ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 7, Issue 3, 2014

ISSN - 0974-2441

Original Article

FORMULATION OF IBUPROFEN LOADED ETHYL CELLULOSE NANOPARTICLES BY NANOPRECIPITATION TECHNIQUE

P.SWATHI[1], A.KRISHNA SAILAJA[2],

[1] Project Assistant, RBVRR Women's College of Pharmacy, Barkathpura, Hyderabad-27, [2]Associate Professor, RBVRR Women's College of pharmacy, Osmania University, Hyderabad-27.

Email: pamulapartiswathi@gmail.com

Received: 15 May 2014, Revised and Accepted: 5 June 2014

ABSTRACT

Objective : The present study was undertaken to prepare and characterize drug loaded Ethyl cellulose nanoparticles using nanoprecipitation technique. The model drug chosen was Ibuprofen.

Methods: These nanoparticles were prepared using nanoprecipitation technique in which the organic phase containing varied proportions of drug and the polymer was added drop wise to the aqueous phase having the stabilizer with continuous stirring. This resulted in the formation of precipitate in the aqueous phase. The stirring was continued for about 2 hours further. Then, the precipitate was collected by subjecting the sample to vacuum filtration and was air-dried.

Results: The best formulation among all the three was determined by comparing the particle size, stability and invitro drug release of all the formulation. F3 was considered as the best formulation with average particle size as 251.1 nm, zeta potential as -25.2 mV, and 86.02 % drug release which was sustained till 8 hours.

Conclusion: F3 formulation i.e.; in which concentration of drug and polymer bears a ratio of 1:2 was concluded as the best because of their smaller particle size and greater stability.

Keywords: Acetone, Ethyl cellulose(EC), Ethanol, Ibuprofen, Nanoparticles, Nanoprecipitation.

INTRODUCTION

The major focus on Novel drug delivery systems during the past two decades is to improve the therapeutic efficacy and safety profile of the drug substances. Colloidal drug delivery systems are considered to be more popular than the matrix or reservoir drug delivery systems. Among all the colloidal systems, Nanoparticles hold promise as drug delivery through various routes due to their greater stability and easier manufacturing ability. These systems are used for specific drug delivery, controlled drug delivery and also for the improvement of bioavailability of the hydrophobic drugs[1].

Nanoparticles are colloidal particles having size below 1 um. The production of these nanoparticle systems can be categorized in to two, based on the specific characteristics in the materials used. First category involves reactive synthesis from solubilized small molecular precursors and the second involves the fabrication of bulk materials into nanostructures. Nanoprecipitation is one of the method that is included under second category. It is widely applicable technique that is less energy consuming and less complex method. The principle behind this technique is the interfacial deposition that occurs due to the displacement of a solvent with the non-solvent. The parameters that influence the formation of the nanoparticles in this method are miscibility of the solvents and the presence of the dilute polymer solutions. The various polymers undergoing this method are macromolecules that can form complexes in the nanoscale range called as Polyplexes, when come in contact with oppositely charged molecules such as genes and proteins.[2]

This method is considered to be the most sensitive and low energy consuming one as it requires low energy costs and no special equipment requirements. The various polymers involved in this technique are not only Poly(lactide), Poly(lactide-co-glycolide) and Poly caprolactone but also other lactones, cellulose ethers and esters like cellulose butyrate acetate, ethyl cellulose, hydroxyl methylpropylcellulose phthalate, cellulose acetophthalate, naturally occurring polymers(gelatin, Arabic gum), poly(vinyl alcohol acetophthalate), copolymers of acrylate acrylate and methacrylate (Eudragit), poly(vinyl pyrrolidone-vinyl acetate), maleic acid derivatives, etc.

It is most suitable method for hydrophobic drugs and the problem arises when a hydrophilic drug has to be encapsulated in the polymeric matrix by this method. The problem can be minimized by adjusting the pH value or by choosing appropriate solvent/non-solvent.[3],[4]

Ethyl cellulose is a semi synthetic material having properties like biocompatibility and degradation to non toxic and readily excreted products. It is a very useful polymer for the preparation of nanoparticle drug delivery system, as is water-insoluble, wall-forming polymer.[5]

The model drug selected for this work was Ibuprofen. It is a non-steroidal anti-inflammatory drug that is used to relieve symptoms of pain of arthritis. Other uses includes primary dysmenorrheal, alleviating fever and reducing inflammation, also helping in showing analgesic, anti-platelet and vasodilation effect.

The objective of the present study includes formulation of nanoparticles containing Ibuprofen using ethyl cellulose as the retardant polymer which will release the drug at the gastrointestinal tract for a prolong duration to promote patient compliance and to evaluate the effect of various process variables on mean particle size, percentage yield, percentage encapsulation efficiency of the formed Ibuprofen nanoparticles.

MATERIALS

Drug : Ibuprofen (Gift Sample)

Polymer : Ethyl Cellulose, obtained from SD Fine Chem. Limited, Mumbai.

Stabilizer : Tween – 20, obtained from SD Fine Chem. Limited, Mumbai.

Solvents : Ethanol, Acetone, obtained from SD Fine Chem. Limited, Mumbai.

METHODOLOGY

Nanoprecipitation technique was adopted for the preparation of Ibuprofen loaded Ethyl Cellulose nanoparticles. The processing parameters like concentration of the drug, polymer and amount of solvents chosen were varied and three different formulations were prepared[6],[7],[8]. In the first formulation(F1), equal quantities of drug and polymer were dissolved in water miscible solvents i.e.; 6ml of Ethanol and 6ml of Acetone respectively. Tween-20 (0.1%) which acts a stabilizer was added to the aqueous phase. Above prepared organic phase was added drop-wise to the aqueous phase with continuous stirring. The appearance of precipitate in the solution was considered as the end point. After the attainment of endpoint, the solution was kept for stirring for about 2 hours. The precipitate was separated from the solution by means of filtration. The obtained precipitate was air-dried to remove the moisture content.

Similarly, in the second formulation(F2), drug and polymer were taken at the ratio of 1:1.5 and were dissolved in 6ml of Ethanol and 10ml of acetone respectively. Further the above steps were repeated. In the third formulation(F3), the amount of polymer taken was doubled when compared to that of the drug. They were dissolved in 6ml of Ethanol and 12 ml of Acetone respectively.

The dried free flowing powder obtained for all the formulations(F1, F2, F3) were then characterized for particle size distribution and zeta potential to ensure that they were within nanosize range and possessed optimum stability respectively. Further, they were evaluated for following parameters like entrapment efficiency, loading capacity and invitro drug release.

Characterization of Nanoparticles

Drug Content and Drug Entrapment Efficiency

Drug content was determined as follows

50 mg from each formulation of prepared drug loaded EC nanoparticles prepared by nanoprecipitation technique, were dissolved in 50 ml of methanol and kept for stirring at 600 rpm for 3 hours respectively. The total amount of the drug in each formulation was determined spectrophotometrically at 221 nm.

Entrapment efficiency and Loading capacity were determined as follows

50 mg from each formulation of prepared drug loaded EC nanoparticles prepared by nanoprecipitation technique, were dissolved in 50 ml of 7.2 pH phosphate buffer and were kept for ultracentrifugation for 40 minutes respectively. Entrapment efficiency and loading Capacity of each formulation was determined using the formula :

$$\text{Entrapment Efficiency} = \frac{\text{Total amount of the drug entrapped}}{\text{Total amount of the drug initially taken}} \times 100$$

$$\text{Loading Capacity} = \frac{\text{Total amount of the drug entrapped}}{\text{Total weight of the nanoparticles taken}} \times 100$$

Particle Size Analysis and Zeta Potential Measurement

The average particle size and size distribution of Ibuprofen loaded EC NP's were determined by dynamic light scattering(DLS), using Horiba Zetasizer.

The Zeta potential(Surface Charge) which indicates the stability of the NP's can be defined as electrokinetic potential that is determined by electrophoretic mobility. Samples were prepared by diluting with water and corresponding zeta potential were measured using Horiba Zeta Sizer.

Determining the size and morphology of the nanoparticles:

Scanning Electron Microscopy is used to determine the shape, size and surface morphology of the nanoparticles. Nanoparticulate suspension is made to obtain Photomicrographs of the drug loaded ethyl cellulose nanoparticles using this SEM.InVitro Drug Release Studies:

The invitro drug release studies were carried out using Arbitary Shaker. The prepared nanoparticles of each formulation were placed in conical flask each and were dispersed using 50 ml of 7.2 pH buffer. The entire system was kept at 37 ± 0.5 ºC with the continuous stirring at 100 rpm. The samples were withdrawn at predetermined intervals and replaced by fresh medium simultaneously. The amount of drug released for each formulation at specific time interval was determined with UV spectrophotometrically at 221 nm.[9], [10]

RESULTS AND DISCUSSIONS

The yield obtained for all the formulation for Drug loaded EC nanoparticles prepared by nanoprecipitation technique were optimum. They were evaluated for above mentioned characters and results obtained were as follows:

Drug Content of the formulations: The drug content for all the formulations were evaluated. It was observed that the NPs of F1 showed a higher drug content value i.e; 93.11%. NPs of F2 and F3 showed drug content values as 84.52% and 88.56% respectively.

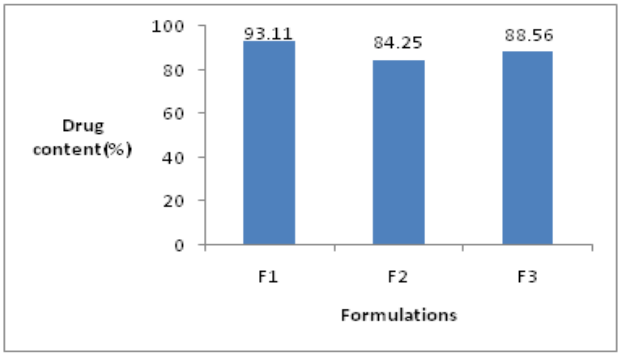

Fig. 1: It shows Drug Content of NPs of various formulations prepared by nanoprecipitaiton technique.

Entrapment Efficiency and Loading Capacity of the formulations : Entrapment efficiency and loading capacity were found to be more for Nanoparticles having higher polymer concentration when compared to drug. The entrapment efficiencies were found to be 77.58%, 88.81% and 95.8% for F1, F2, F3 respectively.

The loading capacities of these formulations i.e; F1, F2, F3 were observed as 56.25%, 35.75%, 43.15% respectively.

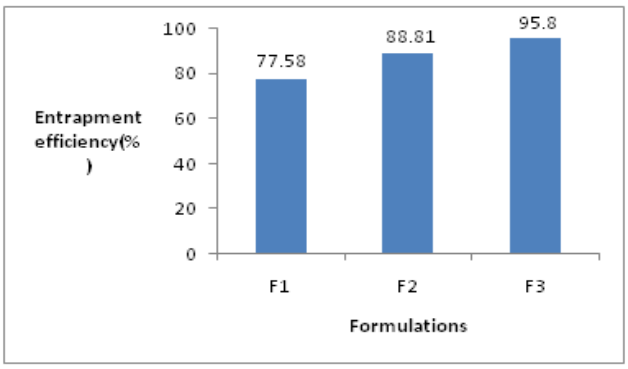

Fig. 2: It shows Entrapment Efficiency of NPs of various formulations prepared by nanoprecipitaiton technique.

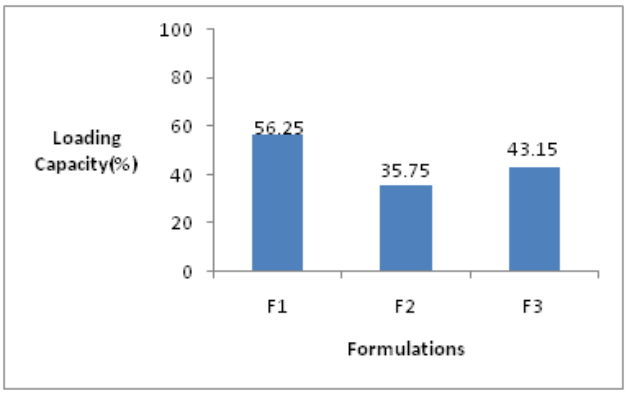

Fig. 3: It shows Loading Capacity of NPs of various formulations prepared by nanoprecipitaiton technique.

Average Particle size and Zeta Potential: The size distribution of the prepared nanoparticles along the mean diameter were measured using particle size analyser. The average particle size of the prepared drug loaded Ethyl Cellulose nanoparticles were recorded. It was found minimum for F3 formulation i.e.; 251.1 nm.

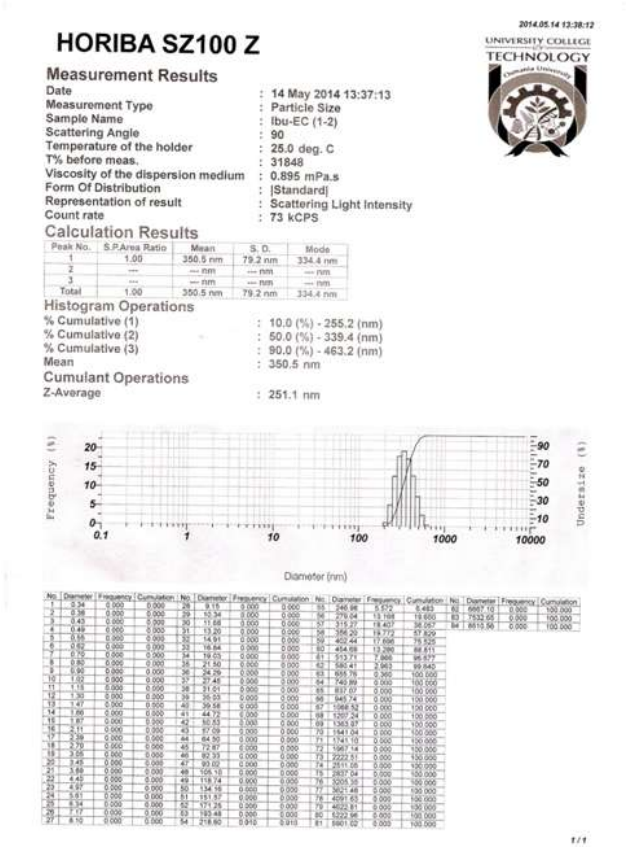

Fig. 4: It shows Particle Size analysis of F3 formulation

Zeta Potential: Zeta potential of the prepared drug loaded Ethyl cellulose nanoparticles were measured using zeta meter. NPs of F3 formulation showed higher stability, bearing a value of -25.2 mV.

Invitro Drug Release Studies : Invitro drug release studies were performed to determine the sustained release nature of the formulations. In F2 and F3 formulations, the drug release was continued upto 8 hours. In a period of 8 hours 86.012% and 79.95% of drug has been released frm F2 and F3. InF1, the drug release continued upto 4 hours. 98.2% of the drug has been released within a time period of 4 hours. From the various plots mentioned, it can be concluded that the drug release from the nanoparticles of the F1 and F3 formulations obeyed zero order kinetics and F2 formulation obeyed first order kinetics, all following fickian diffusion mechanism.

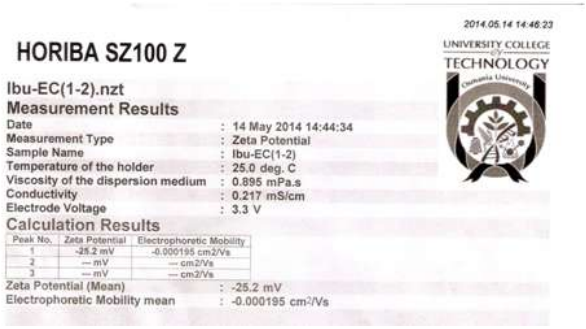

Fig. 5: It shows Zeta Potential of F3 formulation

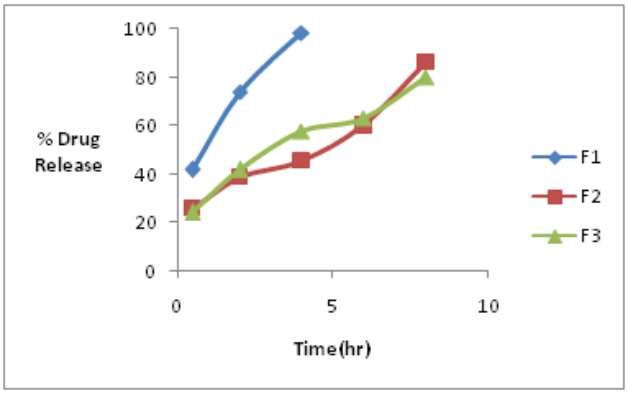

Fig. 6: It shows invitro drug release pattern of NPs of various formulations prepared by nanoprecipitation technique.

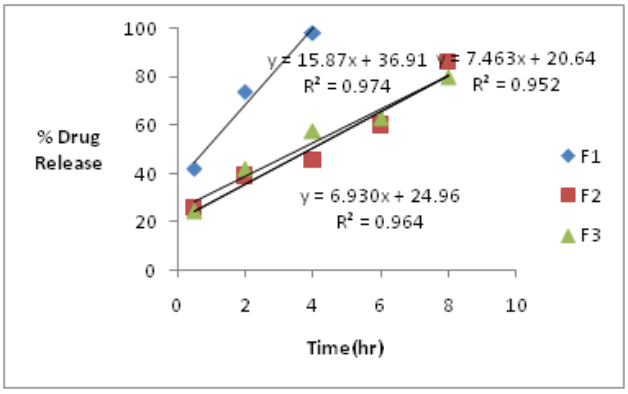

Fig. 7: It shows Zero Order plot of NPs of various formulations prepared by nanoprecipitation technique.

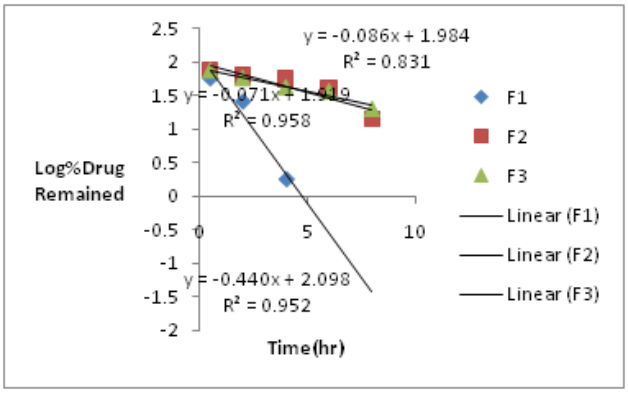

Fig. 8: It shows First Order plot of NPs of various formulations prepared by nanoprecipitation technique.

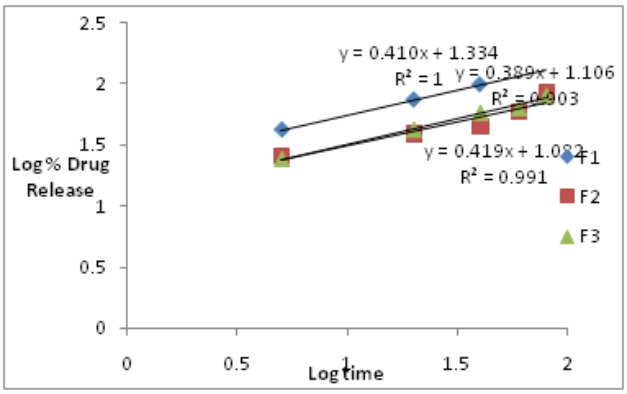

Fig. 9: It shows Peppas plot of NPs of various formulations prepared by nanoprecipitaiton technique.

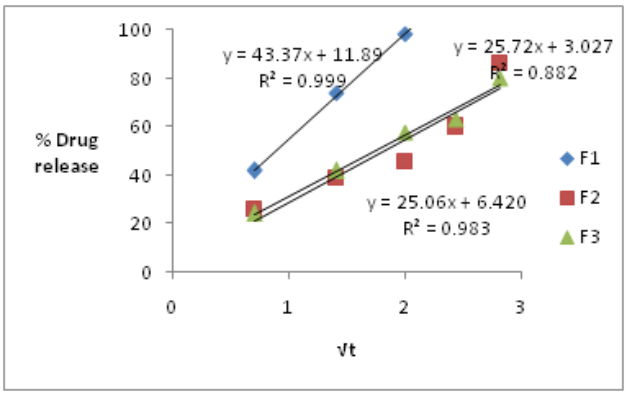

Fig. 10: It shows Higuchi plot of NPs of various formulations prepared by nanoprecipitaiton technique.

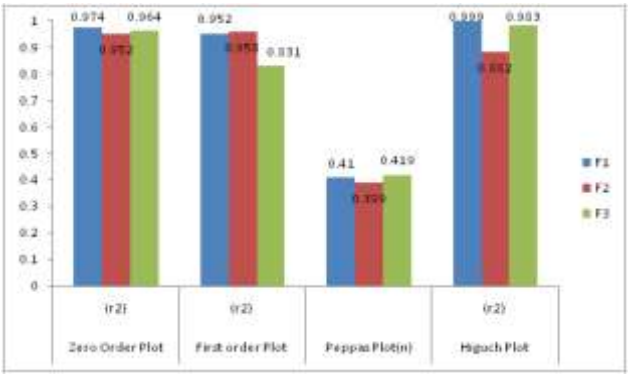

Fig. 11: It shows the parameters determined from the Invitro Release Studies performed on Drug loaded Ethyl cellulose NPs of three different formulations :

DISCUSSION

In this present study attempts have been made to prepare Ibuprofen loaded EC nanoparticles by nanoprecipitation technique. Ibuprofen is a non-steroidal anti-inflammatory drug used in the treatment of Rheumatoid arthritis and Ankylosing spondylitis. In order to obtain the best formulations, the concentration of polymer and solvents were varied by keeping the concentration of drug constant. Three formulations were prepared by varying the concentration of the polymer and organic solvents. The drug, polymer ratio was maintained as 1:1, 1:1.5, 1:2 in formulation 1, 2, 3 respectively. The effect of the polymer concentration on nanoparticle size, stability, drug content, entrapment efficiency, loading capacity was studied.

On comparing the invitro drug release profile of all the formulations, F1 was showing maximum drug release(98.20%) in a time period of 4 hours. The maximum drug release was may be because of the poor entrapment of the drug. Initial burst release indicated the presence of the free drug in higher concentrations. In F2 and F3, the drug release was continued upto 8 hours indicating its sustained release properly. When F2 and F3 formulations were compared, maximum amount of drug has been released from F3(86.012%). In F2 and F3, amount of polymer taken was more when compared to drug. The sustained release nature is thought to be mainly because of the higher concentration of polymer to that of drug. Entrapment efficiency was improved by increasing the polymer concentration from 1:1 to 1:1.5 to 1:2.

CONCLUSION

From the results, it can be concluded that F3 formulation i.e.; in which concentration of drug and polymer bears a ratio of 1:2, is considered to be better than F1 and F2 because of smaller particle diameter(251.1 nm), greater stability(-25.2 mV) and maximum entrapment efficiency(95.8%).

ACKNOWLDGEMENT

The authors would like to thank RBVRR Women's College of Pharmacy, Principal Dr.M.Sumakanth for providing us funds for the work. The authors would like to acknowledge Mrs. K. Sumalatha and Mrs. D. Suvarna for providing us technical assistance.

REFERENCES

1. S.Tamizhrasi, A.Shukla, T.Shivkumar, V.Rathi, J.C.Rathi. Formulation and evaluation of lamivudine loaded polymethacrylic acid nanoparticles, International Journal of Pharm Tech Research 2009;1(3):411-415.
2. Stephanie Homig, C.Remzi Becer and Ulrich S.Schbert. Synthetic polymeric nanoparticles by nanoprecipitation. Journal of Materials Chemistry.
3. Stephanie Schubert, Joesph T.Delaney and Ulrich S.Schubert. Nanoprecipitation and Nanoformulation of polymers: from history to powerful possibilities beyond poly(lactic acid).Soft Matter 2010.
4. Patrick Nardstrom: Formulation of polymeric nanoparticles encapsulating and releasing new hydrophobic cancer drug. Master of Science Thesis in Materials and Nanoptechnology. Sweden; 2011.
5. Avanco G B, Bruschi M.L. Preparation and Characterisation of ethylcellulose microparticles containing propolis. Journal of Basic and Applied Pharmaceutical Science 2008; 29(2):129-135.
6. Pranita Kashyap, Hemant Dhongade, Kamlesh Singh, Afreen Ansari, Pragati Bhagel. Preparation and Evaluation of Acetaminophen Microparicles. International Journal of Medical and Pharmaceutical Sciences 2011; 1(5).
7. Nepolean.R et al. Preparation and Characterization of Nisoldipine Nanoparticles by Nanoprecipitation Method. J.Pharm. Sci. & Res. 2012; 4(11):1989-1994.
8. Jose Mario Barichello, Mariko Morishita, Kozo Takayama and Tsuneji Nagai. Encapsulation of Hydrophilic and Lipophilic Drugs in PLGA Nanoparticles by the Nanoprecipitation Method. Drug Development and Industrial Pharmacy 1999; 25(4) :471-476.
9. Gupta Dilip Kumar, Razdan B.K. Bajpai Meenakshi. Formulation and Evaluation of nanoparticles containing Artemisinin HCL, International Journal of Research and Development in Pharmacy and Life Sciences. March 2014; 3(2): 925-934.
10. A.Krishna Sailaja, P.Amareshwar. Preparation of alginate nanoparticles by desovaltion technique using acetone as desolvating agent. Asian Journal of Pharmaceutical and Clinical Research. 2012; 5(2).
11. A.Krishna Sailaja, P.Amareshwar, P.Chakravarty. Different Techniques for the preparation of Nanoparticles using natural polymers and their application, International Journal of Pharmacy and Pharmaceutical Sciences.2011; 3(2).
12. The Merck Index. An Encyclopedia of Chemicals, drug and biological, Merck Laboratories, 13th Edition. 2001. Pp139.
13. Merodio M,. Arnedo A, Renedo M.J. Irache J.M, Ganciclovir- loaded albumin nanoparticles:characterization and in vitro release properties, European J of Pharmceutical Sciences, (2001); Vol.12(3), 251.
14. Bahareh Azimi, Parviz Nourpanah, Mohammad Rabiee and Shahram Arbab. Producing Gelatin Nanoparticless as Delivery System for Bovine Serum Albumin, Iranina Biomedical Journal. 2014; 18(1): 34-40.

15. Mohanraj VJ, Chen Y Nanoparticles – A Review. Trop. J.Pharm. Res. 2006; 5(1): 561-573.
16. Radhika Ramachandran and Piranamayagam Shanmughavel. Preparation and characterization of biopolymeric nanoparticles for Drug-delivery, Indian Journal of Biochemistry and Biophysics. 2010; 47: 56-59.
17. Vyas S P, Khar R K, Targeted & Controlled Drug Delivery, Novel Carrier Systems, CBS publicarion, 2002, 331-387.
18. Wim H De Jong, Paul Ja Borm. Drug delivery and nanoparticles: Applications and Hazards, Int J Nanomedicine. June 2008; 3(2): 133-149.
19. G.M Barratt, Therapeutic Applications of colloidal drug carriers, Pharm. Sci. Technol. Today 3, 163-171.
20. Jiang B, Hu L, Gao C, Shen J. Ibuprofen loaded nanoparticles prepared by a co-precipitation method and their release properties, Int J Pharm. Nov 2005; 304(1-2): 220-30.
21. Rahimnejad M., M. Jahanshahi*, G. D. Najafpour. Production of biological nanoparticles from bovine serum albumin for drug delivery. African Journal of Biotechnology.2006; Vol. 5 (20): pp. 1918-1923
22. Dongmei Zhao,Xiuhua Zhao,Yuangang Zu,Jialei Li Preparation, characterization, and in vitro targeted delivery of folate-decorated paclitaxel-loaded bovine serum albumin nanoparticles. International Journal of Nanomedicine 2010;5 : 669–677.
23. Truong-Le VL, Walsh SM, Guggino WB, August JT, Leong KW. Gene transfer by DNA-Gelatin nanospheres, Arch. Biochem. Biophys. 1999; 361(1): 47-56.
24. Galindo-Rodriguez S.A, Allemann EH, Fessi, Doelker E. Polymeric nanoparticles for oral delivery of drugs and vaccines: a critical evaluation of in vivo studies, Crit. Rev. Ther. Drug Carr.Syst. 22 (2005) 419–464.
25. Galindo-Rodriguez S.A, Allemann EH, Fessi, Doelker E. Polymeric nanoparticles for oral delivery of drugs and vaccines: a critical evaluation of in vivo studies, Crit. Rev. Ther. Drug Carr.Syst. 22 (2005) 419–464.
26. Nagavarma B V N, Hemant K.S.Yadav, Ayaz A, Vasudha L.S, Shiva Kumar H.G. Different techniques for preparation of polymeric nanoparticles–A Review. Asian Journal of Pharmaceutical and Clinical Research. 2012; 5(3).