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Advancements in Novel Drug Delivery Systems: Techniques for Pre and Post Formulation Analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Novel drug delivery systems (NDDS) are revolutionizing treatment by leveraging progressive technologies to deliver drugs precisely to their targets within the body. This targeted approach enhances therapeutic efficacy while minimizing unwanted side effects. This review delves into the various techniques employed for developing and characterizing NDDS. We focus on the critical role of characterization, encompassing both pre- and post-formulation stages. Pre-formulation techniques explored include physicochemical properties (melting point, solubility, etc.)

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spectroscopic analysis (UV, FTIR), thermal analysis (DSC, TGA), and powder characterization (XRD, polarized microscopy). In addition, post-formulation methods such as NMR spectrometry, atomic force microscopy, and in vitro drug release investigations are covered. By comprehensively characterizing these systems, researchers can optimize their design and formulation, ultimately leading to improved patient outcomes and encouraging improvements in the study and development of pharmaceuticals.

Keywords: Novel drug delivery systems; advanced drug delivery; physicochemical properties; nanomedicine; characterization techniques.

1. INTRODUCTION

Novel drug delivery systems (NDDS) offer advantages over traditional dosage forms, such as first-pass action, large doses, poor availability, instability, and rapid release of pharmaceutical items. NDDS aims to provide continuous, predictable kinetics for medication distribution into the bloodstream, potentially reducing drug-related adverse effects, enhancing patient compliance, and reducing overall medication amount. These systems, including liposomes, nanoparticles, micelles, and hydrogels, offer a wide range of options for drug delivery optimization. Liposomes encapsulate drugs and target specific cells or tissues, while nanoparticles improve drug solubility and stability. NDDS has the potential to revolutionize drug delivery, leading to more effective treatments with reduced side effects [1].

Pre- and post-formulation studies are essential in developing pharmaceutical products to ensure the final product's safety, efficacy, and stability. These studies help identify potential potential issues that may arise during manufacturing or storage, allowing for adjustments to be made early in the development process. By conducting these studies, pharmaceutical companies can optimize their formulations to meet regulatory requirements and ensure that the final product will be safe and effective for patients. Additionally, pre- and post-formulation studies also help to reduce the risk of product recalls and ensure consistent quality throughout the manufacturing process [2].

Understanding the system's physical and chemical characteristics both before and after formulation will help to ensure the new drug delivery system's stability and effectiveness. This comprehensive analysis helps researchers optimize the formulation for targeted drug delivery and maximize therapeutic outcomes. By studying the drug delivery system both before and after formulation, researchers can identify any potential issues that may arise during storage or administration. This allows for adjustments to be made to improve the overall performance and effectiveness of the system. Additionally, understanding the behaviour of the drug delivery system in different physiological conditions can help predict its performance in vivo. This knowledge is crucial for designing effective drug-delivery systems that can successfully deliver therapeutic agents to target tissues or cells.

2. PRE FORMULATION CHARACTERIZATION

2.1 Organoleptic Properties

Organoleptic properties in pharmaceuticals are important characteristics of a substance that the senses, such as taste, smell, appearance, and texture, can perceive. These properties play a crucial role in shaping patient compliance and acceptance of the drug, directly impacting the overall experience of using the product. As a result, pharmaceutical companies frequently prioritize enhancing organoleptic properties to improve the user experience and gain a competitive edge [2].

2.2 Melting Point

The melting point of powder is a crucial factor in determining its physical properties and potential applications. It is often used as a quality control measure in manufacturing processes to ensure the consistency and purity of the final product [3].

The capillary technique is used to determine a drug's melting point. The capillary, measuring 10–15 mm in length and 1 mm in diameter, was loaded with powdered drug and sealed at one end, with the powder remaining within until about 2 mm from the closed end. The capillary was then placed into the digital melting point device [3].

2.3 Solubility Studies

Solubility was determined using the shake-flask method. The solubility was evaluated using several solvents and buffers [4].

The shake-flask method is employed to determine solubility at an equilibrium pH value. This technique involves filling a flask with a sample, shaking it for a specified duration at a set temperature, and then filtering the sample to measure the compound's concentration in the filtrate. This approach calculates thermodynamic solubility rather than kinetic solubility. It reduces the likelihood of forming a supersaturated solution and removes contaminants from the sample through high-performance liquid chromatography (HPLC) analysis, thereby lowering the risk of false positives [5].

2.4 Partition Coefficient

The partition coefficient, a ratio indicating the relative amounts of dispersed substances in an organic and aqueous environment, can be calculated using the following formula:

$$\textbf{Partition coefficient} = \frac{Concentration\ of\ drug\ in\ organic\ phase}{\text{Concentration of drug in aqeuous phase}}$$

By slightly altering the "Shake Flask Method," the partition coefficient was determined. Excessive API was added in a 10ml combination of n-octanol and water (1:1). To achieve equilibrium, the system was produced in triplicate and gently shaken in the separating funnel for an entire day. After the two phases were separated, the partition coefficient was computed using the equation, and UV spectroscopy was used to determine the concentration of API in each phase [6].

2.5 Preparation for Calibration Curve in Phosphate Buffer Solution

A calibration curve is utilized to determine the concentration of an unknown material. A 100-ml standard stock solution is made to produce the drug calibration curve. From this stock, 1, 3, 5, 7, and 10 ml are pipetted out and diluted with distilled water to achieve final concentrations of 0, 0.5, 1, 1.5, 2, and 2.5 µg/ml. These dilutions are then analyzed using a UV spectrophotometer at the maximum wavelength range. The calibration curve is constructed by plotting the absorbance against concentration [7].

2.6 UV Spectrophotometer

A UV spectrometer measures a sample's absorption of UV light to offer both quantitative and qualitative examination of the sample. The ideal solvent is used for the drug's spectrophotometric examination. A plot of absorbance vs. wavelength is typically used to record the UV spectrum. The drug's λmax is determined using a double-beam UV-visible spectrophotometer. The drug was dissolved in methanol to produce a stock solution (0.1 mg/ml). The material was then diluted to yield 2 µg/ml using methanol. To ascertain the drug's λmax, the resultant solution was scanned between 200 and 400 nm [8].

2.7 Fourier Transform Infrared Spectroscopy (FTIR)

Pharmacological excipients were tested for compatibility and possible interactions using Fourier transform infrared (FTIR) analysis. Using an FTIR spectrophotometer, samples were scanned within the 400 cm-1–4000 cm-1 range. Samples were generated using the potassium bromide disk technique, and measurements were made using 20 scans and 4 cm–1 resolution. Significant peaks corresponding to primary functional groups were identified, and the spectra of the following sample were compared [9].

2.8 Isothermal Stress

The researchers followed a method developed by Silva and Cintra to assess how the materials behaved under constant stress (isothermal stress studies). They precisely measured equal weights (1:1 weight ratio) of pure RLX and each excipient mixture. These samples (at least 3 for each mixture) were placed in 5-milliliter glass flasks and stored in an oven at 50 degrees Celsius for 14 days. Afterward, the samples were appropriately diluted with methanol. A validated chromatography technique, adapted from the US Pharmacopeia 38, was then used to quantify the amount of remaining drug (RLX) in each sample [10].

2.9 DSC Analysis

To examine how heat flow altered within the material, researchers employed thermogravimetric analysis with a Dupont TA 2000 (DSC analysis). They experimented with a protective nitrogen environment to guarantee

reliable results. They weighed a precise amount of the dry material and placed it in a sealed aluminum cup. The temperature was then increased from 25 degrees Celsius to 350 degrees Celsius at a rate of 10 degrees Celsius per minute, all while under a flow of nitrogen gas [11].

2.10 TGA Analysis

Researchers used thermogravimetric analysis (TGA) to analyze the polymers used in novel drug delivery systems. They employed an alumina crucible and loaded each sample with 5 milligrams. The experiment occurred in a nitrogen atmosphere with a flow rate of 100 milliliters per minute. The temperature increased from 24 degrees Celsius to 700 degrees Celsius at a rate of 10 degrees Celsius per minute [11].

2.11 XRD Analysis

Researchers employed a method known as wide-angle X-ray diffraction to calculate the d-spacing—the distance between atomic planes—in the crystalline PU sample. They used an instrument with copper Kα radiation, set at 50 kilovolts and 100 milliamps. The instrument also contained a graphite monochromator to filter out unwanted radiation. The X-ray data was collected over a range of angles (2 theta) from 5 to 60 degrees, with measurements taken every 0.02 degrees and a waiting time of 2 seconds between each measurement. Bragg's equation was then used to calculate the d-spacing values from the strongest peaks in the resulting data [12].

$$\boldsymbol{\lambda} = 2(d - spacing)sin\theta$$

2.12 Polarized Microscopy

Scientists examined the samples for uniformity (isotropy) using polarized light microscopy (PLM). They used a specific instrument and image analysis software (Pixel Link). Before performing the analysis, the samples were allowed to rest for at least 5 days to ensure they were stable. The measurements were then carried out at room temperature (25°C) [13].

2.13 Bulk Characterization

2.13.1 Tapped density

Tapped density measures powder's settlement under mechanical tapping, impacting flow properties and packaging efficiency in industries like pharmaceuticals and food processing. It also ensures accurate dosing and uniformity. The volumetric cylinder was tapped for one to two minutes to determine the substance's density. The tapped volume value was then recorded in the measuring cylinder. Then, using the relevant calculation, the taped density was determined [14].

$$\textbf{Tapped density} = \frac{\text{weight of the powder (g)}}{\text{tapped volume (ml)}}$$

2.13.2 Bulk density

Bulk density measures the mass of a material's unit volume, typically in grams per cubic centimeter, providing valuable information about its porosity and compactness. The powder's bulk density was measured by adding 25 grams of powder to a 100-ml measuring cylinder, and the data was recorded using a volumetric cylinder. Next, bulk density was calculated using the appropriate formula [14].

$$\textbf{Bulk density} = \frac{\text{weight of the powder (g)}}{\text{Bulk volume (ml)}}$$

2.13.3 Hauser's ratio

Hauser's ratio is used to assess a powder's followability. An equation developed especially for this purpose calculates the Hauser's ratio [14].

$$\textbf{Hauser's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.13.4 Carr's index

After weighing the ingredients, they are placed in a measuring cylinder. Determine the bulk volume without tapping, then use Carr's method to compute the compressibility index by tapping until the volume stays constant. The following formula can be used to find the compressibility index [14].

$$\textbf{Carr's index (\%)} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

2.13.5 Angle of repose

The angle of repose is defined as the maximum angle between the surface of a powder pile and the horizontal plane. In the experiment, a fixed funnel was positioned 2.5 cm above a flat surface with paper placed underneath. The powder was then poured through the inverted

funnel to measure the diameter of the resulting pile. The angle of repose may be determined by applying the following formula: [14]

$$\textbf{Angle of repose} = \tan^{-1}(\frac{2h}{d})$$

2.14 Stability studies

To assess a novel drug delivery system's chemical, physical, and microbiological stability, stability testing is an essential step in the process. This ensures the product remains safe and effective, maintaining its quality throughout its shelf life. The process involves weighing drugs and excipient samples, combining them in a binary combination, and keeping them in a stability chamber for 12 weeks. After dispensing the samples into glass ampoules, half are sealed without additional processing, and the other is topped with 5% distilled water. Samples are taken out at one-, two, and three-month intervals for examination [15].

2.15 Design of Experiment Approach

To find the best combination of ingredients (material attributes) for the new formulation and identify the most important ones (critical attributes), researchers used a special design method called a 'full factorial 2^3 design'. This method involves testing all possible combinations of three factors at two different levels. They repeated this approach with a separate 'full factorial 2^3 design' to optimize the manufacturing process for the best formulation they identified earlier. In this second experiment, they focused on finding the most crucial process parameters (critical parameters) that affect the outcome. The most successful formulation conditions discovered in the first experiment were then used in the second set of tests [16].

3. POST FORMULATION CHARACTERI-ZATION

3.1 Hardness

The hardness of a tablet is its resistance to crushing or breaking under pressure, crucial for its handling and transport without breaking apart [17].

The Monsanto hardness tester measures tablet hardness in kg/m2. Place one tablet from each formulation between the tester's jaws, apply pressure, and observe until it breaks. Note the reading at which the tablet breaks. The average weight is then noted [17].

3.2 Thickness & Diameter

Measuring tablet thickness ensures uniformity in drug dosage and absorption rates, which is crucial for quality control in pharmaceutical manufacturing processes [18].

A Vernier caliper measures tablet thickness. After inserting each tablet between the caliper's jaws, the reading on the primary scale is noted. The average thickness and diameter of the tablets are calculated using the provided formulas [18].

3.3 Weight Variation

Weight variation measurement evaluates an individual's weight fluctuations over time, offering insights into potential health issues and the effectiveness of weight management plans [19].

Each tablet was individually weighed. The average tablet weight was then calculated by dividing the total weight of the twenty tablets by the number of tablets. Next, the average weight of all the tablets was compared to each tablet's unique weight [19].

3.4 Friability

Friability is the term for a tablet's propensity to lose weight and break less frequently when being transported [19].

The Roche Friabilator measures friability by rotating at 20 to 90 revolutions per minute. Sample tablets are weighed and tested. After running at 25 rpm for four minutes, the device is re-weighed after running for another four minutes [19]. The friability was computed using the formula below:

$$\boldsymbol{Friability} = \frac{\text{Initial Weight } (\text{W1}) - \textit{Final Weight } (W2)}{\text{Initial Weight}} \times 100$$

3.5 DSC Analysis

The researchers used a device called a TA 2000 (made by Dupont) to analyze how heat flow changed within the material (DSC analysis). To ensure accurate results, they experimented with a protective nitrogen atmosphere. They weighed a precise amount of the dry material and placed it in a sealed aluminum cup. The temperature

was then increased from 25 degrees Celsius to 350 degrees Celsius at a rate of 10 degrees Celsius per minute, all while under a flow of nitrogen gas [11].

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$$\boldsymbol{\lambda} = 2(d - spacing)sin\theta$$

3.8 NMR (Nuclear Magnet Resonance)

This analytical instrument provides stereochemistry, repeating distances up to 150 nm, and molecular structure information for compounds in liquid or solid states. It offers complementary approaches, needs less sample preparation, and is non-destructive [20].

3.9 Drug Entrapment Efficiency

The entrapment efficiency of the formulation was calculated using the Mini Column centrifugation technique. A solution was prepared by thoroughly mixing 0.1 g of the formulation with 20 ml of ethanol. This mixture was then diluted to a final volume of 100 ml (0.1% w/v) and centrifuged at 15,000 rpm. A microscope examination of the eluted columns was conducted to ensure no crystals remained. The eluted columns were subsequently diluted with ethanol. The drug concentration was measured using a UV-visible spectrophotometer at a specific λ max [21].

The entrapment efficiency was determined using the formula

$$\textbf{Drug Entrapment} = \frac{\text{Amount of drug entrapped}}{Total\ amount\ of\ drug} \times 100$$

3.10 Zeta Potential

Zeta potential measures particle charge and indicates the stability of drug delivery systems. High zeta potentials suggest stability, while low potentials suggest flocculation. A zeta potential of 30 mV is necessary for electrostatic stability and is influenced by factors such as particle source, electrolyte concentration, pH, hydration, and shape. The zeta potential was measured using a Malvern Zetasizer 2000 HS equipped with a flow-measuring cell to determine the surface charge of particles. Demineralized water was used to dilute 5–10 ml of particle samples to a final volume of 200 ml in a 250 ml sample container at the titrator. The pH was first adjusted to 3 using HCl (1 n) and then titrated to pH 10 with NaOH (0.1 n). Zeta potential measurements were taken at 25°C in 0.5 pH intervals. The device was regularly calibrated using a 50 mV latex standard [22].

3.11 Scanning Electron Microscopy

SEMs, unlike optical microscopes, use an electron beam to observe objects. At the top, an electron cannon fires a concentrated electron stream. Two primary types of electron cannons are field emission guns and thermionic guns, which produce a powerful electric field and heat the filament [23]. The samples were adhered to a polycarbonate substrate and allowed to air dry at room temperature (25 °C). After that, they were dried with carbon dioxide in a critical point dryer and sputter-coated with gold in a metallizer. Finally, a 20 kV accelerating voltage scanning electron microscope was used to analyze them [24].

3.12 Atomic Force Microscopy

Atomic force microscopy is a crucial technique for evaluating the interfacial characteristics of novel drug delivery systems, including surface shape, average roughness, root mean square roughness, and droplet size [25]. Dilute the novel delivery system with distilled water to prevent droplet agglomeration. Apply to a divided mica

substrate, wash, and dehydrate. Adsorption occurs when droplets attract charges on mica and sample surfaces. Capture photos of droplets' dimensions and shapes are used to ascertain shapes and atomic force microscopy is used for resolution [26].

3.13 Transmission electron microscopy

An objective lens concentrates and magnifies the transmitted electrons, which are then utilized to generate the picture. An electron beam interacts with the sample during transmission.

The contrast between TEM images and light microscopic imaging is different due to diffraction, where the electron beam interacts with the material instead of absorption. The plane's orientation affects the diffraction intensity, with some angles diffracted and others transmitted. The specimen is tilted to create specific diffraction conditions. A thin foil must be developed for the sample to permit electron passage. A diluted sample is deposited onto support grids, producing lower dimensions. Under cryogenic conditions, materials are sliced into thin films using an ultramicrotome and diamond knife. The best samples are thin and can withstand intense vacuum [23].

3.14 Scanning tunneling microscopy

This device generates surface images with lateral resolution at the atomic scale. A piezoelectric crystal assists a thin probe with a tip in scanning the surface of the conducting sample, revealing the resulting tunneling current. The underlying mechanism of Scanning Tunneling Microscopy (STM) is quantum tunneling. When the tip and the sample's surface come into close proximity, the applied bias allows electrons to tunnel through the vacuum between them. At low voltages, the tunneling current depends on the sample's local density of states at the Fermi level. In STM, a depth resolution of 0.01 nm and a lateral resolution of 0.1 nm are considered satisfactory.

STM uses a piezoelectric crystal to adjust the distance between the surface and the tip of a sample. It produces images by maintaining a constant force while scanning the surface and plotting the tip's height relative to its lateral position. STM can be used in various environments, including liquid, gas, air, and vacuum, but requires clean surfaces and a sharp tip. Carbon nanotube tips are employed in STM, making it a valuable tool for material characterization [23].

3.15 Raman spectroscopy

Analyzing the Raman scattering, or inelastic scattering, of monochromatic laser light allows for the analysis of a system's vibrational, rotational, and other modes. This approach is known as Raman spectroscopy. An energy shift that results from the interaction of the laser light with phonons tells us about the various phonon modes in the system. Typically, a laser beam illuminates the sample, and a lens collects the electromagnetic radiation from the point of laser contact. This radiation is then directed through a collimator.

The process involves a molecule being excited from its ground state to a vibrationally excited state, producing Stokes Raman scattering. If the molecule is already in a vibrational state, it results in anti-Stokes Raman scattering. For Raman scattering to occur, the molecule must experience a change in polarizability. The Raman shift is determined by the specific vibrational level involved, while the intensity of Raman scattering depends on the change in polarizability. Advanced variations of this technique include surface-enhanced Raman spectroscopy, resonance Raman spectroscopy, and stimulated Raman spectroscopy [23].

3.16 Dynamic Light Scattering

DLS is used to characterize colloidal fluids and nanoparticles. It measures the light scattered from a laser as it passes through the colloidal solution. Analyzing the scattered light's modulation as a function of time allows us to calculate the size of the particles [23].

3.17 A DLS Autocorrelation Function

The decay of a function is influenced by the nanoparticle's diffusion rate, with Brownian motion providing the basis for analysis. The hydrodynamic diameter, determined from scattering intensity measurement, indicates nanoparticle aggregation. Unaggregated solutions have diameters equal to or greater than the TEM size, determined by macromolecules' dimensions and form [23].

3.18 Thermodynamic Stability

It discussed the metastable formulation problem under thermodynamic stability testing. There are

three steps in determining thermodynamic stability:

3.19 Centrifugation

Centrifugation is applied to the nanoemulsions for 30 minutes at 5000 rpm. Phase separation is not evident in the stable preparations. Centrifuging the material to identify whether it is an unstable or metastable emulsion allows for the observation of phase separation [27].

3.20 Heating Cooling Cycle

The evaluated sample is kept at 4° to 45° for at least 48 hours, during which it is exposed to temperature changes. Before each formulation's stability is evaluated, it undergoes six temperature cycles [27].

3.21 Freeze-Thaw Cycle

The formulation's stability is assessed following three cycles of freeze-thaw between 21° and +25° minimum over a 48-hour period. These nanoemulsions are stored at -20°C in a deep freezer for a whole day. They are then removed from the freezer and allowed to thaw to room temperature. The stable nanoemulsions return to their original condition after two to three minutes. 27

3.22 *In-vitro* Analysis

3.22.1 Disintegration

The disintegration test is a crucial procedure for ensuring the proper release of active ingredients in a tablet. It involves placing the tablet in a liquid medium, usually water or gastric fluid, and agitating it while maintaining a constant temperature. The test results record the time it takes for the tablet to disintegrate completely, ensuring its effectiveness in breaking down and providing a therapeutic effect [28].

3.22.2 Dissolution

The study involved drug release dissolution studies in vitro, using a medium maintained at 37 C and diluted up to 900 mL. The dosage form was placed in a dissolving basket, wrapped with a muslin cloth, and rotated at 100 rpm for basket apparatus and 50 rpm for paddle equipment. A sample holder was used to prevent the form from adhering to the vessel's bottom, measuring 5 cm in diameter and 4 cm in height.

To maintain sink conditions, a predetermined number of samples are obtained typically every hour and replaced with new medium. At this moment, 37 C is also maintained as the temperature of the replacement medium. Following the prescribed amount of time, a UV-Vis spectrophotometer set to the medication's wavelength is used to measure the concentration of the desired substance. Calibration curves for the desired drug are developed to estimate the quantity of released medicine [29].

3.22.3 Franz cell apparatus method

For in vitro drug release, the Franz cell device, featuring a diffusion area of 1.79 cm^2 and a receiver chamber capacity of 16 ml, was employed. A pre-wetted synthetic cellulose acetate membrane (Merck, Brazil) was used to separate the donor and recipient compartments. To maintain sink conditions, a physiological solution containing 1% cyclodextrin as a solubilizer was transferred into the receiver chamber. Temperature control for the receptor compartment was maintained at 32°C using Peltier-type equipment and an external thermal bath. Constant stirring was maintained throughout the experiment. To prevent bubbles, the receiver solution was sonicated before the experiment. An equivalent of 10 mg of the formulation was placed on top of the membrane, and the receiving compartment was sealed with Parafilm® once the donor compartment was secured. Samples of 500 µl were taken at 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, and 24 hours, with an equivalent volume of fresh medium added to maintain the conditions. The concentration of the drug in each sample was determined using an established HPLC technique [30].

3.22.4 Membrane diffusion method

Using conventional regenerated cellulose and Spectra, drug release experiments were conducted at 32°C. Take 5g of the formulation and place the receptor solution inside the dialysis chamber for a whole day to conduct the release experiment. The drug concentration in the receptor solution was determined by measuring the wavelength at 350 nm using UV-visible spectroscopy. A surfactant was added to make the solution more soluble in the receptor solution. With a pH of 7.4, 1.5% w/w polysorbate buffer makes up the receptor solution [31].

3.22.5 *In-vivo* Bioavailability Study

The study involved 27 male rats divided into three groups of nine each. One group received the standard formulation, acting as a control. The other two groups received a novel formulation: one with the formulations with active ingredients and the other without the drug for comparison.

Before receiving the treatments, the control group fasted overnight. Then, all groups received their assigned treatment: Control group: Orally administered 7.2mg/kg of active ingredient in water. Blood samples were collected from the rats' eyes (retro-orbital vein) at various times after treatment (0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours). The researchers then separated the blood plasma (liquid part) and extracted the active ingredient from it. This involved Mixing plasma with methanol (a process called deproteination), shaking and spinning the mixture to separate the drug, and then filtering the extracted liquid for analysis. Finally, the amount of active ingredient in the samples was measured using a technique called high-performance liquid chromatography (HPLC) [32].

3.22.6 Release kinetics

The kinetics of drug release were examined using a variety of models. i.e (i) first order; (ii) zero order; (iii) Higuchi model (iv)Model of Korsemeyer Peppas (v)–Crowell Hixson (vi) The Weibull model (vii) Model of Baker Lonsdale (viii) Gompertz model and Hopfenberg model [33].

Zero-order release kinetics: In zero-order release kinetics, drug concentration, and release rate are independent of one another, describing continuous drug release from the delivery device. The following equation can be used to describe zero-order release kinetics.

$$Q = Qo + Kot$$

Qo = First drug released in device, Q= Constant (zero order release), and Q= Drug released quantity in time t [33].

First-order release kinetics: This release kinetics model describes drug release from a system where drug concentration relies on release rate. The drug's release can be described using the following equation [34].

$$dC/dt = -K1C$$

LogC=logCo-K1t/2.303, where C is medication quantity, Co is initial drug release, and K1 is constant.

Higuchi model: The Higuchi model explains drug release using the square root of a time-dependent mechanism in a solid dose form. The following formula can be used to describe the Higuchi model [35].

$$Mt/M\infty = KH * t½$$

The Higuchi model represents cumulative drug release quantity in time t and infinite time, with KH representing the Higuchi constant [35].

Hixson and Crowell Kinetic model: Hixson and Crowell introduced a 1931 concept utilizing drug particle surface area and dosage form cube root to determine drug release rate from solid dosage forms.

$$\frac{(Wo - Wt)1}{3} = KHC * t$$

The drug's initial dosage form amount and release amount at time t is represented by Wo and Wt, respectively, and Hixson Crowell's rate constant, KHC, is used to determine the release rate [35].

Korsemeyer Peppas Model: This model explains the fractional release of drugs over time, represented by an equation, and effectively describes drug release from polymeric systems.

$$Mt/M\infty = Kt\hat{}n \quad \text{or} \quad Log\,(Mt/M\infty) = \log K + n\log t$$

The model, which considers the rate constant K, the exponent of diffusion n, and the proportion of drug release in time t, results in a straight line with a slope of n [36].

Weibull model: Weibull's model can be applied to any dissolution curve to visualize drug release kinetics and drug fraction accumulation in solution.

$$M = Mo1 - e - [(t - T/a)b]$$

The dissolution curve represents drug release and dissolved over time, influenced by parameters a and b, with logarithmic curves indicating quicker release and exponential kinetics indicating slower release [37].

Baker–Lonsdale model: In 1974, Higuchi, Baker, and Lonsdale developed a model to explain controlled pharmaceutical release from spherical matrices, outlined in the following equation.

$$f1 = 3/2[1-(1-Mt/M\infty)^{1}/^{3}]\, Mt/M\infty = kt$$

Researchers can evaluate drug release kinetics by plotting in vitro drug release data with respect to the root of time inverse, focusing on the amount and slope at time t [38].

Hopfenberg model: Hopfenberg developed a mathematical model to estimate the cumulative percent of drug release at time t, representing drug release from dissolving polymer surfaces until the surface area is preserved during degradation [38].

$$Mt/M\infty = 1 - [1 - \frac{kot}{CL}a]\hat{}n$$

Gompertz model: The model is commonly used to represent in vitro dissolution and can be expressed using the following equation [38].

$$X\,(t) = Xmax\; exp[-\alpha e\beta \log t]$$

The formula calculates the percentage of medicine remaining undissolved at time t by analyzing the rate of dissolving per unit time, Xmax, and Xt.

4. CONCLUSION

This study explores various methods used to analyze these novel drug delivery systems, both before and after they are formulated. These methods include checking the melting point of ingredients, how well they dissolve, how stable they are over time, and how readily the drug interacts with different environments. Scientists also develop calibration curves to ensure accurate measurements and use UV analysis to study the drug itself. Beyond these initial tests, researchers delve deeper into the delivery system's physical properties. They measure its hardness, thickness, how easily it crumbles, and the weight variation between units. This ensures consistency and proper functionality. But the most crucial aspect is the drug itself. Scientists assess how much drug is successfully trapped within the delivery system (entrapment efficiency). They also use techniques like DSC (differential scanning calorimetry) and TGA (thermogravimetric analysis) to understand the system's thermal behavior and stability. Finally, the most important test is how well the system releases the drug. In vitro analysis (laboratory studies) simulates the release process, providing valuable insights into how effectively the drug gets delivered. By employing this comprehensive toolbox of characterization techniques, researchers can optimize these drug delivery systems for targeted delivery and controlled release of the medication. This not only ensures the safety and efficacy of the system but also helps identify any potential issues early in the development process. Additionally, advanced analytical tools can shed light on the compatibility and stability of the system's components, guaranteeing its overall quality and reliability in delivering the intended therapeutic benefits.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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