Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 6
Open Access

Development And Assessment Of Floating Microcapsules For Safinamide Mesylate In Parkinson's Therapy

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Cite this paper as: Mugdha Avinash Nandedkar, Dr. Ravindra Dubey (2024) Development And Assessment Of Floating Microcapsules For Safinamide Mesylate In Parkinson's Therapy. Frontiers in Health Informa 4268-4277

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects motor function due to dopamine depletion. Safinamide mesylate, a selective monoamine oxidase-B (MAO-B) inhibitor, is widely used as an adjunct therapy in PD management. However, its therapeutic effectiveness is often limited by poor bioavailability and a short half-life, necessitating frequent dosing. To address these challenges, this study focuses on the development and assessment of floating microcapsules for Safinamide mesylate using a gastro-retentive drug delivery system. Floating microcapsules enhance gastric retention, ensuring sustained drug release and improved absorption in the upper gastrointestinal tract. Various polymers, including HPMC K4M, HPMC K15M, chitosan, and carbopol, were used to optimize buoyancy and control drug release kinetics. The formulated microcapsules were characterized based on particle size, surface morphology, entrapment efficiency, in vitro buoyancy, and drug release profiles. Results demonstrated that the optimized formulation exhibited prolonged gastric retention and controlled drug release, reducing fluctuations in plasma drug levels. The floating microcapsules showed high drug entrapment efficiency and excellent buoyancy, making them a viable alternative to conventional dosage forms. This sustained drug release approach minimizes dose frequency, enhances patient compliance, and potentially improves treatment outcomes for Parkinson's patients. While the in vitro findings are promising, further in vivo and clinical evaluations are required to confirm the efficacy and safety of the developed formulation. This study establishes floating microcapsules as a novel and effective drug delivery system for improving the pharmacokinetic profile of Safinamide mesylate in Parkinson's therapy.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor dysfunction, including tremors, rigidity, and bradykinesia, primarily caused by dopamine depletion in the brain. Safinamide mesylate, a selective monoamine oxidase-B (MAO-B) inhibitor, is widely used as an adjunct therapy to levodopa in managing Parkinson's symptoms. However, its therapeutic efficacy is often limited by its short half-life and irregular absorption in the gastrointestinal (GI) tract. To overcome these challenges, floating microcapsules offer a promising drug delivery system, designed to prolong gastric retention time and enhance bioavailability. Floating microcapsules, based on gastro-retentive drug delivery principles, remain buoyant in the stomach for an extended duration, facilitating sustained drug release and improved absorption. This approach ensures a more consistent plasma drug concentration, potentially reducing fluctuations in therapeutic effects and enhancing patient compliance.

The formulation and evaluation of floating microcapsules for Safinamide mesylate involve advanced polymer-based encapsulation techniques to achieve controlled drug release. The

selection of suitable polymers, such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and sodium alginate, plays a crucial role in maintaining buoyancy and modulating drug release rates. Key evaluation parameters include particle size, surface morphology, drug entrapment efficiency, in vitro buoyancy studies, and dissolution profile analysis. By optimizing formulation factors, floating microcapsules can significantly improve the pharmacokinetic profile of Safinamide mesylate, making it a more effective therapeutic option for Parkinson's disease. The present study aims to develop an efficient floating microcapsule formulation and assess its potential in enhancing the sustained delivery of Safinamide mesylate, ultimately contributing to improved management of Parkinson's disease symptoms.

Need for Floating Microcapsules in Drug Delivery

Oral drug delivery remains the most preferred and convenient route of administration, but it often faces challenges such as poor bioavailability, short gastric retention time, and irregular absorption, especially for drugs with site-specific action in the stomach or upper small intestine. Floating microcapsules, a type of gastro-retentive drug delivery system (GRDDS), address these limitations by prolonging gastric retention, enhancing drug dissolution, and ensuring sustained release. These microcapsules are designed with buoyant materials that allow them to remain in the stomach for extended periods, preventing premature drug transit into the intestines. This is particularly beneficial for drugs with a narrow absorption window in the stomach or those that exhibit reduced solubility in higher pH conditions of the intestines. Additionally, floating microcapsules minimize dose frequency, improving patient compliance and reducing side effects associated with fluctuating plasma drug levels.

For drugs like Safinamide mesylate, used in Parkinson's disease treatment, floating microcapsules offer significant therapeutic advantages. The drug's bioavailability is often compromised due to its short half-life and irregular gastrointestinal absorption. By incorporating Safinamide mesylate into floating microcapsules, a controlled and sustained drug release profile can be achieved, ensuring more consistent plasma concentrations and reducing motor fluctuations in Parkinson's patients. The polymer-based encapsulation also protects the drug from enzymatic degradation in the intestine, further enhancing its stability and efficacy. As a result, floating microcapsules provide an effective strategy to improve drug performance, optimize treatment outcomes, and offer a patient-friendly alternative to conventional dosage forms, making them a crucial advancement in modern drug delivery systems.

Research Methodology

Nelfinavir mesylate, recognized as an official compound in authoritative pharmacopoeias like the Indian Pharmacopoeia (IP) 2010 and Martindale, demands accurate quantitative analysis for quality assurance in pharmaceutical formulations. In the IP, a high-performance liquid chromatography (HPLC) method is outlined for the assay of both Nelfinavir mesylate itself and its tablet formulations. However, the existence of multiple analytical methodologies in the literature underscores the importance of selecting the most suitable technique for the intended application.

Literature surveys exploring the estimation of Nelfinavir mesylate have revealed a variety of analytical approaches, reflecting the diverse needs and capabilities of researchers and industries. Spectrophotometric methods, which measure the absorption of light by the compound, offer simplicity and accessibility, but may lack the specificity and sensitivity required for complex pharmaceutical matrices. Conversely, HPLC methods provide excellent selectivity and sensitivity, making them preferred for pharmaceutical analysis due to their ability to separate and quantify individual components in a mixture accurately.

The choice of analytical method depends on various factors such as the matrix complexity, required sensitivity, selectivity, and precision, as well as the available instrumentation and expertise. While spectrophotometric methods may suffice for preliminary screenings or routine quality control in less complex matrices, HPLC methods are often favored for pharmaceutical

formulations due to their robustness and accuracy. Thus, researchers and analysts must judiciously evaluate the pros and cons of each method to ensure reliable and accurate quantification of Nelfinavir mesylate, crucial for maintaining the efficacy and safety of pharmaceutical products.

Method used for the estimation of Nelfinavir mesylate

A UV-VIS spectrophotometric method based on the measurement of absorbance at 252 nm in methanol stock solution was used in the present research work for the estimation of NLF.

Materials

Procedure For the estimation of NLF in different aqueous fluids the standard solution was subsequently diluted to get a series of dilutions 10, 20, 30, 40 and 50µg/ml of solution and the absorbance was measured at 252 nm (UV-VIS spectrophotometer, SL-150, Elico) against respective blanks. The absorbances were plotted against concentration of nelfinavir mesylate. The absorbance values of NLF at different concentrations in different fluids are given in Table and the calibration curves are shown in Figures. The linearity range of NLF standards were selected based on the solubility of the drug in different buffers. In acidic buffer NLF is more soluble. Hence standards of range 10-50µg/ml were selected. In distilled water, 6.8 pH phosphate buffer and 7.4 pH phosphate buffer solubility of NLF was very low. Hence standards of range 2-10µg/ml were selected.

Validation of the method 1. Reproducibility Reproducibility of the above method was studied by analysing six individually weighed samples of nelfinavir mesylate. The persent relative standard deviation (RSD) of the determination was found to be less than 1.0%.Thus the method is highly reproducible. 2. Interference study The interference of excipients in the analytical method was studied by the following procedure. Accurately weighed amounts of nelfinavir mesylate (NLF) and HPMC, MCC, chitosan, carbopol, sodium bicarbonate or other materials in 1:1 weight ratios were mixed thoroughly. From each sample an accurately weighed powder equivalent to 10mg of NLF was assayed by the above analytical method. The NLF contents were calculated by measuring the absorbance at 252nm and the results are given in Table

Table 1 Estimation of NLF Content in Various Excipients

Excipient	Amount of NLF added (mg)	Amount of NLF estimated (mg)	Percent estimated
HPMC K4M	10	9.86	98.6
HPMC K15M	10	10.21	102.1
HPMC K100M	10	10.23	102.3
AVICEL PH 200	10	9.91	99.1
CHITOSAN	10	10.12	101.2
CARBOPOL	10	9.85	98.5
MCC	10	10.41	104.1
Mg. Stearate	10	10.25	102.5
Talc	10	9.54	95.4
PVP k-30	10	9.91	99.1
PG	10	9.53	95.3
Tween 80	10	9.98	99.8
PEG-400	10	9.95	99.5
BHT	10	9.91	99.1
Ethyl alcohol + water (9:1 ratio)	10	9.99	99.9

Solubility determination

An excessive amount of NLF was introduced into 10 ml of each fluid contained in 25 ml stoppered conical flasks. These mixtures underwent agitation for 24 hours at room temperature (37 ± 0.5ºC) in a rotary flask shaker. After 24 hours of agitation, 1 ml aliquots were drawn and filtered using nylon disc filters (0.45µm). The filtered samples were appropriately diluted if necessary and subjected to NLF assay by measuring the absorbance at 252 nm. Shaking was continued until three consecutive estimations yielded the same result. Solubility experiments were conducted in triplicate to ensure accuracy and reliability of the findings.

Analytical method for estimation of NLF The UV spectrum of NLF is shown in Figure 3.1 and λmax of 252 nm was selected and used for the analysis of NLF in different samples. The λmax of NLF was found to be the same in all the media used in the present work.

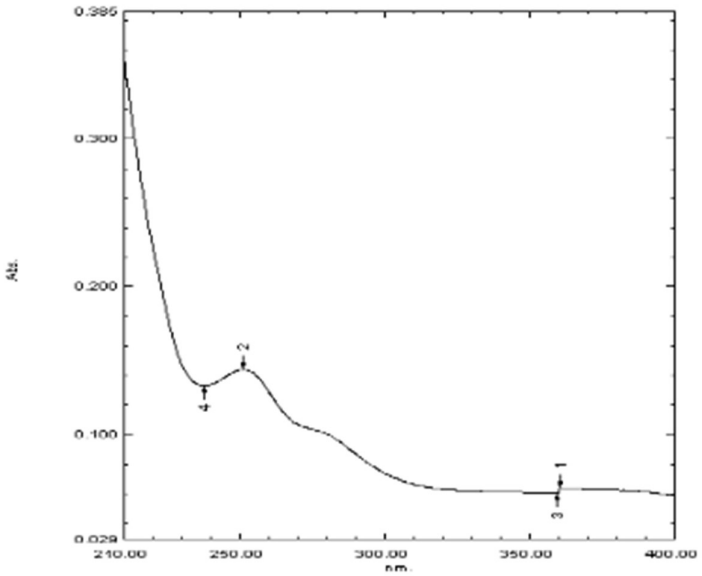

Figure 1: UV Spectrum of NLF

Table 2 Calibration curve for the estimation of nelfinavir mesylate in 0.1N HCl

Nelfinavir Mesylate Concentration (µg/mL)	Absorbance ± SD
10	0.136 ± 0.001
20	0.261 ± 0.002
30	0.390 ± 0.005
40	0.518 ± 0.002
50	0.625 ± 0.005

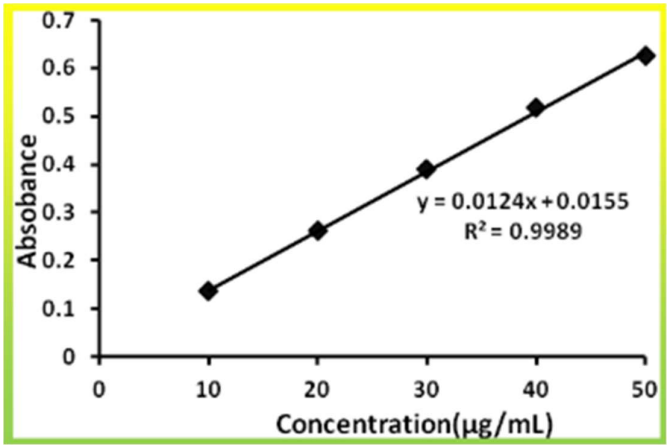

Figure 2: Calibration curve for NLF in 0.1N HCl

The table provides data on the absorbance values measured at different concentrations of nelfinavir mesylate (NLF) in solution. The concentrations of NLF range from 10 µg/mL to 50 µg/mL, with each concentration tested in triplicate. For each concentration, the mean absorbance value is reported, along with the standard deviation (SD) as a measure of the variability among the triplicate measurements. Absorbance is a measure of the amount of light absorbed by a solution at a specific wavelength, typically measured using a spectrophotometer. In this case, the absorbance of the NLF solutions is measured at a wavelength of 252 nm. As the concentration of NLF in the solution increases, more light is absorbed by the solution, resulting in higher absorbance values. From the data presented in the table, it can be observed that there is a clear trend of increasing absorbance with increasing concentration of NLF. As the concentration doubles from 10 µg/mL to 20 µg/mL, the absorbance approximately doubles as well. This trend continues as the concentration increases further, with absorbance values increasing proportionally. The standard deviation values provided alongside the mean absorbance values indicate the degree of variability or precision in the absorbance measurements. A smaller standard deviation suggests that the triplicate measurements are more closely clustered around the mean value, indicating greater precision and reliability in the measurements. the data in the table demonstrate the relationship between the concentration of NLF in solution and the absorbance measured at a specific wavelength, providing valuable information for quantifying the concentration of NLF in solution using spectrophotometric analysis.

Results and Discussion

Soft gelatin capsules are single-unit solid dose forms. They are made of a liquid or semi-solid substance that is surrounded by a one-piece sealed elastic outer shell. The dose form can be globular or oval in shape. They are easy to swallow, keep their contents from oxidising, and have an attractive appearance. Soft gels are effective delivery vehicles for hydrophobic, low melting point, and easily oxidised medicines. The development of a specific soft gelatin capsule formulation entails meticulous attention to both the shell and filler components. Initial steps involve careful selection and optimization of these elements to achieve the creation of a chemically and physically stable product with the desired biopharmaceutical characteristics. The shell of a soft gelatin capsule typically comprises gelatin, either alone or in combination with a plasticizer or water. Additionally, it may incorporate preservatives, colouring and opacifying agents, flavoring agents, sweeteners, and occasionally sugars to enhance chewability. Gastro-resistant chemicals may also be included, along with active compounds under certain circumstances. Meanwhile, the fill formulation is tailored to meet specific requirements for optimal therapeutic efficacy, ensuring that the active ingredients are delivered effectively to achieve the desired pharmacological effect.

Consumer preferences lean significantly towards soft gel capsules over other solid dosage forms. Within the pharmaceutical industry, approximately 75% of solid dosage forms are manufactured as compressed tablets, 23% as hard gelatin capsules, and only 2% as soft gelatin capsules. Results from a market survey reveal that 44.2% of consumers favor soft gelatin capsules, 39.6% prefer tablets, and 19.4% opt for hard gelatin capsules.

Advantages:

A soft gel capsule delivers the medicine to the GIT in the form of a solution, suspension, or emulsion. Thus, dissolution is no longer the rate-limiting step in the absorption process. Absorption occurs faster, more uniformly, and with more intensity. • Soft gel capsules are easier to swallow, conceal odours or disagreeable tastes, and protect the encapsulated component from oxygen and light. • Soft gel capsules may also have greater absorption due to the fill excipient's suppression of P-glycoprotein-mediated drug efflux. • Enzyme-catalyzed breakdown of the drug in the GIT lumen may also contribute to improved absorption. • Soft gels are also used to precisely deliver therapeutic medicines that require ultra-low dosages (e.g., cardiac glycosides, vitamin D analogues).

Challenges:

The soft gel formulations must be protected against two major possibilities: physical migration of the shell and fill components between themselves, as well as migration of the components to the external environment; and physical and chemical interactions between the shell and fill components, or within the shell or fill components. Fill formulations must have the best attributes in terms of viscosity, mix consistency, fill weight uniformity, physical stability, and chemical stability. Some concerns to consider when selecting excipients include solubilized substance crystallisation, drug-excipient interactions, and excipient auto-oxidation.

Orally administered medications often encounter challenges due to effluxion by P-glycoprotein, a transporter that reduces drug bioavailability by transporting absorbed drugs back into the gastrointestinal system. To address this issue, a diverse array of surfactants has been identified with the capability to inhibit this efflux transporter. Soft gel capsules play a crucial role in enhancing the stability of loaded medications by impeding oxygen permeability. This protective barrier helps maintain the integrity and efficacy of the enclosed drugs, ensuring their potency over time.

Drug release kinetics & mechanisms:

Various kinetic models exist to describe the total release of a medication from its dosage form. Given that qualitative and quantitative changes in a formulation can impact drug release and in vivo performance, there's a continuous effort to develop techniques that streamline product development and minimize the reliance on bio-studies. In this context, analysing the rate of NLF release from manufactured dosage forms involved fitting drug release data into a first-order release kinetics equation. This approach not only aids in understanding the release kinetics but also facilitates the optimization of formulations and ensures product quality and performance.

$$\text{Log } C = \log CO - k\, t/2.303.$$

In the first-order release kinetics equation, CO represents the initial concentration of the drug, while k denotes the first-order constant. To determine the value of k, a common approach involves plotting the logarithm of the cumulative percentage of drug remaining unreleased against time. The slope of this plot corresponds to -k, enabling the calculation of the first-order rate constant. This method provides a quantitative measure of the drug release kinetics, allowing for further analysis and optimization of the formulation.

Table 2: Morphological characters of liquid fill formulations of nelfinavir mesylate for soft gels

Formulations	Morphological Character
F1	Homogeneous, clear, no color change.
F2	Homogeneous, clear, no color change.
F3	Homogeneous, clear, no color change.
F4	Homogeneous, clear, no color change.
F5	Homogeneous, clear, no color change.
F6	Homogeneous, clear, no color change.
F7 (placebo)	Homogeneous, clear, no color change.

Table 3: pH values for Liquid fill formulations of nelfinavir mesylate for soft gels

Formulation	pH
F1	7.16 ± 0.23
F2	7.12 ± 0.20
F3	6.96 ± 0.11
F4	7.25 ± 0.15
F5	6.97 ± 0.21
F6	7.03 ± 0.18
F7 (Placebo)	5.41 ± 0.12

The pH values reported for various formulations, ranging from F1 to F7, offer critical insights into their chemical properties and potential physiological interactions. F1 and F2 exhibit slightly alkaline pH levels, with F4 demonstrating a marginally higher pH compared to the rest. Conversely, F3 and F5 appear to have slightly lower pH values. These variations might stem from the specific composition of each formulation, including the presence of different excipients and active ingredients. The pH of F7, serving as a placebo, notably differs from the other formulations, indicating the absence of the active drug component. Understanding these pH profiles is crucial for assessing the formulations' compatibility with biological systems, ensuring optimal drug release, and minimizing potential adverse effects associated with pH-related instabilities. Adjustments to pH levels may be necessary during formulation development to enhance therapeutic effectiveness and patient safety.

Table 4 Percent drug content profile of nelfinavir mesylate liquid fill formulations for soft gels

Formulation	**Percent Drug Content**
F1	98.98 ± 0.34
F2	99.40 ± 0.19
F3	98.89 ± 0.05
F4	99.39 ± 0.18
F5	99.68 ± 0.31
F6	99.24 ± 0.27

The percent drug content data presented for formulations F1 through F6 provides valuable insights into the uniformity and consistency of drug distribution within each formulation. The

results indicate that all formulations maintain drug content within acceptable ranges, with minor variations observed among different formulations. F5 demonstrates the highest drug content percentage, while F3 exhibits the lowest, albeit still within acceptable limits. These variations could arise from differences in formulation composition, manufacturing processes, or analytical techniques used for drug content determination. Overall, the findings suggest that the formulations maintain consistent drug content, essential for ensuring therapeutic efficacy and dosage uniformity across batches. Such data are crucial for quality control measures in pharmaceutical production, facilitating the development of safe and effective medication formulations.

Table 5: Percent moisture absorption of liquid fill formulations for soft gels of nelfinavir mesylate

Formulation	Percent Moisture Absorption
F1	1.19 ± 0.22
F2	1.29 ± 1.16
F3	1.17 ± 0.95
F4	1.82 ± 0.29
F5	2.99 ± 0.44
F6	1.22 ± 0.29

The percent moisture absorption data provided for formulations F1 through F6 offers valuable insights into the moisture uptake characteristics of each formulation. These values indicate the amount of moisture absorbed by the formulations under specific conditions, which is essential for assessing their stability and shelf-life. Generally, lower moisture absorption percentages are desirable as they indicate better stability and reduced risk of formulation degradation. Among the formulations, F3 exhibits the lowest moisture absorption percentage, suggesting relatively better stability in terms of moisture uptake. On the other hand, F5 shows the highest moisture absorption, indicating a higher susceptibility to moisture ingress. Such variations in moisture absorption may be attributed to differences in formulation ingredients, excipients, or manufacturing processes. Monitoring moisture absorption is critical in pharmaceutical formulations as excessive moisture can lead to degradation of active ingredients, alteration of physical properties, and reduced shelf-life. Therefore, these data provide valuable information for quality control and optimization of formulation compositions to ensure stability and efficacy of the final product.

Table 6: Comparative viscosity data for liquid filling formulations

Formulation	Viscosity (cps)
F1	512.82 ± 4.19
F2	515.46 ± 2.98
F3	409.35 ± 3.87
F4	350.38 ± 2.95
F5	509.68 ± 3.86
F6	534.47 ± 3.17

The viscosity data presented for formulations F1 through F6 offer crucial insights into the flow characteristics of each formulation. Viscosity is a key parameter that influences the handling, administration, and stability of pharmaceutical formulations. Formulations with higher viscosity values, such as F2, F5, and F6, may exhibit thicker consistency and slower flow rates compared to formulations with lower viscosity, such as F3 and F4. The differences in viscosity among formulations can be attributed to variations in the composition and concentration of viscosity-modifying agents such as PVP K-30, PEG-400, and Tween 80. Optimizing viscosity is essential to ensure proper filling into dosage forms, such as soft gel capsules, as well as to

enhance patient compliance and drug delivery efficiency. Formulations with viscosity within the desired range can provide adequate coating and protection for the active pharmaceutical ingredient while facilitating uniform distribution within the dosage form. the viscosity data provided here contribute to the comprehensive characterization of the formulations and are instrumental in guiding formulation development and optimization efforts aimed at achieving desired rheological properties for pharmaceutical products.

Conclusion

The development and assessment of floating microcapsules for Safinamide mesylate offer a promising approach to enhancing the drug's therapeutic efficacy in Parkinson's disease management. By employing a gastro-retentive drug delivery system, the floating microcapsules significantly improve gastric retention time, ensuring sustained drug release and better absorption in the upper gastrointestinal tract. The use of polymers such as HPMC, chitosan, and carbopol plays a crucial role in maintaining buoyancy and controlling drug release kinetics. Characterization studies, including buoyancy tests, drug entrapment efficiency, and in vitro release profiling, demonstrate the formulation's potential to provide a stable and controlled drug delivery system, minimizing fluctuations in plasma drug levels. This sustained release mechanism is particularly beneficial for Parkinson's patients, as it helps in reducing motor complications associated with inconsistent drug absorption.

Furthermore, the study highlights the advantages of floating microcapsules over conventional dosage forms, such as improved bioavailability, reduced dosing frequency, and better patient compliance. The optimized formulation ensures a more predictable pharmacokinetic profile, thereby enhancing therapeutic outcomes. While the findings support the potential of floating microcapsules for Safinamide mesylate, further in vivo studies and clinical evaluations are necessary to validate their efficacy and safety in real-world applications. Future research could focus on refining formulation parameters and exploring alternative polymer combinations to achieve even greater efficiency in drug delivery. this study establishes floating microcapsules as an innovative and effective drug delivery system for Parkinson's therapy, offering a step forward in optimizing treatment strategies for better patient outcomes.

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