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Review

Current Trends in Simultaneous Determination of Co-administered Drugs

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Abstract: Recently, high demand of high-throughput analyses with high sensitivity and selectivity to molecules and drugs in different classes with different physical-chemical properties—and a reduction in analysis time—is a principal milestone for novel methodologies that researchers are trying to achieve—especially when analytical procedures are applied to clinical purposes. In addition, to avoid high doses of a single drug that could cause serious side effects, multi-drug therapies are often used to treat numerous diseases. For these reasons, the demand for methods that allow the rapid analysis of mixed compounds has increased in recent years. In order to respond to these needs, new methods and instruments have been developed. However, often the complexity of a matrix can require a long time for the preparation and processing of the samples. Different problems in terms of components, types of matrices, compounds and physical-chemical complexity are encountered when considering drugs association profiles for quantitative analyses. This review addresses not only recently optimized procedures such as chromatographic separation, but also methods that have allowed us to obtain accuracy (precision and trueness), sensitivity and selectivity in quantitative analyses for cases of drug associations.

Keywords: analytical methods; chromatographic procedures; drug associations; hyphenated techniques; biologic matrices; instrument configurations; co-formulation; validation procedures

1. Introduction

Recently, high demand for new formulations and new targeted therapies has led to more sensitive and selective analytical procedures for simultaneous classification, identification and quantification of compounds that show different physical-chemical properties. From a chemical point of view, these compounds may belong to the same chemical class [1,2] or may be different [3]. Moreover, several therapeutic classes (e.g., antihistamines, bronchodilators, mucolytics, anti-inflammatories, antibiotics, etc.) are available on the market that present a low percentage of serious adverse reactions when administered in low doses. Thus, considering the lower occurrence of severe side effects of a low dose of individual drug, the treatment of certain pathologies often involves a combination of medicines. The need for new procedures that allow the simultaneous analysis and bioanalysis of different compounds has been increasing in the last years. When tablet and/or other pharmaceutical forms are analyzed, in order to develop robust procedures for drug quality controls the first step involves the identification of target analytes—often in complex matrices. This step is the key when these compounds are quantified in biologic matrix to evaluate the pharmacokinetic (PK) and pharmacodynamics (PD) parameters for the administration of single drugs or the co-administration. Since dosage changes do not instantly translate into responses or side effects, therapeutic drug monitoring can facilitate dose adjustments. Often, when drugs are administered in

association, the co-administered drug and/or its metabolites may modify the pharmacokinetic parameters of the single active principle via a sort of cross-influence. This can lead to changes in the therapeutic strategies and dosages. The effects can be also positive, related to a higher residence time with better efficacy or lower doses [4]. These phenomena may also be observed when a specific formulation is designed. Some solvents or other additives, such as polyvinylpyrrolidone (PVP) [5] or hydroxy-propyl-methylcellulose (HPMC) [6], may modify the compaction characteristics, mechanical properties, crystal structure and/or the compression properties of final product. HPMC and PVP are polymers that act as a release control element and must possess certain characteristics such as biocompatibility, mechanical strength and permeability to a given drug. These additives can profoundly modify the PK parameters and may be considered at the same level of a "second active compound", due their influence in the drugs release. These polymers strongly influence the release of the drug. A high polymer content causes the formation of a gel layer which slowly erodes by controlling the drug delivery. On the other hand, a small amount of polymer allows a greater penetration of water into the matrix—and a consequent increase in the rate of drug release.

Quality control is fundamental, especially in the search for new synthetic drugs and natural products. It is also an important tool in the fight against drug counterfeiting. Studies on drug stability also allow highlighting the presence of impurities in the final formulation: according to the guidelines of the International Conference on Harmonization (ICH) and other international agencies, all impurities and degradation products that are present beyond a defined threshold must be reported, identified and quantified. In particular, impurities generally present during the synthetic process are often detected and are defined as "*by-products*" or "intermediates".

Taking into consideration the great prevalence and importance of dose-combination in modern therapies, the elaboration of robust and accurate analytical procedures that are able to detect and quantify simultaneously different drugs characterized by different chemical structures represents a new challenge for analysts. The procedures used in quality control must have some characteristics such as reproducibility, transferability, cheapness and speed of analysis. In addition, a validation process must be carried out entirely in order to obtain data that can follow the drug development process [7]. In this review, recent procedures and advantages are treated, both in terms of extraction and instrument configurations in order to highlight the separation conditions, but also to achieve accuracy (precise and trueness), sensitivity and selectivity [8,9] in quantitative analyses for the drug association cases. Various methods concerning the analysis of co-formulated drugs—both in pharmaceuticals and in biologic matrices are reported.

2. Drug Associations: Co-formulations Analyses of Two Different Active Compounds

Prophylactic, curative, palliative or diagnostic purposes is the main target of pharmaceutical drug-association analyses. The final product must satisfy quality standards in addition to respecting safe and effective PK profiles. In this topic are included the main problems related to the drugs association production, especially associated with medicines showing a low therapeutic index, due to the concentration of each compound that is not completely guaranteed. Contamination by impurities not included in the original formula, and/or degradation products is an additional problem, coupled to the simultaneous presence of other active substances that can interfere with a given single drug's stability. In particular, impurities present are often derived from synthetic process. It has been established in the International Conference of Harmonization (ICH) guidelines that all impurities and/or degradation products present over a defined limit must be indicated and quantified. Quantitative analysis using validated procedures aims to verify whether the drug associations not only show the labeled dose of the active ingredient, but also verify the overall product integrity and the absence of degradation products and/or cross interactions between the active principles present in the formulation. In addition, several active ingredients are often present in co-formulations at lower doses than the single formulation. This has the advantage of administering lower doses of active ingredients, which at high doses could cause adverse effects. Analytical assays able to detect more drugs in pharmaceutical formulations, linking in vitro and in vivo characterization of novel formulations are very important, especially when drug development

is carried out using extensive formulation development processes. In this scenario, analytical procedures based on spectroscopic techniques play a key role, due to their high sensitivity, selectivity, ease of use and inexpensiveness. In this case, the use of spectrofluorimetric techniques is often adopted, and no interfering signals due co-formulated drugs are present, as recently reported by Walash et al [10]. In the same way, derivative spectrophotometric procedures also allow analyses of pharmaceutical formulations, as reported for the simultaneous determination of co-formulated binary mixtures for specific treatments [11–25]. In this case, the main problem is related to the possibility of resolving the overlapping peaks phenomena that occurs in a "cumulative" absorbance measure when different signals are recorded. To increase the reliability of this test, it is sometimes recommended that the absorbance at a given maximum value should be within ± 3% of the reference standard. In addition, in some cases, the absorbance ratio of two characteristic wavelengths is also limited. Using derivative spectroscopy in the UV-Vis spectra—and applying spectral corrections according to constant center (CC), ratio difference (RD), mean centering of ratio spectra (MCR), simultaneous equation method, Q-analysis method/absorption ratio, area under curve, or first-order derivative spectrophotometric methods—can enable quantifying two active components in different formulations. Even if spectroscopic procedures are easy and reliable [26], chromatographic methods are generally applied to quality control measurements, especially in co-formulations, as reported in Tables 1–3. High pressure thin layer chromatography (HPTLC) [27–36], capillary electrophoresis (CE) [37,38] high performance liquid chromatography (HPLC) [39–102] or methodologies allow the quantification of targeted compounds in complex pharmaceutical dosage to certify the final commercial product and its stability (also considering the possibility of cross-interactions). In particular, several HPLC procedures have been developed and validated for binary drug-association co-formulation analyses in tablets (Table 1), capsules (Table 2), mixtures or other formulations (Table 3). As highlighted in the column concerning the instrumentation, HPLC coupled with a UV detector is very useful for the simultaneous determination of drugs in pharmaceutical dosage forms. This technique is widely used for higher sensitivity and selectivity. Particular interestingly is the work by Ibrahim and co-workers [53], who used HPLC coupled with fluorescence detection in addition to third-derivative synchronous fluorescence spectroscopy as two complementary methods for the determination of rabeprazole sodium and domperidone after derivatization with 4-chloro-7-nitrobenzofurazan as fluorescence probe. The different physical-chemical properties shown by the active ingredient and its degradation products—or by two different active compounds—represent a further difficulty. These lead to optimizing the extraction and clean-up procedures in order to obtain the best recovery of molecules and/or degradation compounds.

The procedure for mixtures prepared in the laboratory involved standard solutions of the various active compounds in specific ratios that were subsequently diluted to volumes and mixed. The recommended procedure for the calibration curve was then performed. The peak signal was plotted vs. the final concentration of the drug (μg/mL) to generate the calibration curve. For the simultaneous determination of two different active compounds in their co-formulated tablets, the preparation was generally carried out as follows: tablets were weighed and pulverized well. A weighed quantity of the powdered tablet in their pharmaceutical ratio (specific for each active compounds) was transferred into a small conical flask and extracted with organic solvent (mostly methanol). The extract was then filtered into a volumetric flask. The conical flask was washed with few milliliters of methanol. The washings were passed into the same volumetric flask and filled to the volume with the same solvent. Aliquots spanning the working concentration range were transferred into final flasks.

Table 1. High performance liquid chromatography (HPLC) procedures developed and validated for binary drug-association co-formulations analyses in tablets.

Drugs	Instrumentation	Ref.
Domperidone/pantoprazole	HPLC-UV-Vis	[54]
Omeprazole/domperidone	HPLC-UV-Vis	[57]
Rabeprazole sodium/domperidone	HPLC-UV-Vis	[60]
Pantoprazole/domperidone	HPLC-UV-Vis	[62]
Rosiglitazone/glimepiride	RP-HPLC-UV-Vis	[64]
Ilaprazole/domperidone	HPLC-UV-Vis	[39]
Domperidone/lafutidine	HPLC-UV-Vis	[43]
Famotidine/domperidone	HPLC-UV-Vis	[44]
Prulifloxacin/impurities	HPLC-PDA	[52]
Valsartan/amlodipine	HPLC-MS/MS	[67]
Amlodipine/aliskren	HPLC-UV-Vis	[68]
Metformin/vildagliptin	HPLC-UV-Vis	[69]
Valsartan/ezetimibe	HPLC-UV-Vis	[70]
Amlodipine/atorvastatin	HPLC-UV-Vis	[71]
Atorvastatin calcium/pioglitazone hydrochlor	HPLC-PDA	[72]
Rabeprazole sodium/domperidone	HPLC-FLD	[59]
Metformin/gliclazide	HPLC-UV-Vis	[78]
Gliclazide/enalapril maleate	HPLC-UV-Vis	[79]
Artemether/lumefantrine	HPLC-UV-Vis	[80]
Irbesartan/hydrochlorothiazide	HPLC-UV-Vis	[81]
Ranitidine/metronidazole	HPLC-UV-Vis	[82]
Ambrisentan/tadalafil	HPLC-UV-Vis	[83]
Quinapril hydrochlor/hydrochlorothiazide	HPLC-UV-Vis	[84]
Amlodipine besylate/Olmesartan Medoxomil	HPLC-PDA	[85]
Nevirapine zidovudine/lamivudine	RP-HPLC	[86]
Metformin hydrochlor/repaglinide	HPLC-MS/MS	[89]
Irbesartan/hydrochlorothiazide	HPLC-UV-Vis	[90]
Valsartan/amlodipine	HPLC-UV-Vis	[94]
Irbesartan/amlodipine besylate	HPLC-MS/MS	[95]
Entecavir/tenofovir	HPLC-UV-Vis	[96]
Adapalene/benzoyl peroxide	HPLC-UV-Vis	[97]
Alogliptin/metformin	UPLC-MS/MS	[98]
Elbasvir/Grazoprevir	HPLC-UV-Vis	[99]
Naltrexone/bupropion	HPLC-UV-Vis	[100]
Velpatasvir/sofosbuvir	UPLC-PDA	[101]
Metolazone/spironolactone	RP-HPLC-UV-Vis	[102]

Table 2. HPLC procedures developed and validated for binary drug-association co-formulation analyses in capsules.

Drugs	Instrumentation	Ref.
Domperidone/omeprazole	HPLC-UV-Vis	[55]
Omeprazole/domperidone	HPLC-UV-Vis	[36]
Cinitapride/omeprazole	HPLC-UV-Vis	[45]
Esomeprazole/levosulpiride	HPLC-UV-Vis	[41]
Cinnarizine/piracetam	HPLC-UV-Vis	[51]
Omeprazole/domperidone	RP-HPLC	[65]
Celecoxib/Diacerein	HPLC-UV-Vis	[91]

Table 3. HPLC procedures developed and validated for binary drug-association co-formulation analyses in mixtures or other formulations.

Drugs	Instrumentation	Ref.
Cinnarizine/domperidone	HPLC-UV-Vis	[56]
Domperidone/pantoprazole	HPLC-UV-Vis	[58]
Rabeprazole/domperidone	HPLC-UV-Vis	[59]
Pantoprazole/domperidone	HPLC-UV-Vis	[61]
Domperidone/sorbic acid/propylparaben	HPLC-UV-Vis	[63]
Domperidone/rabeprazole	HPLC-UV-Vis	[40]
Domperidone/rabeprazole	HPLC-UV-Vis	[47]
Domperidone/ilaprazole	HPLC-PDA	[48]
Rosuvastatin/ezetimibe	HPLC-PDA	[66]
Metformin Hydrochloride and Telmisartan	RP-HPLC	[73]
Clindamycin/adapalene	HPLC-UV-Vis	[74]
Rosuvastatin/amlodipine	HPLC-UV-Vis	[75]
Fluticasone propionate/salmeterol xinafote	HPLC-UV-Vis	[76]
Gemcitabine/curcumin	HPLC-UV-Vis	[77]
Gatifloxacin/prednisolone acetate	HPLC-UV-Vis	[87]
Finasteride/tamsulosin	HPLC-UV-Vis	[88]
Withaferin a/Z-Guggulsterone	HPLC-UV-Vis	[92]
Atenolol/nifedipine	HPLC-UV-Vis	[93]

As shown in the tables above, all developed methods consider the HPLC-UV-Vis (or PDA) instrument configuration as the best choice, particularly for ease of use, robustness, cheapness and the fact that it does not require highly qualified personnel for its use. Notably, a review study was recently published reporting the importance of HPLC instrumentation in quality control and drug research [26]. The primary developed HPLC methods are simple, sensitive, specific and adequate for the simultaneous quantification of two active compounds in different formulations. The methods have been validated in terms of linearity, intra- and inter-day precision, trueness, limit of quantification (LOQ), limit of detection (LOD) and reproducibility for each analyte and successfully applied to drug chemical stability studies. The method is also suitable for application to other analytical problems, for example, quality control of pharmaceutical formulations or evaluating the chemical stability of referred drugs in mixtures for clinical use.

In this scenario, only in recent years [67,89,95,98] some papers reported the HPLC-MS/MS configuration. These methods show very high selectivity—especially when multiple-reaction monitoring (MRM) or single-reaction monitoring (SRM) mode is adopted. This improves the selectivity and sensibility of the developed assay.

In this case, co-eluted compounds can represent major problems and the procedure can suffer from the matrix effect (ME). The impact of ME on the trueness, precision and robustness of bioanalytical methods is growing in pharmaceutical industry. The matrix composition can represent the limiting step in bioanalytical chemistry and quantitative analysis [103]. In fact, matrices often

contain different components—particularly endogenous phospholipids that can affect the instrumental setting up and the equipment performance. Tang and Kebarle described the ME for the first time. MEs can be described as the difference between the MS signal of analytes in a standard solution and the signal of the same compounds in biologic matrices [104,105]. Differences between standard-solution and biologic samples may depend on a potential competition between analytes and components of matrices for stationary and mobile phases. All these factors can cause some errors in the accuracy and precision of bioanalytical methods. There are various methods for evaluating ME; the most common are the post-column infusion method and the post-extraction spike method. The former is performed by monitoring the instrument response of a constantly infused analyte after injecting an extract from a sample into the system. The post-extraction spike method evaluates MEs by comparing the response of an analyte—in a clean solution—to the response of the analyte spiked into a blank matrix sample, prepared through the same process. While the first approach is limited in that it does not provide a quantitative evaluation of the level of ME obtained, in contrast, the second method quantitatively assesses the effect. When pharmaceutical formulations (tablets, mixtures, capsules) are analyzed, the targeting compounds represent the principal component. A great strategy—often adopted in order to reduce the ME—is the dilution procedure. The injection of small amount increases the performance of analysis, due to the decreased number of components in the sample. In addition, when using the MS instrumentation the injection volume optimization is also required and mandatory in order to increase the source ionization process. The dilution procedure, as well as the injection of small volumes, also decreases the number of molecules competitors to the droplet surface [106,107]. Other scientists have focused on optimizing sample preparation in order to reduce or remove matrix effect. These sample preparation methods include protein precipitation (PPT), liquid–liquid extraction (LLE), silica-based solid-phase extraction (SPE) and polymeric SPE. Comparing all these sample preparation procedures, PPT is the least effective sample preparation technique because fails to remove enough of the plasma components, specifically phospholipids that are known to cause variability in analyte signal intensity in mass spectrometers. Reversed-phase SPE and cation exchange SPE result in significantly lower levels of phospholipids, compared with PPT. Liquid–liquid extraction provides cleaning extracts comparable to cationic SPE. Mixed-mode strong-cation-exchange SPE, which combines the retention mechanisms of reversed-phase and ion exchange, showed the most effective sample clean-up and highest recoveries, leading to minimal matrix effects from biologic samples and excellent recoveries for a range of polar and nonpolar analytes.

3. Drug Associations: Co-formulations Analyses of More Different Active Compounds

Some recently published papers report also the quality control and/or stability evaluation for ternary mixtures of co-formulated principles [52,108–116], highlighting the deep importance and the necessity covered by separation techniques in pharmaceutical fields, from drugs development to final commercial products, as reported in Table 4 (tablets) and Table 5 (mixture). Nowadays, the mixtures of these active components are present in pharmaceutical formulations as capsules and tablets forms. All reported methods consider organic solvents (principally acetonitrile and methanol) and aqueous ones as starting conditions for the development of the reversed-phase chromatographic separation. This kind of chromatography has been generally selected due to the large availability of different stationary phases and robustness with respect to the nature of other chromatographic interactions.

Table 4. Analytical procedures developed and validated for multidrug (n ≥ 3)-association co-formulation analyses in tablets.

Drugs	Instrumentation	Ref.
Sumatriptan succinate/naproxen/domperidone	HPLC-UV-Vis	[50]
Hydrochlorothiazide/Amlodipine besylate/telmisartan hydrochloride	HPLC-UV-Vis	[109]
Aspirin/amlodipine/simvastatin	HPLC-UV-Vis	[110]
Tenofovir disoproxil fumarate/emtricitabine/nevirapine	HPLC	[111]

Table 5. Analytical procedures developed and validated for multidrug (n ≥ 3)-association co-formulation analyses in mixture or other formulations.

Drugs	Instrumentation	Ref.
Tramadol hydrochloride/paracetamol/domperidone	HPLC	[114]
Pantoprazole/rabeprazole/lansoprazole/domperidone	HPLC-UV-Vis	[115]
Domperidone/paracetamol/esomeprazole/lansoprazole	HPLC-UV-Vis	[49]
Paracetamol/aceclofenac/rabeprazole sodium	HPLC-UV-Vis	[42]
Aliskiren hemifumarate/amlodipine besylate/hydrochlorothiazide	CE-UV-Vis	[38]
Sitagliptin/metformine/atorvastatin	HPLC-UV-Vis	[112]
Rabeprazole sodium/mosapride citrate rabeprazole sodium/itopride hydrochloride	HPLC-PDA	[46]
Losartan potassium/glimepiride/metformin	HPLC-UV-Vis	[108]
Dexamethasone/ondasetron/granisetron/tropisetron/azasetron	HPLC-PDA	[116]

Furthermore, the aqueous phase could be added with formic acid (generally at 0.1% to 1%) or other modifiers (trifluoroacetic acid, trichloroacetic acid), in order to improve the mass spectrometry (MS) response or could be buffer (ammonium formiate or ammonium acetate) with concentrations ranged from 25 mM to 100 mM. Interestingly, all papers use standard HPLC columns from 150 cm to 250 cm, with 4.6-mm internal diameter (i.d.) and 5-μm-particle size. In this contest these configurations are very cheap, but don't follow the "green analytical chemistry" rules due to high solvent consumption respect to other configurations such as lower column i.d., the use of not fully environmental-friendly solvents, coupled to eventual persistent bioaccumulation and toxic effects [112].

In order to better follow the GAC rules, possible alternative options could be represented by replacement with green solvents (like ethanol, isopropanol, *n*-propanol, acetone, ethyl acetate, ethyl lactate and propylene carbonate) or the use of shorter columns in order to reduce the single analysis runtime (enhancing the throughput). Another available option could be the use of nano–LC instrumentation that allow the same analytical performances observed in classical configuration, but require smaller solvent volumes.

4. Drug Associations: Co-formulations Analyses in Biologic Matrices

Papers that report the analyses of co-administered drugs in different biologic matrices are described in this section. Since some biologic functions are modified following the co-administration of two drugs, the methods for their determination in vivo helps understand their interactions—especially in metabolism reactions. Very often, the same family of cytochromes (mainly CYP3A4) metabolizes the drugs administered concomitantly. Therefore, the possibility of drug–drug interactions (DDI) is highly probable. For this reason, the development and validation of new analytical methods for the simultaneous determination of two or more drugs in biologic fluids is of utmost importance for drug therapeutic monitoring, pharmacokinetics, bioequivalence and DDI studies.

Regarding validated procedures applied to conventional formulations, in the case of biologic matrices, it can be observed that an increased number of papers consider the HPLC-MS/MS instrument configuration as the better choice (Table 6 and Table 7), even if is expensive and not readily available in most laboratories. A sample treatment step is usually necessary before the instrumental analysis of xenobiotics in the biologic matrices—in order to remove interfering compounds, isolate target analytes and increase the selectivity and sensitivity of the analytical method. In most reported works, the sample pretreatment was carried out with SPE or LLE, involving PPT (with acetonitrile in most cases). HPLC-MS/MS configurations (especially when MRM or SRM acquisition modes are used) permit minimal sample-handling due to the instruments' intrinsic high selectivity and sensitivity [9]. By reducing the pre-analytical steps, the overall recovery methods are generally enhanced, bringing to a quali-quantitative analysis of not only active principles, but also of different compounds derived by degradation or metabolic processes, with a consequent

improvement in terms of LODs and/or LOQs. The proposed methods are simple to perform and validated in terms of linearity, intra- and inter-day precision, trueness, LOQ, LOD and reproducibility. The reported analytical methodologies represent suitable tools for the efficient detection, identification and quantification of these analytes in biologic matrices. This is useful to evaluate clinical therapy efficaciously in order to better evaluate pharmacological dosages for the association. In addition, these methods have the potential for application in therapeutic monitoring of patients under treatment with several drugs, and may be applied in clinical research of drug combination, multidrug pharmacokinetics and interactions studies.

Papers that consider HPLC coupled with UV-Vis [117–140], FLD [118], MS or MS/MS [141–144] detectors are shown in Table 6 and Table 7. When a fluorescence detector was used, the pre-analytical step should involve a derivatizing reagent (for example 4-fluoro-7-nitro-[2,1,3]-benzoxadiazole), especially when the target compounds do not show fluorescence property. The derivatized products can then detected in chromatographic system. Despite these sample treatments, it is often possible to obtain better analytical performance with HPLC-FLD configurations over MS detectors [118], due to the higher intrinsic sensitivity of the FLD detector. The main drawbacks related to MS detectors are related to isobaric compounds—compounds with the same nominal mass, but with a different molecular formula—and isomeric drugs. In these cases, chromatography is of fundamental importance, which is entrusted with the task of solving these compounds, allowing simultaneous analysis in the absence of mutual interference.

The high selectivity achieved with these analytical methods allows studying pharmacokinetic profiles: it is possible to calculate pharmacokinetic parameters such as C_{max} (the maximum serum concentration that a drug achieves in a specified compartment), T_{max} (the time at which the C_{max} is observed), area under the curve (AUC) and the elimination rate constant (K_e).

Table 6. Analytical procedures developed and validated for drug-association analyses in plasma.

Drugs	Instrumentation	Ref.
Domperidone/pantoprazole	HPLC-UV-Vis	[119]
Proton-pump inhibitors/domperidone	HPLC-UV-Vis	[122]
Rosuvastatin/fenofibric acid	HPLC-UV-Vis	[123]
Amlodipine/valsartan	HPLC-UV-Vis	[124]
Metformin/vildagliptin	HPLC-UV-Vis	[69]
Etodolac/pantoprazole	HPLC-PDA	[125]
Furprofen/indoprofen/ketoprofen/fenbufen/ flurbiprofen/indomethacin/ibuprofen	HPLC- PDA	[2]
Eperisone chloride/paracetamol	HPLC- PDA	[3]
Entecavir/tenofovir	HPLC-UV-Vis	[96]
Flubendazole/nitazoxanide	HPLC-UV-Vis	[126]
Omeprazole/tinidazole/clarithromycin	HPLC-UV-Vis	[127]
Diclofenac sodium/papaverine hydrochlor.	HPLC	[128]
Dexamethasone/nefopam	HPLC	[129]
Methotrexate/sulfasalazine	HPLC- PDA	[130]
Prulifloxacin/ulifloxacin	HPLC- PDA	[117]
Metronidazole/meropenem/ciprofloxacin/linezolid/piperacillin	UHPLC-PDA	[132]
Oxytetracycline/tinidazole/esomeprazole	HPLC-PDA	[133]
Acebrophylline/levocetirizine/pranlukast	HPLC-PDA	[135]
Apixabam/dabigatran/rivaroxaban	UHPLC-PDA	[136]
Sildenafil/tramadol	HPLC-UV	[137]
Doxorubicin/curcumin	HPLC-MS/MS	[142]
Sofosbuvir/daclatasvir	UPLC-MS/MS	[143]
Ketoprofen/carprofen/diclofenac	HPLC-PDA	[139]
Anastrozole/letrozole/exemestane	HPLC-PDA	[140]

Table 7. Analytical procedures developed and validated for drug-association analyses in other biologic matrices.

Drugs	Matrix	Instrumentation	Ref.
Diltiazem/quinolones	human serum	RP-HPLC-UV-Vis	[120]
Dorzolomide/timolol	aqueous humor	HPLC-UV-Vis	[122]
Irbesartan/hydrochlorothiazide	urine	HPLC-UV-Vis	[90]
Ciprofloxacin/levofloxacin	saliva	HPLC-PDA	[1]
Octreotide/gabexate mesylate metabolite	pancreatic juice	HPLC-PDA-FLD	[118]
Venlafaxine/vilazodone	human serum	HPLC-PDA	[131]
Amitriptyline/nortriptyline and their hydroxy metabolites	human serum	LC-MS/MS	[144]
Anastrozole/letrozole/exemestane	Whole blood	HPLC-PDA	[140]
Furprofen/indoprofen/ketoprofen/fenbufen/flurbiprofen/ibuprofen	saliva	HPLC-PDA	[138]
Ketoprofen/carprofen/diclofenac	whole blood	HPLC-PDA	[139]

In the pharmaceutical field, the availability of validated methods that allow obtaining a high sensitivity and selectivity even in complex matrices is of fundamental importance. This can be further highlighted when the drugs—in either single or association administration—are delivered through formulations that allow the modification of the parameters of PD and PK [145–148].

5. Conclusions

Biologic cross-interactions are important in the determination of many processes that occur in living systems, especially if drug formulations comprise an association of two or more active principles. The simultaneous presence of these compounds can bring to a cross interaction and to a change in PK parameters. Although, especially for new drug formulations, drug research and drug interactions are the first basal step that must be carefully evaluated before pharmaceutical industry production. Many problems encountered in drug association analyses could also be addressed to the quality of the starting raw material used and ineffective of test used for checking the material. In this contest, analytical chemists play a key role in the drug association formulations development, in all steps required for the characterization, quality control, evaluation of pharmacological properties, drug adulteration. Validated procedures allows analytical chemists to obtain accurate and sensitive analyses with extensive linear responses on several drug classes, often using simple, economic and reproducible HPLC methods.

Another finding from this work may be related to the fact that the literature on the analyses of drugs and their associations was examined to provide a useful tool for the immediate use in the laboratory, so that drugs can be exploited according to the specific needs. Unfortunately, it is not possible to indicate which chromatographic column is better, as this would be not only pure speculation, but also free advertising that falls outside the scientific purposes of a review. This is especially in light of the fact that the choice of the column, in addition to the type of analytes to be examined, depends on the matrix (and therefore on interferents), the instrument configuration used (and the chromatographic pumps), the extraction assay and the clean-up procedure. The final choice of column falls on its capability of provide the best performance according to the overall analytical problem, and not just as a function of the analytes.

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