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RECENT TRENDS IN SIMULTANEOUS ESTIMATION OF CO-ADMINISTERED DRUGS

Sanskar Shrivastava* and Varsha Kashaw

Sagar Institute of Pharmaceutical Sciences, Sagar M.P.

***Corresponding Author: Sanskar Shrivastava**

Sagar Institute of Pharmaceutical Sciences, Sagar M.P.

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ABSTRACT

Recently, to study drugs with different physicochemical properties new methods are being studied so as to achieve analytical methods with a high sensitivity and selectivity along with reduction in the time for analysis. This is very significant in the analytical studies involved in the clinical studies. This is especially true when analytical procedures are applied to clinical purposes. Additionally, multi-drug therapy are frequently utilised to treat a variety of disorders so as to sidestep the major side effects involved with usage of high dosage of single medicine. Thus in recent times this has led to elevation in the requirement of techniques enabling rapid analysis of mixed constituents. New tools and techniques are being studied in order accomplish these needs. Due to the intricacy of the matrix the sample preparation and subsequent processing might be time consuming. Not only this but numerous issues arise in matrices, compounds and components while investigating drug association profiles of physical and chemical nature. This review covers methodologies used for the simultaneous estimation of drugs that in the quantitative analysis provides us accuracy and sensitivity.

INTRODUCTION

Developments in the further selective and precise analytical techniques that aids the simultaneous estimation of compounds with a variety of physicochemical properties owing to the growing need for innovative formulations and targeted medicines. Chemically these molecules may belong to the same class or not.[1,2,3] Moreover, several therapeutic classes (such as antibiotics, bronchodilators, mucolytics, anti-inflammatories, and antihistamines) might be purchased that have a minimal risk of major adverse responses when used at modest doses. In recent years, for simultaneous estimation of chemicals there has been an upsurge in the development of innovative methods. In order to establish robust methods for the control of quality of drugs the first step involves the identification of target analytes. This serves as a crucial parameter in the quantification of pharmacokinetics as well as pharmacodynamic characters. For further dose modification therapeutic drug monitoring may play a significant role. A process known as cross-influence may cause alteration in the pharmacokinetics traits of one active ingredient due to co-administration of the other medication which may cause alteration in the dosage as well as therapeutic approach. This may also lead to positive effects like enhanced efficacy, lowered dosage and increased residence duration.[4] The mechanical, crystal, compaction or compression features of a drug may change with regard to some additive like polyvinylpyrrolidone.[5] or hydroxy-propyl-methylcellulose.[6] which aid as release control elements and essentially possess specific properties like drug permeability, mechanical durability and biocompatibility. These additives with their impact on drug release may be regarded as being on par with a "second active compound" with regard to the pharmacokinetic characteristics. These polymers have a significant impact on how the medication is released. An elevated polymer concentration results in the creation of a gelatinous film that regulates the medication distribution and slowly erodes. Drug release rate may be enhanced since modest quantity of the polymer enables more water to enter the matrix. Quality monitoring is essential, particularly when looking for novel natural and synthetic products. It is a crucial weapon in the struggle against medication fraud. While studying the stability of drug the impurities present may also be identified and quantified.

Given the significant incidence and significance of combination of dosages in contemporary therapeutics, developing reliable and accurate analytical processes that can simultaneously identify and quantify many medicines with various chemical structures provides a new challenge to analysts. The processes used for quality control require a few qualities, like being able to be replicated, transferred, affordable, and quick to analyse. Validation should be done in order to acquire data that

may be employed for the process of drug development.[7] Thus for separation process and to achieve procision along with sensitivity.[8,9] in study of simultaneous estimation, modern methodologies are discussed.

Analytical techniques used in simultaneous estimation

1. Spectrophotometric Techniques
- UV/VIS Spectroscopy
- Derivative Spectrophotometry
- IR Spectroscopy
- Mass Spectroscopy
- NMR Spectroscopy

2. Chromatographic techniques
- High performance liquid chromatography (HPLC)
- Thin layer chromatography (TLC)
- High performance liquid chromatography (HPTLC)
- Gas chromatography (GC)
- Ultra-high performance liquid chromatography
- Column chromatography.

3. Hyphenated Techniques
- LC-IR
- LC-MS
- LC-NMR

2. Co-Formulations Analysis of Two Diverse Active Compounds in Drug Associations

Pharmaceutical drug-association analyses' major focus is on preventative, palliative, therapeutic or diagnostic reasons. Along with adhering to pharmacokinetic profiles that are effective as well as secure, the finished produce must convene to the quality criteria. The primary issues with drug association manufacture are covered in this area, particularly as they pertain to medications with therapeutic index that is diminutive because the strength of individual components is not absolutely definite. The concurrent existence of multiple active chemicals that may impose an effect on the stability of a drug products is unruly. Particularly, contaminants that are present are frequently a result of a synthetic process. The contaminants along with products produced as a result of degradation that are present in surplus of a predetermined level must be as per the norms of ICH, identified and measured using approved methods. Drug associations using the quantitative analysis demonstrates labelled dose of active the active ingredient's along with the overall integrity of the product to ensure there are no cross-reacting active principles or products of degradation existing in the formulation. Additionally, co-formulations frequently contain multiple active substances at lower levels than the original formulation. The benefit of doing this is that active chemicals are administered at lowered dosages, which at large quantities could have negative consequences.

In particular, when medications are developed utilising lengthy formulation development methods, analytical assays that can detect more compounds in preparations and link in vivo and in vitro characterisation of novel formulations are very crucial. With regard to the great sensitivity, selectivity, usability, and affordability, spectroscopic based analytical methods are critical in this situation. As recently reported by Walash et al.,[10] spectrofluorimetric techniques are frequently used in this situation, and no interference signals caused by co-formulated medicines are present. Pharmaceutical formulation analysis is also possible using derivative spectrophotometric techniques.[11–25] The primary issue in this instance is how to deal with the overlying peaks phenomenon that appears in a "cumulative" absorbance amount when various signals are captured.

In the UV-Vis spectra quantification of two active ingredients in various formulations is possible and implying the rectification in the spectra in accordance with ratio difference (RD), constant centre (CC), simultaneous equation method, mean centering of ratio spectra (MCR), Q-analysis method/absorption ratio, first-order derivative or area under the curve methods of spectroscopy,[26] This is shown in Tables 1-3. Capillary electrophoresis, high performance liquid chromatography (HPLC), high pressure thin layer chromatography (HPTLC)[27–36], or additional technologies in the formulation of commercial products help us quantify the targeted components and ensure their stability. For dual drug-association analyses in tablets (Table 1), capsules (Table 2), mixes, or other formulations, numerous HPLC techniques have been devised and validated (Table 3). HPLC when coupled with a UV detector is extremely beneficial with high degree of sensitivity and selectivity for the simultaneous determination in pharmaceutical dosage forms. It was particular intriguing when Ibrahim and colleagues conducted research,[53] for determination of rabeprazole sodium and domperidone using third-derivative synchronous fluorescence spectroscopy along with HPLC coupled with fluorescence detection after derivatization with 4-chloro-7-nitrobenzofurazan as fluorescence probe. The disparity in the physicochemical features between the active pharmaceutical components poses another to get the best molecules and/or degradation chemicals recovered.

Table 1: The designed and validated HPLC techniques for dual drug-association evaluations in tablets.

Drug	Instrumentation	Reference
Ilaprazole/domperidone	HPLC-UV-Vis	[39]
Domperidone/lafutidine	HPLC-UV-Vis	[43]
Famotidine/domperidone	HPLC-UV-Vis	[44]
Prulifloxacin/impurities	HPLC-PDA	[52]
Domperidone/pantoprazole	HPLC-UV-Vis	[54]
Omeprazole/domperidone	HPLC-UV-Vis	[57] [59]
Pantoprazole/domperidone	HPLC-UV-Vis	[60] [62]
Rosiglitazone/glimepiride	RP-HPLC-UV-Vis	[64]
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] [72]
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] [83]
Amlodipine besylate/Olmesartan Medoxomil	HPLC-PDA	[84] [85]
Metformin hydrochlor/repaglinide	HPLC-MS/MS	[86] [89]
Irbesartan/hydrochlorothiazide	HPLC-UV-Vis	[90]
Valsartan/amlodipine	HPLC-UV-Vis	[94]
Irbesartan/amlodipine besylate	HPLC-MS/MS	[95] [96]
Adapalene/benzoyl peroxide	HPLC-UV-Vis	[97]
Alogliptin/metformin	UPLC-MS/MS	[98]
Naltrexone/bupropion	HPLC-UV-Vis	[100]
Velpatasvir/sofosbuvir	UPLC-PDA	[101]
Metolazone/spironolactone	HPLC-UV-Vis	[102]

Table 2: The HPLC techniques created and approved for co-formulation analyses of binary drugs in capsules.

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

Table 3: The established and approved HPLC techniques for dual drug-association.

Drugs	Instrumentation	References
Domperidone/rabeprazole	HPLC-UV-Vis	[40]
Domperidone/rabeprazole	HPLC-UV-Vis	[47]
Domperidone/ilaprazole	HPLC-UV-Vis	[48]
Cinnarizine/domperidone	HPLC-UV-Vis	[56]
Domperidone/pantoprazole	HPLC-UV-Vis	[58]
Rabeprazole/domperidone	HPLC-UV-Vis	[59]
Pantoprazole/domperidone	HPLC-UV-Vis	[61] [63]
Rosuvastatin/ezetimibe	HPLC-PDA	[66] [73]
Clindamycin/adapalene	HPLC-UV-Vis	[74]
Rosuvastatin/amlodipine	HPLC-UV-Vis	[75] [76]
Gatifloxacin/prednisolone acetate	HPLC-UV-Vis	[77] [87]
Withaferin a/ Z-Guggul sterone	HPLC-UV-Vis	[88] [92]
Atenolol/nifedipine	HPLC-UV-Vis	[93]

In the lab, the standard solutions of several active chemicals were utilized in predetermined fractions for the preparation of the mixes followed by preparation of calibration curve by plotting the peak signal against the final concentration of the drug (g/mL). The following steps were done as given: weight of the tablets was taken followed by thorough milling. The powdered tablet was taken in a measured amount and was placed into a tiny conical followed by extraction using an specific organic solvent in required ratio. A few millilitres of methanol were used to wash the conical flask. The same flask was used to collect the washings, and the later solvent was used to fill it to capacity. Aliquots were placed into ultimate flasks spanning the practical concentration range.

The best option, notably due to its usability, robustness, affordability, and the lack of need is the HPLC-UV-Vis by highly skilled employees while using it, as the above tables suggest.[26] The HPLC techniques that have been established are forthright, subtle, precise, and adequate in the simultaneous estimation of active chemicals in various formulations. The techniques have been successfully used to research on the chemical stability of drugs and have been validated in terms of limit of detection, linearity, exactness, authenticity, limit of quantification, for each analyte. The approach is also applicable to several further analytical issues, such as pharmaceutical formulation quality control.

In this situation, co-eluted chemicals may pose significant issues, and the method may experience the matrix effect (ME). The pharmaceutical industry is seeing a growing influence of ME. The composition of matrix may pose as a limiting factor in both quantitative analysis and bioanalytical chemistry.[103] In reality, matrices frequently contain various components, that can impact the configuration of the instrument and the functionality of the apparatus. The The variance amongst analytes' MS signals in standard solutions and the components in the biological matrices might be referred to as a ME.[104,105] Variances between standard and biological samples may be caused by the challenge between the element of matrix and the analytes for the mobile and stationary phases which may additionally modify the exactness of technique. There are several ways to assess ME; the two most popular ones are post-column infusion and post-extraction spike. The former is carried out via analysing the response of the instrument by subsequently infusing the analyte after inserting an extract from a sample into the system. The later method analyses the analyte's reaction in a clean solution in contrast to the response of an analyte spiked into a blank matrix sample. The first strategy has a drawback because it the quantitative assessment of the amount of ME attained is not offered; while the later does so. The diluting technique is a fantastic tactic that is frequently used to lessen ME. As a result of less sample components, a tiny amount of injection improves analysis performance. For speeding up the source ionisation process while using the MS equipment, its necessary to optimize the injection volume. Additionally, the dilution process and small amount injection of sample reduce the quantity of fragments that compete for the surface of.[106,107]

Other researchers have concentrated on improving sample preparation to lessen or eliminate matrix impact. The techniques of sample preparation include protein precipitation, liquid-liquid extraction, silica-based solid-phase extraction (SPE), polymeric SPE. The least efficient sample preparation method is protein precipitation since it is unable to sufficiently remove enough plasma constituents, particularly phospholipids, acknowledged to affect the consistency of analyte signal strength in mass spectrometers. In comparison to PPT, cation exchange silica-based solid-phase extraction and reversed-phase silica-based solid-phase extraction produce much lower quantities of phospholipids. The utmost effectual was mixed-mode strong-cation-exchange SPE which give rise to nominal matrix effects from biologic samples and from a variety of polar and nonpolar analytes provide excellent recovery.

3. Co-Formulations Analysis of More Diverse Active Compounds in Drug Associations

The implication of separation techniques are highlighted in some recently published papers.[52,108-116] This is shown in Table 4 (tablets) and Table 5 (mixture). Pharmaceutical formulations like tablet and capsules have the combinations of active pharmaceutical ingredients. The development of the reversed-phase chromatographic separation owing to the extensive diversity of stationary phases that are available accompanied with the robustness of it has generally taken into account as commencement conditions along with aqueous solvents organic ones.

Table 4: The analytical techniques created and approved for co-formulation assessments of several drugs (n3) in tablets.

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

Table 5: The analytical techniques created and approved for co-formulation assessments of multiple drugs (n3) in mixtures and other formulations.

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

It's interesting to note that all publications use typical HPLC columns with internal diameters of 4.6 mm and particle sizes of 5 m, ranging in length from 150-250 cm. These are tremendously affordable configurations in this competition, nonetheless they interrupt the rules of green analytical chemistry since they devour more solvent than other configurations and use solvents that are not entirely environmentally friendly having toxic and long-lasting bioaccumulation effects.[112]

Alternate selections that might be used to comprise the usage of shorter columns or the substitution of conventional solvents with environmentally friendly ones, such as isopropanol, n-propanol, ethanol, acetone which enhance the throughput. The use of nano-LC apparatus, obliges slighter volumes of solvent, is additional possibility that may be offered.

4. Co-Formulations Analysis in Biologic Matrices for Drug Associations

The approaches regulating biologic activities in vivo aid in understanding drug interactions after the co-administration of two medications various biological functions are altered, particularly in metabolic processes. The medications that are taken concurrently are frequently metabolised by the same family metabolizing enzymes cytochromes, primarily CYP3A4. Drug-drug interactions (DDI) are therefore quite likely to occur. The monitoring, pharmacokinetics, bioequivalence, and DDI research, for the simultaneous quantification of active pharmaceutical ingredients in biologic fluids its vital to develop as well as authentic novel method of analysis.

For validating processes applied to traditional formulations HPLC-MS/MS is a superior option for biological matrices despite being scarce and expensive (Tables 6). A sample treatment step is characteristically obligatory in biomatrices before performing an instrumental analysis of xenobiotics, so that the method has lesser interfering substances, the target analytes are separated and the method is more accurate and precise. HPLC-MS/MS combinations allow for the least amount of sample handling are used owing to their sensitivity.[9] The methods of recovery are enhanced by reduction in the pre-analytical procedures, leading to a qualitative as well as quantitative examination of diverse substances resulting from degradation or metabolic processes in addition to active principles, with a corresponding improvement in terms of LODs and/or other metrics LOQs. The suggested methods have been verified for linearity, intra- and inter-day precision, trueness, LOQ, LOD, and reproducibility. They are also easy to use. The described analytical techniques serve as useful instruments for the quick and accurate detection, identification, and quantification of these analytes in biological matrices. This helps evaluate clinical therapy well so that pharmaceutical dosages for the association can be evaluated more effectively. Additionally, these techniques may be used in clinical research on medication combinations, multidrug pharmacokinetics, and interactions studies, as well as therapeutic monitoring of patients receiving multiple drug treatments.

Tables 6 and 7 display papers that take into account HPLC combined with UV-Vis.[117-140] FLD.[118] MS.[141,144] detectors. The chromatographic apparatus can then be used to detect the derivatized products. It is recurrently probable to accomplish with HPLC-FLD setups over MS detectors better analytical performance with regard to their sensitivity.[118] Chromatography, which is tasked with resolving these substances and enabling simultaneous analysis without cross-interference, is crucial in these situations.

Table 6: The analytical techniques created and approved for plasma drug-association analyses.

Drugs	Instrumentation	References
Furprofen/indoprofen/ketoprofen/fenbufen/ flurbiprofen/indomethacin/ibuprofen	HPLC- PDA	[2]
Eperisone chloride/paracetamol	HPLC- PDA	[3]
Metformin/vildagliptin	HPLC-UV-Vis	[69]
Entecavir/tenofovir	HPLC-UV-Vis	[96]
Prulifloxacin/ulifloxacin	HPLC- PDA	[117]
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]
Etodolac/pantoprazole	HPLC-PDA	[125]
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	[130]
Metronidazole/meropenem/ciprofloxacin /linezolid/piperacillin	HPLC- PDA	[132]
Oxytetracycline/tinidazole/esomeprazole	HPLC- PDA	[133]
Acebrophylline/levocetirizine/pranlukast	HPLC- PDA	[135]
Apixabam/dabigatran/rivaroxaban	HPLC- PDA	[136]
Sildenafil/tramadol	HPLC- PDA	[137]
Ketoprofen/carprofen/diclofenac	HPLC- PDA	[139]
Anastrozole/letrozole/exemestane	HPLC- PDA	[140]
Doxorubicin/curcumin	HPLC-MS/MS	[142]
Sofosbuvir/daclatasvir	UPLC-MS/MS	[143]

It is possible to calculate pharmacokinetic parameters like area under the curve (AUC), Tmax (the time at which the Cmax is observed), Cmax (the maximum serum concentration that a drug achieves in a specific compartment), and the elimination rate constant using these analytical methods with high accuracy. The methods that are sensitive and selective are very essential. When the medications are administered via single or combined routes, this might be further emphasised formulations.[145–148] that permit changing the PD and PK characteristics.

5. CONCLUSIONS

The estimation od several developments that occur in biological systems relies on biologic cross-interactions involving two or more active principles. The components alter the pharmacokinetic features by their interactions. In the formulation of the new drugs in the pharmaceutical industry, prior to the manufacturing the research on medication along with their drug interactions are is a very vital factor.

Numerous issues with drug association analysis can also be attributed to the calibre of the usage of raw material along with the efficacy of the tests conducted on the material. For the formulation development analytical chemists are essential, besides to all processes necessary for depiction, quality control, and the assessment of pharmacological characteristics and drug adulteration. Analytical chemists can obtain precise and extensively linear sensitive assays responses on a variety of drug classes by applying validated methodologies, frequently with straightforward, affordable, and repeatable HPLC techniques.

This study provides insights on the analysis of drug accompanied by their associations, which provided a practical device for the lab's immediate usage so as to exploit pharmaceuticals in accordance with the needs of the moment. Inopportunely, its unfeasible to say which column of chromatography is superior because doing so would amount to nothing more than unsupported speculation that is unrelated to the review's scientific goals. The column choice hinge on the matrix, the configuration of the instrument employed along with the analyte type, the extraction test, the chromatographic pumps, and the method of clean up. The eventual decision of the column to be used is a function of the analytes accompanied by the performance of the column category.

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