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A COMPREHENSIVE REVIEW ON COMPATIBILITY STUDIES OF EXCIPIENTS AND ACTIVE PHARMACEUTICAL INGREDIENTS TARGETING THE CENTRAL NERVOUS SYSTEM

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ABSTRACT

The present review article investigates the crucial role of excipients during the manufacturing of pharmaceutical products, with a key focus on compatibility evaluations of active pharmaceutical ingredients and excipients. The compatibility of excipients and active pharmaceutical ingredients plays a significant role in ensuring the highest quality in drug product manufacturing. This is further explored through compatibility assessments, which contribute significantly to the overall comprehensive development of drug product quality. The detailed methodologies of compatibility studies for different active pharmaceutical ingredients and excipients are delved into in the article, utilizing diverse analytical tools including Differential Scanning Calorimetry, Fourier Transform Infrared spectroscopy, High-Performance Liquid Chromatography, Preformulation, Stability indicating methods, and Scanning Electron Microscopy. The results of various case studies on the compatibility between active pharmaceutical ingredients and excipients are compiled in this review article. A wide range of case studies is covered, addressing different aspects of drug stability and compatibility complexities, considering both the active pharmaceutical ingredient and excipients. Additionally, critical factors such as thermal stability, incompatibility reactions, and compatibility challenges associated with various active pharmaceutical ingredients used in

treating central nervous system disorders, along with their respective excipients, were explored. The current review article highlights the challenges encountered in interpreting compatibility data obtained from various analytical instruments. It recognizes the significance of these challenges and provides a comprehensive exploration, making it a valuable reference for researchers in their future research endeavors.

Keywords: Compatibility, Differential Scanning Calorimetry, Fourier Transform Infrared spectroscopy, High-Performance Liquid Chromatography, Preformulation, Stability indicating methods, Scanning Electron Microscopy

INTRODUCTION

Preformulation is essential aspect in guiding the development of both the drug substance and the drug product. An integral component of preformulation involves conducting compatibility studies between the active pharmaceutical ingredient and excipients. It includes examining the physical and chemical characteristics of the drug substance both independently and in conjunction with excipients. Formulating an active pharmaceutical ingredient (API) typically involves blending it with various excipients to improve manufacturability and optimize the drug's capacity to efficiently deliver the prescribed dose **[1]**. The excipients, along with potential impurities within them, have the capacity to interact with drugs, often facilitating the degradation of valuable active pharmaceutical ingredients **[2]**. Incompatibilities denote interactions between a drug and excipients or other active substances, resulting in alterations to the chemical, physical, and therapeutic properties of the pharmaceutical dosage form **[3]**.

To define, comprehend, and control the quality of the final dosage form and its procedural elements, it is essential to select excipients with one or more specific functional roles. The quality of a formulation depends a lot on stability followed by compatibility of drug substance and excipients. These aspects can be viewed as essential factors for adhering to legal standards regarding the identity, strength, purity, and overall quality of drug products **[4]**. Excipients may contain impurities or generate degradation byproducts, which could potentially result in the degradation of the drug substance **[5]**. Examining the compatibility between the drug substance and excipients can be considered as a most crucial step in the development of a drug product. This procedure contributes in securing the stability and efficacy of drug products, as any incompatibility has the potential to affect their safety and effectiveness. Conducting studies on excipient compatibility assists in the selection of suitable components for the

dosage form. It helps define the drug's stability profile, identify degradation products, and comprehend reaction mechanisms **[6]**.

In pharmaceutical formulations, the active pharmaceutical ingredients come into close contact with one or more excipients. Furthermore, in the majority of the formulations, the amount of excipients surpasses that of the active pharmaceutical ingredient, potentially influencing the API's performance in the formulation. This exchange may influence the safety and effectiveness of the medication, contingent on the method of administration. Therefore, a comprehensive grasp of interactions between drug and excipients is essential when selecting appropriate excipients for a given formulation. To achieve this, it is essential to conduct studies on the compatibility of drugs with excipients **[7-11]**.

ANALYTICAL TOOLS FOR ASSESSING COMPATIBILITY BETWEEN ACTIVE PHARMACEUTICAL INGREDIENTS AND EXCIPIENTS [12]

The following flowchart 1 **(Figure 1)** represents various applicable analytical tools for assessing the compatibility between active pharmaceutical ingredients and excipients.

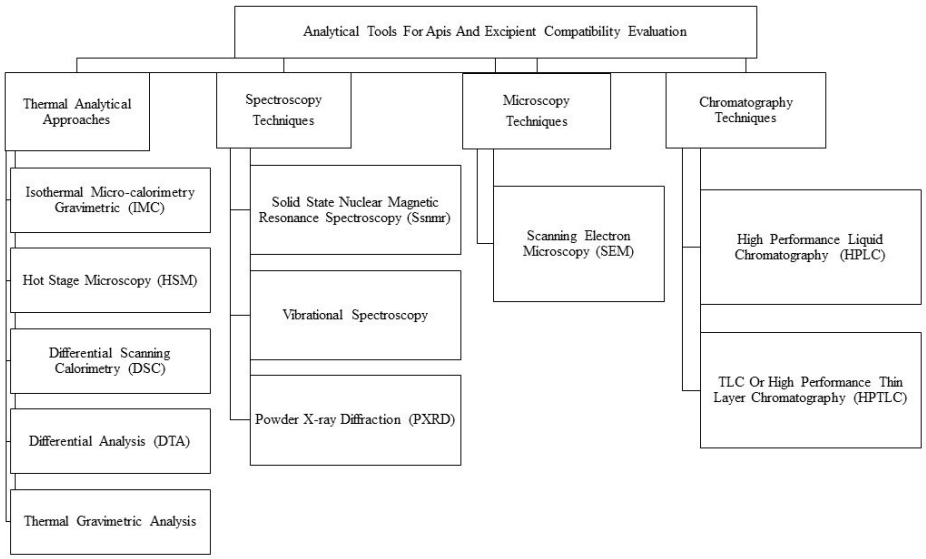

Figure: 1 Analytical Tools for Assessing Compatibility Between Active Pharmaceutical Ingredients and Excipients

Thermal analysis identifies physicochemical incompatibility in compatibility screening studies, offering advantages over traditional methods by providing direct indications aligned with the excipient, reducing the need for extensive sample preparation and saving valuable time **[13]**. Isothermal Micro-calorimetry assesses solid-state pharmaceutical compatibility by measuring minute heat changes, providing meaningful

results without extensive sample preparations and aiding in identifying potential incompatibilities between excipients and APIs. **[14-15]**. Hot Stage Microscopy integrates thermal testing and microscopy for a visual assessment of solid-state interactions, efficiently revealing insights into component dissolution and deterioration not easily discerned by traditional methods like Differential Scanning Calorimetry and Thermogravimetry **[16-19]**. Differential Scanning Calorimetry is a crucial technique for detecting incompatibilities in pharmaceutical formulations. It involves comparing Differential Scanning Calorimetry curves of individual components with those of 1:1 physical blends to reveal potential issues in thermal characteristics. If the elements do not align with each other, the thermal properties of the blends (such as melting point, enthalpy changes, etc.) may appear to correspond to the quantity of elements present **[20-21]**. Differential Thermal Analysis and Differential Scanning Calorimetry stand out as premier analytical techniques for conducting compatibility studies **[22-23]**. Thermogravimetric Analysis serves the dual purpose of determining material structure and evaluating thermal stability, providing crucial insights into weight changes that offer information on composition, oxidative potential, and environmental effects on tested components **[24-26]**. Solid State Nuclear Magnetic Resonance Spectroscopy is an essential and highly selective technique for pharmaceutical solid evaluation, offering insights into chemical relationships, structure, and controlled excipient analysis, recognizing consistency in mixtures, revealing interactions among solid-state pharmaceutical components including active pharmaceutical ingredients and excipients **[27-28]**. Vibrational spectroscopy techniques such as Raman, FTIR, and near IR are essential for evaluating pharmaceutical interactions and characterizing the solid state of APIs, helping identify dehydration, hydrate formation, and morphological changes during processing, providing valuable insights into intermolecular interactions between components **[29-33]**. Powder X-ray Diffraction directly assesses a material's crystal structure, revealing crystalline peaks crucial for dosage form analysis. Incompatibilities during processes like wet granulation can be identified, aiding in detecting changes in API types and polymorphic forms due to moisture presence **[34-35]**. Scanning Electron Microscopy is effective for studying material structures and surfaces, especially for drug additives without chemical or thermal properties. Integration with techniques like DSC, HSM, and FT-IR enhances the classification of incompatible materials **[36]**. Various

chromatographic techniques like HPLC, TLC and HPTLC utilized for compatibility checks during isothermal stress testing, assessing the interaction between pharmaceutical excipients and drugs **[37-39]**.

FORCED DEGRADATION STUDY

Force degradation, a crucial element in establishing the link between drug substance and excipient compatibility, involves subjecting drug ingredients and products to more severe conditions, leading to the generation of byproducts, which when analyzed, enables the assessment of molecule stability **[40]**. These studies are conducted with the main goal is to thoroughly comprehend the pathways of degradation for both drug substance and drug products.

Essentially, studies on forced degradation play a crucial role in creating a degradation profile that mirrors conditions observed in a formal stability study conducted following International Council for Harmonisation guidelines. This approach provides essential insights for pharmaceutical development and ensures compliance with regulatory standards **[41-42]**. The examination of forced degradation can encompass diverse stressed conditions, namely hydrolytic, oxidative, photolytic and thermal as well **[43-47]**.

As previously mentioned, this review article offers detailed insights into the compatibility study of active pharmaceutical ingredients and excipients employed in central nervous system-acting drug treatments. To understand this, it is essential to grasp the concise physiology of the central nervous system, as elucidated in the section below.

OVERVIEW OF THE PHYSIOLOGY OF CENTRAL NERVOUS SYSTEM [48-49]

The nervous system is divided into two primary components: the central nervous system, comprising the brain and spinal cord, and the peripheral nervous system, encompassing all other neural structures. The brain resides within the cranial cavity of the skull, while the spinal cord occupies the vertebral cavity within the vertebral column. A simple diagram representing the neural connections in the central nervous system is presented in the **Figure 2**, given below:

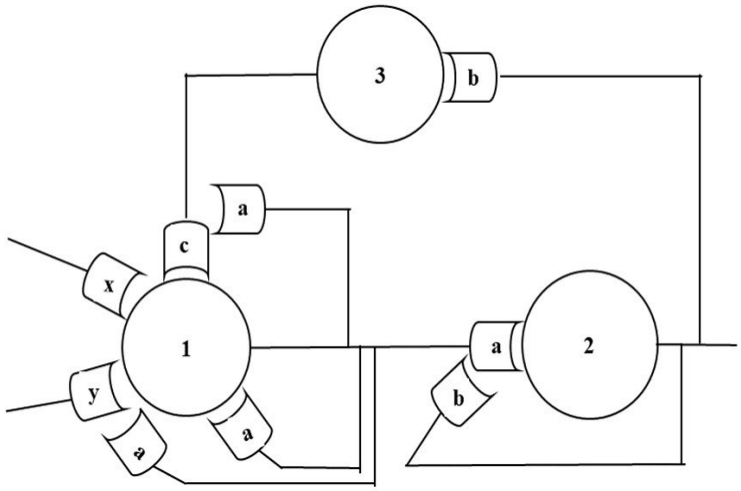

Figure:2 Neural connections in the central nervous system [48-49] (Neurons 1, 2, and 3 release transmitters a, b, and c, respectively, with potential excitatory or inhibitory effects. Neuron 1's boutons connect with neuron 2, itself, and presynaptic terminals of other neurons linked to neuron 1. Additionally, neuron 2 provides feedback to neuron 1 through interneuron 3. The impact of transmitters x and y from other neurons on neuron 1 is also depicted. Despite the simplicity of this network, predicting the effects of drug-induced interference with specific transmitter systems can pose challenges)

Understanding the impact of drugs on brain function is challenging due to complexities such as the intricate neural wiring diagram, involving feedback loops, interneuronal connections, and the influence of glial cells. Predicting the effects of altering neurotransmitter release is difficult, as secondary adaptive reactions, including changes in gene expression, take time to manifest. Clinical benefits often arise from the brain's secondary responses rather than the immediate pharmacodynamic effects of drugs. The blood-brain barrier, crucial in CNS pharmacology, allows or restricts drug penetration based on passive diffusion or transporter-mediated mechanisms. Efflux transporters influence the entry and expulsion of CNS-acting drugs, with individual variations and drug interactions at the transporter level adding further complexity to understanding drug behaviour in the CNS.

CASE STUDIES REPRESENTING COMPATIBILITY STUDIES OF EXCIPIENTS AND ACTIVE PHARMACEUTICAL INGREDIENTS TARGETING THE CENTRAL NERVOUS SYSTEM:

1. Thermal stability and kinetic study of Fluvoxamine stability in binary samples with lactose [50-51]

Fluvoxamine (FLM) is an antidepressant drug categorized as a selective serotonin reuptake inhibitor and is prescribed for the treatment of obsessive or compulsive disorders. In this particular case study, the incompatibility between fluvoxamine and lactose in solid-state mixtures was explored.

Various physicochemical methods, including but not limited to differential scanning calorimetry, Fourier-transform infrared spectroscopy, and mass spectrometry, were employed to assess their compatibility.

Methodology

Differential Scanning Calorimetry Analysis was conducted using a Shimadzu DSC-60 instrument equipped with TA-60 software (version 1.51). Thermal analysis was performed on both fluvoxamine and lactose individually, as well as on a binary mixture of fluvoxamine and lactose (prepared at a 1:1 ratio, w/w) using a tumbling method to ensure uniform blending. Subsequently, Differential Scanning Calorimetry pans containing the prepared samples were subjected to scanning within a temperature range of 25–300°C, employing various heating rates (2.5, 10, and 15 °C/min).

FTIR spectroscopy was employed in the blending of fluvoxamine and lactose at a 1:1 mass ratio. Following the method, 20% (v/w) water was incorporated into each sample. The mixtures were then stored in sealed vials at 70°C for 72 hours. FTIR spectra were initially recorded right after blending and subsequently after specified intervals of storage in an oven. The potassium bromide disc preparation method, utilizing a Bomem MB-100 series instrument, was employed for spectrum acquisition. Data processing of Fourier-transform infrared spectra was carried out using GRAMS/32 version 3.04 software provided.

Mass spectrometry was conducted using the Waters 2695 Quadrupole mass system in positive electron-spray ionization mode.

Result

Differential Scanning Calorimetry (DSC) provided crucial insights into drug-excipient compatibility, offering details on purity, stability, and polymorphic forms of drugs. Analysis of DSC curves for fluvoxamine, lactose, and their combination showed consistent results, confirming compatibility without peaks in the mixture. However, reliance solely on simple DSC thermograms at a single heating rate might mislead formulators about potential incompatibilities. Alternative DSC techniques, like multiple scan methods at varying heating rates, were recommended for a thorough understanding. Furthermore, observed shifts in DSC curves to higher temperatures with increased heating rates emphasized significant influences on temperature ranges and curve shapes, highlighting the need for comprehensive analysis. Kinetic analysis, utilizing methods such as Friedman, Kissinger–Akahira–Sunose, and Flynn–Wall–Ozawa, revealed higher stability of pure fluvoxamine compared to its lactose mixture, indicating the importance of preformulation studies in pharmaceutical development.

Key signals of FLM's C=N stretching and N–H bending at 1624 cm-1 were detected by Fourier-transform infrared spectroscopy, revealing potential interactions between fluvoxamine and lactose after 72 hours at 70°C, underscoring the importance of monitoring molecular changes during storage. Mass spectrometry identified successful condensation products of fluvoxamine with lactose, supported by protonated molecules [M+H]+ of fluvoxamine with an m/z value of 319.0, consistent with reported Maillard type interaction products in a physical mixture with 20% added water stored at 80°C for 24 hours.

Conclusion

Incompatibility between fluvoxamine and lactose was detected through a range of analytical techniques, encompassing Differential Scanning Calorimetry, Fourier-transform infrared, and mass spectrometry. The inadequacy of simple Differential Scanning Calorimetry analysis was evident, with the need for multiple scans revealing elevated activation energies for the pure drug, suggesting possible incompatibility. A cautious recommendation is made to refrain from combining fluvoxamine with lactose in pharmaceutical formulations to enhance drug stability and safety.

2. **Compatibility studies of Donepezil with different excipients by using HPLC and FTIR [52-53]**

Donepezil, a powerful acetylcholinesterase inhibitor, is employed in the treatment of Alzheimer's disease to assist in preserving cognitive functions in patients. Binary blends of Donepezil with excipients are subjected to accelerated temperature storage, and their analysis using HPLC and FTIR reveals potential interactions through altered chromatograms and spectral changes. The study focuses on evaluating the physical and chemical stability of the drug when mixed with excipients, namely is mannitol, microcrystalline cellulose, sodium starch glycolate, Mg-sterate, and talc.

Methodology

Investigations into drug-excipient interactions involved the storage of pure drugs and binary mixtures at 55°C for 20 days, with samples analyzed using HPLC and FTIR techniques.

Donepezil-excipient interactions were assessed through physical powder mixtures of the drug and commonly used excipients for orodispersible tablets. Different ratios, including Donepezil with Mannitol (1:6.4), MCC (1:0.2), SSG (1:0.8), Mg stearate (1:0.2), and talc (1:0.2), were homogeneously mixed, placed in glass vials, and stored at 55°C for 20 days. The samples were subsequently analyzed for related substances using a validated HPLC method. Various analytical validations, including assessments of linearity, accuracy, and precision, were conducted.

For compatibility studies, 100mg of Donepezil was weighed, followed by the addition of 30ml of methanol to a 100ml volumetric flask, which was then shaken for 10 minutes and adjusted to 100ml volume. Sample preparation involved weighing 100mg of Donepezil powder, adding 40ml of methanol to a 100ml volumetric flask, sonicating for 15 minutes, and adjusting the volume to 100ml, after which, in both cases, 1ml of the solution was transferred to another 100ml flask, and the volume was adjusted to the mark using the mobile phase, Methanol: buffer (40:60).

For FTIR analysis, samples were prepared using the potassium bromide pellet method, involving the physical mixing of Donepezil and excipients in different ratios. The resulting mixtures were compressed into pellets and analyzed using a Bruker FT-IR spectrophotometer to detect interactions between the drug and excipients in the wave number region of 4000-500cm^{-1}.

Result

Chromatographic conditions were maintained stably throughout variations in parameters. No immediate interaction between Donepezil and excipients was observed in the analysis, and long-term storage at 55ºC for 20 days indicated no significant interaction, aligning with ICH guidelines for impurities.

In the FT-IR spectra of Donepezil and powder mixtures, no differences were observed, with consistent bands such as C=O (1697) and C-N (1262). The comparison between pure Donepezil and mixed powder spectra showed no changes, even after 20 days at 55°C, suggesting stability.

Conclusion

Donepezil, whether pure or in binary mixtures, remained stable for 20 days at 55°C, showing no changes in peak area, retention time, or additional peaks, confirming its compatibility with examined excipients under specified storage conditions.

3. Assessment of feasibility of maillard reaction between Baclofen and lactose by liquid chromatography and tandem mass spectrometry, application to pre formulation studies [54]

Baclofen, classified as a primary amine, is employed for the therapeutic treatment of spastic movement disorders. This study employs innovative techniques such as HPLC, mass analysis, and FTIR to verify the occurrence of Maillard reactions between the drug and excipients. Simultaneously, it investigates visible spectrophotometry as a less intricate yet valuable method for assessing these reactions in pharmaceutical sciences. The research further introduces a novel stability-indicating HPLC method incorporating an internal standard for the

detection of Maillard reaction products between baclofen and lactose.

Methodology

HPLC analysis was conducted using a Shimadzu system equipped with an auto-injector, system controller, liquid chromatograph, UV–VIS PDA detector, and fraction collector. Samples were injected onto a Hypersil C18-BDS column at ambient temperature using a mobile phase of 13% acetonitrile in a pH-adjusted phosphate buffer. The flow rate was set at 1 mL/min, and detection occurred at 220 nm. Data analysis was performed using Class VP software, and the method was validated for linearity, precision, accuracy, and selectivity with a 3-methyl salicylic acid internal standard.

LC-MS/MS analysis was carried out using a Shimadzu system equipped with a SIL-10AD VP auto-injector, SCL-10A VP system controller, LC10ADVP liquid chromatograph, and DGU-12A degasser. Samples, introduced through a C18 Gemini column, underwent elution with 97% solvent A (0.1% formic acid in water) and 3% solvent B (0.1% formic acid, 90% acetonitrile, 5% methanol, and 5% water). Mass spectrometric detection employed an Applied Biosystems API 2000 triple quadrupole mass spectrometer in positive ion mode, operating in the MRM mode for high selectivity and sensitivity. System settings and data acquisition were managed using Applied Biosystems Analyst version 1.4.1 software.

The formation of brown polymers in Maillard reaction samples was spectrophotometrically monitored using a Spectra Count Packard plate reader. The optical density (OD) at 490 nm was recorded with a Nunc® 96-well-plate.

Infrared spectra were recorded on a Bomem MB100 spectrometer (Bomem, Quebec, Canada), in the range of 400–4,000 cm−1, using KBr disks. The resolution was 4 cm−1, and there were 37 scans/min. The spectrum was a mean of ten consecutive scans on the same sample. Processing of the FTIR data was performed using GRAMS/32 version 3.04.

The baclofen–lactose adduct mixture was prepared by dissolving 0.5 g baclofen and 2.5 g lactose monohydrate in 50 mL of USP borate buffer (0.1 M, pH=9.2) with stirring and ultrasound, adjusted to 25 mM ionic strength, followed by reflux at 60°C for 12 hours and overnight drying. The resulting mixture, dissolved in the mobile phase at 1 mg/mL concentration, underwent analysis using reversed-phase chromatography and LC-MS/MS. Degradation products were generated by heating samples at 90°C (solid) and 60°C (liquid) for 24 and 72 hours, respectively.

Baclofen and lactose, in anhydrous or monohydrate forms, were mixed at 1:1, 1:5, and 1:10 w/w ratios, granulated and

compressed into tablets. After storage in silica-gel-containing desiccators for 10 days, tablets were transferred to sealed containers within silica gel chambers, subjected to temperature variations (25-60°C) and near-zero humidity for 6 months. Analysis involved HPLC DAD, LC-MS/MS, FTIR, and spectrophotometry at 490 nm to assess brown color intensity.

Commercial tablets and screenings were evaluated for solid-state drug-excipient interactions using a modified Serajuddin method, where drug powders with 20% water were incubated at 95°C for 12 hours in sealed glass vials, excluding lactose in controls. HPLC analysis determined remaining drug, while spectrophotometry measured brown color at 490 nm. Screening assessed lactose types, water addition, and magnesium stearate impact, with mixtures analyzed for remaining baclofen, Maillard reaction adducts, and brown color formation in duplicate experiments. Lactose presence in formulations was evaluated per the British Pharmacopoeia by heating lactose (0.25 mg equivalent) with ammonia and water, confirmed by the development of a red color. Tablets from three brands were pulverized, assayed following USP guidelines, and subjected to 24-hour incubation at 95°C for analysis.

Result

The newly developed HPLC method, featuring a unique internal standard, exhibited selectivity, linearity, repeatability, accuracy, and intermediate precision, qualifying it as a stability-indicating technique. HPLC analysis revealed the presence of early-stage Maillard reaction products or an unknown-1 peak in binary/tertiary mixtures of baclofen and lactose, along with magnesium stearate, observed consistently in solid-state formulations (granules and tablets) from various brands, indicating incompatibility due to the Maillard reaction between lactose, a reducing sugar, and baclofen, an amine-containing compound.

Tandem mass spectrometry analysis revealed the occurrence of the Maillard reaction in early-stage Maillard reaction products, showcasing the transformation of baclofen and lactose (in both monohydrate and anhydrous forms). Mass spectrometry had been employed by various researchers to identify condensation products of metoclopramide, amlodipine, and hydrochlorothiazide in a similar fashion. The primary influences on the Maillard reaction in formulated tablets and granules were determined to be physical contact and moisture content, respectively.

FTIR analysis verified the generation of imine in the heated blends. The pivotal aspect of the Maillard reaction's incidence was the progression of brown color development, aligning with contemporary

methodologies employed in this investigation.

Conclusion

The reliability of stability indication by the HPLC technique, featuring a unique internal standard, was demonstrated, while the Maillard reaction between baclofen and lactose was detected by tandem mass spectrometry, cautioning in formulations and emphasizing the need to avoid lactose in baclofen formulations to ensure drug safety, necessitating further research to thoroughly assess the safety profile of Maillard reaction products.

4. **Drug-excipient interactions of Seproxetine maleate hemi-hydrate: isothermal stress methods [55]**

The initial formulation of Seproxetine maleate hemi-hydrate included pregelatinized starch, allowing the creation of gelatin capsule dosage forms at 1 and 20 mg of the free base, intended for storage at temperatures of 25°C and 40°C. Stability at 40°C or 50°C for one month was demonstrated in earlier trials, yet subsequent investigation revealed an increased presence of 1,4-adduct in capsules containing pregelatinized starch at 25°C and 40°C. Isothermal stress assessments on lactose, starch, and talc were conducted to understand this phenomenon and explore potential reformulation options by examining the solid-state reactivity of Seproxetine maleate hemi-hydrate.

Methodology

For isothermal stress testing, 12g batches with 2.2% drug content were prepared, equivalent to a 5mg formulation between the original 1mg and 20mg capsules. Samples, including excipients, were sealed in amber glass containers and stored at 40°C and 50°C. After one, two, or four weeks, individual containers were analyzed for water content using Karl Fisher analysis.

For the analysis of 5 and 20 mg formulations, the contents of one capsule were transferred to a 10 mL vial, and 3 mL (5 mg) or 10 mL (20 mg) of mobile phase was added, followed by capping, shaking, and filtration. The 1 mg formulation involved four capsules in a 10 mL vial with 5 mL acetonitrile, followed by filtration, evaporation, reconstitution, and a second filtration. Two replicates were used for 5 mg, and six for 1 mg and 20 mg formulations in the study. Degradation products were identified through solution storage experiments, storing solutions for two to four weeks in pH 8 buffer, 0.1 N HCl, or pH-adjusted water.

The samples were analyzed by HPLC using a reversed-phase system with UV detection at 215 nm. The mobile phase comprised 40% acetonitrile and 60% triethylamine buffer. These conditions effectively separated process intermediates, formulation components, and degradation products from seproxetine. Additionally, no

interfering peaks were observed from excipients stored at 65°C for two weeks, and quantification of individual degradation products was accomplished using the highllow approach.

Result

Under mild alkaline conditions (pH 8 at 40°C for a month), a significant 1,4-adduct peak was shown in HPLC analysis, while no other impurities increased. Optimal adduct formation in pH-adjusted water (40°C for two weeks) occurred at pH 5.5 to 8.5, with increased fumaric acid indicating an equilibrium with maleic acid. Storage in acidic conditions yielded distinct degradation impurities. In additional experiments, a reference sample of the 1,4-adduct was stored in pH-adjusted water at either room temperature or 40°C for 2 weeks, demonstrating the stability of this adduct with no observed reverse degradation to SMH or maleic acid.

Stability tests at 40°C or 50°C confirmed bulk material stability, but SMH capsules (1 and 20 mg) in a PGS formulation at 25°C and 40°C showed increased 1,4-adduct levels. Three-month storage revealed consistent differences between total related substances and 1,4-adduct, indicating a single reaction mechanism. Despite minor degradation in 20 mg capsules at room temperature, processing factors were considered insignificant. Accelerated 1,4-adduct formation at higher temperatures, with a defined reaction mechanism, supported isothermal stress testing.

During storage, PGS exhibited a slight decrease in water content, likely due to a weakened aluminum cap seal. Reduced starch water content improved stability, with the identified degradation product being the 1,4-adduct. Talc-SMH mixtures produced an amide degradation product. In drug-lactose mixtures, the Maillard reaction causing yellow discoloration after a week remained unidentified.

Initiated by a solid-state interaction between SMH and PGS, forming an exclusive Michael addition adduct, the study explored alternative excipients, revealing a complex process with additional interaction products. Data specific to 1,4-adduct formation in starch-based excipients supported extrapolation to room temperature. Talc-drug interaction data suggested a threshold reaction temperature at 40°C. Lactose data indicated a temperature-dependent leveling off of Maillard product, offering insights into excipient selection and storage conditions.

Conclusion

This investigation unveils three distinct solid-state reactions involving SMH and various excipients. PGS and PGS-D induce a Michael addition reaction, which is less effective in dried material, and temperature equivalences are provided. Talc prompts an amide formation reaction, with unclear

kinetics or a threshold temperature around 40°C, crucial for predicting its occurrence at room temperature. Lactose initiates an exclusive Maillard reaction, with a temperature-dependent equilibrium indicative of a drug-impurity reaction. The findings underscore the importance of avoiding reliance on a single isothermal stress condition, emphasizing the need for a thoughtful excipient selection process based on the drug's solid-state reactivity and the influence of different reactions over the projected shelf life.

5. Solid-state characterization and pharmaceutical compatibility between citalopram and excipients using thermal and non-thermal techniques [56]

Citalopram hydrobromide (CIT) belongs to the antidepressant category known as selective serotonin reuptake inhibitors (SSRIs). The assessment of interactions between drugs and excipients has been conducted using Differential Scanning Calorimetry (DSC), coupled with techniques such as powder X-ray diffraction (PXRD) and solid-state nuclear magnetic resonance (SSNMR). This study aimed to investigate the interactions between the antidepressant citalopram hydrobromide and commonly used excipients, including lactose monohydrate, sodium croscarmellose, hydroxypropyl-methylcellulose, magnesium stearate, microcrystalline cellulose (MC), and starch in binary combinations.

Methodology

The citalopram (CIT) utilized in this investigation was a commercially available product obtained from a pharmacy. To create binary mixtures (BM), the standard inactive components found in CIT tablets were employed: lactose monohydrate (LM), sodium croscarmellose (CRSC), hydroxypropylmethylcellulose (HPMC), magnesium stearate (MS), microcrystalline cellulose (MC), and starch. The binary mixtures of CIT with each chosen excipient were formulated in a 1:1 (w:w) ratio through mixing.

Differential scanning calorimetry and thermogravimetry were performed using a Mettler–Toledo TGA/DSC 1 under a dynamic nitrogen atmosphere. The samples, weighing 5.00 ± 0.03 mg, were analyzed with a heating rate of 10 C min-1 from 25 to 600 C.

Powder X-ray diffraction data were obtained using a Shimadzu XRD-7000 diffractometer with Cu Kα radiation. Scans covered 4–70 (2θ) at a step size of 0.01 (2θ), utilizing a spinning motion of 30 cycles per minute to reduce rugosity effects. Lattice parameters were determined through Rietveld analysis.

Proton-decoupled 13C solid-state NMR spectra were obtained on a Bruker Avance DRX 400 NMR spectrometer using a 4-mm MAS probe. The cross-polarization pulse

sequence employed standard parameters, including a 90-pulse width of 4 μs, a spin lock time of 5000 μs, and a recycle delay of 4.0 s. Adamantane at 29.5 ppm served as the reference.

Result

CIT's thermal stability up to 230°C was demonstrated, as indicated by TG/DTG curves. The two-stage decomposition occurred between 231°C and 430°C. The melting point at 187°C was confirmed by the DSC curve, followed by thermal decomposition at approximately 230°C. The utility of DSC in detecting interactions between pharmaceutical ingredients was highlighted, emphasizing the importance of analyzing melting peaks for potential incompatibility in binary mixtures. Minor changes in drug melting peaks were suggested to signify reduced purity due to component mixing.

The DSC data for various binary mixtures (CIT–starch, CIT–CRSC, CIT–MC, CIT–MS, and CIT–HPMC) suggested no significant interaction, as evidenced by the consistent CIT melting peak and T-onset even in the presence of excipients. Thermogravimetric analysis of CIT–LM revealed decomposition starting at 230°C, coinciding with the melting phase, providing additional insights into potential interaction.

The DSC and TG/DTG curves revealed that LM underwent dehydration at 133–177 °C, followed by CIT melting and LM melting/decomposition. The a-lactose to b-lactose crystalline transition's exothermic event in Figure 4a was concealed by the overlapping CIT fusion event. This suggested that changes in the thermal profile of the CIT–LM mixture signified interactions between components, not just mixing-induced alterations. The thermal curves of binary mixtures essentially overlaid CIT and excipients' isolated curves, indicating the absence of incompatibility between these components, even in the CIT–LM case.

Utilizing PXRD, SSNMR, and DSC, the thermal interactions of binary mixtures with CIT were investigated, focusing on their impact on physical and chemical stability. The analysis, including Riveted assessment, confirmed CIT's crystalline structure under a monoclinic P1 211 space group. PXRD patterns for CIT–starch, CIT–MC, CIT–MS, and CIT–HPMC indicated well-crystallized material with no evident interactions. Notably, CIT–LM exhibited increased peak intensity without altering the crystalline structure, suggesting a distinct behavior in this mixture.

The assignment of CIT in the SSNMR spectrum involved computational predictions and comparison with previously reported spectra. The 13C NMR spectrum

confirmed CIT's structure with specific signals for aromatic, nitrile, benzyl ether, and sp3 carbons. This analysis indicated no significant evidence of chemical interaction between components in the binary mixtures, as the observed changes were smaller than 1 ppm, the typical line width in solid-sample NMR spectra.

Conclusion

The DSC results reveal the absence of interactions between CIT and the evaluated excipients. PXRD demonstrates unaltered CIT crystallinity in the mixtures. Spectra obtained at 27°C show no interactions between the components. These findings hold significance for the development of new CIT formulations incorporating the tested excipients.

6. Analytical study proving alprazolam degradation to its main impurity Triazolaminoquinoleine through maillard reaction [57-58]

Alprazolam, belonging to the 1,4-benzodiazepine class, is utilized for the therapeutic management of anxiety disorders and depression due to its notable potency in affecting the central nervous system.

Methodology

LC methods, both quantitative and qualitative, were executed using a previously validated HPLC method. This method, previously published, allowed simultaneous determination of alprazolam and its impurity, triazolaminoquinoleine. Baseline separation in under 3 minutes was achieved. Isocratic conditions at pH=7.0 with a mobile phase of buffer A/acetonitrile 43:57 (v/v) were employed, and UV detection occurred at 234 nm. Standards and samples were prepared with a target concentration of 0.04 mg alprazolam/mL using a solvent solution (SS) of solution A/acetonitrile (70:30, v/v). Solution A, a 25 mM KH_2PO_4 buffer adjusted to pH 7.0 with KOH, was utilized.

LC methods, utilizing an Agilent 1100 LC system, were employed to monitor the model reaction. Chromatographic conditions included a C18 Ascentis Express 150×2.1 mm, 2.7 µm column at 60 °C. The mobile phase consisted of buffer A/acetonitrile, with a gradient elution program. UV detection occurred at 234nnm for the initial 15 min and at 430 nm until the analysis's completion, utilizing a 20 µl injection volume.

Standard solutions and sample preparation involved using a 70:30 (v/v) mixture of solution A and acetonitrile, where solution A comprised 25 mM acetic acid adjusted to pH 4.0 with 2 M ammonium solution.

Nuclear magnetic resonance analysis was performed on a spectrometer at 298 K in $CDCl_3$, with 1H and 13C spectra acquired. Proton shifts were referenced to TMS at 0 ppm, and carbon shifts to $CDCl_3$ at 77 ppm.

FT-IR analysis on the isolated compound used a Perkin Elmer Spectrum 2000 spectrometer, with data acquisition spanning 4,000 cm−1 to 200 cm−1. Two percent (w/w) pressed discs, employing KBr as a transparent material, were prepared for examination.

UV-VIS spectrophotometric analysis measured brown color development in degraded samples. Samples were prepared by dissolving weighed material in DMSO, sonicating, and filtering before measurement. Weight adjustments were made based on triazolaminoquinoleine content. A calibration curve for the model reaction was established using a stock solution of the analytical standard. The concentration levels ranged from 28.0 to 84.0 µg/mL, measured at 390 nm after dilutions and filtration. A calibration curve for the model's reaction was established using a stock solution of the analytical standard. Dilutions covered a range from 50% to 150%, and concentrations ranged from 28.0 to 84.0 µg/mL, measured at 390 nm. Weighing 25.0 mg of the sample, dissolve it in acetone, and after sonication, filter a 0.5-mL aliquot to a final volume of 5 mL using 0.45 µm nylon filters for reaction mixture quantification.

pH measurements were performed using pH meter on 268.0 mg powder dissolved in milli-Q water, filtered with 0.45 µm nylon filters post-sonication.

Result

Alprazolam and triazolaminoquinoleine were efficiently determined in under 3 minutes using the HPLC method with UV detection. Collaborative triazolaminoquinoleine generation induced by excipients, particularly carbohydrates, with a role played by moisture content, was systematically studied. Each excipient was systematically removed from a pharmaceutical formulation, creating synthetic combinations with alprazolam in a 1:1 (p/p) ratio approach, revealing crucial insights. Notably, the elimination of aluminum hydroxide decreased alprazolam content and increased triazol-aminoquinoleine generation, while lactose removal halted triazol-aminoquinoleine and alprazolam degradation. Sodium docusate, magnesium stearate, and sodium benzoate, sharing a carboxylic moiety, were found to reduce impurity generation, suggesting a catalytic role in degradation. This method efficiently assessed the individual excipient impact on drug stability.

The observed increase in impurity formation upon removing aluminum hydroxide was attributed to the hindered generation of alprazolam due to the excipient's basic pH. Post-degradation, all samples turned brown, except those lacking lactose. Absorbance measurements at 430 nm revealed a strong correlation (r=0.982) between triazolaminoquinoleine content and sample

absorbance, suggesting that lactose may be crucial in both brown color development and triazolaminoquinoleine generation.

pH changes during alprazolam degradation were monitored, revealing a correlation with the linear regression model, suggesting a chemical reaction involving alprazolam ring opening with lactose, leading to triazolaminoquinoleine generation via a Maillard reaction. Challenges of detecting unstable Maillard intermediates were addressed by adding o-phenylenediamine to the reaction mixture for stability.

The study aimed to confirm the ability of alprazolam, under degradation conditions, to form a Schiff base by targeting the electrophilic center of an aldehyde. A model using p-nitrobenzaldehyde as a reagent provided stable intermediates, and the resulting reaction mixture was analyzed with HPLC and LC/MS to obtain structural information on the new compounds.

The reaction mixture (103.4 mg) underwent washing with a 70:30 water/acetonitrile mixture, yielding 38.2 mg with over 99% HPLC-UV purity. The isolated compound, free from interference, was analyzed using proton and carbon NMR, revealing its structure. The NMR spectra of the degradation product closely resembled triazolaminoquinoline, confirming imine generation. Characterization included UV, IR, and MS analysis, with the compound used as an analytical standard. HPLC-UV determined a 40.3% (w/w) content compared to the initial alprazolam, while mass balances showed 100% for all reaction species, providing a comprehensive understanding of the reaction pathway.

Lactose, a tablet diluent in pharmaceutical formulations, was studied for possible replacement with excipients like mannitol, sorbitol, alveosucre, and calcium carbonate. Synthetic mixtures were subjected to heat treatment, revealing improved API stability and reduced impurity generation with nonreducing sugars, particularly calcium carbonate. These findings suggest potential enhancements in the formulation by substituting lactose with selected excipients.

Conclusion

An unforeseen Maillard reaction alters the structure of alprazolam, impeding its recovery through a structural rearrangement. The primary degradation product, Triazolaminoquinoleine, is notably affected by reducing carbohydrate excipients, with lactose identified as the primary contributor to active degradation. Substituting lactose with calcium carbonate or a comparable excipient in the manufacturing process of alprazolam presents a viable solution to enhance stability. These findings provide valuable insights for optimizing pharmaceutical product design.

CONCLUSION

This review underscores the significance of such studies, especially when leveraging

modern analytical techniques, to reveal incompatibilities and gain insights into the chemical and physical stability of diverse drug formulations. The research highlighted in this review utilizes an array of analytical tools, including DSC, FTIR, mass spectrometry, HPLC, among others, to probe the interactions between various drugs and excipients. The findings underscore the crucial importance of meticulously selecting excipients to mitigate incompatibility issues during both production and storage, ultimately ensuring the effectiveness and safety of pharmaceutical formulations.

ABBREVIATION

Doxepin, Differential Scanning Calorimetry (DSC)

Fourier Transform Infrared (FTIR) spectroscopy

High-Performance Liquid Chromatography (HPLC)

Scanning Electron Microscopy (SEM)

Active pharmaceutical ingredients (API)

Isothermal stress testing (IST)

Fluvoxamine (FLM)

Microcrystalline cellulose (MCC)

Sodium starch glycolate (SSG)

Magnesium stearate (Mg stearate)

Retention time (Rt)

Pregelatinized starch (PGS)

Seproxetine maleate hemi-hydrate (SMH)

Tricyclic antidepressants (TCAs)

Kissinger–Akahira–Sunose (KAS)

Flynn–Wall–Ozawa (FWO)

Citalopram hydrobromide (CIT)

Selective serotonin reuptake inhibitors (SSRIs).

Powder X-ray diffraction (PXRD)

Solid-state nuclear magnetic resonance (SSNMR)

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