FORMULATION AND EVALUATION OF RIVAROXABAN NANOSUSPENSIONS

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ABSTRACT:

In the present study, an attempt was made to prepare Nanosuspension of Rivaroxaban is a factor Xa inhibitor used to treat deep vein thrombosis (DVT) and pulmonary embolism (PE). Nanosuspension containing the drug were prepared by precipitation method using combinations of polymers such as PVP K90, Sodium lauryl sulphate (SLS), urea, poloxamer, and methanol. Estimation of Rivaroxaban was carried out spectrophotometrically at 295nm. The Oral Nanosuspension were evaluated for various physical and biological parameters, drug content uniformity, particle size analysis, zeta potential, in-vitro drug release, short-term stability, drug-excipient interactions (FTIR). IR spectroscopic studies indicated that there are no drug-excipient interactions. The formulations F1 to F12 (containing PVP K-90, Urea, SLS, Poloxamer, and Methanol) used different ratio were found to be promising, of that formulation F12 containing combination ofPVP K-90, SLS, Poloxamer, and Methanolshowed 99.65% release at the end of 30 min & it follows zero order drug release kinetics. These formulations have displayed good Nanosuspension strength.

Keywords: Rivaroxaban, Nanosuspension, PVP K90, SLS, poloxamer, Urea and Methanol.

INTRODUCTION:

The formulation of pharmaceuticals successfully depends on a number of factors, including solubility, stability at ambient temperature, compatibility with solvent, excipient, and photostability. Over 40% of the novel chemical entities created to date by drug discovery programmes are lipophilic or have low water solubility.[1,2].There are several formulation strategies available to address the issues of low medication solubility and bioavailability. The traditional methods include micronization, the use of fatty solutions, the use of penetration enhancers or cosolvents, the surface - active scattering method, salt creation, precipitation, etc. Other methods include vesicular systems like liposomes, dispersal of solids, immersion and nanoemulsion techniques, and exclusion complexes with cyclodextrins. These methods show promise as drug delivery systems, but their main drawback is that not all medications can be delivered using them.[3]Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by surfactants.[4]Nanosuspensions consist of the poorly water-soluble drug without any matrix material suspended in dispersion.[5]These can be used to enhance the solubility of drugs that are poorly soluble in water as well as lipid media. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster. This approach is useful for molecules with poor solubility, poor permeability, or both, which poses a significant challenge for the formulators. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without any blockade of the blood capillaries.

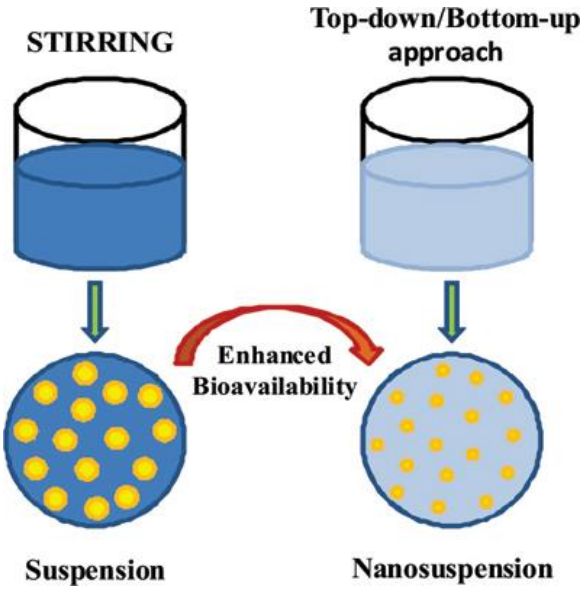

Fig .No.1.Development And Characterization Of Oral Nanosuspension

The suspensions can also be lyophilized and into a solid matrix. Apart from these advantages, it also has the advantages of liquid formulations over others[6].

NANOSUSPENSION MERITS[7]:

- Enhance the solubility and bioavailability of drugs.
- Suitable for hydrophilic drugs.
- Higher drug loading can be achieved.
- Dose reduction is possible.
- Enhance the physical and chemical stability of drugs.
- Provides a passive drug targeting.

DEMERITS:

- Problems are caused by physical stability, sedimentation, and compaction.
- Due to its weight, handling and transportation must be done with caution. incorrect dosage.

Rivaroxaban is used to treat or prevent blood clots (venous thrombo embolism, or VTE). Blood clots can occurin the legs (deep vein thrombosis, DVT) or the lungs (pulmonary embolism, PE) [8].Rivaroxaban has anelimination half-life of 26 hours, and is conventionally dosed once daily with immediate-release tablets.

Rivaroxaban is bcs-II drug having poor aqueous solubility, particularly soluble at pH values above 4.5.

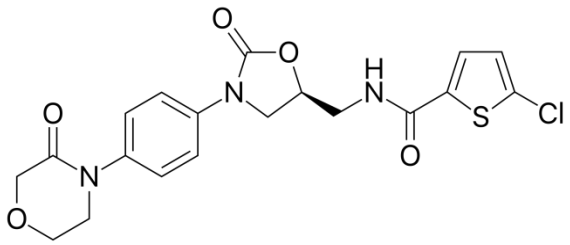

Fig.No.2.Structure of Rivaroxaban

MATERIALS AND METHODOLOGY:

Rivaroxaban,Polyvinylpyrrolidonek-90, sodiumlaurylsulphate,urea,poloxamer, methanol,water,hydrochloric acid.

Nanosuspension Preparation Method:

Method of precipitation

Preparation: Utilizing PVP K-30, UREA, SLS, and Poloxamer 188 as polymers, the consumable nanosuspension of rivaroxaban was made using the nanosuspension precipitation technique.Precipitation technique was used to create a nanosuspension of Rivaroxaban using a variety of carriers and medication. The measured accurately of Rivaroxaban was first taken and dissolved in an organic solvent called acetone in a beaker. The organic phase is the mixture of the medication and acetone. Now that the carriers Urea and PVP have been dispersed in the water and a surfactant (SLS) has been added, the stabiliser solution has been designated as being in the aqueous phase. To ensure equal mixing, this solution was maintained on a magnetic stirrer. The aqueous phase was gradually filled with the organic phase, adding drops at a time, as the magnetic stirrer continued to stir.

PREPARATION OF CALIBRATION CURVE OF RIVAROXABAN :

Procedure forstandard curve in6.8 pH buffer:

10mg of Rivaroxaban was dissolved in 10ml of 6.8 pH Buffer by slight shaking (1000 mcg/ml). 1mlof this solution was taken and made up to 10ml with 0.1N HCL, which gives 100mcg/ ml concentration (stocksolution).Fromthestocksolution,concentrationsof5,10,15,20, 25 and30 µg/mlin 6.8 pH Buffer were prepared. The absorbance of diluted solutionsweremeasuredat295 nm andastandardplotwasdrawnusingthedata obtained.

Table.No.1:Composition of Nanosuspensions of Rivaroxaban precipitation method

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
RIVAROXABAN (5mg/5ml)	40	40	40	40	40	40	40	40	40	40	40	40
PVP-K90	2.5	5	7.5	2.5	5	7.5	-	-	-	2.5	5	2.5
UREA	2.5	5	7.5		-	-	2.5	5	7.5	2.5	5	5
SLS	-	-	-	2.5	5	7.5	2.5	5	7.5	-	-	7.5
POLOXAMER	10	10	10	10	10	10	10	10	10	10	10	10
METHONOL	5	5	5	5	5	5	5	5	5	5	5	5
WATER(ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

RESULTS AND DISCUSSIONS:

Solubility Studies:

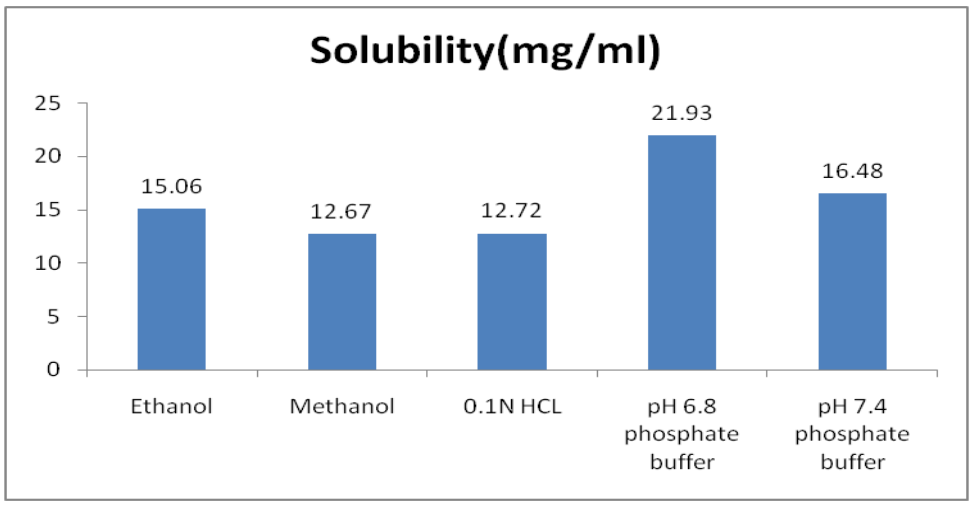

Fig.No.3:Solubility studies of Rivaroxaban

UV Spectrum:

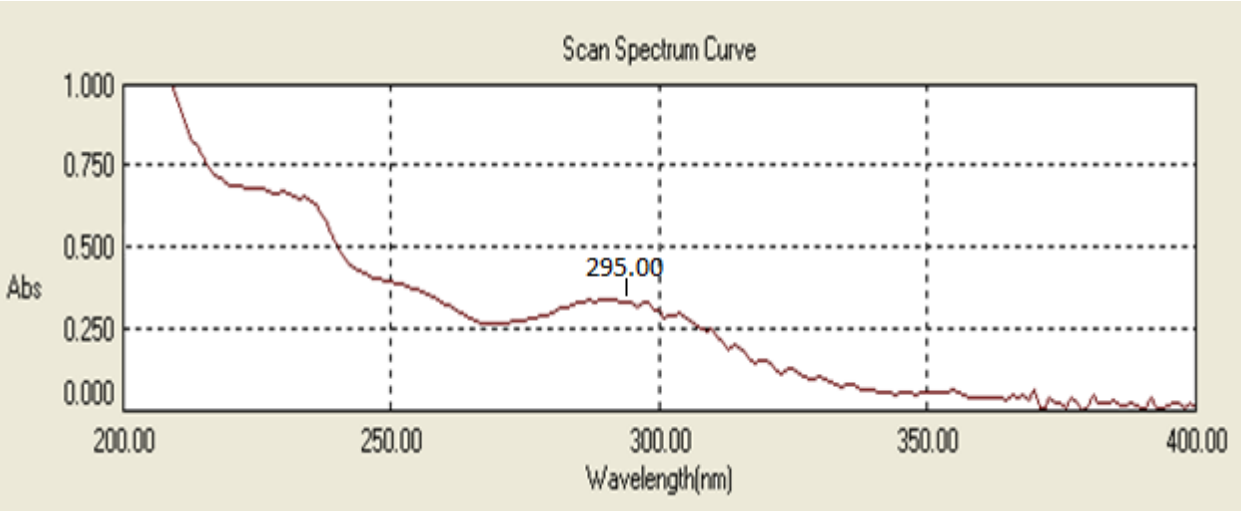

Fig.No.4:UV spectrum of Rivaroxaban

Standard Calibration Curve:

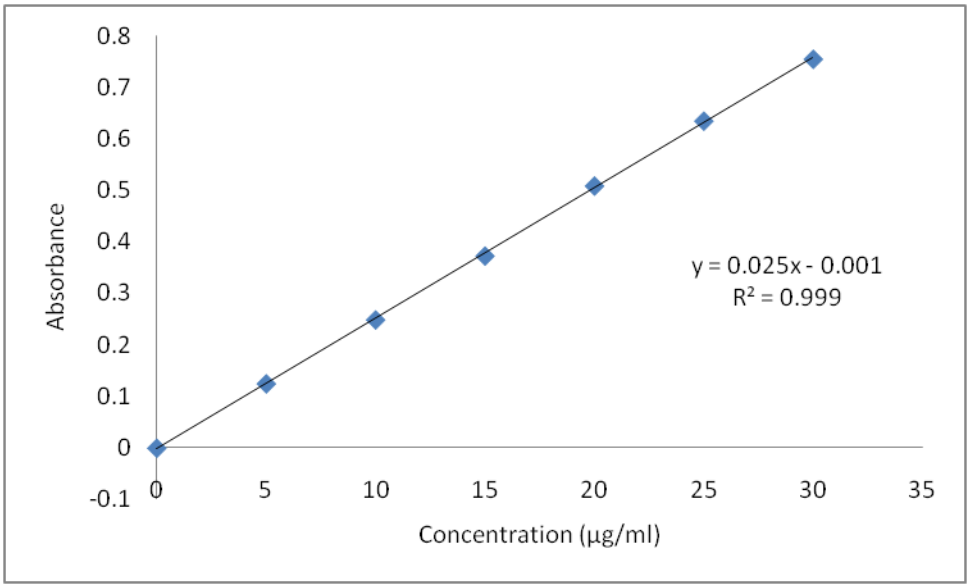

Fig.No.5.Standard calibrationcurve of Rivaroxaban inpH 6.8 Buffer

FTIR Studies:

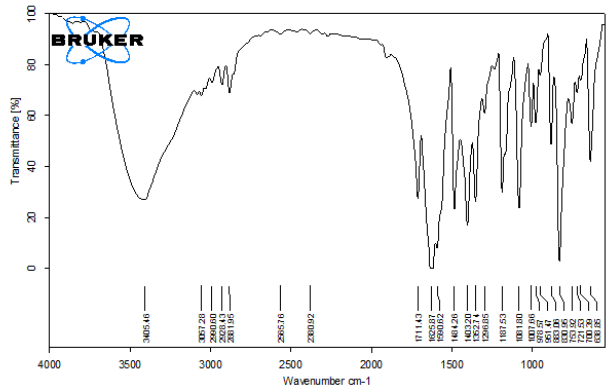

Fig.No.6.IR spectrum of Rivaroxaban

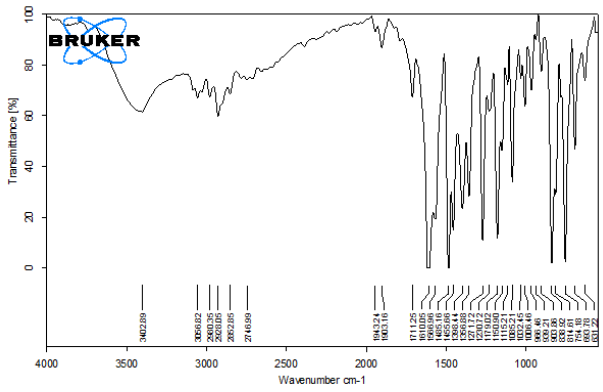

Fig.No.7.IR spectrum of RivaroxabanOptimised Formulation

Scanning Electron Microscopy:

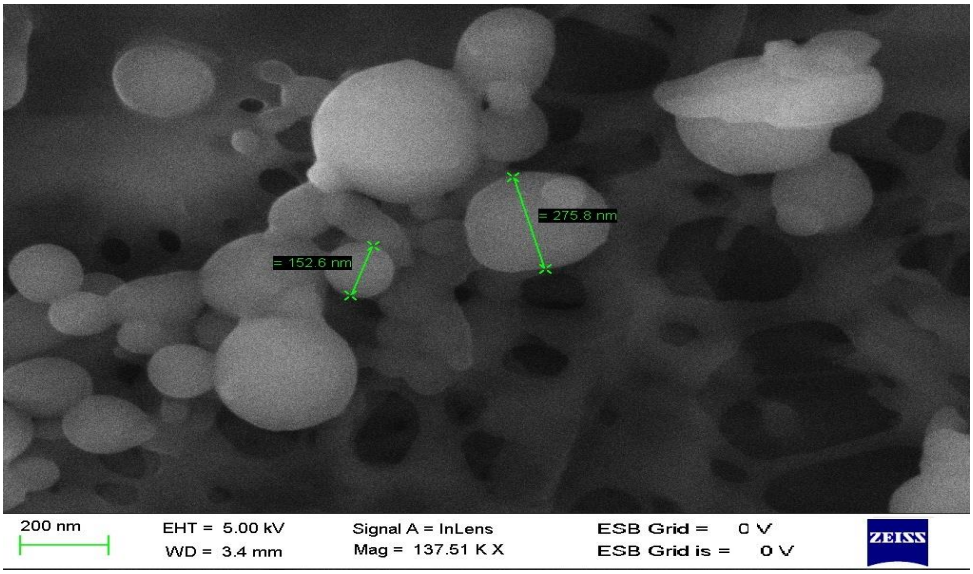

Fig.No.8.Scanning Electron Microscopyof Optimized Formulation

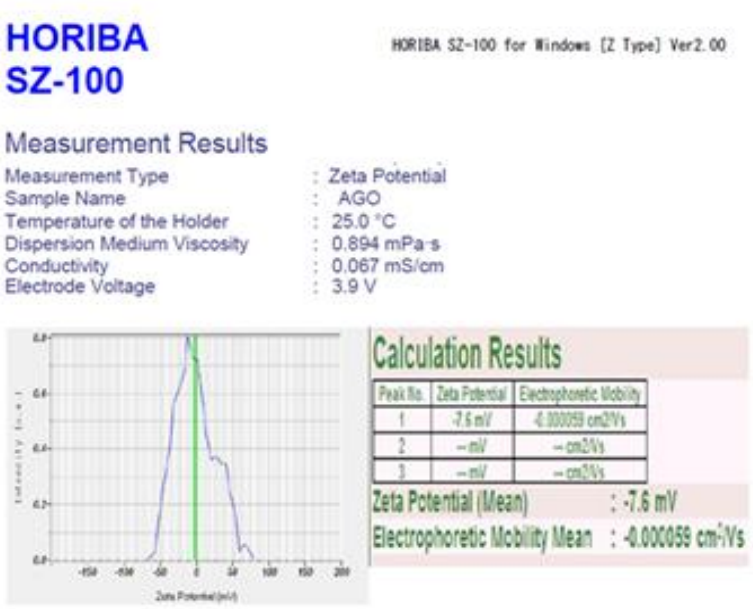

Fig.No.9.Zeta potential value for the optimized formulation (F12)

DISSOLUTION RESULTS:

Table.No.2:*In-vitro* drugrelease data of formulation F1 – F12

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	**0**
5	11.65	22.53	30.45	32.78	46.08	51.64	30.56	32.49	44.84	37.78	42.08	**59.64**
10	24.63	32.18	34.85	42.07	68.63	67.53	34.86	44.18	52.48	44.07	60.63	**68.53**
15	36.86	36.86	49.68	59.94	72.04	79.61	47.75	52.49	69.49	59.94	64.04	**79.61**
20	42.16	47.63	53.49	69.19	76.48	84.49	50.94	60.89	74.52	67.19	71.48	**88.49**
30	52.08	58.35	69.62	75.65	85.65	97.65	62.85	75.49	88.34	74.65	85.65	**99.65**
45	68.65	75.58	78.68	78.45	98.05		79.18	89.04	95.53	79.45	96.05	
60	78.48	88.39	90.65	88.36			85.69	97.61		90.36		

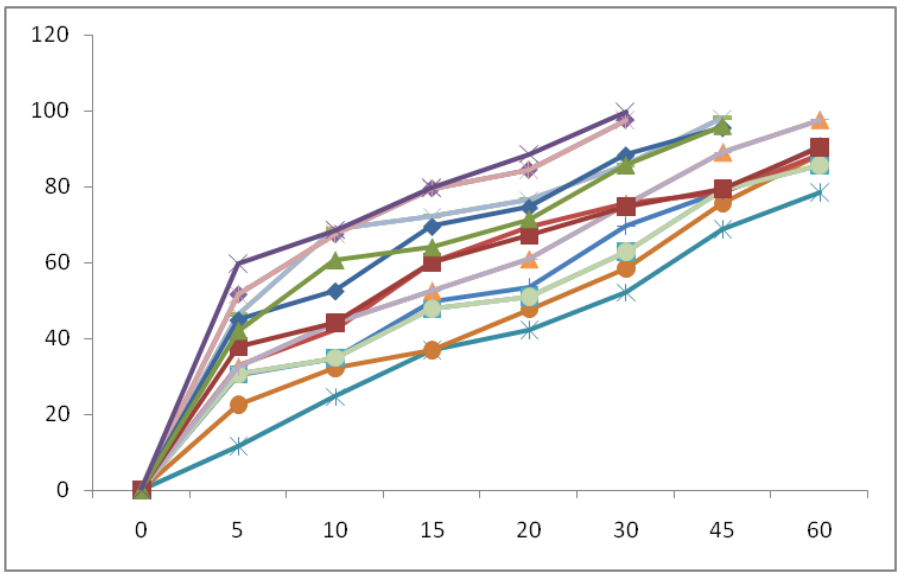

Fig.No.10.Dissolution parameters for theformulations F1-F12

Release Kinetics for Formulation{F12}:

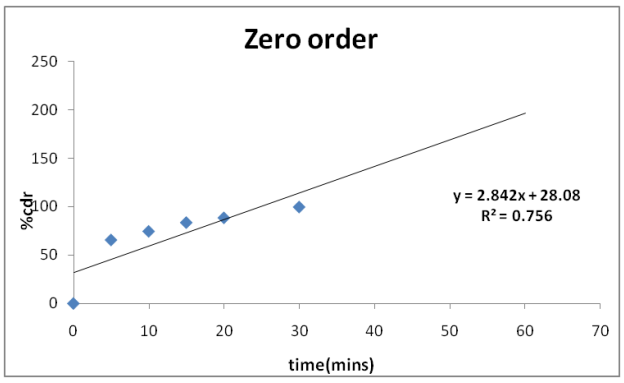

Fig.No.11.Zero order release

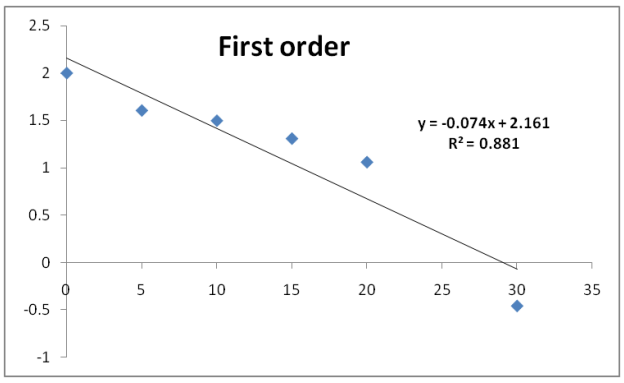

Fig.No.12.First order release

SUMMARY&CONCLUTION:

A factor Xa inhibitor called rivaroxaban is used to treat pulmonary embolism and deep vein thrombosis (DVT) (PE). The medicine is effectively absorbed from the gastrointestinal system, but because of substantial first pass metabolism, its bioavailability is poor. A significant amount of distilled water and combinations of the polymers PVP-k90, urea, methonol, SLS, and Poloxamer were used to generate a nanosuspension containing medication utilising the precipitation technique. Spectrophotometric estimation of Rivaroxaban was done at 295 nm.

By using the capillary technique, the melting point of Rivaroxaban was discovered to be between 177°C and 178°C. The 6.8 pH buffer medium has better solubility than other buffer solutions, according to the aforementioned solubility experiments of other buffers. 6.8 devised a straightforward Spectrophotometric technique for estimating Rivaroxaban.As seen in the picture, the pH buffer medium had a maximum at 295 nm in the Beer's range of 5–30 g/ml. According to the results of the drug excipient compatibility investigations, there are no interactions between the pure drug (rivaroxaban) and the ideal formulation (rivaroxaban with excipients), which suggests there are no physical alterations.The entrapment efficacy of formulation F1 was found to be 83.23%, that of formulation F2 to be 85.15%, that of formulation F3 to be 87.45%, that of formulation F4 to be 96.07%, that of formulation F5 to be 88.23%, that of formulation F6 to be 97.14%, that of formulation F7 to be 93.26%, that of formulation F8 to be 95.15%, and that of formulation F9 to be 97.26%. F10 was discovered to be 82.46%, F11 to be 94.27%, and F12 to be 98.52%. So, 98.52% was found to be the optimal formulation for F12.Surface morphology of Rivaroxaban nanosuspension of optimized formulation (F12) was carried out by scanning electron microscopy (SEM) and which shows that it was acceptable.

The improved formulation's (F12) zeta potential value was discovered to be -7.6 Mv, indicating that it was within acceptable bounds.

The improved formulations' (F12) average nanosuspension particle size was determined to be satisfactory with allowable limits.

According to the aforementioned in vitro investigations, the formulation (F12) including PVP, SLS, and POLOXAMER exhibits the best drug release, with a rate of 99.65% within 30 minutes, whereas the other formulations require between 35 and 60 minutes to release the medication. The best formulation (F12) underwent in vitro release kinetics tests in which it was fitted into zero order and first order, demonstrating that the best formulation adheres to zero order release kinetics with an R2 value of 0.756.

From the present study, the following conclusions can be drawn:

• Rivaroxaban oral nanosuspension may be made utilising the precipitation process and a suitable amount of distilled water in conjunction with the polymers PVP-K90, UREA, METHONOL, SLS, and POLOXAMER.

• It was discovered that every formulation that had been created had an acceptable level of entrapment efficiency, ranging from 82.46% to 98.52% in each case.

• As the amount of polymer rises, the drug release rate drops while the strength of the nanosuspension increases.

• Zero order release kinetics and drug release were seen in optimised formulations of nanosuspensions.

• Studies using IR spectroscopy revealed that there are no interactions between drugs and excipients.

• When compared to all other formulations, F12 is the best formulation, demonstrating 99.65% effective drug release after 30 minutes and adhering to zero order release dynamics

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