74.0
Marquis et al[30]	Tablets, effervescent tablets, chewable tablets, powders, granules	Size Coating Taste Shape	Size was the most commonly reported cause of swallowing difficulties—63% of people with past or ongoing swallowing difficulties said size was the main cause. Coating was the second most commonly reported cause of swallowing difficulties, with 29.3% reporting difficulties with a "sticky tablet." 10.9% of those with past or ongoing difficulties said the "bad taste or smell" of the tablet was the cause of this. The main drawback of powders and granules was their taste. Shape was not mentioned as a trigger of swallowing difficulties.			66.5
Notenboom et al[17]	Tablets, dispersible tablets	Appearance Break marks Size Taste	Difficulties distinguishing between different strengths due to similarities in appearance led to discomfort and clinical deterioration. Breaking of tablets were reported as difficult or painful. 60.7% of problems relating to the taking of medicines were caused by the medicines lodging in the mouth or throat. 35% of problems relating to the taking of medicines were caused by the flavor of medicines, including ferrous fumarate.	100		78.4

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Table 2 (*continued*)

Author	Oral Solid Dosage Form	Formulation Characteristic	Key Findings	% Patients Aged ≥65 y	% Patients Aged ≥60 y	Mean Age, y
Notenboom et al[18]	Tablets, dispersible tablets	Dimensions Surface texture Appearance Break mark Taste	29.6% of use difficulties were due to the dimensions of the dosage form, including problems holding the medicine and problems swallowing. 18.5% of use difficulties were due to the surface texture, which led to problems swallowing and medicines getting stuck in the throat. Of the 16 medicines that got stuck in the throat, 11 were uncoated tablets. 3 use difficulties and 7 use errors were the result of the appearance of oral solid dosage forms (OSDFs), which led to difficulties distinguishing between tablets. 3 use difficulties and 5 use errors were due to break marks not functioning well. 6 use difficulties and 4 use errors were due to the unpleasant taste.	100		78.4
Phillips et al[19]	Tablets	Coating	50% of patients reported no preference for a coated or uncoated formulation. Of those who expressed a preference, 79% preferred the film-coated tablet, the main reasons being that it was “smoother” and “easier to swallow.”		100	82
Rees and Howe[20]	Chewable tablets	Taste Chewiness Grittiness Chalkiness Ease of swallowing Stickiness	Two high-dose preparations of calcium and vitamin D were compared: Calcichew D3 Forte (CDF) and Ad Cal D_3 (ACD). Although these were similar in terms of dose and active constituents, there was a statistically significant difference in all scores except taste, indicating one formulation (CDF) was more acceptable than the other (ACD); overall, 79.8% of patients stated a preference for CDF, 10.6% preferred ACD, and 9.6% had no preference.		100	72.6
Reginster et al[27]	Chewable tablets and sachets	Taste	Mean acceptability score was higher for the tablet than for the powder; however, taste scored the lowest overall acceptability score out of all 5 acceptability variables. An overall significant preference was observed for the chewable tablet; 73.3% of patients aged ≥65 y preferred the tablet.	56.3		66
Rodenhuis et al[28]	Scored tablets	Score line	A total of 24 of 51 negative evaluations of the score line was reported in patients aged ≥60 y, mainly because of a combination of “unequal halves,” “crumbs,” and the tablet being “difficult to break.” The authors report that it was not possible to detect any significant differences between the groups 20-40 y and 60-75 y; however, this was not proven statistically.		50	N/A
Schiele et al[23]	Tablets and capsules	Size Surface Shape Flavor	74.6% of difficulties related to the dosage form were due to size; however, acceptable size was related to the shape. For example, swallowing difficulties were only slightly more frequent with oval tablets that had a length of almost twice the diameter of circular tablets. 70.5% of difficulties related to the dosage form were due to surface. 43.5% of difficulties related to the dosage form were due to shape: hard gelatin capsules, soft gelatin capsules, and oblong tablets caused a greater number of problems in comparison to round and oval tablets. 22.1% of difficulties related to the dosage form were due to “flavor.” NB: The older people included in this study reported fewer swallowing difficulties. Therefore, they reported fewer preferences for dosage form characteristics; eg, approximately 70% of patients without swallowing difficulties reported no preferences for the shape of OSDFs.			61.8

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Table 2 (*continued*)

Author	Oral Solid Dosage Form	Formulation Characteristic	Key Findings	% Patients Aged ≥65 y	% Patients Aged ≥60 y	Mean Age, y
Scott et al[21]	Tablet	Taste Appearance	When exploring the convenience, taste, appearance, efficacy, and tolerability of the tablet vs the liquid, the median scores for both formulations were similar: there were no significant differences between the 2 formulations. The median global acceptability score was marginally higher for the tablet formulation, and the 2 factors that made a significant contribution toward predicting global acceptability of the tablet were taste and appearance.	100		N/A
Vallet et al[22]	Divisible tablet, coated tablet, divisible coated tablet, capsule tablet, orally disintegrating tablet	Taste Size	13% of patients (140 patients) required the dose to be divided as it could not be taken whole. 19% of patients (205 patients) required the use of food or drink to mask the taste or ease swallowing. When exploring medicine "Y" (a psycholeptic drug), differences in subpopulations of patients were found, with a higher acceptability in older patients without swallowing disorders.	100		86.4

taking, removing the dose from the container, and general convenience of taking) found that taste was given the lowest overall acceptability score.[24,27] The unpleasant taste of chewable formulations led to some older people swallowing the tablet whole instead of chewing,[17] and the issue of taste was also highlighted as a drawback of dispersible formulations.[16,18,30]

Appearance

Difficulties distinguishing between different strengths because of similarities in appearance led to discomfort and clinical deterioration,[17] although sometimes additional markings such as embossments could help patients differentiate tablets.[18] Smaller tablets, including mini tablets, were difficult to see, especially for older people with visual impairments.[16] Conversely, large tablets can lead to a psychological block and anxiety before taking medication.[18]

The type of dosage affected older people's views on appearance. Concerns were raised in relation to the appearance of granules, which were considered the least acceptable "alternative dosage form" alongside chewable tablets in older people.[16] Furthermore, when comparing tablet and liquid formulations of alendronic acid, there was a general trend for the liquid to perform better in terms of appearance, although this difference was not statistically significant.[21]

No study was identified that directly investigated the impact of color on acceptability of oral solid dosage forms within the older population. A preference survey conducted across ages found color to have little importance; however, this survey looked primarily at preference for soft gels.[26] A further study on generic substitution that found external characteristics, including the color of prescription medication, were less significant than familiarity.[29]

Discussion

As far as the authors are aware, this is the first systematic review that has focused on how the characteristics of oral solid dosage forms affect acceptance and adherence in older people. A preliminary review to identify studies investigating the appropriateness of medication for older patients was performed in 2015.[31] This preliminary review looked at the "appropriateness" of all medication, including the route of administration, drug delivery technology, and frequency of dosing.[31] Both the preliminary review and this one support the urgent need for further research in this area, with the present review highlighting a specific gap in relation to formulation characteristics. In particular, 3 key areas were identified by this review that require further research: the dimensions, palatability, and appearance of oral solid dosage forms.

The dimensions and palatability of oral solid dosage forms both affect swallowability, and inappropriate characteristics in either category can lead to patients modifying the drug product. Manipulating dosage forms is a source of medication error and harm[32] and can lead to nonadherence.[33] Although palatability has been extensively researched (13 of the 16 included studies explored some aspect of palatability), further work is needed in the final category—appearance. This area is especially significant for older people who often use external characteristics rather than the product label to recognize their medication.[2] Studies in the adult population have found that the use of multiple medications increases the likelihood of a preference toward brightly colored tablets,[34] and bichromatic dosage forms (those with 2 colors) aid rapid identification of the tablet.[35] The risk of clinical deterioration due to similarities in appearance was supported by only 1 study in this review,[17] highlighting the urgent need for further research in this area.

This review is of particular relevance for clinicians working with older people; 1 in 9 older community-dwelling adults have symptoms that amount to dysphagia that are likely to be under-reported and under-recognized.[36] Older people with degenerative neurologic conditions such as dementia are at highest risk of dysphagia, as the cognitive impairment impairs their feeding and swallowing abilities; however, dysphagia is again often not recognized in these patients.[37] As patients rarely report any difficulties, health care professionals should proactively enquire about practical problems.[15,17,30] Pharmacists in particular can then use this information to select a dosage form that causes fewer swallowing difficulties.[17,23] Where no suitable oral solid formulation is available, this may involve collaboration between professionals to provide an alternative such as a liquid formulation. However, there is a greater need to ensure acceptable palatability for these preparations, and studies have found that liquids are a suboptimal alternative to oral solid dosage forms in patients with swallowing difficulties.[38] Health care professionals must therefore work closely with patients to understand their attitudes toward their treatment and share decision making on formulation choice with older patients.

This systematic review was conducted by an interdisciplinary team with expertise in formulation and clinical pharmacy. It used standard systematic methods to conduct an extensive literature search and screen relevant studies. The protocol was registered on PROSPERO prior to screening to reduce potential for bias. However, a key

limitation is the inherent lack of research in this area. The inclusion criteria for the study were broad, although only 5 studies were identified that directly investigated this phenomenon in older people.[16,19–22] Furthermore, there was a lack of data on ethnicity and on whether improvements in formulation led to any changes in clinical outcomes. Five studies were found to be sponsored by or receive funding from the pharmaceutical industry.[21,24–27] Research was mainly conducted in affluent countries, and the inclusion of English-language studies only may limit generalizability.

The 3 qualitative studies gave a deeper insight into the challenges older people face when managing medication; however, all focused on general medication-taking practices. Further qualitative work should aim to specifically focus on formulation characteristics, looking in particular at the 3 categories identified from this review. This qualitative work should also aim to involve a wider range of people involved in an older person's therapy. The systematic review found a single study that involved General Practitioners, in which their awareness of swallowing difficulties was assessed;[23] however, no studies were identified that involved formal or informal caregivers.

Eight of the 16 studies included in the review included younger adults, and the findings highlight preferences for dosage forms that are easy to swallow.[23,25,26,30] It would therefore be valuable for future research to consider a patient-centric drug product for older people in comparison to that for the general adult population in order to highlight any significant differences.

Conclusions and Implications

Adherence to medication is complicated by a number of drug therapy–associated factors in older people, namely, the number of medications, duration of treatment, tablet characteristics, and the dosage regimen. Although the majority of these are difficult to modify, ensuring that patients receive an acceptable formulation is a key intervention that can help reduce nonadherence. Manufacturers must take into account the practical problems older people may encounter when considering the dimensions, palatability, and appearance of the final drug product. These characteristics should be optimized to aid visual identification and swallowability. Medical providers and pharmacists have an important role in ensuring that these patient-centric drug products are prescribed and dispensed appropriately so that patients receive the most suitable formulation. Future work must therefore take a multidisciplinary approach so that gaps in perceived responsibilities in this area can be identified and addressed.

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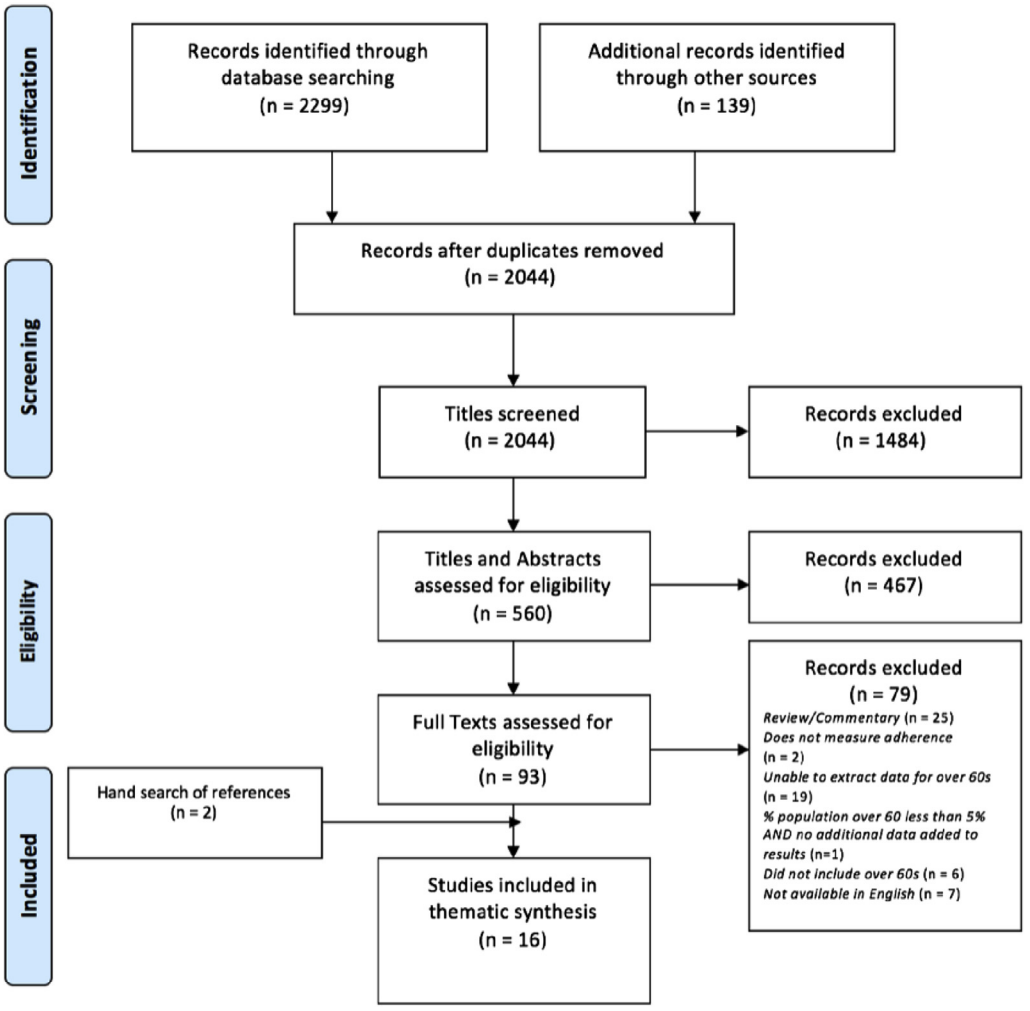
Appendix



Supplementary Figure 1. PRISMA Flow Chart depicting the main stages of the systematic review process.

Supplementary Table 1
PRISMA Checklist

Section/Topic	No.	Checklist Item	Reported on Page No.
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	6 and Supplementary Table 2
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 and Supplementary Table 2
Search	8	Present full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplementary Table 2
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	7, 25-32
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	Supplementary Table 4
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	N/A
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	24
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	25-32
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study (1) simple summary data for each intervention group and (2) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Table 4
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy makers).	15-20
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-20
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	Title Page

Supplementary Table 2
Search Strategy for Systematic Review

MEDLINE Search Strategy (May 2019)	
1	1) ((MH=(Chemistry, Pharmaceutical)) OR TS= Pharmaceutical design OR TS= dosage form design OR TS= medic* design OR TS= drug product design OR TS= pharmaceutical formulation OR TS= drug formulation OR TS= medic* formulation OR TS= formulation factors OR TS= patient centric OR TS= patient-centric OR TS= physical characteristics OR TS= physical attributes OR TS= appearance OR TS= tablet dress OR MH=(Patient-Centered))
2	2) ((MH=(Administration, Oral) OR TS= "Oral solid" OR TS= "oral dosage" OR TS= "solid oral" OR TS= "solid dosage" OR TS= *tablet* OR TS= *capsule* OR TS= chewable OR TS= orodispersible OR TS= effervescent OR TS= "small tablet$" OR TS= "mini tablet$" OR TS= "hard capsule$" OR TS= "soft capsule$" OR TS= "fixed dose combination$"))
3	3) (((MH=(Patient Compliance OR Medication Adherence OR Treatment Refusal OR Patient Preference))))
4	4) TS= elderly OR TS= aged OR TS= older OR TS= geriatric OR TS= "over 60"
5	1 AND 2 AND 3 AND 4
Cochrane Library Search Strategy (May 2019)	
1	("pharmaceutical design" or "dosage form design" or "medic* design" or "drug product design" or "pharmaceutical formulation" or "drug formulation" or "medic* formulation" or "formulation factors" or "patient centric" or "patient-centric" or "physical characteristics" or "physical attributes" or appearance or "tablet dress") in Title Abstract Keyword
2	("Oral solid" or "oral dosage" or "solid oral" or "solid dosage" or *tablet* or *capsule* or chewable or orodispersible or effervescent or "small tablet" or "mini tablet" or "hard capsule" or "soft capsule" or "fixed dose combination") in Title Abstract Keyword
3	(appropriate* OR acceptab* OR usab* OR swallow* OR dysphagia OR prefer* OR persist* OR adhere* OR complian* OR nonadhere* OR non-adhere* OR noncomplian* OR non-complian* OR concordan*) in Title Abstract Keyword
4	(elderly OR aged OR older OR geriatric OR "over 60")
5	1 AND 2 AND 3 AND 4
Scopus (May 2019)	
1	TITLE-ABS-KEY ("Pharmaceutical design" OR "dosage form design" OR "medic* design" OR "drug product design" OR "pharmaceutical formulation" OR "drug formulation" OR "medic* formulation" OR "formulation factors" OR "patient centric" OR "physical characteristics" OR "physical attributes" OR appearance OR "tablet dress")
2	TITLE-ABS-KEY ("Oral solid" OR "oral dosage" OR "solid oral" OR "solid dosage" OR *tablet* OR *capsule* OR chewable OR orodispersible OR effervescent OR "small tablet" OR "mini tablet" OR "hard capsule" OR "soft capsule" OR "fixed dose combination")
3	TITLE-ABS-KEY (appropriate* OR acceptab* OR usab* OR swallow* OR dysphagia OR prefer* OR persist* OR adhere* OR complian* OR nonadhere* OR non-adhere* OR noncomplian* OR non-complian* OR concordan*)
4	TITLE-ABS-KEY (elderly OR aged OR older OR geriatric OR "over 60")
5	1 AND 2 AND 3 AND 4
Web of Science (May 2019)	
1	TS= "Pharmaceutical design" OR TS= "dosage form design" OR TS= "medic* design" OR TS= "drug product design" OR TS= "pharmaceutical formulation" OR TS= "drug formulation" OR TS= "medic* formulation" OR TS= "formulation factors" OR TS= "patient centric" OR TS= "patient-centric" OR TS= "physical characteristics" OR TS= "physical attributes" OR TS= appearance OR TS= "tablet dress"
2	TS= "Oral solid" OR TS= "oral dosage" OR TS= "solid oral" OR TS= "solid dosage" OR TS= *tablet* OR TS= *capsule* OR TS= chewable OR TS= orodispersible OR TS= effervescent OR TS= "small tablet$" OR TS= "mini tablet$" OR TS= "hard capsule$" OR TS= "soft capsule$" OR TS= "fixed dose combination$"
3	TS= Appropriate* OR TS= acceptab* OR TS= usab* OR TS= swallow* OR TS= dysphagia OR TS= prefer* OR TS= persist* OR TS= adhere* OR TS= complian* OR TS= nonadhere* OR TS= non-adhere* OR TS= noncomplian* OR TS= non-complian* OR TS= concordan*
4	TS= elderly OR TS= aged OR TS= older OR TS= geriatric OR TS= "over 60"
5	1 AND 2 AND 3 AND 4
Google Scholar Search Strategy (June 2018)	
1	"Oral Solid"
2	Adherence
3	"Older"
4	1 AND 2 AND 3

Other Sources: 1. BASE (May 2019)"oral solid" "adherence" "older" 2. EThOS (May 2019)"oral" AND "adherence" AND "older people" 3. OpenGrey (May 2019)("oral") AND (adherence) AND (older OR elderly OR geriatric OR "over 60") 4. WoS Conference Proceedings: Conference Proceedings Citation Index- Science (CPCI-S) –1990-present (May 2019)TOPIC: (oral AND (older OR elderly OR geriatric) AND adherence).
"Over 60s" was defined as the included population for this review in order to ensure all relevant studies were identified. The scoping search found a number of studies that had potentially relevant data for this systematic review but that defined or categorized the older person as "over 60."

Supplementary Table 3
Reasons for Exclusion

No.	Study Name	Reason for Exclusion
1	Aleksovski A, Dreu R, Gašperlin M, Planinšek O. Mini-tablets: A contemporary system for oral drug delivery in targeted patient groups. Expert Opin Drug Deliv 2015;12:65-84.	Review from which no additional references were found
2	Andersen O, Zweidorff OK, Hjelde T, Rodland EA. Problems when swallowing tablets. A questionnaire study from general practice. Tidsskr Nor Lageforen 1995;115:947-949.	Only available in German
3	Argoff CE, Kopecky EA. Patients with chronic pain and dysphagia (CPD): Unmet medical needs and pharmacologic treatment options. Curr Med Res Opin 2014;30:2543-2559.	Review from which no additional references were found
4	Bayer AJ, Day JJ, Finucane P, Pathy MSJ. Bioavailability and acceptability of a dispersible formulation of levodopa-benserazide in parkinsonian patients with and without dysphagia. J Clin Pharm Ther 1988;13:191-194.	Does not explore the formulation characteristics that affected preference for each formulation
5	Bhosle M, Benner JS, Dekoven M, Shelton J. Difficult to swallow: Patient preferences for alternative valproate pharmaceutical formulations. Patient Prefer Adherence 2009;3:161-171.	1.2% (5 participants) aged ≥65 y and no data provided that would added to results
6	Bitter I, Treuer T, Dilbaz N, et al. Patients' preference for olanzapine orodispersible tablet compared with conventional oral tablet in a multinational, randomized, crossover study. World J Biol Psychiatry 2010;11:894-903.	Participants aged 18-65 y; however, unable to extract data for older people
7	Blanco MA, Prieto M, Mearin F, et al; El Grupo Del Estudio LAN/41/01. Evaluation of preferences in patients with gastroesophageal reflux disease and dysphagia concerning treatment with lansoprazole orally disintegrating tablets. Gastroenterol Hepatol 2009;32:542-548.	Only available in Spanish
8	Boateng J. Drug delivery innovations to address global health challenges for pediatric and geriatric populations (through improvements in patient compliance). J Pharm Sci 2017;106:3188-3198.	Commentary from which no additional references were found
9	Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. Expert Opin Drug Deliv 2007;4:37-45.	Review from which no additional references were found
10	Buckalew LW, Ross S. Medication property effects on expectations of action. Drug Dev Res 1991;23:101-108.	Unable to extract data for older people on preferences for formulation characteristics. Focus is more on perceived indications based on color.
11	Casian T, Bogdan C, Tarta D, et al. Assessment of oral formulation-dependent characteristics of orodispersible tablets using texture profiles and multivariate data analysis. J Pharm Biomed Anal 2018;152:47-56.	Participants aged 22-57 y
12	Channer KS, Virjee JP. The effect of formulation on oesophageal transit. J Pharm Pharmacol 1985;37:126-129.	Unable to extract data for older people because of differences in mean age between the groups given differing formulations; focus on esophageal transit rather than patient acceptability.
13	Chu XY, Gao CH, Ge C, Gao CS. Progress in researches of patient-centric individualized formulation approaches. Chin J New Drugs 2018;27:409-416.	Only available in Chinese
14	Danileviciute V, Adomaitiene V, Sveikata A, et al. Compliance in psychiatry: Results of a survey of depressed patients using orally disintegrating tablet. Medicina (Kaunas) 2006;42:1006-1012.	Only available in Lithuanian
15	De Argila CM, Ponce J, Marquez E, et al. Acceptability of lansoprazole orally disintegrating tablets in patients with gastro-oesophageal reflux disease: ACEPTO study. Clin Drug Invest 2007;27:765-770.	Unable to extract data for older people
16	Denneboom W, Dautzenberg MGH, Grol R, De Smet PAGM. User-related pharmaceutical care problems and factors affecting them: The importance of clinical relevance. J Clin Pharm Ther 2005;30:215-223.	Does not explore formulation as defined for the review
17	Derosa G, Romano D, Bianchi L, et al. Metformin powder formulation compared to metformin tablets on glycemic control and on treatment satisfaction in subjects with type 2 diabetes mellitus. J Clin Pharmacol 2015;55:409-414.	Does not explore the formulation characteristics that affected preference for each formulation
18	Desai RJ, Sarpatwari A, Dejene S, et al. Differences in rates of switchbacks after switching from branded to authorized generic and branded to generic drug products: Cohort study. BMJ (Clin Res Ed) 2018;361:k1180.	Does not explore the formulation characteristics that impacted the rates of switchbacks in sufficient detail for the review
19	Drumond N, Van Riet-Nales DA, Karapinar-Carkit F, Stegemann S. Patients' appropriateness, acceptability, usability and preferences for pharmaceutical preparations: Results from a literature review on clinical evidence. Int J Pharm 2017;521:294-305.	Review from which no additional references were found
20	Faisal W, Farag F, Abdellatif AAH, Abbas A. Taste masking approaches for medicines. Curr Drug Deliv 2018;15:167-185.	Review from which no additional references were found
21	Forough AS, Lau ET, Steadman KJ, et al. A spoonful of sugar helps the medicine go down? A review of strategies for making pills easier to swallow. Patient Prefer Adherence 2018;12:1337.	Review—additional reference (Schiele et al, 2013) retrieved
22	Goyanes A, Scarpa M, Kamlow M, et al. Patient acceptability of 3D printed medicines. Int J Pharm 2017;530:71-78.	Participants aged 18-45 y
23	Grady H, Kukulka MJ, Ono T, Nudurupati SV. Evaluation of physical characteristics of dexlansoprazole orally disintegrating tablets. Pharm Technol 2018;42:30-37.	Unable to extract data for older people
24	Hanning SM, Lopez FL, Wong ICK, et al. Patient centric formulations for paediatrics and geriatrics: Similarities and differences. Int J Pharm 2016;512:355-359.	Review from which no additional references were found

(*continued on next page*)

Supplementary Table 3 (*continued*)

No.	Study Name	Reason for Exclusion
25	Hey H, Jørgensen F, Sørensen K, et al. Oesophageal transit of six commonly used tablets and capsules. BMJ 1982;285:1717-1719.	Focus on esophageal transit of medication rather than patient adherence or acceptance
26	Howell EH, Senapati A, Hsich E, Gorodeski EZ. Medication self-management skills and cognitive impairment in older adults hospitalized for heart failure: A cross-sectional study. SAGE Open Med 2017;5:2050312117700301.	Does not explore formulation as defined for the review; focus more on the impact of cognitive impairment on health literacy
27	Ibrahim IR, Izham MM, Al-Haddad M. Consumer preferences and perceptions towards the use of colored oral solid dosage forms in Baghdad. Arch Pharm Pract 2010;1:15.	Unable to extract data for older people
28	Imai K. Alendronate sodium hydrate (oral jelly) for the treatment of osteoporosis: Review of a novel, easy to swallow formulation. Clin Interv Aging 2013;8:681-688.	Review from which no additional references were found
29	Jamison J, Sutton S, Mant J, De Simoni A. Barriers and facilitators to adherence to secondary stroke prevention medications after stroke: Analysis of survivors and caregivers views from an online stroke forum. BMJ Open 2017;7:e016814.	Does not explore formulation in older people as defined for the review
30	Kakuda TN, Berckmans C, De Smedt G, et al. Single-dose pharmacokinetics of pediatric and adult formulations of etravirine and swallowability of the 200-mg tablet: results from three phase 1 studies. Int J Clin Pharmacol Ther 2013;51:725-737.	Unable to extract data for older people; mean age 49 y for swallowability study
31	Kelly J, D'Cruz G, Wright D. A qualitative study of the problems surrounding medicine administration to patients with dysphagia. Dysphagia 2009;24:49-56.	Does not explore formulation as defined for the review; focus more on health care professionals' administration of medication
32	Kraemer S, Chartier F, Augendre-Ferrante B, et al. Effectiveness of two formulations of oral olanzapine in patients with schizophrenia or bipolar disorder in a natural setting: Results from a 1-year European observational study. Hum Psychopharmacol 2012;27:284-294.	Unable to extract data for older people
33	Lam PW, Lum CM, Leung MF. Drug non-adherence and associated risk factors among Chinese geriatric patients in Hong Kong. Hong Kong Med J 2007;13:284-292.	Does not explore formulation factors that may lead to nonadherence as defined for the review
34	Lenahan JL, McCarthy DM, Davis TC, et al. A drug by any other name: Patients' ability to identify medication regimens and its association with adherence and health outcomes. J Health Commun 2013;18:31-39.	Does not explore formulation factors which may impact adherence or acceptance as defined for the review
35	Liu F, Ranmal S, Batchelor HK, et al. Patient-centred pharmaceutical design to improve acceptability of medicines: Similarities and differences in paediatric and geriatric populations. Drugs 2014;74:1871-1889.	Review from which no additional references were found
36	Liu Y, Li P, Qian R, et al. A novel and discriminative method of in vitro disintegration time for preparation and optimization of taste-masked orally disintegrating tablets of carbinoxamine maleate. Drug Dev Ind Pharm 2018;44:1317-1327.	In vivo testing carried out in 6 healthy volunteers; unable to extract data for older people
37	Lopez FL, Bowles A, Gul MO, et al. Effect of formulation variables on oral grittiness and preferences of multiparticulate formulations in adult volunteers. Eur J Pharm Sci 2016;92:156-162.	Participants aged 20-25 y
38	Lumbreras B, Lopez-Pintor E. Impact of changes in pill appearance in the adherence to angiotensin receptor blockers and in the blood pressure levels: A retrospective cohort study. BMJ Open 2017;7.	Does not explore the formulation characteristics in detail that may lead to a change in adherence
39	Mackenzie-Smith L, Marchi P, Thorne H, et al. Patient preference and physician perceptions of patient preference for oral pharmaceutical formulations: Results from a real-life survey. Inflamm Intest Dis 2018;3:43-51.	Unable to extract data for older people
40	Marquez-Contreras E, Gil V, Lopez J, et al. Pharmacological compliance and acceptability of lansoprazole orally disintegrating tablets in primary care. Curr Med Res Opin 2008;24:569-576.	Unable to extract preferences for formulation characteristics for older people
41	Matuszewski K, Kapusnik-Uner J, Man M, et al. Variation in generic drug manufacturers' product characteristics. Pharm Ther 2018;43:485-504.	Does not measure impact of formulation on adherence or acceptance as defined for the review
42	McGillicuddy A, Kelly M, Sweeney C, et al. Modification of oral dosage forms for the older adult: An Irish prevalence study. Int J Pharm 2016;510:386-393.	Does not explore the formulation characteristics that led to swallowing difficulties and the resulting modifications
43	McGillicuddy A, Kelly M, Crean AM, SAHM LJ. Understanding the knowledge, attitudes and beliefs of community-dwelling older adults and their carers about the modification of oral medicines: A qualitative interview study to inform healthcare professional practice. Res Social Adm Pharm 2019.	Conference Abstract (published paper not yet available)
44	Mehuys E, Dupond L, Petrovic M, et al. Medication management among home-dwelling older patients with chronic diseases: Possible roles for community pharmacists. J Nutr Health Aging 2012;16:721-726.	Does not explore the formulation characteristics that cause the practical problems when taking medicines
45	Miehlke S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut 2016;65:390.	Does not explore the characteristics of each formulation that led to the patient's preferred preference
46	Miller CA. Safe medication practices: Administering medications to elders who have difficulty swallowing. Geriatr Nurs 2003;24:378-379.	Review from which no additional references were found
47	Ogata I, Yamasaki K, Tsuruda A, et al. Some problems for dosage form based on questionnaire surveying compliance in patients taking tamsulosin hydrochloride. Yakugaku zasshi: Journal of the Pharmaceutical Society of Japan 2008;128:291-297.	Only available in Japanese

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Supplementary Table 3 (*continued*)

No.	Study Name	Reason for Exclusion
48	Papanastasiou A, Kalantzi L. Innovation in formulation development for older people. J Aging Sci 2018;6:2.	Review from which no additional references were found
49	Park C, Meghani NM, Amin HH, et al. Patient-centered drug delivery and its potential applications for unmet medical needs. Ther Deliv 2017;8:775-790.	Review from which no additional references were found
50	Patel MX, De Zoysa N, Bernadt M, David A. Depot and oral antipsychotics: Patient preferences and attitudes are not the same thing. J Psychopharmacol 2009;23:789-796.	Does not explore formulation characteristics of the oral antipsychotics as defined for the review
51	Patsalos PN, Russell-Jones D, Finnerty G, et al. The efficacy and tolerability of chewable carbamazepine compared to conventional carbamazepine in patients with epilepsy. Epilepsy Res 1990;5:235-239.	Does not explore the formulation characteristics that led to a preference for either formulation
52	Pepić I, Lovrić J. Challenges in patient-centric oral dosage form design—The example of sumamed®. Medicus 2018;27:171-175.	Only available in Croatian
53	Pereira BC, Isreb A, Forbes RT, et al. "Temporary Plasticiser": A novel solution to fabricate 3D printed patient-centred cardiovascular "Polypill" architectures. Eur J Pharm Biopharm 2019;135:94-103.	Unable to extract data for older people (only in vitro testing conducted)
54	Perkins AC, Wilson CG, Frier M, et al. Esophageal transit of risedronate cellulose-coated tablet and gelatin capsule formulations. Int J Pharm 1999;186:169-175.	Does not measure patient adherence or acceptance, rather looks at esophageal transit
55	Quinn HL, Hughes CM, Donnelly RF. Novel methods of drug administration for the treatment and care of older patients. Int J Pharm 2016;512:366-373.	Review from which no additional references were found
56	Reilly TM. Medication management in the elderly: Major opportunity for advances in drug delivery & formulation technologies. Drug Deliv Technol 2009;9:52-57.	Review from which no additional references were found
57	Roger A, Fortea J, Mora S, Artés M. Ebastine fast-dissolving tablets versus regular tablets: Acceptability and preference in patients with allergic rhinitis. Expert Rev Clin Pharmacol 2008;1:381-389.	Sample excludes older people
58	Roger Reig A, Plazas Fernandez MJ, Galvan Cervera J, et al. Acceptance survey of a fast dissolving tablet pharmaceutical formulation in allergic patients. Satisfaction and expectancies. Allergol Immunopathol 2006;34:107-112.	Unable to extract data for older people
59	Roman B. Patients' attitudes towards generic substitution of oral atypical antipsychotics: A questionnaire-based survey in a hypothetical pharmacy setting. CNS Drugs 2009;23:693-701.	Unable to extract data for older people
60	Roose SP. Compliance: The impact of adverse events and tolerability on the physician's treatment decisions. Eur Neuropsychopharmacol 2003;13:S85-92.	Review from which no additional references were found
61	Sajatovic M, Thompson TR, Nanry K, et al. Prospective, open-label trial measuring satisfaction and convenience of two formulations of lamotrigine in subjects with mood disorders. Patient Prefer Adherence 2013;7:411-417.	Unable to extract data for older people
62	Satyanarayana DA, Kulkarni PK, Shivakumar HG. Gels and jellies as a dosage form for dysphagia patients: A review. Curr Drug Therapy 2011;6:79-86.	Review from which no additional references were found
63	Schwartz JI, Yeh KC, Berger ML, et al. Novel oral medication delivery system for famotidine. J Clin Pharmacol 1995;35:362-367.	Unable to extract data for older people on the formulation characteristics of the wafer and tablet that led to patient preference
64	Serrano-Castro PJ, Mauri-Llerda JA, Garcia A, et al. Treatment adherence with levetiracetam: a non-interventionist retrospective observation-based study. Rev Neurol 2016;62:481-486.	Only available in Spanish
65	Slavkova M, Breitkreutz J. Orodispersible drug formulations for children and elderly. Eur J Pharm Sci 2015;75:2-9.	Review from which no additional references were found
66	Stegemann S, Gosch M, Breitkreutz J. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. Int J Pharm 2012;430:197-206.	Review from which no additional references were found
67	Stegemann S, Ternik R. L, Onder G, et al. Defining patient centric pharmaceutical drug product design. AAPS J 2016;18:1047-1055.	White paper; no additional references found
68	Tahaineh L, Wazaify M. Difficulties in swallowing oral medications in Jordan. Int J Clin Pharm 2017:39:373-379.	Unable to extract data for older people
69	Tao D, Wang T, Wang T, Qu X. Influence of drug colour on perceived drug effects and efficacy. Ergonomics 2018;61:284-294.	Unable to extract data for older people
70	Thirion O, Neggazi N, Almaqdissi A, et al. "Patient centric design": Contribution to medicine safety. STP Pharma Pratiq 2014;24:347-351.	Review article from which no additional references were found
71	Trenfield SJ, Awad A, Goyanes A, et al. 3D printing pharmaceuticals: Drug development to frontline care. Trends Pharmacol Sci 2018;39:440-451.	Review from which no additional references were found
72	Trivedi MR, Patel HH, Dave RH. A Review on tablet scoring: Background, history and current regulatory considerations. Br J Pharm Res 2017;20.	Review from which no additional references were found
73	Van Riet-Nales DA, Hussain N, Sundberg KAE, et al. Regulatory incentives to ensure better medicines for older people: From ICH E7 to the EMA reflection paper on quality aspects. Int J Pharm 2016;512:343-351.	Review from which no additional references were found
74	Walsh J, Ranmal S. R, Ernest TB, Liu F. Patient acceptability, safety and access: A balancing act for selecting age-appropriate oral dosage forms for paediatric and geriatric populations. Int J Pharm 2018;536:547-562.	Review from which no additional references were found

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Supplementary Table 3 (*continued*)

No.	Study Name	Reason for Exclusion
75	Wight LJ, Vandenburg MJ, Potter CE, Freeth CJ. A large scale comparative study in general practice with nitroglycerin spray and tablet formulations in elderly patients with angina pectoris. European J Clin Pharmacol 1992:42:341-342.	Does not explore the characteristics of each formulation that led to the patient's preferred preference
76	Williams B, Shaw A, Durrant R, et al. Patient perspectives on multiple medications versus combined pills: a qualitative study. QJM 2005;98:885-893.	Does not explore the formulation characteristics in detail that impact acceptability as defined for the review
77	Yanze MF, Duru C, Jacob M, et al. Rapid therapeutic response onset of a new pharmaceutical form of chloroquine phosphate 300 mg: Effervescent tablets. Tropic Med Int Health 2001;6:196-201.	Participants aged between 19-51 y
78	Zanardi R, Colombo L, Marcheggiani E, et al. Paroxetine drops versus paroxetine tablets: Evaluation of compliance in a six-month study. Riv Psichiatr 2013;48:261-267.	Unable to extract data for older people
79	Zgraggen L, Fare PB, Lava SAG, et al. Palatability of crushed SS-blockers, converting enzyme inhibitors and thiazides. J Clin Pharm Ther 2012;37:544-546.	Participants aged between 24-50

Supplementary Table 4
Quality Appraisal of Included Studies Using the MMAT*

First Author	1. Qualitative Studies†					Pharma Sponsored or Funding‖
	1.1. Is the Qualitative Approach Appropriate to Answer the Research Question?	1.2. Are the Qualitative Data Collection Methods Adequate to Address the Research Question?	1.3. Are the Findings Adequately Derived From the Data?	1.4. Is the Interpretation of Results Sufficiently Substantiated by Data?	1.5. Is There Coherence Between Qualitative Data Sources, Collection, Analysis and Interpretation?	
Kelly[18]	Yes	Yes	Yes	Yes	Yes	No
Notenboom[20]	Yes	Yes	Yes	Yes	Yes	No
Notenboom[21]	Yes	Yes	Yes	Yes	Yes	No
First Author	2. Randomized Controlled Trials§					Pharma Sponsored or Funding
	2.1. Is Randomization Appropriately Performed?	2.2. Are the Groups Comparable at Baseline?	2.3. Are There Complete Outcome Data?	2.4. Are Outcome Assessors Blinded to the Intervention Provided?	2.5 Did the Participants Adhere to the Assigned Intervention?	
den Uyl[27]	Yes	Can't tell	Yes	No	Yes	Yes
Hofmanová[28]	Yes	Can't tell	Yes	Yes	Yes	Yes
Philips[22]	Can't tell	Can't tell	No	Can't tell	Yes	No
Rees[23]	Can't tell	Yes	Yes	Yes	Yes	No
Reginster[30]	Yes	Can't tell	No	No	No	Yes
First Author	3. Quantitative Nonrandomized Studies					Pharma Sponsored or Funding
	3.1. Are the Participants Representative of the Target Population?	Are Measurements Appropriate Regarding Both the Outcome and Intervention (or Exposure)?	3.3. Are There Complete Outcome Data?	3.4. Are the Confounders Accounted for in the Design and Analysis?	3.5. During the Study Period, Is the Intervention Administered (or Exposure Occurred) as Intended?	
Scott[24]	Yes	Yes	No	Yes	Yes	Yes
Vallet[25]	Yes	Yes	Yes	Yes	Can't tell	No
First Author	4. Quantitative Descriptive Studies‡					Pharma Sponsored or Funding
	4.1. Is the Sampling Strategy Relevant to Address the Research Question?	4.2. Is the Sample Representative of the Target Population?	4.3. Are the Measurements Appropriate?	4.4. Is the Risk of Nonresponse Bias Low?	4.5. Is the Statistical Analysis Appropriate to Answer the Research Question?	
Heikkilä[32]	Yes	Yes	Yes	Yes	Yes	No
Jones[29]	No	No	Can't tell	Can't tell	No	Yes
Liu[19]	Yes	Yes	Yes	Can't tell	Yes	No
Marquis[33]	Yes	Yes	Can't tell	No	Yes	No
Rodenhuis[31]	Can't tell	Can't tell	Can't tell	Can't tell	No	No
Schiele[26]	Yes	Yes	Can't tell	Can't tell	Yes	No

Notes to Quality Appraisal: *All included studies had clear research questions and collected data that addressed the research question. †The 3 qualitative studies (18, 20, 21) scored highly, with all using semistructured interviews to collect data from which quotes were extracted and used to illustrate the interpretation of the results. ‡The quality of the 6 quantitative descriptive studies (19, 26, 29, 31-33) varied, with 2 studies scoring very low because of unclear sampling strategies, a nonrepresentative sample, uncertainty over the validity of the survey used and few details reported in relation to the analysis of data. §All 5 randomized crossover studies (22, 23, 28, 30, 49) investigated the formulation of oral solid dosage forms directly; however, the quality of these studies again varied, with 1 study scoring very low because of insufficient details in the reporting of the study to enable the quality to be assessed. ‖Five studies (24, 27-30) received financial support from or were sponsored by the pharmaceutical industry, 3 of which were randomized crossover studies (27, 28, 30) and 2 of which studied calcium and vitamin D Formulations (27, 30). The quality of these again varied, with 1 study in particular having scoring very low because of irrelevant sampling strategies and an unrepresentative sample (29).