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Quantification of Pharmaceutical Excipients: An Overview

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ABSTRACT

The quantitative analysis of bulk materials, drug formulations, drug products, impurities, and biological products containing pharmaceuticals and their metabolites is challenging in the field of pharmaceutical research. It is also complicated to choose the best method. Pharmacokinetic studies frequently make use of quantitative or qualitative studies of a drug and its metabolite. Developing a generic product with quantitative equivalence, which increases regulatory flexibility, seems to be the ultimate aim. Knowing the exact components of reference items and their concentrations is extremely helpful when developing generic formulations. The quantitative composition of the dosage forms is kept secret by the innovators. In such a situation, the quantitative formula of the dosage form is being decoded by generic manufacturers through reverse engineering. To quantify them, we need reliable, non-destructive analytical tools. In this article, we covered excipient quantification techniques, analytical data reports, challenges, and applications.

Keywords: Excipients, Quantitative analysis, HPLC, chemometrics, Multivariate curve resolution

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INTRODUCTION

Pharmaceutical industries are constantly improving in terms of drug manufacturing in terms of various dosage forms, and it contains active pharmaceutical ingredients as well as excipients. Excipients are fundamental and crucial parts of pharmaceutical formulations even though they are pharmacologically inactive substances. The importance of excipients, which not only enhance dosage form adherence but also have an impact on the formulation's technology and performance, is frequently overlooked. Excipients are being recognized as more valued than ever by pharmaceutical companies, particularly in the production of solid dosage forms such as capsules and tablets [1]. Solid formulations usually contain a range of excipients in addition to the drug (binders, lubricants, solubilizers, disintegrants, glidants, etc.). The quantity and concentration of active pharmaceutical substances have a crucial role in defining pharmacokinetics and stability of dosage form [2]. Even in small amounts, these inert excipients have the potential to affect the final drug product's characteristics, quality, stability, and/or performance. Furthermore, the effectiveness, quality, and patient safety of the product depend on knowing the exact concentrations of the API and excipients in the final dosage form [3]. As a result, it's crucial to define and thoroughly quantify these excipients along with the drug in the formulation. Many pharmaceutical excipients are insensitive to traditional methods of analysis or require a lengthy development process, making them difficult to quantify. The development of analytical methods that enable non-invasive, non-destructive, and real-time blend uniformity analysis has become a topic of interest in academia and industry. Researchers have investigated the use of such methods as Terahertz spectroscopy (THz) [4], FT-Raman spectroscopy with multivariate curve resolution (MCR) [5], Near-infrared (NIR) spectroscopy, and High-performance liquid chromatography system with UV detector/ Evaporative light scattering detector (ELSD)/Refractive index detector (RID) [6]. Furthermore, recent improvements in chemometric techniques may provide additional tools for quantifying API and excipient component compositions in the final dose form [7].

Pharmaceutical excipients

Excipient, which means "other than," is derived from the Latin word, which also means "to except" [8]. Excipients are compounds other than the active pharmaceutical ingredient (API) that have undergone proper safety evaluation and are purposefully included in a drug delivery system to help with the processing, enhance stability, and improve the overall safety and effectiveness of the active drug, according to the IPEC-International Pharmaceutical Excipients Council [9].

Properties of ideal excipients:

Excipients should be chemically and physically stable throughout the shelf life of the product, chemically and pharmacologically inert, should serve the intended purpose efficiently, acceptable organoleptic characteristics should be economical, should be non-toxic, and non-irritant [10].

Classification of excipients: [11, 12]

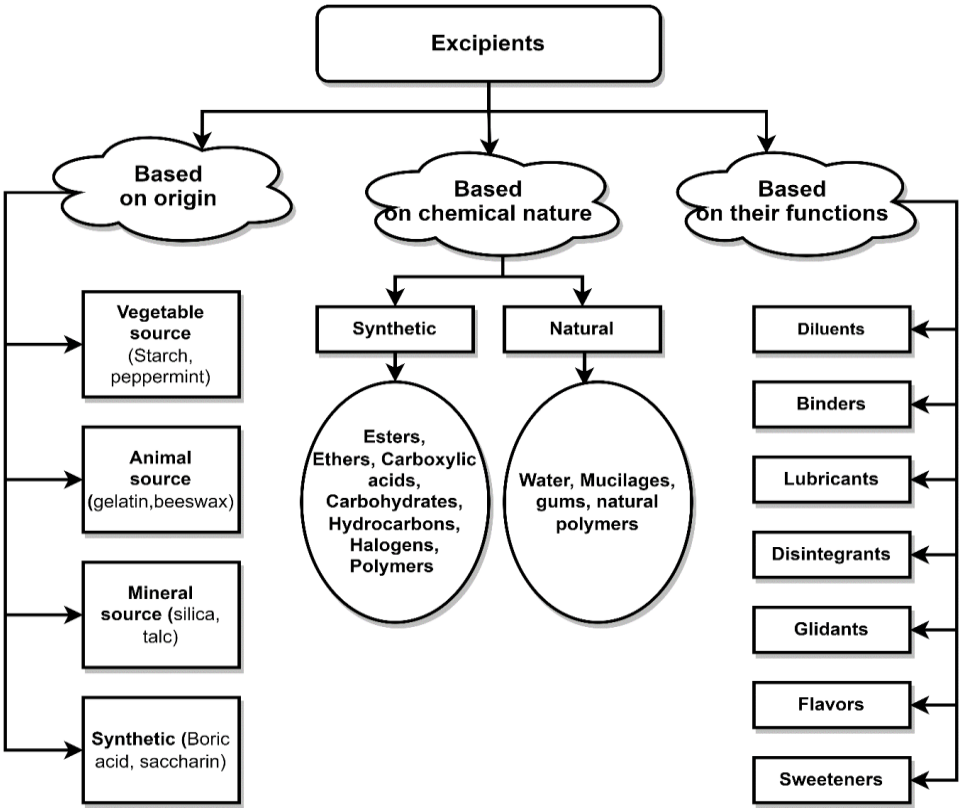

Figure 1: Schematic diagram of classification of pharmaceutical excipients

Qualitative analysis

The subjective investigation is another name for qualitative analysis. It is a branch of science that looks at the analysis of the chemical makeup of a substance present in a sample.

Qualitative analysis techniques

Selective and sensitive analytical methods for Qualitative analysis of analytes are essential for the successful conduction of drug studies. Several methods are useful for the quantification of the sample. The selection of a particular method was driven by suitable authentic standards [13]. Physical techniques and chemical techniques can be used to categorize them widely. Physical qualities like density and light absorption are measured using physical techniques. A few techniques such as atomic emission spectroscopy (AES), X-ray fluorescence (XRF) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and others. In chemical methods, measurement is based on chemical reactions like neutralization, precipitation, etc. Methods include titration (volumetric analysis), gravimetric analysis, and others [14].

FT-IR (Fourier Transform - Infrared Spectroscopy)

In FT-IR, an interferometer composed of a beam splitter, a moving mirror, and a stationary mirror receives infrared light from an infrared light source. Light is divided by the beam splitter into two optical beams, one of which is focused on a stationary mirror and the other on a moving mirror. The signal that emerges from the interferometer is the consequence of these two beams "interfering" with one another because one beam's path is fixed and the other's is continually changing due to the movement of its mirror. The outcome signal is known as an interferogram [15]. A fundamental principle used in quantitative FT-IR spectra is the Bouguer–Beer–Lambert law.

$$A = klc$$

where "A" stands for the sample absorbance as measured at the specified frequency, 'k' stands for the molecular absorptivity at the frequency constant, and 'l' stands for the source beam's pathlength through the sample. The concentration of the sample is 'c', This law states that the concentration of each component determines the relationship between the intensity of the absorption bands in a homogeneous mixture or solution [16].

AES (Atomic emission spectroscopy)

The atoms in the sample are thermally excited and emit light at a specific wavelength during relaxation, which is different for each element [17]. Anyone can measure an analyte's concentration by measuring the emission spectrum, which is a collection of emission lines. The intensity of emission is dependent on the atom or ion density. An element's concentration in an unknown sample can be calculated by plotting a working curve of line intensity against known concentrations of the element obtained from measured intensities of its spectral lines [18].

XRF-X-ray fluorescence spectroscopy:

The identification of elements is facilitated by the use of XRF spectroscopy, an elemental analysis method based on the idea that when activated by an external energy source, individual atoms release x-ray photons of a particular energy or wavelength [19]. Measured fluorescent intensities are converted into analyte concentrations in quantitative XRF analysis [20].

Titrimetry:

Traditional quantitation analytical methods like titration rely on accurately measuring the volume of an analytical standard that is gradually added to the sample to measure the analyte's reaction quantitatively. The titrant is the solution containing the component being titrated, and the titrant is the reagent solution that is added to react stoichiometrically with the analyte. Titrimetric analysis divided into several categories based on the type of reaction that occurs. They include acid-base, redox, complexometric, and precipitation titration, all of which rely on visual end detection [21].

Gravimetry:

This analytical approach involves precipitating the analyte, separating the precipitation, and weighing the ultimate outcome in order to quantify the analyte. Thermogravimetry, physical gravimetry, electron disposition, and precipitative gravimetry are the four different types of gravimetric analysis [22].

Quantification of pharmaceutical excipients:

The purpose of quantification of the pharmaceutical excipients is for developing generic drug products. Pharmaceutical industries will not label the identity and quantity of excipients that are used in the dosage form so, it is helpful in characterizing the competitive drug products in the market [23, 24]. The role of quantification of excipients is to identify the batch-to-batch variations, distinguish the major and minor excipients, and assess the distribution of excipients in the dosage formulation During the manufacture of pharmaceuticals, it will have importance in monitoring the changes [25].

Various analytical techniques are employed for the quantification of excipients

Pharmaceutical industries are becoming more productive in manufacturing drugs and utilizing a number of advanced techniques for the quantification of drugs and excipients.

HPLC- High-performance liquid chromatography

It is an analytical chemistry separation technique quantify the number of components in a mixture and identifying each one. Pumps are used to push a pressured liquid solvent through a stationary phase (column) made up of solid materials while containing the sample mixture. As the components flow out of the column, they separate slightly as a result of each component in the sample interacts with the adsorbent material in column [26]. This method most commonly used in the pharma industry for various identification purposes. A variety of excipients found in pharmaceutical products can be quantified using HPLC and various detectors. For example, quantification of mannitol in the dosage form, as mannitol lacks a UV chromophore, the HPLC analysis required alternative detectors for quantitation in that case Several non-UV absorbing compound detectors plays a key role, such as ELSD, RID, and mass spectrometry (MS), can be used. More flexibility for the examination of the formulation's sieve fractions possibly substantially varied mannitol contents. it could be provided by improved method linearity, coefficient of precision. We can determine the concentrations of active drugs, mannitol, and other excipients by analyzing sieve fractions of formulations.

SEC-Size exclusion chromatography

SEC is a method for separating molecules depending on their molar masses or size; occasionally,

molecular weight and separation are caused by the packing material's pore size[27]. SEC with ELSD can be used to quantify hydroxyl-propyl methylcellulose (HPMC). As HPMC is non-volatile and lacks UV chromophore, we can use ELSD as a detection method. ELSD works on the principle that it detects the non-volatile particles that scatter light. According to the equation Signal Intensity = $\alpha[\text{analyte}]^{\beta}$, the signal intensity of the ELSD detector is directly proportional to the analyte concentration, and the parameters are directly influenced by the particle size, volatility of the analyte, mobile phase flow rate, nature, and temperature of the drift [28].

GC-Gas chromatography:

Gas chromatography (GC) is a popular form of chromatography. For the purpose of separation, the studying substances that may be vaporized without decomposing [29]. This technique helps to determine the excipients from the dosage form and one of the examples is to be used for the quantitation of sodium dodecyl sulfate (SDS) and other alkyl sulfonates in aqueous samples. SDS acts as a wetting agent and emulsifier in pharmaceutical formulations. To increase sensitivity, this technique relies on converting SDS to 1-dodecanol at the GC injection port at a high temperature, then this degradation product will be used to analyze SDS concentration. For that need to prepare the standard solutions of SDS and plot the standard plot between peak area and concentration. The peak area correlates with the amount of SDS in the solution [30].

UV- spectroscopy:

The excipients having chromophores can be directly quantified by using UV absorbance readings. These excipients are fully ionized and separated as ions based on their electrophoretic mobility by capillary electrophoresis. Organic acids like fumaric acid and maleic acid can be detected by using 200nm and can also be quantified [31].

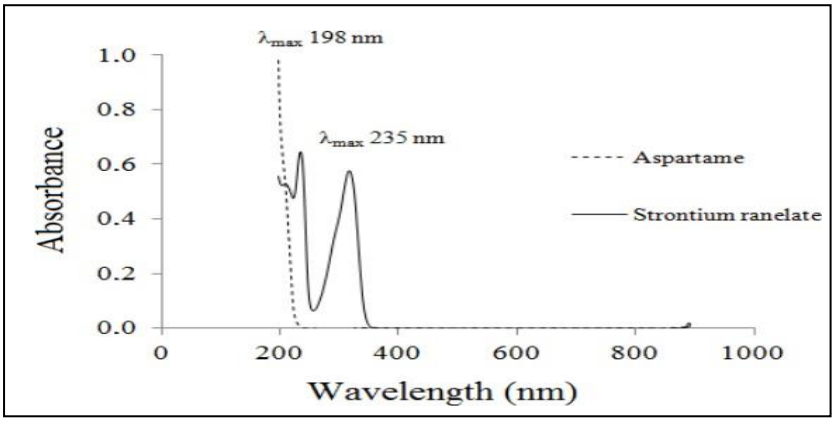

Figure 2: **UV spectrum of strontium ranelate and aspartame** [3]

Carvalho *et al* showed the determination of aspartame using UV-spectroscopy. Capillary zone electrophoresis (CZE) was used to separate aspartame and showed UV absorption at 198nm, also

the determination of strontium ranelate at a wavelength of 235nm. In figure 2, We can observe the drug and aspartame are at particular wavelengths and the amount can be determined by using absorbance values [32].

NIR-Near-infrared spectroscopy:

In way of comparison to what takes place in the mid-infrared frequencies, the near-infrared region of the electromagnetic spectrum corresponds to combination bands, high-energy vibrational transitions and overtones resulting in low-intensity bands that are frequently heavily overlapped and challenging to directly interpret [33]. Due to the intrinsic qualities of this method, which allow for rapid, non-invasive, and non-destructive high throughput analysis with little to no sample requirement, making NIR ideal for real-time assessment when there are many highly correlated predictors, chemometric methods are used to process spectral data in this technique. In this framework, partial least squares regression was the most commonly used algorithm. PLS models can accurately quantify the variables to be predicted [34].

NIR spectral acquisition:

Spectra are obtained from light signals that pass through the optical head and are transferred to the microprocessor via radiofrequency using the aspect plus and process explorer software. After plotting the calibration models for different blend components, use the Online Unscrambler Predictor (OLUP) software to upload them into the process explorer. Process Explorer was connected to the OLUP using specific protocols to obtain in-line quantification of each blend component. The NIR spectra of individual components can be seen in figure 3.

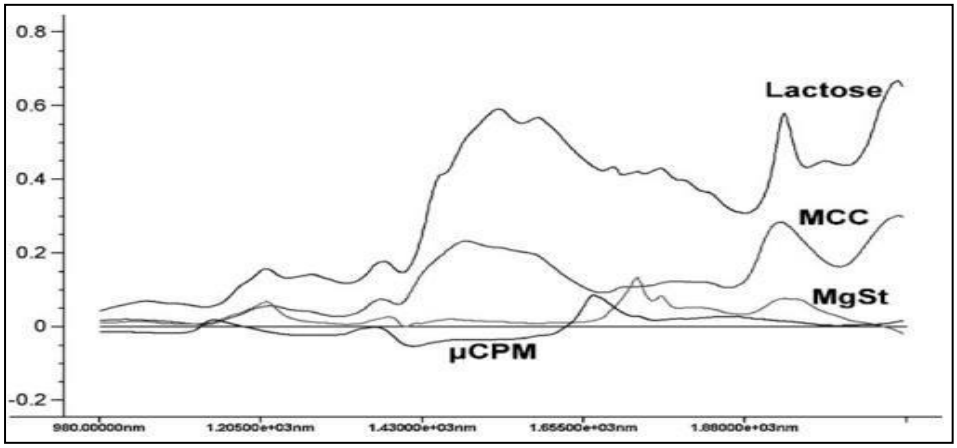

Figure 3: Raw NIR spectrum of the individual blend components [1].

FT-Raman spectroscopy with multivariate curve resolution (MCR)

Raman spectroscopy is a useful tool for identifying and quantifying chemicals, in particular API and excipients in drug analysis. To know about the distribution of excipients in tablet form, there is a need to combine them with an imaging technique called Raman mapping. However, it is

necessary to carry out chemometric approaches for the accurate quantitative determination of API along with its excipients [35].

Multivariate curve resolution (MCR):

It is based on the mathematically decomposing the instrumental response of spectral data to produce pure spectra maps it showing the component distribution in the sample under imaging. The quantification of salicylic acid with excipients was explained by Haslet Eksi-Kocak et al. The bands at 477 cm-1, 1085 cm-1 and 1635 cm-1 for starch, lactose, salicylic acid respectively, were chosen for Raman distribution maps. The Raman intensity change were indicated by the scale bar. In all spectroscopic analyses, the instrumentation was set up to work optimal with pure excipients and APIs.

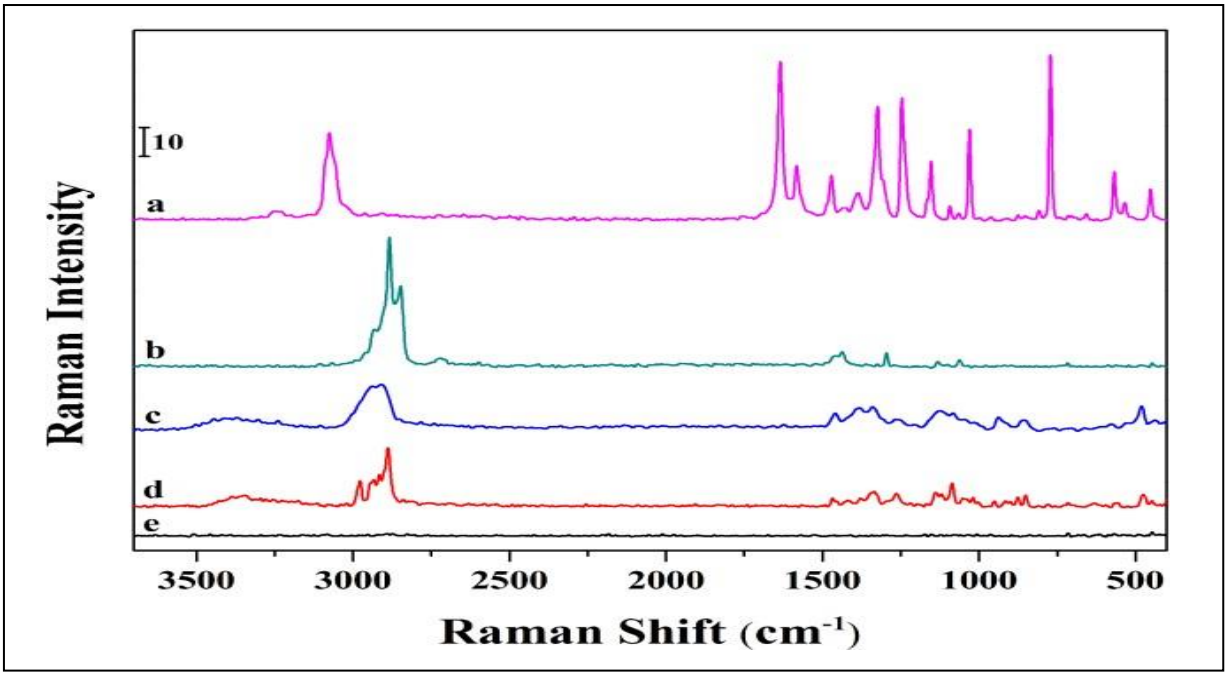

Figure 4: FT-Raman spectra of (a) pure salicylic acid, (b) Mg-stearate, (c) starch, (d) lactose and (e) Aerosil

Raman mapping may be used to implement several PLS models for low-content quantification in powders. PLS (partial least squares discriminant analysis), ICA (independent component analysis), PCA (principal component analysis), cluster analysis, and multivariate curve resolution (MCR) are some methods for analyzing data [36].

RRS-Resonance Rayleigh scattering method:

When the wavelength of Rayleigh scattering is close to the molecular absorption band, RRS is produced. Molecular structure, form, size, state of combination, charge distribution, and other variables are all provided by RRS. RRS is a highly sensitive analytical technique that can be used to determine both inorganic and organic substances [37]. This new analytical technique is crucial for

studying the precise and sensitive quantification of excipients for quantity monitoring, with the best example being the determination of polyvinyl pyrrolidine concentration (PVP). PVP is a water-soluble polymer with excellent cohesion, biocompatibility, thermal stability, and film-forming properties. As a result, determining the PVP concentration is critical. Because the RRS of PVP is weak in solutions, we can use eosin y (EY) as a probe; when the two react, the RRS intensities are greatly increased. The intensity of scattering was proportional to the concentration of PVP.

Figure 5 shows that after forming a binding product, the intensities of PVP and EY are weak, but the RRS is greatly increased [38]

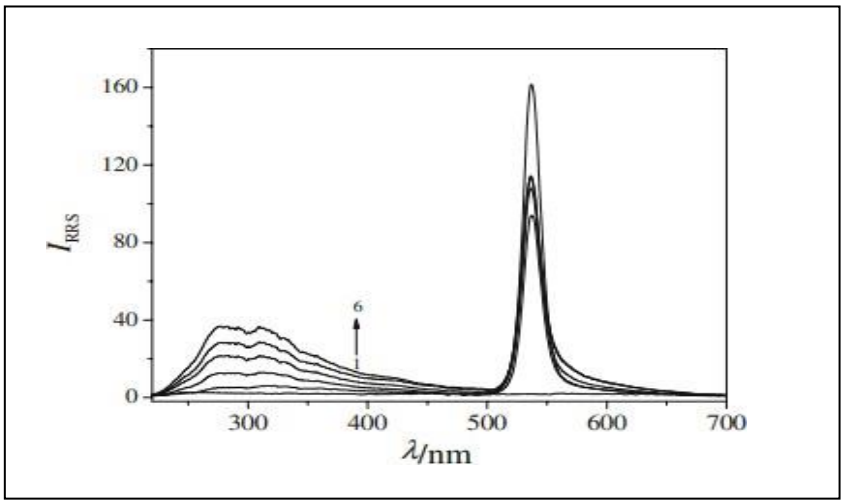

Figure 5: Resonance Rayleigh scattering spectra[38].

THz- Terahertz spectroscopy:

Because of its unique properties, THz technology is used in the pharmaceutical industry. THz waves have the unique ability to penetrate a variety of materials that are normally impervious to other types of electromagnetic radiation [39]. The identification and quantification of polymorphic forms or hydrates of excipients are some of the applications of terahertz in the pharmaceutical industry. The extraction of critical information from THz spectra and the correlation of THz spectra with the concentrations of pharmaceutical excipients are critical steps in this method. Theophylline and excipients quantification was carried out by Huiquan Wu et al. using THz spectroscopy techniques. They did this by mixing tablet powder with polyethylene (PE) powder, compressing the mixture into transparent discs, taking THz spectra, converting the spectra to an optical density (OD), and converting the OD to a ratio between raw sample disc transmission spectra (T sample) and blank disc (TPE) spectra obtained under identical acquisition conditions, as follows:

OD =log10 (T sample/TPE)

Data analysis methods such as the characteristic peak method and multivariate data analysis method were used for quantitative analysis[40]. The characteristic peak method identified a constituent's characteristic peak and correlated the integrated absorbance with tablet concentration. Both PLS and principal component regression (PCR) were used in multivariate data analysis.

FAAS-Flame atomic absorption spectroscopy:

The principle involved in this technique is that ground state metals absorb light at a specific wavelength. By utilizing flame metal ions in a solution are converted to an atomic state. When a correct wavelength of light is supplied, the amount of light absorbed is measured and a reading for concentration can be obtained[41]. It is a very common technique for detecting metals and metalloids and is frequently used to quantify magnesium ions in formulated preparations or alone. It is an expeditious and highly delicate method for the determination of magnesium. Magnesium stearate act as a lubricant in solid dosage forms. As it is used in very low concentrations, its monitoring and controlling of its levels are of paramount importance. In this technique, the linearity of responses can be studied by using magnesium standard solutions with varying concentrations [42]. By plotting the absorbance of each solution versus its magnesium concentration, its determination can be done. We can use magnesium amount to refer to magnesium stearate using the equation i.e., each 591.3 mg magnesium stearate is equivalent to 24.305mg. The main drawback of this technique is it can be used to determine total magnesium from excipient, but cannot differentiate between magnesium coming from talc or magnesium stearate [43].

LIBS-Laser-induced breakdown spectroscopy

It is a type of atomic emission spectroscopy In this spectroscopy a high-energy laser pulse is used as an excitation source. A pulsed laser beam is focused on to sample to form a microplasma. The emission from the excited sample is analyzed through optical emission spectroscopy to infer the elemental composition of the sample[44]. This technique finds its application in the quantitation of lubricant magnesium stearate in tablets. The concentration of magnesium stearate is obtained by forming a simple calibration curve of the intensity (counts) of the magnesium spectral line emitted from the laser-induced plasma using internal standardization to eliminate the matrix effect [45]. In this quantitation, carbon is used as an internal standard as its concentration in the sample will not depend on the lubricant concentration. In figure 6, we can observe the Mg518.36 line and strong carbon line at 496 nm approximately and other diatomic emissions.

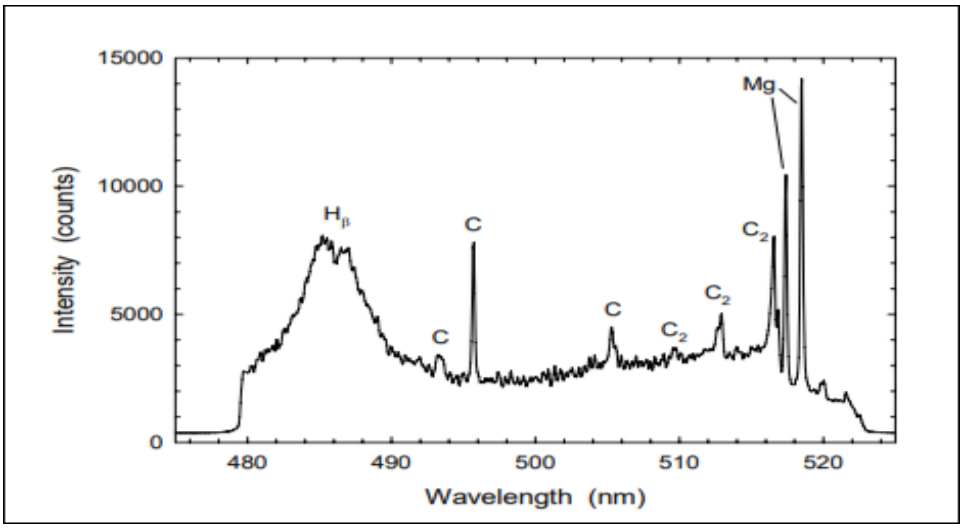

Figure 6: A spectrum of LIBS

Table 1: Analytical method reports based on the quantification of excipients and drugs.

S.No	Excipient /API	Dosage form/Sample	Quantification method	Application/Use	Ref
1	Paracetamol with maize starch, sodium carboxymethyl cellulose and microcrystalline cellulose	Tablets	DSC, FT-IR	Excipients Effect on paracetamol release	46
2	Paracetamol and Hypromellose	Solid sample	DSC, FT-IR, Raman Spectroscopy	Study of Interactions Between API and Excipients	47
3	Aceclofenac with retard tablet excipients	Tablets	DSC, FT-IR	Compatibility studies	48
4	Commonly used excipients	biopharmaceutical products	HPLC	Direct and simultaneous estimation of excipients	49
5	Tetrahydro curcumin (THC)	Bulk drug and formulation	HPLC	Development of sensitive, cost-effective method.	50
6	Clotrimazole	Vaginal gelatin film	HPLC	Quantification of Drug in the gelatin film formulation	51
7	Alcohols and ethylene glycol	Plasma samples	headspace GC	Determination of toxic compounds	52
8	Diethylamine, triethylamine and cyclopropylamine	API	GC	Quantifications of the chemical level in active ingredients	53
9	Amlodipine Besylate and Olmesartan Medoxomil	Binary and ternary mixture of sample	HPLC	Drug-Excipient Compatibility Study	54
10	Formaldehyde	Pharmaceutical Excipient mixture	Headspace GC-FID	Simple and economic GC-FID technique for quantification	55
11	Drug Substance and Excipients	Nano formulations	HPLC-ELSD & UV	Quantification of excipients in nanomedicines	56
12	HPMC and Dodecyl β-D-Maltoside	Nanosuspensions	SEC-ELSD	Simultaneous quantification	57
13	Lactose in drugs	NA	HPLC	Quantification of lactose and lactose free drugs	58
14	Nifidipine and excipients	Matrix tablets	DSC, FT-IR	Quantification of excipients in matrix formulations	59
15	Drug Substance and Excipients	Tablets	NIR-CI	Determination of compositions and distribution of coated and uncoated tablets.	60
16	Polymeric Excipients and Atenolol	Solid dosage forms	DSC, FT-IR, PXRD,	Drug-Excipient Compatibility Study	61
17	Triclosan and Flurbiprofen	Nano-formulation.	DSC, FT-IR, PXRD.	Drug-Excipient Compatibility Study	62
18	Amlodipine and Benazepril	Pure and fixed dose	HPLC	Development and validation	63

		combination			
19	Diclofenac	Tablets	HPLC	Development and validation	64
20	levothyroxine	Tablets	HPLC	Stability indicating validation	65

(Size exclusion chromatography (SEC) with evaporative light scattering detector (ELSD), Near Infrared-Chemical Imaging (NIR-CI), Fourier transform infrared (FTIR) spectroscopy, and powder X-ray diffraction (PXRD)

Chemometrics approach in Quantification of pharmaceutical excipients

In recent years, the majority of research analysis has used chemometrics to understand the differences or variation in the data matrix. Chemometrics is the application of statistical and mathematical approaches to analytical data to enable the maximal collection and extraction of usable information. Supervised methods such as PCR-Principal compound regression, PLS-partial least square, and unsupervised methods such as PCA-Principal compound analysis, and CA-cluster analysis are the two classifications of chemometrics methods. Table 2 reviews the analysis method based on the data from various analytes with excipients collected using chemometrics.

Table 2: Analytical method reports based on chemometrics

S.no	Analyte	Dosage form/ Sample	Quantification method	Chemometrics method	Ref
1	Caffeine anhydrate	Tablets	NIR	PLS	66
2	Atenolol, Amiloride hydrochloride, and Chlorthalidone	Tablets	HPLC	PLS and PCR	67
3	**Pseudoephedrine hydrochloride and Ibuprofen**	Tablets	UV-Visible	PLS	68
4	Acetaminophen and Ascorbic acid	Tablets	UV-Visible	PLS and PCR	69
5	Melatonin and Pyridoxine	Tablets	spectrofluorimetric and spectrophotometric	PLS and PCR	70
6	Amiloride, Propranolol and Dipyridamole	Tablets	**Spectrofluorometric**	PARAFAC	71
7	Meloxicam and its excipients	Tablets	NIR, HPLC	SNV, PLS and PCR	72
8	Antipyrine	Granules	NIR	PCR	73
9	Naproxen and Diflunisal	Suppositories	HPLC	CLS, PCR and PLS	74
10	Drotaverine hydrochloride and Nifuroxazide.	Capsules	UV-Visible	PCR, CLS, and PLS	75
11	β-blockers (Bisoprolol, atenolol, sotalol, metoprolol, carvedilol, propranolol, and nebivolol).	Tablets and capsules	HPLC	GA-PLS, PCR, PLS	76
12	Daphnia magna metabolites	Natural samples	GC-MS	MCR-ALS	77
13	Theophylline, Methylparaben, Diphenhydramine, Guaiphenesin, Propylparaben and Sodium benzoate.	syrup	UV-Visible, HPLC	PLS and PCR	78

14	Selamectin	Topical formulations	NIR	PLS	79
15	Lansoprazole, Amoxicillin and Clarithromycin	Commercial preparation	HPLC	PCR and PLS.	80
16	Miconazole nitrate and Nystatin	Tablets	HPLC, UV-Visible	CLS, PLS, and PCR	81

Standard Normal

Variate (SNV)

Standard Normal

Variate (SNV)

PLS-Partial least square test, PCR- Principal compound regression, PARAFAC-Parallel factor analysis, SNV- Standard normal variance, GA-PLS- Genetic algorithm Partial least square, MCR-ALS- Multivariate curve resolution-alternating least squares)

Challenges and advantages:

It is crucial to incorporate spectroscopic methods and chemometric modelling strategies into quantification since this enables the extraction of crucial data for a product or process's design, monitoring, and management. Pharmaceutical companies use reverse engineering methods to extract formulations from novel products; throughout this process, quantitative excipient information will be crucial to comprehend formulation science, greatly increasing the likelihood of developing a bioequivalent product. While it might be challenging to quantify complicated material in sample preparation and integrations, particularly in bioanalytical, nano-preparation. Excipient quantification has a wide range of applications in the pharmaceutical industry, including studies on the compatibility of drugs and excipients, stability indications of validation, development and validation, and excipients' effects on drug release, among others.

CONCLUSION:

Finally, we came to the conclusion that in order to build a pharmaceutical product that is trustworthy and consistent, it is essential to fully characterize pharmaceutical solids, from the active pharmaceutical ingredient through excipients, physical mixes, and placebo to the final therapeutic product. Excipient quantification requires a high level of expertise as well as equipment. We also suggest various analytical methods for quantifying active and inactive substances with the chemometric, like some other computational approaches leads to improve the quantification methodologies. Using chemometric models may increase study knowledge about excipients and simplify the complex excipient analysis.

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