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RESEARCH ARTICLE

Synthesis, Application and Evaluation of Bismuth Sulfide (Bi_2s_3) Metal Nanoparticles as Nanocarriers for Poorly Soluble Class II Drug Clarithromycin

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Abstract

Objective: The aim of this study was to evaluate the effect of bismuth sulfide Bi_2S_3 metal nanoparticles as carries on the pharmaceutical properties and biologic activity of Biopharmaceutical Classification System (BCS) class II drug clarithromycin (CLA). Methods: Bismuth sulfide (Bi_2S_3) nanoparticles synthesized by chemical co-precipitation technique, during which CLA loaded (incorporation method). Characterizations techniques including atomic force microscopy (AFM), X-ray diffraction (XRD) and fourier transform infra-red spectroscopy (FTIR) were used for particle size and particle size distribution, crystal lattice and compatibility, respectively. USP puddle apparatus type II (in phosphate buffer solution pH 7.4) was used for *in-vitro* release study. Disc diffusion method was the technique used to test the antibacterial activity of blank Bi_2S_3 nanoparticles; free CLA (as control) and CLA loaded metal nanoparticles. Results: CLA was loaded successfully with synthesized Bi_2S_3 nanoparticles by physical interaction without any chemical modification, as approved by FTIR. Particle size of CLA was reduced from 116.17 to 95.5 nm after loading process with uniform particle size distribution (as measured by AFM). *In vitro* release study demonstrated complete release of CLA from Bi_2S_3 nanoparticles after 120 min, indicating significant*increase in the solubility and dissolution profile of CLA after loading process. XRD spectrum showed lattice transition from crystalline into amorphous structure. Susceptibility test displayed significant*potentiation of antibacterial activity at all tested concentrations against gram +ve bacteria *Staphylococcus aureus* and *Bacillus subtilis* after loading of CLA with Bi_2S_3 nanoparticles, while gram –ve bacteria *E. coli* showed no response for CLA before and after loading process. Bi_2S_3 nanoparticles showed no antibacterial activity against all tested bacterial cultures. Conclusion: The use of synthesized metal Bi_2S_3 nanoparticles, as nanocarriers, was applied successfully as an attractive delivery system for the improvement in the solubility, dissolution profile and biologic activity of BCS class II drug CLA.

Keywords: *Class II drug; Clarithromycin (CLA); Bismuth sulfide (Bi_2S_3) nanoparticles.*

Introduction

Clarithromycin (CLA) is a broad spectrum semisynthetic macrolide antibiotic that produce its antibacterial activity by interfering with the synthesis of bacterial protein, where CLA binds to the 50S ribosomal subunit of susceptible bacteria and therefore hinder translocation of aminoacyl transfer RNA and thereby inhibit protein synthesis[1, 2].

CLA is used in the treatment of bacterial infections in respiratory tract, skin soft tissue, acute maxillary sinusitis, tonsillitis, pharyngitis, chronic bronchitis, pneumonia, as well as in *Chlamydia* and *Helicobacter pylori* infections [3]. CLA belong to class II of Biopharmaceutical Classification System (BCS), where drug present with high permeability and low solubility (0.33mg/ml)[4, 5]. To improve this low solubility of CLA many techniques were used, most importantly nanotechnology, as an attractive approach[6]. Because of CLA low aqueous solubility, slow rate of dissolution and therefore less amount of drug in solution with reduced absorption.

Additionally, extensive first pass metabolism and pH dependent solubility of CLA, leading to low bioavailability (50 - 55%) of CLA after oral administration[7]. That is why class II drugs of BCS assigned as having dissolution

rate limited absorption[8]. In the recent years, the application of nanotechnology as a delivery system approach was the scope to upgrade the physiochemical properties and performance of many drugs, where nanotechnology is the understanding and control of matter at nearly 1 to 100 nm dimensions[9, 10]. Medically, nanotechnology has numerous applications such as in the delivery of therapeutic drugs as well as in the development of treatments for a variety of diseases and disorders[11, 12]. Nanotechnology, by particle size reduction, can increase efficacy of many drugs and thereby minimize the risk of incidence of their side effect and toxicity [11, 13, 14].

As carriers for drug, many types of nanoparticles have been utilized to improve their pharmaceutical and biological properties. For example liposomes, niosomes, nanotube, nanocrystal, micelles and other materials[15, 16]. Another type of nanomaterials used, as nanocarriers, is metal inorganic nanoparticles. Metal nanoparticles are particles of metal, metal oxide or metallic composition presenting with at least one length scale in the range of nanometer. Because of their very small nano-size scale, these nanostructures appeared with significantly advanced and diverse physical, chemical, and biological properties[17, 18].

Bismuth sulfide (Bi_2S_3) nanoparticles, a member of inorganic nanoparticles, utilized in this study as a nano-carrier module for CLA. Medically, bismuth sulfide (Bi_2S_3) nanoparticles used in computed tomography (CT) imaging [19, 20]. The aim of the following study was to synthesize and characterize metallic-nanoparticles, (Bi_2S_3) nanoparticles, as a novel drug delivery system to improve and modulate the pharmaceutical (particularly solubility) and / or biological (antimicrobial spectrum) properties of low soluble BCS class II drugs. CLA used as a model drug for this study, as it belongs to class II drugs in the Biopharmaceutical Classification System (BCS).

Materials and Methods

Materials

Clarithromycin (CLA) Jiangsu Yew Pharmaceutical Co. Limited (China); sodium sulfide ($Na_2S.10H_2O$) Thomas Baker Co. Limited (India); bismuth nitrate Bi $(NO_3)_3.6H_2O$ Qualikems Fine Chem Co. Ltd. (India); acetone C_3H_6O Sigma Chemical Co. Limited (USA); dimethyl sulfoxide (DMSO) LobaChemie Pvt. Ltd (India).

Methods

Synthesis of Metal Nanoparticles, Bismuth Sulfide (Bi_2S_3)

Chemical co-precipitation technique was used to synthesize bismuth sulfide (Bi_2S_3) nanoparticles, where 0.1 M of disodium sulfide $Na_2S.10H_2O$ aqueous solution was titrated (10 drops per min) of onto 0.1 M of bismuth nitrate $Bi(NO_3)_3.6H_2O$ aqueous solution with specialized conditions (vigorous stirring at 1100 rpm and heating at 80 °C) using a magnetic stirrer (Dragon Lab, USA).

As dropping proceed, the color of bismuth nitrate aqueous solution was altered from white into black color. After completion of the titration, stirring continued vigorously at 1100 rpm and the temperature was hold constant at 80 °C for 3 h. Black sticky nanoparticles of Bi_2S_3 were produced, which was then filtered. After filtration, Bi_2S_3 nanoparticles were washed using deionized water. Then, to ensure complete drying, put Bi_2S_3 nanoparticles in silica gel containing desiccators for 3 days [21, 22].

$$3Na_2S + 2Bi\ (NO_3)_3 \rightarrow Bi_2S_3 + 6NaNO_3$$

Loading of Drug, Clarithromycin, with Bi_2S_3 Nanoparticles

Loading of CLA with Bi_2S_3 nanoparticles was achieved during synthesis process of Bi_2S_3 nanoparticles. A technique known as incorporation method, where CLA added in the last step of Bi_2S_3 nanoparticles synthesis before the completion of disodium sulfide titration. Where 0.1 M of CLA was prepared using acetone as a solvent. When titration completed, stirring was continued for 3-4 h. Finally, the metallic nanoparticles loaded drug were filtered, washed by deionized water and then dried in silica gel containing desiccator to be collected [23-26].

Characterization Techniques of Drug Loaded Bi_2S_3 Nanoparticles

X-ray Diffraction (XRD)

To evaluate the effect of loading process on crystal nature of CLA, XRD instrument (Shimadzu, Japan) was utilized on CLA before and loading with Bi_2S_3 nanoparticles. Instrument was equipped with Cu-Ka at

radiation of λ = 1.54060 Å, voltage 40 Kv and electrical current of 30 mA. A range of 0 to 60 degrees with axis θ-2θ was applied and scanning speed of 5 °/min[27].

Fourier Transform Infra-red spectroscopy (FTIR)

FTIR instrument (Shimadzu Japan) used to demonstrate the compatibility as well as the effect of loading process of CLA with Bi_2S_3 nanoparticles on the functional groups and chemical structure of the drug. FTIR performed using potassium bromide (KBr) disc with spectroscopy (4000-500 cm^{-1}) [28, 29].

Atomic Force Microscopy (AFM)

AFM instrument (Augestrom advance Inc., USA) used for detection of average particle size of CLA before and loading process with Bi_2S_3 nanoparticles as well as to demonstrate particle size distribution [30]. Samples of solid powder dissolved using methanol, then few drops were poured separately on a silica glass plate and left to dry at room temperature residue on the plate for 2 and 3 dimensional imaging by AFM instrument [31].

Drug Entrapment Efficiency, Loading and Yield Percentages [32-34]

The entrapment efficiency percent of the entrapped CLA calculated using the following equation:

$$\text{Entrapment Efficiency \%} = \frac{\text{weight of drug in nanoparticles after incorporation(actual)}}{\text{weight of drug before incorporation(theoretical)}} \times 100\%$$

The loaded CLA with Bi_2S_3 nanoparticles percent calculated as follow:

$$\text{Loading \%} = \frac{\text{weight of drug in nanoparticles}}{\text{weight of nanoparticles loaded with the drug}} \times 100\%$$

While the yielded drug percent by Bi_2S_3 nanoparticles calculated using equation below:

$$\text{Yield \%} = \frac{\text{weight of nanoparticles after drug incorporation(actual)}}{\text{weight of nanoparticles and drug before incorporation(theoretical)}} \times 100\%$$

In Vitro Drugs Release Study

In vitro release profile of CLA from Bi_2S_3 nanoparticles accomplished using puddle dissolution apparatus, USP type II rotating apparatus (Copley, UK), at 37 ± 0.5 °C under rotating speed of 100 rpm. Samples of unloaded CLA (100 mg) and CLA loaded with Bi_2S_3 nanoparticles (equivalent 100 mg of CLA) dispersed each separately in 500 mL phosphate buffer solution with pH 7.4. Then, 5 mL samples withdrawn at pre-determined time intervals and replaced with the same volume of phosphate buffer fresh media after each withdrawal. The withdrawn samples then filtered and the content of determined spectrophotometrically using UV-Visible spectrophotometer (Shimadzu, Japan) at 210 nm, each experiment was analyzed in triplicate [35, 36].

Antibacterial Susceptibility Test

Disc diffusion technique used for antibacterial sensitivity test, it performed for unloaded CLA, CLA loaded Bi_2S_3 nanoparticle and blank Bi_2S_3 nanoparticles. The test performed against two types of gram +ve bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and one type of gram –ve bacteria (*E.coli*). Where serial diluted concentrations (500, 250, 125 and 62.5 µg/mL) of unloaded CLA and an equivalent concentration of CLA loaded with Bi_2S_3 nanoparticles used. Dimethyl sulfoxide (DMSO) solvent used for samples preparation; Muller Hinton agar was the culture medium used for each sample for 24 h and at 37 °C [37, 38].

Statistical Analysis

The experiments performed in triplicates. Quantitative data comparison for antibacterial activity of CLA, before and after loading process, analyzed using one-way and two-way ANOVA tests. Student T-Test used for quantitative data comparison during *in vitro* release experiment. Results expressed as mean ± standard deviation (SD). SPSS package for windows (version 13, SPSS Inc., Chicago, IL, USA) was the used statistical analysis program and the statistical significance for each test (*P* value) adapted was less than 0.05.

Results

Fourier Transform Infra-red Spectroscopy (FTIR)

FTIR spectrum of unloaded CLA (fig. 1 A) displayed bands for multiple hydroxyl groups (OH) in the backbone structure at the range (3469 – 3419 cm^{-1}), while bands at 1730 cm^{-1} and 1691 cm^{-1} assign to the two carbonyl groups of ester and ketone respectively. Aliphatic groups (CH_3 and CH_2) appeared in the expected stretching area (asymmetrical and symmetrical) in the range (2974-2781 cm^{-1}), while the finger prints area showed the bending bands of the drug. The FTIR spectrum of loaded CLA with Bi_2S_3 nanoparticles (Fig.1 B) displayed the same functional groups for unloaded CLA with small shifting.

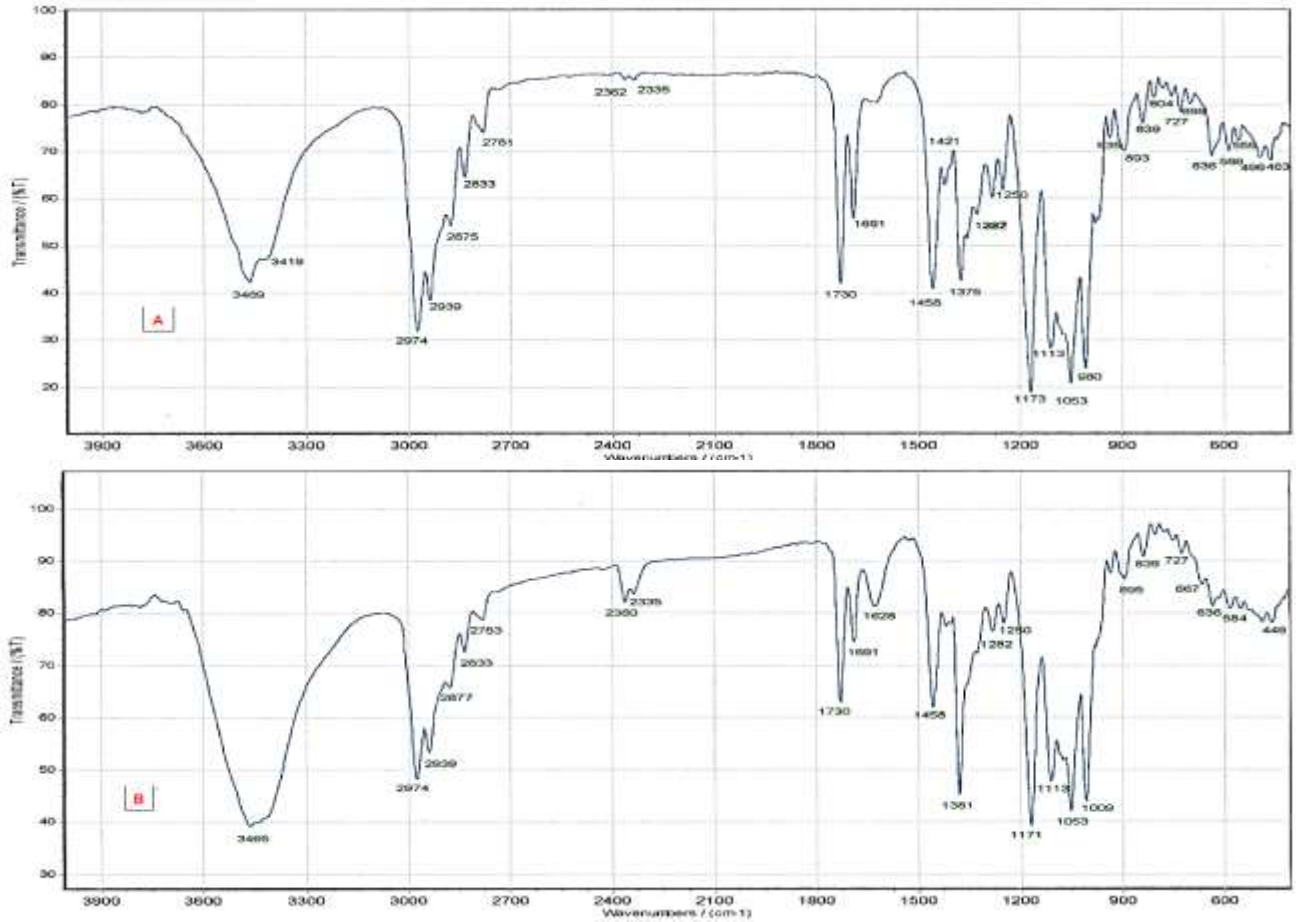

Fig. 1: FTIR of (A) unloaded CLA and (B) CLA loaded Bi_2S_3 nanoparticles

X-ray Diffraction (XRD)

The X- ray spectrum of unloaded CLA (fig. 2A) showed sharp narrow intense diffraction peaks with high multiplicity, this indicate the highly crystalline structure of unloaded drug. After loading of CLA with Bi_2S_3 nanoparticles, the X-ray (fig. 2 B) was diffracted with non-intense nor- sharp diffraction peaks giving arise to crystal lattice transformation into amorphous drug molecules.

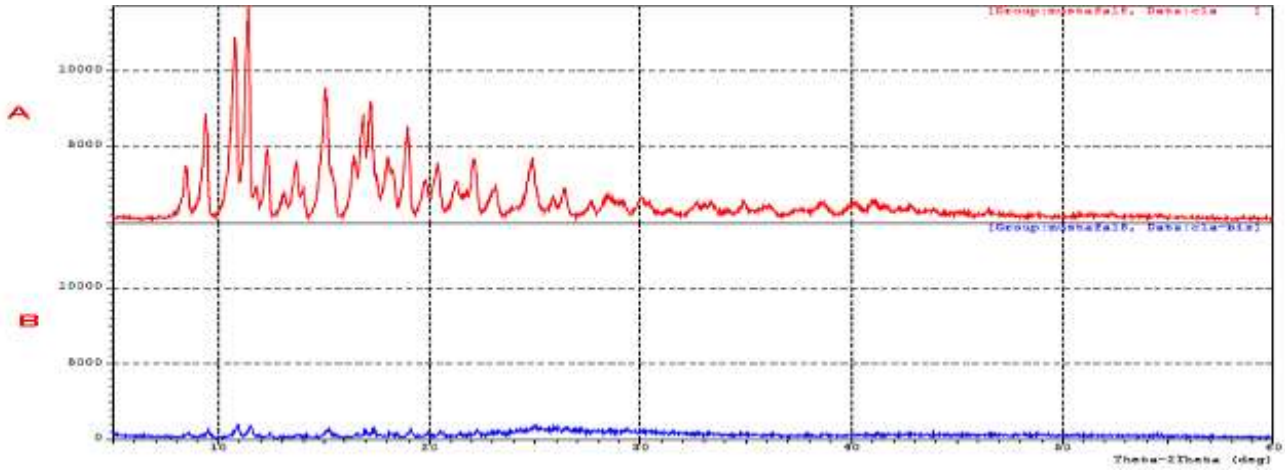

Fig. 2: PXRD of (A) unloaded CLA and (B) CLA loaded Bi_2S_3 nanoparticles

Atomic Force Microscopy (AFM)

Average particle sizes images (2 and 3 dimensional images) determined by AFM for CLA before (Fig. 3A) and after (Fig. 3B) loading with Bi_2S_3 nanoparticles were found 116.17 and 95.5 nm respectively, indicating particle size reduction of CLA after loading process. Particle size distribution was also detected using AFM instrument and displayed more symmetrical (pyramidal shaped) as well as more fine distribution of CLA particles after loading on Bi_2S_3 nanoparticles (Fig. 4 A) than that of unloaded CLA (Fig. 4 B).

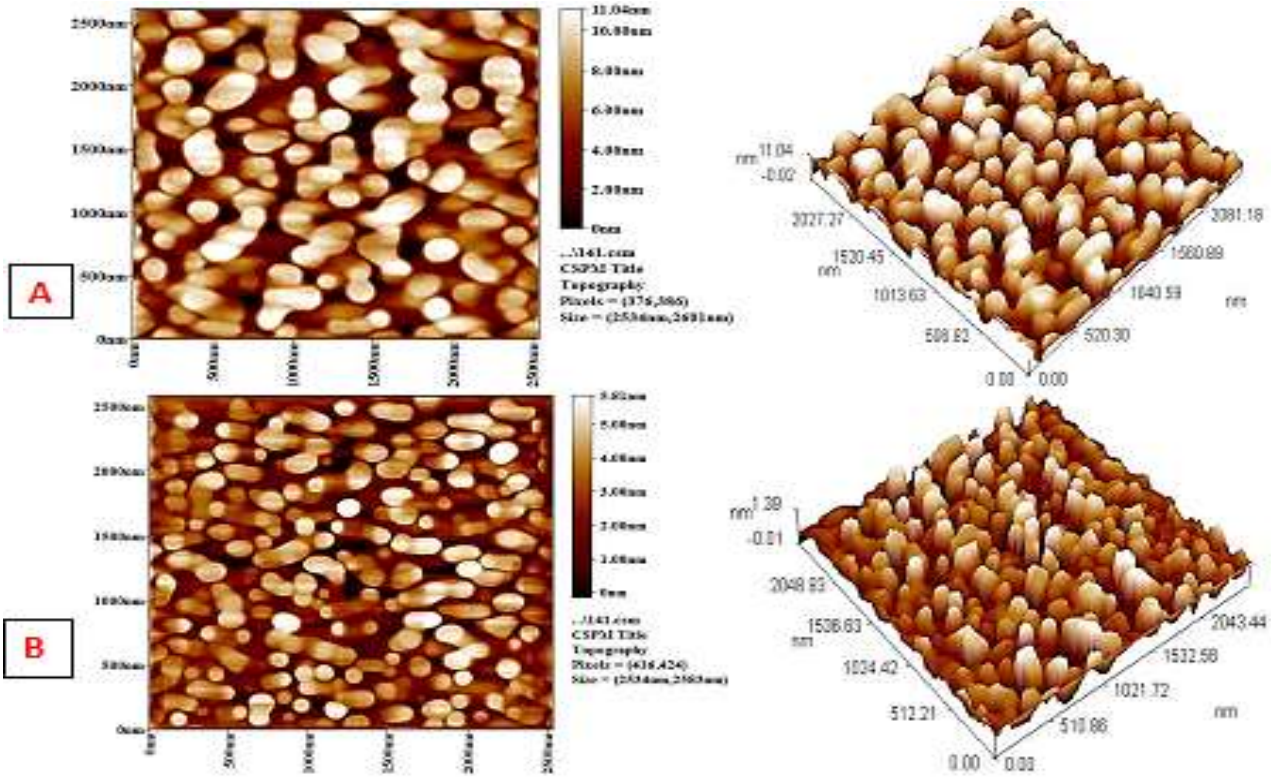

Fig. 3: AFM (2 and 3 D) images of (A) unloaded CLA and (B) CLA loaded Bi_2S_3 nanoparticles

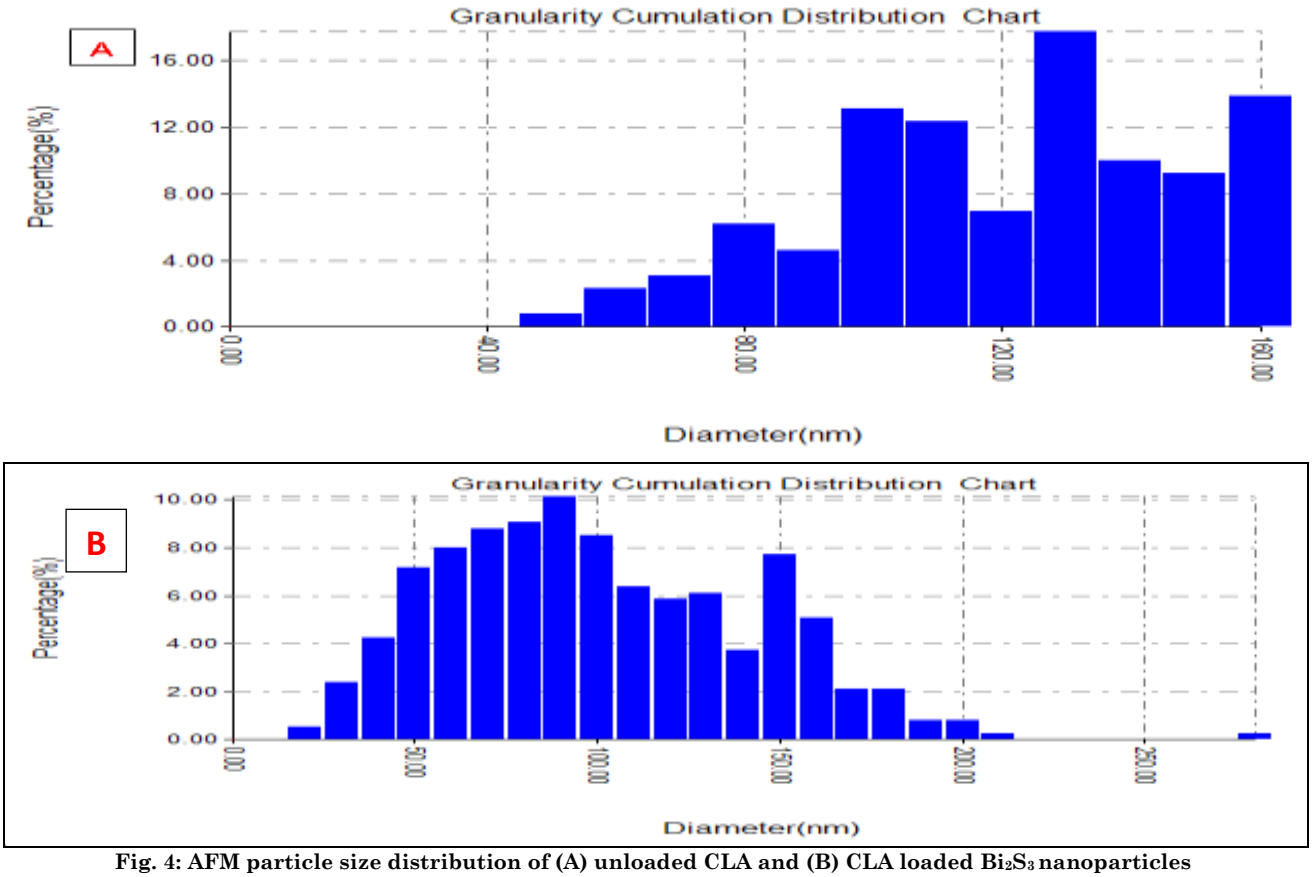

Fig. 4: AFM particle size distribution of (A) unloaded CLA and (B) CLA loaded Bi_2S_3 nanoparticles

Drug Entrapment Efficiency, Loading and Yield Percentages

The entrapped drug percent for CLA was found 98.79%, while the percent of loaded drug with Bi_2S_3 nanoparticles was found 92.66%. The yielded drug percentage was found 65.88%.

In Vitro Drug Release Study

The *in vitro* release pattern of CLA from Bi_2S_3 nanoparticles (Fig.5 B) in phosphate buffer solution with pH 7.4 and showed significantly*improved solubility and dissolution profile after loading with Bi_2S_3 nanoparticles when compared with the dissolution profile of unloaded drug (Fig. 5 A).

Where after 120 min CLA completely (100%) released from Bi_2S_3 nanoparticles while unloaded CLA dissolution profile showed only 30% dissolution of the drug.

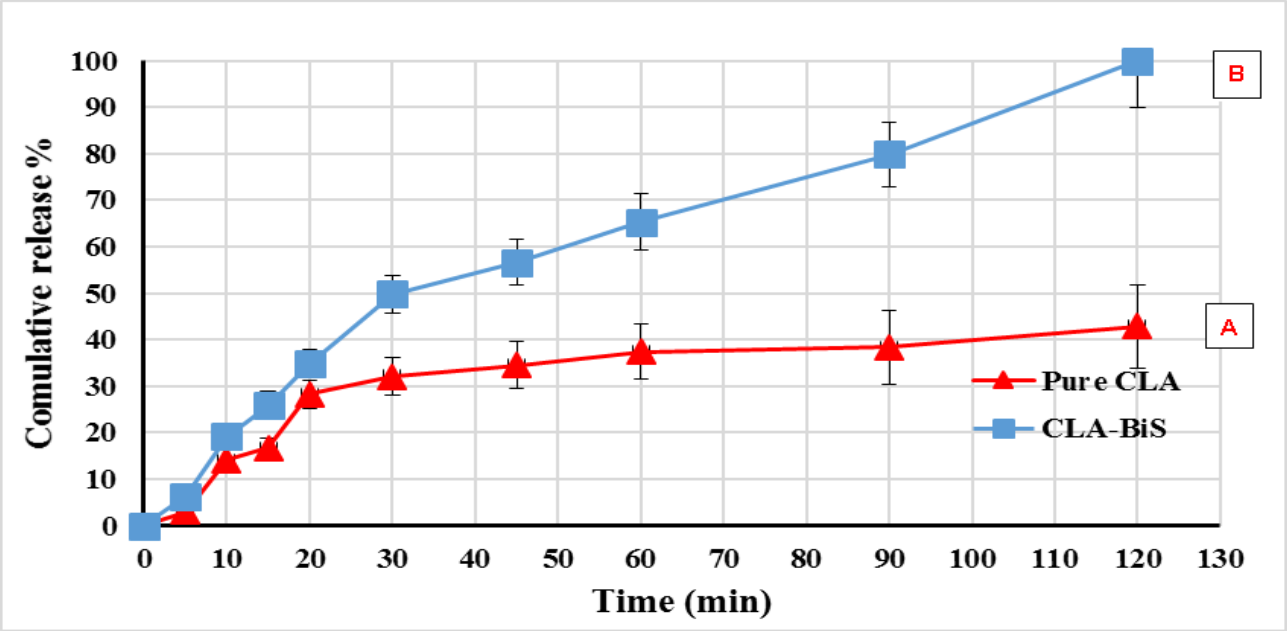

Fig. 5: *In vitro* profile of (A) unloaded CLA and (B) CLA loaded Bi_2S_3 nanoparticles. Data represent mean (n=3) ±SD

Antibacterial Susceptibility Test

The susceptibility test of CLA (Table1) before and after loading process with Bi_2S_3 nanoparticles showed significantly* increased antibacterial activity at all concentrations used against gram +ve bacteria *Staphylococcus aureus* and *Bacillus subtilis* after loading with Bi_2S_3 nanoparticles. While the test against gram -ve bacteria *Escherichia coli* showed no antibacterial activity, nor for unloaded CLA neither for loaded drug at all tested concentrations.

Table 1: Antibacterial activity of unloaded CLA, CLA loaded Bi_2S_3 nanoparticles and blank Bi_2S_3 nanoparticles represented as inhibition zone in millimeter (mm)

Sample	*Staphylococcus aurous*				*Bacillus subtilis*				*Escherichia coli*			
	Concentration µg/mL											
	62.5	125	250	500	62.5	125	250	500	62.5	125	250	500
DMSO	_	_	_	_	_	_	_	_	_	_	_	_
Blank Bi_2S_3 nanoparticles	_	_	_	_	_	_	_	_	_	_	_	_
unloaded CLA	21	22	22	24	18	20	21	23	_	_	_	_
CLA loaded Bi_2S_3 nanoparticles	31	33	35	38	32	34	34	35	_	_	_	_

Discussion

Nanoparticles of Bi_2S_3 were synthesized and loaded successfully with CLA; the loading process was achieved physically by attractive or physical complex formation without any chemical reaction between Bi_2S_3 nanoparticles and CLA. FTIR spectra of CLA before and after loading process as comparative showed similar main functional

groups of CLA with small shifting after loading with Bi_2S_3 nanoparticles indicating the physical complex creation without any chemical reaction [39].

The particle size reduction of the prepared loaded CLA assessed by AFM device approve the nano-sized particles of CLA after loading process with accompanied alterations in its physical and pharmaceutical properties of the very small produced particles**,** where the *in vitro* release and dissolution profile study showed significantly*enhanced solubility of CLA after loading with Bi_2S_3 nanoparticles, this enhanced solubility might be a result of particle size reduction within nano-range (1-100 nm) and thereby increased effective surface area of exposed drug particles to the dissolution medium and significantly*enhanced solubility which in turn lead to increase in absorption and bioavailability of already poor soluble drug, CLA [40-42].

Another explanation of enhanced solubility was attributed to the transformation of CLA particles from highly crystalline low soluble structure into amorphous highly soluble molecules [43-46]. This alteration in the morphism of molecules was detected using X-ray instrument which displayed narrow intense sharp diffraction peaks of unloaded crystalline CLA, while after loading process with Bi_2S_3 nanoparticles the diffracted peaks were diminished and the sharp peaks were disappeared.

The high loading, entrapment efficiency and yield percentages (92.66%, 98.79% and 65.88%) give indication of effective and uniform process of CLA loading with Bi_2S_3 nanoparticles as well as excellent compatibility between drug and Bi_2S_3 nanoparticles without chemical degradation or cross interaction between them[47].

The highly loaded and entrapped CLA to Bi_2S_3 nanoparticles give evidence of enough drugs being carried by Bi_2S_3 nanoparticles to the targeted site and hence the desired biologic activity will be obtained. Disc diffusion method used to test the antibacterial activity was achieved against gram +ve bacteria *Staphylococcus aurous* and *Bacillus subtilis* and showed significantly* increased activity at all serial diluted concentrations used.

This potentiation of biologic activity could be attributed to the enhanced penetration rate of reduced nano-sized particles into pathogenic bacteria and thereby enhanced effective concentration of CLA within bacteria and potentiating activity [48-50].

This increased activity might be utilized to decrease number and amount of conventional dosage form doses to decrease potential side effects and increase patient compliance. The reduction in particle size of CLA molecules might also cause huge increase in effective exposed surface area of drug particles to the microorganism membrane resulting in enhanced penetration and activity [51, 52].

The enhanced solubility of loaded CLA with Bi_2S_3 nanoparticles can bring CLA into solution faster than that of unloaded drug and thereby enhanced available CLA for absorption into blood stream and increased bioavailability which can reach targeted area with high concentration [53-55]. *E. coli* showed no response to both, unloaded and loaded CLA.

Conclusion

The utilization of nanotechnology as a novel drug delivery system for poorly soluble class II drug CLA, give rise for significantly*increase in the solubility and in the antibacterial activity after loading with Bi_2S_3nanoparticles as an effective nanocarriers. The increased antibacterial activity and solubility (hence absorption and bioavailability) of CLA after loading process give rise to decrease number of doses and drug content per dose to avoid side effect and enhance patient compliance.

Declaration of Interest

The author declares no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Author Contribution

This study was self-funded and was written, achieves experimental and analytical work and revised by the author.

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