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DEVELOPMENT AND INVITRO CHARACTERIZATION OF CLARITHROMYCIN LOADED CHITOSAN NANOPARTICLES

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ABSTRACT

The present study was aimed to develop a nanoparticulate drug delivery system of Clarithromycin using polymer (Chitosan). The polymer enhances the binding of Clarithromycin nanoparticles in specific or targeted site with sustained release of drug increasing therapeutic efficacy. These nanoparticles may also reduce the dose frequency with desired therapeutic response. All batches of nanoparticles (F1-F10) were prepared by nano precipitation method. The entrapment efficiency of the optimized formulation F7 (drug 50mg, Chitosan 75mg, β –cyclodextin 10 mg) was 99.38 ±0.08 and *invitro* drug release was 98.46% after 24 hours. It also obey the zero order, follows diffusion and erosion mechanism of release. Surface morphology of optimized formulation (F7) indicated that lrbesartan nanoparticles were found to be in average nanometer range(358.4nm) and showed ideal surface morphology. The stability test performed revealed that the formulation (F7) showed no change in its characters. The optimized formulation (F7) was also examined for zeta potential determinations. The formulation(F7) showed maximum deviation of 9.16 mV which demonstrated that the particles are separate and highly repelling property found to be more useful in decreasing opsonization and favors target specificity. The developed Clarithromycin nanoparticle formulation increases water solubility, reduces thedose frequency and improves the bioavailability of drug.

KEYWORDS: Nanoparticulate, Drug Delivery System, Clarithromycin, Chitosan.

INTRODUCTION

In the last 50 years, material researchers have been extensively studying how to exploit nanoparticles and nanostructured materials in different biomedical and healthcare sectors.[1] The term "NP" usually defines minute particles of matter (1 to 100 nm in diameter), but other names can be used to describe larger particles (up to 500 nm in diameter). For example, nanorods, nanowires, and nanofibers are nanoparticles with a diameter in the 1–100 nm range but with one dimension outside the nanoscale dimension.[2] Nanostructured materials are nanomaterials with one dimension in the nanoscale range (<100 nm) and are made of a single material or multiple materials. Therefore, nanostructured materials are composed of interlinked parts in the nanoscale range.[3] Nanoparticles and nanostructured materials can be made of simple materials (e.g., metal, carbon, polymer)[4], of composites (e.g., polymer-metal, silica-metal, graphene-metal), or in the core-shell form.[5,6,7,8]

Nanomaterials are typically synthesized by one of two main approaches, i.e., bottom-up approach and top-down approach. Among all the methods, recently, the synthesis of nanomaterials by physical vapor deposition, chemical vapor deposition, electrospinning, 3D printing, biological synthesis, and supercritical fluid have gained importance, which is mingled with other methods to improve the synthesis efficiency.[9,10] Nanomaterials display many interesting features, such as superior mechanical performance, the possibility of surface functionalization, large surface area, and tunable porosity, compared to their bulk materials.[11,12,13] These outstanding features explain why nanomaterials are the perfect candidates in the biomedical sector for the production of tissue-engineered scaffolds (e.g., blood vessels, bone), drug delivery systems (gene therapy, cancer treatments, drugs for chronic respiratory infections), chemical sensors[4,5], biosensors[6,7], and wound dressings.[14,15] Remarkably, several studies suggest that ancient civilizations in India, Egypt, and China used nanotechnology (metallic gold) for therapeutic purposes in 2500 BC.[16] Nanomaterials' discrete features can complicate the assessment of the effects and the toxicity risk associated with their use in a biological environment. Indeed, nanomaterials' chemical composition, size, shape, surface charge, area, and entry route in the body can influence their biological activities and effects.[17]

Clarithromycin is a macrolide antibiotic used for the treatment of a wide variety of bacterial infections such as acute otitis, pharyngitis, tonsillitis, respiratory tract infections, uncomplicated skin infections, and helicobacter pylori infection. Development of nanoparticles are one of the emerging fields of nanotechnology with several potential application in drug delivery, clinical medicine and research as well as in other discipline. The use of nanoparticles as drug carrier system is a very attractive controlled drug release. The bioavailability of the valsartan after oral administration is low (60%) with higher variability. The present study was aimed at developing nanoparticle of Clarithromycin in order to improve the bioavailability and efficacy. Clarithromycin is a poorly water soluble drug. To increase solubility of the drug and reducethe dose frequency and improve the bioavailability the study was aimed at nanoparticle of Clarithromycin. Thus the present work is to Develop and characterize a nanoparticulate drug delivery system.

METHODOLOGY

INSTRUMENTS AND MATERIALS USED

Table No. 1: Materials Used.

MATERIALS	SOURCE
Clarithromycin	Hetero Laboratory Ltd.
Chitosan	Micro labs, Hosur.
β cyclodextrine	Micro labs, Hosur.
Potassium dihydrogen phosphate	S.D.Finechemicals, Boisar
Disodium hydrogen phosphate	S.D.Finechemicals, Boisar.
Sodium Hydroxide	S.D.Finechemicals, Boisar
Ethanol	S.D.Finechemicals, Boisar

EXPERIMENTAL INVESTIGATIONS

CONSTRUCTION OF STANDARD CURVE FOR CLARITHROMYCIN UV Spectroscopy Method

Clarithromycin is estimated spectrophotometrically at 220 nm and it obey Beer-Lambert` s Law inthe range of 5-50 mcg /ml.

Detrminatiion of Absorbance maximum (λ_{max})

Clarithromycin was dissolved in phosphate buffer saline pH 7.4 Solution with 50 µg/ml concentration was prepared by suitable dilution. The solution was scanned in UV spectrophotometer at 200 to 400 nm using phosphate buffer saline pH 7.4 as blank. Absorbance maximum was determined as 220 nm. The drug was later quantified by measuring the absorbance at 220 nm in phosphate buffer saline pH 7.4

Preparation of release media

1.38gm of disodium hydrogen phosphate, 0.19gm of potassium dihydrogen phosphate and 8gm of sodium chloride was dissolved in sufficient amount of distilled water and produced 1000ml. pH was adjusted to 7.4

4.5.2. Standard curve for Clarithromycin (By UV method) [90]

A stock solution of Clarithromycin was prepared by dissolving 50mg of pure drug in pH 7.4 phosphate buffer saline in a 100ml volumetric flask. From the above stock solution, 10ml of solution was pipetted out into a 100ml volumetric flask and made upto the mark. From the secondary stock solution, 1ml, 2ml, 3ml, 4ml upto 10ml were taken and diluted to 10ml to obtain the concentrationof 5 to 50 µg/ml.The absorbance of the solutions were measured against the blank in a UV spectrophotometer. A calibration curve was obtained at 220 nm for a series of concentration in the range of 5 to 50 µg/ml.

Table 2: Calibration Curve of Clarithromycin.

Concentration(µg/ml)	Absorbance at 220nm
5	0.097
10	0.197
15	0.298
20	0.381
25	0.494
30	0.587
35	0.678
40	0.781
45	0.877
50	0.966

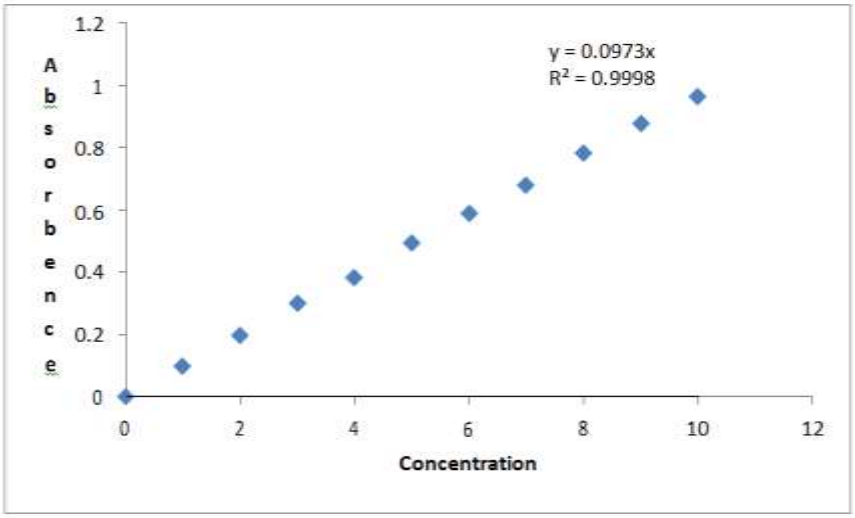

Fig: 1: Standard Curve For Clarithromycin.

PREFORMULATION STUDYIR studies

Identification of the pure drug was performed using IR spectroscopy. IR spectroscopy (using Perkin Elmer) by KBr pellet method carried out on drug. They are compressed under 15 tones pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000-400cm^{-1} in a spectrophometer and peaks obtained were identified.

METHOD OF PREPARATION OF CLARITHROMYCIN NANOPARTICLE NANOPRECIPITATION METHOD

All batches of nanoparticles were prepared by nanoprecipitation method. The required quantity of polymer dissolved in 3ml ethanol, and drug was dissolved in 3ml of ethanol, added finally both were mixed together and added β-cyclodextrin. The mixer was homogenized in vortex mixture for 1 min and then the Final volume of the preparation was to 10ml. Then this preparation was centrifuged at 15000rpm at 4^{0}c for half an hour. The supernatant was discarded and precipitate was washed 3times with distilled water. The nanoparticles thus obtained were dried overnight in oven at 60^{0}c and stored in desiccators.

The prepared formulation were characterized for loading efficiency, entrapment efficiency, particle size, particle size distribution, zeta potential and drug polymer compatability studies.

Table 3: Various Composition of Nanoparticles Formulation.

FORMULATIONCODE	DRUG (Clarithromycin)in mg	PAV in mg	β CYCLODEXTRIN
F1	50	25	5
F2	50	50	5
F3	50	75	5
F4	50	100	5
F5	50	25	10
F6	50	50	10
F7	50	75	10
F8	50	100	10
F9	50	25	15
F10	50	50	15

RESULTS AND DISCUSSION

DEVELOPMENT OF CLARITHROMYCIN NANOPARTICLES

All batches of nanoparticles were prepared by nanoprecipitation method. The required quantity of polymer dissolved in 3ml ethanol, and drug was dissolved in 3ml of ethanol, added finally both were mixed together and added β-cyclodextrin. The mixer was homogenized in vortex mixture for 1 min and then the Final volume of the preparation was to 10ml. Then this preparation was centrifuged at 15000rpm at 4^{0}C for half an hour. The supernatant was discarded and precipitate was washed 3 times with distilled water. The nanoparticles thus obtained were dried overnight in oven at 60^{0}C and stored in desiccators.

Formulations with different ratios of polymer were prepared, several physiochemical characteristics of nanoparticles such as particle size determination, drug release profile, were investigated and stability of optimized formulation at various temperature was evaluated.

DRUG AND POLYMER COMPATABILITY STUDIES BY FTIR[27,76]

Identification of the pure drug was performed using IR spectroscopy. IR spectroscopy (using Perkin Elmer) by KBr pellet method carried out on drug. They are compressed under 15 tones pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000-400cm^{-1} in a spectrophometer and peaks obtained were identified.

Table 4: I.R Spectra Data For Pure Clarithromycin.

Wave no. (cm$^{-1)}$	Group Assigned
1730.21	C=O – Stretching
1408.06	C=C – Stretching
1099.46	C-N - Stretching

Table 5: I.R Spctera Data for Physical Mixture.

Wave no.(cm$^{-1)}$	Group Assigned
1734.01	C=O – Stretching
1409.06	C=C – Stretching
1099.43	C-N - Stretching

REPORT

In FTIR spectra the peaks of physical mixture was compared with the original spectra. Same peaks were observed, indicates no possible molecular interaction between the drug and the polymer.

ENTRAPMENT EFFICIENCY OF NANOPARTICLES

The entrapment efficiency of Clarithromycin nanoparticles was prepared by nano precipitation method. The formulation F1(Clarithromycin 50 mg with 25 mg of Chitosan and β -cyclodextrin) shows less entrapment value of 60.16% this may be the due to repulsiveforce between drug and the polymer.

Table No: 6 Entrapment efficiency of Clarithromycin nanoparticles

Formulation Code	Drug(mg)	Chitosan(mg)	β cyclodextrin(mg)	Ethanol	Entrapment Efficiency(%)
F1	50	25	5	2%	60.16±0.14
F2	50	50	5	2%	64.15±0.17
F3	50	75	5	2%	68.28±0.15
F4	50	100	5	2%	71.12±0.09
F5	50	25	10	2%	88.23±0.12
F6	50	50	10	2%	94.26±0.18
F7	50	75	10	2%	99.38±0.08
F8	50	100	10	2%	87.42±0.09
F9	50	25	15	2%	85.35±0.06
F10	50	50	15	2%	82.25±0.04

In formulation F2 Polymer concentration was increased (Clarithromycin 50 mg with 50mg of Chitosan and 5 mg β -cyclodextrin) the entrapment efficiency was to 64.15%. Further increase in polymer concentration in formulation F3 (Clarithromycin 50 mg with 75 mg of Chitosan and 5mg β -cyclodextrin)entrapment efficiency was 68.28%. Further increase in polymer concentration in formulation F4 (Clarithromycin 50 mg with 100 mg of Chitosan and5 mg β -cyclodextrin) entrapment efficiency was 71.12%. Formulation F5, F6, was carried out by same process as like previous formulation but changes in polymer concentration 25mg, 50mg, 50 mg of Clarithromycin and10 mg β -cyclodextrin was taken. The entrapment efficiency was found to be F5,88.23% for F6,94 .26%.

Formulation F7 was carried out by increasing the polymer concentration same (Clarithromycin 50 mg with 75 mg of Chitosan and 10 mg β -cyclodextrin) the entrapment efficiency was increased to 99.38%.

Formulation F8 was carried out by increasing the concentration (Clarithromycin 50 mg with 100 mg of Chitosan and 10 mg β -cyclodextrin) which give the percentage of entrapment efficiency was 87.42% but In F8 the *invitro* release of drug shows less than F7 formulation. So F7 formulation is optimized and further study was carried out.

Further formulation F9 and F10 was carried out in same process, drug and polymer concentration (Clarithromycin 50 mg with 25 and 50mg of Chitosan and 15 mg β -

cyclodextrin) the Entrapment efficiency is F9 85.35%, F10 82.25% From the above result formulation F7 shows highest percentage of entrapment efficiency of 99.38%. So hence this formulation was optimized and further study was carried out.

In F1,F2,F3, F4 formulations, when increasing the polymer concentration the entrapment efficiency is not satisfactory limit. Nanoparticle using 5 mg β - cyclodextrin showed lower entrapment.

So further increasing the concentration of β – cyclodextrin in F5, F6 and F7 formulations. (Clarithromycin 50 mg with 25 mg 50mg and 75 mg of Chitosan and 10 mg β -cyclodextrin). In this formulations the entrapment efficiency was F5 for 88.23%, F6 for 94.26% and F7 for 99.38%.In this the optimum entrapment efficiency obtained in F7.

Further increase the concentration of β –cyclodextrin in formulation F8, F9 and F10.

The entrapment efficiency also decreased.

IN VITRO DRUG RELEASE PROFILE OF NANOPARTICLES

- The *in-vitro* drug release of Clarithromycin nanoparticles can be carried out by membrane diffusion method for 24 hrs.
- The *in-vitro* drug release of Clarithromycin nanoparticles with Chitosan and β –cyclodextrin.
- The *in-vitro* drug release of formulation F1 (Clarithromycin 50 mg with 25mg of Chitosan and 5 mg β -cyclodextrin) The percentage of *in vitro* drug release was 97% in 9 hrs.
- The formulation F2 was carried out by the increasing the polymer concentration (Clarithromycin 50 mg with 50mg of Chitosan and 5 mg β -cyclodextrin) The percentage of *in vitro* drug release was found to be 96.40% in 11 hrs.
- The formulation F3 was carried out by further increasing in polymer concentration (Clarithromycin 50 mg with 75 mg of Chitosan and 5 mg β - cyclodextrin) The percentage of drug release was found to be 98.44% in 13 hrs.
- The formulation F4 was carried out by further increasing in polymer concentration (Clarithromycin 50 mg with 100mg of Chitosan and 5 mg β - cyclodextrin). The percentage drug release found to be 96.2% in 16 hrs.
- The formulation F5 was carried out by further increasing in polymer concentration (Clarithromycin 50 mg with 25 mg of Chitosan and 10 mg β - cyclodextrin). The percentage drug release was found to be 98.0% in 19 hrs.
- The formulation F6 was carried out by further increased in polymer concentration (Clarithromycin 50 mg with 50mg of Chitosan and 10 mg β - cyclodextrin). The percentage drug release was found to be 94.42% in 24 hrs.
- The formulation F7 was carried out by combination of (Clarithromycin 50 mg with 75mg of Chitosan and 10 mg β -cyclodextrin). The percentage of drug release wasfound to be 98.46% in 24 hrs.
- The formulation F8 was carried out by the combination of increasing the polymer concentration of (Clarithromycin 50 mg with 100mg of Chitosan and 5 mg β - cyclodextrin) percentage drug release was found to be 88% in 24 hrs.
- The formulation F9 was carried out by the combination of increased polymer concentration (Clarithromycin 50 mg with 25 mg of Chitosan and 15 mg β - cyclodextrin) percentage of drug release was found to be 95% 14 hrs.
- The formulation F10 was carried out by the combination of increased polymer concentration (Clarithromycin 50 mg with 50mg of Chitosan and 15 mg β - cyclodextrin) percentage of drug release was found to be 96.4% 17 hrs.
- From the above formulation (F1-F10) confirms that the percentage of drug release was satisfactory in formulation F7 and it shows higher percentage of drug release of 98% for 24 hrs. So it was selected as a optimized formulation.

When increasing the polymer concentration the *in vitro* drug release also increased toa certain extent in the drug and polymer ratio up to 1:1.5

Further the polymer concentration is increased in F8 formulation the *in vitro* drug release increased but not extend upto 24hrs. So F7 was selected as a optimized formulation.

COMPARITIVE INVITRO RELEASE STUDY OF CLARITHROMYCIN NANOPARTICLE FORMULATIONS F1 TO F10

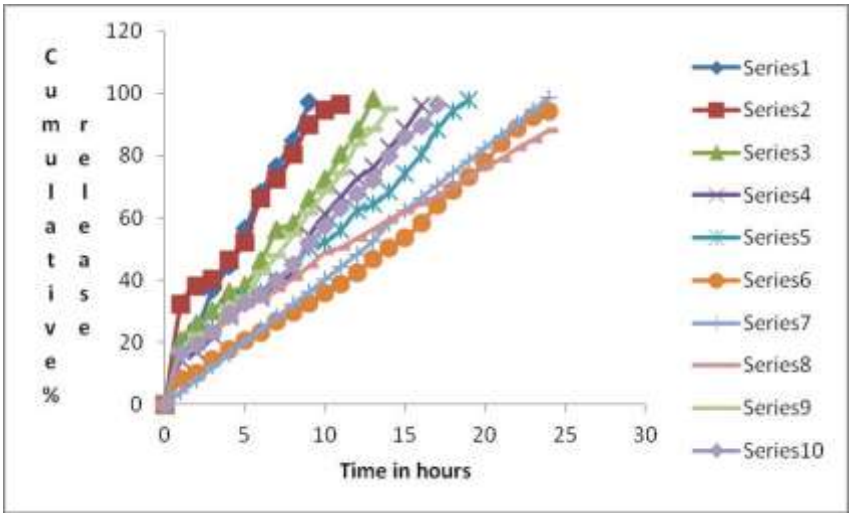

Figure: 2

SCANNING ELECTRON MICROSCOPY

The surface characteristics of optimized formulation (F7) particle size were studied by scanning electron microscope. SEM image of prepared nanoparticle formulation shows the coating of polymer mixture on drug particles. The appearance of nanoparticles in scanning electron microscope is in granule form, which indicates a thin and uniform coating over the drug. SEM image revealed that the Clarithromycin nanoparticles were in nano size range, and smooth spherical in shape in this F7 Formulation.

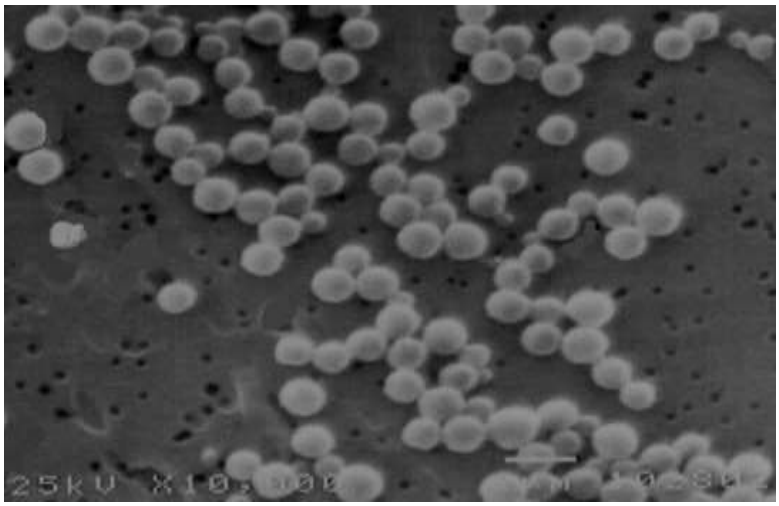

Fig. No. 3: SEM IMAGE OF F7.

SURFACE CHARGE (ZETA POTENTIAL)

The zeta potential of a nanoparticles is commonly used to characterize the surface charges property of nanoparticles. It reflects the electrical potential of particles influenced by the composition of the particles band the medium in which it is dispersed. When nanoparticles formulations are administered through intravenous route they are easily identified and detected by the phagocytes. The particle size and the hydrophobicity surface ofthe nanoparticles determine the adsorption of blood components (proteins) called as opsonins. The opsonin in turn decides the fate of the nanoparticles. Binding of these opsonins on to the surface is known as Opsoniazation. Non modified nanoparticles were rapidly opsoniazed and gets easily eliminated from the body. Hence, to increased minimize the opsoniazation and to prolong the circulation of nanoparticles *invivo*.

The zeta potential of the nanoparticle formulation with Chitosan (formulation F7) particles which present in the formulation are de-aggregated and remain same and more stable in the substance and zeta potential (mV) is 38 mv and zeta Deviation (mV) is 9.16 and conductivity (mS/cm) is 0.899. So this polymer is more suitable for nanoparticles preparation and the result shows smooth surface character and efficient repelled action and it decreases the opsoniazation.

STABILITY STUDIES OF CLARITHROMYCIN NANOPARTICLES[75]

The stability studies of optimized nanoparticle formulation F7 was carried our for 3 months. The test was performed in three conditions 4°C, Room temperature and 45°C/70% RH. At the time interval of one month the nanoparticle formulation were evaluated for entrapment efficiency. The stability of nanoparticles formulation was more stable in refrigerator (4°C) when compared to room temperature and at (45°C/70% RH)

Table 7: Stability Studies for Clarithromycin Nanoparticle.

S.NO	Storage Condition	Test parameters	1st month	2th month	3rd month
1	4°C	pH colour stability	7.5 Clear & colour less 97.46	7.5 Clear& colour less 96.47	7.5 Clear & colour less 95.46
2	Room Temperature	pH colour stability	7.4 Clear & colour less 93.41	7.4 Clear & colour less 92.42	7.3 Clear & colour less 91.42
3	Accelerationcondition at 45°C/70% RH	pH Colour Stability	7.4 Clear & colourless 90.42	7.3 Clear & colourless 88.24	7.3 Clear & colourless 86.41

Kinetics of drug release for optimized formulation F7

The optimized formulation F7 was introduced in to graphical treatment for kinetic of drugrelease.

IN VITRO DRUG RELEASE FORMULATION F7

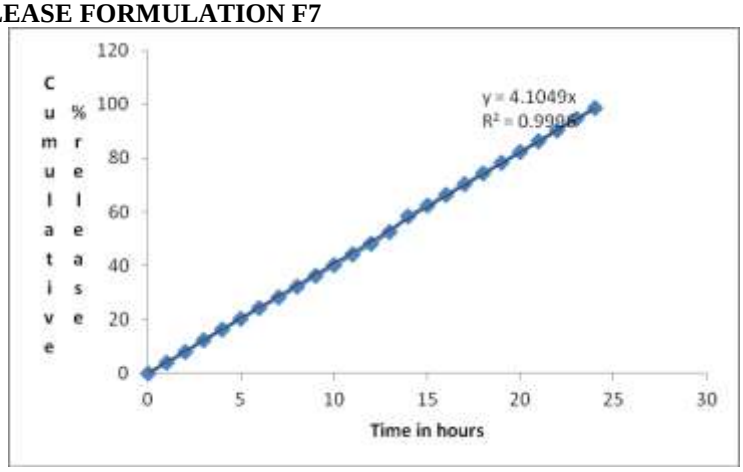

Fig. No. 4: Zero Order Plot for formulation F7.

Regression=0.999

The optimized formulation F7 of nanoparticles is more suitable for parentral administration it shows good *invitro* release kinetic study. The zero order plots were obtained by plotting cumulative percentage drug release versus time. The regression value is 0.999.

HIGUCHI 'S PLOT

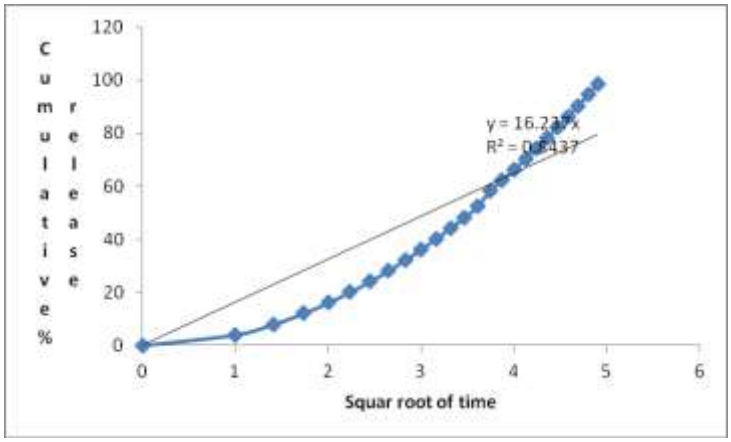

Fig. No. 5: HIGUCHI' S PLOT FOR FORMULATION F7.

Regression=0.843

Higuchi plot was made by plotting cumulative percentage % drug release against square root of time. The regression value was found to be 0.843.This indicates that diffusion is one of the mechanism of drug release.

KORSEMEYER PLOT

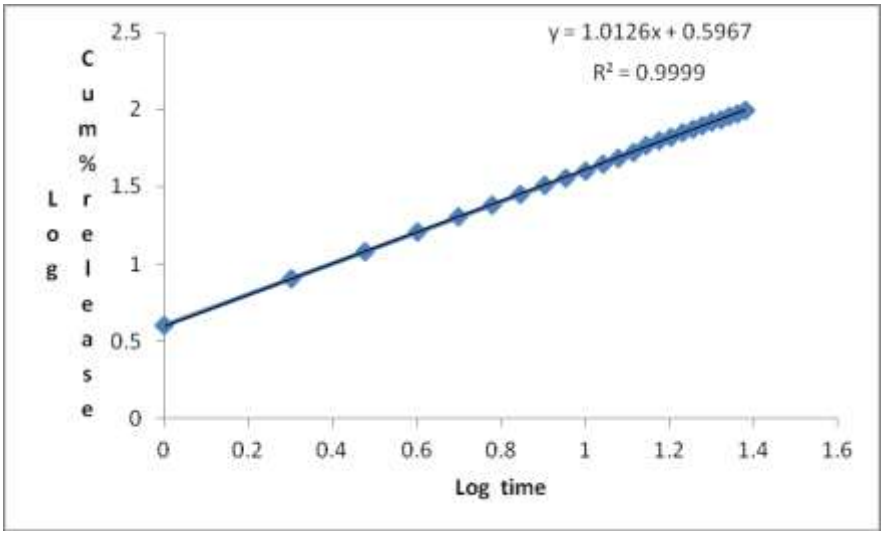

Fig. No. 6: KORSEMEYER'S PLOT FORMULATION F7.

The graph was plotted between log cumulative % of drug release and log time. The n'value was found to be 1.0126 indicated may nonfickian diffusion mediated.

Kinetic of drug release of first order for optimized formulation F7

The optimized formulation F7 was introduced into graphical treatment for kinetics of drugrelease.

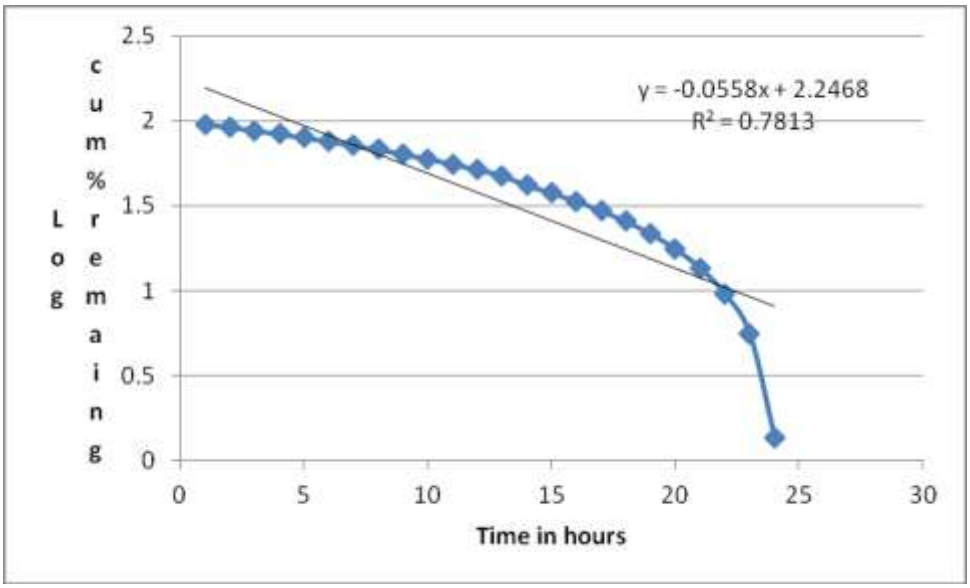

Fig. No. 7: First order plot for formulation F7.

Regression = 0.7813

The optimized formulation F7 of nanoparticles is more suitable for parentral administration it shows the *invitro* release kinetic study. The first order plots were obtainedby plotting log remaining cumulative percentage drug release versus time. The regression value is 0.7813.

SUMMARY AND CONCLUSION

The present study was aimed to develop a nanoparticulate drug delivery system of Clarithromycin using polymer (Chitosan). The polymer enhances the binding of Clarithromycin nanoparticles in specific or targeted site with sustained release of drug increasing therapeutic efficacy. These nanoparticles may also reduce the dose frequency with desired therapeutic response.

All batches of nanoparticles (F1-F10) were prepared by nano precipitation method.

The entrapment efficiency of the optimized formulation F7 (drug 50mg, Chitosan 75mg, β –cyclodextin 10 mg) was 99.38 ±0.08 and *invitro* drug release was 98.46% after 24 hours. It also obey the zero order, follows diffusion and erosion mechanism of release.

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The stability test performed revealed that the formulation (F7) showed no change in its characters. The optimized formulation (F7) was also examined for zeta potential determinations.

The formulation(F7) showed maximum deviation of 9.16 mV which demonstrated that the particles are separate and highly repelling property found to be more useful in decreasing opsonization and favors target specificity.

The developed Clarithromycin nanoparticle formulation increases water solubility, reduces the dose frequency and improves the bioavailability of drug.

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