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The era of fake medicines: Investigating counterfeit medicinal products for erectile dysfunction disguised as herbal supplements

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ABSTRACT

Sales of substandard and falsified medical products (SF) are rising rapidly everywhere around the globe. The wide and easy access to these products is an alarming issue to the global health systems and undermined the health of patients, especially with the thrive of online commerce. To tackle this threat to public health, new ways to access these products should be identified and detection technologies should be strengthened. The overarching aim of this study was to investigate if herbal supplements sold online claiming to be natural alternatives to Viagra® were amongst these SF medical products and how effective different analytical techniques are in providing information about these products. 3 products which claimed to be herbal supplements for men sexual performance were purchased from an e-commerce platform. Two products were received as unregistered generic sildenafil citrate tablets manufactured in India (and thus different to the products information on the website) while one product was received in the same packaging as shown on the website, claiming to be an herbal product. Nevertheless, all products were proven to contain sildenafil citrate, the active pharmaceutical ingredients in Viagra® after the comprehensive analytical tests. The results elucidated that the quality standards for the unregistered generic sildenafil citrate tablets were fulfilled according to the British Pharmacopeia, but the falsified product failed the quality tests and contained approximately 200 mg sildenafil citrate, which is equivalent to 2-fold of the daily maximum dose. Furthermore, physical characterisations, including powder x-ray diffraction and thermal analysis were performed and revealed that the polymorphic forms of sildenafil citrate were different, demonstrating the importance of employing thermal analysis in addition to the conventional analysis techniques for the substandard and falsified medical products. These techniques provided valuable insights into the physical form of the active ingredient in these products. What is more, the ease with which these SF products were obtained and confirmed to be misleading consumers emphasises the need for tighter regulation for e-commerce websites in line with those enforced on online pharmacies.

1. Introduction

Substandard and falsified medicines (SF) is a growing threat to the healthcare system. A study by the World Health Organisation (WHO) in 2017 found that approximately 10% of medicines in developing countries were falsified or substandard (World Health Organization, 2017a). SF medicines are classified by the Member State Mechanism and WHO global surveillance and monitoring system into 3 categories, substandard, unregistered/unlicensed, and falsified medicines (World Health Organization, 2017b). Substandard medical products are authorized medicines that failed to fulfil either the specifications or the quality standards, or both, while unregistered/unlicensed medical products are medical products that are sold or distributed without authorization from the respective regulatory authority in that country or region. Falsified medical products are produced to deliberately disguise their identity, composition, or source (Callister, 2019). The latter two types of medical products are the focus of this study. The causes for the surge of SF medicines are numerous, which include the unaffordable price tags of medicines (Blackstone et al., 2014), lacking legal and steady supply, deficiency of awareness for the potential dangers of SF medicines (Buckley and Gostin, 2013)(), and trying to obtain highly restricted prescription-only medicines (POM) without a legitimate prescription as patients self-diagnose and self-prescribe (Funestrand et al., 2019).

Poor regulations and pharmaceutical governance also allow

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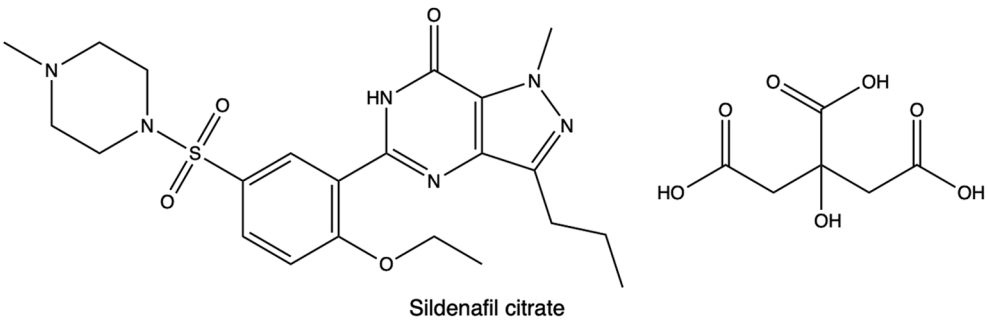


Fig. 1. Chemical structure of sildenafil citrate.

Table 1
Common methods of screening counterfeit medicines (Alfarsi et al., 2021; Bartle and Myers, 2002; Cranwell et al., 2017; Martino et al., 2010; Urban, 2016 (Buckley and Gostin, 2013).

Methods	Description
high-performance liquid chromatography (HPLC)	A chromatographic technique was used to separate mixtures to identify and quantify the proportions of individual components.
thin-layer chromatography (TLC)	A chromatographic technique is used to separate non-volatile mixtures, which can be used to identify compounds and determine their purity.
Gas chromatography (GC)	A chromatographic method that can be used to separate and analyze complex mixtures that can be evaporated.
Mass spectrometry (MS)	An analytical technique that can identify sample components based on the mass-to-charge ratio (m/z).
Fourier transform IR spectroscopy (FTIR)	Spectra was used to identify the functional groups with absorption frequency in the drug component.
Vibrational spectroscopies (Raman or IR)	The non-destructive chemical analysis scattering spectroscopy technique can be used to screen the quality of pharmaceutical preparations through coatings and capsules.
Nuclear magnetic resonance spectroscopy (NMR)	A spectroscopy technique that can determine molecular structure.
Broadband acoustic resonance dissolution spectroscopy (BARDS)	An acoustic spectroscopy that monitors and characterises the disintegration of tablets and blends during the dissolution in a solvent

individuals, who disregard the legislation, easier access to falsified medicines (Ghanem, 2019). In the UK, any website intending to sell medicines to the public must register with the Medicines and Healthcare products Regulatory Agency (MHRA) and present a Distance Selling logo on the website to allow members of the public to identify them (Medicines and Healthcare products Regulatory Agency, 2015). However, selling products that are claimed to be herbal or food supplements online is not regulated, which is a loophole and a new route to sell falsified and unlicensed medicines without regulation.

One of the most prevalent examples of SF medicines was Viagra®, which contains sildenafil citrate (Jackson et al., 2010). Sildenafil is a phosphodiesterase-5 inhibitor, administered via the oral route for erectile dysfunction (ED), with the chemical structure shown in Fig. 1. ED is defined as the consistent inability of the male to attain or maintain a penile erection sufficient for satisfactory sexual intercourse (Health, 1993). The maximum recommended dose for sildenafil is 100 mg per day. Common side effects include anaemia, anxiety, headache, vasodilation, and insomnia (Joint Formulary Committee, 2021). Although higher doses of sildenafil citrate produced a significant improvement in ED for patients who do not respond to 100 mg, studies have shown that 63% of people taking 150–200 mg experienced adverse reactions including headaches, facial flushing, visual disturbances, and indigestion (McMahon, 2002).

The global security department in Pfizer conducted a study in 2011, where 22 claimed to be authentic Viagra® tablets were ordered online and 77% amongst those tablets were counterfeit (Campbell et al., 2012). Albeit the reclassification of 50 mg sildenafil citrate film-coated tablets from a prescription-only medicine (POM) to pharmacy medicine (P) in November 2017 in the UK (Medicines & Healthcare products Regulatory Agency, 2017), large financial and emotional incentives to purchase them via alternative routes remain. The high cost of the drug discourages patients from purchasing genuine medicine, in preference to the cheaper SF medicines. Moreover, there is a stigma attached to ED, resulting in patients seeking alternative sources to pharmacy to avoid disclosing their condition to a healthcare professional, where the over-the-counter purchase of Viagra Connect® still requires the patients to complete a health questionnaire and be screened by the pharmacist to ensure the patient meets the criteria to purchase Viagra Connect®. It is estimated that 13–28% of men aged 40–80 years old are affected by erectile dysfunction (ED) and are anxious about the failure of their sexual response (Steidle et al., 2007), but the cardiovascular morbidities could prevent them from purchasing the tablets from the pharmacy. Sildenafil is contraindicated for unstable angina, myocardial infarction, history of non-arteritic anterior ischaemic optic neuropathy (Joint Formulary Committee, 2021). In addition, patients who are not fit for vasodilation or sexual activity, suffer from genetic diseases of retinal phosphodiesterase are not suitable for treatment with sildenafil (Joint Formulary Committee, 2021; Lim et al., 2002). Therefore, these patients either need a prescription from a doctor or might seek alternative sources.

There is an increasing number of herbal or food supplements sold online claiming to improve men sexual performance, with claims that they do not contain sildenafil. However, these products are neither regulated nor require any form of health screening, and they could be falsified or illegal products. Taking counterfeit medicines not only could have suboptimal therapeutic effects but also pose serious health risks that could potentially lead to death (Blackstone et al., 2014). Thus, taking SF supplements equally cause these dangerous health risks, exposing patients to unknown ingredients, overdosing, and different drugs. In addition, incorrect label information and instructions could also result in overdosing and increase the likelihood of experiencing adverse events, while incomplete descriptions of certain ingredients in the product may cause interaction with other drugs (Jackson et al., 2010).

The European Union Intellectual Property Office (EUIPO) estimated that about EUR 16.5 billion was lost in sales and over 80,000 jobs in pharmaceutical and related sectors were impacted due to counterfeiting. The European Union (EU) 2019 Status Report on IPR Infringement reported that EUR 9.6 billion in sales, which accounted for 3.9% of the total sales, was lost by the European pharmaceutical industry between 2012 and 2016 (The European Intellectual Property Office, 2019), whereas the counterfeiters contributed to nearly a quarter of the turnover from India's pharmaceutical industry of USD 4.2 billion in 2003 (OECD, 2016). Thus, the sales of counterfeit medicines possess

enormous financial impacts, displacing the sales of the legitimate products (OECD/EUIPO, 2020).

An important aspect indicated by the WHO to combat substandard and falsified medical products is detection (World Health Organization, 2017b). However, there are "high quality" SF medicines circulating on the market that are difficult to identify with careful visual inspection solely (Buckley and Gostin, 2013)(). Thus, comprehensive analytical methods have been employed for detecting SF medicines. A summary of common qualitative and quantitative analysis techniques currently used to identify counterfeit medicines are shown in Table 1. Despite these analytical technologies being crucial to detect SF medicines, the use of chromatography, spectroscopy and mass spectrometry mainly focus on identifying and quantifying the active pharmaceutical ingredients. Physical properties of the API in SF medicine are equally important and should also be characterised. API could exist as amorphous materials, monomorphic and polymorphic crystals, which could subsequently impact the solubility, bioavailability, dissolution rate and other tablets properties. Therefore, solid-state analytical techniques could also distinguish between counterfeit and genuine medicines (Bugay, 2001), such as powder X-ray diffraction analysis (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) (Stofella et al., 2019), dielectric spectroscopy (DS), Terahertz pulsed spectroscopy (TPS) (Guo et al., 2013). However, these techniques are less commonly used in the detection of SF medical products, especially thermal analysis and PXRD. We believe characterising the physiochemical properties of the pharmaceutical ingredients in the SF drugs is equally important as other established characterisation techniques. These powerful techniques could provide fast and simple detection of SF products. In addition, combining two techniques to simultaneously collect two sets of results from the same sample during the same test can provide valuable insights into properties such as polymorphic phase transitions (Buanz et al., 2015).

DSC measures the temperature and enthalpy associated with transitions in materials such as melting, crystallization and decomposition as a function of temperature and time in a fixed atmosphere (Ekere et al., 2017), which could determine the melting point, thermal stability, purity, polymorphism, hydration and solvation behaviour of medical products. TGA measures the weight changes of a substance as a function of temperature and time. Consequently, it possesses the ability to quantify decomposition, oxidation, decarboxylation, loss of water, solvent and plasticizer of a pharmaceutical product (Lin, 2016). Lastly, PXRD could differentiate between genuine and falsified medicines by interpreting the interplanar distance, deflection angle and intensity of deflection, which provides information about the medicine's qualitative composition (Jendrzejewska et al., 2018). In addition, in vitro dissolution test is also suitable for identifying the quality of counterfeit drugs. This is because the content of API in the formulation and the choice of excipients will significantly affect the dissolution profile, which can be used to identify the authenticity of the sample by the low or exceeding the dissolution profile (Gaudiano et al., 2012).

In this study, we first investigated the authenticity of several claimed herbal or food supplements for men sexual performance procured online and identified what types of products were received. Then, these products were evaluated by the solid-state characterization technique we advocated, and subsequently compared with pure sildenafil reference and Viagra Connect® tablets. This study is aimed to investigate this type of products that are sold as herbal supplements but could be SF medicines and demonstrate the importance of characterizing the physical properties in SF medicines in addition to the ordinary characterization techniques. It also aims at highlighting the ability of these techniques in differentiating the physical properties of the API between authentic and illicit products.

2. Materials and methods

2.1. Materials

Viagra Connect® 50 mg film-coated tablets, manufactured (Pfizer Ltd, New York City, USA), were purchased from Boots the Chemist (Nottingham, UK) in London. Three herbal alternatives which claimed to contain 100% herbal ingredients for enhancing men sexual performance, namely Vairelax capsules, Via-Max tablets, and Love tablets were purchased from the online e-commerce website eBay (San Jose, CA, USA). Two batches of reference standards for sildenafil citrate were purchased from Sigma Aldrich (St Louis, MO, USA). Hydrochloric acid used was of analytical grade.

2.2. Methods

2.2.1. Procurement and visual evaluation

Two keywords, namely "herbal v" and "blue pill", were monitored over two weeks on two popular e-commerce marketplaces - amazon and eBay from 28/05/2021 to 11/06/2021. Three products, namely Vairelex capsule, Via-Max, and Love tablets were selected and purchased from eBay, based on the availability at the time of purchase. Viagra Connect® tablets were purchased from a registered pharmacy in London directly to ensure their authenticity. Upon receiving the delivery, the packaging of the products and the content inside the box if any, were photographed for the record.

2.2.2. Dimensions and hardness measurements

The width, thickness and hardness of the tablets were measured using an ERWEKA TBH 125 hardness tester (ERWEKA GmbH, Heusenstamm, Germany) based on a method modified from the British Pharmacopoeia 2022 with only three replicates tested for each product (COMMISSION., 2021).

2.2.3. Weight and content uniformity

Weight uniformity was assessed with a method adapted from the British Pharmacopeia, with the weight of only 10 units measured individually. The weight of tablets was measured directly, while the weight of the content of the capsule was obtained by subtracting the mass of the empty capsule shell from the total weight of the capsule. The acceptable criteria were 5% and 10% derivation from the average mass for the dosage forms according to the British Pharmacopeia 2022 (BP), for tablets weighted above 250 mg and capsules weight less than 300 mg respectively (COMMISSION., 2021).

Content uniformity was also assessed with a method adapted from the British Pharmacopeia 2022 (COMMISSION., 2021). 5 units of the tablets were randomly selected and ground into a powder with a pestle and mortar. 50 mg of the ground sample was first dissolved in 50 mL of 0.1 M HCl. Subsequently, 1 mL of the solution was filtered with a 0.22 μm filter (Merck Millipore, Darmstadt, Germany) and further diluted to 25 mL with 0.1 M HCl solution. UV absorbance of the samples was measured at 290 nm using a UV–visible light spectrophotometer (Cole-Parmer, St Neots, UK). Capsules were first opened before assaying the drug content as discussed above. Individual content in the range between 85 and 115% of the average content is deemed acceptable.

2.2.4. Physical characterisations

The tablets were first ground into a powder with a pestle and mortar, while the content of the capsules was first emptied from the capsule shells before conducting the physical characterisations.

2.2.4.1. Fourier-transform infrared spectroscopy. Analysis of the sildenafil citrate and the samples from the herbal alternatives was performed using a Spectrum 100 FTIR spectrometer equipped with an attenuated total reflectance (ATR) sampling accessory (Perklin Elmer, Waltham,

Table 2
Details of the herbal alternatives monitored on two e-commerce platforms and the unit cost for each product; Viagra Connect® are included for comparison.

Platform	Product	Claimed content	Unit cost (£)	Purchased
Boots	**Viagra Connect ®**	**Sildenafil**	**4.4**	**Yes**
eBay	Via-Max tablet	100% natural food supplement	0.5	Yes
	Vairelex capsule		0.52	Yes
	Love tablet		0.45	Yes
	Mellow Pharmaquests Pills	Plant extracts	1.2	No
	VMANPLUS Sex Pills	100% natural food supplement	0.5	No
Amazon	Herbal N+	Plant extracts	1.5	No
	Crazy dik		2.0	No
	Viamen capsule	100% natural food supplement	1.0	No

USA) in the range of 650–4000 cm^{-1} and with a resolution of 8 cm^{-1}. Each sample was scanned 16 times.

2.2.4.2. Thermogravimetric analysis. Thermogravimetric analysis of all samples was performed on a Discovery TGA (TA Instruments, New Castle, DE, USA). 3–5 mg of sample was added in a tared aluminium pan (TA Instruments, New Castle, DE, USA). The samples were then heated from 40 °C to 300 °C at a temperature ramp of 10 °C/min. Experiments were conducted at a nitrogen gas purge flow rate of 25 mL/min. Data were analysed using Trios software (TA Instruments, New Castle, DE, USA).

2.2.4.3. Differential scanning calorimetry. Tests were performed on 3–5 mg of the samples, which was added to a Tzero aluminium pan, which was sealed with a hermetic lid (TA instrument, New Castle, DE, USA). A pinhole was punctured in the lid to release the moisture during heating. The analysis was carried out with a Q2000 differential scanning calorimeter (TA Instruments, New Castle, DE, USA). The calorimeter was calibrated for cell constant and enthalpy (156.6 ± 0.5 °C, enthalpy = 28.72 J/g ± 3%) at the heating rate used with indium standard before the experiment according to the manufacturer's instructions. The sample was heated directly from 0 °C to 250 °C at a temperature ramp of 10 °C/min and under a flow of 50 mL/min nitrogen gas. Data were recorded with the TA Advantage software package and analysed using TA Universal Analysis with transition temperatures taken as peak maxima and enthalpy values calculated using the sigmoidal integration function.

2.2.4.4. Simultaneous differential scanning calorimetry-synchrotron X-ray diffraction. Experiments were performed at the Diamond Light Source using the Joint Engineering, Environment and Processing (JEEP) Beamline I12. A monochromatic X-ray beam of wavelength = 0.234 Å, and a diameter of 0.5 mm were used. A Pilatus 2 M CdTe detector was fitted 2 m behind the sample. Using the calibration procedure described in the literature, the sample-detector distance and beam wavelength had been calibrated with cerium dioxide (CeO2) (Hart et al., 2013). Patterns were recorded by collecting data for 4 s, with a 2 s pause. Powder samples were placed in Tzero aluminium pans and sealed with pin holed Tzero hermetic lids. The sealed pans were placed in a TA Instruments Q20 differential scanning calorimeter (TA Instruments, New Castle, DE, USA) with a refrigerated cooling system (RCS). In the experimental area, the DSC was mounted onto the sample stage. It had already been modified to allow the passage of a synchrotron beam. In the RCS, 5 mm entry and 10 mm exit holes were made, and in the DSC furnace, 3 mm entry and 5 mm exit holes were drilled. The DSC was calibrated before for cell contact and enthalpy using indium standard (melting onset temperature = 156.6 ± 0.5 °C, enthalpy = 28.72 J/g ± 3%), according to the manufacturer's instructions. Two aluminium hermetic lids were used to raise the pans inside the DSC furnace to centre the sample in the beam direction; these pans were also included in the calibration. A nitrogen purge gas (50 mL/min) was used throughout.

Data were collected with TA Instruments Advantage software and initially analysed with TA Universal Analysis software. DAWN Science Workbench was first used to mask regions of unrepresentative spots of high intensity in the 2D Pilatus data caused by the large grain/crystal size of the samples. The same software was used to convert the 2D data into 1D diffraction patterns. DSC measurements were performed at a heating ramp rate of 10 °C/min from 0 °C to 250 °C and one powder pattern was recorded per degree centigrade.

2.2.5. Dissolution tests

Dissolution of sildenafil from the products was tested by an ERWEKA DH 1520 dissolution tester (ERWEKA GmbH, Heusenstamm, Germany) with the paddle apparatus, based on a method adapted from the British Pharmacopoeia 2022 (COMMISSION., 2021). The rotation speed was 100 rpm while the vessel temperature was maintained at 37.0 ± 0.5 °C. 0.1 M HCl was used as the dissolution medium, to simulate the gastric condition. 5 mL of dissolution medium were taken at seven time points; 5, 10, 15, 30, 45, 60, and 120 min, followed by replenishment of fresh warmed 0.1 M HCl. 4 mL of the samples were filtered through cellulose-based 0.22 μm filters (Merck Milipore, Darmstadt, Germany) and further diluted to 25 mL with 0.1 M HCl. Sildenafil was assayed by UV–Vis spectroscopy at the wavelength of 290 nm using a UV–Vis spectrometer (Cole-Parmer, St Neots, UK). Drug concentrations were calculated using pre-determined calibration curves (r^2 = 0.9998). The experiment was replicated independently three times and the results were presented as the mean value ± standard derivation. Dissolution profiles were compared using similarity factor (f_2), which was calculated for the three suspected SF products in comparison to Viagra Connect® as described before (Costa et al., 2003).

3. Results

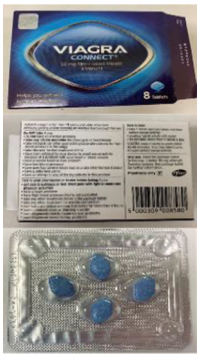
3.1. Procurement and visual evaluation

Eight claimed to be natural food or herbal products for men sexual performance which were monitored on the e-commerce platforms as shown in Table 2, all of which claimed to contain either 100% natural food supplement or plant extracts. Interestingly, all products claimed to contain ginseng extracts and thus three products were purchased to verify their authenticity. The unit costs for these herbal alternatives, ranged from £ 0.5 to £ 2, which were much lower in cost than that of the Viagra Connect®, which costs £ 4.4 per tablet. The low unit costs for these herbal alternatives might account for their popularity and attractiveness online, given that Viagra Connect® is now available over the counter and is readily accessible to patients in pharmacies.

Upon receipt of the purchased products, photos of the packaging and the content after box opening, if any, were taken (Table 3). Both products named Via-max and Love tablets on the website were received as strips of 100 mg sildenafil citrate tablets manufactured by an unknown manufacturer and Hab Pharmaceuticals & Research Limited respectively, and thus they were different from the claims on the e-commerce platform. The brand names of the tablets received were Sildamax for Via-max, which was exported by Agron India Ltd. The latter was marketed under the brand name Abhigra-100 by Abhiflax Pharma Chem Pvt. Ltd. The tablets appeared in signatory diamond shape and with a blue coating, but the blue coating was brighter in colour compared to Viagra Connect®. No patient information leaflet or medicine box was given, but both tablets were in date according to the information provided on the strips. Neither of the manufacturers was registered with the Medicine Healthcare Regulatory Agency (MHRA), nor did the products have market authorization in the UK at the time of writing.

The manufacturer Hab Pharmaceuticals & Research Limited could be identified in the list of manufacturers of drugs for COVID-19 published

Table 3
Summary of claimed and observed ingredients list of the authentic Viagra Connect® and falsified herbal alternatives with pictures of the received items.

Sample name	Pictures of the products received	Claimed ingredients on the website	Ingredient on the packaging	Contain sildenafil	Authenticity
Viagra connect® tablet		Sildenafil citrate, microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium, Hypromellose, titanium dioxide (E171), lactose, triacetin, indigo carmine aluminium lake (E132)	Sildenafil citrate, microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium, Hypromellose, titanium dioxide (E171), lactose, triacetin, indigo carmine aluminium lake (E132)	Yes	Authentic
Via-Max tablet (Received as Sildamax tablets)		Microcrystalline cellulose, dicalcium phosphate, vitamin C (ascorbic acid), L-arginine oats, alfalfa extract (oat), Korean ginseng (ginseng) extract, modified corn starch, zinc sulfate, anti-caking agent: Silicon dioxide, magnesium stearate, coating, HPMC, E464 colour E127	Sildenafil citrate, Brilliant blue, Indigo Carmine	Yes	Unregistered generic
Love tablet (Received as Abhigra-100 tablets)		Oat (Avena Sativa) extract, Korean Ginseng (Panax) extract, Vitamin C, L-Arginine, Zinc	Sildenafil citrate Brilliant blue	Yes	Unregistered generic
Vairelex capsule		Ginseng Panax, Fructus Lycii, Rhizoma Polygonati, Semen Ziziphi Spinose, Flos Caryophlli, Cortex Cinnamomi, Semen Alli Tuberosi	Ginseng (Panax Ginseng), Fructus Lycii (Goji Berry), Rhizoma Polygonati, Semen Ziziphi Spinosae, Flos Caryophylli (Dried Cloves), Cortex Cinnamomi, Semen Alli Tuberosi	Yes	Falsified medicine

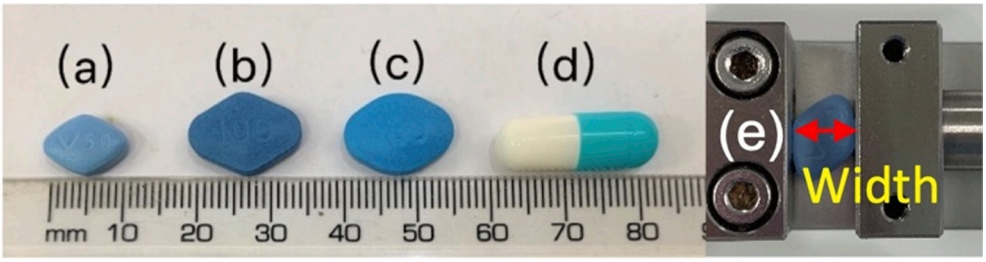


Fig. 2. Images of units of (a) Viagra Connect® (b) Sildamax, and (c) Abhigra-100 tablets, and (d) Vairelex capsules. (e) The orientation of the tablets in the tablet hardness machine. The scale is in mm.

by the Government of Maharashtra, which indicated that the company is a legitimate and approved drug manufacturer (Government of Maharashtra, 2020). However, the registration status of Sildamax and Agron India Ltd could not be confirmed, due to the absence of an official registration list for the pharmaceutical companies or products. Interestingly, the product was published on the health blog of the Public Health Nigeria (Public Health Nigeria, 2020), which supports that the products are generics. Importing a small number of unlicensed drugs for personal use is legal in the UK but distributing or selling without a product license is illegal in the UK. As these products are highly likely

Table 4
Dimensions and hardness of tablet products (expressed as mean ± SD) (n = 3).

Sample	Width (mm)	Thickness (mm)	Hardness (N/mm^2)
Viagra Connect®	4.40 ± 0.03	7.96 ± 0.04	179 ± 13
Abhigar-100	5.77 ± 0.01	10.91 ± 0.08	140 ± 11
Sildamax	5.49 ± 0.09	10.34 ± 0.01	231 ± 37

generics but are not licensed in the UK, they were classified as unregistered generics.

Meanwhile, the Vairelex capsules were received in a secondary packaging with an identical appearance and ingredients list as claimed online. However, the capsules were in an un-labelled gold packaging and appeared as white and turquoise capsules without any marking. The manufacturer was unknown, despite CH Traderes Ltd being shown as the distributor on the box. The product was in-dated according to the expiry date on the box. As the product claimed to contain natural food supplements, such as ginseng, goji berry, Rhizoma Polygonati, suanzaoren, cloves, cinnamon, Chinese leek seed, and so on. Thus, the product should not theoretically contain any drugs for erectile dysfunction. If the capsules contain sildenafil, then it would be considered a falsified medicine, of which the active ingredient was deliberately mislabelled.

In summary, all the herbal alternatives ordered online are most likely SF medical products, and the descriptions claimed online does not match the actual ingredients in the products.

3.2. Dimensions and hardness measurements

Dimensions and hardness measurements were conducted on tablet products only. Owing to the signatory diamond shape of the sildenafil tablets, the orientation of the tablets in the tablet hardness machine was crucial. As the tablets were oriented with one side of the diamond-shaped tablet aligned with the press to attain the highest stability, the width of the tablets was defined as the red arrow shown in Fig. 2(e). The longer diagonals (length) were in between 1 and 1.5 cm for all three tablets, with Viagra Connect® being the shortest as shown in Fig. 2(a), whilst the capsule was about 2 cm in length.

The Viagra Connect® tablets were also smaller in width and thinner than the other unregistered generic counterparts, as it contains the lowest amount of sildenafil, as shown in Table 4. The sizes of the Sildamax and Abhigra-100 tablets were similar, as both claimed to contain 100 mg sildenafil. Interestingly, the hardness of the tablets did not correlate to their dimensions, with Sildamax being the hardest to break while Abhigar-100 tablet was the softest. This discrepancy is likely due to differences in the formulation and different excipients in the tablets, which were not specified on the packaging. Moreover, the tabletting parameters and manufacturing processes, such as granulation or direct compression, could also impact the solid fraction and the hardness of the tablets, but this information could not be found.

3.3. Weight and content uniformity

Despite the method being adapted from BP, a proportional

Table 5
Results of weight and content uniformity tests for all products (expressed as mean ± SD).

Sample	Weight uniformity (n = 10)			Content uniformity (n = 5)		
	Weight (mg)	Criterion	Result	Content (mg)	Criterion	Result
Viagra Connect®	311.2 ± 2.5	Average ± 5%	Pass	58.3 ± 1.1	Average ± 15%	Pass
Abhigar-100	653.3 ± 7.8		Pass	122.9 ± 3.4		Pass
Sildamax	628.7 ± 15.4		Pass	122.4 ± 4.0		Pass
Vairelex	207.9 ± 20.6	Average ± 10%	Failed (2 out of 10)	199.8 ± 25.8		Failed (2 out of 5)

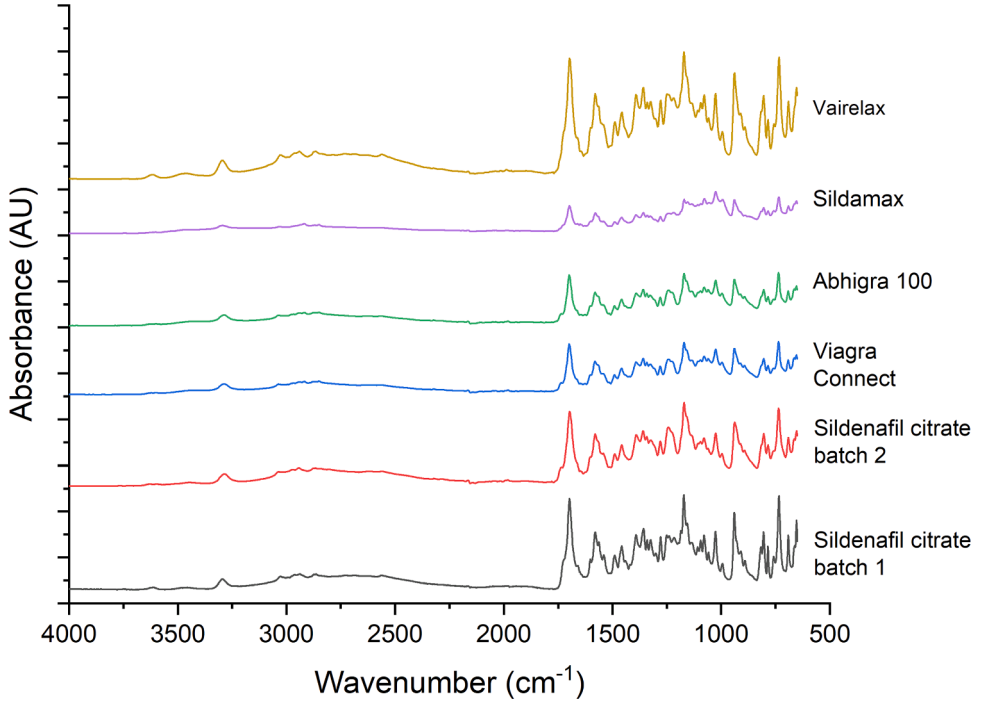


Fig. 3. FTIR spectra of sildenafil citrate references and all four products.

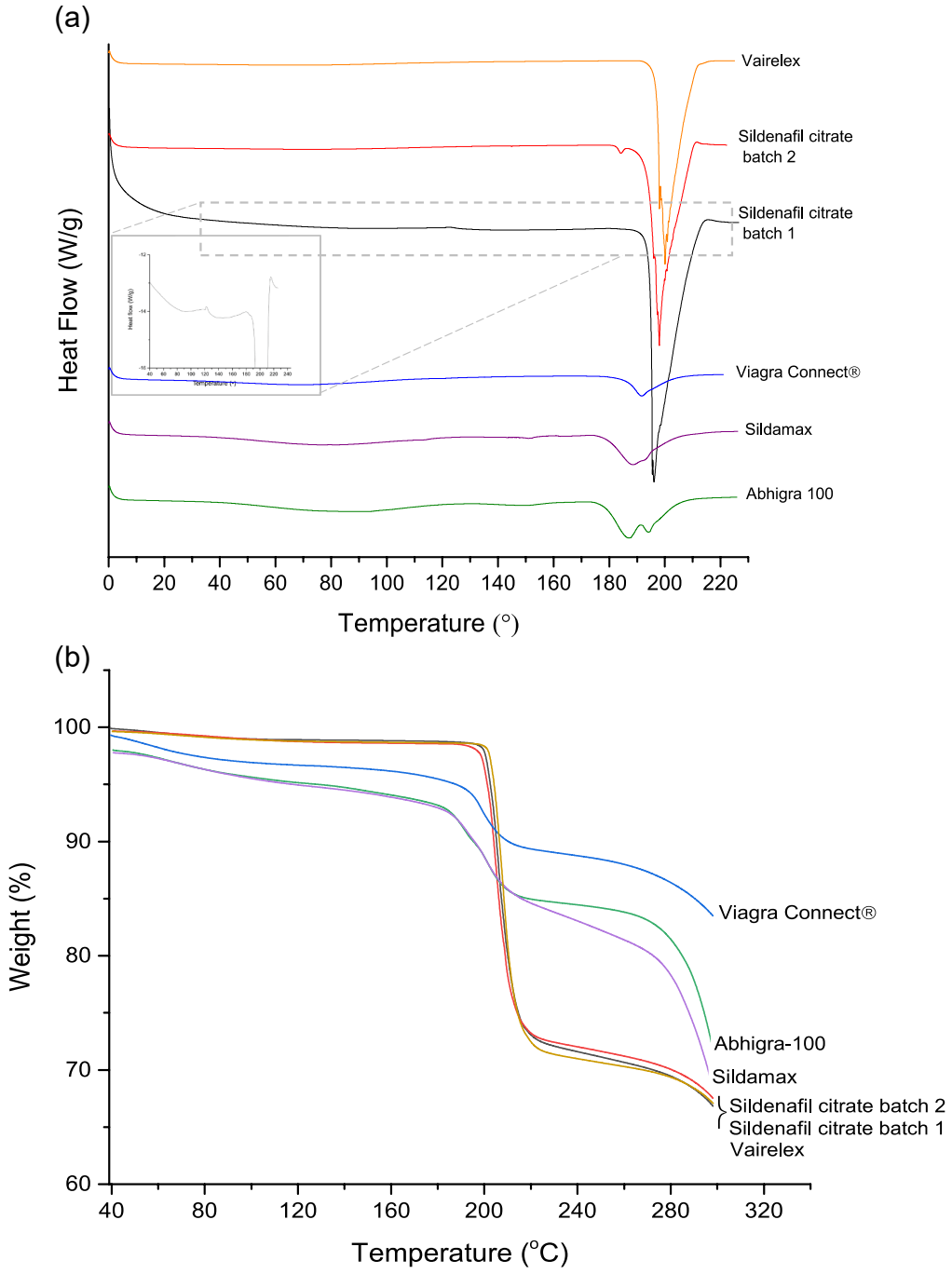


Fig. 4. (a) DSC and (b) TGA thermograms of sildenafil citrate references and all four products.

adjustment of the BP standards for weight and content uniformity was used as the acceptance criteria in this study. Less than or equal to 1 unit failing the criteria as shown in Table 5 was considered acceptable for both weight and content uniformity. All Viagra Connect®, Sildamax and Abhigra-100 tablets fulfilled the criteria for both weight variation test and content uniformity, which elucidated that the quality of the tablets was acceptable and maintained, albeit two of the tablets were unregistered generics.

Conversely, two individual Vairelex capsules did not meet the requirements for both weight variation test and content uniformity, exceeding the acceptable limits for these tests. Although the packaging of the capsules claimed they contain only herbal extracts, the content measured in the test referred to sildenafil citrate and thus confirmed its presence in the capsules. The results demonstrated a poor quality of the capsules as a falsified medicine and that good manufacturing practices (GMP) were not in place, which could, in turn, impact the optimum therapeutic activity and bioavailability (Nasrin et al., 2011). Any potential variation in sildenafil content is likely linked to the capsule content weight variation observed.

3.4. Physical characterisations

3.4.1. Fourier-transform infrared spectroscopy

The FTIR spectra of the sildenafil references, Vairelex capsules, genuine and unregistered generic sildenafil tablets were shown in Fig. 3 and S1. In the spectrum of sildenafil citrate, the weak band at about 3298 cm^{-1} in the spectrum is attributable to N-H stretching in the amide group, while the medium peak in between 1500 and 1600 cm^{-1} is due to

Table 6
Summary of endothermic transitions in the temperature range of 165–225 °C and the mass loss in the temperature range of 40–225 °C.

Sample	Endothermic transitions 165–225 °C		% Mass loss 40–225 °C	
	T_1 (°C)	T_2 (°C)/ΔH_f (J/g)	less than 120 °C	165–225 °C
Sildenafil citrate reference batch 1	na	195.7 ± 0.8/ 360 ± 5	0.8 ± 0.2	26.3 ± 0.4
Sildenafil citrate reference batch 2	184.8 ± 1.2	198.0 ± 0.5	1.1 ± 0.2	26.3 ± 0.4
Viagra Connect®	na	191.3 ± 0.3	2.0 ± 0.6	6.7 ± 0.2
Abhigar-100	187.0 ± 0.04	193.8 ± 0.2	3.1 ± 0.1	9.0 ± 0.1
Sildamax	187.3 ± 0.3	192.5 ± 0.1	3.0 ± 0.1	9.4 ± 0.1
Vairelex	na	198.0 ± 0.1/ 329 ± 13	0.9 ± 0.01	27.0 ± 0.1

*Enthalpy values (ΔH_f) were only reported for Vairelex and sildenafil citrate reference batch 1 due to overlapping peaks in other samples. A small shoulder is observed in Vairelex sample at ~200 °C.

the N-H bending. Moreover, the sharp peaks at 1358 cm^{-1} and 1172 cm^{-1} are associated with the S═O symmetrical and asymmetric stretching respectively. The absorption peak at 1703 cm^{-1} is related to the C═O stretching, while the small band at about 2920 cm^{-1} corresponds to the C—H stretching in the alkanes. Another moderate to sharp band at 1000–1300 cm^{-1} corresponds to C—N stretching (Seçilmiş Canbay and Doğantürk, 2019).

The FTIR spectra of the Viagra Connect®, Sildamax, Abhigra-100 and Vairelex all showed a high degree of similarity, which elucidated that all dosage forms contain sildenafil citrate. However, the shift in bands and variation of the transmittances are likely to result from the purity of API and the difference of excipient/adjuvant ratio (Coelho Neto and Lisboa, 2017). Thus, the discrepancy between the tablets and the reference was more pronounced than with Vairelex, where its FITR spectra were almost identical to pure sildenafil citrate. This suggests that capsules most likely contain high percentage of sildenafil citrate powder (or even only the drug with no excipients).

3.4.2. Thermal analysis

Crystal polymorphism of the API is crucial in any pharmaceutical dosage form in addition to its chemical identity, as the former could impact the dissolution profiles, bioavailability, solubility, and stability of the drug. Three polymorphic forms of sildenafil citrate – Form I to III were previously reported in the literature (Badwan et al., 2001). Here we tested the sildenafil citrate references, Viagra Connect®, Vairelex capsule and the unregistered generics with DSC and TGA. Their thermograms are shown in Fig. 4a and 4b, respectively and the summary of the values of mass loss and endothermic phase transition temperatures are given in Table 6.

In the DSC thermograms, sharp large endothermic peaks at ~196 °C were observed for the sildenafil reference batches, which is likely corresponded to the melting of the most thermally stable form. The result indicates that sildenafil citrate in the references was mainly in Form I as the melting point reported for this form was 199.0–199.5 °C in the literature. The small shoulder in the endothermic peak in reference batch 2 at ~195 °C, reveals that another metastable Form II is likely to be present in the sample, as the melting point for this form was reported to be 192.5–195.3 °C (Badwan et al., 2001). An additional smaller endothermic peak at 184.30 °C was also observed in batch 2, which is likely due to the melting of a metastable form – Form III. The reference melting point for this form was 186.0 °C (Melnikov et al., 2003). The results suggest that sildenafil citrate reference batch 2 is predominantly in Form I crystals but Form II and III crystals co-exist, while batch 1 is most likely only Form I crystals.

Furthermore, very small exothermic transitions are also observed before the endothermic peaks in both reference batches, at about 127 °C and 146 °C in batches 1 and 2, respectively. This is an important observation as it could suggest a phase transition occurring before the main melting transition. These transitions were further investigated with simultaneous DSC-XRD analysis discussed in detail in the next section.

TGA results, on the other hand, also revealed the moisture and citrate contents in the sildenafil. A minimal weight (0.8%) was lost in pure

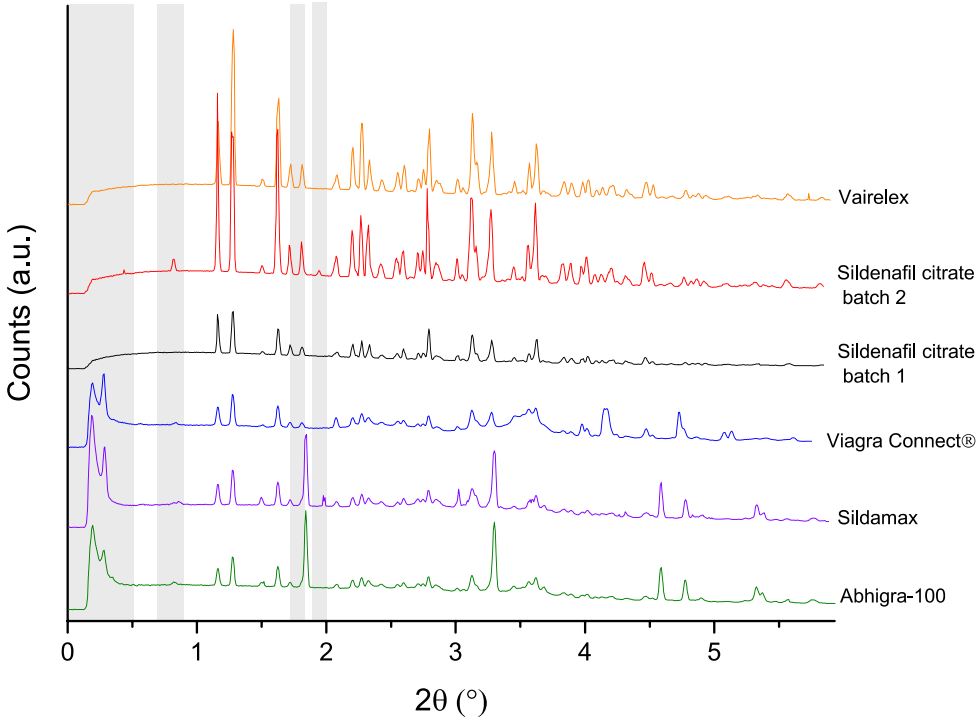


Fig. 5. Powder X-ray diffraction patterns of sildenafil citrate references and all four products at 40 °C; regions of clear differences between samples are highlighted.

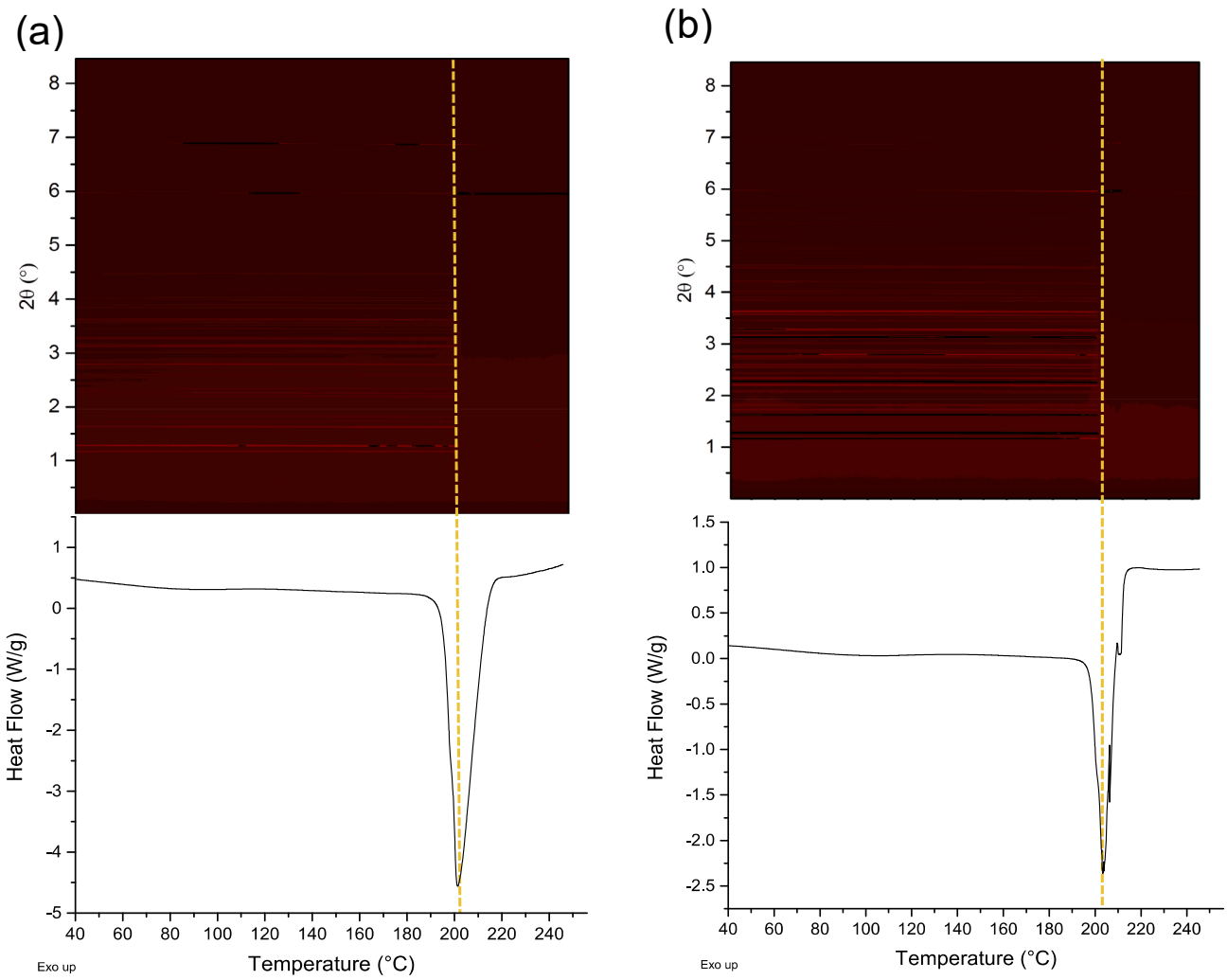


Fig. 6. DSC-XRD data for (a) sildenafil citrate reference batch 1 and (b) Vairelex capsules. Top: A contour plot of the diffraction data and Bottom: the corresponding DSC thermograms. Regions with a noticeable change in diffraction patterns are indicated with dashed lines. Some residual reflections persist above 6° arising from diffraction by the furnace elements.

sildenafil citrate from 40.0 to 120 °C due to evaporation of both free and bound moistures. Sildenafil citrate exhibits a three-step thermal decomposition profile, with 26% weight loss observed above 165 °C being the first decomposition step, where the citrate degraded, agreeing with the reported value in the literature (Melnikov et al., 2003). The second decomposition step was onset from 245 °C, but it was not complete due to the maximum temperature set at 300 °C. This step is likely due to the decomposition of sildenafil.

It is worth noting that Vairelex showed a similar profile as the pure sildenafil citrate (batch 1), of which both TGA and DSC results agreed. Similar moisture content was present in the Vairelex, with 0.9% of the weight loss due to moisture evaporation. The citrate decomposition step occurred at the same temperature range with a weight loss of 27%. The weight loss also agrees with the reported literature and the reference, which points out that the content of the capsules is only sildenafil citrate. Meanwhile, in the DSC thermogram, an endothermic peak at 200 °C was presented in Vairelex, which was similar to sildenafil citrate reference batch 1 (polymorph I). The additional spike at 198 °C revealed that a small amount of Form II crystal was also presented. Based on the enthalpy of fusion values, it is estimated that Vairelex capsules contained very close to pure Form I sildenafil citrate at a purity of ~92%, which is equivalent to 191 mg sildenafil citrate in weight. The calculation agrees with the result obtained in content uniformity, which reveals that DSC could also be employed to estimate the drug content.

Meanwhile, shifts and shape changes of the endothermic peak were observed in the DSC thermogram for all ground samples of the Viagra Connect®, Sildamax, Abhigra-100 tablets, in comparison to those of the sildenafil citrate references. The shift was due to the interaction between the components in the formulation (Maria and Noordin, 2014). All tablets contained sildenafil, but the decrease of the onset melting temperature, suppression of peak height, and the widening of the melting range pointed that the presence of impurities due to the excipients (Maria and Noordin, 2014). An endothermic peak at 191 °C was shown in the DSC thermogram for Viagra Connect®, which demonstrated that the sildenafil citrate was in Form II. Endothermic peaks at 187 °C and 192 °C were identified for Sildamax tablets, which demonstrated that both metastable Forms II and III were present in the sample. A double melting peak was observed at 187–193 °C in the DSC thermogram for Abhigra-100 tablets, where sildenafil citrate crystal probably underwent a sequential melting-recrystallization-melting process, transiting between Form II and III.

Compared with pure sildenafil citrate, the TGA thermogram demonstrated that the moisture content of Viagra Connect®, Sildamax and Abhigra-100 were much higher, with 2–3% weight loss due to moisture evaporation. The moisture content of the tablets was namely, in ascending order, Viagra Connect®, Abhigra-100 and Sildamax. Only 6–9% weight loss was contributed by the citric acid degradation for these samples, which are likely due to the presence of other excipients in

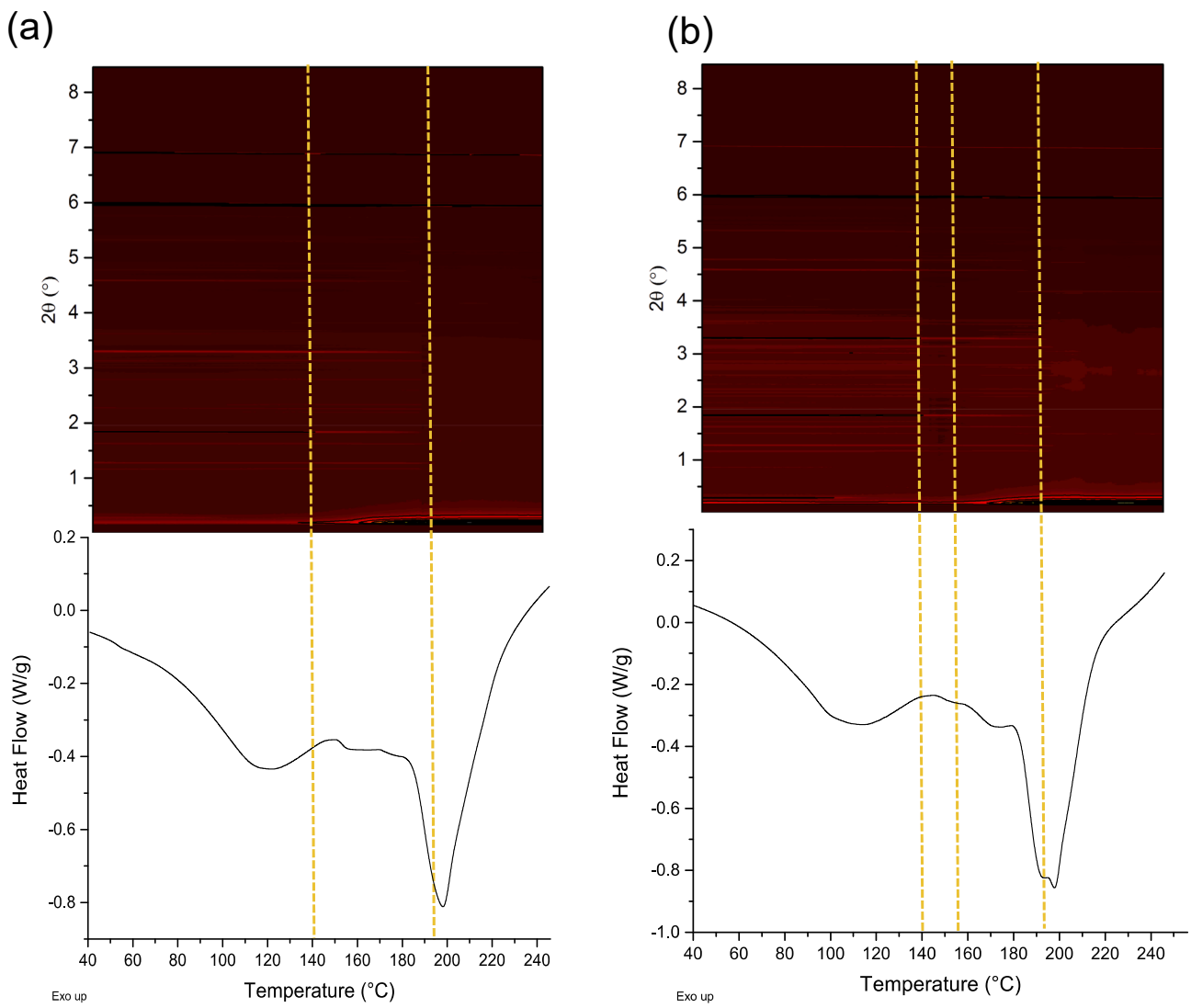


Fig. 7. DSC-XRD data for (a) Abhigra-100 tablets and (b) Sildamax tablets. Top: A contour plot of the diffraction data and Bottom: the corresponding DSC thermograms. Regions with a noticeable change in diffraction patterns are indicated with dashed lines. Some residual reflections persist above 6° arising from diffraction by the furnace elements.

these products and lower the proportion of sildenafil citrate in the samples.

3.4.3. Simultaneous differential scanning calorimetry-synchrotron X-ray diffraction

Characterisations of the nature of crystalline material is key in understanding the impact of the different arrangements of the same API into various polymorphic forms on the properties of the solid dosage form of that API. Powerful techniques such as X-ray diffraction are still the main method for characterizing polymorphic forms. Powder X-ray diffraction gives valuable information about polycrystalline materials, which is what most APIs exists as in pharmaceuticals (Ameh, 2019). Combining PXRD with DSC has been proven to provide valuable insights into phase transitions of polymorphic forms (Clout et al., 2016) and this would be useful for investigating SF medicines. Here we employed simultaneous DSC and synchrotron PXRD to investigate the SF products.

PXRD patterns were collected alongside the DSC thermograms for all samples in this study. Diffraction patterns collected at 40 °C are depicted in Fig. 5. All four products showed clear diffraction peaks for sildenafil citrate, supporting the findings from the other analytical tests that all products contained sildenafil citrate. It is observed that the tablet formulations have diffraction peaks below 0.5°, which are most likely due to the excipients as they are absent from the reference samples. Their absence from the capsule sample is also consistent with the results from the other tests that suggested the product mainly contains sildenafil citrate and a small number of excipients if any.

In addition, extra Bragg's peaks below 1° observed in the reference sildenafil citrate batch 2, which are absent from batch 1, also support the results that indicated the presence of more than one polymorphic form of sildenafil citrate. The same peaks are present in Viagra Connect® and the tablets products, while Vairelex capsules' pattern matches that of sildenafil citrate reference batch 1, both consistent with the findings from the DSC results.

The full diffraction data are presented as contour plots with the corresponding DSC thermograms (Figs. 6 and 7, S2). Regions of noticeable change are indicated with dashed lines. Selected PXRD patterns at regions of interest are presented in Figs. 8, S2 and S3. It can be observed in Fig. 8a that there is a split of the diffraction peaks at 2q 2.1° correspond to the exothermic transition observed in the DSC results for sildenafil citrate reference batch 1. This suggests a phase transition most likely a solid–solid transition. What is more, the first endothermic peak observed in the DSC results for sildenafil citrate batch 2 at 187 °C is accompanied by the disappearance of diffraction peaks at 2q 0.8° followed by the complete disappearance of the diffraction peaks at the

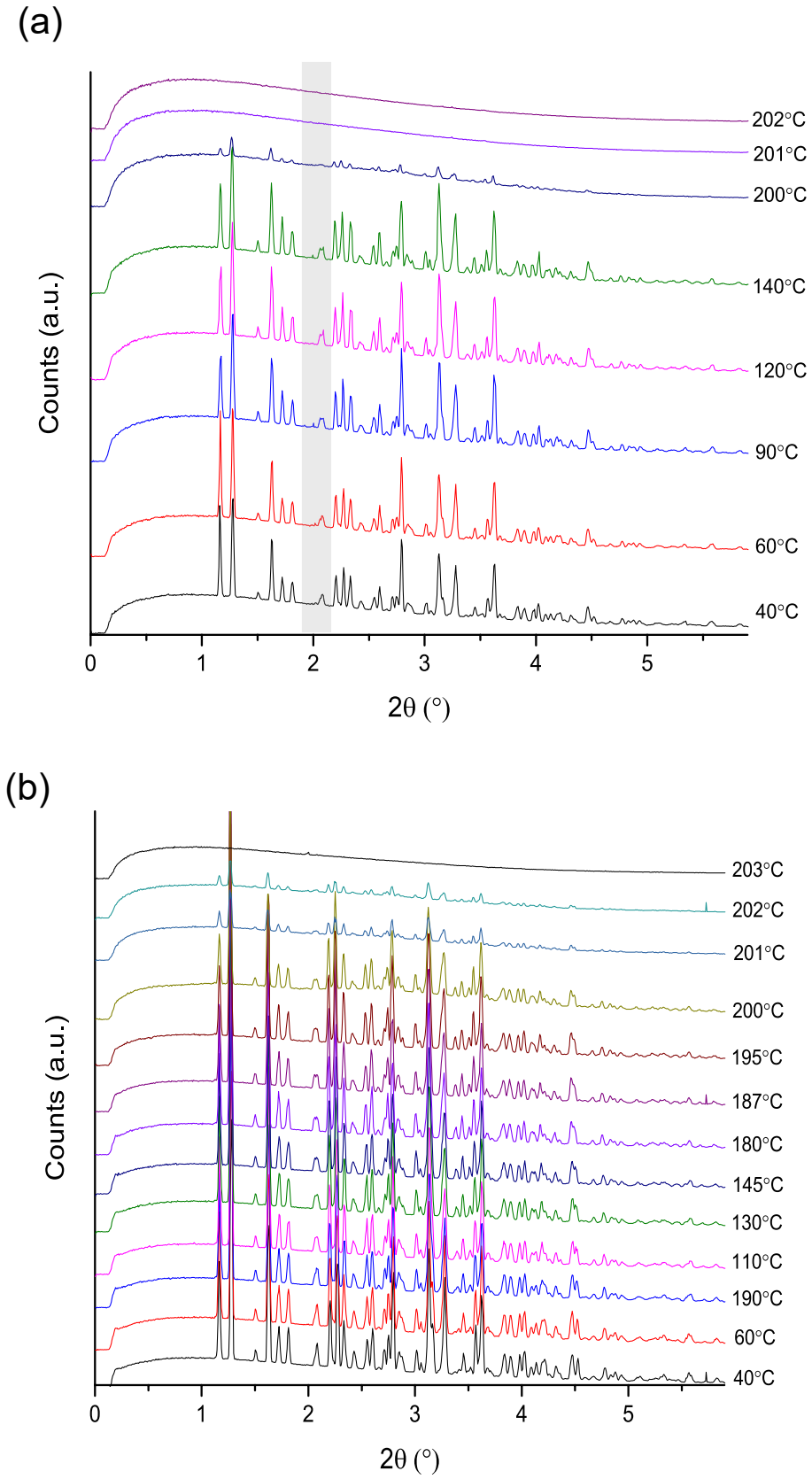


Fig. 8. Powder X-ray diffraction patterns of (a) sildenafil citrate reference batch 1 and (b) Vairelex capsules.

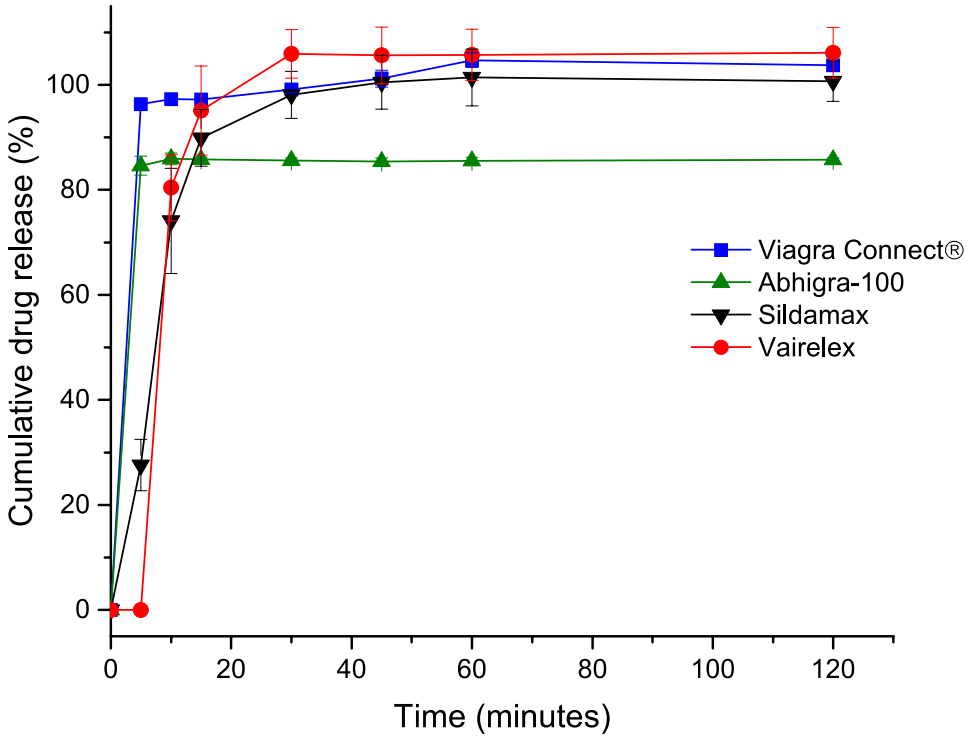


Fig. 9. Dissolution profiles of all products over 2 h in 0.1 N HCl; some error bars are too small to be observed on the graph.

temperature of the second endothermic peak (Fig. S3a). This supports the findings that the two endothermic peaks are the melting of forms II/III and I, respectively.

The DSC-PXRD results for the tablets products are also consistent with the results from the previously mentioned analytical test. For example, Viagra connect® results in Fig. S3b show disappearance of diffraction peaks at 0.5 and 0.8° after 145 °C followed by the disappearance of the full pattern at 195 °C, corresponding to the two endothermic peaks observed in the DSC thermogram, supporting the observation of the sample containing two polymorphic forms of the API. Similar behaviour is observed for the other two tablets.

Moreover, extra peaks below 0.3° are observed in the PXRD diffraction patterns of the three tablet products, which along with other peaks, persist after the full melting of the API, which are due to the presence of excipients. Such peaks are not observed for the capsule's product, which shows complete disappearance of the diffraction peaks at the melting point of sildenafil citrate. This supports the findings from the other tests which suggests that the capsules only contain sildenafil citrate without excipients.

The results also highlight the complexity of the polymorphic landscape of sildenafil citrate and the phase transitions of its polymorphs. The combination of two powerful techniques provided more insights into these phase transitions that were not previously reported. This could provide further explanation to the impact of polymorphism on product performance that could be revealed by tests such as dissolution testing. For example, the two generic tablet products appear to have somewhat similar DSC thermograms but there are differences in the diffraction patterns, noticeably the presence of a diffraction peak at 2° in Sildamax product which is absent in the Abhigra-100 tablet sample. This makes the pattern of the latter more similar to Viagra Connect® than the former, which might suggest similar release proprieties to be expected. Nonetheless, there is also a difference in the diffraction peak at 1.8° which is more prominent in the generic tablet products than in Viagra Connect®. These differences might be reflected in the dissolution profiles of the products.

3.5. Dissolution test

The dissolution profiles of sildenafil from the authentic Viagra Connect® and illicit alternatives are shown in Fig. 9. The dissolution tests were performed in 0.1 M HCl using BP apparatus over 2 h, which replicates the release in the stomach. The total sildenafil citrate content in each dosage form was determined in the content uniformity test as the information claimed on the packaging of the SF products are likely inaccurate and not trustworthy.

Release of sildenafil was observed within 60 min for all tablets and capsule tested. The fast release in the tablets was likely due the presence of disintegrant, while disintegration of the capsule was generally fast and was the only barrier before dissolution of the pure sildenafil powder contained. Interestingly, similar release profiles were observed between Viagra Connect® and the Abhigra-100 tablets, where most of the sildenafil from the Viagra Connect® and Abhigra-100 tablets was achieved in the first 5 min. However, only 85% of the drugs were released in the Abhigra-100 tablets, compared to the full release in Viagra Connect®. Meanwhile, the release of the Abhigra-100 tablets peaked at 15 min and plateaued afterwards. The faster release of Abhigra-100 tablets is probably related to the tablet hardness, where the tablet was the softest amongst all test products. Interestingly, the release rate was double for the Abhigra-100 tablets compared to Viagra Connect®, as it contains a two-fold amount of sildenafil citrate.

The release for Sildamax was much slower than Viagra Connect® and Abhigra-100 tablets, with less than half released in the first 5 min. Then, the release was more gradual, and an almost full release was observed at 45 min. The cause of the slower release is likely multifarious, including the composition of the film coating and powder blends, compression parameters and granulation, but none of these details was available. Polymorphism is also a possible factor as noted from the DSC-PXRD results that Viagra Connect® and Abhigra-100 tablets have similar patterns, but Sildamax has some differences. One way to compare dissolution profiles is to use the similarity factor (*f2*) with a value above 50 indicates the two dissolution profiles to be similar by no more than 10% difference between sample points. Dissolution profiles of all three

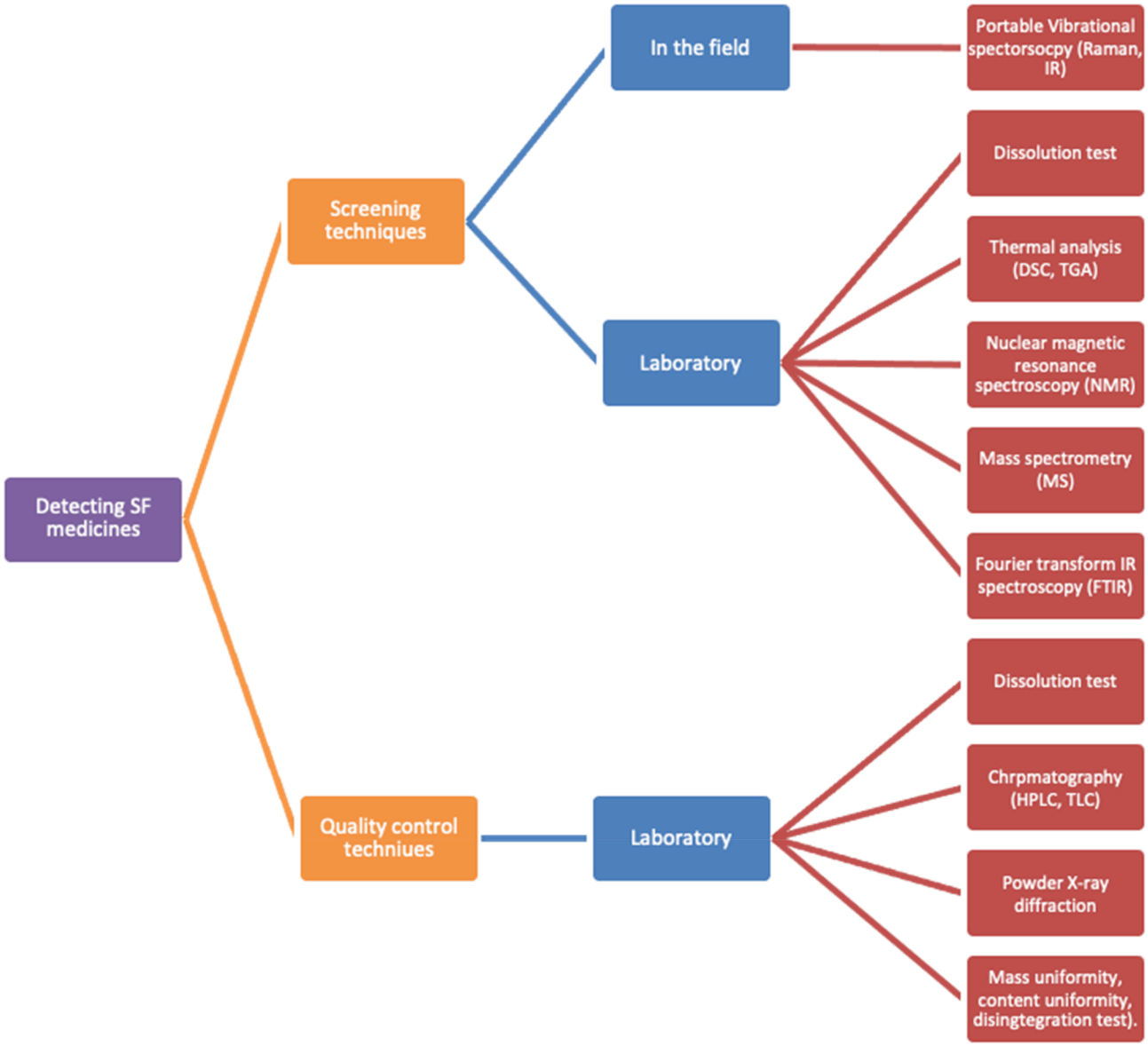


Fig. 10. Suggested categorising of analytical techniques used for the detection of SF medicine. The list of examples is not exhaustive, and more techniques can be added.

SF products were shown to be different to Viagra Connect® tablets' profile with *f2* values of 18, 25 and 46 for Vairelex, Abhigra-100 and Sildamax, respectively.

Nevertheless, all these parameters could be reflected by the hardness of the tablets, except the coating composition. The hardness of the tablet is therefore an important factor in the dissolution rate (Kitazawa et al., 1975). The Sildamax tablet was shown to be the hardest amongst all test products, which indicates that the porosity of the tablets is the lowest and the wettability of the tablets is impaired. The results reiterate that the formulation and properties of the tablets hugely impact the drug release, even though they are made by generic companies and the quality is maintained.

Surprisingly, the drug profile for the Vairelex capsule has the closest resemblance to the Sildamax tablets (f_2 value is 46 compared to 21 for Abhigra-100). The capsule shell had to be disintegrated before drug release in the Vairelex, which resulted in a delay of release for the first 5 min and followed by a rapid increase. The drug release was peaked at 30 min and was followed by a slow decrease over time. The slow release in the Vairelex could be explained by the polymorphism of sildenafil. Since the capsule contains nearly pure sildenafil citrate powder, the dissolution is governed by the solubility of the sildenafil citrate, where crystal polymorphism plays an important role. Vairelex mainly contains Form I sildenafil citrate, while the others contain Form II and III. Form I polymorph is the most thermally stable and thus has a lower solubility than the metastable form II and III. More importantly, the peak drug release was equivalent to 200 mg of sildenafil citrate or four Viagra Connect® tablet, which reveals that taking one capsule is over the maximum dose of 100 mg per day. According to the BP 2022, tablets and capsules for immediate release are required to release 80% of the content within 45 min (COMMISSION., 2021). The results demonstrated that all products fulfilled the requirements from BP.

The WHO has a recommendation of the 'virtuous circle', which is an approach that involves three areas of actions; prevent, detect, and respond (World Health Organization, 2017b). The 'detect' element highlights the importance of improving detection technologies in the field and the laboratory. Based on this, we suggest categorising the analytical techniques into screening techniques and quality control (QC) techniques, and further dividing them into either suitable for use in the field or the laboratory. The level of expertise and training needed to use these techniques depends on whether they are for screening or QC. This

is one element of how they can be implemented in regions with limited expertise and resources and the actions needed to improve their use. The other element would be the varying cost associated with such techniques. This highlights where the focus of research and development of these techniques should be, which would be in the areas of providing low cost in the field and laboratory screening techniques and in providing adequate training to staff. The techniques discussed in this study fall under the screening laboratory and/or QC laboratory techniques, as summarised in Fig. 10.

4. Conclusions

This study demonstrated how it was possible to easily purchase falsified and unregistered medical products disguised as herbal supplements online. Three claimed herbal supplements for men sexual performance were purchased from an e-commerce platform, where all products claimed to only contain herbal substances but were proved to contain sildenafil citrate, the active pharmaceutical ingredient in Viagra®. Two products received were unregistered generic tablets and one product was a falsified medical product.

A comprehensive analysis was performed on these products, to determine the chemical identity and the quality of the products, including dissolution, Fourier transformed infrared spectroscopy, weight and content uniformity tests. The qualities of the unregistered generic sildenafil citrate tablets fulfilled the British Pharmacopeia, but the falsified product failed the quality standard and contained approximately 200 mg sildenafil citrate, which is equivalent to 2-fold of the daily maximum dose. Moreover, the release profiles from the tablets also varied between products, with the unregistered generic tablets and falsified capsules possessing a slower release of sildenafil citrate than in Viagra Connect®.

Physical characterisations, including powder X-ray diffraction and thermal analysis, were also performed, which reveals the difference in the physical forms of the active pharmaceutical ingredients between the test products. The results highlight the benefit of employing different analytical techniques to investigate substandard and falsified products, with approaches such as simultaneous DSC and powder XRD providing valuable insights into the physical form of the active ingredient in these products, their phase transitions, and the possible impact they have on the product performance. Further work is needed to demonstrate the full applicability of solid-state techniques for combating SF medicines.

The findings of this study highlight the need for tighter regulations on the selling of products that claim therapeutic effects on e-commerce websites even if they are portrayed as herbal supplements. The recent regulations applied to online pharmacies should be extended to these websites to prevent harmful health consequences to the public. It is also important to increase awareness among the public of the danger of purchasing health products through these websites and the routes of reporting fake products to the authorities such as through the Yellow Card Scheme in the UK and the FDA MedWatch in the United States. All SF products in this study were reported to the UK's MHRA.

CRediT authorship contribution statement

Hei Ming Kenneth Ho: Conceptualization, Investigation, Formal analysis, Writing – review & editing. **Zhaoan Xiong:** Investigation, Formal analysis, Writing – original draft. **Hui Ying Wong:** Investigation, Writing – original draft. **Asma Buanz:** Conceptualization, Investigation, Formal analysis, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hei Ming Kenneth Ho reports financial support was provided by Engineering and Physical Sciences Research Council. Asma Buanz reports financial support was provided by Diamond Light Source Ltd.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2022.121592.

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