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Formulation And Evaluation Of Clarithromycin Nanosuspension

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ABSTRACT:

Background: Oral administration is the preferred route for drug delivery, but many drugs face challenges due to poor water solubility. This leads to inadequate bioavailability and variability in plasma levels. Macrolide antibiotics like clarithromycin (CAM) often have low bioavailability, with only about half of their active content being soluble.

Objectives: The primary aim of this study was to enhance the bioavailability of clarithromycin by developing a stable nanosuspension using the nano precipitation technique. Specific objectives included evaluating the physicochemical properties of the formulations and assessing their drug release profiles.

Materials and Methods: Clarithromycin was processed using the nano precipitation technique to create four formulations (F1-F4) with varying concentrations of Poloxamer 188 (stabilizer) and Sodium Lauryl Sulfate (SLS) (surfactant). The resulting nanosuspensions were analyzed for particle size, zeta potential, and polydispersity index, while compatibility studies confirmed no significant chemical changes between the drug and excipients.

Results: The formulations exhibited drug content ranging from 65 ± 0.3% to 98 ± 0.12%. Average particle sizes were measured between 96.4 nm and 511.7 nm across the formulations. Formulation 4 (F4) demonstrated the most desirable stability and characteristics. F4 had the highest cumulative percentage of drug release in 30 minutes, indicating an optimal formulation for enhanced bioavailability.

Conclusion: The nano precipitation technique enhanced the solubility and bioavailability of clarithromycin, with formulation F4 showing the best stability and drug release profile. This suggests its potential for improving therapeutic efficacy. Further studies are recommended to investigate its in vivo performance.

KEYWORDS*: Nanosuspension, Clarithromycin, Nano-precipitation, Particle size, In-vitro drug release.*

1. INTRODUCTION:

Due to its simplicity and ease of use, the verbal method of medication management is the most recommended method. Additionally, it has benefits including less adverse effects, ease of consumption, patient acceptance, and painless administration. Because 40% of newly created drug moieties are hydrophobic in nature, formulation scientists have been concentrating increasingly on the development of innovative medication delivery methods in recent years.[1-3] The best method for boosting absorption and, consequently, bioavailability is to prepare a nano solution that exhibits an increase in permeability and solubility. Pharmaceutical a submicron colloidal dispersion of drug particles at the nanoscale is called nanosuspension suspended as a dispersion and stabilized by surfactants. The drug particles are poorly water soluble and do not contain any matrix material.[4-6]Since more and more poorly water-soluble medications are being launched in the pharmaceutical era, drugs with low aqueous solubility are becoming a bigger problem in the creation of new drugs.[7-9] The drug's permeability, solubility, and capacity to dissolve in a medium all affect how bioavailable it is.[10-12] One major obstacle to a drug's therapeutic efficacy with regard to its mode of delivery is bioavailability.[13-15] The method by which solid medication particles dissolve in physiological fluid surrounding them is known as dissolution. One of the main problems with the clinical application Class II of the Biopharmaceutics Classification System (BCS) medications is their low water solubility.[16-18] The Poorly soluble BCS Class II medications' solubility, rate of dissolution, and bioavailability can be improved by using conventional methods like mucoadhesive microspheres, cyclodextrin complexation, solid dispersion, liposomes, salt creation, pH changes, micronization, chemical modification, self-emulsifying systems, microemulsions, nanoparticles, and nanosuspensions. Using these techniques, the medication is prepared and kept as a nanoparticle, which is subsequently suspended to produce nanosuspensions in a liquid, typically water.[19-23] An increasingly common method for increasing solubility is the use of nanosuspensions. In a top-down approach, One way to make nanosuspensions is to shrink the size of big drug particles to nanoscale, or in a bottom-up approach, by precipitating dissolved molecules into crystals. Zirconium beads and stabilizer were utilized in the top-down media milling procedure to mechanically grind the medication and create nanosuspensions. Media milling is easy to scale up and does not require organic solvents like other nano scaling methods do.[24-27]

The medication is agitated into an aqueous phase after being dissolved in an organic phase,resulting in supersaturation and crytal formulation.[28] A stabilizer is used to keep the generated nanoparticles stable. A medication classified as Clarithromycin, a member of BCS Class II, has poor solubility and high permeability.[29,30] The problem of solubility and bioavailability is frequently addressed using the nanosuspension technique.[31,32]

2.MATERIALS AND METHOD:

Materials:

Clarithromycin is a gift sample from Murli Krishna Pharma Pvt. Ltd., Ranjangaon. Chitson, Poloxamer 188, Ethyl acetate were procured from Chemdyes corporation, Rajkot and SLS were procured from Sourav scientific, Pune.

Methods:

The process of nano precipitation has been utilized to create polymeric nanoparticles. Clarithromycin drug was completely dissolved in organic solvent that is ethyl acetate. Then organic phase prepared after that solution was filtered through 0.45 µm size to remove precipitated impurities. Separately anti solvent phase was prepared by dissolving polymer chitosan and Poloxamer 188 and surfactant Sodium Lauryl Sulfate (SLS) in distilled water. The aqueous phase was prepared. After that organic phas was injected drop wise into prepared anti-solvent phase by using mechanical stirrer at 4000 RPM for 1 hour. Using a probe sonicator, the resulting nanosuspension was ultrasonically sonicated for various time period. Temperature was maintained at 37 ± 1°C and formulation was stored in suitable container. As shown in Table No.2 and Fig. 1

Table No. 1: Formulation of Clarithromycin Nanosuspension

Formulation Code	Drug (mg)	Polymers		SLS (Surfactant) (mg)	Ethyl acetate (Solvent) (ml)	Water (ml)
		Chitosan (mg)	Poloxamer 188 (mg)			
F1	50	0.33	10	4	10	100
F2	50	0.33	30	4	10	100
F3	50	0.99	10	8	10	100
F4	50	0.99	30	8	10	100

Fig. 1: Formulation of Different Batches of Clarithromycin Nanosuspension

3.CHARACTERIZATION OF OPTIMIZED NANOSUSPENSION:

1. Total Drug Content:
   At 211 nm, The UV-Visible spectrophotometer was used to measure the drug content. After making the nanosuspension, one milliliter was extracted and diluted using a pH of 7 Phosphate Buffer.
2. Particle size analysis:

The SZ-100 instrument from Horiba Scientific was used to measure the particle size. Because particle size affects surface area and porosity, it is essential to assess it in order to ensure product bioavailability, efficiency, and half life.

3. Zeta potential:
   One significant and easily measured measure The zeta potential is a measure of colloidal dispersions stability. The strength of the electrostatic force between nearby, similar the amplitude of the zeta potential indicates the presence of charged particles in dispersion. The stability of nanoparticles in suspension and the primary driver of their initial adsorption onto the cell membrane are both influenced by the zeta potential, which is based on the surface charge. The particle size determines the endocytotic absorption rate following adsorption.
4. Polydispersity Index (PI):
   The distribution measuring molecular weights of polymer chains inside a certain polymer is indicated by the polydispersity index (PI); Heterogeneity in cross-linking, network formation, chain length, branching, and hyper-branching will become more unpredictable as the PDI value increases.
5. Drug Entraptment Efficiency (DEE):
   Using spectrophotometry, the entrapment efficiency or percentage of integrated indomethacin in was calculated at 211 nm. After centrifuging the aqueous sample for five minutes at 5000 r.p.m., the

amount of free drug was discovered in the supernatant. The amount of integrated drug was calculated by subtracting the free drug from the original drug.

The percentage efficiency (EE %) could be achieved by the following equation: Entrapment efficiency (%) = W initial drug – W free drug/ W initial drug X 100

6. *In-vitro* drug release study:

The method of dialysis membrane diffusion was applied. 10 ml of the nanosuspension were added to the diffusion cell device. Using a dialysis (donor compartment) with the nanosuspension. The amount of medication released from the nanosuspension was monitored while it was fixed in a water jacketed beaker containing 300ml of 7 pH phosphate buffer. For a full day, the system was maintained at 37±1ºC. Using a magnetic stirrer, the contents of the beaker were stirred. To keep the sink condition, Every so often, 5 ml of the sample was taken out of the receptor compartment and wrapped out for fresh medium. The UV spectrophotometer was used to measure the amount of medication dissolved at a wavelength of 211 nm.

4.RESULTS:

Preparation of calibration curve of clarithromycin:

A calibration curve for clarithromycin was developed by measuring absorbance at 211 nm. at various concentration in 7 pH Phosphate buffer. The resultant calibration curve is displayed in Table No. 2 and Fig. 2

Table No. 2: Calibration curve clarithromycin measured using UV Spectrophotometery at 211 nm

Sr. No.	Concentration (µg/ml)	Absorbance at 211 nm
1	0	0
2	2	0.081
3	4	0.1602
4	6	0.2391
5	8	0.3227
6	10	0.3995

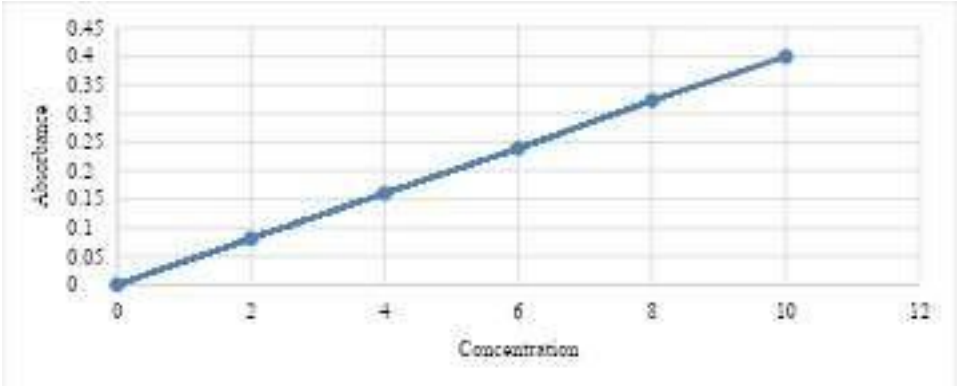


Fig. 2: Calibration curve clarithromycin measured using UV Spectrophotometery at 211 nm

FTIR Study:

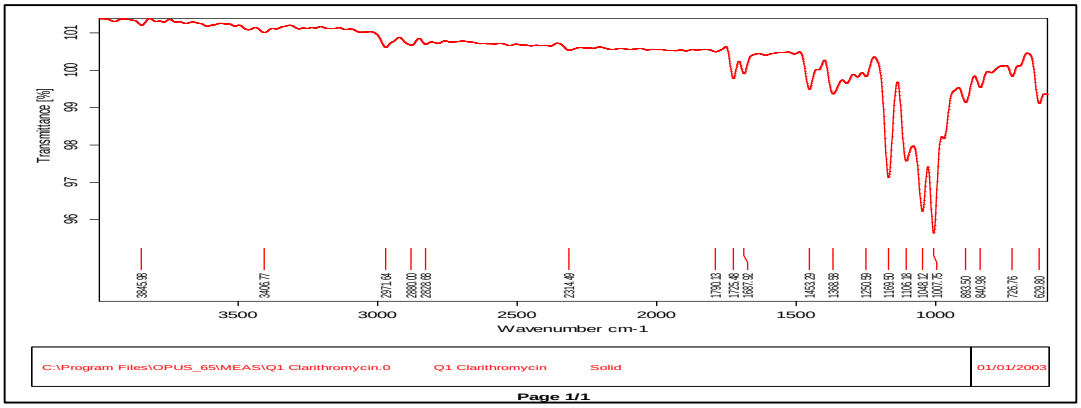


Fig. 3: FTIR Spectrum of Clarithromycin

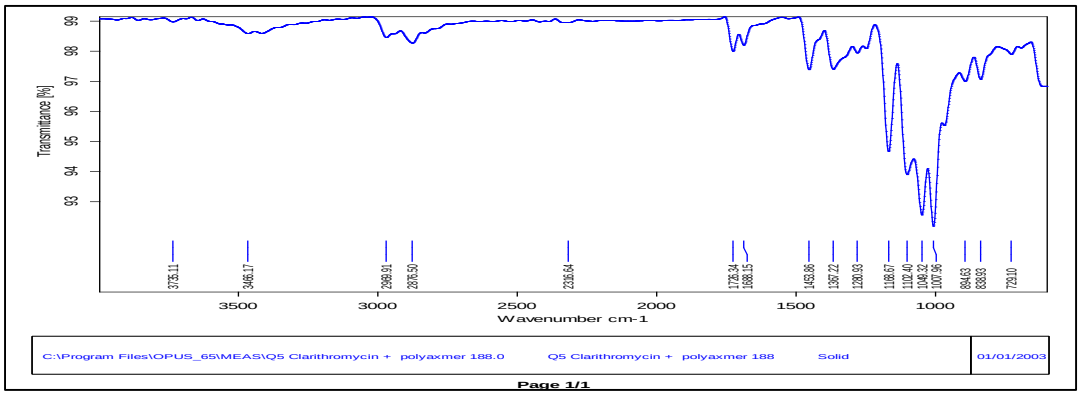


Fig. 4: FTIR Spectrum of Clarithromycin + Poloxamer 188

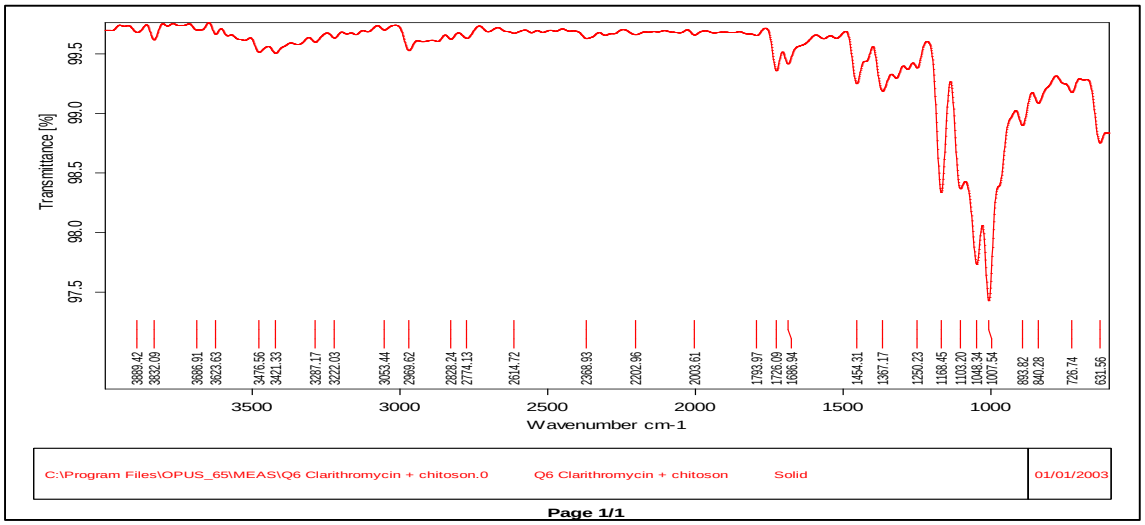


Fig. 5: FTIR Spectrum of Clarithromycin + chitosan

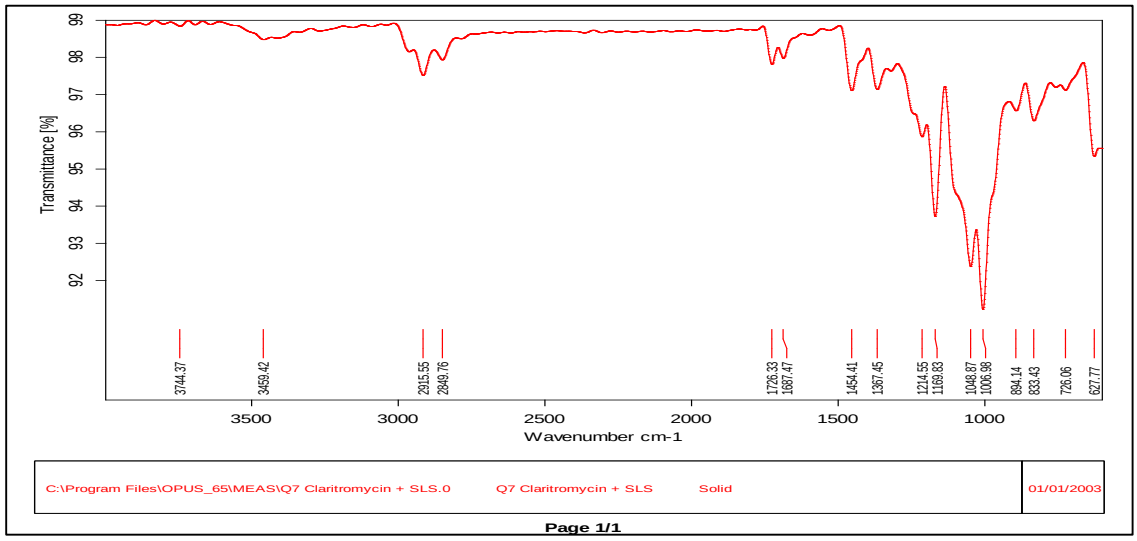


Fig. 6: FTIR Spectrum of Clarithromycin + SLS

From the FTIR spectra Figures 3 to 6, various functional groups of pure drug physical mixture and formulation of clarithromycin were observed. From the characteristics bands at 3406cm^{-1} represents O-H(free), 2876cm^{-1} represents N-H (stretching), 1453cm^{-1} represents C-H (stretching), 1688cm^{-1} represents C=N (stretching), 1725cm^{-1} represents C=O (stretching), 1453cm^{-1} represents C-H (bending), 1368cm^{-1} represents S=O (stretching), 1009cm^{-1} represents C-O (stretching), 1007cm^{-1} represents CO-O-CO (stretching). It demonstrated that the addition of excipients and subsequent formulation of the dosage form did not alter the functional group.

5.Characterization of Optimized Nanosuspention:

Total Drug Content:

All of the formulations' combined medication contents range from 53± 13% to 98± 11%, the optimized formulation F4 showed 98±10% and the results are shown in Table No. 3 and Fig.6

Table No. 3: Total Drug Content of Clarithromycin Nanosuspension

Formulation code	% Drug content
F1	61 ± 0.12%
F2	86± 0.17%
F3	53± 0.13%
F4	98 ± 0.11%

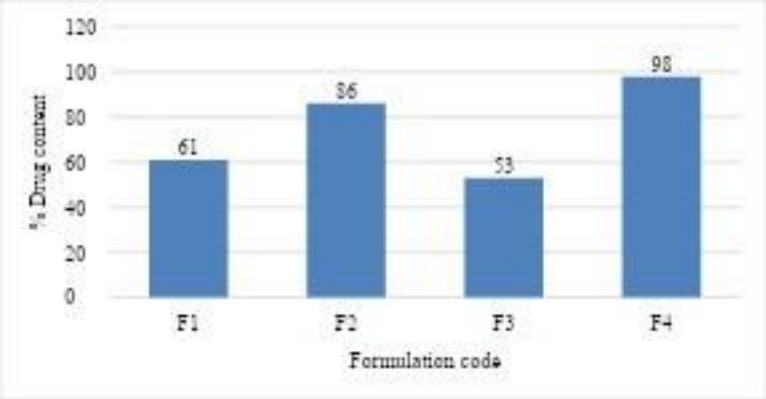


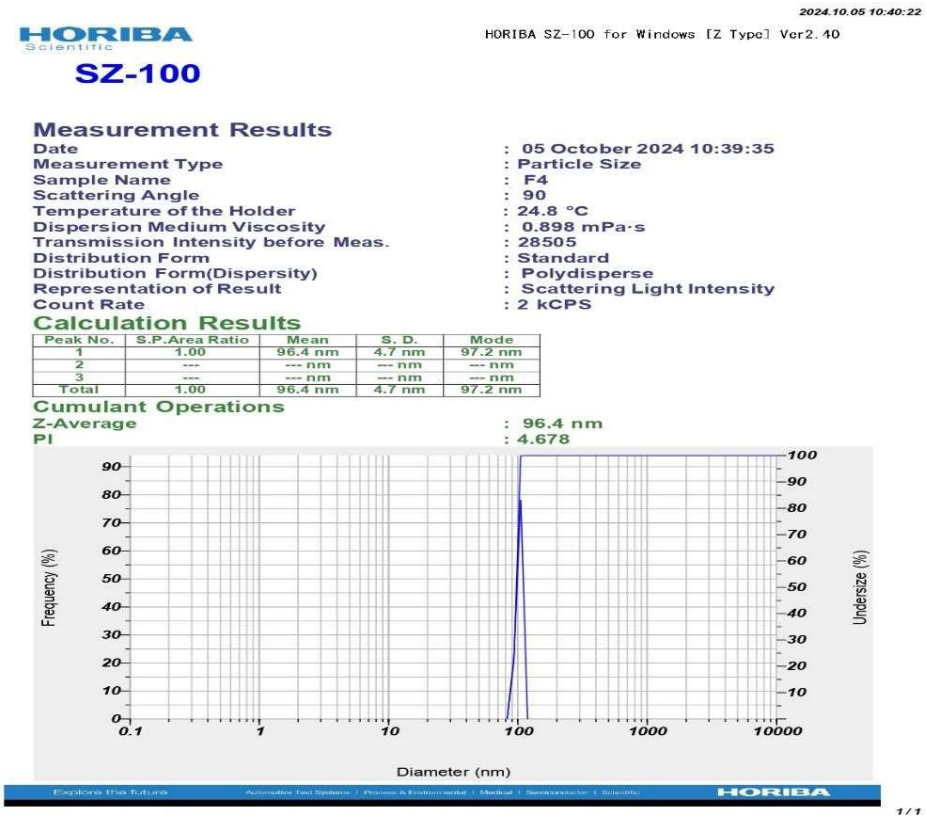
Fig. 6:Total Drug Content of Clarithromycin Nanosuspension

Particle size:

Particle size and dispersion were crucial factors in determining solubility. Particle size that contributes to the pure drug's increased solubility, dissolution, and bioavailability. The results are displayed in the Table 4. It was discovered that The mean particle size of the F1 to F4 batches was between 96.4 to 511.7 nm. The optimized batch of F4 formulation shown in Table No. 4 and Figure 7.

Table No. 4: Particle size of clarithromycin nanosuspension

Batch code	Particle size in nm
F1	458.0
F2	212.5
F3	511.7
F4	96.4



nanometer

Fig. 7: Optimized batch F4 formulation of clarithromycin nanosuspension

Polydispersity Index (PID):

The Particle Size Distribution degree is indicated by the Polydispersibility Index. The stability of the nanosuspension is preserved by the broad particle distribution shown by the high value of the Polydispersibility Index.The outcomes are displayed in Table No.

Table No. 5: Polydispersity index of clarithromycin nanosuspension

Batch code	Polydispersbility index
F1	462
F2	218
F3	522
F4	98.14

Zeta potential:

When electrostatic and sterric stabilization are coupled, A zeta potential of at least ±20 mV is preferred, but a maximum of ±50 mV is necessary. Table No. 6 present the outcomes of the stable system that was created by the valve of F4, which displayed the intended value.

Table No. 6: Zeta potential of Clarithromycin nanosuspension

Batch code	Zeta potential
F1	-49.7
F2	-47.0
F3	-51.3
F4	-48.1

In-Vitro Dissolution study:

The results of the in vitro breakdown of various clarithromycin samples are displayed in Fig. 8 in order to observe that increasing the Clarithromycin's rate of dissolution is accelerated by creating a nanosuspension by nano precipitation. Unmilled benidipine appears to dissolve at a low rate (65 ± 0.3%). Owing to the factorial design, the clarithromycin nanosuspension F4 optimized formulation exhibits an enhanced dissolution rate, with nearly 98 ± 0.12% of the drug dissolving during the first half-hour

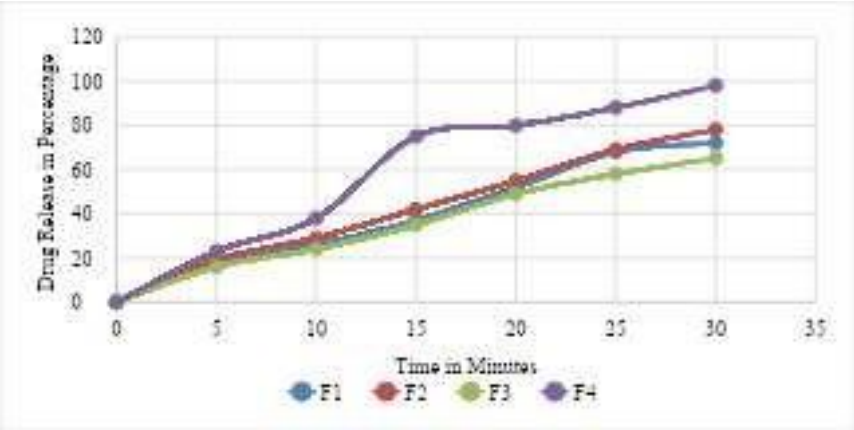


Fig. 8: *In Vitro* Drug Rlease of Batches of Clarithromycin Nanosuspension

6.DISCUSSION:

The study successfully developed a calibration curve for clarithromycin, measured at 211 nm using UV spectrophotometry, confirming its suitability for quantitative analysis. The absorbance data indicated a linear relationship, validating the calibration curve for future assessments of drug concentration.

FTIR analysis revealed that the addition of excipients did not alter the functional groups of clarithromycin, indicating compatibility and stability in the formulations. The observed peaks corresponding to various functional groups suggest that the structural integrity of clarithromycin was maintained throughout the formulation process.

The total drug content of the formulations varied, with the optimized formulation F4 demonstrating a high content of 98 ± 0.11%. This suggests effective incorporation of the drug into the nanosuspension.

Particle size is crucial for solubility and bioavailability; the mean sizes ranged from 96.4 to 511.7 nm, with F4 exhibiting the smallest size, which is favorable for enhanced dissolution. The polydispersity index values indicated a broad particle distribution, which can contribute to the stability of the nanosuspension.

Zeta potential measurements indicated that F4 had a stable system with a value of -48.1 mV, well within the desired range for electrostatic stability, suggesting good formulation stability.

In vitro dissolution studies showed that the optimized F4 formulation significantly improved the dissolution rate of clarithromycin, with nearly 98 ± 0.12% of the drug released within the first 30 minutes. This rapid release underscores the effectiveness of the nanosuspension approach in enhancing bioavailability.

Overall, the findings support the potential of clarithromycin nanosuspensions, particularly formulation F4, for improving therapeutic efficacy through enhanced solubility and dissolution rates. Further investigations, including in vivo studies, are warranted to confirm these results in clinical settings.

7. CONCLUSION:

The formulation of clarithromycin nanosuspensions using Sodium Lauryl Sulfate (SLS) as a surfactant, in combination with poloxamer 188 and chitosan, represents a significant advancement in drug delivery systems. This approach addresses the challenges associated with the poor solubility and bioavailability of clarithromycin, a commonly prescribed antibiotic. The nanosuspension method allows for the nanoscale particle size reduction, which greatly increases the drug's surface area and, as a result, its rate of breakdown. During the formulation process, the volume of the organic phase and the surfactant concentration are optimized.we were able to achieve a stable nanosuspension with improved solubility characteristics. This not only facilitates better absorption in the gastrointestinal tract but also enhances the overall therapeutic efficacy of the drug. The incorporation of biocompatible polymers such as chitosan and poloxamer 188 not only stabilizes the formulation but may also contribute to sustained release profiles and reduced side effects, thereby increasing patient compliance.
Furthermore, the flexibility in adjusting formulation parameters provides a tailored approach to address specific clinical needs, making this method highly versatile. Overall, the development of clarithromycin nanosuspensions holds promise for improving treatment outcomes in infections where this antibiotic is indicated, ultimately leading to better patient adherence to therapy and more effective management of bacterial infections. Future research may explore the long-term stability and in vivo efficacy of these formulations to fully realize their potential in clinical applications.

8. CONFLICT OF INTEREST:

The authors declare no conflict of interest related to this research
.

9. ABBREVATIONS:

CAM:Clarithromycin; BCS: Biopharmaceutics Classification System; SLS: Sodium Lauryl Sulfate; DEE: Drug Entrapment Efficiency; PDI: Polydispersity Index; UV: Ultraviolet; FTIR: Fourier Transform Infrared Spectroscopy; RPM: Revolutions Per Minute; pH: Potential of Hydrogen

10. AUTHOR CONTRIBUTION:

KM and AS designed the study and performed the experiment, AB and SK collected the data, AK and SP analysed the data, SJ and RM prepared the manuscript. All authors read and approval of final manuscript.

11. SUMMURY:

In order to improve the bioavailability of clarithromycin, a macrolide antibiotic with low water solubility, this study used the nano precipitation approach to create a stable nanosuspension. Stabilizer and surfactant concentrations were varied in four formulations (F1–F4). F4, the improved formulation, had the best in vitro drug release (98 ± 0.12% in 30 minutes), the smallest particle size (96.4 nm), the highest drug content (98 ± 0.11%), and a good zeta potential (-48.1 mV). Clarithromycin's structural integrity was validated throughout formulation by compatibility tests using FTIR. According to the results, clarithromycin nanosuspensions in particular, formulation F4 significantly increase solubility and therapeutic efficacy, which calls for more in vivo research. In clinical settings, this strategy presents a viable way to improve clarithromycin's efficacy.

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