Preparation And Characterization Glipizide Loaded Nanoparticles

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***Abstract*—Glipizide is a second-generation sulfonylurea widely used in the management of type 2 diabetes mellitus; however, its therapeutic efficacy is limited by poor aqueous solubility, variable gastrointestinal absorption, and short biological half-life, leading to frequent dosing and fluctuating plasma drug levels. The present study aims to develop and characterize glipizide-loaded nanoparticles to enhance its solubility, sustain drug release, and improve oral bioavailability.**

Glipizide-loaded nanoparticles were prepared using a suitable polymeric system such as poly (lactic-co-glycolic acid) (PLGA) or chitosan by the nanoprecipitation/emulsification–solvent evaporation method. The formulation variables, including polymer concentration, drug-to-polymer ratio, surfactant concentration, and stirring speed, were optimized to obtain nanoparticles with desirable physicochemical properties. The prepared nanoparticles were characterized for particle size, polydispersity index (PDI), and zeta potential using dynamic light scattering techniques. Drug entrapment efficiency and drug loading capacity were determined by UV-visible spectrophotometry.

Compatibility between glipizide and excipients was evaluated using Fourier Transform Infrared Spectroscopy (FTIR), while the physical state and crystallinity of the drug were analyzed by Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) studies. Surface morphology of the nanoparticles was examined using Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM). In vitro drug release studies were performed using suitable dissolution media to assess the release kinetics and mechanism.

The results demonstrated that glipizide was successfully encapsulated within the nanoparticles, producing a nanosized, stable formulation with sustained drug release characteristics. The developed glipizide-loaded nanoparticles show promise as an effective oral drug delivery system for improved diabetes management.

***Index Terms*—Glipizide; Nanoparticles; Polymeric drug delivery system; Nanoprecipitation; Entrapment efficiency; Sustained release; Characterization; Type 2 diabetes mellitus; PLGA; Chitosan**

I. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Type 2 diabetes mellitus accounts for the majority of diabetic cases worldwide and is commonly managed with oral hypoglycemic agents. Despite the availability of several antidiabetic drugs, achieving optimal glycemic control remains a challenge due to issues such as poor drug solubility, low bioavailability, frequent dosing, and associated side effects.

Glipizide is a second-generation sulfonylurea widely prescribed for the treatment of type 2 diabetes mellitus. It acts by stimulating insulin release from pancreatic β-cells, thereby reducing blood glucose levels. Although glipizide is effective, its therapeutic application is limited by poor aqueous solubility, variable gastrointestinal absorption, short elimination half-life, and rapid metabolism, which necessitate frequent dosing and may result in fluctuating plasma drug concentrations. These limitations can lead to reduced patient compliance and suboptimal therapeutic outcomes.

Nanotechnology-based drug delivery systems have gained significant attention in recent years as an effective approach to overcome the limitations of conventional dosage forms. Among these, polymeric nanoparticles offer several advantages, including reduced particle size, enhanced surface area, improved solubility of poorly water-soluble drugs, protection of drug from degradation, and the ability to provide controlled and sustained drug release. Nanoparticles can also improve oral bioavailability

and minimize dose-related side effects by maintaining therapeutic drug levels over an extended period.

The preparation of drug-loaded nanoparticles involves various techniques such as nanoprecipitation, emulsification–solvent evaporation, solvent diffusion, and ionic gelation methods. Selection of an appropriate polymer and preparation technique plays a crucial role in determining the physicochemical properties, stability, and drug release behavior of nanoparticles. Polymers such as poly (lactic-co-glycolic acid) (PLGA), chitosan, and other biodegradable polymers are commonly used due to their biocompatibility and safety.

Characterization of nanoparticles is essential to ensure reproducibility, stability, and performance of the formulation. Key parameters such as particle size, polydispersity index, zeta potential, drug entrapment efficiency, surface morphology, and in vitro drug release behavior provide critical insights into the quality and therapeutic potential of the nanoparticle system. Analytical techniques including Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and Scanning or Transmission Electron Microscopy (SEM/TEM) are commonly employed to assess drug–polymer compatibility, crystallinity, and surface characteristics.

Therefore, the present study aims to develop and characterize glipizide-loaded nanoparticles using suitable polymers and preparation methods to enhance its solubility, improve bioavailability, and achieve sustained drug release. The successful development of such a nanoparticulate system may provide a promising alternative to conventional oral dosage forms for effective management of type 2 diabetes mellitus.

II. MATERIALS AND METHODS

1. MATERIALS USED

Thematerialsusedforthepreparationofnanotechnology-basedoralantidiabetic formulations are enlisted in Table 1.1.

S. No.	Name	Grade	Company Name
1	Glipizide	Pharmaceutical	Swapnroop Drugs and Pharmaceuticals, Aurangabad, India
2	Metformin HCl	Pharmaceutical	Mankind Pharma, Paonta Sahib, India
3	Palmitic acid	A.R.	Sigma-Aldrich, India
4	Stearic acid	A.R.	Sigma-Aldrich, India
5	PluronicF127	A.R.	Sigma-Aldrich, India
6	Polyvinyl alcohol	A.R.	Sigma-Aldrich, India
7	PolyvinylpyrrolidoneK30	A.R.	S.D. Fine Chem. Ltd., Mumbai
8	Streptozotocin	R.G.	Sigma St. Louis MO, USA
9	Chloroform	L.R.	Molychem, Mumbai
10	Methylene chloride	L.R.	Molychem, Mumbai
11	Ethyl acetate	L.R.	Molychem, Mumbai
12	Petroleum ether	L.R.	Molychem, Mumbai
13	KBr	A.R.	S.D. Fine Chem. Ltd., Mumbai
14	Potassium di-hydrogen phosphate	A.R.	S.D. Fine Chem. Ltd., Mumbai
15	Tween80	L.R.	Hi-Media Laboratories, Mumbai
16	Potassium dihydrogen orthophosphate	A.R.	S.D. Fine Chem. Ltd., Mumbai

PREFORMULATION STUDIES

Preformulation studies were carried out to obtain prior information on the physicochemical properties of the drug and excipients, which is essential for the development of a stable and effective nanoparticle formulation. These studies help in understanding the behavior of the drug during formulation development and reduce time and cost in later stages. The preformulation parameters evaluated included

organoleptic properties, melting point, solubility, loss on drying, UV spectroscopic characteristics, partition coefficient, and drug–excipient compatibility.

ORGANOLEPTIC EVALUATION

The pure drug samples were examined visually for color and odor, and the observations were recorded.

DETERMINATION OF MELTING POINT

The melting point of glipizide and metformin was determined using the capillary method with a melting point apparatus. A small amount of drug was filled in a sealed capillary tube and heated gradually. The temperature at which the drug started melting was noted.

SOLUBILITY STUDIES

The solubility of glipizide and metformin hydrochloride was determined in various solvents including water, chloroform, methylene chloride, dimethylformamide, and 0.1 N NaOH. An excess amount of drug was added to each solvent, vortexed for 2 minutes, and equilibrated at 37 ± 0.5 °C for 24 hours. The solutions were filtered and analyzed using a UV–Visible spectrophotometer.

LOSS ON DRYING

Accurately weighed 1 g of drug was placed in a hot air oven at 105 °C until a constant weight was obtained. The percentage loss on drying was calculated.

DETERMINATION OF ΛMAX OF GLIPIZIDE

A solution of glipizide (10 µg/ml) was prepared in phosphate buffer pH 7.4 and scanned between 200–400 nm using a UV–Visible spectrophotometer. The λmax of glipizide was found to be 274 nm.

PREPARATION OF STANDARD CALIBRATION CURVE OF GLIPIZIDE

A stock solution of glipizide (100 µg/ml) was prepared in phosphate buffer pH 7.4. Dilutions of 2.5–15 µg/ml were prepared and their absorbance was measured at 274 nm to construct the calibration curve.

DETERMINATION OF ΛMAX OF METFORMIN

A 10 µg/ml solution of metformin in phosphate buffer pH 7.4 was scanned between 200–400 nm. The λmax of metformin was found to be 232 nm.

PREPARATION OF STANDARD CALIBRATION CURVE OF METFORMIN

A stock solution of metformin (100 µg/ml) was prepared in phosphate buffer pH 7.4. Dilutions ranging from 2–16 µg/ml were prepared and analyzed at 232 nm using a UV–Visible spectrophotometer.

DETERMINATION OF PARTITION COEFFICIENT

The partition coefficient of the drugs was determined using the shake flask method. 1-Octanol and phosphate buffer (pH 7.4) were mutually saturated for 24 hours. Equal volumes of both phases were taken, and a known quantity of drug was added. The mixture was shaken for 24 hours at 37 °C, allowed to separate, and centrifuged. Drug concentration in each phase was determined spectrophotometrically at respective λmax values. The experiment was performed in triplicate (n = 3).

III. RESULTS AND DISCUSSION

ORGANOLEPTIC STUDIES OF GLIPIZIDE

The glipizide received from the industrial supplier was found to be as per reported specifications (British Pharmacopoeia, 2015a). The results of these parameters are shown in Table 2.1.

TABLE 2.1: RESULTS OF PHYSICAL APPEARANCE, MELTING POINT, SOLUBILITY AND LOSS ON DRYING OF GLIPIZIDE

S. No.	Parameter	Result
1.	Physical appearance	White, odorless crystalline powder
2.	Melting point analysis	208 ±2 ºC
3.	Solubility	Practically insoluble in water, slightly soluble in Methylene chloride and acetone, soluble in chloroform, dissolve in 1 M sodium hydroxide.
4.	Losson drying	PassedasperBritishPharmacopoeia,2015

PREPARATION OF STANDARD CURVE OF GLIPIZIDE

The standard graph (Figure 2.2) of glipizide in phosphate buffer at pH 7.4 was prepared (2.5-20 µg/ml) to calculate the amount of drug released from glipizide nanoparticle formulations in *in-vitro* drug release study. The λ_{max} 274 was used for analysis. Regression coefficient (r^2= 0.9963) indicates the accuracyof the estimation.

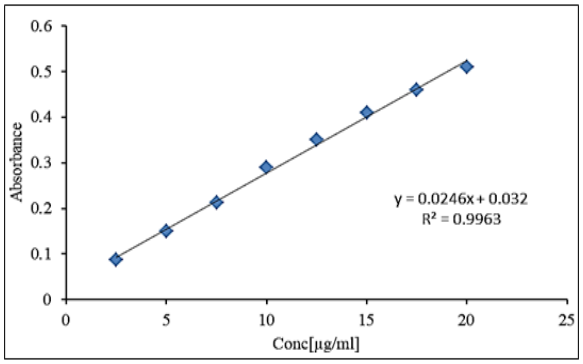

FIGURE 2.2: STANDARD GRAPH OF GLIPIZIDE IN PHOSPHATE BUFFER SOLUTION PH 7.4 (2.5-20 MG/ML)

PARTITIONCOEFFICIENT

The partition coefficient directly influences the permeability of the drug through the biological membrane, which could be approximated by measuring partition coefficient of drugin1-octanol: wateror1-octanol: phosphate buffer(pH7.4) system. The partition coefficient of glipizide in 1-octanol: water and 1-octanol: phosphate buffer (pH 7.4) was 1.634 ± 0.141 and 1.576 ± 0.172, respectively. The above values suggested the lipophilic nature of glipizide.

IV. COMPATIBILITY STUDIES

FTIRANALYSIS

FTIR spectra provide a distinct idea about interaction(s) between diverse functional groups existing in drug and excipients (Mukherjee *et al*., 2005; Mukherjee *et al*., 2008). The possible interactions between PAF127, PVP K30, glipizide, physical mixture and optimized GN1 were investigated by comparing the FTIR peaks.

The IR spectra of pure glipizide (Figure 2.3) exhibited peaks at 3250.44 cm^{-1}(-NH stretching), 2941.02 cm^{-1} (C-H stretching), 1690.44 cm^{-1} (C=O stretching), 1649.88cm^{-1}(-CONH- stretching), 1591.28 cm^{-1}(C=C aromatic stretching), 1461 cm^{-1}(C-Haromaticbending),1337.27,1160.14cm^{-1}(O=S=O), which are also detected in the physical mixture and GN1. There was no significant shift in peaks were detected in the physical mixture and optimized GN1 as compared to spectra of PAF127, PVA, and pure glipizide (Figure 2.4). This indicates that the glipizide and excipients used were compatible and suitable for current investigation.

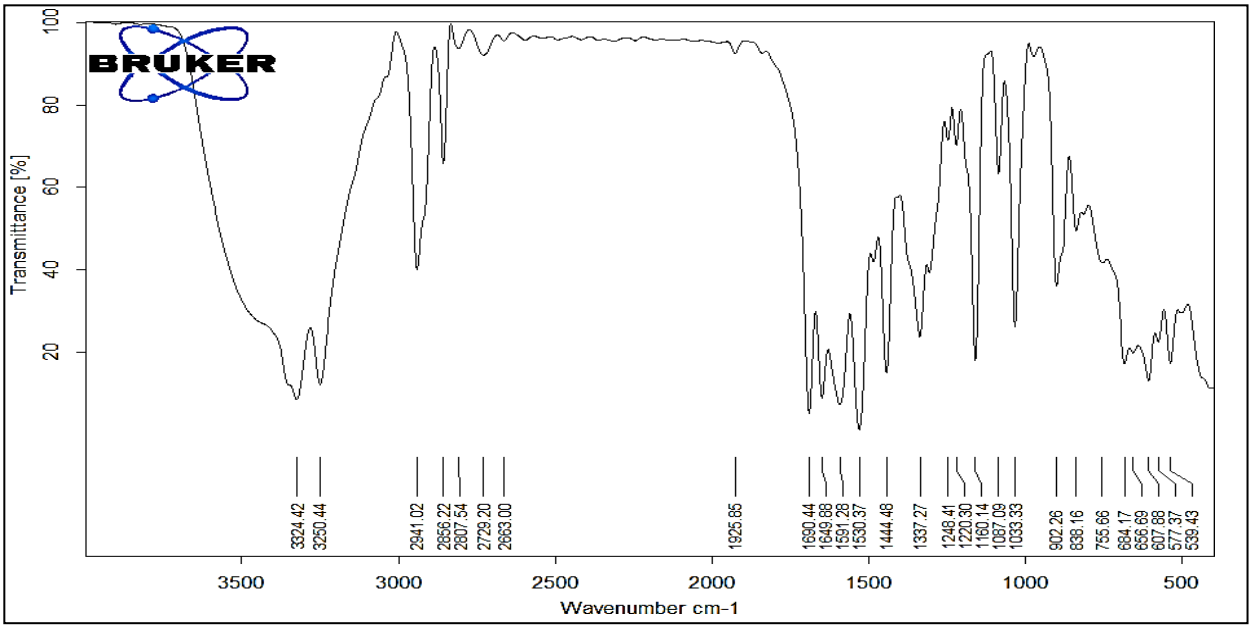

FIGURE 2.3: FTIR SPECTRA OF PURE GLIPIZIDE

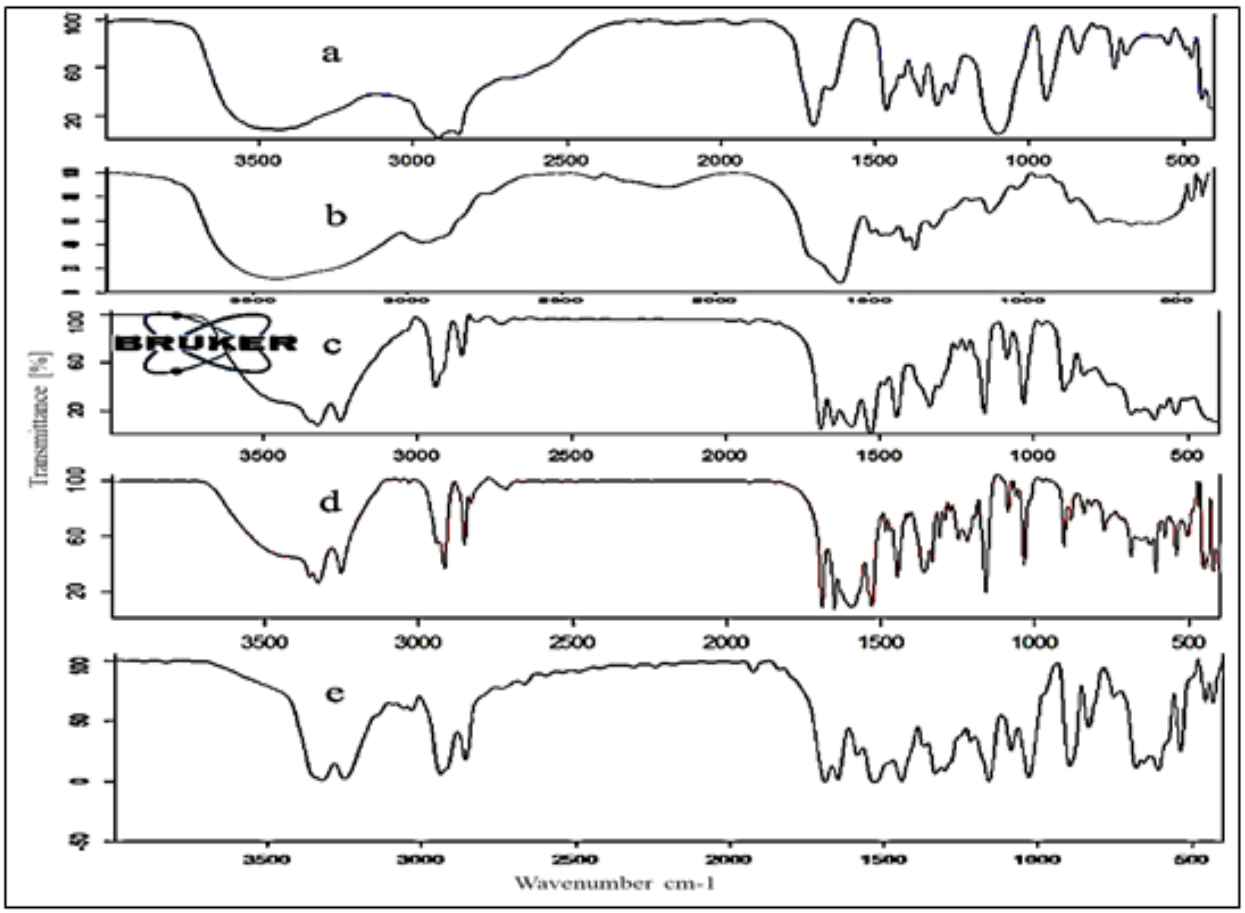

FIGURE 2.4: FTIR SPECTRA OF (A) PAF127, (B)PVPK30, (C) PUREGLIPIZIDE, (D)PHYSICAL MIXTURE AND (E) GN1

DSC ANALYSIS

It was found to be useful in the examination of thermal properties of then an o particle, providing quantitative and qualitative manifests about the physicochemical state of the drug inside the nanoparticles as well as drug-excipients interactions (Ramazani *et al*., 2017).

The characteristic sharp endothermic peak at 212.18 ºC was observed for pure glipizide (Figure 2.5) which was absent in PAF127 (Figure 2.6) copolymer. PVPK30 (Figure 2.6) showed an endothermic peak at 98.3 ºC. The small melting peak was observed for GN1 compared to pure glipizide but which was not significant. This proposed that the glipizide was entrapped within polymeric nanoparticles and present in the amorphous or molecular state (Rawat *et al*., 2010). Hence, there was no significant interaction between glipizide and polymeric excipients. The selection of excipients was done on the basis of results of FTIR and DSC analysis and further studies were extended.

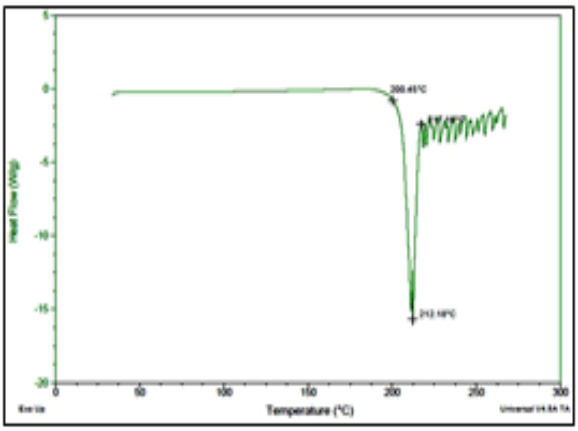

FIGURE 2.5: DSC THERMO GRAM OF PURE GLIPIZIDE

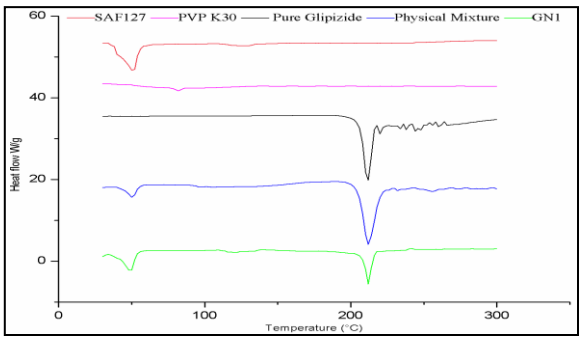

FIGURE 2.6: DSC THERMOGRAMS OF PAF127, PVP K30, PURE GLIPIZIDE, PHYSICAL MIXTURE AND GN1

XRD ANALYSIS

The XRD patterns of the PAF127 copolymer and PVP K30 showed a diffused spectrum having fewer peaks suggested semi-amorphous nature. The XRD patterns of glipizide's howed several sharp peaks which were found to be in line with the previous report (Dash *et al*., 2015). The characteristic sharp diffraction peaks due to pure glipizide and diffused peaks of PAF127 copolymer and PVP K30 can be seen in the physical mixture. After being formulated into nanoparticles, the XRD pattern of GN1 showed comparatively fewer sharp peaks with reduced intensity and has partially amorphous nature. This decreased intensity shows the reduced crystalline properties due to distortion of crystal lattices of the drug in polymeric nanoparticles (Mokale *et al*., 2016). The comparison of XRD spectra of excipients, pure glipizide, physical mixture and GN1 are shown in Figure 2.7.

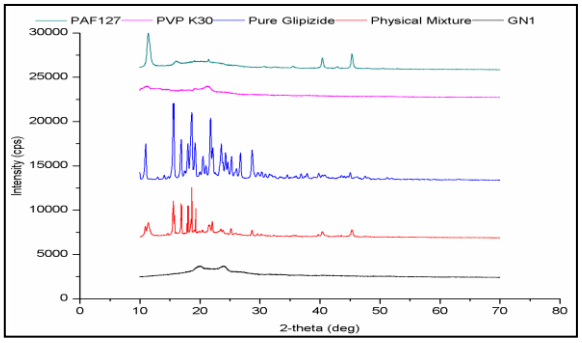

FIGURE 2.7: XRD PATTERNS OF PAF127, PVA, PURE GLIPIZIDE, PHYSICAL MIXTURE ANDGN1

V. CONCLUSION

Nanotechnology-based oral drug delivery systems offer improved bioavailability and sustained drug release, addressing the limitations of conventional antidiabetic therapy. In this study, glipizide and metformin nanoparticles were developed using Penta block copolymers to enhance solubility and reduce dosing frequency. Optimized formulations showed nanosized particles, sustained drug release following the Higuchi model, improved bioavailability, effective blood glucose control for up to 24 hours, and no toxicity in animal studies. These findings suggest that Penta block copolymers are promising carriers for oral antidiabetic nanoparticle formulations, though further clinical evaluation is required.

REFERENCES

[1] Arunachalam, A., Reddy, V.R., Shankar M. (2013). Nanomedicine: A novel class of drug delivery system. Asian J Res Pharm Sci Biotechnology 1(1), 35-39.

[2] Ahmad, S. (2007). Nanotechnology in drug delivery: Introduction and recent developments. Internet J Nanotechnology 2(1), 1-5.

[3] Allémann, E., Leroux, J.C., Gurny, R., Doelker, E. (1993). *In vitro* extended-release properties of drug-loaded poly (DL-lactic acid) nanoparticles produced by a salting- out procedure. Pharm Res 10, 1732-1737.

[4] Anselmo, A.C., Mitragotri,S.(2016).Nano particles in the clinic. Bioeng Trans l Med 1, 10-29. Arias, J.L., Gallardo, V., Ruiz, M.A., Delgado, A.V. (2007). Ftorafur loading and controlled release from poly(ethyl-2-cyanoacrylate) and poly (butyl cyanoacrylate) nanospheres. Int J Pharm 337, 282-290.

[5] American Diabetes Association (2010). Diagnosisandclassificationofdiabetesmellitus.DiabetesCare33(Supp 1), S62-S69

[6] Barakat, N.S., Bintaleb, D., Al Salehi, A.S. (2012). Target nanoparticles: An appealing drug delivery platform. J Nanomed Nanotechnol 3, 552-558.

[7] Barichello, J.M., Morishita, M., Takayama, K., Nagai, T. (1999). Encapsulation of hydrophilic and lipophilic drugs in PLGA nanoparticles by

the nanoprecipitation method. Drug Dev Ind Pharm 25, 471-476.

[8] Bhowmik, D., Chiranjib, C.R., Jayakar, B. (2009). Role of nanotechnology in novel drug delivery system. J Pharm Sci Technol 1, 20-35.

[9] Bobo, D., Robinson, K.J., Islam, J., Thurecht, K.J., Corrie, S.R. (2016). Nanoparticle- based medicines: A review of FDA approved materials and clinical trials to date. Pharm Res 33, 2373-2387.

[10] Boisseau, P., Lou baton, B. (2011). Nanomedicine, nanotechnology in medicine. ComptesRendusPhys12,620-636.

[11] Campos, D.A.M., Sánchez, A., Alonso, M.J. (2001). Chitosan nanoparticles: A new vehicle for the improvement of the delivery of drugs to the ocular surface, application to cyclosporin

[12] A. Int J Pharm 224, 159-168.Choi, C., Chae, S.Y., Nah, J.W. (2006). Thermosensitive poly(n-isopropylacrylamide)-b-poly(caprolactone)nanoparticles for efficient drug delivery system. Polymer 47, 4571-4580.