European Journal of Pharmaceutical Sciences 208 (2025) 107042

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Pharmaceutical quality of herbal medicinal products and dietary supplements – a case study with oral solid formulations containing *Lavandula* species

Banaz Jalil [a,*], Michael Heinrich [a,b,*]

[a] Pharmacognosy and Phytotherapy, UCL School of Pharmacy, London, United Kingdom
[b] Department of Pharmaceutical Sciences and Chinese Medicine Resources, Chinese Medicine Research Center, College of Chinese Medicine, China Medical University, Taichung, Taiwan

ARTICLE INFO

Keywords:
Oral dosage forms
Lavandula
Pharmaceutical performance
Soft gel capsules
Disintegration
Herbal medicinal products

ABSTRACT

The effectiveness and safety of regulated herbal medicinal products and dietary/food supplements are key areas of research. However, limited evidence exists of their pharmaceutical performance quality (including the standard in the respective pharmacopeial monographs). We evaluated the applicability of the European Pharmacopoeia general chapter protocols for disintegration testing of oral dosage forms using 73 products containing *Lavandula* species. Several *Lavandula* species, hybrids and cultivars are important medicinal plants globally in the phytopharmaceuticals and dietary/food supplement industry, including *Lavandula* Mill., traditionally used to treat conditions linked to nervousness and sleep disorders. We evaluate the pharmaceutical performance quality, particularly the *in vitro* disintegration and the phytochemical quality of 73 *Lavandula* oral dosage forms of single and multi–ingredients with different regulatory statuses. The phytochemical quality testing showed that 63 % of products contain less or none of the main marker compounds (e.g., linalool, linalyl acetate, and cineole). There was also considerable variability of the main marker compounds between products, with some containing 'often/sometimes undeclared' and significant amounts of rapeseed and sunflower oils as excipients. The pharmaceutical performance quality testing showed that 30 % of oral solid formulations always failed the disintegration testing (seven soft gels, ten hard shells, and five tablets/caplets). Pass rates for gelatine-based capsules were higher than for non-gelatine (cellulose-based) capsules. Overall, our findings highlighted problems with the pharmaceutical performance and phytochemical quality of the investigated products. These results have implications for the interpretations of the benefits and risks of phytopharmaceuticals used as compared to dietary/food supplements.

1. Introduction

The regulatory status of herbal medical products varies among different systems also within Europe. There is a large group of products which are fully licensed medicines in some countries (esp., Austria, Germany, Poland, and Switzerland), while the same products are regulated under the European Traditional Herbal Regulation scheme (European Medicines Agency, 2004) in others or are sold as dietary/food supplements without a medical regulation. At the same time, products without pharmaceutical/medical regulation are commonly sold globally. Due to their chemical complexity, they pose unique challenges in the context of pharmaceutics, and a common concern relates to low quality and adulteration (Villani et al., 2015; Booker et al., 2016; Gafner et al., 2023; Orhan et al., 2024), resulting in important public health concerns.

Every year, many publications describe the effects of Herbal Medicinal Products (HMPs) and Dietary/food Supplements (DSs) and their potential for pharmaceutical development. In addition to pharmacokinetic aspects, the safety and effectiveness of these products in humans are central to assessing the bioavailability of active metabolites/marker compounds, which is often unknown or considered to be very low (Gurley, 2011, 2012; Rathaur and Johar, 2019; Sorkin et al., 2020; Di Lorenzo et al., 2021; Floyd et al., 2022). Human physiology, genetic factors, formulation and phytochemical/physicochemical properties define the bioavailability of an active substance. However, pharmaceutical performance quality remains an overlooked aspect for licensed

* Corresponding authors.
E-mail addresses: b.jalil@ucl.ac.uk (B. Jalil), m.heinrich@ucl.ac.uk (M. Heinrich).

https://doi.org/10.1016/j.ejps.2025.107042
Received 10 October 2024; Received in revised form 3 February 2025; Accepted 11 February 2025
Available online 12 February 2025

and regulated HMPs as well as DSs. Most available HMPs and DSs are formulated as gelatine or cellulosic capsules or various tablet formulations. Previous research generally focused on the active ingredients (extracts or individual metabolites) (i.e., phytochemical quality) of finished products and the primary starting materials (Villani et al., 2015; Booker et al., 2016; Gafner et al., 2023; Orhan et al., 2024) along the value chains and in different regulatory contexts (Heinrich, 2015). In contrast, this study takes a novel approach in looking at the dosage form performance, and pharmaceutical quality of oral dosage formulations used either as a regulated medicine or a dietary supplement/botanical available on the global market.

1.1. Formulation aspect (dosage form performance) of herbal medicinal products and dietary/food supplements

Generally, the dosage form performance assesses whether a tablet, capsule or liquid gel capsule can disintegrate and release its contents into gastrointestinal fluids within a time that facilitates absorption and, thus, bioavailability. Dosage forms that quickly disintegrate and readily release their active metabolites generally exhibit better bioavailability than those with inferior performance traits. In effect, this process is an in vitro means of gauging the rate and extent of phytochemical release into simulated gastric or intestinal fluids using standardised conditions and equipment (Azarmi et al., 2007; Floyd et al., 2022). Therefore, the efficacy and safety of oral HMPs and DSs dosage forms are based on the design and performance of the formulations into which they are incorporated and delivered to consumers and patients. Products that fail in vitro disintegration and dissolution tests may also fail to disintegrate and release ingredients properly in vivo. Consequently, their active ingredients presumably cannot be fully absorbed, and expected health benefits may not be achieved. Poor disintegration and dissolution may also result in safety concerns, e.g., oral dosage forms that do not disintegrate properly may cause local irritation or inflammation, gastric upset, and, in rare cases, gastrointestinal obstructions. Hence, dosage form performance testing is essential to detect the release from dosage forms that may occur because of improper formulation design or manufacturing processes (i.e., coatings, lubricants, disintegrants, batch-to-batch consistency, over-drying, and over-compression) (Gray et al., 2014). For example, the nature, composition, and inert materials used in manufacturing typically exhibit different disintegration, dissolution and breakdown properties (Gusev et al., 2020). Dosage form performance testing is a well-established tool in pharmaceutical quality control for oral dosage forms and a core element of drug development. However, the regulatory standards for dosage forms performance testing for HMPs and DSs are much more complicated than for chemically defined medicines due to their complex nature, the selection of analytical markers, solubility determination and selection of suitable dissolution media.

At present, most HMPs and DSs (i.e., marketed and formulated (commercial) products also known as 'botanicals') available on the global market do not have specific dosage form testing methods in their respective monographs in the national pharmacopoeias (e.g., European (British) Pharmacopoeia, Korean and Japanese Pharmacopeia). In addition, they are not required to abide by the general chapters and requirements for oral dosage forms in their respective pharmacopoeias. The focus in these pharmacopoeias is on the authenticity and quality of the starting plant material (i.e., raw material), not the dosage form performance of finished products. It remains up to individual manufacturers to test and develop methods for the dosage form performance of their products, which then can become unique characteristics for specific products.

In the United States, assessing the dosage form performance of 'botanicals' is different, and there is a strong push towards developing DS monographs of commonly used ones. In the United States Pharmacopoeia (USP), under the specific DS monographs, there is a general section for 'performance testing', which highlights that the supplement should comply with the general guidance for 'dosage forms' testing unless specific dosage form testing is required in the monographs for a particular dietary supplement (i.e., at present, there is very limited specific DS dosage form testing and the majority of DS have to comply with the 'Dosage Forms' requirements under the 'General Guidance'). The focus seems to be on the most widely used groups of supplements. However, DSs are not required by law to meet USP standards. In response to this, a few recent projects funded and led by teams based at the Office of Dietary Supplements (ODS), National Institutes of Health (NCCIH) and the United States Department of Agriculture (USDA) investigated the dosage form performance of specific DSs with the aim to explore the USP General Chapter on Dosage forms of dietary supplements and asses its applicability for the development and implementation of dietary supplements specific monographs (Gusev et al., 2020; Andrews et al., 2021; Brzezińska et al., 2021; Lyu et al., 2021; Ekong et al., 2022) (see Table 1, for more details). It is now emerging as a key area of research that is relevant both for HMPs and DSs.

Recommendations were also made to the National Institutes of Health's National Center for Complementary and Integrative Health policy for "Natural Product Integrity" to consider including satisfactory performance quality of dosage forms as a requirement for funding to avoid inconsistent results in clinical trials (Gusev et al., 2020). In response, the section '*Considerations of Dosage Form Disintegration and Dissolution' is updated under 'Grants and Funding'* section. Here, investigators are strongly encouraged to consider, prior to initiation of tests of pharmacokinetics or efficacy, whether disintegration and dissolution (requisite first steps towards bioavailability) have been evaluated for the putative bioactive(s) in their oral dosage form products (https://ods.od.nih.gov/Funding/ProductQualityResources.aspx).

HMPs and DSs, based on aromatic medicinal plants (i.e., plants which are rich in essential oils) are utilised in different dosage forms, including oral and topical formulations as single or multiple ingredients products and for a wide range of therapeutic and self-care needs (Baser and Buchbauer, 2021). In addition, the pharmaceutical formulation of aromatic plants poses specific challenges to preserve and protect the active ingredients or marker compounds (i.e., essential oils) during storage while releasing them completely after oral intake. The volatile character of essential oils requires a leakproof dense formulation that disintegrates in the gastrointestinal tract. Therefore, we selected HMPs and DSs based on *Lavandula* species products. As of October 2024, there were 509 clinical trials with lavender as the investigational product registered with (https://trialsearch.who.int/), and 77 clinical trials with lavender as the investigational product were registered with clinicaltrials.gov. To the best of our knowledge, no studies have investigated the dosage form performance of orally formulated (e.g., soft gels, hard shell capsules, tablets and caplets) *Lavandula* species products, including different HMPs and DSs available on the global market. At present, there is no data except for studies funded or led by ODS, NCCIH, and USDA teams on the extent of the issues, opportunities, and challenges of formulation and dosage form performance of HMPs and DSs available on

Table 1
Summary of the previous studies into the dosage form performance of dietary/food supplement.

Study	Number of products tested	Pass rates of the products tested	References
Green tea products (single and multiple ingredients)	28 and 34	55 % and 67 %	(Gusev et al., 2020)
Turmeric products	52	83 %	(Andrews et al., 2021)
Cranberry products	36	84 %	(Ekong et al., 2022)
Beetroot based products	31	80 %	(Brzezińska et al., 2021)

the global market, especially those utilised in clinical trials.

1.2. Potential therapeutic and safety concerns arising from poor phytochemical and pharmaceutical quality of Lavandula species products

Several *Lavandula* species are important aromatic and medicinal plants with great economic value for phytopharmaceuticals, food, perfumery, cosmetics, and aromatherapy. The genus *Lavandula* comprises 39 species, and many hybrids and over 20 years ago about 400 registered cultivars were recorded (Lis-Balchin, 2002), with three main cultivated species being used to produce essential oils, including fine lavender oil, spike lavender oil and lavandin oil, with several uses (Table 2). There are differences between these oils in terms of the active ingredients/main marker compound contents, with fine lavender oil being mainly investigated for its biological and clinical activities (Edwards et al., 2015). Fine lavender oil is generally considered safe (GRAS) to be consumed in oral dosage or topical forms without serious adverse reports in the literature. For example, Silexan® is a high-quality fine lavender oil, licensed as active ingredient in medicines for the relief of mild anxiety disorders (Dold et al., 2023; Kasper and Eckert, 2024), registered as Herbal Medicinal Product (HMP), Traditional Herbal Medicinal Product (THMP), listed medicine, or natural health product in numerous countries (under brand names such as Kalms Lavender, Lasea®, Laitea®, Laseaxan®, Lavekan®, Seremind®, or Laila), and as a food supplement (under the brand names CalmAid® and Lavela) in the United States (Empowered By Evidence, 2024). In some recent reports, fine lavender oil could possess a weak potential for skin sensitisation effects (Tisserand and Young, 2014). Reports about prepubertal gynecomastia cannot be regarded as specific. For example, if used in a safety assessment, a non-characterised or chemically poorly characterised herbal extract or a finished product leads to misleading and invalid data, which cannot be used for an evidence-based assessment of other medical preparations derived from such a botanical drug (Heinrich et al., 2022). Importantly, adverse reaction reporting must ascertain reproducibility, as in all other fields of research (Heinrich et al., 2022). The European regulation requires a warning statement on fine lavender oil content and the labelling requirements within the list of cosmetic allergens. After oxidation, linalool degrades to linalool hydroperoxides, which is why skin sensitisation could occur. The International Fragrance Association require that linalool contain the least possible peroxide value. In addition, spike lavender oil and lavandin oil contain a higher amount of linalool and camphor compared to fine lavender oil. Topical application of camphor is linked to allergic contact dermatitis. Based on the established toxicity of camphor-containing products (Love et al., 2004), they are not recommended for children.

Consequently, the adulteration or substitution of fine lavender oil with the lowest oil quality, such as spike lavender oil or lavendin oil, can occur, which may also pose a high risk to consumers. Adulterations or substitution can occur intentionally or accidentally; however, intentional adulteration seems to occur more frequently, and it is economically motivated (Lis-Balchin, 2002; Baser and Buchbauer, 2015). For example, a case study in France found the direct mixing of synthetic chemicals with purely distilled lavender oil (Lis-Balchin, 2002; Baser and Buchbauer, 2015), mainly non-declared to the consumer. With the regular increase in the innovation of oral dosage formulation of these products, as well as the increase in pre-clinical and clinical research conducted using these products as investigational products, the research and the wider understanding of the pharmaceutical performance quality remains unsatisfactory and limited.

Table 2
The main species of *Lavandula* with their phytochemical quality and uses of the essential oils.

Species	Phytochemical quality of essential oil	Uses
Fine/true Lavender oil/ flower: *Lavandula angustifolia* subsp. *angustifolia* (an infraspecies of *Lavandula angustifolia* Mill.) – syn.: *Lavandula officinalis* Chaix	It produces the highest quality of oil in terms of the main active ingredients/marker compounds contents when grown at altitudes between 600 - 1400 m	It is mainly used in medicine, perfumes and cosmetics
Spike Lavender oil: *Lavandula latifolia* Mill.	It grows at lower altitudes preferring warmer regions yields three times the quantity of L. *angustifolia*, but it is of lowest quality in terms of the main active ingredients/marker compounds contents	It is mainly used as raw material in industrial perfumes and fragrance industries and as a natural food flavouring agent
Lavandin oil: *Lavandula* x *intermedia* Emeric ex Loisel	Produces very high yields of lowest quality oil as compared to L. *angustifolia* in terms of the main active ingredients/marker compounds contents and grows at lower altitudes between 200 and 1000 m	Its preferentially used in personal care and hygiene products

2. Material and methods

2.1. Sample descriptions

Seventy-three products ($n = 73$) for oral intake were obtained from different global suppliers, including pharmacies, retail outlets and over the Internet. Our selection strategy was to access *Lavandula* products that were readily available to consumers on the global market. The samples consisted of *Lavandula* species products, soft gel capsules ($n = 34$), hard shell capsules ($n = 26$), tablets and caplets ($n = 13$) claiming to be L. *angustifolia* ($n = 71$) and L. *latifolia* ($n = 2$), respectively. 27 products solely contained *Lavandula* essential oil or flower extract (plus excipients), and 46 were multiple ingredients combined with other constituents such as herbal extracts, vitamins, and minerals (Fig. 1). In terms of the regulatory statuses of the products, few products were registered/licensed in Europe as (traditional) herbal medicinal products ($n = 3$), containing Silexan®, which are labelled in this study as LS1, LS24, and LS25), and the majority were not registered as medicinal products and are available as listed medicine or dietary/food supplements ($n = 70$), including Silexan®: LS21, LS22, LS23). All products are readily available to consumers globally, including the European, Australian, Canadian, and United States markets. The products were marketed for various indications and claims, including restlessness, anxiety disorders and improving sleep quality in adults and children. In addition, Different concentrated essential oils claiming to contain L. *angustifolia* (including Silexan® as authenticated essential oil ($n = 1$), which is labelled in this study as LO16), *Lavandula* species essential oils ($n = 6$), and other essential oils, including clary sage, hyssop, camphor, and eucalyptus ($n = 4$) oils, were also included in this study (for more details about the range of the products included in this study, and the products descriptions, see Table S1 in Supplementary material).

2.2. Phytochemical analysis

2.2.1. Preparation of standard solutions and samples

The reference standard solutions of linalool, linalyl acetate and cineole were prepared individually at concentrations of 5 µl, 5 µl and 10 µl in 1.0 ml of toluene, respectively. For the preparation of soft gel capsules (liquid samples), approximately 0.25 ml (the equivalent of two dosage units were mixed) were measured individually into a 10 ml reaction tube, and 5 ml of a mixture of equal volumes of methanol and heptane was added. Heptane and methanol are immiscible. This effect was used to separate the excipients (e.g., rapeseed oil and/or sunflower oils) and the active substance since excipients can interfere with the chromatographic analysis of the active substance. The mixture was

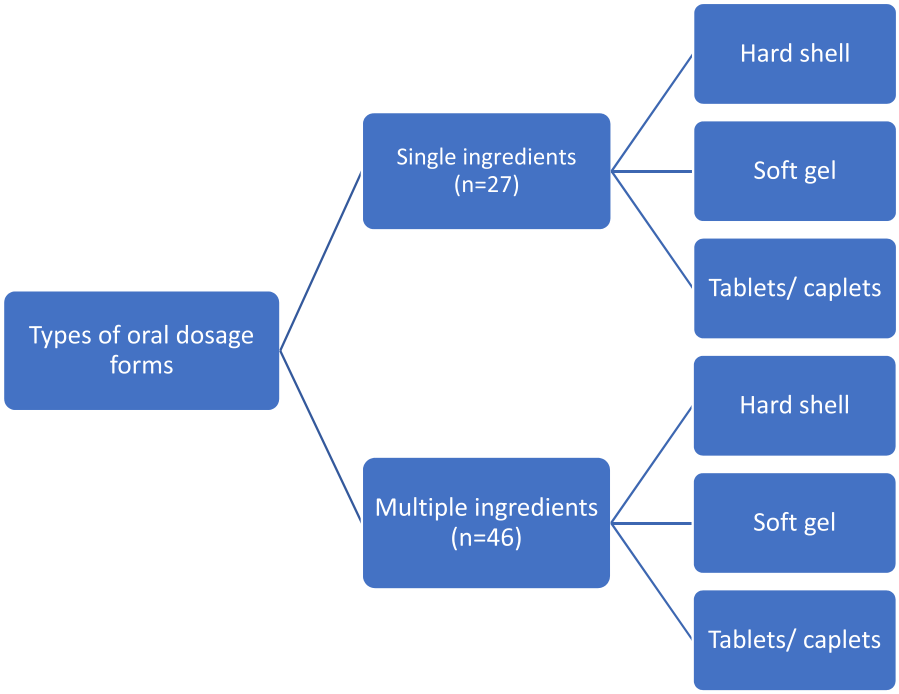

Fig. 1. Schematic description of the *Lavandula* species products, including the different oral dosage forms investigated in this study and which are available on the global market ($n = 73$).

sonicated for 30 min at room temperature, and then the two layers were separated. The methanol solution layers containing the active substance were transferred into individual vials and then submitted for High-Performance Thin Layer Chromatography (HPTLC) analysis at 5 µl injection volumes. For the preparation of hard-shell capsules and tablets/caplets (solid samples), approximately 500 mg (the equivalent of two dosage units were mixed) were weighed individually into 10 ml reaction tubes, and 5 ml of toluene was added. The resultant solution was sonicated for 30 min at room temperature and then filtered. The supernatant solution was transferred into individual vials and then submitted for HPTLC analysis at 5 µl injection volumes. For the preparation of the different essential oils, approximately 0.25 ml was transferred individually into 10 ml reaction tubes, and 5 ml of toluene was added. The resulting solution was sonicated for 30 min at room temperature. The supernatant solution was transferred into individual vials and then submitted for HPTLC analysis at 5 µl injection volumes. For the HPTLC analysis, multiple dosage units were mixed, weighed and used for sample preparations, and two different batch numbers of products were analysed; the respective experiments were repeated three times.

2.2.2. Chromatography

The HPTLC analysis for single- and multi-ingredient lavender products was performed on 200.0*100.0 mm silica gel 60 F 254 HPTLC glass plates (Merck, Germany) in accordance with the European Pharmacopoeia (Ph. Eur.) 11.0 identification of lavender oil (European Pharmacopeia, 2023a). Standard solutions and samples 5 µl were applied on the plate as bands 8.0 mm wide using the CAMAG spray-on technique with Semi-automatic CAMAG Linomat 5. Bands were applied at a distance of 8.0 mm from the lower edge of the plate and 20 mm from the left and right edges. The space between bands was 11 mm, and the number of lanes per plate was 15. The development distance was 70.0 mm from the lower edge of the plate using the CAMAG Automatic developing chamber (ADC2). The temperature and the relative humidity within the developing chamber (ADC2) were 23 °C and 33 %, respectively. Mobile phase (ethyl acetate R, toluene R (5:95)). The derivatisation of plates was performed through the automatic CAMAG spraying device (Speed: 3) with anisaldehyde reagent using the ultra-blue nozzle and heated to 100 °C for 5 min on the TLC plate heater. The plates were documented using CAMAG Visualizer under white light, UV 254 nm, and UV 366 nm with visionCATS software (version 3.1).

2.3. Dosage form performance testing methods

Single- and multi-ingredient lavender products were tested for disintegration in accordance with the European Pharmacopoeia (Ph. Eur.) 11.0 general monograph for dosage forms (European Pharmacopeia, 2023a). Six capsules or tablets for each product were individually immersed and agitated in the appropriate media for 15, 30, 60, and 120 min for uncoated tablets, soft gel, hard shell capsules, coated tablets (immediate-release formulations), and delayed-release formulations, respectively as per Ph. Eur. 11.0. Products were immersed in the media containing 0.1 M hydrochloric acid at 37 C, 50 paddle rpm. According to the Ph. Eur. (11.0) standards for oral dosage forms, disintegration was considered complete when any residue remaining on the screen of the test apparatus (except fragments of insoluble coating or capsule shell) was a soft mass having no palpably firm core after 15, 30, 60, 120 min respectively for different oral dosage forms. At the end of the test, the number of units disintegrated was recorded, and if the capsule/tablet was still in one piece, notes were taken on how close it was to the original size/shape. The remaining capsules and tablets were cut open to examine whether the content was dry or wet. Any dry content was considered as a failure to disintegrate. If one or two units failed to disintegrate, then an additional 12 units were evaluated, and the batch passed at this second level if at least 16 of 18 disintegrated in the specified time. Products in capsules were categorised as cellulose-based (non-gelatin) or gelatin-based shells by reviewing label information. Cellulose capsules were listed as vegetarian, veggie or vegan capsules, and the “Other ingredient” box listed shell materials as cellulose, vegetable cellulose, modified cellulose, hydroxypropyl methylcellulose (HPMC) or, less frequently, pullulan. For the dosage form testing, two different batch numbers of products were tested; the respective experiments were repeated three times.

2.4. Other chemicals, apparatus and instrumentations

Mettler Toledo electronic balance, Serial no AG245, Ultrasound bath, model D-78224, Serial no 004472044, Fisherbrand, UK.

3. Results

3.1. Phytochemical HPTLC method optimisations

The development and optimisation of a method of analysis consists of several steps. For the HPTLC analysis, sample extractions for different dosage forms, injection volumes and the detection and derivatisations were assessed and optimised. The temperature and relative humidity were also considered. Only one parameter was changed at a time to obtain comparable and reproducible results. The HPTLC method for the soft gel capsules was optimised from a standardised method for the identification of lavender of aetheroleum (essential oil) as per the Ph. Eur. (11.0) (European Pharmacopeia, 2023b). The sample extraction method was developed and optimised using equal volumes of methanol and heptane instead of Toluene R solely as described by Ph. Eur. This allows the equal partition and separation of the polar and non-polar components (mainly due to the amount of excipients added to these products) of *Lavandula*-containing products. This process, as identified by the initial HPTLC analysis, showed that most products contain a significant volume of excipients of vegetable oils (e.g., sunflower oil and/or rapeseed oil), which interfered with the analysis. The amounts were occasionally added in high volumes to fill the soft gel capsules, diluting the volume of lavender oil needed; hence also, less lavender oil is contained in these capsules, interfering with the chemical analysis, which may lead to false identification of *Lavandula* containing products as high-quality products.

3.2. Phytochemical HPTLC analysis of different oral dosage forms

The HPTLC plates were developed, evaluated visually, and compared to the reference standards. Comparisons of the different *Lavandula* species products were only assessed with the same or similar dosage forms, e.g., soft gels, hard shells, caplets and tablets. The sample extraction procedure and the injection volumes were kept the same for all the samples of the same dosage forms, and the daily dosage units were also considered.

Out of 73 chemically tested oral dosage form products, 28 contained less of the main marker compounds linalyl acetate (intense violet zone at the average Rf value of 0.55 ± 0.03), linalool (intense violet zone at the average Rf value of 0.26 ± 0.03) and cineole (weak violet-brown zone at the average Rf value of 0.37 ± 0.03) (nine soft gel capsules, 12 hard shell capsules, and seven tablets and caplets), and, in some cases, only trace amounts of the main marker compounds were present (Table 3 and Fig. 2–4). In addition, 18 products did not contain any main marker compounds (two soft gel capsules, ten hard shell capsules, and six tablets and caplets) (Table 3 and Figs. 2–4).

Although the three main marker compounds in the essential oils claiming to contain *Lavandula angustifolia Mill.* were in higher concentrations than the reference standards, there were no significant differences between the essential oils except for LO14 (Fig. 5). However, compared to the main marker compounds, our finding shows that clary sage and hyssop have chemical profiles similar to those of *Lavandula angustifolia Mill.* essential oils (Fig. 6).

3.3. Dosage form performance testing

The disintegration testing method was based on the standardised method for disintegration testing of the oral dosage form as described in the Ph. Eur. (11.0). The method remained the same for all dosage forms, e.g., soft gels, hard shells, caplets and tablets, except for whether the products were immediate or delayed-release dosage forms as per the product packaging and leaflets. Attempts to conduct the dissolution testing of different dosage forms of the *Lavandula* species products were not successful. This is because in order to assess the release of active substances of *Lavandula* species products, three main marker compounds - linalyl acetate, linalool and cineole - have to be analysed individually as the percentage of the absorbed drug. These marker compounds show limited UV absorbance, as well as these compounds, have low solubility rates in the assay; hence, it was not possible to accurately assess the percentage of drug release (i.e., the percentage of the absorbed drug) within 70-minute intervals based on the three main marker compounds found in *Lavandula* products. Out of 72 tested products for dosage form performance, 50 always passed the disintegration testing (23 soft gel capsules, 20 hard shell capsules, and seven tablets and caplets), and 22 always failed the disintegration testing (seven soft gel capsules, 10 hard shell capsules, and five tablets and caplets) (Table 4). In addition, the pass rates for gelatine-based capsule shells were higher ($n = 26$) compared to cellulose-based capsule shells ($n = 9$), with some products not clearly declaring the capsule shell materials (Tables 5 and 6).

Table 3
Summary of phytochemical analysis testing results (HPTLC analysis) of *Lavandula* species products ($n = 73$).

Types of formulation	HPTLC analysis results (3 trials) as compared to the main marker compounds			Total
	Contained the main marker compounds	Contained less or trace amounts of the main marker compounds	Did not contain any of the main marker compounds	
Soft gel capsules or products contained essential oils inside the capsule shell	23	9	2	34
Hard shell capsules	4	12	10	26
Tablets/caplets	0	7	6	13
Total	27	28	18	73

63 % of the investigated *Lavandula* containing products contain less or none of the main marker compounds.

3.3.1. Dosage form performance testing 1: Lavandula containing products as single or primary ingredients

Twenty-seven ($n = 27$) products with *Lavandula* oil or dried flower extract as the only or primary ingredients were tested over 18 months. Across the two batches of tested products, 16 products always passed the disintegration testing (12 soft gel capsules and four hard shell capsules), ten always failed the disintegration testing (4 soft gel capsules, three hard shell capsules, and three tablets and caplets). Agitation times to achieve disintegration ranged from 7.6 to 30 min. Retests were also conducted on randomly selected product batches that initially passed ($n = 4$) or failed ($n = 4$); the tests showed consistent outcomes (Table 5).

3.3.2. Dosage form performance testing 2: Lavandula containing products as multiple ingredients (complex matrices)

Forty-five ($n = 45$) products containing *Lavandula* oil or dried flower extract as multiple ingredient products were tested over 18 months. Across the two batches of the tested product, 34 always passed the disintegration testing (10 soft gel capsules, 17 hard shell capsules, and seven tablets and caplets), and 12 always failed the disintegration testing (3 soft gel capsules, seven hard shell capsules and two tablets and caplets) failed the disintegration testing. Agitation times to achieve disintegration varied from 8.1 min to 120 min. Retests were also conducted on randomly selected product batches that initially passed ($n = 5$) or failed ($n = 5$); the tests showed consistent outcomes (Table 6).

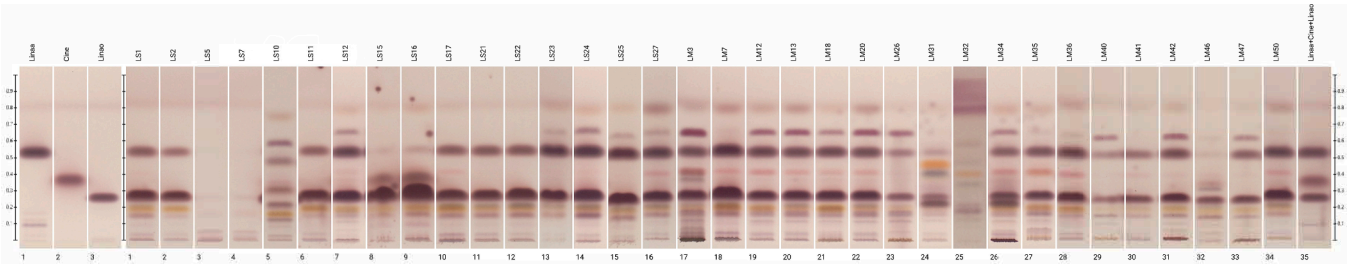

Fig. 2. HPTLC comparison image of *Lavandula* soft gel products represented as bands ($n = 34$). Tracks 1–3 and 35 represent reference standards (linalool, cineole, and linalyl acetate). Tracks 1–34 represent the investigated soft gel capsules (LS represents single-ingredient products, and LM represents multiple-ingredient products). LS1, LS24 and LS25 are registered as herbal medicinal products, and all other products are available as dietary/food supplements on the global market.

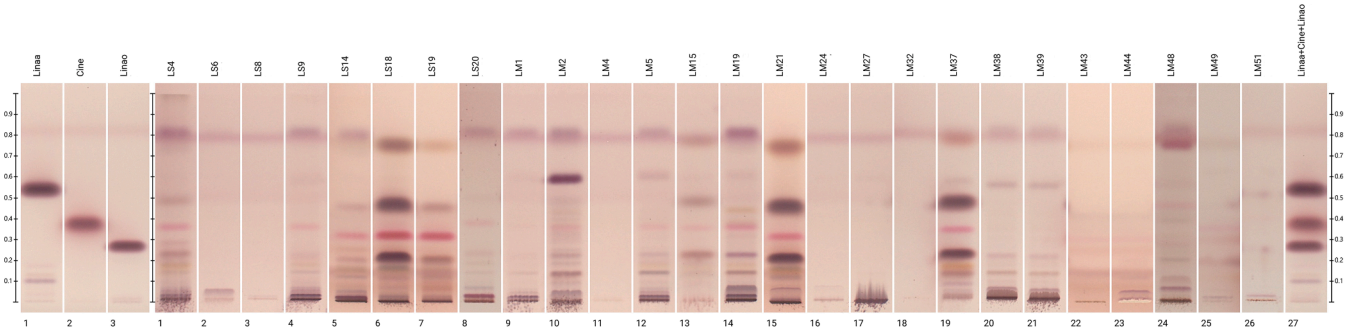

Fig. 3. HPTLC comparison image of *Lavandula* hard shell products represented as bands ($n = 26$). Tracks 1–3 and 27 represent the reference standards (linalool, cineole, and linalyl acetate). Tracks 1–26 represent the investigated hard-shell capsules (LS represents single-ingredient products, and LM represents multiple-ingredient products). All products are available as dietary/food supplements on the global market.

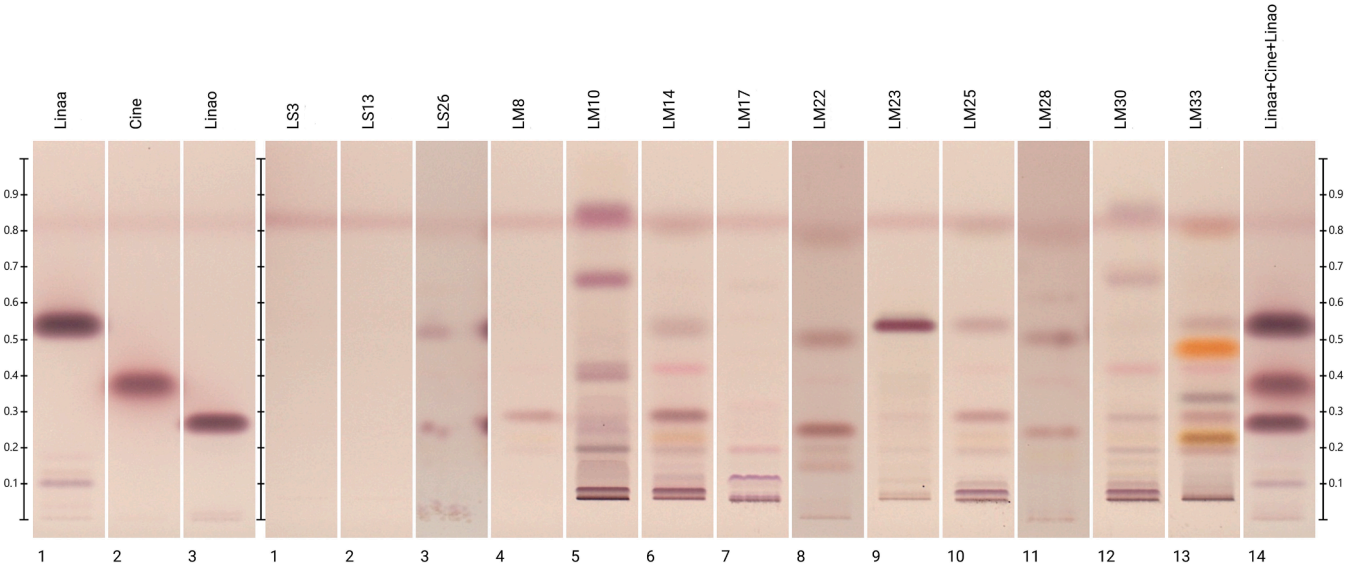

Fig. 4. HPTLC comparison image of *Lavandula* tablets and caplets products represented as bands ($n = 13$). Tracks 1–3 and 14 represent reference standards (linalool, cineole, and linalyl acetate). Tracks 1–13 represent the investigated tablets and caplets (LS represents single-ingredient products, and LM represents multiple-ingredient products). All products are available as dietary/food supplements on the global market.

4. General discussions

The overarching objective of this work is to assess the pharmaceutical quality of regulated HMPs and DSs available on the global market using a novel approach, a combination of an assessment of the disintegration performance of the pharmaceutical form and the chemical composition of the products. *Lavandula*-containing products were selected as a case study since this is a fast-emerging group of products with increased pharmaceutical importance and therapeutic potential (as well as dietary or food supplements) and its diverse regulatory statutes on the global markets.

Our findings showed that 30 % of the investigated *Lavandula*-containing products did not pass the disintegration testing in neutral and/or acidic medium per the Ph. Eur. (11.0) recommendations (see Table 4). Previous limited studies assessing the pharmaceutical quality of specific DSs available on the market have highlighted this issue, where several

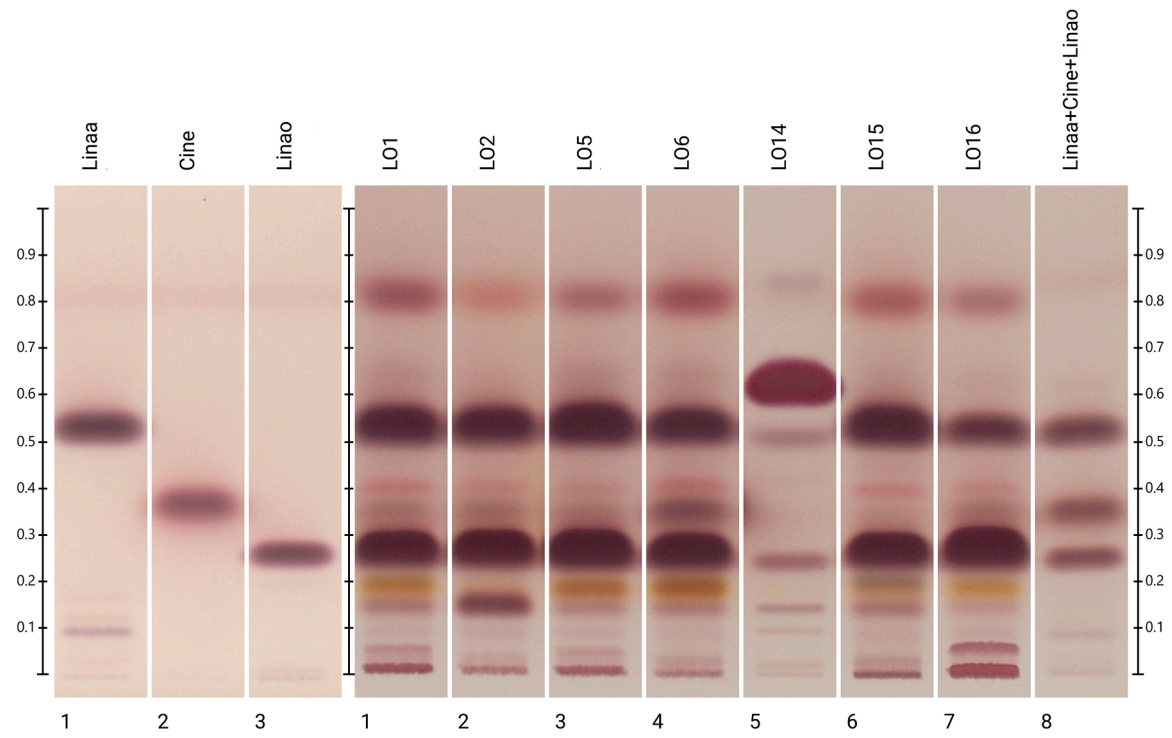

Fig. 5. HPTLC comparison image of *Lavandula* essential oils represented as bands ($n = 7$). Tracks 1–3 and 8 represent the reference standards (linalool, cineole, and linalyl acetate). Tracks 1–7 represent *Lavandula angustifolia Mill.* essential oils (LO represents concentrated essential oils). LO16 is Silexan® as an authenticated L. *angustifolia* essential oil, and all other products are available as essential oils on the global market.

products do not pass the dosage form performance testing (Gusev et al., 2020; Andrews et al., 2021; Brzezińska et al., 2021; Lyu et al., 2021; Ekong et al., 2022) (see Table 1).

Central to assessing the safety and efficacy of pharmaceutical products (including HMPs and DSs) in humans is determining the bioavailability of the active ingredients or marker compounds that are also key to pre-clinical effectiveness. Many phytochemicals have poor oral bioavailability stemming from two major factors, e.g., human physiology and phytochemical physico-chemical properties. Other challenges may include lipophilicity and poor solubility, making them less bioavailable. Many phytochemicals are also substrates for various efflux transporters expressed on the apical surface of intestinal enterocytes, affecting their uptake from the gut lumen (Gurley, 2012; Floyd et al., 2022). From an evolutionary perspective, the ingestion of plants significantly impacts human development so that we, as a species, readily biotransform phytochemicals through either enzymatic metabolism in the gut or liver parenchyma or via gut microflora. Collectively, all these challenges may render phytochemicals inadequately bioavailable. In effect, these challenges and others are generally addressed during the formulation of a pharmaceutical product.

There are several reasons why HMPs or DSs products do not pass the pharmaceutical quality testing, e.g., the capsule composition (i.e., gelatin vs cellulosic), old or outdated gelatin capsules may also bleb and not adequately disintegrate, certain phytochemicals may induce cross-linking of polysaccharide chains in hydroxypropylmethylcellulose capsules, compromising disintegration and dissolution results (Gusev et al., 2020), resulting in certain mixtures of phytochemicals not being suitable for certain oral dosage forms. In our findings, it was challenging to pinpoint specific reasons why a product did not pass the disintegration testing (Fig. 7); this is due to the diversity of the formulations investigated here, the multi-ingredients nature of a product, and the overall lack of guidelines or recommendations for assessing this category of pharmaceutical products in pharmacopoeias. One issue could be a potential interaction between the main marker compounds of HMPs or DSs with the capsule shell material, which was reported as an issue with green tea extract-based products (Glube et al., 2013); however, further studies need to be designed and conducted with specific HMPs and DSs assessing the different capsule shell materials with various marker compounds of interest in these products.

Regulatory authorities do not require HMPs and DSs to undergo the same stringent testing procedures as pharmaceutical formulations (i.e., medicines) before they can be marketed and during production. Therefore, unless the manufacturer makes a label claim, supplements can be marketed based on safety data and traditional use (demonstrating plausible therapeutic benefits based on experience over at least three decades (Heinrich, 2015). However, the same factors affecting the bioavailability and efficacy of medicines also apply to HMPs and DSs, and hence, proper formulation design and testing is a crucial step in the development of efficacious and safe HMPs and DSs. Our finding show that is not the case with many poorly regulated DSs available on the global market as well the extent of this issue is not yet known and is limited as this is not systemically assessed or investigated for HMPs and DSs on the global market.

In addition, 63 % of investigated products also contained less or none of the three main marker compounds for *Lavandula* species. We found that in some instances, lavender oil was substituted (i.e., diluted) with less expensive options, such as vegetable oils, including sunflower or rapeseed oils. These products will then qualitatively pass the analysis as lavender oil since they contain three main marker compounds. However, less amount quantitively, and these oils are presented as excipients on the product packaging, where they exceeded the amount of lavender oil contained in these products (Fig. 2), therefore, the HPTLC methods were optimised accordingly. Previous studies have reported the issues of adulteration of HMPs and DSs (Villani et al., 2015; Booker et al., 2016, 2018; Upton et al., 2020; Gafner et al., 2023; Orhan et al., 2024). The essential oils of lavender are high-value, hence, they are considered at high risk of adulteration (Baser and Buchbauer, 2015). The risk of adulteration is considered around 90 %, particularly with lower costs lavandin essential oils (*Lavandula x intermedia* Emeric ex Loisel) or spike lavender (*Lavandula latifolia Mill.*) (Lis-Balchin, 2002; Baser and

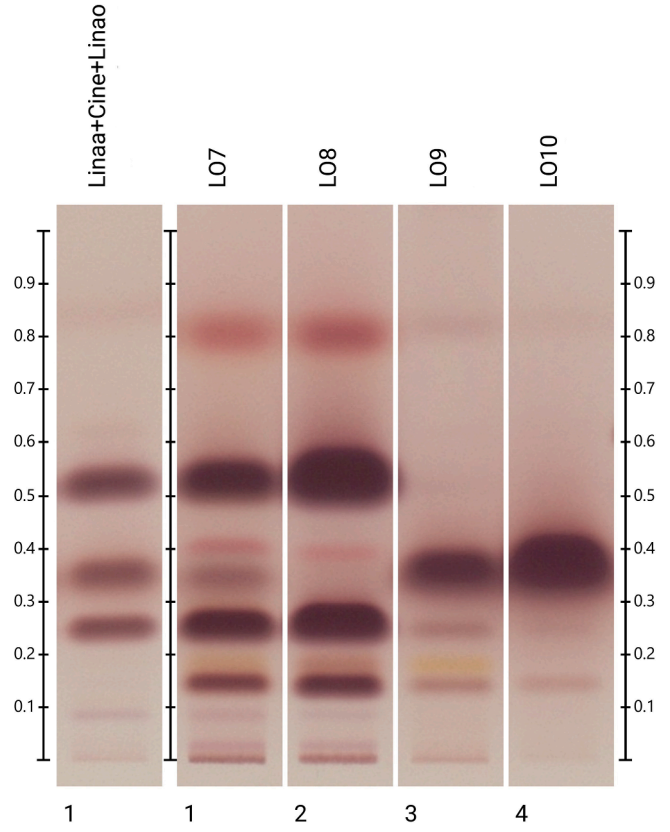

Fig. 6. HPTLC comparison image of other essential oils represented as bands ($n = 4$). Track 1 is the mixture of reference standards (linalool, cineole, and linalyl acetate). Tracks 2–4: LO7 represents hyssop, LO8 represents clary sage, LO9 represents camphor, and LO10 represents Eucalyptus oils (LO represents concentrated essential oils). All products are available as essential oils on the global market.

Table 4
Summary of dosage form performance testing results (Disintegration testing) of *Lavandula* species products ($n = 72$).

Types of formulation	Disintegration testing results (3 trials)		Total
	Pass	Fail	
Soft gel capsules	23	7	30
Hard shell capsules	20	10	30
Tablets/caplets	7	5	12
Total	50	22	72

30 % of the investigated *Lavandula* contained products did not pass the dosage form performance testing.

Buchbauer, 2015; Schmidt, 2020).

In comparison, with the investigated products here, products that contained higher amounts of cineole and camphor, were considered chemically more in line with the chemical composition of lavandin, therefore, the additions of camphor as the fourth marker compound could be recommended for more accurate results. In addition, the higher amounts of linalool and cineole could indicate spike lavender (Fig. 2, samples LS15 and LS16). Clary sage (*Salvia sclarea,* Lamiaceae), Spanish sage (*Salvia officinalis* subsp. *lavandulifolia* (Vahl) Fams, syn. *Salvia lavandulifolia* Vahl, Lamiaceae*)*, rosemary (*Salvia rosmarinus* Spenn., *syn. Rosmarinus officinalis* L., *Lamiaceae*), Ho wood [*obtained from Camphora officinarum* Boerh. ex Fabr. *Cinnamomum camphora* (L.) J.Presl, Lauraceae], eucalyptus (*Eucalyptus globulus* Labill., Myrtaceae) or rosewood (*Aniba rosodora* Ducke, *Lauraceae)* oils or fractions of these oils were also reported as potential essential oils adulterants for lavender oil

Table 5
Disintegration test results for single ingredients *Lavandula* products (LSs).

Product ID	Dosage Form	Type of capsule shell material / coating materials	Testing results
LS1	Soft gel	Gelatin based capsule shell	Pass
LS2	Soft gel	Gelatin (bivine) based capsule shell	Fail
LS3	Caplet	Hydroxypropyl methylcellulose	Fail
LS4	Hard shell	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Fail
LS5	Soft gel	Gelatin based capsule shell	Pass
LS6	Hard shell	Gelatin based capsule shell	Pass
LS7	Soft gel	Gelatin based capsule shell	Pass
LS8	Hard shell	Gelatin based capsule shell	Fail
LS9	Hard shell	Gelatin based capsule shell	Pass
LS10	Soft gel/ pearls	Gelatin based capsule shell	Pass
LS11	Soft gel	Gelatin based capsule shell	Pass
LS12	Soft gel	Gelatin based capsule shell	Pass
LS13	Tablet	Microcrystalline cellulose (not clearly stated)	Fail
LS14	Hard shell	Vegetable capsules (not cleared stated)	Pass
LS15	Soft gel	Gelatin based capsule shell	Fail
LS16	Soft gel	Gelatin based capsule shell	Fail
LS17	Soft gel/ granules	Gelatin based capsule shell	Pass
LS18	Hard shell	Microcrystalline cellulose based capsule shell	Fail
LS19	Hard shell	Vegetable capsule (not clearly stated)	Pass
LS20	Hard shell	Gelatin based capsule shell	Fail
LS21	Soft gel	Gelatin based capsule shell	Pass
LS22	Soft gel	Gelatin based capsule shell	Pass
LS23	Soft gel	Gelatin based capsule shell	Pass
LS24	Soft gel	Gelatin based capsule shell	Pass
LS25	Soft gel	Gelatin based capsule shell	Pass
LS26	Tablet	Microcrystalline cellulose (not clearly stated)	Fail
LS27	Soft gel	Gelatin based capsule shell	Fail

N = 27 number of tested products.

(Lis-Balchin, 2002; Burfield, 2003; Schmidt, 2020). In our analysis, here, using the same methodology and based on the three main marker compounds, we showed that the chemical composition of clary sage, as well as hyssop [*Dracocephalum officinale* (L.) Y.P.Chen & B.T.Drew, syn.: *Hyssopus officinalis* L., Lamiaceae] (which is not clearly reported in the literature as adulterant), is similar to that of *Lavandula angustifolia* Mill. oil (Fig. 6), while, for camphor or eucalyptus are more prominent for cineole, with limited content for linalool in terms of chemical composition. These findings all confirm that these essential oils could be used as an adulterant and be analysed with similar chemical methods applied here. However, it is not possible to accurately detect or identify them using the method. One approach could include camphor and thujone as additional marker compounds to this analysis.

Our findings provide insights into an emerging but so far little-researched aspect of the quality and safety of HMPs and DSs. This work calls for further research on the quality of specific formulations used both in supplements and medicines. Assessing the product formulations is needed in all studies that examine the bioavailability (including the safety and efficacy) of HMPs and DSs in animal and human trials and in a rigorous manner as pharmaceutical products on the market (i.e., products used orally and that solely contain synthetic compounds). Oral dosage forms that quickly disintegrate and readily release their active ingredients into gastrointestinal fluids generally exhibit better bioavailability than those with inferior performance traits. Consequently, the material of the capsule itself, the excipients used and blended into these products or medicinal plant extracts must also be subjected to performance quality testing to ensure that the products are disintegrated in a timely manner and the correct (adequate) concentrations needed in animal or human use including of course, in clinical studies, are delivered. Collectively, these findings highlight a significant issue with these products in terms of their formulation and phytochemistry (i.e., authenticity). This translates into concerns associated

Table 6
Disintegration test results for multiple ingredients *Lavandula* products (LMs).

Product ID	Dosage Form	Capsule shell material / coating materials	Testing results
LM1	Hard shell	Vegetable cellulose based capsule shell (hydroxypropyl methylcellulose)	Fail
LM2	Hard shell	Not clearly stated	Pass
LM3	Hard shell with oil inside	Not clearly stated	Fail
LM4	Hard shell	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Fail
LM5	Hard shell	Vegetable cellulose based capsule shell (hydroxypropyl methylcellulose)	Fail
LM7	Soft gel	Vegetable gelatin (modified from starch, glycerol and carrageenan)	Pass
LM8	Caplet	Not clearly stated	Pass
LM12	Hard shell (Delayed release duo capsules)	Cellulose based capsule shell	Pass
LM13	Hard shell (Delayed release duo capsules)	Gelatin (fish) based capsule shell	Pass
LM14	Tablet	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Pass
LM15	Hard shell	Vegetable capsule (derive de cellulose)	Fail
LM17	2-Phase caplet	Microcrystalline cellulose and essin acid esters of mono- and diglycerides from food grade acids	Fail
LM18	Soft gel with oil and suspended particles inside	Soft starch-based capsule (modified from corn starch, glycerin E422, carrageenan, water, sodium carbonate)	Pass
LM19	Hard shell	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Fail
LM20	Hard shell (Delayed release duo capsules)	Cellulose based capsule shell	Pass
LM21	Hard shell	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Pass
LM22	Tablet	Hypromellose (not clearly stated)	Pass
LM23	Caplet	Polyvinly alcohol (PVP), polyethylene glycol	Fail
LM24	Hard shell	Gelatin based capsule shell	Pass
LM25	Tablet	Pea starch	Pass
LM26	Soft gel with oil and suspended particles inside	Gelatin based capsule shell	Pass
LM27	Hard shell	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Pass
LM28	Tablet	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Pass
LM29	Hard shell	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Fail
LM30	Caplet	Not clearly stated	Pass
LM31	Soft gel	Peanut oil gelatin based capsule shell	Fail
LM32	Hard shell and soft gel	Hard shell: gelatine based (corn starch); for soft gel gelatine based (peanut oil)	Hard shell (pass), and soft gel (fail)
LM33	Effervescent tablet	Not clearly stated	Pass
LM34	Soft gel	Gelatin based capsule shell	Fail
LM35	Soft gel	Vegetable gelatin (plantaarrdige glycerine)	Pass
LM36	Soft gel/pearls	y	Pass
LM37	Hard shell	Gelatin (fish)	Pass
LM38	Hard shell	Vegetable cellulose	Pass
LM39	Hard shell	Vegetable cellulose based capsule shell (hydroxypropyl methylcellulose)	Pass
LM40	Soft gel with oil and suspended particles inside	Gelatin based capsule shell	Pass
LM41	Soft gel	Not cleared stated (glycerol)	Pass
LM42	Soft gel	Gelatin based capsule shell	Pass
LM43	Hard shell	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Pass
LM44	Hard shell	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Pass
LM46	Soft gel	Not clearly stated (100 % natural origin capsule material)	Pass
LM47	Soft gel	Gelatin (fish) based capsule shell	Pass
LM48	Hard shell	Hypromellose (not clearly stated)	Pass
LM49	Hard shell	Vegetarian capsule (cellulose)	Pass
LM50	Soft gel	Not clearly stated	Pass
LM51	Hard shell	Cellulose based capsule shell (hydroxypropyl methylcellulose)	Pass

N = 45 number of tested products.

with these products when utilised in pre-clinical and clinical trials for their safety and efficacy (Heinrich et al., 2022), but also for healthcare professionals or the general public who recommend or use these products regularly (Jalil et al., 2022).

5. Conclusions

This is the first study looking into the dosage form performance (pharmaceutical quality) of HMPs and DSs available on the global market. It will improve the understanding of the effects and importance of these HMPs or DSs formulations and research on the efficacy and bioavailability of HMPs or DSs in animal or human trials. It goes beyond previous studies, which, in essence, looked at the quality of the botanical material used and the extracts derived from these. In general, products regulated as medicines showed good performance characteristics. The study is relevant not only for *Lavandula* species products but also for other HMPs more generally. Ongoing research focuses on a more detailed assessment of the chemical composition of *Lavandula*-containing products (Jalil et al. (n.d.) under preparation)). These studies will guide our understanding of HMPs or DSs formulation and also build a foundation to improve the reported outcomes of pre-clinical studies and clinical trials investigating HMPs and DSs efficacy, safety and bioavailability. With the lack of adequate dosage form testing and reporting in studies utilising HMPs and DSs products, results of the risks and benefits would vary, be overstated/understated and/or falsely reported and interpreted. Equally important is the chemical characterisation and authentication of the investigational products in these studies. The study highlights the need for quality assurance beyond defining the chemical composition (e.g., in a pharmacopoeia) and the urgent need for better quality assurance with HMPs and DSs. The differences in regulatory statutes governing medicinal products and dietary/food supplements on the global market (Heinrich et al., 2024) (i.e., using *Lavandula* species products as a case study) may contribute to a limited understanding of the potential risks and benefits of these products, particularly HMPs (i.e., medicinal products) for their utilisations in addressing the challenges faced by the global healthcare systems.

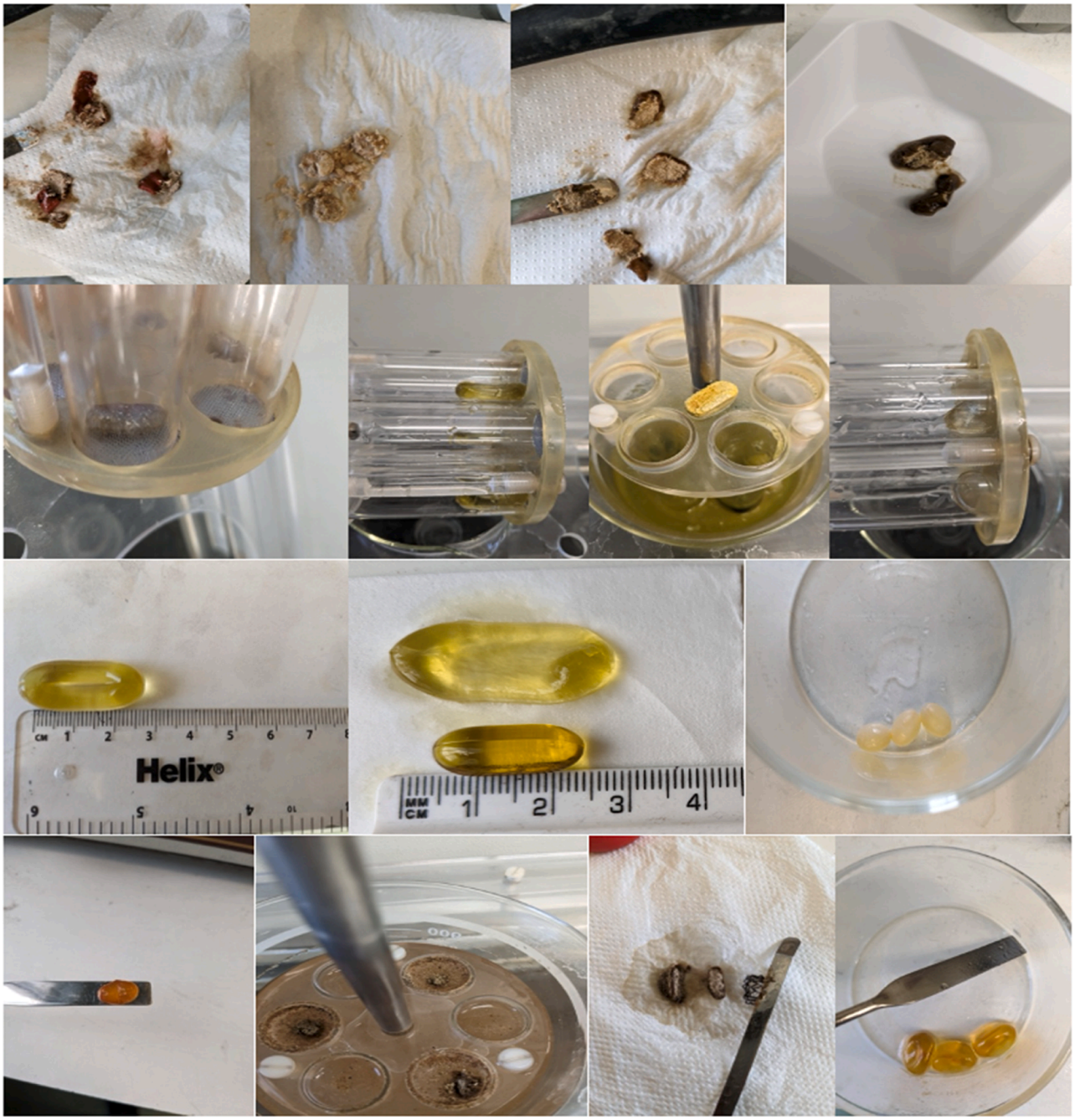

Fig. 7. Disintegration testing results for selected products that did not pass the disintegration testing, including examples of all different dosage forms tested in this study ($n = 72$).

Funding

This project was funded through a charitable donation by Dr. Willmar Schwabe GmbH & Co. KG, Germany, manufacturer of Silexan®. The donor had no influence on the analysis and interpretation of the data but supported the study, for example, through the supply of difficult-to-obtain products.

CRediT authorship contribution statement

Banaz Jalil: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Michael Heinrich:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Conflict of interest

The authors declare no conflict of interest. BJ's position was funded through a charitable donation by Dr. Willmar Schwabe GmbH & Co. KG, Germany, manufacturer of Silexan®.

Acknowledgement

The authors are grateful to Prof Catherine Tuleu for their support with pharmaceutical performance testing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2025.107042.

Data availability

The original contributions presented in this study are included in the article/Supplementary materials; further inquiries can be directed to the authors.

References

Andrews, K., Gusev, P., Savarala, S., Tey, P.-T., Oh, L., Bautista, R., Atkinson, R., Bahadur, R., Pehrsson, P., Dwyer, J., 2021. Comparison of label claims, measured curcuminoid content and dosage form performance quality with industry standards for turmeric dietary supplements. Curr. Dev. Nutr. 5, 5140296.

Azarmi, S., Roa, W., Löbenberg, R., 2007. Current perspectives in dissolution testing of conventional and novel dosage forms. Int. J. Pharm. 328, 12–21.

Baser, K.H.C., Buchbauer, G., 2015. Handbook of Essential Oils: Science, Technology, and Applications. CRC Press, Boca Raton.

Baser, K.H.C., Buchbauer, G., 2021. Handbook of Essential Oils: Science, Technology, and Applications. CRC Press.

Booker, A., Agapouda, A., Frommenwiler, D.A., Scotti, F., Reich, E., Heinrich, M., 2018. St John's wort (Hypericum perforatum) products–an assessment of their authenticity and quality. Phytomedicine 40, 158–164.

Booker, A., Jalil, B., Frommenwiler, D., Reich, E., Zhai, L., Kulic, Z., Heinrich, M., 2016. The authenticity and quality of Rhodiola rosea products. Phytomedicine 23, 754–762.

Brzezińska, J., Szewczyk, A., Brzezicha, J., Prokopowicz, M., Grembecka, M., 2021. Evaluation of physicochemical properties of beetroot-based dietary supplements. Foods 10, 1693.

Burfield, T., 2003. The adulteration of essential oils-and the consequences to aromatherapy and natural perfumery practice. In: International Federation of Aromatherapists Annual General Meeting. London, UK.

Di Lorenzo, C., Colombo, F., Biella, S., Stockley, C., Restani, P., 2021. Polyphenols and human health: the role of bioavailability. Nutrients 13, 273.

Dold, M., Bartova, L., Volz, H.-P., Seifritz, E., Möller, H.-J., Schläfke, S., Kasper, S., 2023. Efficacy of Silexan in patients with anxiety disorders: a meta-analysis of randomized, placebo-controlled trials. Eur. Arch. Psychiatry Clin. Neurosci. 273, 1615–1628.

Edwards, S.E., da Costa Rocha, I., Williamson, E.M., Heinrich, M., 2015. Phytopharmacy: An evidence-Based Guide to Herbal Medicinal Products. John Wiley & Sons.

Ekong, J., Oh, L., Haile, E., Andrews, K., Gusev, P., Pehrsson, P., Bahadur, R., Dwyer, J., Kuszak, A., Costello, R., 2022. Sampling plan for a study of cranberry dietary supplements (DS) for the dietary supplement ingredient database (DSID). Curr. Dev. Nutr. 6, 6009279.

Empowered By Evidence. 2024. *Empowered by evidence database* [Online]. Available: https://empoweredbyevidence.org/ebe-database/(Accessed 5 January 2025).

European Medicines Agency. 2004. *Herbal medicinal products* [Online]. Available: https://www.ema.europa.eu/en/human-regulatory-overview/herbal-medicinal-products (Accessed 1 September 2024).

European Pharmacopeia. 2023a. *Dosage forms* [Online]. Available: https://www.edqm.eu/en/european-pharmacopoeia-ph.-eur.-11th-edition (Accessed 10 October 2024).

European Pharmacopeia. 2023b. *Lavender oil* [Online]. Available: https://www.edqm.eu/en/european-pharmacopoeia-ph.-eur.-11th-edition (Accessed 10 October 2024).

Floyd, Z.E., Ribnicky, D.M., Raskin, I., Hsia, D.S., Rood, J.C., Gurley, B.J., 2022. Designing a clinical study with dietary supplements: it's all in the details. Front. Nutr. 8, 779486.

Gafner, S., Blumenthal, M., Foster, S., Cardellina, J.H., Khan, I.A., Upton, R., 2023. Botanical ingredient forensics: detection of attempts to deceive commonly used analytical methods for authenticating herbal dietary and food ingredients and supplements. J. Nat. Prod. 86, 460–472.

Glube, N., von Moos, L., Duchateau, G., 2013. Capsule shell material impacts the in vitro disintegration and dissolution behaviour of a green tea extract. Results Pharma Sci. 3, 1–6.

Gray, V.A., Cole, E., Toma, J.M.R., Ghidorsi, L., Guo, J.-H., Han, J.-H., Han, F., Hosty, C. T., Kochling, J.D., Kraemer, J., 2014. Use of enzymes in the dissolution testing of gelatin capsules and gelatin-coated tablets–revisions to dissolution< 711>and Disintegration and dissolution of Dietary supplements< 2040. Dissol. Technol. 21, 6–20.

Gurley, B.J., 2011. Emerging technologies for improving phytochemical bioavailability: benefits and risks. Clin. Pharmacol. Ther. 89, 915–919.

Gurley, B.J., 2012. Pharmacokinetic herb-drug interactions (part 1): origins, mechanisms, and the impact of botanical dietary supplements. Planta Med. 78, 1478–1489.

Gusev, P.A., Andrews, K.W., Savarala, S., Tey, P.-T., Han, F., Oh, L., Pehrsson, P.R., Dwyer, J.T., Betz, J.M., Kuszak, A.J., 2020. Disintegration and dissolution testing of green tea dietary supplements: application and evaluation of United States pharmacopeial standards. J. Pharm. Sci. 109, 1933–1942.

Heinrich, M., 2015. Quality and safety of herbal medical products: regulation and the need for quality assurance along the value chains. Br. J. Clin. Pharmacol. 80, 62–66.

Heinrich, M., Jalil, B., Abdel-Tawab, M., Echeverria, J., Kulić, Ž., McGaw, L.J., Pezzuto, J.M., Potterat, O., Wang, J.-B., 2022. Best practice in the chemical characterisation of extracts used in pharmacological and toxicological research—The ConPhyMP—Guidelines. Front. Pharmacol. 13, 953205.

Heinrich, M., Reiken, B., Roether, B., Müller, A., Rumsch, J., Symma, N., 2024. Consensus statement on the outcome of the European Herbal Health Products Summit–Which way forward? Planta Med. 90, 1052–1055.

Jalil, B., Naser, A.Y., Prieto, J.M., Heinrich, M., 2022. Herbal supplements in Jordan: a cross-sectional survey of pharmacists' perspectives and knowledge. BMJ Open 12, e057405.

Kasper, S., Eckert, A., 2024. Silexan in anxiety, depression, and related disorders: pharmacological background and clinical data. Eur. Arch. Psychiatry Clin. Neurosci. 1–15.

Lis-Balchin, M., 2002. *Lavender: The Genus Lavandula* London. Taylor & Francis, UK.

Love, J.N., Sammon, M., Smereck, J., 2004. Are one or two dangerous? Camphor exposure in toddlers. J. Emerg. Med. 27, 49–54.

Lyu, W., Omar, T., Patel, H., Rodriguez, D., Ferruzzi, M.G., Pasinetti, G.M., Murrough, J. W., Muzzio, F.J., Simon, J.E., Wu, Q., 2021. Dissolution study on grape polyphenol hard gelatin capsule dietary supplements. Front. Nutr. 8, 780260.

Orhan, N., Gafner, S., Blumenthal, M., 2024. Estimating the extent of adulteration of the popular herbs black cohosh, echinacea, elder berry, ginkgo, and turmeric–its challenges and limitations. Nat. Prod. Rep.

Rathaur, P., Johar, K., 2019. Metabolism and pharmacokinetics of phytochemicals in the human body. Curr. Drug Metab. 20, 1085–1102.

Schmidt, E., 2020. Production of Essential Oils. CRC Press.

Sorkin, B.C., Kuszak, A.J., Bloss, G., Fukagawa, N.K., Hoffman, F.A., Jafari, M., Barrett, B., Brown, P.N., Bushman, F.D., Casper, S.J., 2020. Improving natural product research translation: from source to clinical trial. FASEB J. 34, 41–65.

Tisserand, R., Young, R., 2014. Essential Oil Safety: A Guide For Health Care Professionals. Elsevier Health Sciences, Edinburgh: UK.

Upton, R., David, B., Gafner, S., Glasl, S., 2020. Botanical ingredient identification and quality assessment: strengths and limitations of analytical techniques. Phytochem. Rev. 19, 1157–1177.

Villani, T.S., Reichert, W., Ferruzzi, M.G., Pasinetti, G.M., Simon, J.E., Wu, Q., 2015. Chemical investigation of commercial grape seed derived products to assess quality and detect adulteration. Food Chem. 170, 271–280.