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APPLICATION OF FAST NON- INVASIVE SOLID STATE ANALYSIS ON COUNTERFEIT TRACING OF PHARMACEUTICAL DRUG EXCIPIENTS

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Near-infrared (NIR) spectroscopy has long been used for quantitative and qualitative analysis. It offers the advantages of being rapid and non-destructive technique. Pharmaceutical analysis is always concerned with active pharmaceutical ingredients (APIs), while no focus is done on the analysis of excipients used in pharmaceutical dosage forms. In this study, the NIR spectra of most commonly used excipients are presented, the interpretation of such spectra can be used as a reference in counterfeit tracing during pharmaceutical analysis. In this article, twenty two excepients are studied which fall into seven classes: disaccharides [β-lactose anhydrous, α-lactose monohydrate and sucrose], polysaccharides [corn starch, wheat starch, sodium starch glycolate, maltodextrin, croscarmellose sodium, microcrystalline cellulose, hydroxypropyl cellulose and hypromellose (hydroxypropylmethyl cellulose)], a fatty acid and its salt [stearic acid and magnesium stearate], a carboxylic acid salt [potassium sorbate] inorganic compounds [calcium carbonate, dibasic calcium phosphate, silicon dioxide and talc], an anionic surfactant [sodium lauryl sulphate (sodium dodecyl sulphate)] and unclassified compounds [calcium ascorbate, candelilla wax and polyvinylpyrrolidone]. Counterfeit tracing was applied for samples representing each class of excipients by examination of their NIR spectra followed by comparison with the related spectra of the standards.

Keywords: *NIR spectroscopy; excipients; pharmaceuticals*

INTRODUCTION

NIR spectroscopy is now being widely used in quality control laboratories for quantitative and qualitative analysis of raw materials and also for quantitative analysis of final products. The wide applicability of NIR spectroscopy is mainly because it is a fast, easy, non-destructive technique that requires minimal sample preparation with least amount of sample[1-11] .

It has been found that most researches are concerned with APIs rather than the pharmaceutical excipients. Excipients were reported to have their own role during both manufacture and administration of pharmaceutical dosage form (either medicated or non-medicated). The tablet size and capsulated powder amount could be increased by using diluents. The enhancement of cohesiveness of the powders to be granulated easily during tablet formulation could be achieved by using binders. Furthermore, during tablet compression and ejection, the granules inter-friction could be reduced using suitable lubricant. Also, a suitable disintegrant could be used to aid tablet disintegration. Finally, the taste and final appearance could be improved by using the appropriate flavouring and coloring agent[12].

In this study, the NIR spectra of different classes of excipients are studied and

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interpreted. Such spectra can be used as a reference during analysis of medicated and non- medicated dosage form to ensure purity and counterfeit tracing of excipients.

The analysis of excipients, whether quantitatively or qualitatively is very crucial in the field of quality assurance of medicated or non-medicated dosage forms. Both, purity and identity of excipients must be checked to avoid counterfeits[13-18]. In that field, NIR spectroscopy is a fast and non-destructive technique that could be used to detect counterfeits.

Experimental

MATERIALS

The studied twenty-two excipients are shown in Table 1. This table indicates the supplier and the category of each excipient. The selection criteria of excipients studied in this article were their appearance in articles concerned with medicated and non-medicated dosage forms. For counterfeit tracing, samples of β-lactose anhydrous, corn starch, stearic acid, calcium carbonate, sodium lauryl sulphate and calcium ascorbate were kindly supplied by NODQAR (National organization of drug quality and research) El-Giza, Egypt.

Table 1: The suppliers of studied excipients and their role in medicated and non- medicated dosage form.

The excipient	Company	Functional Category
β-Lactose anhydrous	Alfa Aesar	Binding agent, directly compressible tabletting excipient
α-Lactose monohydrate	Alfa Aesar	Binding agent, directly compressible tabletting excipient
Sucrose	Alfa Aesar	Coating agent and granulating agent
Corn Starch	Alpha Pharma	Glidant, tablet and capsule diluent
Wheat Starch	Alpha Pharma	Glidant, tablet and capsule diluent
Sodium starch glycolate	Bepharm	Disintegrant, dissolution aid and suspending agent
Maltodextrin	Sigma Aldrich	Coating agent, tablet and capsule diluent
Croscarmellose sodium	Advanced Technology & Industrial Co., Ltd	Disintegrant and dissolution aid
Microcrystalline cellulose	Sigma Aldrich	Absorbent and suspending agent
Hydroxypropyl cellulose	Alfa Aesar	Coating agent and emulsifying agent
Hypromellose	Alfa Aesar	Suspending agent and viscosity-increasing agent
Stearic acid	Sigma Aldrich	Lubricant, emulsifying and solubilising agent
Magnesium stearate	Sigma Aldrich	Tablet and capsule lubricant
Potassium sorbate	Alfa Aesar	Preservative
Calcium carbonate	Merck	Buffering agent and coating agent
Dibasic calcium phosphate	Sigma-Aldrich	Tablet and capsule diluent
Silicon dioxide	Sigma-Aldrich	Flow agent in tablets
Talc	Sigma-Aldrich	Glidant and anticaking agent
Sodium lauryl sulfate	Alpha Pharma	Anionic surfactant and detergent
Calcium ascorbate	Bepharm	Antioxidant in pharmaceutical manufacturing.
Candelilla wax	Sigma-Aldrich	A carrier for food additives and in cosmetics industry
Polyvinylpyrrolidone	Sigma-Aldrich	Binder and suspending agent

NIR spectroscopy

FT-NIR spectra were collected in triplicate employing a Bruker Optics MPA-FTNIR spectrometer with an integrating sphere and auto-sampler together with a fiber-optic probe was used for these measurements. OPUS Version 5.0 (Ettlingen, Germany) was used for interpretation of information. Integrating sphere specimen vials were placed within the auto-sampler and measured in sequence. Spectra were collected through the bottom of transparent glass vial and 10 scans (~ 7 s accumulation times) with a spectral resolution of 8 cm-1 within the range 800-2500 nm using the reflectance mode. Individual sample vials were rotated between triplicate scans to make sure representative spectra. Triplicate scans were averaged to get one spectrum for every sample.

Spectral preprocessing

Baseline correction was carried out by GRAMS AI package, because a scatter effect in the form of a base line shift was observed in the spectra. This mainly occurs due to diversity in sample material shape which is easily detected visually. GRAMS AI package was also used to export all the NIR spectra into Galactic*SPC.

RESULTS AND DISCUSSION

The investigated excipients names, suppliers and role in formulations are listed in Table 1. But it is well known that one excipient can serve for many purposes. For example, maltodextrin serves as a diluent and a coating agent. So it was found better to classify excipients in our study on basis of chemical composition rather than their function as excipients. On that basis, our study focused on sugars (disaccharides and polysaccharides), fatty acids and their salts, carboxylic acids and their salts, inorganic compounds, anionic surfactants and other unclassified compounds. The NIR bands and intensities for the studied excipients and their corresponding Figures numbers are given in Table 2.

Table 2: The NIR bands, intensities and figures numbers for each pharmaceutical excipients (very weak bands are not listed).

The pharmaceutical excipient	The NIR bands (wavelength, nm) and intensities	Figure
β-Lactose anhydrous	1012 (w), 1224 (w), 1479 (s), 1567 (ms), 2081 (s,sh), 2105 (s), 2265 (mw), 2291 (mw), 2314 (mw), 2370 (mw)	1a
α-Lactose monohydrate	1206 (w), 1453 (s,sh), 1535 (s), 1578 (s,sh), 1934 (s), 1976 (w,sh), 2094 (s), 2117 (s,sh), 2257 (mw), 2280 (mw), 2291 (w,sh), 2319 (mw), 2348 (w), 2358 (w,sh), 2475 (mw)	1b
Sucrose	982 (w), 1195 (w), 1372 (w), 1437 (s), 1502 (m,br), 1552 (m,sh), 1691 (mw), 1726 (w), 2013 (mw), 2075 (s), 2146 (m,sh), 2180 (mw,sh), 2249 (mw), 2277 (mw), 2317 (mw), 2337 (w,sh), 2417 (w)	1c
Corn Starch	1202 (w), 1453 (s), 1533 (ms,sh), 1765 (w,br), 1930 (s), 2100 (ms), 2283 (m), 2312 (m), 2477 (w)	2a
Wheat Starch	1202 (w), 1453 (s), 1533 (ms,sh), 1765 (w,br), 1930 (s), 2100 (ms), 2283 (m), 2312 (m), 2477 (w)	2b
Sodium starch glycolate	1202 (w), 1453 (s), 1533 (ms,sh), 1765 (w,br), 1930 (s), 2100 (ms), 2283 (m), 2312 (m), 2477 (w)	2c
Maltodextrin	1202 (w), 1453 (s), 1533 (ms,sh), 1765 (w,br), 1930 (s), 2100 (ms), 2283 (m), 2312 (m), 2477 (w)	2d
Croscarmellose sodium	1003 (w), 1213 (mw), 1458 (ms), 1547 (m,sh), 1765 (mw,br), 1927 (s), 2102 (m), 2285 (m), 2312 (m,sh), 2476 (w)	3a
Microcrystalline cellulose	1214 (w), 1375 (w), 1482 (s), 1526 (s,sh), 1770 (w), 1928 (s), 2105 (s), 2271 (m), 2337 (m), 2478 (m)	3b

Table 2: Continued.

Hydroxypropyl cellulose	1155 (w,sh), 1185 (m), 1203 (m,sh), 1456 (s), 1539 (m,sh), 1682 (m), 1694 (m), 1732 (m), 1754 (m,sh), 1928 (s), 2088 (ms,br), 2267 (s), 2302 (s), 2467 (w)	3c
Hypromellose	1198 (m,br), 1450 (s,br), 1538 (m,sh), 1717 (s,br), 1765 (m,sh), 1927 (s), 2076 (m,br), 2273 (s), 2332 (m,sh), 2390 (w), 2470 (w)	3d
Stearic acid	931 (w), 1212 (m), 1394 (m), 1419 (m), 1731 (s), 1765 (ms), 2312 (s), 2353 (ms), 2416 (m,br)	4a
Magnesium stearate	931 (w), 1212 (m), 1394 (m), 1419 (m), 1731 (s), 1765 (ms), 1934 (mw), 2312 (s), 2353 (ms), 2416 (m,br)	4b
Potassium sorbate	1163 (m), 1199 (m), 1391 (w,br), 1670 (w,sh), 1697 (s), 1710 (s), 1751 (s), 1778 (ms), 1881 (w), 2016 (w), 2049 (w), 2105 (w), 2138 (m), 2148 (mw,sh), 2166 (m), 2185 (m), 2301 (m,sh), 2330 (s), 2369 (m), 2398 (mw), 2442 (w), 2462 (mw)	4c
Calcium carbonate	1412 (s), 1865 (w,sh), 1902 (m,sh), 1959 (s), 2211 (m), 2345 (m)	5a
Dibasic calcium phosphate	1354 (w,sh), 1420 (ms), 1785 (m), 1865 (mw,sh), 1899 (m,sh), 1951 (s), 2211(w)	5b
Silicon dioxide	1403 (m), 1442 (mw,sh), 1897 (s), 1935 (m,sh), 2216 (m,br)	5c
Talc	949 (w), 1390 (s), 1398 (mw), 2229 (w), 2289 (ms), 2312 (s), 2392 (m), 2432 (w), 2467 (mw)	5d
The pharmaceutical excipient	The NIR bands (wavelength, nm) and intensities	Figure
Sodium lauryl sulfate	1214 (m), 1391 (mw), 1429 (mw,br), 1730 (ms), 1764 (m), 1949 (mw), 2281 (m,sh), 2310 (s), 2349 (ms), 2398 (m,br)	6a
Calcium ascorbate	997 (w), 1194 (w), 1455 (s), 1943 (s), 1961 (m,sh), 2031 (mw,sh), 2039 (m), 2044 (mw,sh), 2091 (m), 2114 (ms), 2169 (mw), 2185 (w), 2260 (w), 2273 (w), 2284 (w)	6b
Candelilla wax	932 (w), 1212 (m), 1394 (m), 1417 (mw,br), 1731 (s), 1765 (m), 2291 (mw,sh), 2312 (s), 2353 (m), 2389 (w), 2442 (w,sh)	6c
Polyvinylpyrrolidone	1185 (m,br), 1437 (m,br), 1528 (w,sh), 1712 (m,br), 1934 (s), 2159 (mw), 2279 (ms), 2351 (w,sh)	6d

Br, broad; m, medium, s, strong, sh, shoulder, w, weak.

Disaccharides

Disaccharides were the first studied group of excipients namely, sucrose, α-lactose monohydrate β-lactose anhydrous. Lactose is a natural disaccharide consisting of galactose and glucose, lactose exists in three different forms: β-lactose anhydrous, α-lactose anhydrous andα-lactose monohydrate and[19]. Monohydrate form of α-lactose is usually used as diluent in solid oral dosage form[20]. The natural disaccharide; sucrose consists of glucose and fructose. Sucrose is obtained from different sources such as beet and sugar cane. Unlike lactose, sucrose is found in only one crystalline form.

The studied disaccharides NIR spectra in the range of 800-2500 nm consist of numerous bands of varying intensities (Figure 1). The two polymorphic forms of lactose under study can be readily differentiated by the strong O-H deformation combination band at 1934 nm characteristic of α-lactose monohydrate (Figure 1b) such band is not shown in β-lactose anhydrous NIR spectrum (Figure 1a). Sucrose, in turn, can be readily distinguished from the two forms of lactose by its strong first overtone O-H stretching band at 1437 nm (Figure 1c).

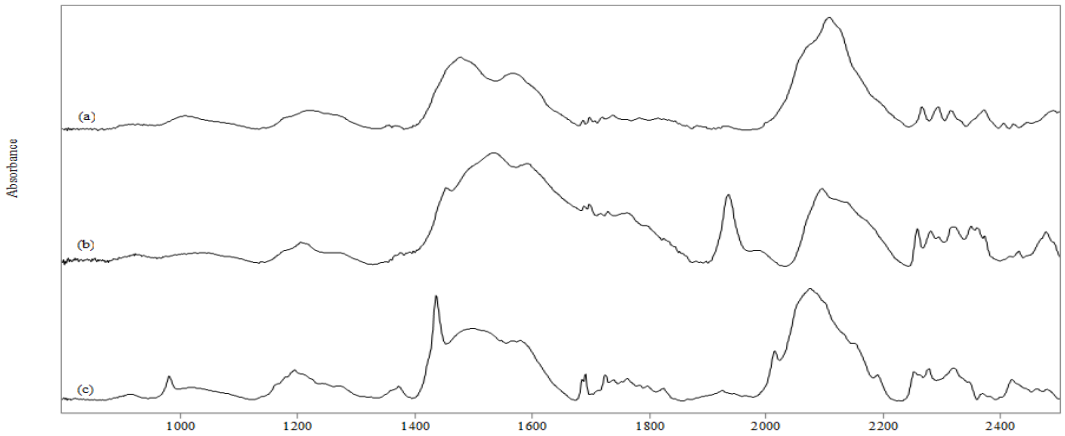

Fig. 1: The NIR spectra of disaccharides: (a) β-lactose anhydrous, (b) α-lactose monohydrate and (c) sucrose.

Polysaccharides

Near-infrared spectra of eight polysaccharides in the region of 800-2500 nm are shown in Figures 2 and 3. Polysaccharides serve many roles in pharmaceutical formulations; as binders [hydroxypropyl cellulose, microcrystalline cellulose, hypromellose, maltodextrin and starch], diluent [starch, , maltodextrin and microcrystalline cellulose] and disintegrant [sodium starch glycolate, starch, and croscarmellose sodium (internally cross-linked sodium carboxymethylcellulose)] in both direct compression and wet granulation[12].

Figure 2 (a-d) presents the NIR spectra of starch derivative excipients which are corn starch, wheat starch, sodium starch glycolate and maltodextrin. The general appearance of these four NIR spectra is quite similar. NIR spectroscopy cannot be reliably used to differentiate between starches and relevant compounds such as maltodextrins[21].

Figure 3 (a-d) presents the NIR spectra of cellulose derivative excipients which are croscarmellose sodium, microcrystalline celullose, hydroxypropyl cellulose and hypromellose. Despite the common NIR spectral features, each excipient has its own NIR spectral signature. Crosacarmellose sodium and microcrystalline cellulose are characterized by the medium combination C-H stretching bands at 2312 and 2271 nm, respectively. Hydroxypropyl cellulose is characterized by the medium second overtone C-H stretching band at 1203 nm, the medium first overtone C-H stretching bands at 1682, 1694, 1732 and 1754 nm and the strong combination C-H stretching band at 2302 nm, while hypromellose is characterized by the combination C-H stretching bands at 2273, 2332 and 2390 nm of varying intensities.

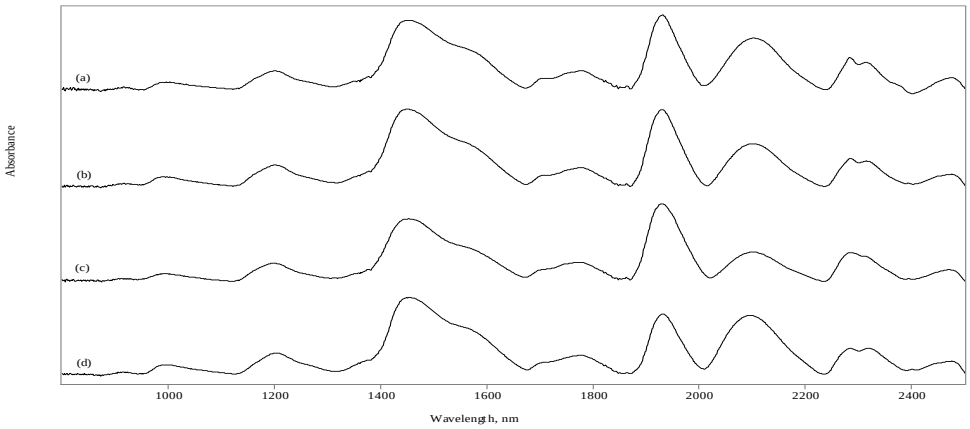

Fig. 2: NIR spectra of polysaccharides: (a) corn starch, (b) wheat starch, (c) sodium starch glycolate and (d) maltodextrin.

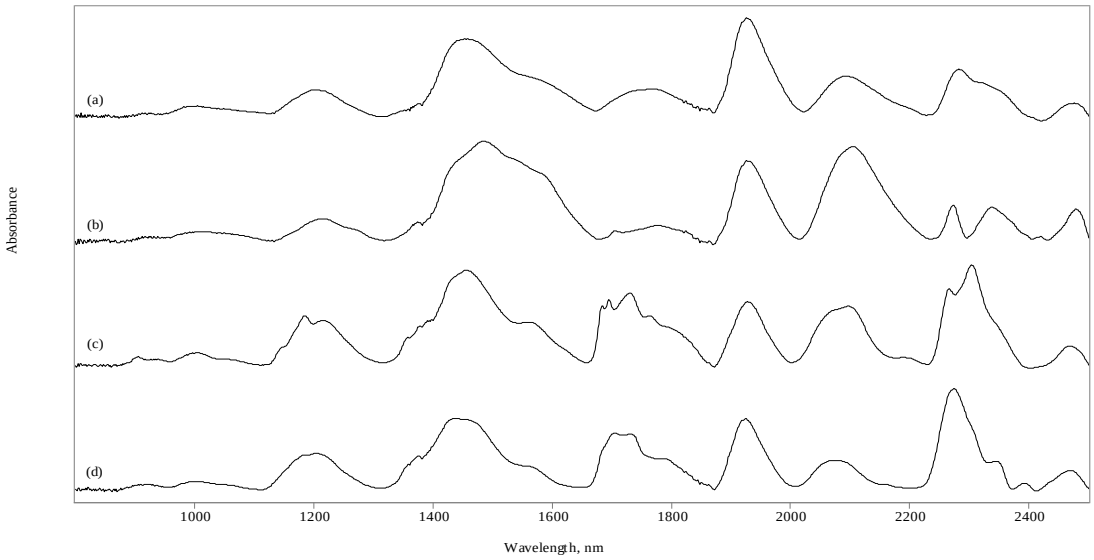

Fig. 3: NIR spectra of polysaccharides: (a) croscarmellose sodium, (b) microcrystalline cellulose, (c) hydroxypropyl cellulose and (d) hypromellose.

A fatty acid and its salt and a carboxylic acid salt

Stearic acid is a saturated fatty acid, used as a lubricant in making tablets and capsules. It is also used as an emulsifying and solubilizing agent[22]. Magnesium stearate –mainly used for lubrication during manufacture of capsules and tablets- exists in the form of white fine powder. Potassium sorbate is primarily used as a preservative[12].

The NIR spectra of stearic acid, magnesium stearate and potassium sorbate in the region of 800-2500 nm are presented in Figure 4 (a-c). The NIR spectra of stearic acid and magnesium stearate are very similar with slight variations in the peak intensities. The only difference between the NIR spectra of stearic acid and magnesium stearate is that, the medium weak O-H deformation combination band at 1934 nm is recorded only in the NIR spectrum of magnesium stearate, which could be attributed to the absorption of some moisture by the sample under investigation. The NIR spectrum of potassium sorbate is easily distinguished from other two NIR spectra presented in Figure 4; this is attributed to the fact that compounds such as stearates, waxes and hydrocarbons have long aliphatic chain which dominates the spectra by $–CH_2$ groups making them indistinguishable from each other[23].

Inorganic compounds

In Figure 5 (a-d), four inorganic compounds are presented. Calcium carbonate and dibasic calcium phosphate are employed as diluents in solid pharmaceutical dosage forms. Silica is applied as flow agent in tablet manufacturing. Talc was previously used for lubrication and as a diluent during manufacture of tablets and capsules, is not likely used nowadays[12].

The NIR spectra of these inorganic compounds (Figure 5) show only a few bands, because they show little vibrational modes. Calcium carbonate exists in three polymorphic forms namely, calcite, aragonite and vaterite, of which calcite shows the highest stability[24] and is shown in Figure 5a. Calcium phosphate exists also in three different forms, namely, monobasic, dibasic and tribasic[25]. The NIR spectrum of dibasic calcium phosphate is presented in Figure 5b. The NIR spectrum of silicon dioxide (Figure 5c) has only five NIR spectral features at 1403, 1442, 1897, 1935 and 2216 nm. The last spectrum in Figure 5 is of talc ($3MgO.4SiO_2 .H_2O$) which has no characteristic NIR spectral features in the region of 1400-2250 nm.

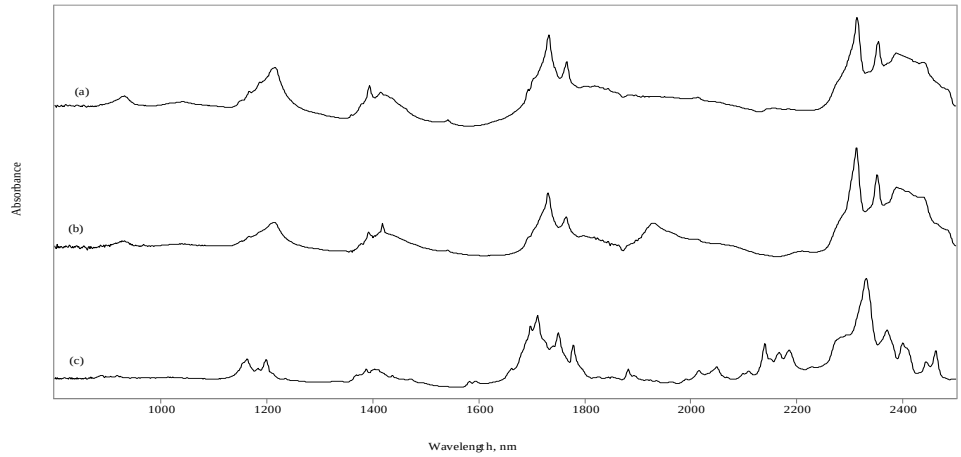

Fig. 4: NIR spectra of: (a) stearic acid, (b) magnesium stearate and (c) potassium sorbate.

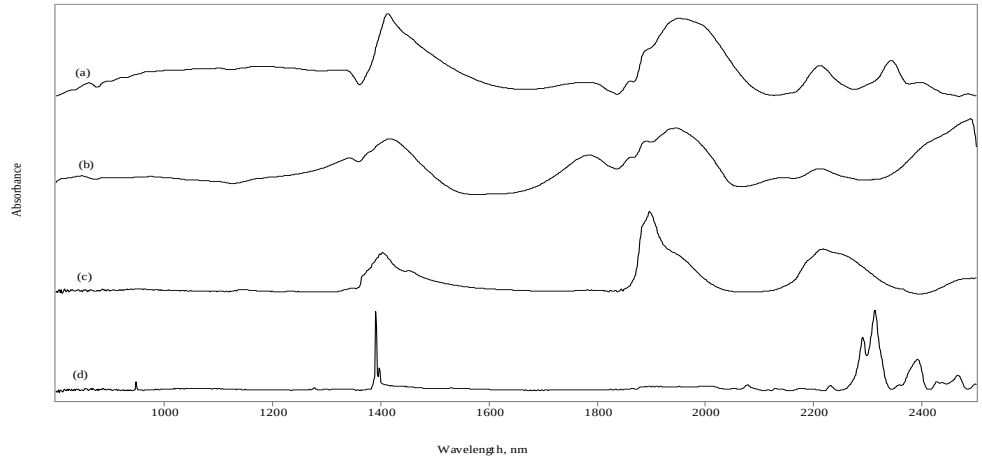

Fig. 5: NIR spectra of inorganic compounds: (a) calcium carbonate, (b) dibasic calcium phosphate, (c) silicon dioxide and (d) talc.

.An anionic surfactant and the other unclassified compounds

Anionic surfactants, mainly sodium dodecyl phosphate, are widly used in formulations. Other unclassified compounds in this database include calcium ascorbate, candelilla wax and polyvinlypyrrolidone (PVP). Calcium ascorbate is a white to slightly yellow, practically odorless, crystalline powder, has vitamin C activity and used as an antioxidant in pharmaceutical manufacturing and in food industry[26]. Candelilla wax is a yellowish-brown, hard, brittle, lustrous solid and used as a carrier for food additives (including flavors and colors) and in cosmetics industry[12]. The last unclassified excipient is polyvinylpyrrolidone (povidone, PVP), used as a solubilizer, a binder, suspending agent, coating agent, as a viscosity increasing agent and stabilizing agent[12]. The NIR spectra in the region of 800-2500 nm of these four excipients are presented in Figure 6 (a-d).

Sodium lauryl sulfate (Figure 6a) is characterized by the medium second overtone C-H stretching band at 1214 nm, the medium strong and medium first overtone C-H stretching bands at 1730 and 1764 nm, respectively and the medium shoulder, strong, medium strong and medium broad combination C-H stretching bands at 2281, 2310, 2349 and 2398, respectively.

Calcium ascorbate (Figure 6b) is characterized by the strong first overtone O-H stretching band at 1455 nm, the strong combination band between the fundamental stretching and deformation vibrations of the O-H bond at 1943 nm[2] and the two medium and the medium strong combination O-H stretching bands at 2039, 2091 and 2114 nm, respectively.

The skeleton of candellila wax consists mainly of n-alkanes (usually odd number from C29 to C33) along with esters of acids and alcohols (usually with even number from C28 to C34). It also contains sterols, free alcohols, free acids, mineral matter and neutral resins. Its NIR spectrum (Figure 6c) is characterized by the medium second overtone C-H stretching band at 1212 nm, the medium combination C-H stretching band at 1394 nm, the strong and medium first overtone C-H stretching bands at 1731 and 1765 nm, respectively and the strong and medium combination C-H stretching bands at 2312 and 2353 nm, respectively.

The last excipient in this NIR specral database is PVP (Figure 6d) which is characterized by medium broad second overtone C-H stretching band at 1185, medium broad first overtone C-H stretching band at 1712 nm and medium strong combination C-H stretching band at 2279 nm.

Samples representing different classes of excipients

samples used for counterfeit tracing were examined through NIR scanning, the obtained spectra were compared with the relevant standards (Figures 7&8) the samples were found to be pure with no counterfeits, this is clear from the absence of any ambiguous bands in the spectra of the samples when compared with the standards.

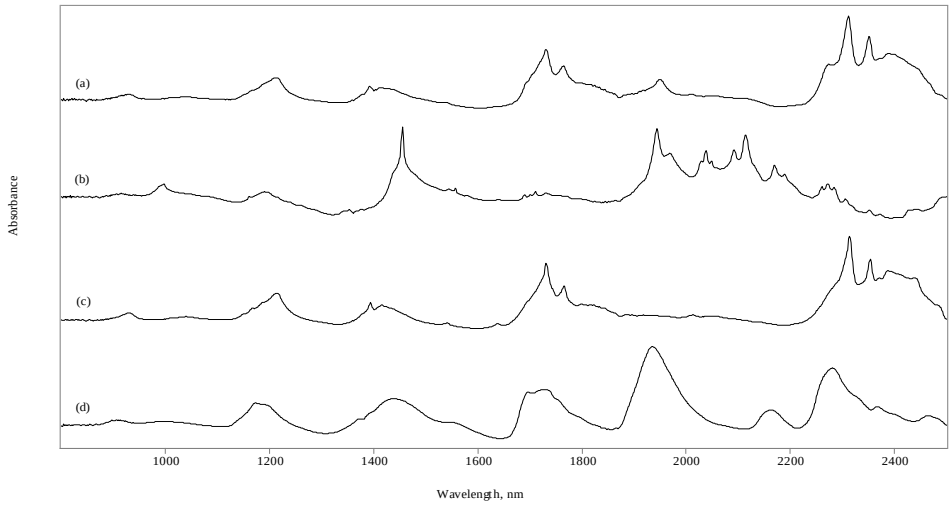

Fig. 6: NIR spectra of: (a) sodium lauryl sulfate, (b) calcium ascorbate, (c) candelilla wax and (d) PVP.

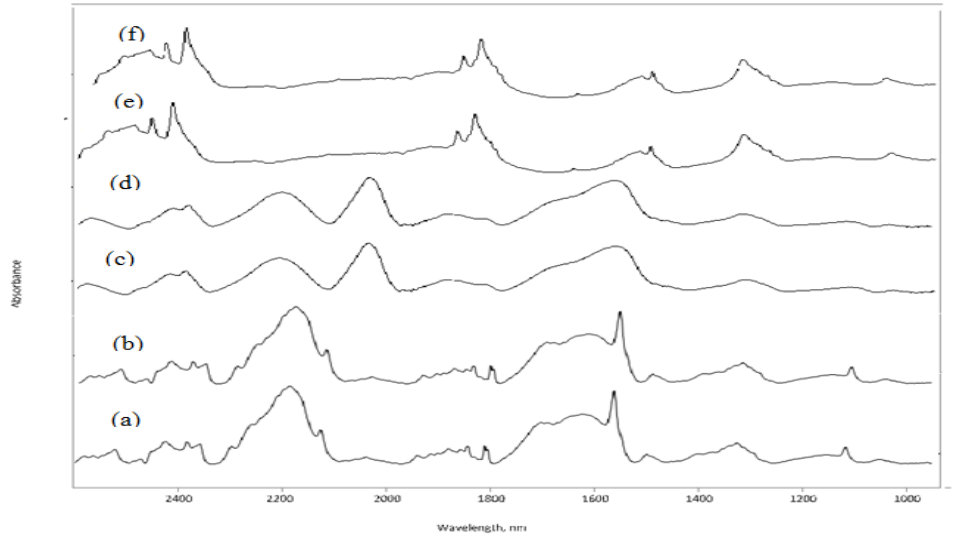

Fig. 7: NIR spectra of (a) ß- lactose anhydrous standard, (b) ß- lactose anhydrous sample, (c) corn starch standard, (d) corn starch sample, (e) stearic acid standard, (f) stearic acid sample.

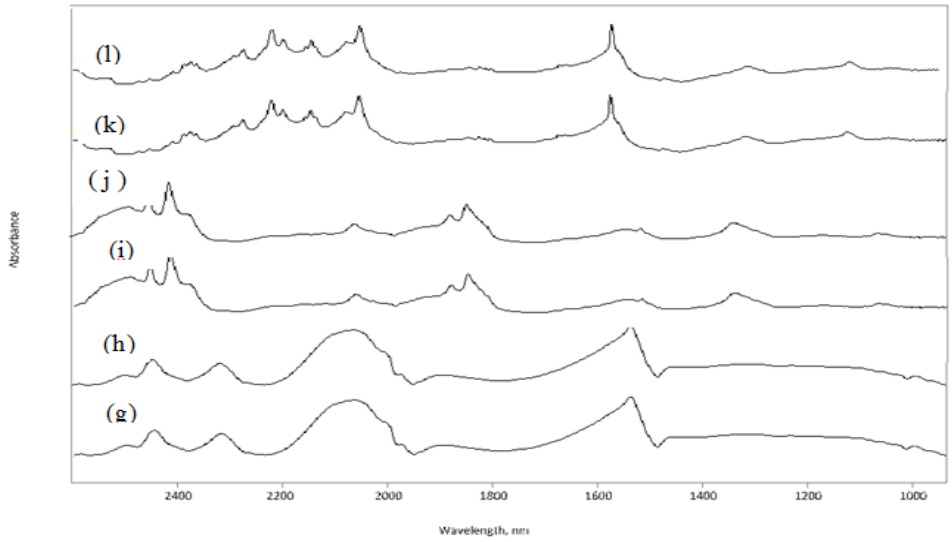

Fig. 8: (g) calcium carbonate standard (h) calcium carbonate sample (i) sodium lauryl sulphate standard, (j) sodium lauryl sulphate sample, (k) calcium ascorbate standard and (l) calcium ascorbate sample.

Conclusion

The NIR spectra of twenty-two of the most commonly used pharmaceutical excipients are studied and the corresponding NIR bands are illustrated in this work. Excipients perform several functions in the pharmaceutical processes, so they were classified into seven categories based on their chemical structures. The method was applied for counterfeit testing of some samples by comparison with the relevant spectra of their standards. NIR spectroscopy proved to be a very useful method for non- destructive counterfeit tracing of excipients in both medicated and non- medicated dosage forms.

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تطبيق تحليل الحالة الصلبة السريع وغير الجراحي على التتبع المزيف لسواغات الأدوية الصيدلانية

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لطالما استخدم التحليل الطيفي للأشعة تحت الحمراء القريبة (NIR) للتحليل الكمي والنوعي. إنه يوفر مزايا كونها تقنية سريعة وغير مدمرة. يهتم التحليل الصيدلاني دائمًا بالمكونات الصيدلانية الفعالة (APIs)، بينما لا يتم التركيز على تحليل السواغات المستخدمة في أشكال الجرعات الصيدلانية. في هذه الدراسة ، يتم تقديم أطياف NIR للسواغات الأكثر استخدامًا ، ويمكن استخدام تفسير هذه الأطياف كمرجع في تتبع التزييف أثناء التحليل الصيدلاني. في هذا المقال ، تمت دراسة اثنين وعشرين مادة خارجية تقع في سبع فئات: السكاريد [بيتا لاكتوز لا مائي ، ألفا لاكتوز أحادي الهيدرات والسكروز] ، السكريات المتعددة [نشا الذرة ، نشا القمح ، نشا الصوديوم جلايكولات ، مالتوديكسترين ، كروسكارميلوز الصوديوم ، السليلوز الجريزوفولفين ، هيدروكسي بروبيل السليلوز وهيدروميلوز (هيدروكسي بروبيل ميثيل السليلوز)] ، حمض دهني وملحه [حامض دهني وستيرات المغنيسيوم] ، ملح حمض الكربوكسيل [سوربات البوتاسيوم] مركبات غير عضوية [كربونات الكالسيوم ، فوسفات الكالسيوم ثنائي القاعدة ، ثاني أكسيد السيليكون والتلك] ، الأنيق الفاعل بالسطح [كبريتات لوريل الصوديوم (كبريتات دوديسيل الصوديوم)] والمركبات غير المصنفة [أسكوربات الكالسيوم ، شمع كانديلا والبولي فينيل بيروليدون]. تم تطبيق التتبع المزيف للعينات التي تمثل كل فئة من السواغات عن طريق فحص أطياف NIR الخاصة بهم متبوعًا بالمقارنة مع أطياف المعايير ذات الصلة.