Virtualization and real-time analysis of pharmaceutical and food products by near infrared spectroscopy

Dong Sun

Tesi doctoral

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Directores: Dr. Manel Alcalà Bernàrdez

Prof. Dr. Marcelo Blanco Romia

Departament de Química

Facultat de Ciències

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Chapter 8

Identification of formulations in the retail pharmaceutical stores with MicroNIR

8. Identification of formulations in the retail pharmaceutical stores with MicroNIR

The NIRS qualitative ability is enjoyed by the business users widely. As the development of the miniaturization process, the spectrometer becomes portable and user-friendly. This ability also can be used by the normal person. In this study, the application of MicroNIR for customers who buy drugs in the retail pharmaceutical stores was investigated. Real time identification of drugs was carried out in a simple, rapid and economic way. 223 formulations from 94 laboratories were includes into the NIR library. Standard and factorization algorithms were chosen to calculate the library which included 3 levels in total. The internal and external validations have been done in order to evaluate the library. The results showed that all the samples have been uniquely identified.

Key word: MicroNIR, NIR library, drug identification, retail pharmaceutical store

8.1   Introduction

The drug quality has to be well control from the raw materials to the final products. Specially, the quality control of the products in the pharmaceutical stores is a work which asks for a great effort. The counterfeit medicines in the retail stores hurt not only the business benefit but also the public health directly[1]–[3]. The World Health Organization (WHO) defined that ´´a counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source.[4]´´ Some of them don´t contain the correct ingredients, some don´t contain sufficient active ingredient and some use the fake packaging. Enterprises and government regulators are trying their best to identify those products. Several methods have been used to help us, such as UV-Vis, IR, AAS, NMR, MS, TLC, HPLC and GC[5]–[10]. Most of the qualitative methods are applied with instruments which need strict operation environment and they are destructive. Structures of these analytical instruments were designed depending on requirements of factories or research labs. However, normal customers of pharmaceutical stores still can´t use them ensure their own safety. Because they are lack of professional knowledges and can´t afford an instrument mentioned above. In order to offer customers the self-protection ability, there is a demand in the facilitation of the identification process and the miniaturization of instrument.

The NIRS is a technology which could identify the counterfeit products in the retail stores. Comparing to the wet chemistry, it is nondestructive, rapid and simple. The benchtop NIR spectrometers have already been used to analyze the pharmaceutical process, such as raw materials, blending uniformity. API content and so on[11]–[13]. The miniaturization of the instrument makes the NIRS can be applied not only to business users but also to normal customers. The MicroNIR (Viavi Solutions Inc. USA) is a portable instrument whose dimension is (diameter x height) 45 x 42mm and the weight<60g. It has a LVF coupled with a linear detector array which creates a splitting system that is capable of providing the spectral range from 1158.800nm to 2153.100nm. There is no movable component so it is possible to work in a vibrating environment. It´s operating system can be installed in a tablet and data can be communicated with the instrument by the USB 2.0. Besides, the electric power is conducted through the same USB interface. Features mentioned above make the MicroNIR become a practical tool for normal customers. The NIR library was the pattern recognition method worked with the MicroNIR in this study. It encompassed all the variables in the samples to be tested, so the unknown substances can be identified. Instead of developing a specific method for each drug,

the NIR library qualifies all types of drugs directly in a simple, rapid and economic way. The library can be operated by the computer automatically so the operators could understand the system easily and don´t have to get a professional knowledge background.

In this study, the portable MicroNIR was applied to acquire spectra of drugs which were collected in the retail stores. The NIR library was constructed to identify these drugs. The combination of these two technologies was applied to simplify the identification process of drugs and brought customers a powerful tool to safeguard their rights and interests.

8.2   Experiment

8.2.1   Spectra acquisition

The spectra of samples were acquired with the MicroNIR. The integration time was 13500us and scan number was 50. The running temperature of instrument was between 45-55 °C.   Background reference was renewed every 1 hour. Tablet, capsule and powder samples were placed in a glass cuvette which was on the top of spectrometer. An appropriate accessory was used to fix the distance between the spectrometer window and the sample. Spectra of different parts of sample were acquired. so that chemical and physical variables can be collected as much as possible. The experiment was operated inside a black box which has reduced the influence of natural light, In total. 223 formulations from 94 laboratories were includes into the NIRS library and 1654 spectra were acquired.

8.2.2   Data processing

Spectra were divided into two sets, the calibration set and the prediction set. The library was calculated with OPUS Spectroscopy Software 7.5 (Bruker. Germany). Standard and factorization algorithms were chosen to calculate the library. The Standard algorithm calculates the Euclidean distance between the test and reference spectra. See equation 8.1

$$D = \sqrt{\sum_k (a(k) - b(k))^2}$$
Equation 8.1

Where $a(k)$ and $b(k)$ are the ordinate values of the a and b spectra. The sum incorporates all selected k data points.

The Factorization algorithm represents spectra as linear combinations of factor spectra (loadings). see equation 8.2 and equation 8.3

$$a = T_{1a} * f_1 + T_{2a} * f_2 + \cdots + T_{ia} * f_i$$
Equation 8.2

$$D = \sqrt{\sum_i (T_{ia} - T_{ib})^2}$$
Equation 8.3

Where a is the original spectrum. f is the factor spectra. T is the scores. D is the distance between the two spectra a and b.

The raw spectra were preprocessed with 1st derivative and vector normalization in order to reduce the baseline shift and offer clear signal peaks. Wavelength ranges of every sub-library were selected to locate the most useful peaks. The thresholds of each drug were calculated with the confidence level from 95-99%. The quality of NIR library was evaluated by the internal and external validation. Selectivity of the validation was calculated as following:

$$S = \frac{D}{T_1 + T_2}$$
Equation 8.4

Where S is the selectivity, D is the distance between two average spectra and T is threshold value of the sample cluster.

The S < 1 means clusters are overlapped with each other. S = 1 means they are contacted and S > 1 means they are separated.

8.3   Results and discussion

8.3.1   Library structure

There are 3 levels in the whole library, one general library, fourteen sub-libraries in the 2nd level and three sub-libraries in the 3rd level. Library spectra of each formulation were selected according to their representativeness. The spectra which have represented all the physical and chemical variables were included in to the library. 1092 spectra were contained in calibration sets and 574 spectra were contained in prediction sets finally. The general library included 223 formulations, the 2nd level sub-libraries included 50 drugs and 3rd level sub-libraries included 7 drugs.

8.3.2   Library construction

The standard (Euclidean distance) method was used to construct the general library. The raw spectra were preprocessed with 1st derivative, smoothing points five. In this way, more peaks have appeared and the differences between spectra were enlarged. Fig. 8.1 shows the plots of raw spectra after (a) baseline correction and (b) 1st derivative, smoothing points five. We can find that signal peaks in (b) are much more than in (a). Table 8.1 shows the names of formulations included in the general library.

(a)   (b)
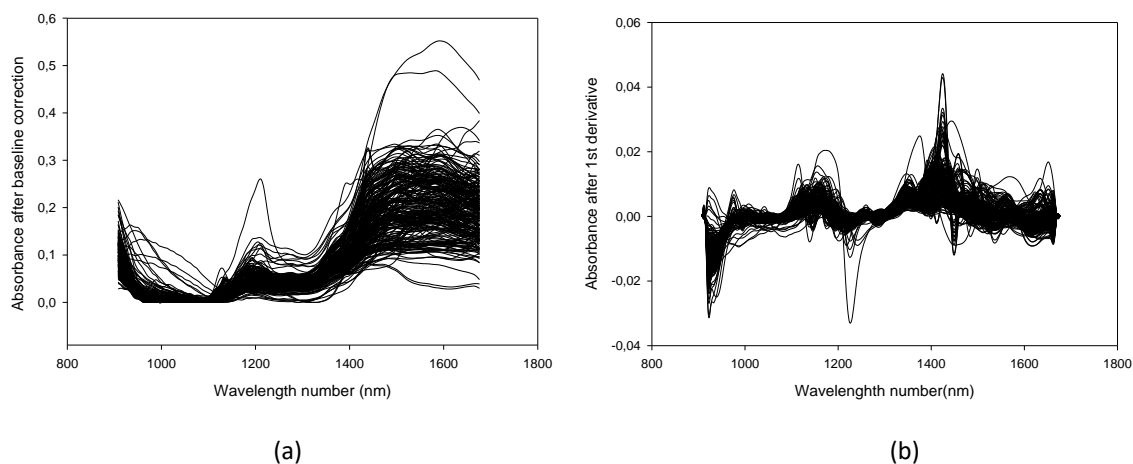
Fig. 8.1 Spectra after (a) baseline correction and (b) 1st derivative. smoothing points five.

Table 8.1 The name list of formulations included in the general library

| Library	Name of formulations	
General	ACALKA 1080 mg COMPRIMIDOS DE LIBERACION PROLONGADA	LEXATIN 3 mg CAPSULAS DURAS
	ACENAM 1250 mg COMPRIMIDOS EFERVESCENTES	LISINOPRILHIDROCLOROTIAZIDA 20 MG12.5 MG COMPRIMIDOS EFG
	ACETILCISTEINA STADA 600 mg COMPRIMIDOS EFERVESCENTES EFG	LIZIPAINA LIZIPAINA
	ACICLOVIR PHARMAGENUS 200 mg COMPRIMIDOS EFG	LOETTE DIARIO 10020 microgramos COMPRIMIDOS RECUBIERTOS CON PELICULA
	ACIDO ACETILSALICILICO STADA 100 MG COMPRIMIDOS GASTRORRESISTENTES EFG	LORATADINA BEXAL 10 mg COMPRIMIDOS EFG
	AERIUS 5 MG COMPRIMIDOS RECUBIERTOS CON PELICULA	LORATADINA NORMON 10 mg COMPRIMIDOS EFG
	AERO RED 40 mg COMPRIMIDOS MASTICABLES	LORAZEPAM CINFA 5 mg COMPRIMIDOS EFG
	AKINETON RETARD	LOSARTANHIDROCLOROTIAZIDA KERN PHARMA 10025 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG
	ALDACTONE 25 mg COMPRIMIDOS RECUBIERTOS CON PELICULA	LYRICA 75 mg CAPSULAS DURAS
	ALDOCUMAR 1 mg COMPRIMIDOS	MASDIL 60mg COMPRIMIDOS
	ALMAX 500 mg COMPRIMIDOS MASTICABLES	METAMIZOL NORMON 575 mg CAPSULAS EFG
	ALOPURINOL MUNDOGEN 300 mg COMPRIMIDOS EFG	MINODIAB 5 mg COMPRIMIDOS
	AMLODIPINO TEVAGEN 5 mg COMPRIMIDOS EFG	MONOLITUM FLAS 30 mg COMPRIMIDOS BUCODISPERSABLES
	AMOXICILINA CINFA 500 mg POLVO PARA SUSPENSION ORAL EFG	MONUROL 3 G GRANULADO PARA SOLUCION ORAL EFG
	AMOXICILINA NORMON 750 mg COMPRIMIDOS EFG	MUCIPLAZMA 500 mg CAPSULAS DURAS
	AMOXICILINAACIDO CLAVULANICO CINFAMED 500 mg125 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG	NAPROXENO NORMON 500 mg COMPRIMIDOS EFG
	AMOXICILINAACIDO CLAVULANICO MYLAN 500125 mg COMPRIMIDOS CON CUBIERTA PELICULAR EFG	NATECAL D COMPRIMIDOS MASTICABLES
	ANACLOSIL 500 mg CAPSULAS	NERVOBION CAPSULAS DURAS
	ARKOCAPSULAS ECHINACEA capsulas duras	NEXIUM MUPS 40 mg COMPRIMIDOS GASTRORRESISTENTES
	ASPIRINA 500 mg COMPRIMIDOS	NOLOTIL 575 mg CAPSULAS DURAS
	ASPIRINA C 400 mg240 mg COMPRIMIDOS EFERVESCENTES	OMEPRAZOL CINFAMED 20 mg CAPSULAS DURAS GASTRORRESISTENTES EFG
	Aspirine UPSA 500 mg comprime effervescent	OMEPRAZOL PENSA 20 mg CAPSULAS DURAS GASTRORRESISTENTES EFG
	ATARAX 25 mg COMPRIMIDOS RECUBIERTOS CON PELICULA	OMEPRAZOL RATIOPHARM 20 mg CAPSULAS DURAS GASTRORRESISTENTES

ATENOLOL NORMON 50 mg COMPRIMIDOS RECUBIERTOS EFG	OMEPRAZOL SANDOZ FARMACÉUTICA 20 MG CÁPSULAS DURAS GASTRORRESISTENTES EFG
ATORVASTATINA STADA GENERICOS 40 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG	OMEPRAZOL STADA 40 mg CAPSULAS DURAS GASTRORRESISTENTES
BETAHISTINA NORMON 16 mg COMPRIMIDOS EFG	OMEPRAZOL TARBIS 20 mg CAPSULAS DURAS GASTRORRESISTENTES EFG
BIODRAMINA 20 mg CHICLES MEDICAMENTOSOS	Omeprazol teva
BIODRAMINA 50 mg COMPRIMIDOS	OMNIC OCAS 0.4 mg COMPRIMIDOS DE LIBERACION PROLONGADA RECUBIERTOS CON PELICULA
BIODRAMINA CAFEINA COMPRIMIDOS RECUBIERTOS	OPIREN FLAS 30 mg COMPRIMIDOS BUCODISPERSABLES
Bisoprolol + Escitalopram	ORBENIN 500 mg CAPSULAS
BONESIL D FLAS 1500 mg400 UI COMPRIMIDOS BUCODISPERSABLES	OXCARBAZEPINA NORMON 600 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG
CEFUROXIMA CINFA 500 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG	PANTOPRAZOL STADA GENERICOS 40 mg COMPRIMIDOS GASTRORRESISTENTES EFG
CETIRIZINA TEVA 10 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG	PARACETAMOL AUROVITAS 1 G COMPRIMIDOS EFG
CHICLIDA 25 mg COMPRIMIDOS PARA CHUPAR	PARACETAMOL CINFA 1 g POLVO EFERVESCENTE EFG
Chloreven BIO	PARACETAMOL KERN PHARMA 1 g COMPRIMIDOS EFG
CIPROFLOXACINO CINFA 250 mg COMPRIMIDOS RECUBIERTOS EFG	PARACETAMOL KERN PHARMA 650 mg COMPRIMIDOS EFG
CIPROFLOXACINO CINFA 500 mg COMPRIMIDOS RECUBIERTOS EFG	PARACETAMOL MABO 1 g COMPRIMIDOS EFG
CIRCULYMPHE 60comp	PARACETAMOL MYLAN 1 g COMPRIMIDOS EFG
CLAMOXYL 1g COMPRIMIDOS	PARACETAMOL NORMON 500 mg COMPRIMIDOS EFG
CLAMOXYL 500 mg CAPSULAS	PARACETAMOL TARBIS 1 g COMPRIMIDOS EFG
COD-EFFERALGAN 500 mg 30 mg comprimidos efervescentes	PARACETAMOLCODEINA KERN PHARMA 500 mg30 mg COMPRIMIDOS EFG
COLCHIMAX 0.55 mg COMPRIMIDOS	PARAPRES 4 mg COMPRIMIDOS
CONDROSAN 400 mg CAPSULAS DURAS	PASTILLAS DEL DR. ANDREU
DACORTIN 2.5 mg COMPRIMIDOS	PECTOX LISINA 2.7 g granulado
DACORTIN 30 mg COMPRIMIDOS	PLANTABEN POLVO EFERVESCENTE
DALACIN 300 mg CAPSULAS DURAS	POLARAMINE 2 mg COMPRIMIDOS
DEFLAZACORT CINFA 30 mg COMPRIMIDOS EFG	PRAVASTATINA DAVUR 10 mg COMPRIMIDOS EFG
DEXKETOPROFENO CINFA 25 MG COMPRIMIDOS RECUBIERTOS CON PELICULA EFG	PREDNISONA ALONGA 50 mg COMPRIMIDOS
DIAMICRON 30 mg COMPRIMIDOS DE LIBERACION MODIFICADA	PREDNISONA KERN PHARMA 30 mg COMPRIMIDOS EFG

DIAZEPAN LEO 5 mg COMPRIMIDOS	RAMIPRIL TEVAGEN 5 MG COMPRIMIDOS EFG
DICLOFENACO CINFA 50 mg COMPRIMIDOS GASTRORRESISTENTES EFG	RAMIPRILHIDROCLOROTIAZIDA STADA 2.5 MG12.5 MG COMPRIMIDOS
DICLOFENACO RATIOPHARM 50 mg COMPRIMIDOS GASTRORRESISTENTES	RANITIDINA CINFA 300 mg COMPRIMIDOS RECUBIERTOS PELICULA EFG
DOLOCATIL 1 g COMPRIMIDOS EFG	RANITIDINA TARBIS 150 mg COMPRIMIDOS RECUBIERTOS EFG
DOLOCATIL 1 g POLVO PARA SOLUCION ORAL	RELIF 1g COMPRIMIDOS
DOLOTREN RETARD 100 mg CAPSULAS DURAS DE LIBERACION PROLONGADA.	RHODOGIL 750.000 U.I.125 mg COMPRIMIDOS RECUBIERTOSPELICULA
DOXAZOSINA NORMON 4 mg COMPRIMIDOS EFG	RINIALER 10 mg COMPRIMIDOS
DOXICICLINA NORMON 100 mg GRAGEAS	RINO-EBASTEL 10 mg120 mg CAPSULAS DURAS DE LIBERACION MODIFICADA
DOXIUM FUERTE 500 mg CAPSULAS DURAS	ROBAXIN 500 mg COMPRIMIDOS
DULCO LAXO COMPRIMIDOS RECUBIERTOS	SALVACOLINA 2 mg COMPRIMIDOS
Duloxetina Hidrocloruro	SEREPROSTAT 80 mg COMPRIMIDOS RECUBIERTOS CON PELICULA
EFFERALGAN 1 G	SERTRALINA CINFA 100 mg COMPRIMIDOS RECUBIERTOS PELICULA EFG
EMCONCOR 5 mg COMPRIMIDOS RECUBIERTOS CON PELICULA	SERTRALINA MYLAN 50 mg COMPRIMIDOS RECUBIERTOS PELICULA EFG
EMCONCOR COR 2.5 mg COMPRIMIDOS RECUBIERTOS CON PELICULA	SILODYX 8mg capsulas duras
ENALAPRIL BD- MABO 20 mg COMPRIMIDOS BUCODISPERSABLES EFG	SINTROM 4 mg COMPRIMIDOS
ENALAPRIL CINFA 5 mg COMPRIMIDOS EFG	SPASMOCTYL 40
ENALAPRIL CINFA 10 mg COMPRIMIDOS	STOPCOLD 5 mg120 mg COMPRIMIDOS DE LIBERACION PROLONGADA
ENALAPRIL KERN PHARMA 20 mg COMPRIMIDOS EFG	STREPSILS CON LIDOCAINA PASTILLAS PARA CHUPAR
ENALAPRIL MYLAN 5 mg COMPRIMIDOS EFG	SULFINTESTIN NEOMICINA COMPRIMIDOS
ENALAPRIL RATIOPHARM 5 mg COMPRIMIDOS EFG	SUMIAL 10 mg COMPRIMIDOS RECUBIERTOS CON PELICULA
ENALAPRIL STADA 20 mg COMPRIMIDOS EFG	SUMIAL 40 mg COMPRIMIDOS RECUBIERTOS CON PELICULA
ENALAPRILHIDROCLOROTIAZIDA CINFA 2012.5 mg COMPRIMIDOS EFG	TAMSULOSINA MYLAN 0.4 mg CAPSULAS DURAS DE LIBERACION MODIFICADA EFG
ENANTYUM 25 mg COMPRIMIDOS	TARDYFERON 80 mg COMPRIMIDOS RECUBIERTOS
ENANTYUM 25 mg. GRANULADO PARA SOLUCION ORAL	THERVAN 40 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG
ESOMEPRAZOL ACTAVIS GROUP 40 MG COMPRIMIDOS GASTRORRESISTENTES EFG	TIORFAN 100 mg CAPSULAS DURAS
ESPIDIFEN 600 mg GRANULADO PARA SOLUCION ORAL SABOR MENTA EFG	TOPIRAMATO QUALIGEN 200 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG
EUTIROX 25 microgramos COMPRIMIDOS	TORECAN GRAGEAS

EUTIROX 150 microgramos COMPRIMIDOS	TRAMADOL CINFA 50 mg CAPSULAS DURAS EFG
EXFORGE 5 mg 160 mg COMPRIMIDOS RECUBIERTOS CON PELICULA	TRANGOREX 200 mg COMPRIMIDOS
FEBRECTAL NIÑOS SUPOSITORIS	TRANXILIUM 5 mg CAPSULAS DURAS
FERBISOL 100 mg CAPSULAS GASTRORRESISTENTES	TROMALYT 300. CAPSULAS DURAS DE LIBERACION PROLONGADA
FERO-GRADUMET 105 mg COMPRIMIDOS DE LIBERACION PROLONGADA	TRYPTIZOL 75 mg COMPRIMIDOS RECUBIERTOS CON PELICULA
FLATORIL 500 microgramos200 mg CAPSULAS DURAS	UNIKET 40 mg COMPRIMIDOS
FLUCONAZOL CINFA 150 mg CAPSULAS DURAS EFG	VALSARTAN CINFA 160 mg COMPRIMIDOS RECUBIERTOS PELICULA EFG
FLUIMUCIL FORTE 600 mg COMPRIMIDOS EFERVESCENTES	VALSARTAN KERN PHARMA 320 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG
FLUOXETINA CINFA 20 mg COMPRIMIDOS DISPERSABLES EFG	VARIDASA COMPRIMIDOS
FLUTOX 10 mg. COMPRIMIDOS RECUBIERTOS	VELMETIA 50 mg1000 mg COMPRIMIDOS RECUBIERTOS CON PELICULA
FORTASEC 2 mg capsulas duras	VENLAFAXINA NORMON 75 mg COMPRIMIDOS EFG
FORTECORTIN 4 mg COMPRIMIDOS	VENLAFAXINA RETARD TEVA 150 mg CAPSULAS DURAS DE LIBERACION PROLONGADA EFG
FRENADOL COMPLEX GRANULADO PARA SOLUCION ORAL	VENLAFAXINA SANDOZ 75 mg COMPRIMIDOS EFG
FURANTOINA 50 mg COMPRIMIDOS	VENORUTON 1 g POLVO PARA SOLUCION ORAL
Furosemida	VENTOLIN 4 mg. COMPRIMIDOS
FUROSEMIDA CINFA 40 mg COMPRIMIDOS EFG	VESOMNI 6 MG0.4 MG COMPRIMIDOS DE LIBERACION MODIFICADA llisa
GEMFIBROZILO STADA 600 mg COMPRIMIDOS EFG	VESOMNI 6 MG0.4 MG COMPRIMIDOS DE LIBERACION MODIFICADA numeros
GEMFIBROZILO STADA 900 mg COMPRIMIDOS EFG	VID ROJA
GLICLAZIDA TEVA 30 mg COMPRIMIDOS LIBERACION MODIFICADA EFG	VOLTAREN RETARD 75 mg COMPRIMIDOS DE LIBERACION MODIFICADA
HEMICRANEAL COMPRIMIDOS	XICIL 1500 MG POLVO PARA SOLUCIÓN ORAL EFG
HIDROFEROL 0.266 MG CAPSULAS BLANDAS	YURELAX 10 mg CAPSULAS DURAS
HIDROXIL B12-B6-B1 COMPRIMIDOS RECUBIERTOS	ZALDIAR 37.5 mg325 mg COMPRIMIDOS RECUBIERTOS CON PELICULA
IBUPROFENO KERN PHARMA 600 mg GRANULADO PARA SOLUCION ORAL EFG	ZONISAMIDA TEVA 25 MG CAPSULAS DURAS EFG
IBUPROFENO KERN PHARMA 600 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG	CEFUROXIMA CINFAMED 250 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG
IBUPROFENO KERN PHARMA 600 mg GRANULADO EFERVESCENTE EFG	ENALAPRIL BELMAC 2.5 mg COMPRIMIDOS
IBUPROFENOCINFA 600 mg GRANULADO SOLUCION ORAL	DUODART 0.5mg0.4mg capsulas duras

IDAPTAN 20 mg COMPRIMIDOS RECUBIERTOS CON PELICULA	DITROPAN 5 mg COMPRIMIDOS
ILVICO COMPRIMIDOS RECUBIERTOS	DIAZEPAN NORMON 5 mg COMPRIMIDOS
INDAPAMIDA NORMON 2.5 mg COMPRIMIDOS RECUBIERTOS EFG	CEFIXIMA NORMON 400 mg CAPSULAS EFG
Inulac Tablets	CETIRIZINA CINFA 10 mg COMPRIMIDOS RECUBIERTOS CON PELICULA EFG
JALRA 50 mg COMPRIMIDOS	CARBOCISTEINA LISINATO STADA 2.7 G GRANULADO PARA SOLUCION ORAL EFG
LACTIBIANE REFERENCE	ATORVASTATINA TEVAGEN 20 mg COMPRIMIDOS RECUBIERTOS PELICULA EFG
LANSOPRAZOL TEVA 30 mg COMPRIMIDOS BUCODISPERSABLES EFG	AUGMENTINE 500125mg COMPRIMIDOS RECUBIERTOS CON PELICULA
LEVITRA 10 mg COMPRIMIDOS BUCODISPERSABLES	AVIDART 0.5 mg CAPSULAS BLANDAS
LEVOFLOXACINO ALMUS 500 MG COMPRIMIDOS RECUBIERTOS CON PELICULA EFG	BETAHISTINA NORMON 8 mg COMPRIMIDOS EFG
	DIGOXINA TEOFARMA 0.25 mg COMPRIMIDOS

The 951.46-1663.81nm range was selected to construct the general library, see Fig. 8.2. The noise which is located before 951.46 nm or after the 1663.81 nm was too high and would affect the qualitative ability of library.
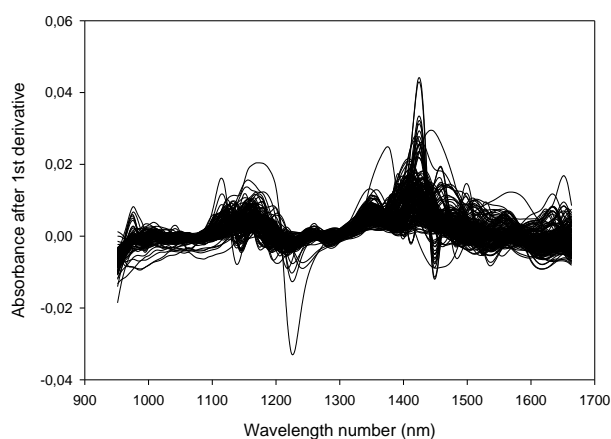
Fig. 8.2 Preprocessed spectra within 951.46-1663.81nm

The sub-libraries in 2nd level have applied Standard and Factorization methods. Ten sub-libraries were calculated with factorization method and the other four were calculated with standard methods. Ten sub-libraries spectra were preprocess with 1st derivative, smoothing points five and vector normalization. And four were preprocessed with 1st derivative, smoothing points five. The sub-libraries in 3rd level have applied factorization method. Two sub-libraries spectra were preprocessed with 1st derivative, smoothing points five and one was preprocess with 1st derivative, smoothing points five and vector normalization. Table 8.2 shows the names of formulation included in sub-libraries.

Table 8.2 The name list of formulations included in sub-libraries

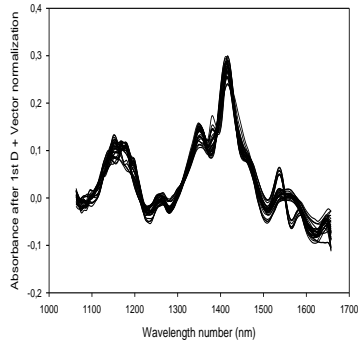| Library	Name of formulations
A	Aerius 5mg film-coated tablets.
	Atenolol normon 50mg coated tablet EFG.
	Bisoprolol normon 2.5mg film-coated tablet EFG.
	Escitalopram ratio 20mg film-coated tablet EFG.
B	Amoxicilina normon 750mg coated tablet EFG.
	Clamoxyl 1g tablet
C	Dolocatil 1g tablets EFG.
	Paracetamol 650mg Kern pharma tablets EFG.
	Paracetamol Mabo 1g tablet EFG.
D	Betahistine normon 16mg tablet EFG.
	Betahistine normon 8mg tablet EFG
E	Dacortin 30mg tablet.
	Eutirox 25mg tablet.
	Eutirox 150mg tablet.
	Predinsone alonga 50mg tablet.
	Prednisone Kern pharma 30mg tablet EFG
E-1	Eutirox 25mg tablet.
	Eutirox 150mg tablet
F	Dacortin 2.5mg tablet.
	Deflazacort cinfa 30mg tablet EFG.
	Fortecortin 4mg tablet.
	Polaramine 2mg tablet
G	Dalacin 300mg hard capsule.
	Silodyx 8mg hard capsule
H	Emconcor 5mg film-coated tablet.
	Emconcor 2.5mg film-coated tablet.
I	Aldocumar 1 mg tablet.
	Loratadine bexal 10mg tablet EFG.
	Loratadine normon 10mg tablet EFG.
	Parapres 4mg tablet.
	Enalapril belmac 2.5mg tablet.
	Digoxina teofarma 0.25 mg tablet
I-1	Loratadine bexal 10mg tablet EFG.
	Loratadine normon 10mg tablet EFG
J	Paracetamol Avrovitas 1g tablet EFG.
	Paracetamol Mylan 1g tablet EFG.
K	Gemfibrozilo Stada 600mg tablet EFG.
	Gemfibrozilo Stada 900mg tablet EFG
L	Enalapril Mylan 5mg EFG.
	Minodiab 5mg tablet.
	Uniket 40mg tablet
M	Sertraline Cinfa 100mg film-coated tablet EFG.
	Sertraline Mylan 50mg film-coated tablet
N	Losartan/Hidroclorotiazide Kern pharma 100/25mg film-coated tablet EFG.
	Sumial 10mg film-coated tablet.
	Sumial 40mg film-coated tablet.
	Thervan 40mg film-coated tablet EFG
N-1	Sumial 10mg film-coated tablet.
	Sumial 40mg film-coated tablet.
	Thervan 40mg film-coated tablet EFG

In Table 8.3 the parameters of general library and sub-libraries were listed.

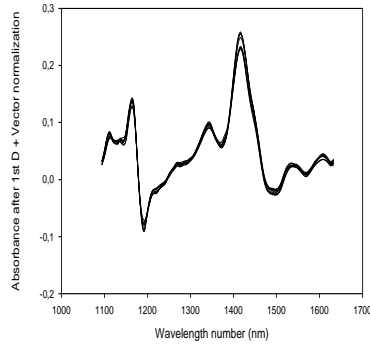*Table 8.3 Parameters of general library and sub-libraries*

Library name	NO. sample	Identification level	Preprocessing method	Range(nm)	Model
General	223	1	First derivative (5 points)	1663.81-951.46	Standard
A	3	2	First derivative (5 points)+Vector normalization	1657.62-1062.96	Factorization
B	2	2	First derivative (5 points)+Vector normalization	1632.84-1093.93	Factorization
C	3	2	First derivative (5 points)+Vector normalization	1651.42-1075.35	Factorization
D	3	2	First derivative (5 points)	1477.98-1403.65	Factorization
E	5	2	First derivative (5 points)+Vector normalization	1645.23-1106.32	Standard
E-1	2	3	First derivative (5 points)+Vector normalization	1657.62-1112.51	Factorization
F	4	2	First derivative (5 points)+Vector normalization	1639.03-1453.2	Standard
G	2	2	First derivative (5 points)+Vector normalization	1651.42-1093.93	Factorization
H	2	2	First derivative (5 points)+Vector normalization	1378.87-1217.82	Factorization
I	6	2	First derivative (5 points)+Vector normalization	1626.65-1100.13	Standard
I-1	2	3	First derivative (5 points)	1447.01-1409.84	Factorization
J	2	2	First derivative (5 points)	1440.81-1335.51	Factorization
K	2	2	First derivative (5 points)	1360.29-1106.32	Factorization
L	3	2	First derivative (5 points)+Vector normalization	1533.73-1124.9	Factorization
M	2	2	First derivative (5 points)	1186.85-1118.71	Factorization
N	4	2	First derivative (5 points)+Vector normalization	1632.84-1341.7	Standard
N-1	3	3	First derivative (5 points)	1626.65-1093.93	Factorization

The preprocessing methods and the spectral range selection are important tools to help identify drugs in the sub-libraries, because drugs in the sub-libraries have similar spectra normally and these tools reduce the similarity of spectra and increased specificity of spectra. The spectral ranges of the sub-libraries were selected according to their characteristic peaks. The peaks which have explained the most significant differences between drugs were chosen to calculate sub-libraries. Fig 8.3 shows the spectral ranges of every sub-library. The peak position and the peak intensity of different drugs in these ranges are not the same. Therefore, drugs can be identified by the NIR library.
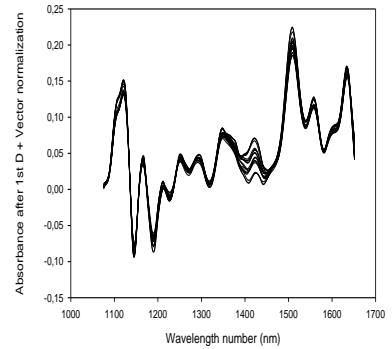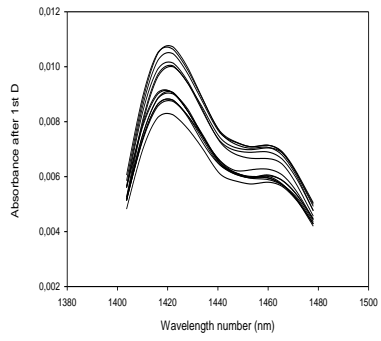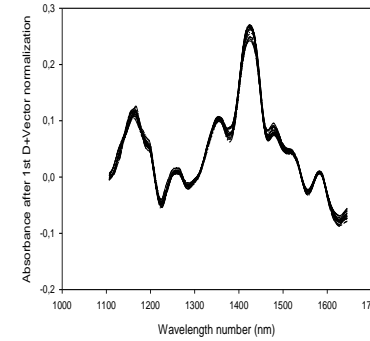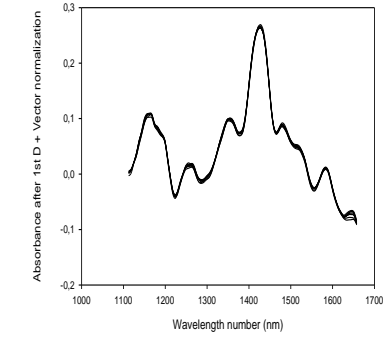
A

B

C

D

E

E-1

F

G

H

I

I-1

J

<div align="center">K</div>

<div align="center">L</div>
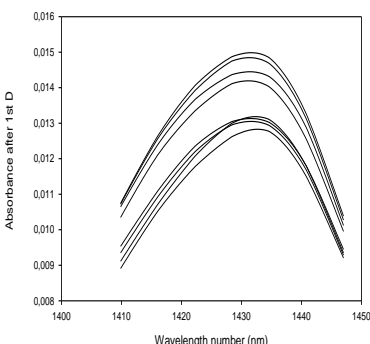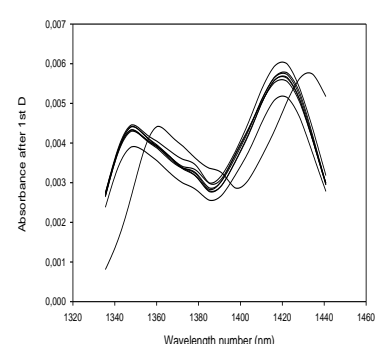

<div align="center">M</div>
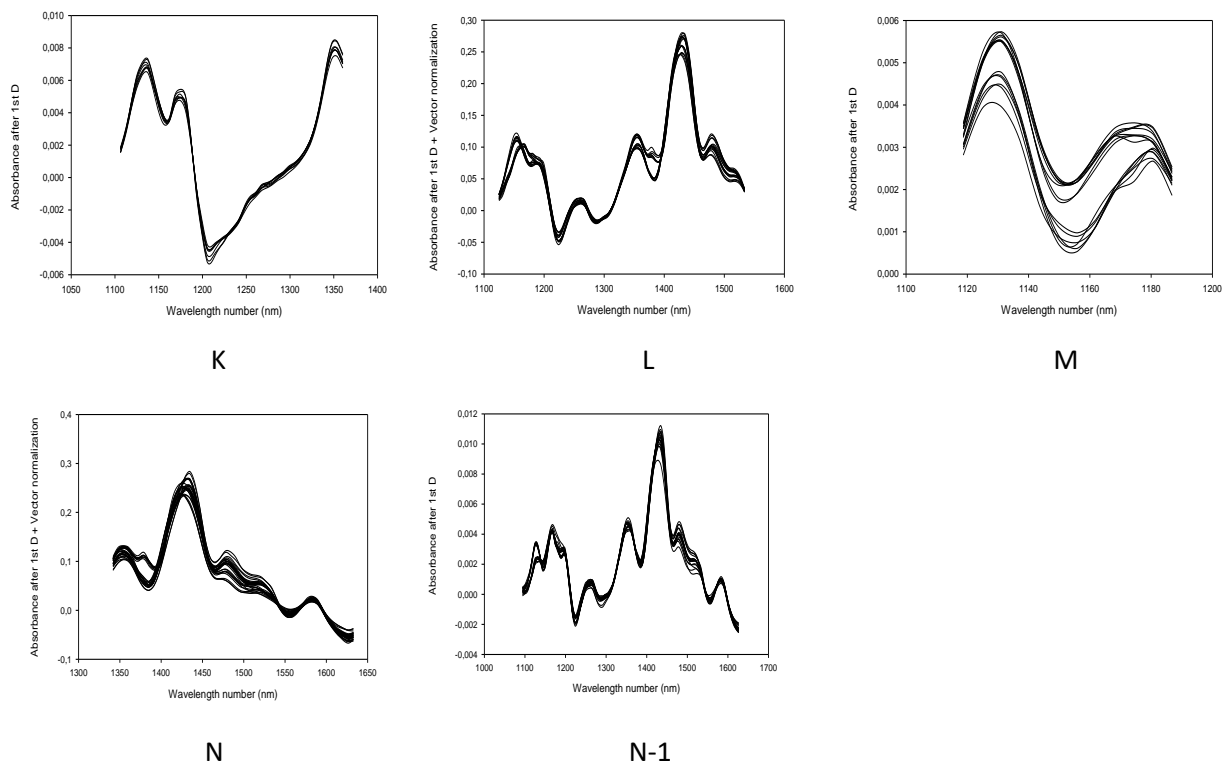

<div align="center">N</div>

<div align="center">N-1</div>
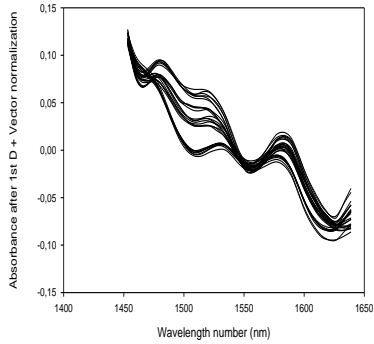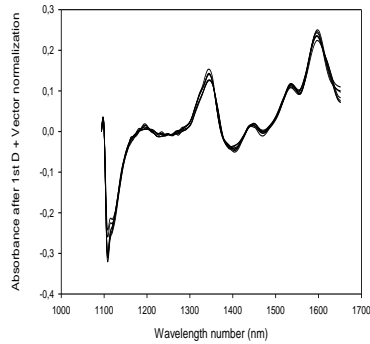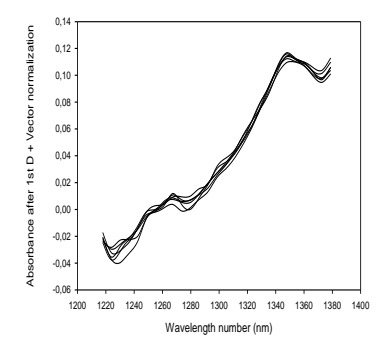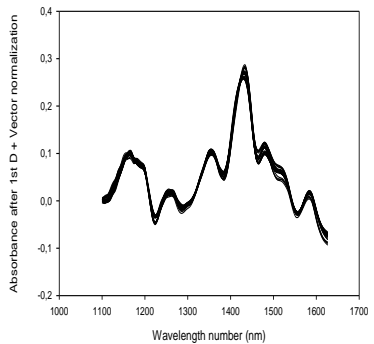
Fig. 8.3 Spectral ranges of sub-libraries

Fig 8.4 shows the distribution of reference spectra in the sub-libraries which were constructed with factorization method. Points in the same color were belonged to the same cluster and they were plotted with the value of scores. Some of them used two scores to calculated plots and some used one. After score selecting, all the clusters can be identified clearly according to their plots.
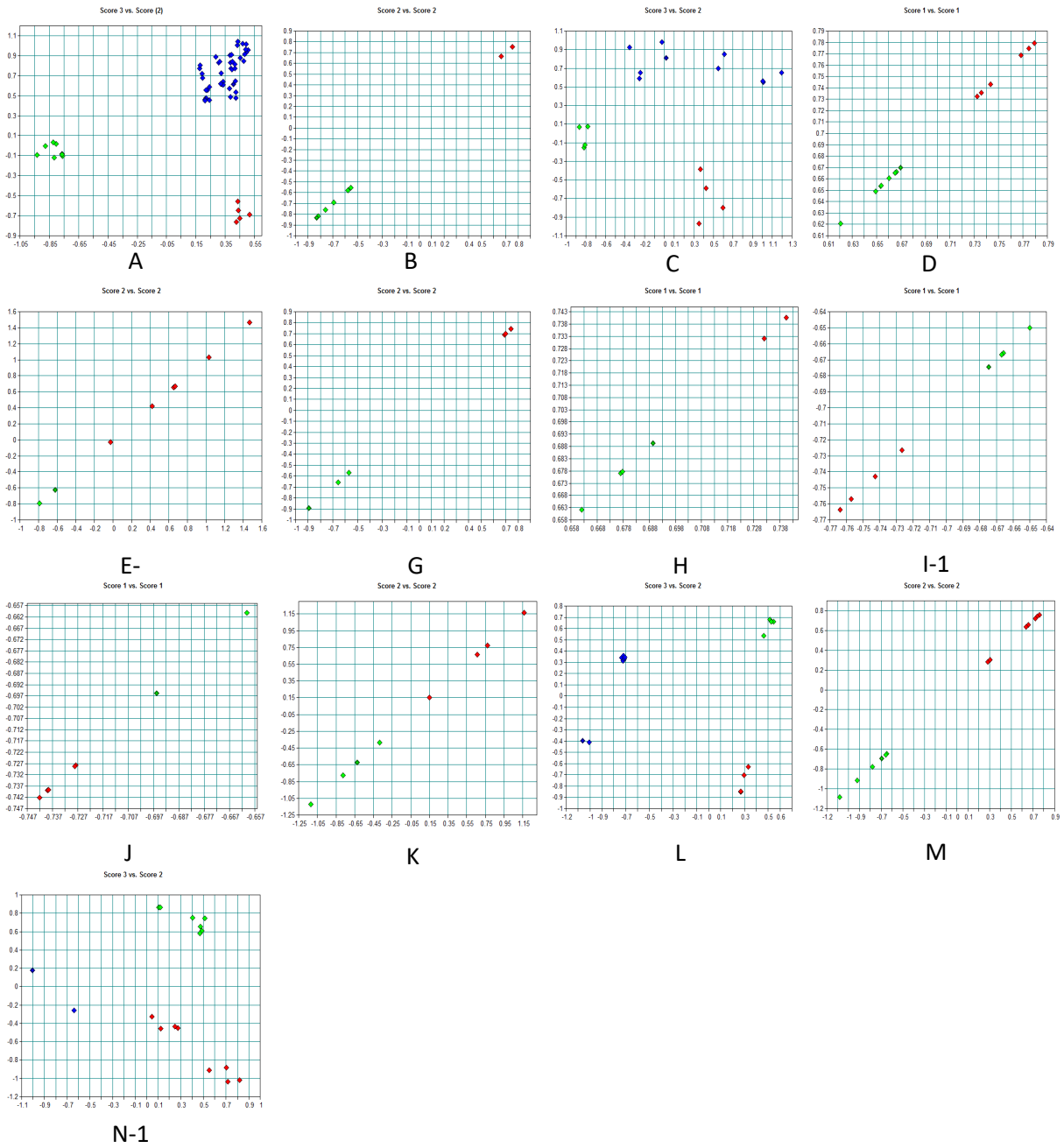
Fig 8.4 Distribution plots of reference spectra calculated with factorization method

8.3.3 Library validation

The internal validation has been carried out with the reference spectra and formulations can be uniquely identified by the NIR library. Then, the library was validated with spectra acquired with external samples by the MicroNIR. 574 spectra of 223 kinds of drugs were tested in total. Fig. 8.5 shows the validation result.
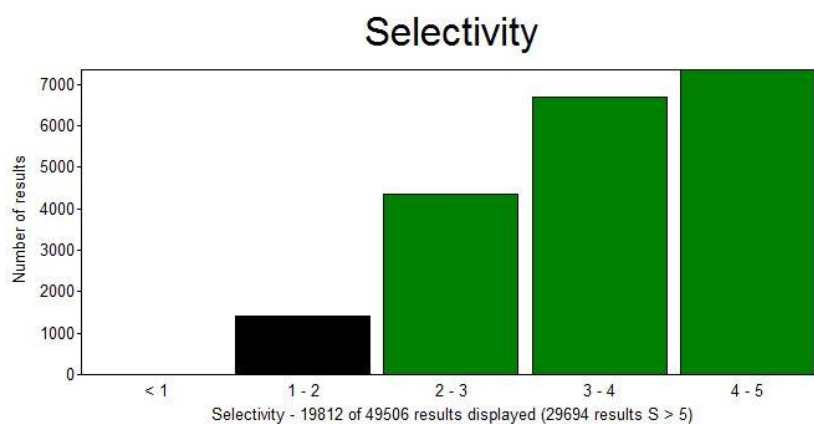
Fig. 8.5 Selectivity of the external validation

Most of the S values were larger than 2 and there was no value smaller than 1. Besides, the proportion of the value between 1 and 2 was much lower than others. All samples were separated fully without any confusion. The selectivity result shows us that the NIR library has a good performance in the identification of these solid drugs.

8.4 Conclusion

In this study, the NIR library was applied together with the MicroNIR spectrometer. The internal and external validations have shown us that this pattern recognition method is suitable for the identification of solid drug products. The miniaturization of spectrometer makes the NIRS expand its user range from research labs and business level to the customer level. Therefore, customers who need to buy drugs in the retail pharmaceutical store could use this nondestructive method to validate the drug quality at real time. It will reduce the amount of counterfeit drugs in the trading session effectively.

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