Complementary classification of solid oral dosage forms in ambient conditions by desorption electrospray ionization mass spectrometry and transmission Raman spectroscopy

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Abstract

Discrepancies or defects in active ingredients, excipients and coatings that form solid oral dosage forms can both impact product quality and provide hallmarks of off-brand or counterfeit products. There is therefore a need for rapid and continuous analytical techniques that can assess and classify product differences of intact samples at- or near the production line, or in analytical labs, ideally without resorting to product dissolution.

Here we test the ability of two rapid ambient chemical characterization methods to discriminate between solid dosage forms: desorption electrospray ionization mass spectrometry and transmission Raman spectroscopy. These two techniques are highly complementary, offering greater sensitivity to the analysis of the surface and the tablet bulk, respectively. The data sets generated were then used to test a variety of classification algorithms including linear discriminate analysis, tree-based methods, a simple neural network, and support vector machines (SVM). The highest performing algorithms for DESI-MSI were the SVM, with an additional performance boost when used with a polynomial kernel. For transmission Raman data, a linear discriminant analysis (LDA) model was found to be the most effective.

Introduction

Inconsistencies in active ingredients, excipients, the thickness and integrity of coatings and the presence of impurities in solid oral dosage forms all negatively affect their performance. Inferior quality attributes can be useful to identify off-brand or counterfeit products. There is a need for rapid and continuous analytical techniques that can assess and classify product differences of intact samples at- or near the production line, or in analytical labs, ideally without resorting to product dissolution [1]. Rapid measurement tools are particularly important to enable continuous monitoring, necessary to support the change from batch to continuous manufacturing. Analytical methods are required to monitor both the actives, coatings and consistency of the product: For example, in addition to the total API content, insight is also needed on degradation products, impurities, (co-) crystallinity/presence of polymorphs, and content uniformity. The ability to monitor tablet coating thickness and integrity is of great importance, particularly for functional coatings, such gastro-resistance, which would be compromised by insufficient thickness, or the occurrence of cracks in the film [2].

Quantitative analysis of pharmaceutical tablets is routinely performed by HPLC which offers accurate and sensitive measurements of the active ingredient(s) and excipients, in addition to the presence of any contaminants. However, solution-based analytical methods are destructive and labor-intensive.

Mass spectrometric methods can provide unlabeled identification, both of expected ingredients in known samples and of contaminants or components of unknown formulations. Ambient ionization mass spectrometry approaches including DESI (desorption electrospray ionisation) and DART (direct analysis in real time) facilitate the desorption and ionization from the surface of samples at atmospheric conditions, without dissolution or additional sample preparation. They are therefore potentially useful tools for rapid assessment of solid oral dosage forms

Optical spectroscopy techniques offer rapid, non-destructive analysis, including polymorphic identification [3], and are also able to measure insoluble ingredients. They have consequently been exploited for in-line process analytical testing and as quality control tools [1]. For example, infra-red-based techniques (FTIR and DESI [4]; and NIR and Mid-IR spectroscopy classification of MDMA containing tablets [5] Near infrared is the most commonly used process analytical tool [1], however Raman spectroscopy provides complementary information and has grown in popularity in recent

years, since it provides more distinct spectral features, and is better-suited to analysis in aqueous environments owing to the relatively weak strength of the Raman O-H band. Technological advancements have facilitated miniaturization, increased speed and reduced cost, resulting in more widespread implementation. [6]

Ambient ionisation mass spectrometry of tablets

Desorption electrospray ionization uses a charged electrospray of organic solvent which, when directed at the sample surface in proximity to the mass spectrometry inlet, desorbs ions from the sample which may be taken up into a mass spectrometer [7]. As this process takes place at ambient pressure and with a flexible geometry, the technique is suited for the analysis of a wide range of samples including explosives on surfaces [8], fingerprints [9], plants [10] and tissues [11,12]

One of the early descriptions of DESI-MSI was in the profiling of tablets [13]. Chen et al demonstrated the use of DESI-MS to profile tablets containing loratadine, folic acid, acetaminophen (paracetamol), aspirin, melatonin or caffeine. Optimization of DESI parameters including voltage, solvent delivery and capillary temperature facilitated analysis at up to three scans per second. Subsequent studies using DESI-MS of tablets have focused on targeted analysis for active ingredients. For example, the identification MDMA and amphetamine derivatives in ecstasy tablets [14], counterfeit artesunate antimalarial tablets [15,16] and antiviral capsules [17].

For ambient mass spectrometry to be deployable in the field for counterfeiting applications, or in manufacturing environments for QA/QC, the mass spectrometer must be compact. Several designs for small field-deployable mass spectrometers have been demonstrated with DESI MS sources [18,19].

Each of these applications has targeted expected components of the tablet of interest, predominantly active ingredients or excipients. However, in manufacturing QA/QC and counterfeit-detection applications, additional information on unexpected changes in active or excipient source or quality, as well as the introduction of contaminants may be of importance. Untargeted multivariate and machine learning approaches are therefore of interest to determine differences between samples using all spectral information.

Classification approaches for mass spectrometry applications are proving powerful in a range of applications. The two most widespread applications of classification in mass spectrometry are in disease diagnosis and determination of bacterial type [20]. A range of classification algorithms have been applied to mass spectrometry and spectroscopy data. PLS-DA is most commonly reported, although a range of algorithms including neural networks, and support vector machines [21] have been reported. Several publications have evaluated different classification algorithms but unsurprisingly the optimal algorithm depends greatly on the nature of the input data. A summary of classification and other data analysis for proteomics can be found here [22] and for metabolomics here [23]. Classification approaches are becoming more accessible through modeling tools with consistent grammar and data structure, and their integration into mass spectrometry software [ScilsLab,Waters software] [23].

Notably, classification of rapid evaporative ionization MS enables real-time classification of tissue types during surgery [24]. Classification of REIMS data has also found applications in food security [25] and bacterial speciation [26]. Classification approaches have also been widely employed in mass spectrometry imaging data, particularly in the classification of cancerous tissue [27]

Raman spectroscopy analysis of tablets

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2. Ordered list item
    a. Sub-item
    b. Sub-item
        i. Sub-sub-item
3. Ordered list item
    a. Sub-item

- List item
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- List item

subscript: H_2O is a liquid

superscript: 2^{10} is 1024.

unicode superscripts^{0123456789}

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Putting each sentence on its own line has numerous benefits with regard to editing and version control.

Line break without starting a new paragraph by putting
two spaces at end of line.

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Heading 1

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Heading 3

Heading 4

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A heading centered on its own printed page

Horizontal rule:

`Heading 1`'s are recommended to be reserved for the title of the manuscript.

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Citation tags (i.e. aliases) can be defined in their own paragraphs using Markdown's reference link syntax:

Referencing figures, tables, equations

Figure 1

Figure 2

Figure 3

Figure 4

Table 1

Equation 1

Equation 2

Quotes and code

> Quoted text

> Quoted block of text
>
> Two roads diverged in a wood, and I—
> I took the one less traveled by,
> And that has made all the difference.

Code `in the middle` of normal text, aka `inline code`.

Code block with Python syntax highlighting:

```
from manubot.cite.doi import expand_short_doi

def test_expand_short_doi():
    doi = expand_short_doi("10/c3bp")
    # a string too long to fit within page:
    assert doi == "10.25313/2524-2695-2018-3-vliyanie-enhansera-copia-i-
        insulyatora-gypsy-na-sintez-ernk-modifikatsii-hromatina-i-
        svyazyvanie-insulyatornyh-belkov-vtransfetsirovannyh-geneticheskih-
        konstruktsiyah"
```

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Figures

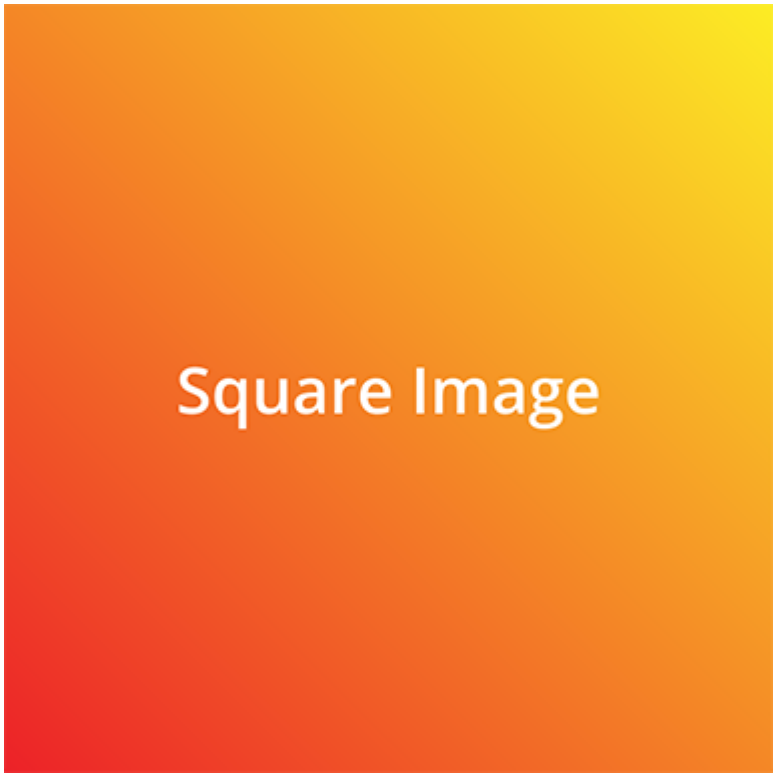

Figure 1: A square image at actual size and with a bottom caption. Loaded from the latest version of image on GitHub.

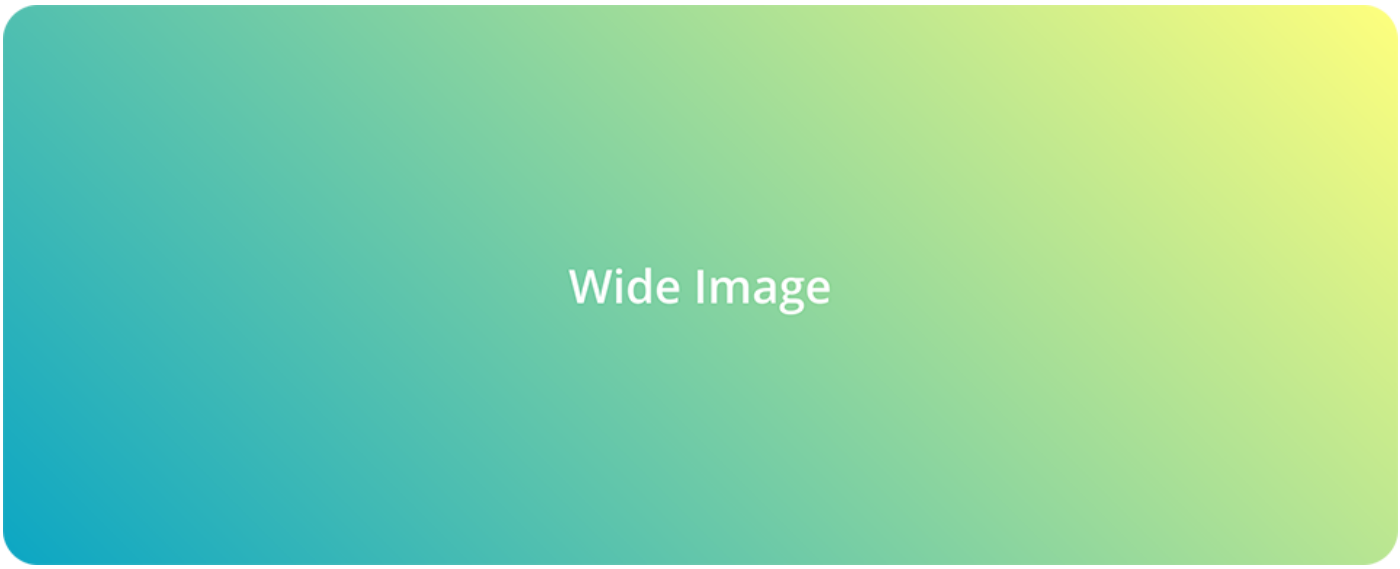

Figure 2: An image too wide to fit within page at full size. Loaded from a specific (hashed) version of the image on GitHub.

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Figure 4: A vector `.svg` image loaded from GitHub. The parameter `sanitize=true` is necessary to properly load SVGs hosted via GitHub URLs. White background specified to serve as a backdrop for transparent sections of the image.

Tables

Table 1: A table with a top caption and specified relative column widths.

Bowling Scores	**Jane**	**John**	**Alice**	**Bob**
Game 1	150	187	210	105
Game 2	98	202	197	102
Game 3	123	180	238	134

Table 2: A table too wide to fit within page.

	Digits 1-33	**Digits 34-66**	**Digits 67-99**	**Ref.**
pi	3.14159265358979323 846264338327950	28841971693993751 0582097494459230	78164062862089986 2803482534211706	`piday.org`
e	2.71828182845904523 536028747135266	24977572470936999 5957496696762772	40766303535475945 7138217852516642	`nasa.gov`

Table 3: A table with merged cells using the `attributes` plugin.

	Colors	
Size	**Text Color**	**Background Color**
big	blue	orange
small	black	white

Equations

A LaTeX equation:

$$\int_0^\infty e^{-x^2} dx = \frac{\sqrt{\pi}}{2} \tag{1}$$

An equation too long to fit within page:

$$x = a + b + c + d + e + f + g + h + i + j + k + l + m + n + o + p + q + r + s + t + u + v + w + x + y + z + 1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9 \tag{2}$$

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