International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 9, Issue 9, 2017

Original Article

PREPARATION AND EVALUATION OF CLARITHROMYCIN LOADED BISMUTH SULFIDE (Bi_2S_3) NANOPARTICLES UTILIZING NANOTECHNOLOGY AS A NOVEL DRUG DELIVERY SYSTEM

MUSTAFA R. ABDULBAQI

Department of Pharmaceutics, College of Pharmacy, Al-Bayan University, Baghdad, Iraq
Email: drmustafa1986@yahoo.com

Received: 22 Mar 2017 Revised and Accepted: 13 Jul 2017

ABSTRACT

Objective: This study was designed to improve the solubility and biological activity of class II drug clarithromycin (CLA) by utilizing the nanotechnology as a novel drug delivery system.

Methods: Bismuth sulfide (Bi_2S_3) nanoparticles were synthesized using chemical co-precipitation technique, while the loading of clarithromycin (CLA) with bismuth sulfide (Bi_2S_3) nanoparticles was achieved using incorporation method. The loading process, as well as particle size reduction, were evaluated using x-ray diffraction (XRD), furrier transformed infrared (FTIR) and atomic force microscopy (AFM). *In vitro* release study was performed using USP paddle apparatus type II in phosphate buffer solution pH 7.4. Disc diffusion method was the technique used to test the antibacterial activity of CLA before and after loading process.

Results: Loading of CLA with Bi_2S_3 nanoparticles was accomplished successfully accompanied with particle size reduction within nano range as measured by AFM. *In vitro* release study showed a significant* increase in solubility and dissolution profile of CLA after loading process, which was also proven using XRD that indicate transformation from crystalline into more soluble 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.

Conclusion: The solubility, as well as the antibacterial activity of CLA, were improved significantly* after preparation of nanotechnology based drug delivery system through the utilization of metal nanoparticles, Bi_2S_3, as nanocarriers for CLA.

Keywords: Nanotechnology, Clarithromycin (CLA), Bismuthsulfide (Bi_2S_3) nanoparticles

DOI: http://dx.doi.org/10.22159/ijpps.2017v9i9.19805

INTRODUCTION

Clarithromycin (CLA) is a semisynthetic antibacterial macrolide antibiotic that inhibits synthesis of a protein of bacteria, it binds to the 50S ribosomal subunit of susceptible organisms and therefore prevents translocation of aminoacyl transfer RNA and inhibition of protein synthesis [1]. CLA is used for respiratory tract infection, skin soft tissue infection, Chlamydia infection, acute maxillary sinusitis, helicobacter pylori infection, tonsillitis, pharyngitis, chronic bronchitis and pneumonia [2]. According to biopharmaceutical classification system (BCS), CLA belongs to class II which means the drug had low solubility of 0.33 mg/ml [3] and high permeability and therefore to overcome bioavailability problems, nanotechnology has been utilized [4]. This low aqueous solubility results in a slow rate of dissolution after oral administration and thereby the low amount of drug in solution and low absorption in addition to first pass metabolism and pH dependent solubility of CLA, all these factors lead to low bioavailability (not more than 50%) [5].

This is the reason for assigning class II drugs of BCS as having dissolution rate limited absorption [6]. The application of nanotechnology as a novel approach for drug delivery was the scope for the elaboration of physiochemical and performance of many drugs in the recent years, where nanotechnology is the understanding and control of matter at nearly 1 to 100 nm dimensions [7, 8]. Nanotechnology has numerous medical applications as a therapeutic drug delivery system as well as in the development of the treatment for a variety of diseases and disorders [9]. Nanotechnology can increase the efficacy of drugs and thereby reducing doses number and decreasing the risk of side effect and toxicity [10]. Many types of nanoparticles have been utilized as carriers for drugs to improve their pharmaceutical and biological properties known as nanocarriers, for example, liposomes, niosomes, nanotube, nanocrystal, micelles and other materials [11, 12]. Inorganic nanoparticles are a part of nanomaterials used as nanocarriers and defined as 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 improved and diverse physical, chemical, and biological properties [12, 13]. Bismuth sulfide (Bi_2S_3) is a member of inorganic nanoparticles that have been utilized in this study as the nanocarrier for clarithromycin. Bismuth sulfide (Bi_2S_3) nanoparticles used medically in computed tomography (CT) imaging [14]. The aim of the following study was to prepare and evaluate a nanotechnology based drug delivery system as a novel drug delivery system to improve and advance the pharmaceutical (particularly solubility) and/or biological (antimicrobial spectrum) properties of low soluble class II drugs. CLA was the 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 (Na2S. XH_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) Loba Chemie Pvt. Ltd (India).

Methods

Synthesis of bismuth sulfide (Bi_2S_3) nanoparticles

Chemical co-precipitation method was the technique used to synthesize Bismuth sulfide (Bi_2S_3) nanoparticles and involve the titration (10 drops per min) of 0.1 M of disodium sulfide $Na_2S.10H_2O$ aqueous solution onto 0.1 M of bismuth nitrate Bi $(NO_3)_3.6H_2O$ aqueous solution with special conditions (vigorous stirring at 1100 rpm and heating at 80 °C) using a magnetic

stirrer (Dragon Lab, USA). When dropping was started, the color of the aqueous solution of bismuth nitrate was changed from white into black color. After finishing the titration, stirring was continued vigorously at 1100 rpm and temperature the temperature was hold constant at 80 °C for 3 h. The resulted black sticky product of Bi_2S_3 nanoparticles was then filtered and washed using deionized water before being dried using silica gel containing desiccators [15].

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

Loading of clarithromycin with Bi_2S_3 nanoparticles

Loading of CLA with Bi_2S_3 nanoparticles was performed in the last step of Bi_2S_3 nanoparticles synthesis (incorporation method) which involves the addition of the drug in the last step of nanoparticles synthesis before the titration of sodium sulfide has been completed, where 0.1 M of CLA added using acetone as a solvent. When titration completed, the stirring was continued for 3-4 h and finally filtered, washed using deionized water to be desiccated and collected [16, 17].

Characterization techniques of CLA loaded Bi_2S_3 nanoparticles

X-ray diffraction (XRD)

XRD instrument (Shimadzu, Japan) was utilized to detect the effect of loading process of Bi_2S_3 nanoparticles on the nature and lattice property of CLA.

Hence, XRD was performed for CLA before and after loading process. Instrument was equipped by the use of Cu-Ka radiation of λ = 1.54060 Å and voltage 40 Kv with electrical current of 30 mA. A range of 0 to 60 degrees with axis θ-2θ was applied and scanning speed of 5 °/min [18].

Fourier transform infra-red spectroscopy (FTIR)

The nature of functional groups of CLA was characterized before and after loading with Bi_2S_3 nanoparticles by the use of FTIR instrument (Shimadzu Japan) to detect whether loading process cause any chemical modification of the drug. FTIR was used with spectroscopy (4000-500 cm^{-1}) and using potassium bromide disc [19].

Atomic force microscopy (AFM)

Shape, particle size and size distribution of unloaded CLA and CLA after loading with Bi_2S_3 nanoparticles were characterized by the use AFM instrument (Augestrom advance Inc., USA)[20]. Solid powdered samples were dissolved using methanol and then few drops were poured separately on a silica glass plate and left to dry at room temperature residue on the plate to be scanned using AFM instrument [21].

Drug entrapment efficiency, loading and yield percentages [22-24]

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

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

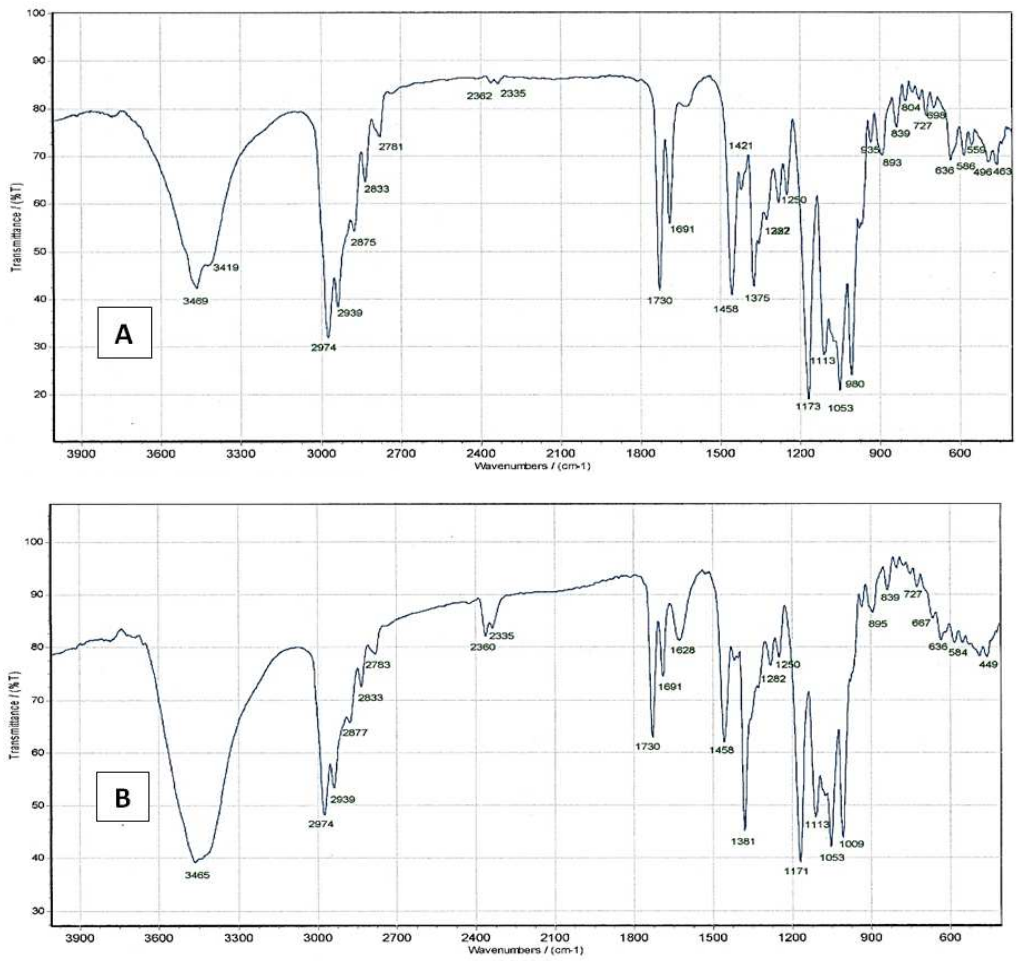


Fig. 1: FTIR of (A) unloaded clarithromycin (CLA) and (B) clarithromycin (CLA) loaded bismuth sulfide (Bi_2S_3) nanoparticles

In vitro drug release study

The *in vitro* release of CLA from Bi_2S_3 nanoparticles was accomplished by the use of paddle apparatus, USP type II rotating (Copley, UK), at 37+0.5 °C and rotating speed of 100 rpm. An equivalent 100 mg of CLA loaded with Bi_2S_3 nanoparticles and 100 mg of unloaded CLA samples were dispersed each separately in 500 ml phosphate buffer solution with a pH 7.4. Samples of 5 ml were withdrawn at programmed time intervals and replaced with the same volume of phosphate buffer fresh media after each withdrawal. The withdrawn samples were then filtered and CLA content was determined spectrophotometrically using UV-Visible spectrophotometer (Shimadzu, Japan) at 210 nm, each experiment was analyzed in triplicate [25, 26].

Antibacterial susceptibility test

Disc diffusion method was the technique used and it was achieved for CLA loaded Bi_2S_3nanoparticles in comparison with unloaded CLA and blank Bi_2S_3 nanoparticles. The test was performed against two types of gram+ve bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and one type of gram–ve bacteria (*E. coli*) using 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. Dimethyl sulfoxide (DMSO) was the solvent used to prepare samples and Muller Hinton agar was the culture medium used where each sample was cultured for 24 h at 37 °C [27-29].

Statistical analysis

The experiments were performed in triplicates and the quantitative data comparison for biologic activity of CLA was analyzed using one-way and two-way ANOVA tests, while Student T-Test was used for of quantitative data comparison of *in vitro* release. Results were expressed as mean±standard deviation. 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 withBi_2S_3 nanoparticles (fig. 1 B) displayed the same functional groups for unloaded CLA with small shifting.

X-ray diffraction (XRD)

The x-ray spectrum of unloaded CLA (fig. 2A) showed sharp narrow intense diffraction peaks with high multiplicity, this indicates the highly crystalline structure of the 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.

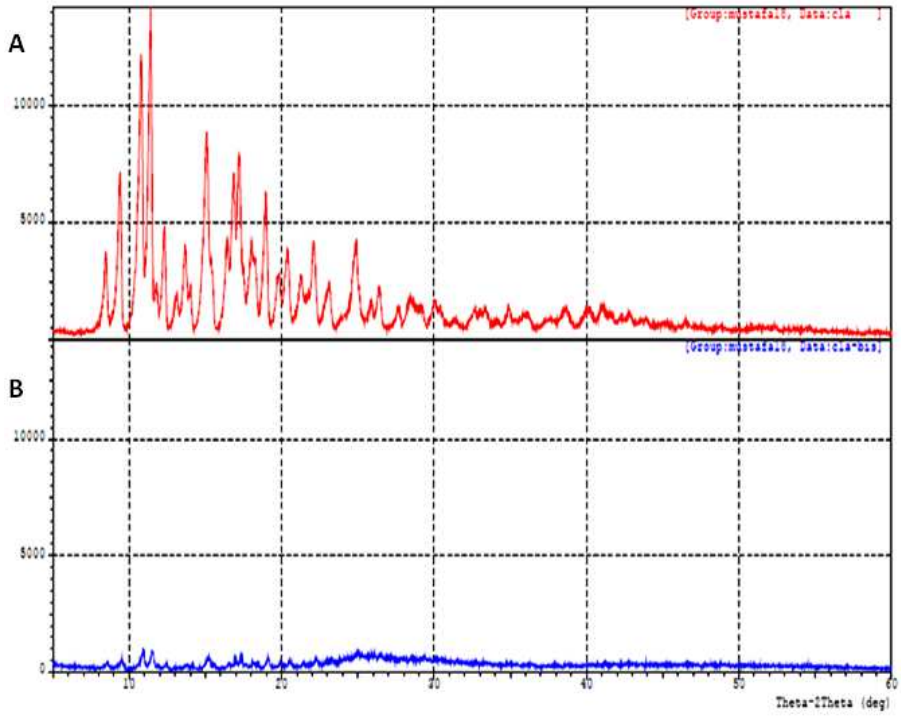


Fig. 2: XRD of (A) unloaded clarithromycin (CLA) and (B) clarithromycin (CLA) loaded bismuth sulfide (Bi_2S_3) nanoparticles

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 the more fine distribution of CLA particles after loading on Bi_2S_3 nanoparticles (fig. 4 A) than that of unloaded CLA (fig. 4B).

Drug entrapment efficiency, loading and yield percentages

The entrapped drug percent for CLA was found 98.79%, while the percent of the 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 7.4and 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.

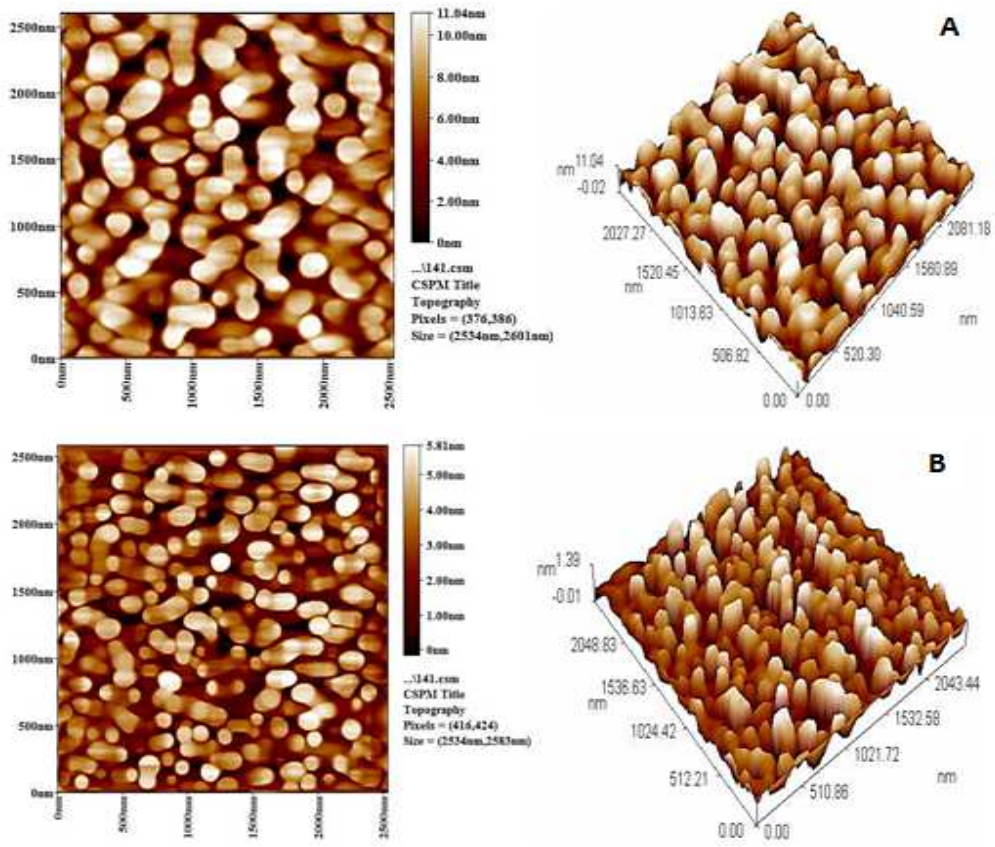
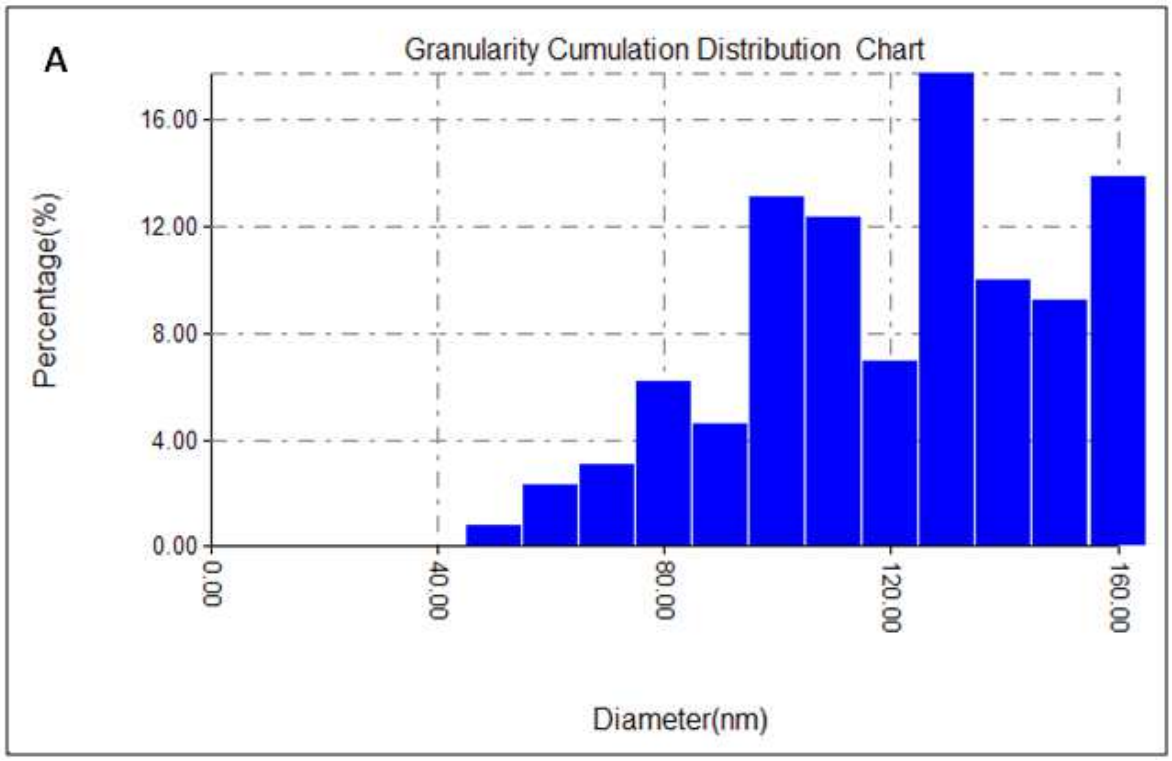


Fig. 3: AFM (2 and 3 D) images of (A) unloaded clarithromycin (CLA) and (B) clarithromycin (CLA) loaded bismuth sulfide (Bi_2S_3) nanoparticles



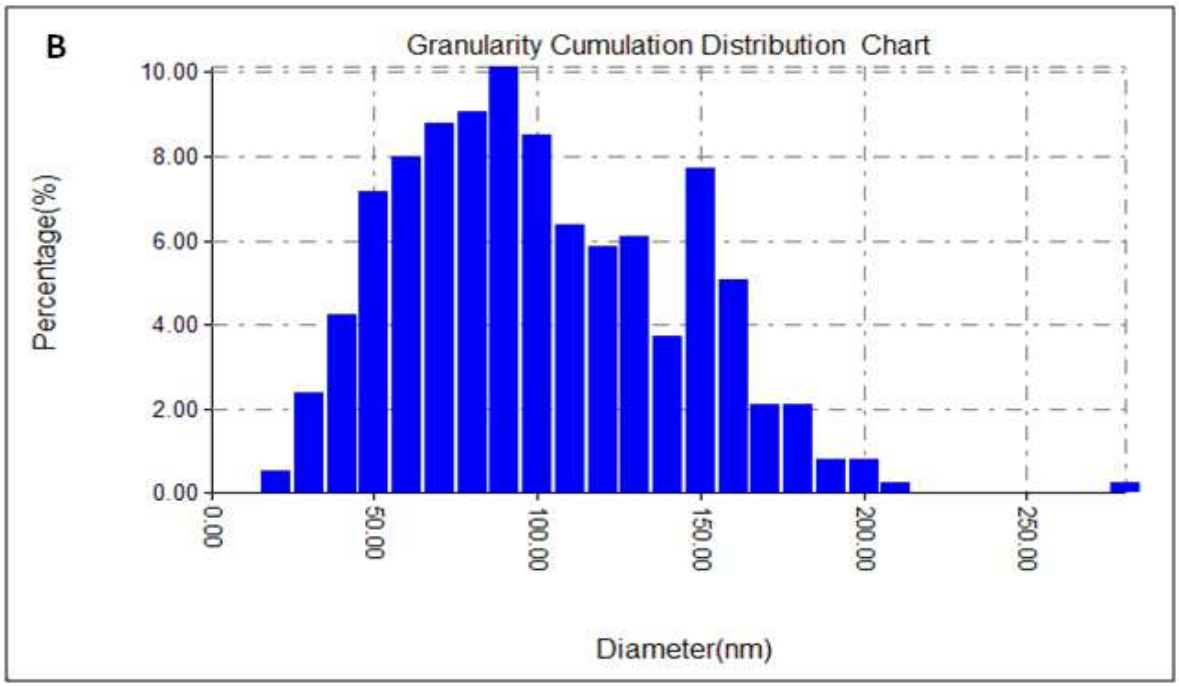


Fig. 4: AFM particle size distribution of (A) unloaded clarithromycin (CLA) and (B) clarithromycin (CLA) loaded bismuth sulfide (Bi_2S_3) nanoparticles

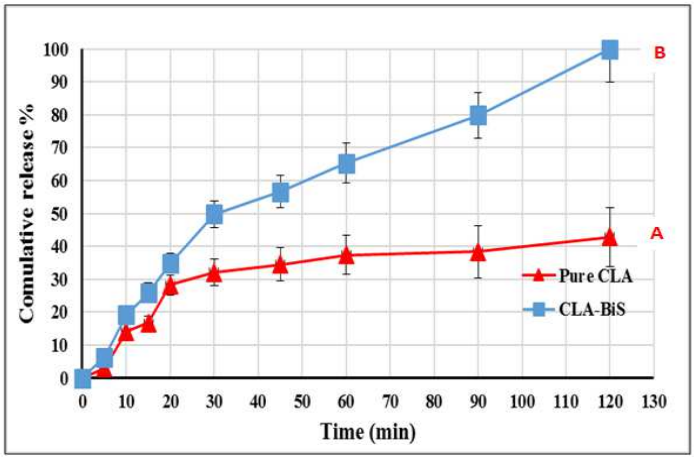


Fig. 5: *In vitro* profile of (A) unloaded clarithromycin (CLA) and (B) clarithromycin (CLA) loaded bismuth sulfide (Bi_2S_3) nanoparticles. Data represent mean (n=3)+SD

Antibacterial susceptibility test

The susceptibility test of CLA (table 1) 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 withBi_2S_3 nanoparticles. While the test against gram $^-$ve bacteria *Escherichia coli* showed no antibacterial activity, nor for unloaded CLA did neither for loaded drug at all test concentrations.

Table 1: Antibacterial activity of unloaded clarithromycin (CLA), clarithromycin (CLA) loaded bismuth sulfide (Bi_2S_3) nanoparticles and blank bismuth sulfide (Bi_2S_3) nanoparticles represented as inhibition zone in milliliter (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
Dimethyl sulfoxide (DMSO)	_	_	_	_	_	_	_	_	_	_	_	_
Blank bismuth sulfide (Bi_2S_3) nanoparticles	_	_	_	_	_	_	_	_	_	_	_	_
Unloaded clarithromycin (CLA)	21	22	22	24	18	20	21	23	_	_	_	_
Clarithromycin (CLA) loaded bismuth sulfide (Bi_2S_3) nanoparticles	31	33	35	38	32	34	34	35	_	_	_	_

DISCUSION

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 [30]. 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 [31, 32]. Another explanation of enhanced solubility was attributed to the transformation of CLA particles from the highly crystalline low soluble structure into amorphous highly soluble molecules [33-36]. 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 an indication of the effective and uniform process of CLA loading with Bi_2S_3 nanoparticles as well as excellent compatibility between the drug and Bi_2S_3 nanoparticles without chemical degradation or cross interaction between them.

The highly loaded and entrapped CLA to Bi_2S_3 nanoparticles give evidence of enough drug 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 serially 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 the effective concentration of CLA within bacteria and potentiating activity [37-39].

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 a huge increase in effective exposed surface area of drug particles to the microorganism membrane resulting in enhanced penetration and activity [40, 41]. 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 the blood stream and increased bioavailability which can reach targeted area with high concentration [42, 43]. *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 clarithromycin (CLA), give rise for a significantly* increase in the solubility and in the antibacterial activity after loading with Bi_2S_3 nanoparticles as effective nanocarriers. The increased antibacterial activity and solubility (hence absorption and bioavailability) of CLA after loading process give rise to decrease the number of doses and drug content per dose to avoid side effect and enhance patient compliance.

ACKNOWLEDGEMENT

Author is grateful to Al-Bayan University for their support and encouragement. Special thank for the central service lab/College of Science for performing the analytical methods in this study.

AUTHOR CONTRIBUTION

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

CONFLICT OF INTERESTS

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

REFERENCES

1. Chellat MF, Raguz L, Riedl R. Targeting antibiotic resistance. Angew Chem Int Ed 2016;55:6600-26.
2. Akre HS, Mundhada DR, Bhaskaran S, Asghar S, Gandhi GS. Dry suspension formulation of taste masked antibiotic drug for pediatric use. J Appl Pharm Sci 2012;2:166-71.
3. Mishra R, Gautam S, Prasad RK, Patel A, Sahu A. Solubility enhancement of clarithromycin using solid dispersion and effervescence assisted fusion technique. Res J Pharm Tech 2016;9:677-86.
4. Wen H, Jung H, Li X. Drug delivery approaches in addressing clinical pharmacology-related issues: opportunities and challenges. AAPS J 2015;17:1327-40.
5. Lotfipour F, Valizadeh H, Milani M, Bahrami N, Ghotaslou R. Study of antimicrobial effects of clarithromycin loaded PLGA nano particles against clinical strains of helicobacter pylori. Drug Res 2016;66:41-5.
6. Mohammadi G, Hemati V, Nikbakht MR, Mirzaee S, Fattahi A, Ghanbari K, *et al. In vitro* and *in vivo* evaluation of clarithromycin–urea solid dispersions prepared by solvent evaporation, electrospraying and freeze drying methods. Powder Tech 2014;257:168-74.
7. Sharma R, Rather MA, Vijaykumar Leela R, Saha H, Purayil P, Babu S, *et al.* Preliminary observations on the effect of nano-conjugated pheromones on clarias batrachus (Linnaeus, 1758). Aquaculture Res 2014;45:1415-20.
8. Caroling G, Tiwari SK, Ranjitham M, Suja R. Biosynthesis of silver nanoparticles using aqueous broccoli extract-characterization and study of antimicrobial, cytotoxic effects. Asian J Pharm Clin Res 2013;6:165-72.
9. Safari J, Zarnegar Z. Advanced drug delivery systems: nanotechnology of health design a review. J Saudi Chem Soc 2014;18:85-99.
10. Daughton CG, Ruhoy IS. Lower-dose prescribing: minimizing "side effects" of pharmaceuticals on society and the environment. Sci Total Environ 2013;443:324-37.
11. Torchilin VP. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. Nat Rev Drug Discovery 2014;13:813-27.
12. Kapil A, Aggarwal G, Harikumar S. Nanotechnology in novel drug delivery system. J Drug Delivery Ther 2014;4:21-8.
13. Chen G, Roy I, Yang C, Prasad PN. Nanochemistry and nanomedicine for nanoparticle-based diagnostics and therapy. Chem Rev 2016;116:2826-85.
14. Fang Y, Peng C, Guo R, Zheng L, Qin J, Zhou B, *et al.* Dendrimer-stabilized bismuth sulfide nanoparticles: synthesis, characterization, and potential computed tomography imaging applications. Analyst 2013;138:3172-80.
15. Mesquita PR, Almeida JS, Teixeira LS, Silva AFd, Silva LA. A fast sonochemical method to prepare 1D and 3D nanostructures of bismuth sulfide. J Brazi Chem Soc 2013;24:280-4.
16. Singh R, Lillard JW. Nanoparticle-based targeted drug delivery. Exp Mol Pathol 2009;86:215-23.
17. RA Mustafa, KM Nidhal, HD Ashour. Loading of clarithromycin and paclitaxel on synthesized CdS/NiO nanoparticles as promising nanocarriers. Int J Pharm Pharm Sci 2016;8:322-33.
18. Wang Z, Xie C, Luo F, Li P, Xiao X. P25 nanoparticles decorated on titania nano tubes arrays as effective drug delivery system for ibuprofen. Appli Surf Sci 2015;324:621-6.
19. Kamarudin N, Jalil A, Triwahyono S, Artika V, Salleh N, Karim A, *et al.* Variation of the crystal growth of mesoporous silica nanoparticles and the evaluation to ibuprofen loading and release. J Colloid Interface Sci 2014;421:6-13.

20. Amini R, Brar SK, Cledon M, Surampalli RY. Intertechnique comparisons for nanoparticle size measurements and shape distribution. J Haz Toxi Radioactive Waste 2015;20:1-8.
21. Chicea D. Using AFM topography measurements in nanoparticle sizing. Rom Rep Phys 2014;66:778-87.
22. Fan B, Xing Y, Zheng Y, Sun C, Liang G. pH-responsive thiolated chitosan nanoparticles for oral low-molecular weight heparin delivery: *in vitro* and *in vivo* evaluation. Drug Delivery 2016;23:238-47.
23. Yang X, Trinh HM, Agrahari V, Sheng Y, Pal D, Mitra AK. A nanoparticle-based topical ophthalmic gel formulation for sustained release of hydrocortisone butyrate. AAPS PharmSciTech 2016;17:294-306.
24. Sunita L. Preparation and characterisation of bora rise aceclophenac microspheres. Asian J Pharm Clin Res 2015; 8:247-9.
25. Shahbaziniaz M, Foroutan SM, Bolourchian N. Dissolution rate enhancement of clarithromycin using ternary ground mixtures: nanocrystal formation. Iran J Pharm Res 2013;12:587-98.
26. Jafari S, Maleki-Dizaji N, Barar J, Barzegar-Jalali M, Rameshrad M, Adibkia K. Methylprednisolone acetate-loaded hydroxyapatite nanoparticles as a potential drug delivery system for treatment of rheumatoid arthritis: *in vitro* and *in vivo* evaluations. Eur J Pharm Sci 2016;91:225-35.
27. Esfandi Eh, Ramezani V, Vatanara A, Najafabadi AR, Hadipour Moghaddam SP. Clarithromycin dissolution enhancement by preparation of aqueous nanosuspensions using sonoprecipitation technique. Iran J Pharm Res 2014;13:809-18.
28. Zahran M, Ahmed HB, El-Rafie M. Surface modification of cotton fabrics for antibacterial application by coating with AgNPs–alginate composite. Carbohydr Polym 2014;108:145-52.
29. Kalaiyarasu T, Karthi N, Manju V. *In vitro* assessment of the antioxidant and antibacterial activity of green synthesized silver nanoparticles from Digitaria radicosa leaves. Asian J Pharm Clin Res 2016;9:297-302.
30. Sun SB, Liu P, Shao FM, Miao QL. Formulation and evaluation of PLGA nano particles loaded capecitabine for prostate cancer. Int J Clin Exp Med 2015;8:19670–81.
31. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, *et al.* Pharmaceutical particle technologies: an approach to improve drug solubility, dissolution and bioavailability. Asian J Pharm Sci 2014;9:304-16.
32. Dizaj SM, Vazifehasl Z, Salatin S, Adibkia K, Javadzadeh Y. Nanosizing of drugs: effect on dissolution rate. Res Pharm Sci 2015;10:95–108.
33. Jog R, Burgess DJ. Pharmaceutical amorphous nanoparticles. J Pharm Sci 2017;106:39-65.
34. Censi R, Di Martino P. Polymorph impact on the bioavailability and stability of poorly soluble drugs. Molecules 2015;20:18759-76.
35. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B 2015;5:442-53.
36. Babu NJ, Nangia A. Solubility advantage of amorphous drugs and pharmaceutical cocrystals. Crys Groand Des 2011;11: 2662-79.
37. Raffi M, Hussain F, Bhatti T, Akhter J, Hameed A, Hasan M. Antibacterial characterization of silver nanoparticles against E. coli ATCC-15224. J Mater Sci Tech 2008;24:192-6.
38. Liu Y, Busscher HJ, Zhao B, Li Y, Zhang Z, Van der Mei HC, *et al.* Surface-adaptive, antimicrobially loaded, micellar nano carriers with enhanced penetration and killing efficiency in staphylococcal biofilms. ACS Nano 2016;10:4779-89.
39. Rodrigues LR. Microbial surfactants: fundamentals and applicability in the formulation of nano-sized drug delivery vectors. J Colloid Interface Sci 2015;449:304-16.
40. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotech 2015;33:941-51.
41. Junyaprasert VB, Morakul B. Nanocrystals for enhancement of oral bioavailability of poorly water-soluble drugs. Asian J Pharm Sci 2015;10:13-23.
42. Chogale MM, Ghodake VN, Patravale VB. Performance parameters and characterizations of nanocrystals: a brief review. Pharmaceutics 2016;8:1-18.
43. Attari Z, Bhandari A, Jagadish P, Lewis S. Enhanced ex vivo intestinal absorption of olmesartan medoxomil nano-suspension: preparation by combinative technology. Saudi Pharm J 2016;24:57-63.

How to cite this article

- Mustafa R Abdulbaqi. Preparation and evaluation of clarithromycin loaded bismuth sulfide (Bi_2S_3) nanoparticles utilizing nanotechnology as a novel drug delivery system. Int J Pharm Pharm Sci 2017;9(9):115-121.