OPTIMIZING SOLUBILITY AND BIOAVAILABILITY OF TICAGRELOR-LOADED NANOPARTICLES

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Abstract

The reduction in particle size methods have advanced through investigative methods to an advanced a commercial drug system for administration in recent years. Compared to conventional drug delivery methods, nanoparticles can offer several benefits due to their high clarity, excessive drugs potency, controlled release capability, versatility in management routes, and ability to deliver water-soluble and water-resistant molecule of drug.

Goals:

This research aimed to improve the dissolution and solubility of the medication, a drug that is not well soluble in water. It was accomplished by producing as well as evaluating nanoparticles of ticagrelor made by solvent evaporation technique. One antiplatelet medication that is water-resistant is ticagrelor. Three formulations had been created, as well as distinct stabilizing chemicals are utilized at varying dosages, including hydroxypropyl methyl cellulose (HPMC) and poloxamer 188 (PXM). The drug to stabilizer proportions employed in order create the nanoparticles were 1:0.5, 1:1, and 1:2.

Keywords: *Ticagrelor, Controlled release, Cardiovascular drugs, Nanoparticles, antiplatelet therapy.*

1.INTRODUCTION

With extensive knowledge gathered in a variety of biotechnology, biomedical engineering, and nanotechnology sectors, the area of innovative system of drug delivery is developing at an exponential rate. Nanotechnology, or the creation of nanoscale structures containing the API, is used in several of the more modern formulation techniques. The National Nanotechnology Initiative (NNI) defines nanotechnology as the research and use of materials that range in size from around from 1 to 100 nm.

The general objective of medicine and nanotechnology is the same: adopting a controlled and targeted medication delivery technique to diagnose as precisely and early as possible and to treat as effectively as possible without any side effects. Nanostructures are solid substances or granular dispersions that range in particle size from 10 to 1000 nanometer.

The drugs are attached to a matrix of nanoparticles, dissolved, trapped, or encapsulated. The preparation method might result in the production of nanoparticles, nanospheres, or nanocapsules. The medicine is enclosed within a hollow that is surrounded by a unique polymer membrane in nanocapsules, as opposed to nanospheres, which are matrix systems in which the drug is evenly and physically dispersed. Because they can target a particular tissue, move around for a duration of time, deliver proteins, peptides, and mutations, and serve as carriers of DNA in gene treatment. Biodegradable polymeric nanoparticles, particularly those coated with hydrophilic molecules like HPMC-, have recently been investigated as possible drug delivery vehicles. Nanoparticles are composed of three layers since they are not simple molecules:

(a) The outermost layer of the which is functionalizable by a variety of metal ions, polymers, surfactants, and small molecules;
(b) The outer layer, that's entirely distinct to its center chemically; as well as
(c) The center, whose is essentially the NP's center and is sometimes referred regarded as the NP proper.

Poor solubility of drug candidates can lead to a lot of issues the study along with growth of pharmaceuticals. The rate of dissolution of the medication in water is a crucial factor in determining how quickly it dissolves, and a poor solubility can often lead to a low bioavailability of medications taken orally.

Additionally, a medication may have dissolution-limited absorption if its water solubility is less than 100 µg/mL. In this case, increasing the dosage may be required unless the level of drug in the blood drops within the medicinal product content range. For only poorly soluble medicines, the dissolution rate frequently determines the rate at which the medication is absorbed. The difficulty these medications face is increasing their solubility or rate of dissolution.

Additionally, dissolving enhances bioavailability and absorption. These formulation techniques, which aim to enhance the solubility of weakly soluble compounds, are constantly being introduced. An improvement in the medication solubility, surface area, or formulation in its dissolved state can all be used to improve poorly soluble medications.

Many methods, including its micronization, adsorption onto high surface area carriers, lyophilization, co-grinding, and inclusion complex formation, have been used to develop oral delivery systems for drugs that improve the rate of dissolution and, consequently, the absorption efficiency of a water-insoluble drug. Nanotechnology, which contains appealing nanoparticles that have attracted a lot of interest in the past 10 years, is one of these several approaches for enhancing solubility.

Particulate dispersions or solid particles between 10 and 1000 nm in size is known as polymeric nanoparticles (PNPs). Despite their small size, atoms and molecules have a rather large surface area, which allows for a significant increase in the portion of these particulates on their outermost surfaces.

The mass of the molecule and formula for ticagrelor are $C_{23}H_{28}F_2N_6O_4S$ (522.57 gm/mole). At normal temperature, the crystallized powder ticagrelor has a solubility of around 3.5µg/ml in water. With a solvent made from organic materials such asThe purpose of this study is to formulate and assess ticagrelor nanoparticles employing solvent antisolvent technology to increase the weakly water-soluble medication's bioavailability and the rate of dissolving.

1.1.EMULSION SOLVENT EVAPORATION METHOD

This process involves dissolving premade polymers, like poly (d.l-lactic co-glycolic acid), or polylactic acid, with a solvent made from organic materials such as acetone, ethyl acetate or chloroform. In order to create an oil-in-water emulsion, the loading medication is typically dissolved in the polymer solution before being moved to an aqueous phase that contains a surfactant, like polyvinyl alcohol. Maintaining the homogenization process for an adequate amount of time can help the organic solvent evaporate. The nanoparticles are gathered by ultracentrifugation at the conclusion of the homogenization time. To obtain the required particle size and other characteristics, process variables can be changed, including the kind of organic solvent, the rate and duration of homogenization, and the ratio of polymer to organic solvent.

2. MATERIALS

S.NO	INGREDIENT	USES
1	Ticagrelor	API-antiplatelet medication
2	Hydroxypropyl methylcellulose (HPMC)	Polymer
3	Dimethyl formamide (DMF)	Solvent
4	Poloxamer 188	Surfactant
5	Distilled water	Dispersion medium

Table 1: Presents the ingredients along with their respective uses

EQUIPMENT

S.NO	NAME	PURPOSE
1	Mechanical stirrer	Homogenizer
2	Centrifuge	Separate nanoparticles
3	Lyophiliser (freeze dryer)	Remove solvent from suspension

Table 2: The equipment employed in the study along with their intended purposes are detailed

3. METHODOLOGY

Making ticagrelor nanoparticles

Techniques for solvent evaporation/extraction were used to create ticagrelor nanoparticles. Two phases are prepared independently in this process. There are two distinct phases: the organic phase and the aqueous phase.

- A specific quantity of ticagrelor, a pure medication and polymer has been fully dissolved in DMF.
- The resulting solution was gradually dropped into a volume of water that contained poloxmer 188 as an external phase at a steady speed.
- A rapid connectivity homogenizer was utilized to break down the resulting mixture in different agitation speeds of 10,000, 15,000, and 20,000 rpm while being maintained in an ice-water bath.

Figure 1: Illustrate the magnetic stirrer was used to ensure uniform mixing during the formulation process

- At room temperature, the resulting oil-in-water (O/W) emulsion was gently agitated for two hours in order to remove the organic solvents.
- Then, for one hour, the nanosuspensions were centrifuged at 37000 rpm at 20 °C.

Figure 2: The centrifuge employed in the experimental procedure is presented

- A lyophilizator was used to lyophilise the obtained nanoparticles after they had been cleaned three times with distilled water using a previously published centrifugation technique.

Figure 3: The lyophiliser utilized in the experimental process is depicted

- Powdered nanoparticles were obtained and gathered.

Formulas for the composition of ticagrelor nanoparticles.

Ingredients	F1	F2	F3
Ticagrelor	0.9g	0.5g	**1g**
HPMC	0.54g	1g	**2g**
DMF	5ml	10ml	**20ml**
Poloxomer 188	0.6g	0.5g	**1g**
Distilled water	10ml	15ml	**30ml**

Table 3: It represents the formulation Ticagrelor drug loaded nanoparticles

4. EVALUATION OF NANOPARTICLES

Advanced microscopic techniques like at Surface Force Microscopy (AFM), Electron Transmission Imaging (TEM), and Electron Beam Surface Analysis (SEM) are used in order to measure the size, shape, and charge on the surface of nanoparticles. The size distribution, charge, and average particle diameter every individual have an impact on the nanoparticles' in vivo distribution and physical stability. Using electron microscopy techniques to determine the general shape of polymeric nanoparticles can be very helpful in determining their spotential toxicity. Both the in vivo performance, the outermost charged of the nanoparticles affects a polymer dispersion's stability in nature.

- FTIR
- SEM
- Surface charge potential

4.1.Fourier Transforms Infra-Red Spectroscopy

The FTIR (Shimadzu IR Spirit) can be used to determine the medication's and the polymer's possible chemical bonds and stability.

Figure 4: It illustrates a FTIR sample press maker

Separate samples were combined with 200–400 mg of potassium bromide, and the samples were compacted in a hydraulic press (Athena Technology ISO 9001:2015, Model no: AT HP 15, Capacity 15 ton) for two minutes at a pressure of 200 kg/cm² to create pellets. By positioning the pellets in the light path, polymer, drug-loaded nanoparticles, and the native drug were examined. All samples were scanned using an average of 32 interferograms at an average resolution of 2 cm across the 4000-400 cm range.

Figure 5: It illustrates the image FTIR spectrophotometer

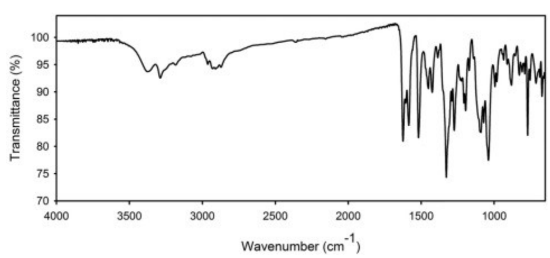

Figure 6: This figure shows that FTIR of ticagrelor

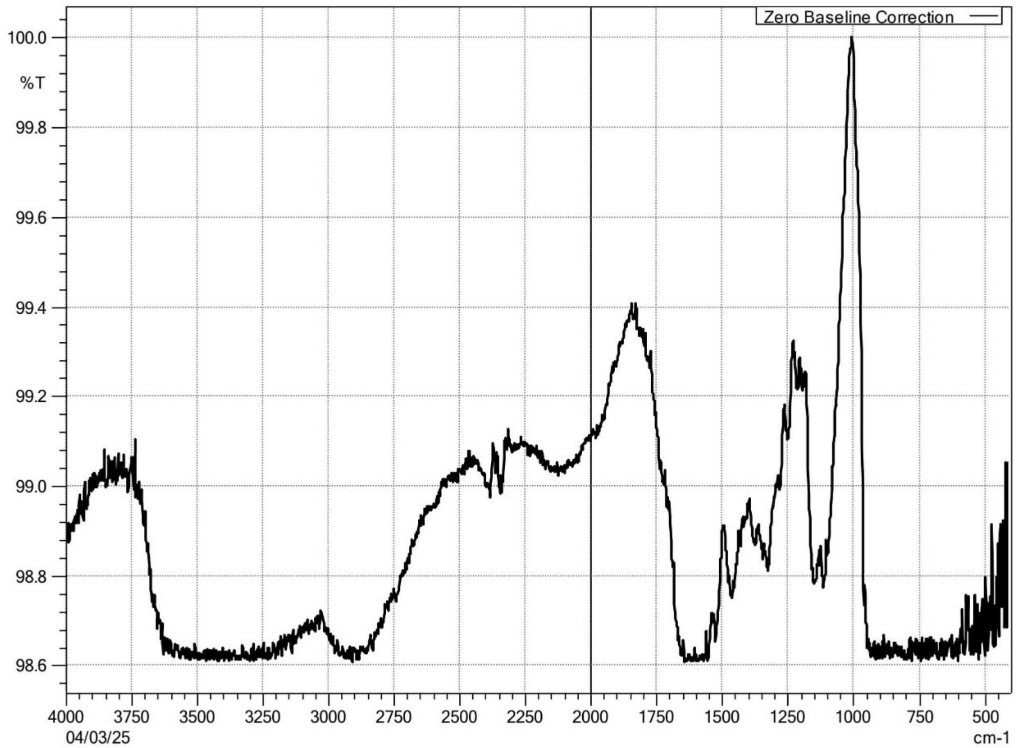

Figure 7: It shows that FTIR of Ticagrelor loaded nanoparticles

Frequency(cm^{-1})	Absorption Intensity	Group Identification	Mode of Vibration
~3400~3400	Broad/strong	-OH (hydroxyl)	O–H stretching (HPMC, Poloxamer 188, minor from Ticagrelor)
~~ 2920	Medium	$-CH_2/-CH_3$ (alkyl)	C–H stretching (Poloxamer 188, HPMC backbone)
~1730−1720~1730 −1720	Medium	C=O (carbonyl)	C=O stretching (DMF solvent traces, HPMC acetyl groups)
~1650~1650	Medium	C=C or C=O stretching / amide	C=C stretching (Ticagrelor aromatic system), amide in DMF
~1450−1370~1450 −1370	Weak	C–H bending	CH_2 bending vibrations

			(Poloxamer 188, HPMC)
~1100−1050~1100−1050	Strong	C–O–C / C–O (ether groups)	C–O–C stretching (Poloxamer 188 as well as HPMC ethers)
~840−720~840−720	Medium	Aromatic C–H Stretching (from the line)	Ring of aromatic vibrations (Ticagrelor)

Table 4: Summary of FTIR Results for Ticagrelor-Loaded Nanoparticles

To verify the chemical integrity and inter-component interactions, the Fourier Transforms Infra-Red Spectroscopy of the Ticagrelor-loaded nanoparticles made with HPMC, Poloxamer 188, and Dimethylformamide (DMF) was examined. Around 3400 cm^{-1}, a broad and strong absorption band was seen. This band corresponds to O–H stretching vibrations and is mostly caused by the hydroxyl groups found in HPMC and Poloxamer 188, with Ticagrelor contributing slightly. The stretching vibrations of the aliphatic -CH_2 and -CH_3 groups, which are representative of the polymeric backbone of HPMC and the surfactant Poloxamer 188, are attributed to the peaks at about 2920 cm^{-1}.

The C=O stretching vibrations are attributed to a medium-intensity peak that was seen in the 1730–1720 cm^{-1} region. This suggests that HPMC contains acetyl groups or leftover DMF solvent. In addition, a noticeable band at about 1650 cm^{-1} is linked to the aromatic rings in Ticagrelor's C=C stretching vibrations, as well as potential amide I bands from DMF residues. C-H bending vibrations are responsible for the peaks that show up between 1450 and 1370 cm^{-1}, which is again in line with the contributions of HPMC and Poloxamer 188.

The existence of ether linkages, which are typical of both HPMC and Poloxamer 188 structures, is confirmed by a prominent band seen between 1100 and 1050 cm^{-1} that corresponds to C–O–C and C–O stretching vibrations. Finally, aromatic C–H bending vibrations, which correspond to the aromatic framework of ticagrelor, are responsible for the peaks seen at approximately 840–720 cm^{-1}. Ticagrelor was successfully trapped in the nanoparticulate matrix without undergoing any chemical alteration, according to the FTIR data, which also indicate that there were no notable chemical interactions between Ticagrelor and the excipients.

4.2. Scanning Electron Microscopy

Direct visualization and morphological analysis are provided by scanning electron microscopy. (JEOL, JSM-IT200 Purchased under RUSA).

Figure 8: Illustrates the scanning electron microscope (SEM) used in this study

Although the electron beam surface analysis-based technique has several benefits over morphological as well as sizing studies, they don't reveal much about the actual population average or size distribution A conductive metal, such as gold, should be applied to the nanoparticle solution using a sputter coater after it has been dried into a powder and placed on a sample holder for a scanning electron microscope analysis. A concentrated, finely focused electron beam is then utilized to scan the sample. Secondary electrons emitted by the sample surface are analyzed to determine the surface characteristics of the sample. The nanoparticles must also be able to survive vacuum, and the polymer could be harmed by the electron beam. The average size determined by SEM is comparable to the results on the dispersion of light under dynamic conditions. These methods were also expensive, time-consuming, and often require additional data regarding size distribution.

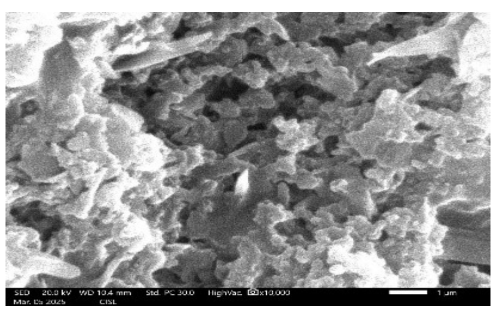

Figure 9: Surface morphology at 10,000× magnification (1 µm scale).

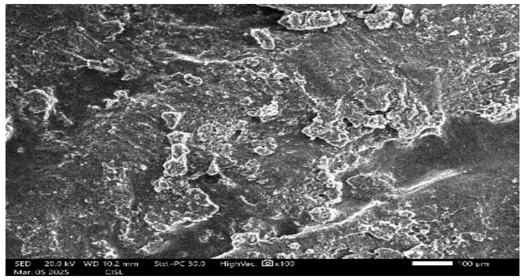

Figure 10: Surface morphology at 100× magnification (100 µm scale).

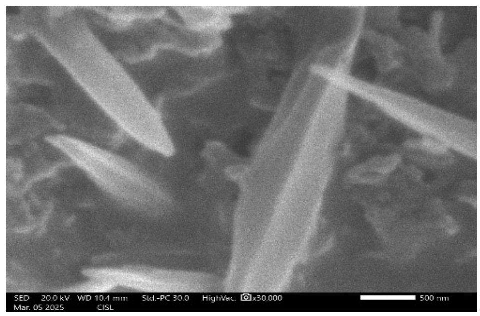

Figure 11: Surface morphology at 30,000× magnification (500 nm scale).

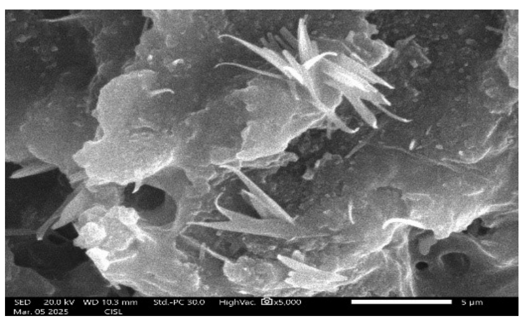

Figure 12: Surface morphology at 5,000× magnification (5 µm scale).

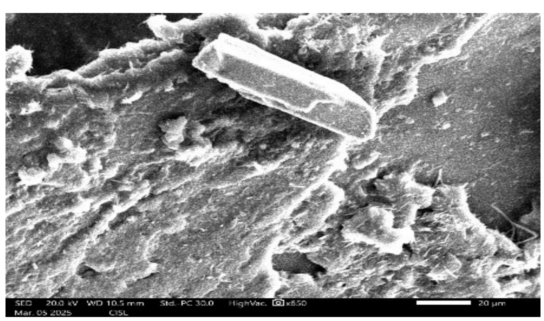

Figure 13: Surface morphology at 650× magnification (20 µm scale).

The SEM image reveals irregularly shaped and aggregated nanoparticles with rough surface morphology. This indicates successful nanoparticle formation, though further optimization may be needed to improve uniformity and reduce agglomeration.

4.3. SURFACE CHARGE POTENTIAL

A Malvenzetasiver method is employed to ascertain the value for the nanoparticles' surface charge and particle size. Nanoparticles' surface charge type and intensity are crucial because they affect how they interact with the biological environment and how they interact electrostatically with bioactive substances. By using the surface charge potential for the nanoparticles, the stability of colloids is examined. This potential serves as a proxy for the surface charge. The surface of shear and the outer Helmholtz plane may differ from one another. Zeta potential measurement enables predictions regarding colloidal dispersion's storage stability. High zeta potential values—whether positive or negative—are necessary to provide stability and stop particle aggregation. It is then possible to forecast the level of surface hydrophobicity using the values of the zeta potential. Information on the specific type of substance coated on the surface or enclosed in the Nano capsules can also be obtained from the surface charge potential.

Size of the surface charge potential (mV)	Interpretation behavior of stability
0-5 mV	Quick coagulation or swelling (high instability)
10-30 mV	Incipient instability (particles begin to aggregate)
30-40 mV	Moderate stability (partial resistance to aggregation)
40-60 mV	significant stability (sufficient repulsive forces)
>61 Mv	outstanding stability (highly resistant to aggregation)

Table 5: It represents the Ticagrelor drug stability

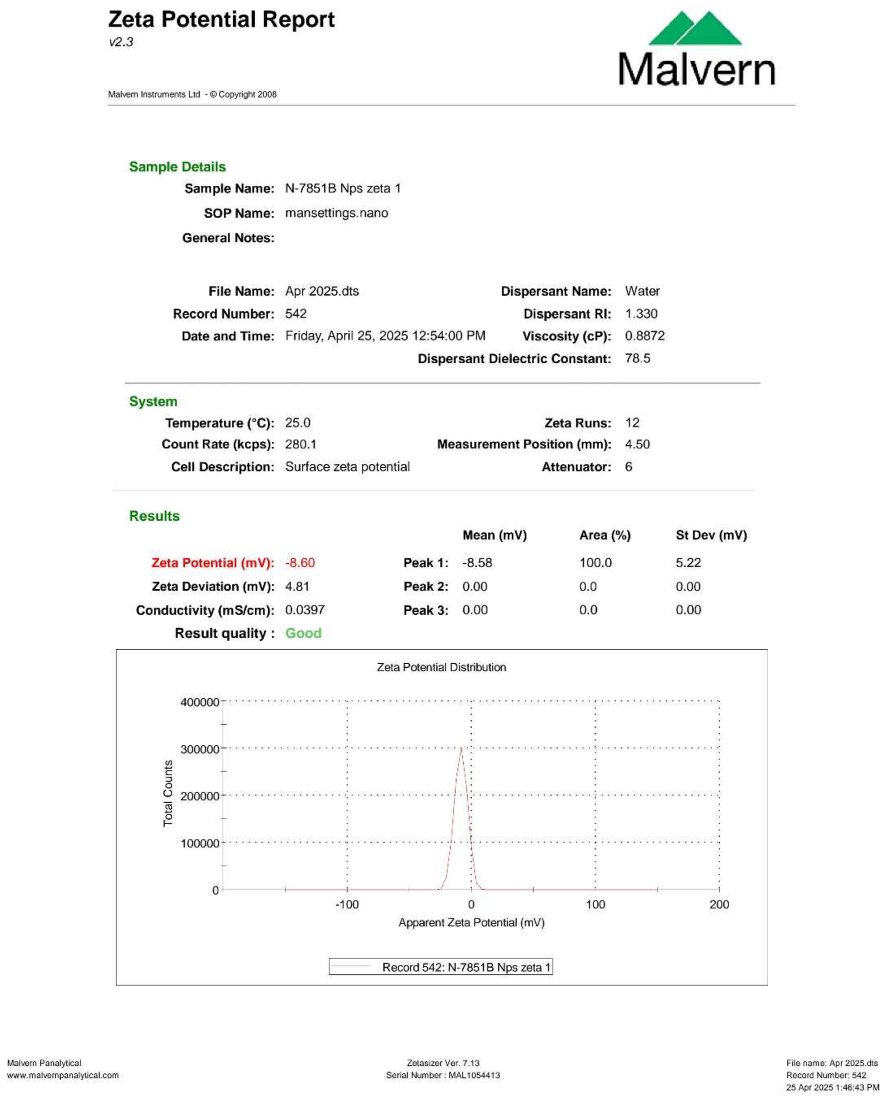

Figure 14: It depicts the zetapotential report of Ticagrelor loaded nanoparticles formulation

The zeta potential measurement of the formulated nanoparticles showed a value of 8.60 millivolts, indicating moderate colloidal stability in the aqueous dispersant medium. Although values above ±30 millivolts are generally considered ideal for electrostatically stable nanoparticles, the observed zeta potential suggests that the system may rely on additional stabilization mechanisms such as steric hindrance or surfactant presence. The narrow peak and low deviation indicate uniformity in particle charge distribution, which supports consistent behavior in suspension. Overall, the results reflect acceptable stability for preliminary formulation studies and potential for further optimization in drug delivery applications.

5. RESULT AND DISCUSSION

To enhance the drug's dissolving characteristic and bioavailability, the current work prepared ticagrelor-loaded nanoparticles using a solvent evaporation approach. One gram of ticagrelor, two grams of hydroxypropyl methylcellulose (HPMC), one gram of poloxamer 188 (PXM), twenty milliliters of dimethylformamide (DMF) as the solvent, and thirty milliliters of distilled water as the dispersion medium were used to create a particular formulation. Because of solvent dispersion and precipitation, nanoparticles spontaneously formed when the organic phase containing ticagrelor and stabilizers was introduced into the aqueous phase. The uniform and steady appearance of the resultant dispersion suggested that the medication and stabilizing agents interacted effectively. There was no discernible phase separation or aggregation, indicating strong physical stability.

The resulting nanoparticles had a uniform and somewhat small size dispersion and were in the nanometer range. In order to increase the surface area available for dissolution, the particle size was adequately lowered. In order to reduce particle development and stop aggregation both during and after formation, HPMC, a polymeric stabilizer, and PXM, a surfactant, were essential. The formulation's relatively negative surface charge, as revealed by zeta potential studies, helped to stabilize the nanoparticles in suspension electrostatically. Preventing particle aggregation and preserving long-term dispersion stability depend on this characteristic.

Through solvent evaporation, the chosen formulation approach—which combined ticagrelor with HPMC and PXM—successfully generated stable, evenly distributed nanoparticles. Dimethylformamide was a good solvent choice because it can dissolve both hydrophilic and lipophilic substances, which encourages the creation of homogeneous nanoparticles when they diffuse into water. This technique shows how to improve the administration of poorly soluble medications in a useful and effective way. The findings lend credence to the possibility of using this nanoparticle technology to enhance the oral bioavailability and therapeutic efficacy of ticagrelor and related substances. By adopting a solvent evaporation/extraction approach and a biphasic system consisting of an organic phase (ticagrelor, HPMC in DMF) and an aqueous phase (distilled water containing Poloxamer 188), ticagrelor nanoparticles were successfully produced. High-speed homogenization, solvent removal, and lyophilization all helped to create the nanoparticles.

Three formulations (F1, F2, and F3) were constructed with varied quantities of the medication, polymer, solvent, and surfactant to study their effect on nanoparticle production and properties.

Composition F3 outperformed the other two formulations in terms of stability, homogeneity of nanoparticles, and likely drug loading efficiency. More stable nanoparticles were produced as a result of improved encapsulation and emulsification brought about by the higher quantities of HPMC and Poloxamer 188 in F3. Better ticagrelor and polymer solubilization was made possible by the larger volume of DMF (20 mL) employed in F3, which also supported the establishment of a uniform and evenly distributed organic phase—a crucial component for the best possible nanoparticle growth when introduced to the aqueous phase.

Additionally, the oil-in-water emulsion was better stabilized during high-speed homogenization due to the increased concentration of Poloxamer 188 (1 g) in the aqueous phase of F3. This improved stability during solvent evaporation and resulted in finer droplet size. Better dispersion of the generated nanoparticles and effective diffusion of the organic solvent were also guaranteed by the higher volume of water (30 mL) in F3. Nanoparticles were successfully separated by centrifugation at 37,000 rpm, and a finely powdered form was obtained by washing and lyophilization. Comparing the lyophilized nanoparticles from F3 to those from F1 and F2, it was found that the latter had reduced agglomeration and improved flowability.

In conclusion, the findings show that Formulation F3 had the best profile because it had the best medication, polymer, and surfactant concentrations as well as a more effective solvent system. Together, these elements improved the stability and production of nanoparticles, making F3 the most effective formulation among those examined.

6.CONCLUSION

In conclusion, this study successfully demonstrated the incorporation of Ticagrelor into nanoparticles without any chemical modification, as confirmed by FTIR analysis. The findings indicate that Ticagrelor was effectively encapsulated within the nanoparticulate matrix, with no significant chemical interactions with the excipients. However, the SEM imaging revealed irregularly shaped and aggregated nanoparticles, highlighting the need for further optimization to improve particle uniformity and reduce agglomeration. Additionally, the zeta potential measurement suggests moderate stability in an aqueous medium, indicating that the formulation could benefit from enhanced stabilization strategies to improve dispersion performance. Overall, while the initial results are promising, further refinement is necessary to achieve a more uniform and stable nanoparticle formulation for potential therapeutic applications.

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