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Formulation development and evaluation of Bexagliflozin loaded nano emulsion

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Abstract:

The goal of the current endeavour is to identify and create a bexagliflozin small emulsion that can effectively cure diabetes. Bexagliflozin is advised in order to assist people with diabetes with type 2 diabetes improve the control of their glucose levels when combined with a good diet and regular exercise. Additionally, bexagliflozin's absorption through the mouth is limited (in the range of fifty to seventy percent). The purpose of this effort was to create nanoemulsion formulations incorporating bexagliflozin and assess their effectiveness in vitro. nanoemulsion made up of distilled water, Tween eighty, a co-surfactant (The polyethylene glycol 400), various oils (oleic acid), containing 0.01% bexagliflozin. The ultrasonic technologies for processing is used to create a variety of water-in-oil nanoemulsion. In vitro drug release studies, stability studies, thermodynamic durability tests, FTIR, pH, and viscosity were conducted on the nano-emulsion formulations.

Keywords: bexagliflozin, viscosity, nanoemulsion, polyethylene glycol.

Introduction

The condition known as diabetes mellitus is the term used by doctors to describe a group of diabetes-related conditions that are characterized by high levels of blood sugar (glucose) because of either inadequate insulin production, an inappropriate hormonal cellular reacting, or both. Patients sometimes experience polyphagia, dizziness, or increased sensations of feeling full or thirsty, and polyuria to occur or frequent urine, as signs of high blood glucose levels. The definition of people with diabetes and its history: Greek for "siphon" is the term hyperglycemia***[1][Kumar CR,1992].*** The Greek physician Aretus the Cappadocian named the disease diabainein in the second century A.D. According to him, some persons have polyuria, which is the spilling of water like a siphoning The term "diabetes" was coined when the the medieval period Latin word diabetes was incorporated into English.

The word "nanoemulsion" describes a combination of two insoluble substances, one of which is spread in the continuous the subsequent stage. Nanoemulsions can be used to create oil in water (O/W) or water in oil (W/O)***[2](Pongsumpun et al., 2020).*** Nano-emulsions are spherical, solid substances with an unpredictable surface that is lipophilic and negatively charged***[3](Jaiswal & Dudhe, 2015).*** Nanoemulsions have great potential for improving therapeutic efficacy and delivering medications due to their micron-sized size. Advanced nano-

droplet devices are used for systemic in nature controlled, and targeted drug administration***[4](Shaker et al., 2019).***

Since varied droplet dimensions can be created depending on the method utilized, preparation procedures can have an impact on the long-term security of emulsions. Bexagliflozin is an exceptionally selective and potent inhibitor of sodium-glucose co-transporter 2 (SGLT2). A methylene bridge, two ring-like structures and glucose make up the three fundamental parts of bexagliflozin, which are similar to those of other SGLT2 antagonists. SGLT2, which is more expressed in the renal system compared to additional isoforms like SGLT1, is responsible for 60% to 90% of kidneys hypoglycemia re-uptake***[5][Zhang W, et al 2011, Azzam O 2021 et al].***

Material and Methods

Charaterization and Identification of Drug and Excipients

Physical Appearance: Powder, white to light yellow

Color/Form: Solid

Odor: None.

Melting point Determination

The bexagliflozin the sample's melting point has been identified using the tube-capillary method. The medication was put into the bottom of one of the ends of the capillary tube. A melting point instrument was then used to determine the temperatures at which the drug completely melted after the capillary tube had been filled. After three attempts at the experiment, the typical melting point was established. The standard characteristics specified in the drug datasheet were compared to the measured melting point. Table 4.2 provides the results of the melting point measurements in the results and the discussion in the chapter***[6][The Japanese Pharmacopoeia].***

Spectrophotometry

Ten milligrams of the bexagliflozin experimental drug was dissolved in 10 millilitres of methanol to achieve a 1000 µg/ml concentration. The standard working combination had an absorbance of 10 µg/ml after the prescribed stock remedy was suitably diluted with methanol. Following that, the suggested working solution was scanned between 200 and 400 nm using an ultraviolet (UV) spectrophotometer. The maximal absorbance peak (λ max) and ultraviolet (UV) light spectroscopy were measured and compared to typical pharmacological spectra. The UV spectrum of the bexagliflozin sample and similar bexagliflozin spectra are shown in figures 4.1 and 4.2 of the results and commentary section***[6][The Japanese Pharmacopoeia].***

FTIR Spectroscopy

The KBr technique was used to change the drug's consonant absorption. A very little amount of the drug sample and already-dried KBr powder were mashed in a clean mortar and pestle to reduce the drug to extremely small particles since the infrared beam breaks up large particles and alters the inclined foundation of the spectrum. As the die is being transferred, powder is equally placed to the seven millimetre collar. For a little time, such as one minute, the die is placed with the powder in the readily accessible KBr press, which can be a pneumatic press, to produce a pellet. Following removal of the pellet from the die, it was placed in the FTIR sample container (Perkin Elmer Spectrum One). Next, the 600–4000 cm-1 range is recorded using the program Spectrum 1***[7][Tugarova A V et al].***

Excipients selected for the nano emulsion formulation

Bexagliflozin's biological characteristics and the chemical and physical characterization of the excipients were the main observations that influenced the creation of the bexagliflozin nanoemulsion.

Screening of Oil

Using surfactants and co-surfactants, a homogeneous solution was initially prepared for the creation of the nano-emulsion formulations. In the oil stage, the most important need for screening is usually the drug's loading efficacy. In this phase, however, excessive drug solubility is deemed acceptable. In an Eppendorf tube, 15 mg of the medication was held in a millilitre of oil state for at least 15 days at room temperature in order to examine and pursue drug equilibrium***[8][Villar A M S, et al].***

Screening of surfactants

Surfactants are essential for the production of nano-emulsions; non-ionic surfactants are commonly employed because to their remarkable preparation properties and ease of combining with other ingredients. Compared to both cationic and anionic surfactants, these substances are safer and less dangerous. Tween-20 and Tween-80 are said to have the finest solubility and mixing properties in the oil stage***[9][Basalious E B et al].***

Screening of co-surfactants

Because of their potent ability to combine with oil, which lowers surface tension, co-surfactants are frequently used to create nano-emulsions. These are the sole explanations for how they were selected. The creation of a bexagliflozin nano-emulsion had to rely on its solubility in water and mixability with the other additive materials once the lipidic component was assessed***[10][Nepal P R et al].***

Drug solubility determination

To assess the ability of drug excipients, including oil stage, co-surfactants, along with surfactants, to dissolve surplus drug, the excess was combined in a 1.0 ml Eppendorf tube. If the medicine was sufficiently mixed, the procedure was repeated using a vortex mixer and 2.0 ml of more medication that was put into an eppendorf tube. After that, the eppendorf tubes were kept at 25 ±5℃ for around 48 hours to achieve equilibrium. The drug sample was rotated at 3000 revolutions per minute for 10 minutes after 48 hours. The total quantity of medicine mixed with different additives at this particular formula was measured using an ultraviolet (UV) spectrophotometer. For this, a model-make equipment is used. The supernatant is then filtered through a 0.45µm membrane that has been adequately moistened with methanol***[11][Zeng L et al].***

Formulation of bexagliflozin nanoemulsion

Characterization of Nanoemulsion Formulation

Droplet size distribution

This nanoemulsion mixture was diluted with pure water to investigate the zeta potential, PDI, and droplet size. The core of ZetaSizer is the dynamic light scattering technology (DLS). To ascertain the droplet size and PDI of the produced mixtures that satisfied the specifications for stable and clear tiny emulsions, ZetaSizer Nano ZS (Malvern 1000) was utilized. Each sample was measured three times. An experiment was carried out, and the results were recorded***[12][Garg V et al].***

Measurement of electrical conductivity

A type 611E computerized conductance meter was used to measure the electrical conductivity of the formulation. Administering a KCl solution at a temperature of 25 ´C was the primary method utilized to calculate the conductmeter simulation's cell constant. After that, 1.0 ml of the mixture was removed, and its platinum electrodes were dipped sequentially in a beaker with a 10 ml capacity. The conductance significance was then displayed by the conductmeter, and it was recorded until the gadget showed a continuous value. The conductivity of the distribution method was observed during operations after all the ingredients were carefully mixed and each formulation was gradually diluted with the water constituent in the container***[13][Daar J, Khan A, et al].***

Morphological evaluation of bexagliflozin nano emulsion formulation

The specimen was put in a tiny drop on wax-coated paper, and an external 400 mesh copper-made rectangular grid was used. After that, 10 millilitres of two per cent w/v uranyl acetate were used to colour and preserve the sample for a brief period of time. An electron microscope equipped with transmission was used to examine the preparation's appearance and structure. Morgani, the defendant, used a TEM equipment running at 70kV to record the material's surface contouring.

Determination of pH

A computerized pH meter called the Symphony SB70P pH Meter was used to measure the pH of the nanoemulsions. The data were presented as the mean and standard deviation (mean ±SD), with each measurement being performed in triplicate at room temperature (25 ◦C)***[14][Attwood D].***

Determination of Refractive Index

The Atago Refractometer, model number Rx 5000i, was first calibrated using milli-q water at 20 to 25 0C. The same procedure was used to determine the refractive index for the other formulations after just one teaspoon of drug-loaded nanoemulsion was inserted into the instrument's the specimen platform, the lid was closed, the operating temperature was adjusted to across 20 and 25 Celsius temperatures, and the amounts that popped up on the display were recorded***[15][Shafiq-un-Nabi S et al].***

Determination of Viscosity

An examination of the composition of the nano-emulsion was conducted rheologically employing a Brookfield viscometer equipped with a 61 spindle. 5 similar quantities (100 ml) containing the nano-emulsion mixture were put into 5 different 150 ml beakers labelled F1, F2, F3, F4, along with F5. To capture the rheological characteristics, the device was configured with a predetermined temperature of 25 °C and shearing speeds of 10, 20, 40, along with 50. To reduce errors, measurements of each nano-emulsion formulation have been taken three times***[16][Dasgupta S et al].***

In-Vitro drug study

Tablet USP in vitro release studies were conducted using the USP XXIII dissolving experiment apparatus. Utilizing a USP paddle-style dissolving apparatus, the dissolution study was carried out at 37 +/- 50 degrees Celsius with a paddle predominance of 100 rpm. Each of the two dissolving media types used included 900 millilitres of 0.1 percent a solution of hydrochloric acid with a pH of 7.4 MIPB. Upon loading the collected nanoemulsion into an empty capsule, it was placed in a container. The results at 267 nm were compared to a blank using a UV Spectrophotometer after samples were removed at different times***[17][Chouksey R et al].***

Thermodynamic Stability study

At temperatures ranging from 4 to 45° Celsius, the appliance's six separate cooling and heating procedures occur over the period of 48 hours. The components of the long-term nano-emulsion at 4 and 45 degrees Celsius were centrifuged for around 30 minutes at 3500 revolutions per minute to confirm that the phases were separated***[18][Talegaonkar S et al].***

Results and Discussions

UV Spectroscopy

The identification of the drug sample that was gathered and the components used to create the nano-emulsion technology were confirmed by preliminary research into this project. Bexagliflozin is effectively characterized by a range of analytical methods, such as chemical analysis, chromatography principles, and spectrum evaluation. The organoleptic characterization revealed that the sample included a white to light yellow powdered with no smell. The thing they were measuring was measured. Methanol was used to assess the UV spectrum of the drug sample. A spectrum analysis reveals a sample using λmax measurement of 295 nm. After the drug had been obtained in its natural state of a solvent, its UV spectrum was analyzed in order to develop the drug sample examination procedure. Each of the drug estimation methods in solvent is shown visually.

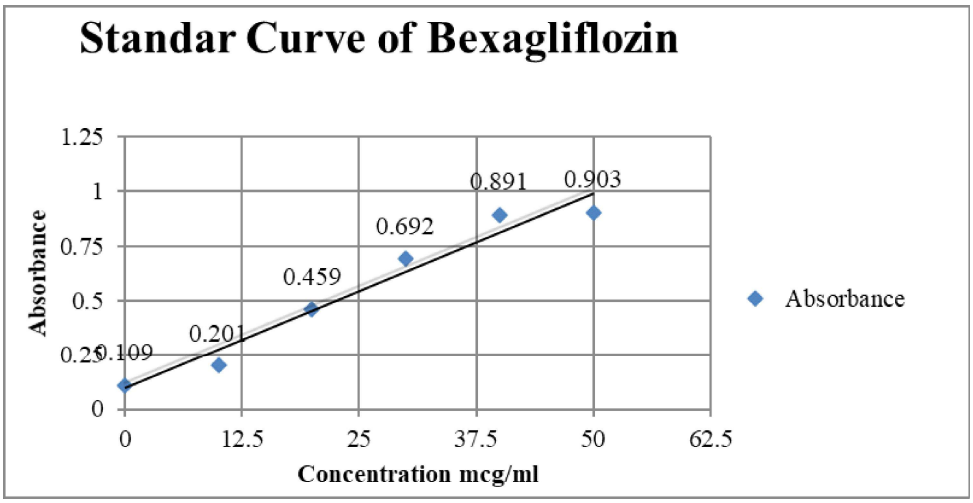


Fig 1: Standard bexagliflozin curve in methanol

FTIR Spectrum Data

The drug's characteristics Using the KBr pellet approach, the total mass of the sample's FTIR spectrum is calculated, and the range of values is 4000 and 600 cm-1. Explain that the main requirement for pre-formulation investigation into the creation and production of bexagliflozin compositions is drug-excipient compatibility. For a month, the medication and the excipient were kept in different proportions as a pre-concentrate combinations to evaluate drug-excipient appropriateness testing. After a while, this mixture was taken out and checked for variations in the powder's colour and composition.

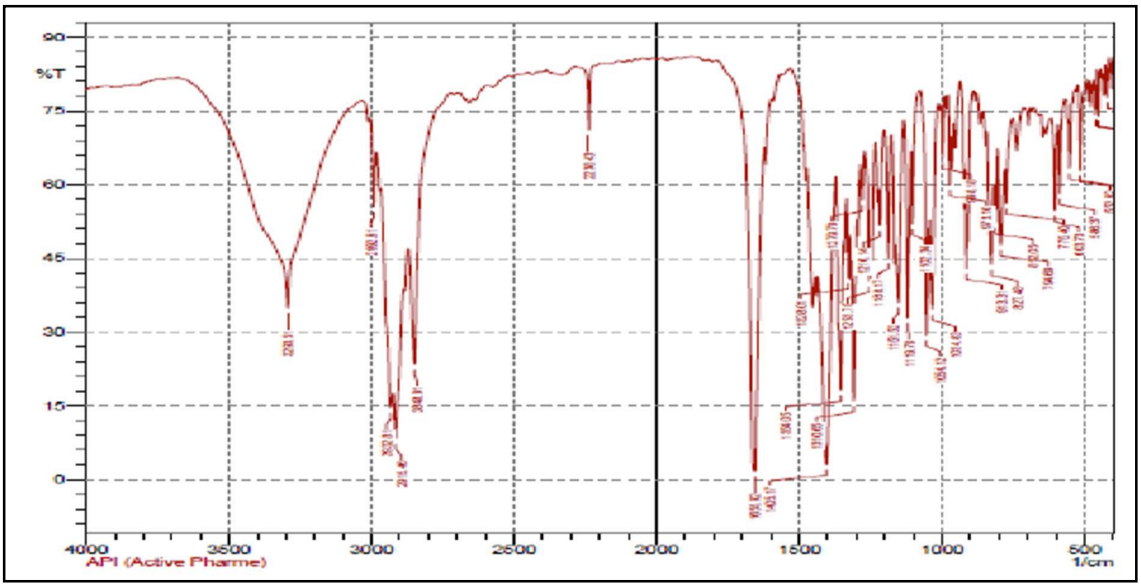


Fig 2: FTIR spectrum of Bexagliflozin

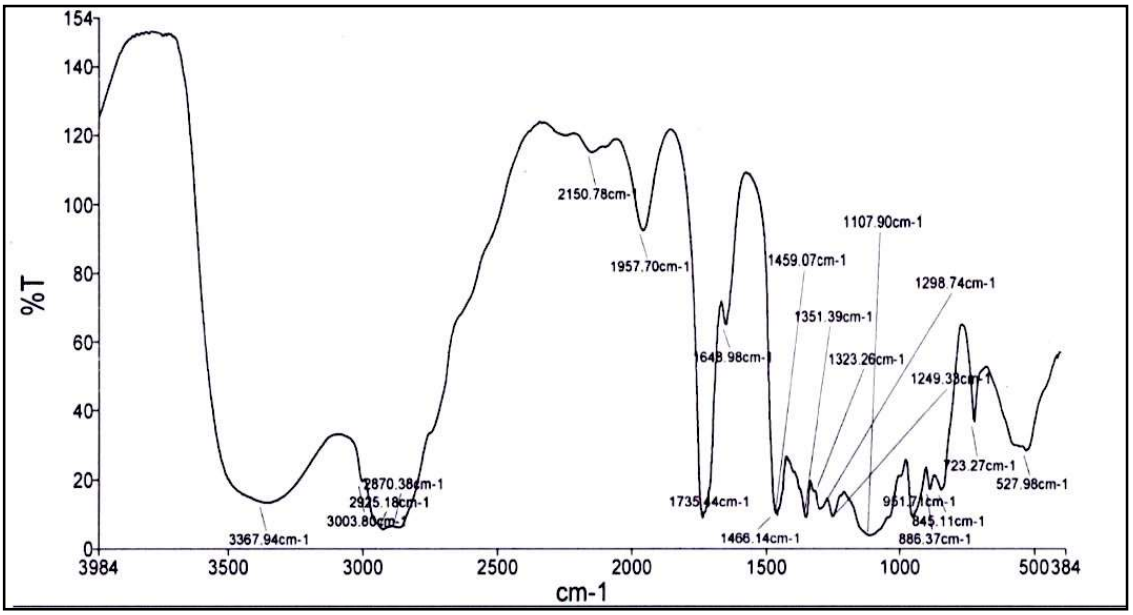


Fig 3: Oleic acid + S-mix + Bexagliflozin FTIR Spectrum (Tween 80:PEG 400)

Drug Solubility

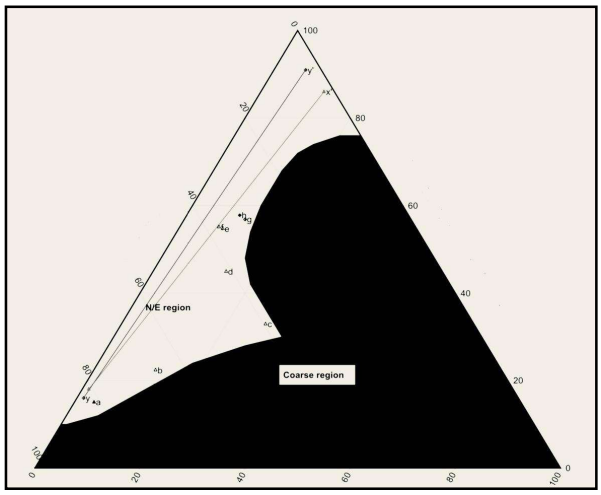
A nanoemulsion's composition is based on the drug's solubility and miscibility in a range of excipients, such as surfactant and oil phase, including co-surfactant. The many excipients that the medicine must dissolve in to create a formulation are listed. The medication was shown to be most soluble in oleic acid and PEG 400, with solubility values of 20–45 mg/ml, 40 mg/ml, along with 28 mg/ml, respectively. The compatibility of excipients such as co-surfactant, oil phase, along with surfactant must all be assessed before they can be used in the nano-emulsion production platform.

OILS		**SURFACTANT**		**CO-SURFACTANT**	
Castor Oil	6mg/ml	Tween 80	32mg/ml	Polyethylene 200	28mg/ml
Oleic acid	35mg/ml	Tween 20	18mg/ml	Polyethylene 400	41mg/ml
Almond oil	4mg/ml				
Cardamom oil	14mg/ml				

Table 1: Drug Solubility

Ternery Phase Diagram

The ternary diagram of phases is a tool used to identify different ternary variables that are mixed in certain regions and regulate the formation of miscellar, reverse-misceller, coarse formulations, and nano-emulsion bi-continuous processes. These types of systems are highly helpful in early formation research on nano-emulsion in identifying a feasible dissemination system when a certain portion of the Smix, oil, as well as water phase were obtained. The components of the oil-containing phase were preserved while the pseudo-ternary phase description was drawn using five different Smix ratios. As can be seen in the image, the ternary
phase representation was created using Smix (Tween-80/PEG-400 at a 1:1 ratio); oleic acid is the main ingredient in the oil-based phase, while distilled water and a water-based titration technique are used in the liquid phase. The makeup of each phase was shown.



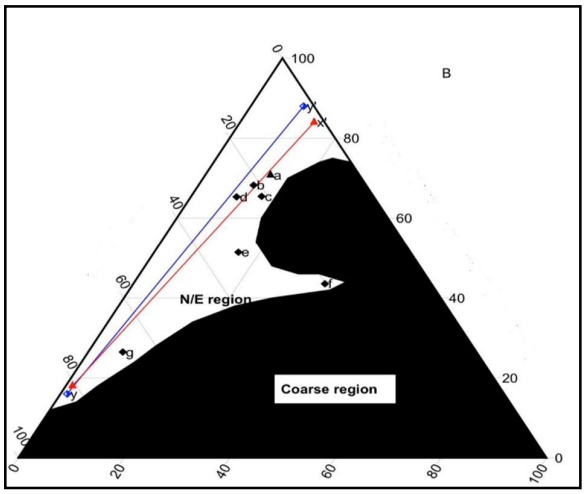


Fig 4: Diagram of the ternary phase shown at (1:1) Water, oleic acid, and the Smix ratio
Figure 5: Ratio 1:1.5 shows the ternary phase diagram. Olive oil, water, and the Smix ratio

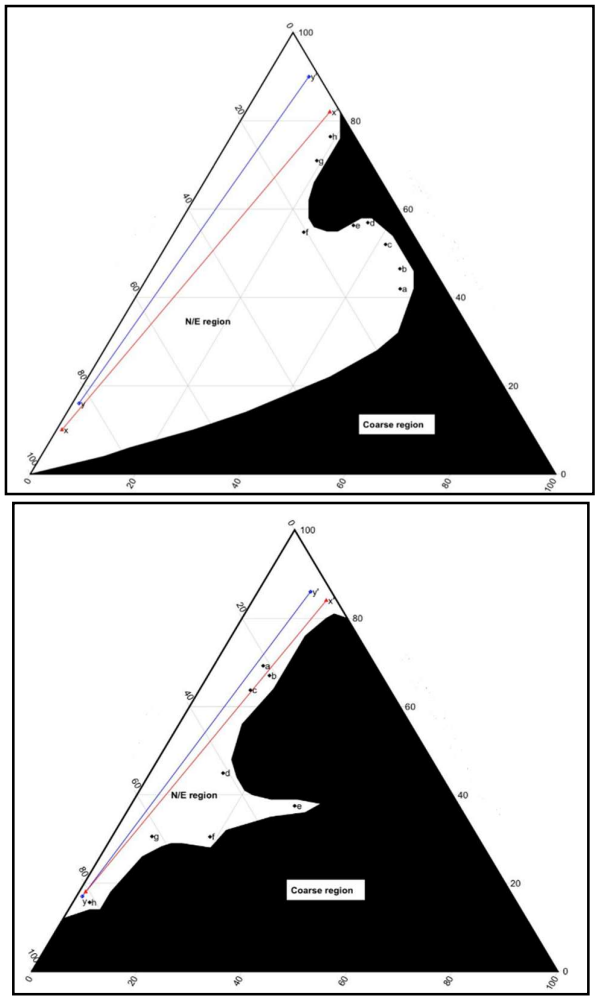


Figure 6: Drawing of the ternary phase diagram at (1.5:1) Smix ratio, water-based, and oleic acid
Figure 7: Drawn at (1:2) is a ternary phases diagram. Olive oil, water, along with the Smix ratio

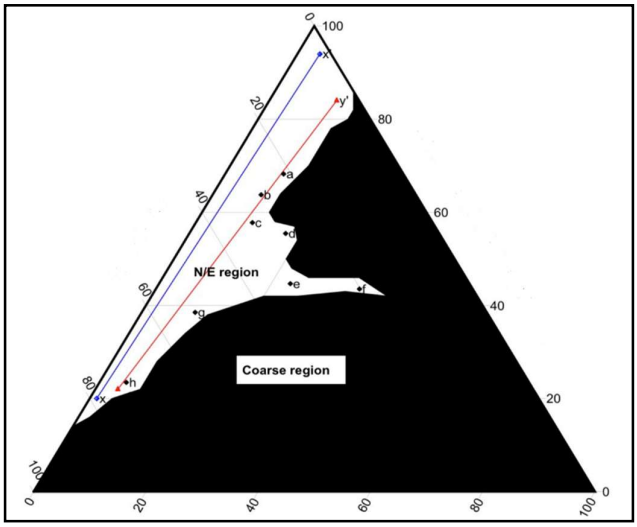


Figure 8: Diagram of the ternary phase shown at (2:1) Water, oleic acid, as well as the Smix concentration

Formulation of Bexagliflozin Nano-emulsion Formulation

After combining a proportionate combination of Smix with oil phase, the water-based preparation is made. After that, the medication is added and loaded one by one while being continuously agitated and sonicated. The foundation of the formulations is the quantity of the medication and the configuration of the water-based phase, which were kept at 0.01% and 10.3% by weight, respectively.

Characterisation of the formulation

Droplet Size Distribution

The nano-emulsion's polydispersity value and globule size were determined using the Malvern Zeta-Sizer Micro sequence. A thorough graphical depiction is given in figures, which were produced after the data was acquired. Each combination resulted in globules with a similar range of sizes between 27.02 and 333.7 nm. The formulation's median globule has a better chance of matching the nanoemulsion's characterization (50–200 nm) when combined with the lowest polydispersity index, which shows a similar droplet size.

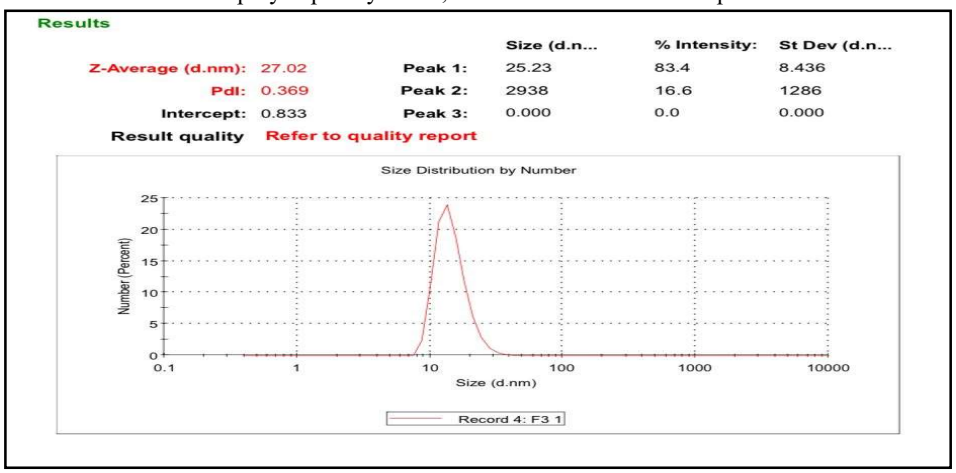


Fig 9: Droplet size and distribution of final formulation

Morphology study of formulation

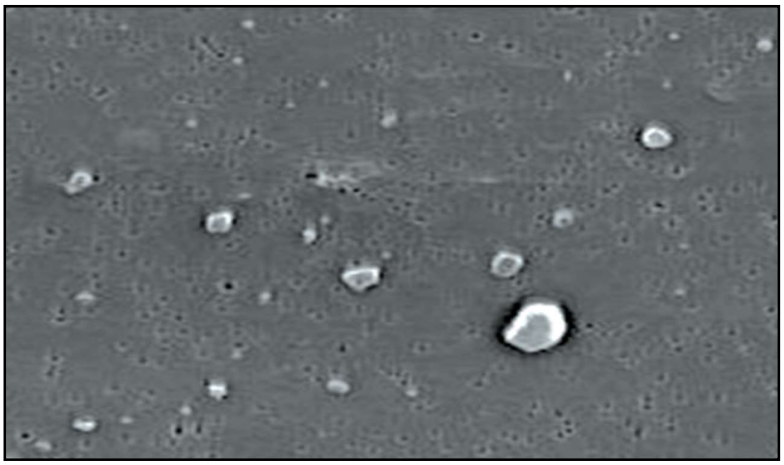


Fig 10: Morphology of nano emulsion formulation

Refractive Index

The reflective indices of all the nano-emulsion formulations were found to range from 1.3621 or 1.3793 at around 20 0C and from 1.3684 to 1.3741 at around 25 ^{0}C.

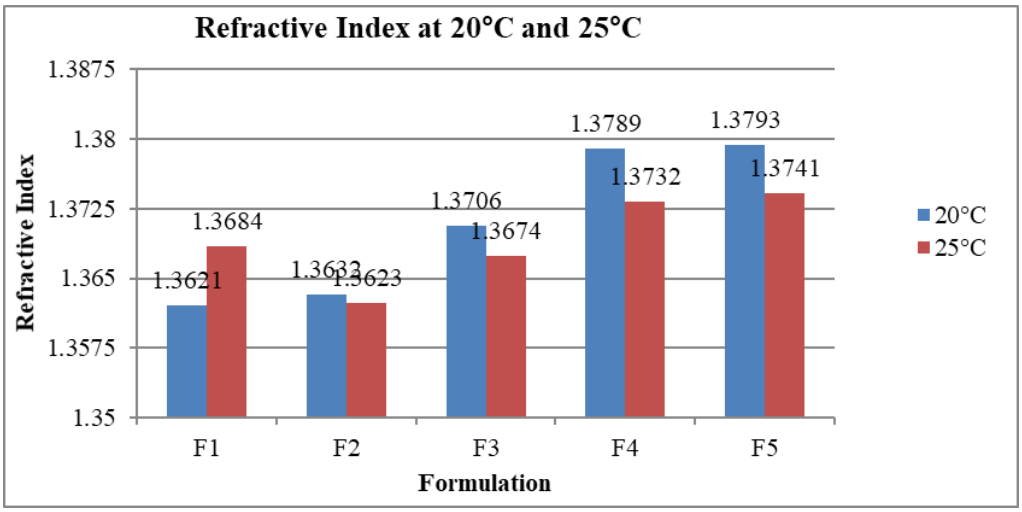


Fig 11: Refractive index of formulation at different temp.

pH Study

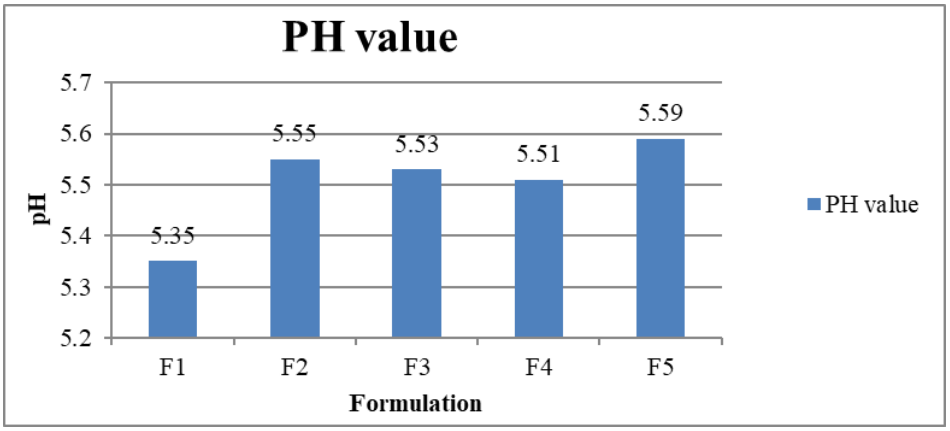


Fig 12: pH value of the different Formulations

Electrical Conductivity Study

This study explains the evolution of several ministructures and their rearrangement from an oil continuous state to a water sustained phase. The creation of a bi-continuous phase with electrical conductivity comparable to an o/w sort nano-emulsion occurred when the water component was added up to 250 µl.

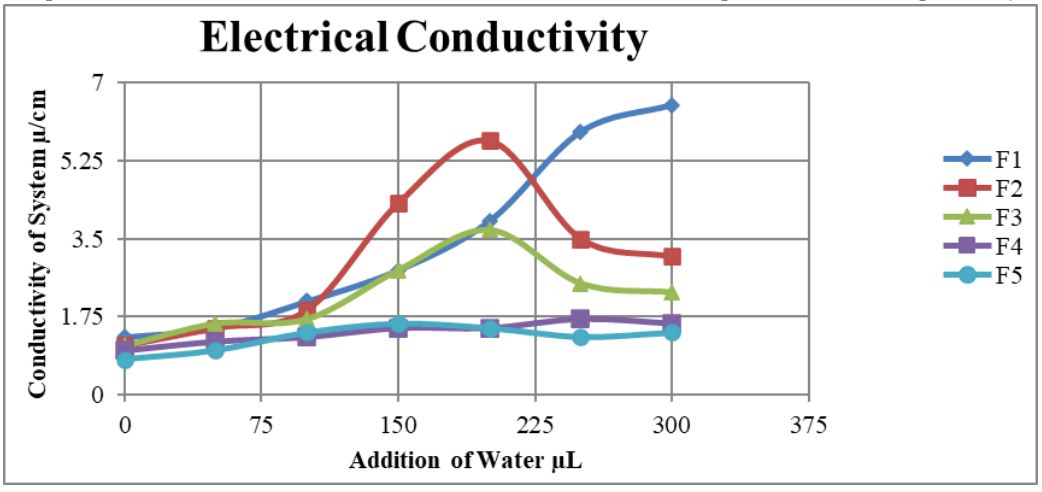


Fig 13: Electrical conductivity of different formulation

Viscosity Study

Table 3.7 provides the overall thickness of the nano-emulsion design, which is shown graphically and statistically in Figure. Viscosity (cP) and cladding ratios (10, 20, 40, & 50) were displayed on the formulation's schematic.

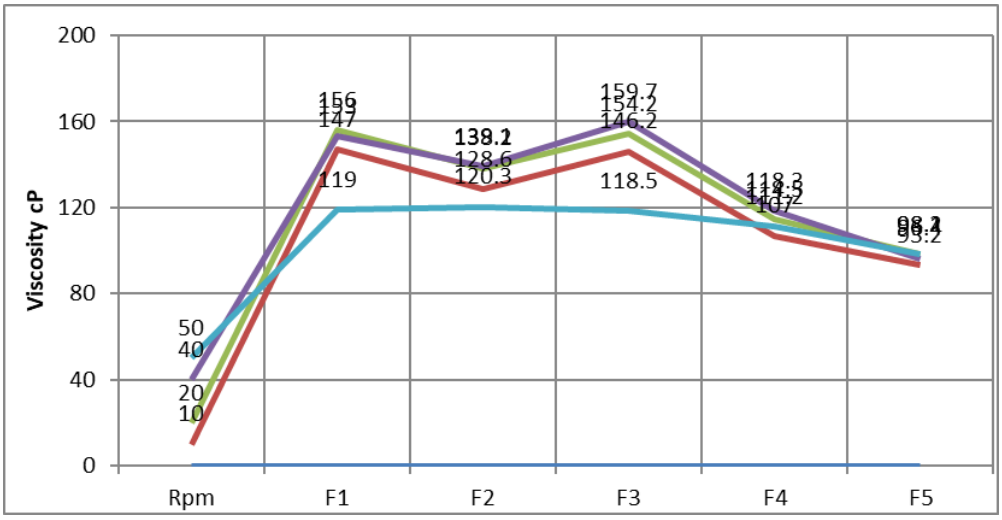


Fig 14: Viscosity of the nano-emulsion formulation

In-Vitro Drug Release Study

The in vitro releasing properties of each mixture were combined in Figure. It took some time for the nanoemulsion to dissolve, according to the results. Accordingly, nanoemulsion may be utilized for offering an anti-diabetic effect. The results also showed that the drug will remain in the circulation and release progressively in the gastrointestinal tract, demonstrating that the composition of the bexagliflozin nanoemulsion meets the criteria for an effective drug delivery system.

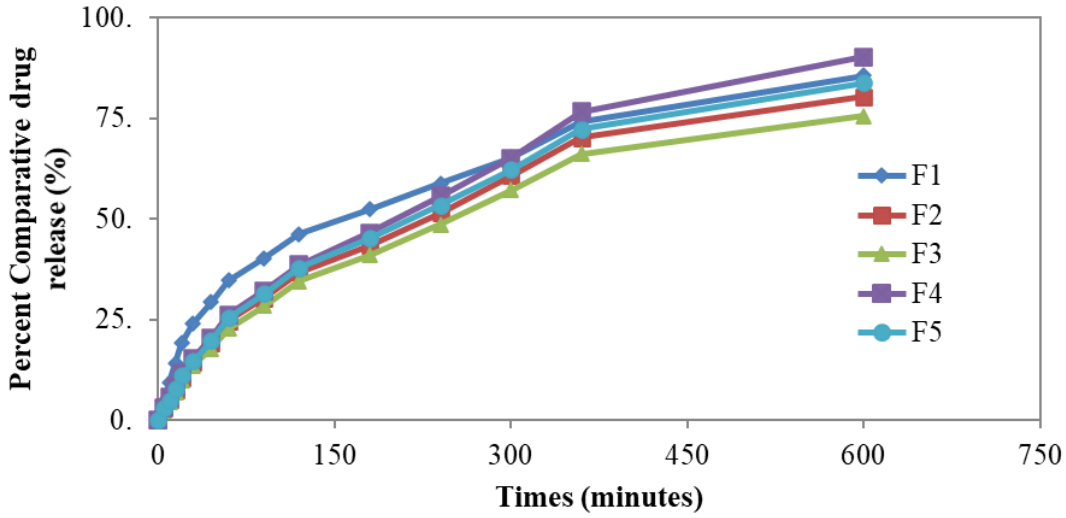


Fig 15: In-Vitro drug release study

Conclusion

In order to improve usage and dissolveability, the current study concluded that bexagliflozin is incorporated into nanoemulsion formulations utilizing an ultrasound treatment technique. Five formulations were developed in line with the architecture of the nano-emulsion. The recently identified composition of the nanoemulsion is denoted by codes F1, F2, F3, F4, along with F5. Several evaluation criteria, such as the size of the droplets presentation at 27.02 nm, the thermodynamic equilibrium test, TEM, pH of 5.59, electric conductivity, viscosity, and index of refraction of 1.3741, indicate that F5 is a better fit than F1 to F4. The Accelerated Stability test findings have shown that every combination remains consistent during the course of the investigation.

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