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FORMULATION AND EVALUATION OF GLICLAZIDE NANOSUSPENSION BY PRECIPITATION METHOD

Paladugu Raja Saran*[a], R. B. Desireddy[b], G. Sivareddy[c], G. Suresh[d], G. Avulaiah[e], G. Naga Durga Prasad[f], K. Raghavendra Rao[g]

Nalanda Institute of Pharmaceutical Sciences, Kantepudi Guntur.
Research Scholar, Jawaharlal Nehru Technological University, Kakinada.

***Corresponding Author: Paladugu Raja Saran**

Nalanda Institute of Pharmaceutical Sciences, Kantepudi Guntur.

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ABSTRACT

In the present study, an attempt was made to prepare Nanosuspension of Gliclazide which is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Nanosuspension containing the drug was prepared by precipitation method using combination of polymers such as PVP K-30, poloxamer (407), Sodium lauryl sulphate (SLS), and acetone. Estimation of Gliclazide was carried out spectrophotometrically at 232nm. The Oral Nanosuspension were evaluated for various physical and biological parameters, drug content uniformity, particle size analysis, zeta potential, in-vitro drug release, short-term stability, drug-excipient interactions (FTIR). IR spectroscopic studies indicated that there are no drug-excipient interactions. The formulations F1 to F9 (containing PVP K-30,Eudragit S 100, SLS, Poloxamer (407), and Acetone) used different ratio were found to be promising, of that formulation F9 containing Eudragit S 100 and PVP K-30 releases 99.43% at the end of 20min & it follows first order drug release kinetics. These formulations have displayed good Nanosuspension strength.

KEYWORDS: Gliclazide, Nanosuspension, PVP K-30, SLS, poloxamer (407), and Methanol.

INTRODUCTION

Nanosuspension

The nanotechnology is presently gaining attention from researchers and pharmaceutical world. In the pharmaceutical field, the term "nanoparticle" is usually used to describe submicron sized particles. The drug of interest is dissolved, entrapped or encapsulated within the particles. Nanoparticle technologies have been used as important strategies to deliver drugs, including peptides and proteins, vaccines and more newly nucleotides.[1] In pharmaceutical field, nanosuspension, nanoemulsion, self nanoemulsifying drug delivery system, solid lipid nanoparticle (SLN) etc are covered under nanotechnology area.

A nanosuspension consists of drug nanocrystals, stabilizers, typically surfactants or polymeric stabilizers, and a liquid dispersion medium. Drug nanocrystals are pure solid drug particles with a mean particle size less than 1 μm, generally between 200 nm and 500 nm.6 Although the term nanocrystals implicates a crystalline structure, the particles can be crystalline, partially crystalline or absolutely amorphous. The dispersion medium can be water, mixtures of water and other non-aqueous media or non-aqueous media. Nanosuspension permits delivery of drugs that are poorly soluble in water or unstable in biological fluids.

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1μm in size. Reduction of drug particles to nanometer range leads to an enhanced dissolution rate not only because of increased surface area but also because of saturation solubility. The increase in the saturation solubility and solution velocity of nanoparticle is due to increase of vapour pressure of the particles.[2]

Method of Preparation of Drug Nanosuspension

Nanosuspensions can be prepared using different techniques, which could be classified generally in two groups based on the principle on which the nanorange is achieved. Top down production, in which the size of drug macrosuspension is reduced up to nanosuspension and second is bottom up technique in which the drug nanoparticles are assembled from a solution of drug by controlling the rate and growth of nuclei formed.[3]

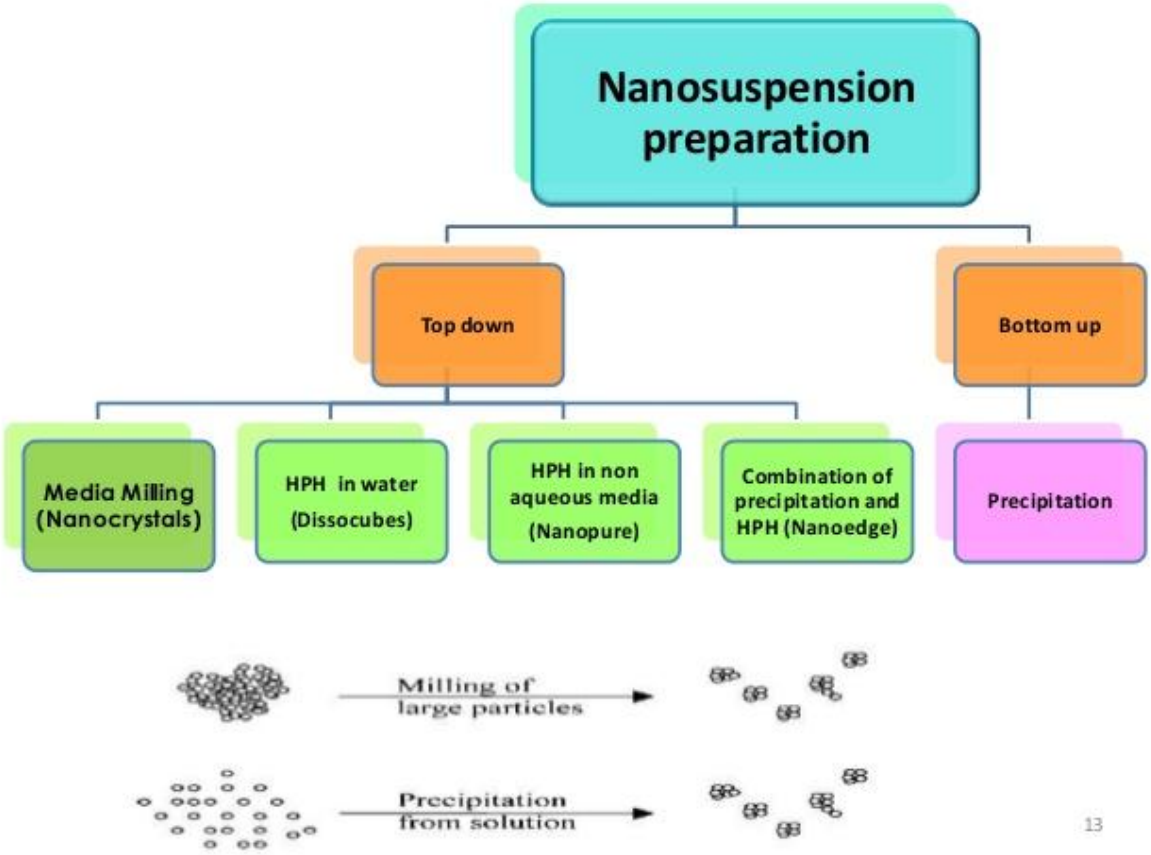
Bottom up technique

a) Nanoprecipitation

b) Supercritical fluid technology

c) Using microemulsions and emulsions as templates.

Top down technique
a) Media milling
b) Dry co-grinding
c) High pressure homogenization



Schematic representation of nano-suspension preparation

Bottom up Technique
Nanoprecipitation

In the precipitation method the poorly water-soluble drugs are dissolved in a suitable solvent and the solution is added into a miscible anti-solvent with stirring and/or agitation. Stabilizers are used to avoid the spontaneous aggregation of molecules. Final morphology of nanoparticles are affected by factors such as types of solvents, the volume ratio of antisolvent to solvent, stirring speed, amount of drug etc.[4]

Nucleation and crystal (particles) growth of drug particles from a supersaturated solution involves in the precipitation process. The supersaturated solution is a solution in which the concentration of solute exceeds the saturation or equilibrium solute concentration at a given temperature. Thus, a supersaturated solution is not at equilibrium, and crystallization of the solute occurs in order to move about the solution towards equilibrium. After initial particle nucleation, both nucleation and crystal growth attempt to take the supersaturated solution to equilibrium. The time required for crystallization depends on the driving force of supersaturation.

The nucleation velocity decreases with increasing surface energy and increases with increasing temperature and degree of supersaturation. High nucleation rates offer the potential to create a large number of submicron particles in the final dispersion, as long as the growth can be seized by stabilizers. Precipitation method is used in both the chemical and pharmaceutical industries for the production of nanoparticles.[5] Solvent evaporation and salting out are the usual precipitation technologies, having common the drawbacks of poor control over particle morphology and particle size and size distribution producing a wide range of particle sizes.[6]

Precipitation process has also been joined with high shear processing. Precipitation of friable materials for subsequent fragmentation under conditions of high shear and/or thermal energy covered under the NANOEDGE technique a registered trademark of Baxter International Inc. and its subsidiaries.[7] It is accomplished by a combination of rapid precipitation and high-pressure homogenization. Rapid adding of a drug solution in to an antisolvent direct to sudden supersaturation of the mixed solution, and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favored at high supersaturation when the solubility of the amorphous state is exceeded. It has been reported that nanosuspensions are successfully prepared by precipitation techniques.[8]

Advantage

- Simple process
- Ease of scale up
- Low cost equipment

Disadvantage

- Drug has to soluble at least in one solvent and that this solvent needs to be miscible with a non-solvent.
- Growing of drug crystals needs to be limit by surfactant addition

Chemically Gliclazide is [1-(3-azabicyclo (3,3,0) oct- 3-yl)-3-p-tolylsulfonylurea]. It is a second generation hypoglycemic sulfonylurea which is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM). Gliclazide is a white crystalline powder, relatively insoluble in water. The pKa of Gliclazide is 6.6. It exhibits slow GI absorption rate and inter individual variations of its bioavailability. Oral bioavailability of drug in rang of 79 to 81 percent. Half-life of drug is about 10hr. Thus solubility enhancement and dissolution enhancement of Gliclazide from its dosage form is an important issue for its in vivo bioavailability and therapeutic efficacy.[9]

AIM & OBJECTIVES

AIM

The aim of the present work is to develop oral Nanosuspension of Gliclazide by precipitation method and to evaluate it.

OBJECTIVES

- To perform Preformulation studies for the pure drug.
- To construct standard calibration curve for gliclazide.
- To perform Drug-Excipient Compatibility Studies.
- To formulate and develop the Nanosuspension and formulations.
- To find out drug content for all the prepared nanosuspensions.
- To determine drug entrapment efficiency for all the prepared nanosuspensions.
- To evaluate the formulation by establishing drug release kinetics using various dissolution models.
- To establish *In–vitro* drug release compliance with the established criteria.
- To establish stability studies of the final formulation, for the selected oral Nano suspension.

MATERIALS AND METHODOLOGY

Materials

Excipients and Chemicals

All the materials used in the formulations, evaluation and other experiments are listed below. The chemicals procured for the study are of laboratory reagent grade. The double distilled water was used in all experiments.

Table 1. List of Materials Used.

S.NO	Materials	Manufactured by
1	Gliclazide	Sri Krishna Pharmaceuticals, Hyderabad
2	Eudragit S 100	Colorcon, Goa
3	Poloxamer 407	Colorcon, Goa
4	Sodium Lauryl Sulphate	SD Fine chem., Mumbai
5	PVP K30	SD Fine chem., Mumbai
6	Acetone	Rankem chemicals, Hyderabad
7	Hydrochloric Acid	Rankem chemicals, Mumbai
8	Potassium Dihydrogen phosphate	Merck, Mumbai
9	Sodium hydroxide	Merck, Mumbai
10	Distilled Water	SD Fine chem., Mumbai

Equipments used: Following equipments were used for preparation and evaluation.

Table 2. List of Equipment and Instruments.

S.NO	Equipment	Manufacturer	Model No
1	Electronic Weighing Balance (0.001mg-200gm)	Shimadzu, Japan	BL-220H
2	Digital melting point apparatus	Contech instruments	CDMP-300
3	Dissolution test apparatus	Electrolab, TDT-06N	
4	UV- Visible spectrophotometer	Shimadzu, Japan	UV-1700
5	Magnetic stirrer	Remi, Ahmedabad	1MLH
6	FTIR spectroscopy	Shimadzu, Japan	1700S
7	Digital pH meter	ELICO	101
8	DSC	Shimadzu	DSC-60
9	SEM	JEOL, Japan	JSM 5200
10	PCS	Malvern Zetasizer	
11	Zeta potential	Malvern Zetasizer	
12	Stability Chamber	Thermolabs	TH 80S/G

PLAN OF WORK

Methods

Pre-formulation studies

Prior to the development of nanosuspension form, it is essential that certain fundamental physical and chemical properties of the drug molecule alone and when combined with excipients are determined. This first learning phase is known as pre-formulation. The overall objective of the pre-formulation is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass produced. The goals of pre-formulation studies are:

- To evaluate the drug substance analytically and determine its necessary characteristics, and
- To establish its compatibility with different excipients.
- Spectroscopic study
- Identification of pure drug

Organoleptic properties

The colour, odour and taste of the drug were recorded using descriptive terminology.[10]

Determination of Melting Point

The temperature at which the first particle of the substance completely melts is regarded as melting point of the substance. The temperature at which the first particle starts to melt and last particle completely melts is regarded as the range of melting point. Melting point of the drug was determined by capillary tube method.

Solubility studies of Gliclazide

Solubility of Gliclazide was carried out in different buffers as follows:

1) Purified water
2) 0.1 N hydrochloric acid (HCl), (pH 1.2) USP
3) Phosphate buffer pH 6.8, USP

Preparation of different buffer media

pH 1.22 buffer: 85 ml of 0.2 M HCl was added to 50 ml of 0.2 M potassium chloride solution and volume was made up to 200 ml in volumetric flask.

pH 6.8 Phosphate Buffer: Placed 50.0 ml of 0.2 M potassium dihydrogen phosphate in a 200-ml volumetric flask and 22.4 ml 0.2 M sodium hydroxide was added, then made up the volume with water.

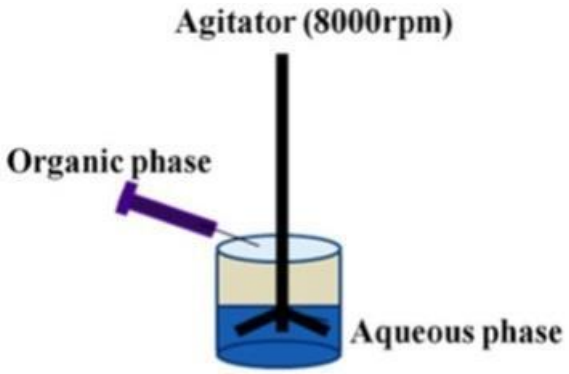
0.2M Potassium Dihydrogen Phosphate: Dissolved 27.218 g of potassium dihydrogen phosphate in water and dilute with water to 1000 ml.

0.2M Sodium Hydroxide: Dissolved 8.0 g of sodium hydroxide in 1000 ml.

Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 hrs at 25^0C under constant vibration. Solubility of Gliclazide was determined at 25 ± 1^0C. The solubility of Gliclazide in distilled water and different buffers was determined by shake flask method. According to this method the drug was added in surplus to different aqueous mediums like distilled water, 0.1N HCl, pH6.8 Phosphate buffer. The flasks were closed with aluminium foil and constantly agitated at room temperature 25 ± 1^0C for 24 hrs using mechanical shaker. After 24hrs, the solution was filtered through a 0.45 µm membrane filter. The filtrates were diluted suitably, and amount of drug solubilised was then estimated by measuring the absorbance at 232nm using UV-VIS spectrophotometer against corresponding solvent blank.

Preparation of Nanosuspension

Nanosuspensions were prepared according to nanoprecipitation method given by Fessi et al. with slight modification. ERLPO polymer and specified quantity of drug were dissolved in acetone at 40°C to form uniform organic solution. The prepared organic solution was then injected slowly dropwise with the help of a syringe into an aqueous phase containing 2%(w/v) P-188 kept under high-speed mechanical agitation of 8,000 rpm to get desired nanodispersion (Fig. 1). Prepared nanosuspension was then stirred magnetically at 500 rpm at room temperature for 12 h to evaporate organic solvent. Complete evaporation of acetone was determined by spectrophotometric method using vanillin. The volume was then adjusted with the addition of triple distilled water to recover loss in volume. All samples were prepared in triplicate. Drug/polymer ratio and agitation time was varied keeping other parameters constant.[1]



Evaluation Parameters of Nanosuspensions

- Particle size analysis:
- Particle Charge (Zeta Potential)
- % Drug Content:
- Apparent Solubility:
- Dissolution Studies:
- Scanning Electron Microscopy (SEM):
- Powder X-Ray Diffraction (PXRD):
- Stability studies:
- Flow Properties
- Stability of Nanosuspensions

Evaluation of Nanosuspension

Organoleptic properties

The color, odor and taste of the drug were recorded using descriptive terminology and found to be yellow crystalline powder, bitter taste and odourless.

Determination of melting point

The melting point of Gliclazide was found to be in range of 168°C which was determined by capillary method. Fine powder of Gliclazide was filled in glass capillary tube (previously sealed on one end). The capillary tube is tied to thermo meter and the thermometer was placed in fire. The powder at what temperature it will melt was noticed.

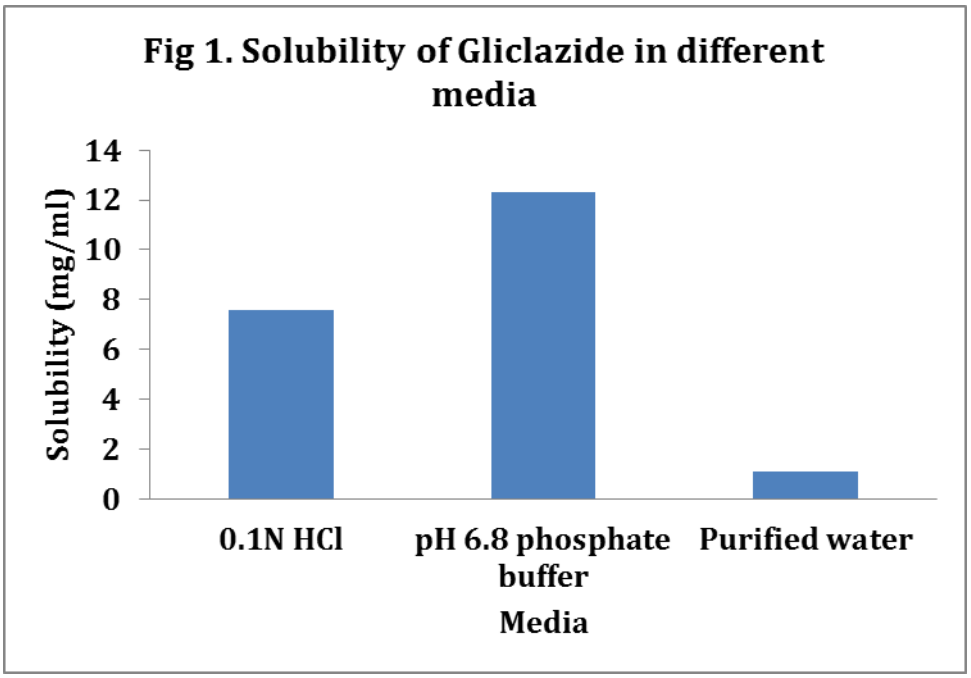
Saturation Solubility

Saturation solubility was carried out at 25^0C using pH 6.8 phosphate buffer, 0.1 N HCl and purified water. Gliclazide has shown highest solubility in pH 6.8 phosphate buffer, as well as in 0.1N HCl (Table 6.1 and Figure 6.1). It is p**ractically insoluble in water.** The solubility of Gliclazide in pH 6.8 phosphate buffer was almost similar which is in the range of 5-20 mg/ml, indicating the high solubility of the drug was in acidic pH.

From the above conducted solubility studies in various buffers we can say that pH 6.8 phosphate buffer has more solubility when compared to other buffer solutions due to reason gliclazide is a weak acid with good lipophilicity. Results show that gliclazide has poor solubility in the acidic media and its solubility increases as the ph becomes more alkaline. This confirms the selection of pH 6.8 phosphate buffer as dissolution medium.

Table 3. Solubility Data Determination of Gliclazide in Various pH Media.

Media	Solubility(mg/ml)
0.1N HCL	7.56
pH 6.8 phosphate buffer	12.33
Purified water	1.08



Solubility of Gliclazide in Different Media

Compatibility Studies

Compatibility study is important to understand the interaction between the drug and polymers. It saves costs and it makes easier to choose a few excipients from the long list of excipients for a better formula.

Drug- excipients interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between drug and the polymers used.

No prominent difference was observed in the principal IR peaks of Gliclazide, Optimized stabilisers, physical mixture formulations upon comparison with the peaks of drug and stabiliser alone, which may considered that Gliclazide, Eudragit S100, Poloxamer and PVP are compatible enough without any interactions.

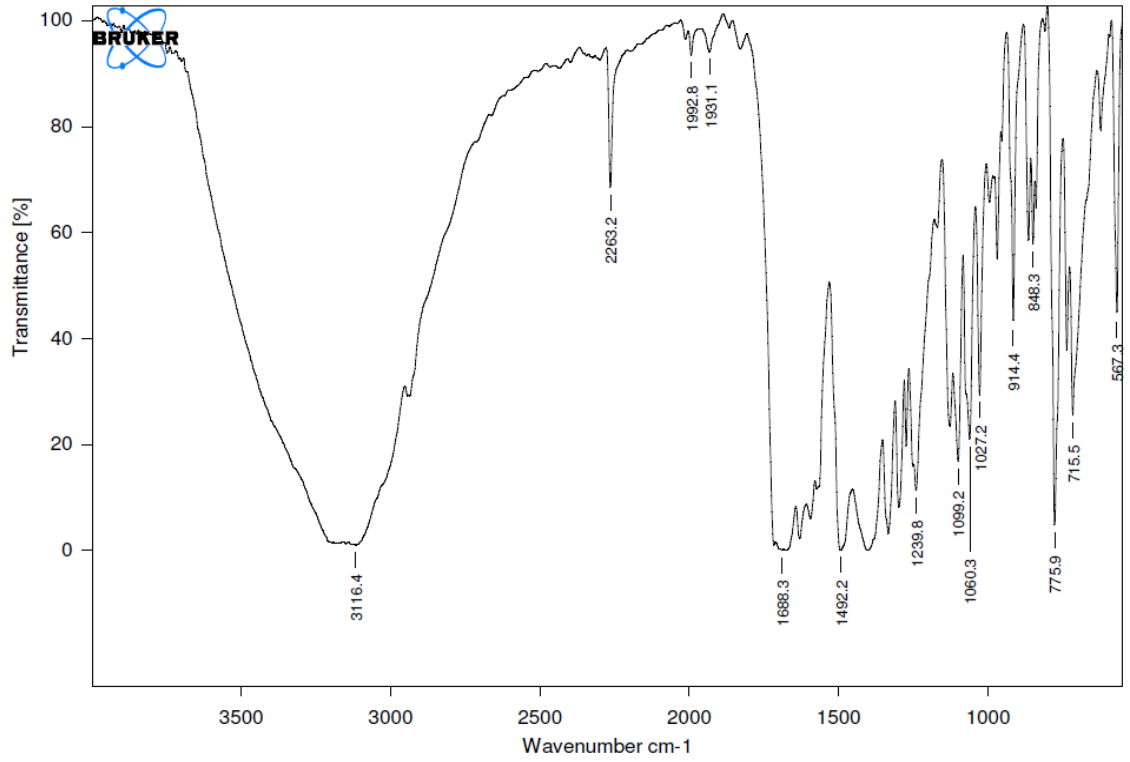


Fig 2. IR spectrum of Gliclazide pure.

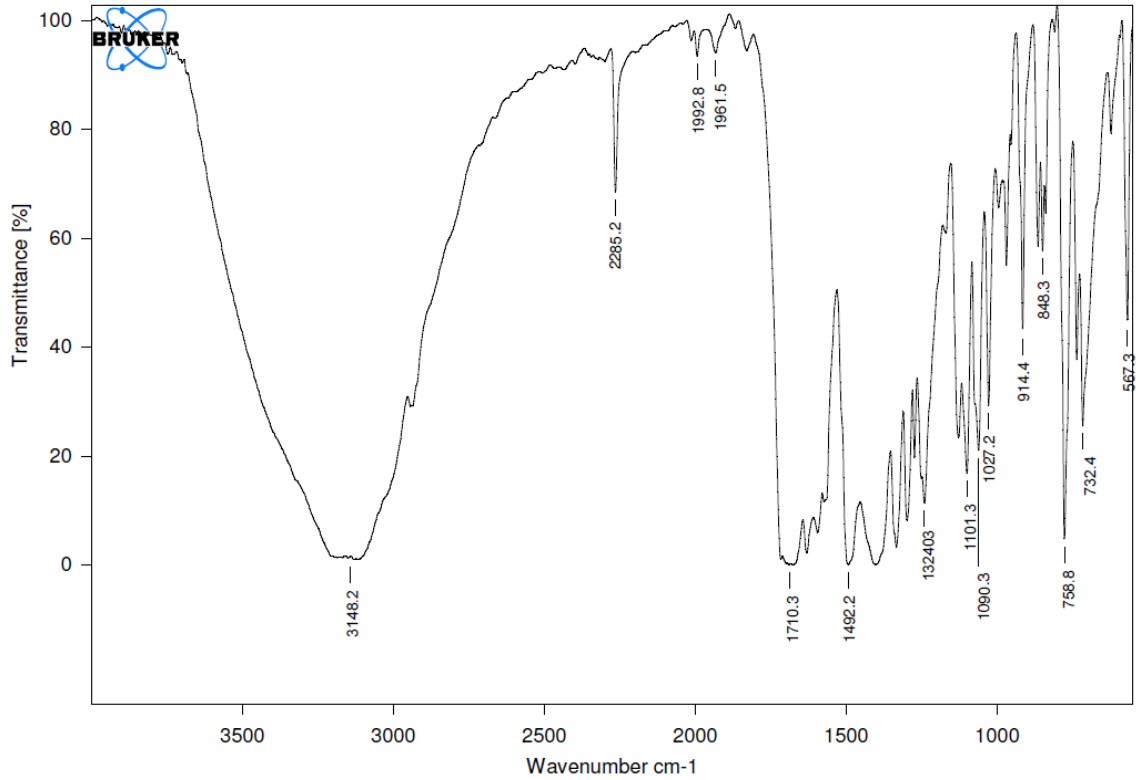


Fig 3. IR spectrum of Gliclazide best formulation.

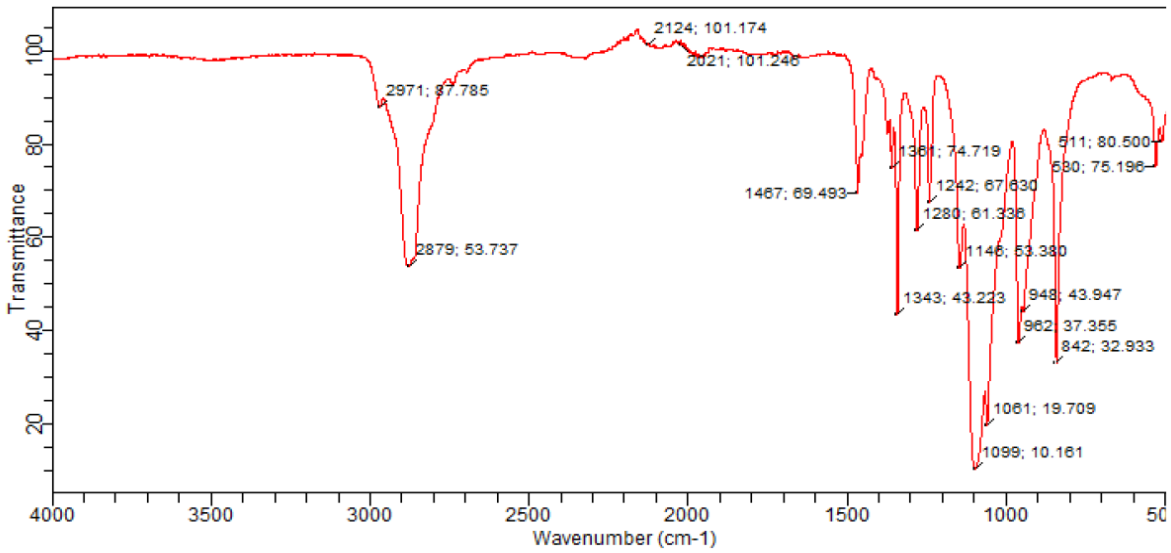
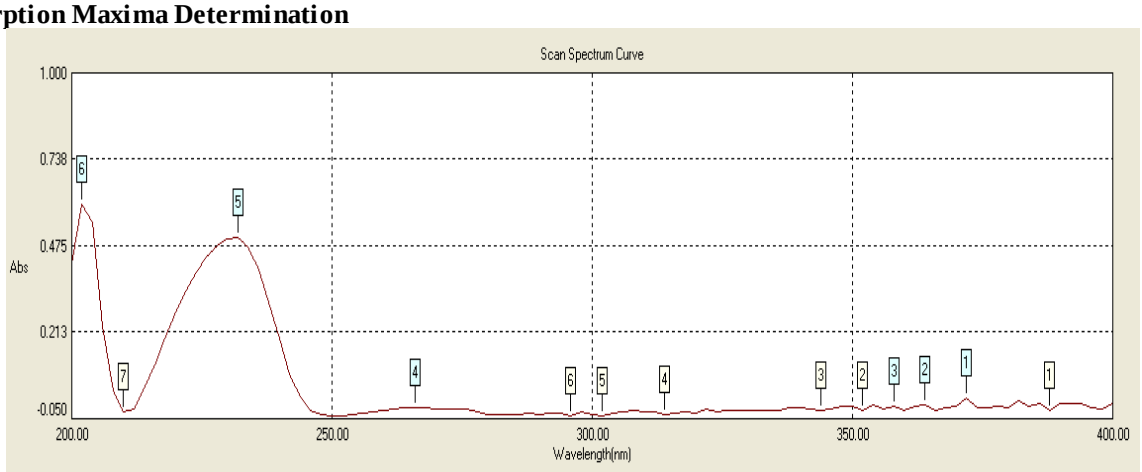


Fig 4. FTIR graph for Polaxomer.

From the drug excipient compatibility studies we observed that there are no interactions between the pure drug (Gliclazide) and optimized formulation (Gliclazide+ excipients) which indicates there are no physical changes.

UV- Spectrum Analysis of Drug
Absorption Maxima Determination



Spectrum curve of Gliclazide
The maximum absorbance of the Gliclazide in 6.8 phosphate buffer was found to be 232nm. Hence the wavelength of 232nm was selected for analysis of drug in dissolution media.

Calibration Curve Determination
The standard calibration curve shown linearity, through that the drug obeys Beers and Lamberts law in the concentration range of 5 to 30µg/mL. A standard graph was plotted by keeping the known concentration on X – axis and obtained absorbance on Y – axis. The values of calibration curve of Gliclazide with 6.8 phosphate buffer were given below.

Table 4. Standard graph of Gliclazide (λ_{max} 232 nm).

Concentration(µg/ml)	Absorbance
0	0
5	0.123
10	0.274
15	0.433
20	0.587
25	0.741
30	0.889

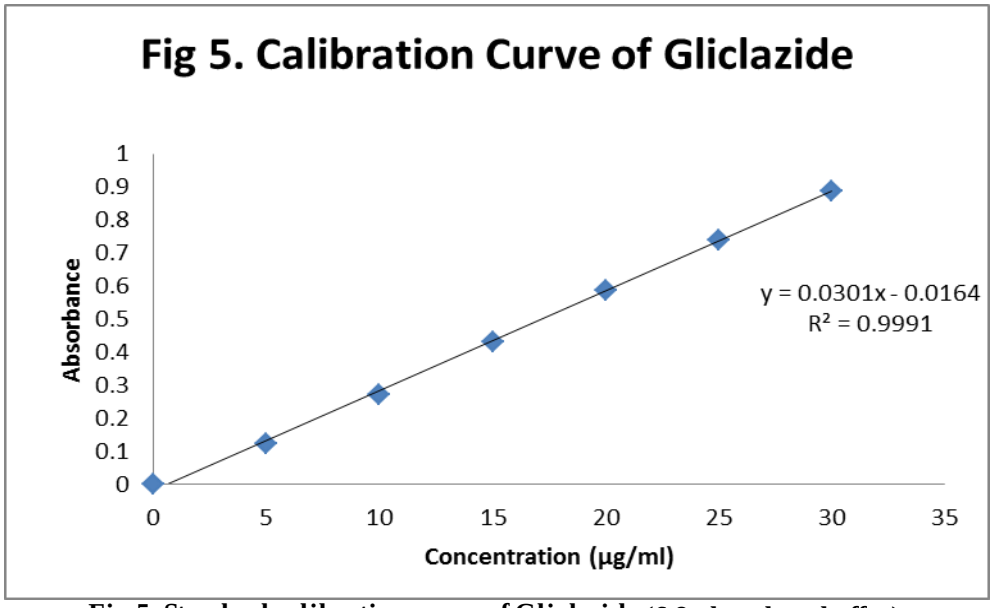


Fig 5. Standard calibration curve of Gliclazide (6.8 phosphate buffer).

Linear relationship was observed between concentration of drug solution (5-30µg/ml) and absorbance in 6.8 phosphate buffer The coefficient of correlation (R^2)was found to be 0.999, indicating that drug solution obeys Beer's- Lambert law in the concentration range of 5-30µg/ml.

Hence it was concluded that dissolution samples can be analyzed in 6.8 phosphate by measuring absorbance at 232 nm using UV-Visible Spectrophotometer.

Drug content:- The drug content of the formulated Nanosuspension was found in the range of 93.26 to 99.87% respectively.

Table 5. Formulated Nanosuspension of Drug content.

Formulation code	Mean % drug content
F1	93.26
F2	94.02
F3	93.89
F4	94.33
F5	95.78
F6	96.20
F7	95.58
F8	96.48
F9	99.87

The percentage of drug content of formulation F1 was found to be 93.26%, formulation F2 was found to be 94.02%, formulation F3 was found to be 93.89%, formulation F4 was found to be 94.33%, formulation F5 was found to be 95.78%, formulation F6 was found to be 96.20%, formulation F7 was found to be 95.58%, formulation F8 was found to be 96.48%, and finally formulation F9 was found to be 99.87%.

Entrapment efficacy:- The entrapment efficacy of the formulated Nanosuspension was found to be in the range of 72.55% to 96.30% respectively.

Table 6. Entrapment Efficiency of Gliclazide Nanosuspension.

Formulation Code	Entrapment Efficiency
F1	72.55±0.07
F2	73.10±0.64
F3	72.99±0.46
F4	78.62±0.29
F5	80.21±0.60
F6	82.19±0.47
F7	88.54±0.54
F8	94.63±0.06
F9	96.30±0.97

The entrapment efficacy of formulation F1 was found to be 72.55%, formulation F2 was found to be 73.10%, formulation F3 was found to be 72.99%, formulation F4 was found to be 78.62%, formulation F5 was found to be 80.21%, formulation F6 was found to be 82.19%, formulation F7 was found to be 88.54 %, formulation F8 was found to be 94.63 %, and finally formulation F9 was found to be 96.30%.

Zeta potential: The measurement itself is a particle electrophoresis, the particle velocity is determined via the doppler shift of the laser light scattered by the moving particles. The field strength applied was 20 V/cm. The electrophoretic mobility was converted to the zeta potential in mV using the Helmholtz-Smoluchowski equation. At standard measuring conditions (room temperature of 25^0 C, water) this equation can be simplified to the multiplication of the measured electrophoretic mobility (μm/cm per V/cm) by a factor of -12.8, yielding the ZP in mV.

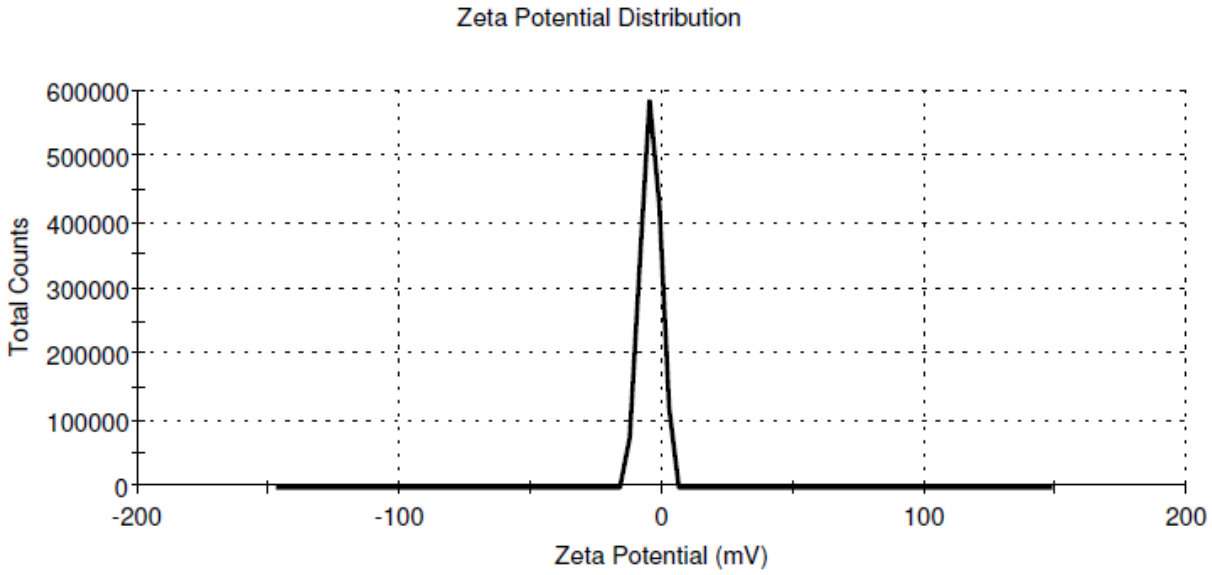


Fig 6. Graph Showing Zeta Potential of Optimzed Formulation (F9).

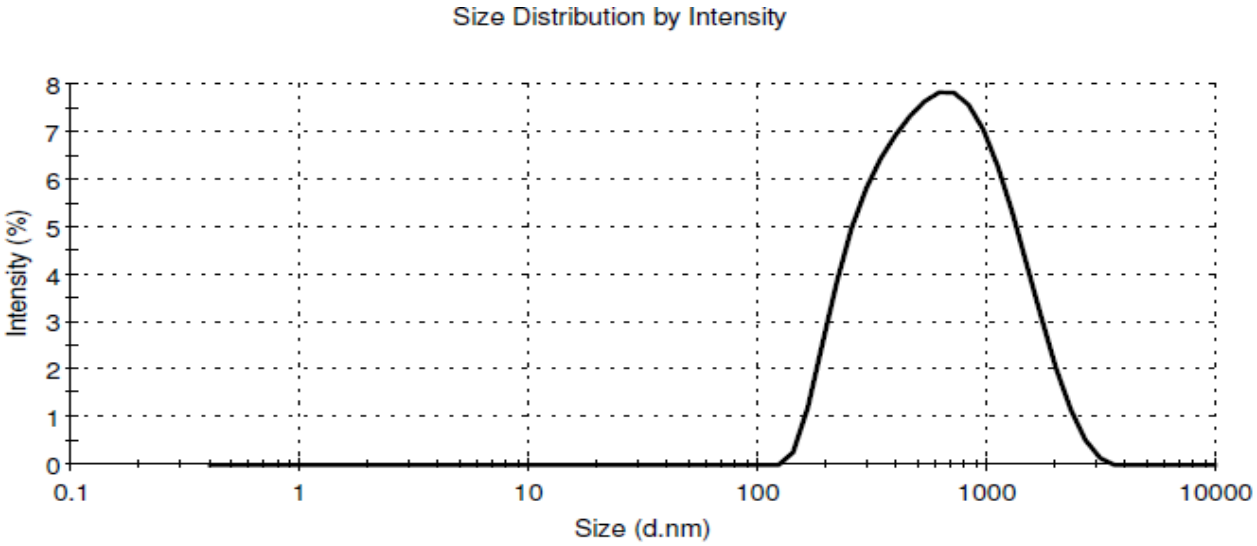


Fig 7. Graph Showing Particle Size Distribution of Optimzed Formulation (F9).

Table 7. Dissolution parameters for the formulations of Nanosuspensions of Gliclazide.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	28.22±0.26	33.12±0.02	36.65±0.27	40.11±0.35	49.98±0.07	53.31±0.06	60.22±0.01	68.87±0.13	72.56±0.652
10	37.45±0.02	45.45±0.11	49.97±0.31	55.12±0.41	61.02±0.19	63.56±0.31	71.44±0.93	76.65±0.86	79.08±0.23
15	46.60±0.68	53.21±0.14	60.11±0.10	68.74±0.16	74.44±0.11	76.55±0.55	79.78±0.46	84.74±0.33	87.84±0.08
20	59.64±0.17	67.40±0.19	71.23±0.07	75.54±0.54	81.17±0.27	87.79±0.73	85.56±0.04	92.02±0.15	99.40±0.134
25	68.78±0.10	78.89±0.85	79.89±0.14	84.88±0.38	88.89±0.52	92.67±0.89	93.25±0.54	97.72±0.05	
30	79.45±0.28	85.67±0.11	86.65±0.12	93.22±0.72	95.56±0.33	97.88±0.11	98.97±0.15		
45	87.88±0.62	90.20±0.36	93.33±0.00	96.66±0.26					

From the above *In-vitro* studies we can say that of all the formulations (F9) shows best drug release of 99.40% within 20 minutes where as all the other formulations takes about 30 to 45 minutes to release the drug.

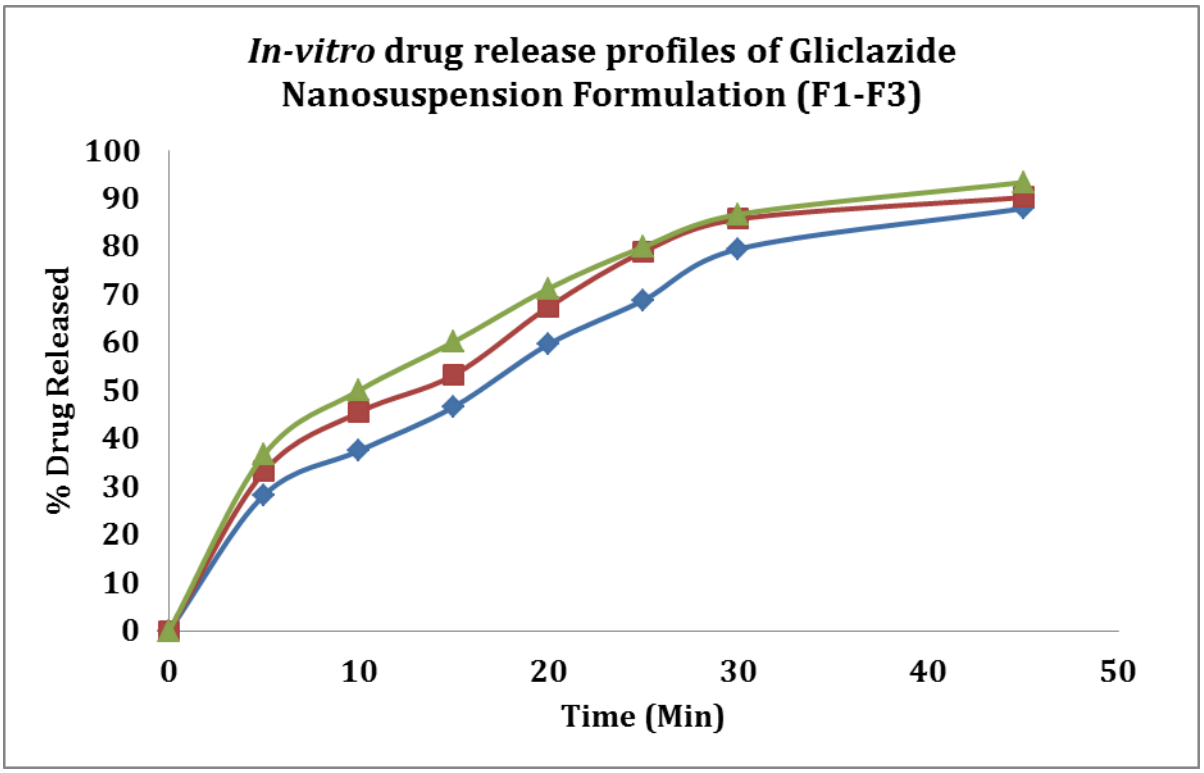
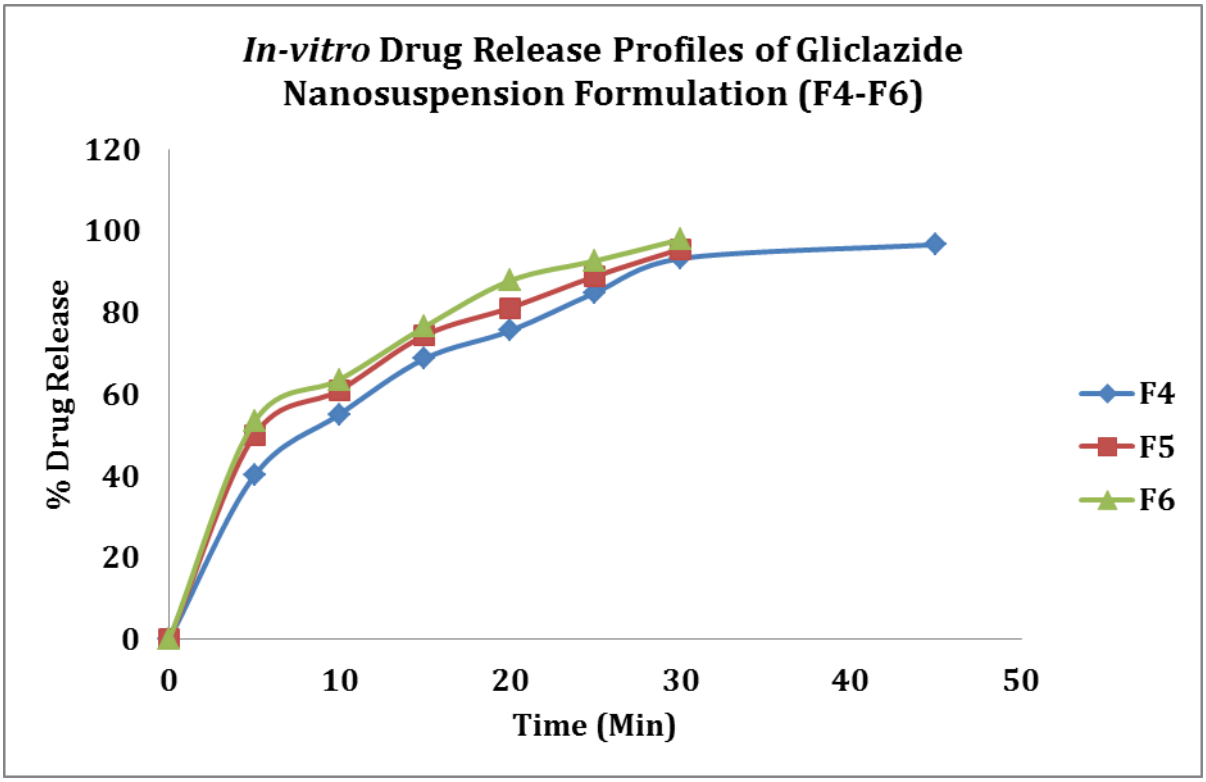


Fig 8. Comparision of dissolution profiles Nanosuspension formulation (F1-F3).



Comparision of dissolution profiles Nanosuspension formulation (F4-F6)

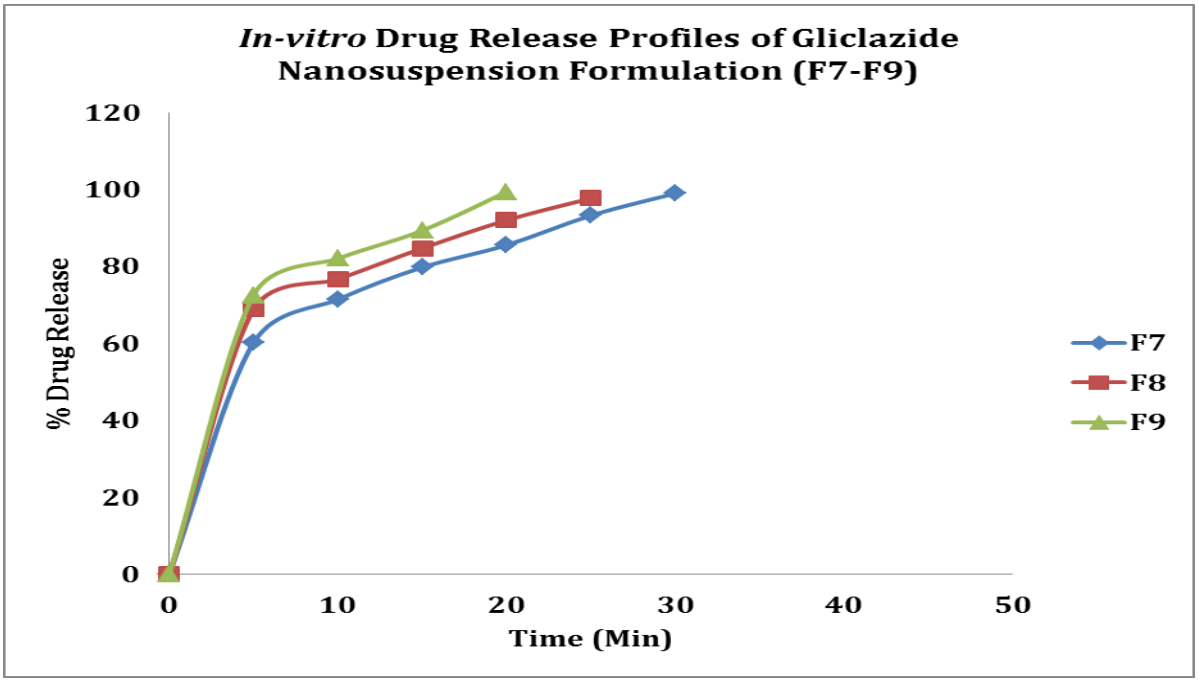


Fig 9. Comparision of dissolution profiles Nanosuspension formulation (F7-F9).

Analysis of the release data

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process. As a model dependent approach, the dissolution data was fitted to five popular release models such as

Zero order

First order

Diffusion and exponential equations

The order of drug release from nanosuspension formulations was described by using zero order or first order kinetics.

The drug release from the Nanosuspension was explained by using mathematical model equations such as zero order, first order, and equation methods. Based on the regression values it was concluded that the optimized formulation F9 follows first order kinetics having R^2 value 0.846.

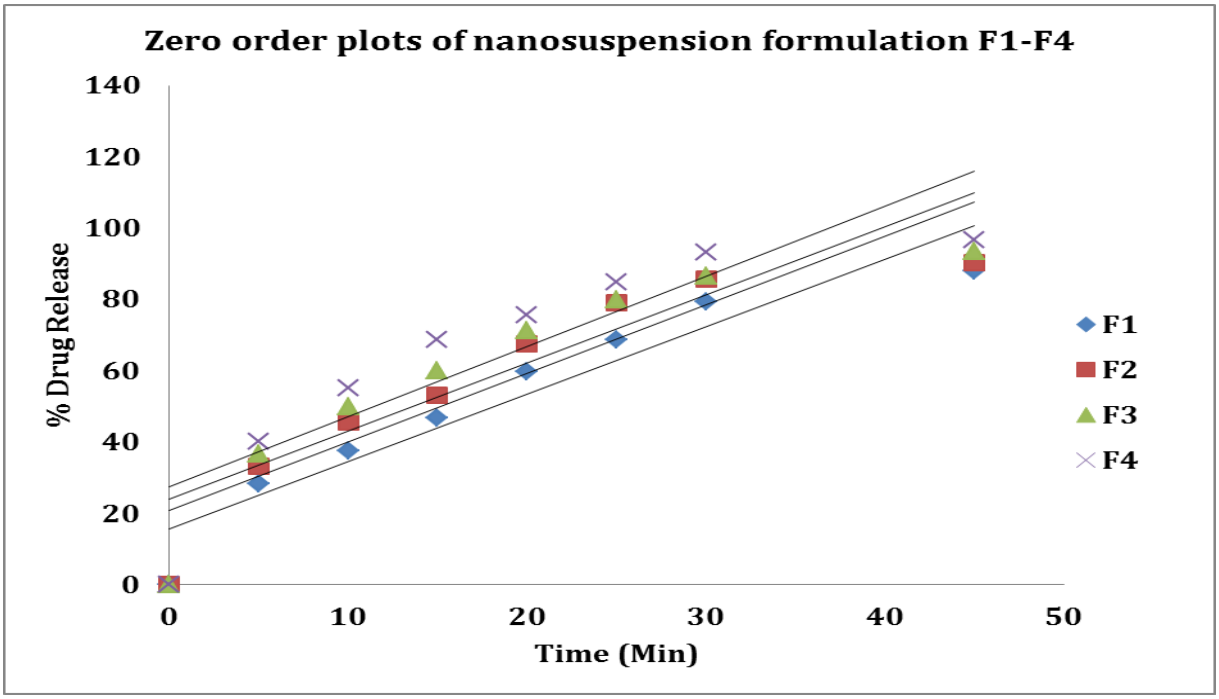


Fig 10. Zero order kinetic plots for nanosuspension formulation F1-F4

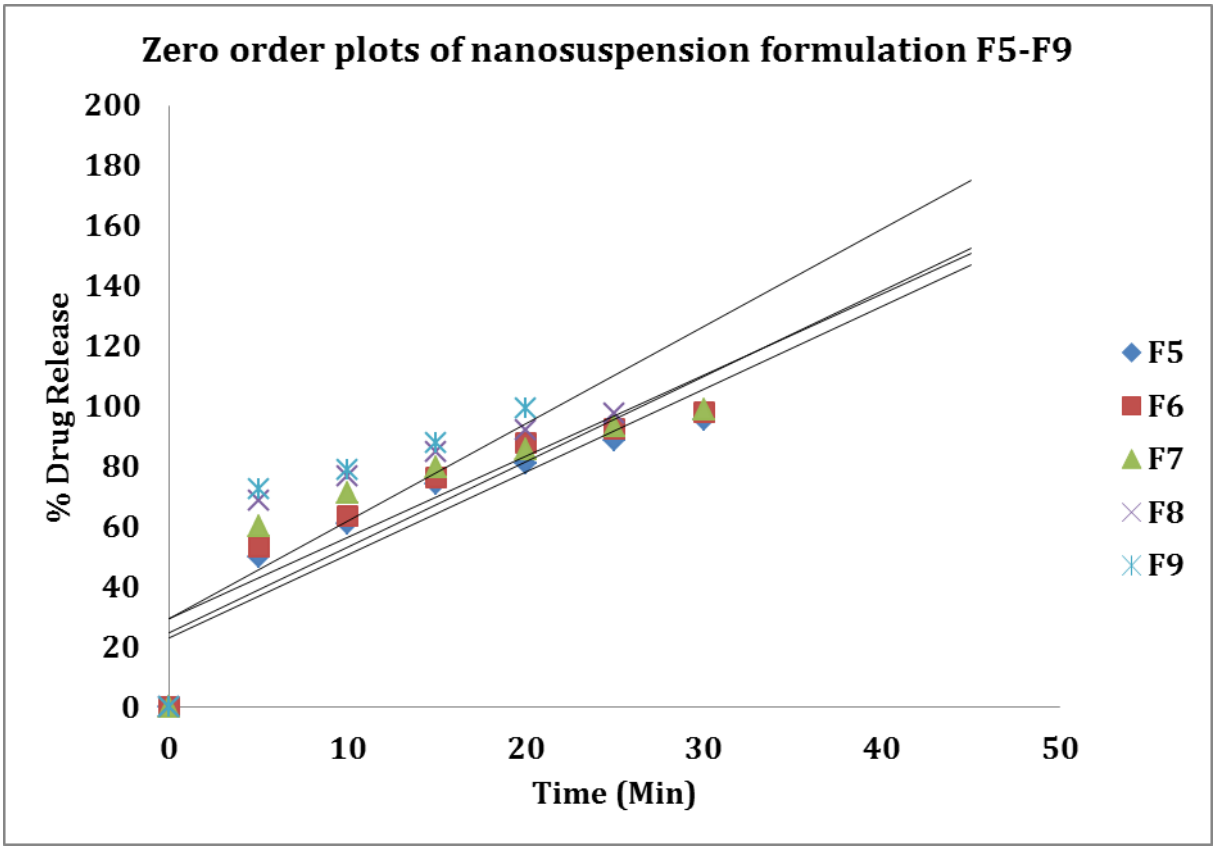


Fig 11. Zero order kinetic plots for nanosuspension formulation F5-F9.

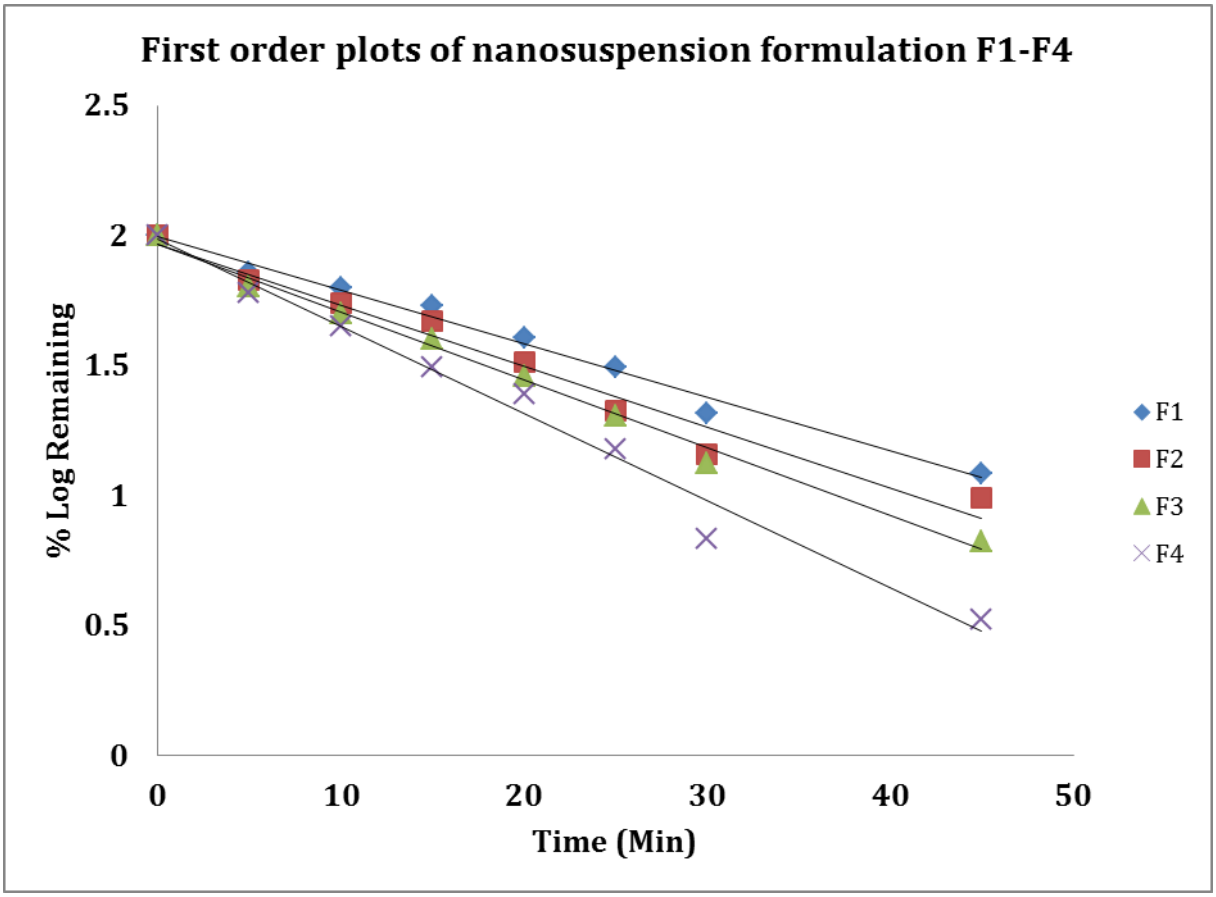


Fig 12. First order kinetic plots for nanosuspension formulation F1-F4.

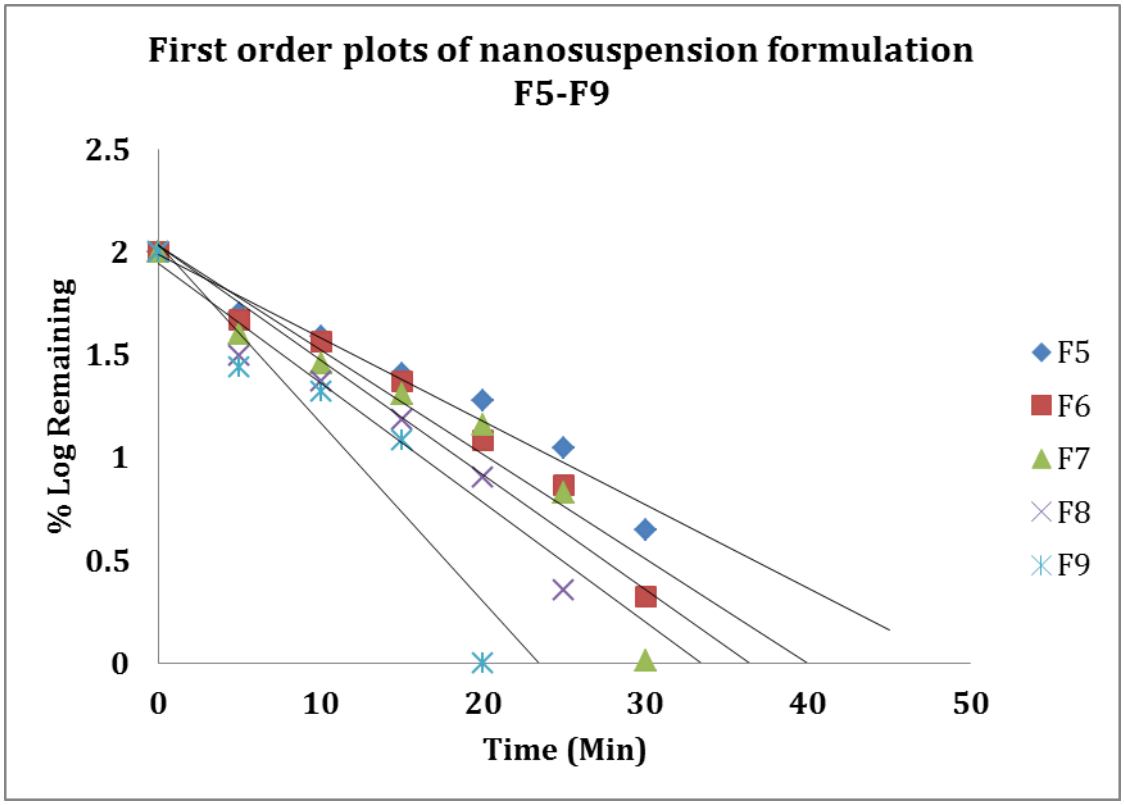


Fig 13. First order kinetic plots for nanosuspension formulation F5-F9.

Table 8. Kinetic Data of Gliclazide Nanosuspension Formulations.

Sl. No	Formulation	Zero order (R^2)	First order (R^2)
1	F1	0.095	0.987
2	F2	0.846	0.969
3	F3	0.826	0.992
4	F4	0.789	0.980
5	F5	0.836	0.967
6	F6	0.823	0.961
7	F7	0.756	0.895
8	F8	0.713	0.952
9	F9	0.745	0.985

6.1.7 Stability study

Stability studies of the optimised formulation F12 was subjected to three different temperature conditions, i.e., 4-8 ^{0}C (refrigerator), room temperature (25±2^0 C) and 45±2 ^{0}C (Stability Chamber). The measurement of drug content, *Invitro* drug release profile was performed and shown in following tabular columns table 6.7. It can be inferred from the observed data that the prepared nanosuspension F9 was stable after 3 months of storage at different temperature condition.

Table 9. Drug content data of Optimised formulation (F9).

SI.No.	Formulation code	1st day (%)	30thday (%)	60thday (%)	90thday (%)
1	F12	99.89	98.21	98.68	99.24

Table 10. *In vitro* drug release data of the Optimised formulation (F9).

Time(min)	1st day	30th day	60thday	90thday
0	0	0	0	0
2	9.4	10.54	9.72	9.69
4	15	16.71	14.24	17.01
6	29.32	32.82	27.69	30.26
8	43.16	47.64	39.1	48.21

10	59.4	60.97	55.18	62.97
12	73.5	74.22	71.87	77.24
14	81.62	85.8	82.12	86.28
16	99.29	96.54	94.36	99.12
18	-	100.94	102.54	-

SUMMARY

Gliclazide is an oral antihyperglycemic agent used for the treatment of non-insulin- dependent diabetes mellitus (NIDDM). It belongs to the sulfonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release. Gliclazide has been shown to decrease fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin (HbA1c) levels (reflective of the last 8-10 weeks of glucose control). Gliclazide is extensively metabolized by the liver; its metabolites are excreted in both urine (60-70%) and feces (10-20%).

Nanosuspension containing drug was prepared by precipitation method by using combinations of polymers PVP K-30, Eudragit S 100, acetone, SLS, Poloxamer 407, and quantity sufficient of distilled water. Estimation of Gliclazide was carried out spectrophotometrically at 232 nm.

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