

Formulation and Characterization of Glimepiride Nanosuspension to Improve the Solubility and Release of Drug

Radheshyam Samanta^{1*}, Pravati Deo², Ranjit Kumar Sutar³, Hrushikesh Behera³, Tamal Deb Goswami¹ and Ayush Panda⁴

¹Department of Pharmaceutics, Kalinga Institute of Pharmaceutical Sciences, Biruan, Balasore, 756060, Odisha, INDIA

²Department of Pharmachemistry, Kalinga Institute of Pharmaceutical Sciences, Biruan, Balasore, 756060, Odisha, INDIA

³Department of Pharmacology, Kalinga Institute of Pharmaceutical Sciences, Biruan, Balasore, 756060, Odisha, INDIA

⁴Department of Pharmacy, Kalinga Institute of Pharmaceutical Sciences, Biruan, Balasore, 756060, Odisha, INDIA

*Corresponding Author: radheshyamsamanta93@gmail.com



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ABSTRACT

The present research work attempt to formulation and characterization of glimepiride nanosuspension made of polyethylene glycol 400 and polyvinyl pyrrolidone K30 with the help of antisolvent precipitation method was developed. These glimepiride containing nanosuspension were evaluated their particle size and size distribution, zeta potential, saturation solubility, drug entrapment efficiency and drug content uniformity. In addition, in vitro drug release was performed. After evaluation, different evaluated parameters like their zeta potential, saturated solubility, drug entrapment efficiency, drug content uniformity was showing valuable result to maintain the stability of nanosuspension. Also in vitro release of drug firstly high in phosphate buffer (pH- 7.8), after one hours the release rate maintain sustainly to all formulation specially GNS5 then other. This is because increase the concentration of polymers composition. So this research work, it was clearly stated that the formulation of glimepiride nanosuspension prepared by addition of suitable polymeric mixture, namely polyethylene glycol 400 and polyvinyl pyrrolidone K30 with others ingredients to improve the solubility and sustain release the drug for a prolong periods of time which is very useful to other insoluble drugs.

Keywords- Nanosuspension, Antisolvent, Polyethylene Glycol, Polyvinyl Pyrrolidone.

I. INTRODUCTION

Nanotechnology has prompted the rise of another field called nanomedicine, which includes the utilization of nanotechnology in drug development, improves and offers many all the more energizing guarantees of new diagnoses and cures [1]. A newer approach for drug delivery for poorly water-soluble compounds has gained lot of attention. Where in the drug is presented in the form of nanometer-sized particles/crystals that can be dispersed in a colloidal solution by having a stabilizer on the surface of nanoparticles. Nano sizing alludes to the way toward diminishing the size of active pharmaceutical ingredient (API) to the submicron level [2]. Drug candidates with poor water solubility pose significant challenges in the

pharmaceutical industry and research. One major issue is the potential loss of dose-response linearity, which can result in unexpected drug breakdown after administration. This can negatively impact patient adherence and reduce bioavailability. Additionally, because these substances are not easily soluble in water, their absorption can vary between fed and fasted states, leading to further complications [3]. To improve solubility and bioavailability, a variety of drug delivery systems are employed, including nanomedicines, liposomes, lipid-based solid nanoparticles, polymeric micelles, quantum dots, nanosuspensions, and nano-emulsions. Nanosuspensions are colloidal dispersions that contain drug particles smaller than 1 micrometer (μm) and are characterized by their fine dispersion and biphasic nature. These systems can enhance drug

adsorption and bioavailability, potentially reducing the conventional oral dosage required [4]. According to the modified Noyes-Whitney equation, reducing drug particle size increases the surface area, thereby accelerating the dissolution rate. Additionally, the Ostwald-Freundlich equation suggests that smaller particle sizes lead to increased saturated solubility due to higher dissolution pressure. Nano-suspensions are particularly useful for drugs in Biopharmaceutical Classification System (BCS) classes II and IV, as they improve solubility [5]. They offer notable benefits in drug delivery, especially for hydrophobic drugs, by increasing drug loading and therapeutic efficiency while decreasing the necessary dose. These systems also address stability issues and allow for passive drug targeting. They are favored for their ease of manufacturing and scalability, making them viable for large-scale production. Stabilizers are often included to maintain long-term stability. For oral administration, nano-suspensions can lead to faster onset of action and enhanced bioavailability [3, 5]. When used intravenously, they provide rapid dissolution and targeted delivery to specific tissues. Injections, whether subcutaneous or intramuscular, may experience reduced tissue irritation with nano-suspensions. They also improve bioavailability via ocular and pulmonary routes, and are particularly advantageous for drugs with high log P values, enhancing their solubility and effectiveness. Furthermore, nano-suspensions can be integrated into a range of dosage forms, including tablets, pellets, hydrogels, and suppositories, providing versatility for various therapeutic applications [6].

Nanosuspensions are submicron colloidal scatterings of nanosized drug particles that are stabilized by surfactants. Nanosuspension is helpful in enhancement of dissolvability of drugs that are least soluble in water and lipid media. This philosophy is important for molecules with poor solubility, poor permeability or both which represents a huge test for the formulators [7]. Nanosuspensions are liquid dispersion which contains solid drug nanoparticles that are stabilized by surfactant and/or polymer. A nanosuspension not just illuminates the issues of least dissolvability and bioavailability yet, in addition, modifies the drug pharmacokinetics and that improves safety and viability of drugs. If there should arise an occurrence of drugs that are insoluble in both water and inorganic media as opposed to utilizing lipoid systems, nanosuspensions are utilized as a formulation strategy [8]. Nanosuspension formulation strategy is most suitable for the molecules with high log P value, large dose and high melting point. The usage of nanotechnology to formulate least water dissolvable drugs as nanosuspension offers the opportunity to address the nature of the deficiency related with this class of drugs. Nanosuspension has been accounted to improve absorption and bioavailability; it may diminish the dose of the conventional oral dosage forms. Drug

particle size reduction prompts an expansion in surface area and therefore in the rate of dissolution as portrayed by the Nernst-Brunner and Levich alteration of the Noyes-Whitney equation. Besides, enhancement in saturation dissolvability is proposed by particle size reduction because of an expanded dissolution pressure clarified by the Ostwald-Freundlich equation [9]. An enhanced measure of amorphous drug fraction could initiate higher saturation dissolvability. In nanosuspension technology, the drug is kept up in the required crystalline state with decreased particle size, prompting an enhanced dissolution rate and as needs be improved bioavailability. Medications enclosed inside nanosuspensions exist in the pharmaceutically satisfactory crystalline or amorphous state [10]. Over 40% of drugs suffer from poor water solubility, which complicates their formulation into conventional dosage forms. This issue is even more challenging for Class II drugs, which are poorly soluble in both aqueous and organic media. For such compounds, particularly those that are water-insoluble but oil-soluble with high log P values, preparing nano-suspensions is often a preferred approach. To address the problems of low solubility and bioavailability, various techniques can be employed, including micronization, co-solvency, oily solutions, salt formation, liposomes, emulsions, microemulsions, solid dispersions, and β -cyclodextrin inclusion complexes [7, 8]. Nanosuspensions offer significant benefits for drugs with poor solubility and low permeability, which are major challenges in formulation. Common issues associated with poorly soluble compounds include: Low bioavailability, Difficulty in optimizing lead compounds based on efficacy and safety, Variability in bioavailability between fed and fasted states, Lack of proportionality between dose and response, Suboptimal dosing strategies, Dependence on harsh excipients, such as excessive co-solvents and other additives, Requirement for extreme pH conditions to enhance solubilisation. [10]. by addressing these challenges, nano-suspensions provide a promising solution for improving drug solubility and therapeutic effectiveness. Nano-suspensions differ from traditional suspension formulations in that the particle length distribution of solid debris is typically less than 1 μm (0.1nm-1000nm), with an average particle size range of 200-600nm. Pharmaceutical suspensions typically require particle sizes ranging from 1 to 50 μm . Nano-suspensions improve total bioavailability by increasing surface location and saturation solubility through particle length discounting. This machine cannot be executed using normal milling techniques [5, 7, 9]. Nanosuspensions offer potential advantages such as reduction of dose as well as cost of therapy, avoiding dose dumping in the body, minimizing fast/fed state plasma level 5 fluctuations and intersubject variability. These advantages have driven towards faster development of nanosuspension technology during last few decades. Various methods are utilized for the formation of

nanosuspension, including cosolvency, solid dispersion, inclusion complexation, cryogenic technique, salt formation, solvent-antisolvent method, supercritical fluid process, emulsification-solvent evaporation technique and media milling techniques [8, 11].

In this present work, glimepiride nanosuspension made of polyethylene glycol 400 and polyvinyl pyrrolidone K30 with the help of antisolvent precipitation method was developed. These glimepiride containing nanosuspension were evaluated their particle size and size distribution, zeta potential, saturation solubility, drug entrapment efficiency and drug content uniformity. In addition, in vitro drug release was performed.

II. METHODOLOGY

2.1 Materials

- Glimepiride was a gift sample from Ajanta Pharma. Pvt. Ltd., India
- Other materials were purchased from different sources like

- Polyethylene glycol 400 and polyvinyl pyrrolidone K30: Sigma Aldrich, USA.
- Methanol and Sodium lauryl sulfate: Loba Chemie Pvt. Ltd., India
- All other chemicals and reagents used were of analytical grade.

2.2 Formulation of nanosuspension of glimepiride

Nanosuspension containing Glimepiride were prepared by antisolvent precipitation method. Overall five batches were formulated using different ratios of Polyethylene glycol 400 and polyvinyl pyrrolidone K30. In this method, the drug glimepiride was dissolved in methanol (organic phase). The polymer PVPK30 and PEG400 were added to 50 mL of distilled water (aqueous phase). The organic phase was drop wise added to the aqueous phase with syringe at room temperature by the addition of sodium lauryl sulphate as a suspending agent and stirred at 1200 rpm for 1 h on magnetic stirrer [12-19]. The formulations of different batches prepared by antisolvent precipitation technique were represented in Table 1.

Table 1: Formula of different ingredients used to prepare glimepiride nanosuspension

Ingredients	Formulation Code				
	GNS1	GNS2	GNS3	GNS4	GNS5
Glimepiride (mg)	5	5	5	5	5
Polyethylene glycol 400 (mg)	10	15	20	25	30
Polyvinyl pyrrolidone K30 (mg)	10	15	20	25	30
Water (ml)	50	50	50	50	50
Methanol (ml)	5	5	5	5	5
SLS (%)	2	2	2	2	2

2.3 Evaluation of particle size and particle size distribution

The nanosuspensions prepared by antisolvent precipitation technique were subjected to particle size analysis using Beckman Coulter (RQ-121 D, Beckman Coulter India Pvt. Ltd., Mumbai, India). Prior to analysis, the dehydrated glimepiride suspension was immersed in double-distilled water and sonicated for duration of one minute then allow to this instruments at 25 °C by this instruments. For determination of particle size distribution DLS method are used to calculate PDI [20].

2.4 Evaluation of zeta potential and saturation solubility

With Zetasizer, the zeta potentials were determined (Malvern instruments ZS 90) at room temperature. To make sure the drug reached the saturation point, an excess of pure glimepiride was added to 5 ml of water. By adding an excessive amount of distilled water, a similarly saturated solution of glimepiride nanosuspension was also produced. These solutions underwent a 24-hour mechanical shaking period at 37°C, followed by a 3-minute centrifugation at 10,000 rpm. After that, the saturated solutions were

diluted to the appropriate concentration. At 228 nm, the drug's concentration was determined by UV spectroscopy [21].

2.5 Evaluation of drug entrapment efficiency and drug content uniformity

The entrapment efficiency of GLM loaded nanosuspensions was evaluated indirectly by estimating the untrapped glimepiride. Briefly, the amount of untrapped drug was first separated from nanosuspension by centrifugation at 20000 rpm for 30 min at 4±0.5 °C using cool ultracentrifuge and was analyzed from supernatant spectrophotometrically (1601 UV-vis spectrophotometer, Shimadzu, Kyoto, Japan) at λ_{max} 228 nm (n=3) [22]. The percent entrapment efficiency (%EE) was determined by applying following equation:

$$\% \text{ Entrapment efficiency (\%EE)} = \frac{(\text{Total drug taken} - \text{Drug in supernatant liquid})}{\text{Total drug taken}} \times 100$$

The drug content uniformity was check by taking this suspension in 10 ml of phosphate buffer, pH 7.8. The sample was sonicated for 15 minutes and

filtered using 0.22 μ membrane filter and after sufficient dilution, the amount of drug was determined spectrophotometrically at 228 nm [23].

2.6 Evaluation of in-vitro drug release study

For pure GLMP and GLMP-NP, an in vitro release investigation was conducted using 900 ml of pH 7.8 phosphate buffer. Glimepiride and glimepiride nanosuspension were dispersed separately in to 3 ml pH 7.8 phosphate buffer and this dispersion was filled in a dialysis tube and tied from both ends. These tubes then dispersed in dissolution test apparatus containing release media maintaining a $37 \pm 0.5^\circ\text{C}$ temperature while the paddles are rotating at 75 rpm. After a duration of 0, 5, 10, 15, 30, 45, and 60 minutes, 5 ml sample aliquots were obtained and. Every time, release media was replaced with 5 ml media. At 228 nm, the drug's concentration was determined by UV spectroscopy [24, 25]

2.7 Statistical analysis

All determined data are expressed as mean $\pm$ standard deviation (Here n = 5).

III. RESULTS AND DISCUSSION

3.1 Preparation of glimepiride containing nanosuspension

In generally suspension was more reliable, economical, and easy to handling dosage system as compare to another system of those drugs having large extent absorbed in small intestine. Previously many similar works reported in this area [26-30], Here this nanosuspension was designed by addition of different ratios of Polyethylene glycol 400 and polyvinyl pyrrolidone K30 with the help of antisolvent precipitation method which achieving good solubility of glimepiride drug and release the drug with in a therapeutically ranges to developed the system.

3.2 Particle size and particle size distribution

Nanosuspensions were analyzed for particle size and polydispersity index (PDI). The differences in the particle size of nanosuspension formulations prepared with variable ratios of polymer and drug were utilized to find out the optimized formulation. The particle sizes of all formulation range of 183-302 nm with PDI of 0.253-0.323 while particle size for GNS1 nanosuspension was found to be 183 nm with PDI 0.253. In general (showing Table 2), drug delivery systems with PDI value higher than 0.5 shows large size distributions and have the tendency to aggregate. Closer the value of PDI to zero more will be the homogeneous nanosuspension formed. The results projected the GNS1 formulation having average particle size 180 nm and PDI 0.253 due to low polymeric concentration present in formulation GNS1 revealed that the optimized nanosuspension formulation was found to be homogeneous with uniform distribution.

Table 2: Particle size and PDI of glimepiride nanosuspension

Formulation Code	Particle Size (nm)	PDI (%)
GNS1	183	0.253
GNS2	118	0.278
GNS3	245	0.297
GNS4	275	0.313
GNS5	301	0.323

3.3 Zeta potential and saturated solubility

It is well known that particle size and zeta potential are significant characteristics, which suggest the physiochemical behaviours of the formulation, involving dissolution velocity, saturation solubility and physical stability. Zeta potential indicates the stability of the nanoparticles to be stably dispersed in suspension. Zeta potential was determined by measuring the electrophoretic mobility of particles in the electrical field using same instrument. The value of zeta potential is a judgment of the electrical charge at the surface of particles that ensures the physical stability of fabricated nanosuspensions. A minimum zeta potential of ± 30 mv is required where as in case of combined electrostatic or for steric stabilizer, a zeta potential of ± 20 mv would be sufficient. At 25°C zeta value for formulation GNS1 was found to be 32.16 mV, respectively. So it concludes that FG1 formulation having more stability as compared to other formulation. The high value of zeta potential (more than ± 30 mV) shows electrostatic repulsion between particles. Electrostatic repulsion causes the particles to repel each other and avoids aggregation, which shows good stability. Zeta potentials of all formulations were shown in Table 3. Drastic enhancement in the solubility of the glimepiride was observed when it was formulated as nanosuspension. The solubility of different formulation ranges from 95 ± 7.8 to 112 ± 6.3 , while GNS1 exhibited 112 ± 6.3 enhancements in saturation solubility as compiled in Table 3.

Table 3: Zeta potential and saturated solubility of glimepiride nanosuspension

Formulation Code	Zeta potential (mV)	Solubility ($\mu\text{g/ml}$)
GNS1	32.16	112 ± 6.3
GNS2	29.35	110 ± 6.9
GNS3	25.45	103 ± 7.6
GNS4	22.29	100 ± 7.5
GNS5	19.03	95 ± 7.8

3.4 Drug entrapment efficiency and drug content uniformity

The drug entrapment efficiency of formulations prepared by antisolvent precipitation method is represented in Table 4. These tables depicted that among all formulations, GNS1 showed highest %EE *i.e.* 82.04 ± 1.50 %. When the amount of these polymers was increased gradually then decreases in %EE was observed. The increased drug entrapment efficiency was due to formation of polymeric matrix. The drug content uniformity also increase when the ratio of polymer was present in this suspension in low that means the best formulation GNS1 showing the value of 90.35 ± 0.34 due to the high drug entrapment efficiency. The value of drug entrapment efficiency and drug content uniformity was shown within the value of 70.19 ± 1.26 to 82.04 ± 1.50 and 87.77 ± 0.57 to 89.48 ± 0.75 respectfully.

Table 4: Drug entrapment efficiency and drug content uniformity of glimepiride nanosuspension

Formulation Code	Drug entrapment efficiency (%)	Drug content uniformity %
GNS1	82.04 ± 1.50	88.35 ± 0.34

GNS2	78.15 ± 1.18	89.48 ± 0.75
GNS3	74.32 ± 1.98	87.03 ± 0.57
GNS4	70.19 ± 1.26	88.63 ± 0.42
GNS5	78.17 ± 1.39	86.77 ± 0.29

3.5 In vitro drug release

In vitro release of glimepiride from this suspension has been given on Figure 2. In 30 min more than 50% drug release was observed from GNS1 formulation. The release was, however, sustained thereafter for the whole period of the study. The enhanced burst release can be attributed to leaching of drug from the polymer and increase in free drug content. Another probable reason for enhanced burst release may be the erosion of nanoparticles. The *in vitro* dissolution data revealed that formulation GNS1 exhibited better drug release as compared to that of formulation after 60 min in PBS pH 7.4 although all other formulation also showing sustain release of drug after 30 minutes. Here the formulation GNS1 showing high drug release as compare to GNS2, GNS3, GNS4 and GNS5 because increase level of polymer concentration.

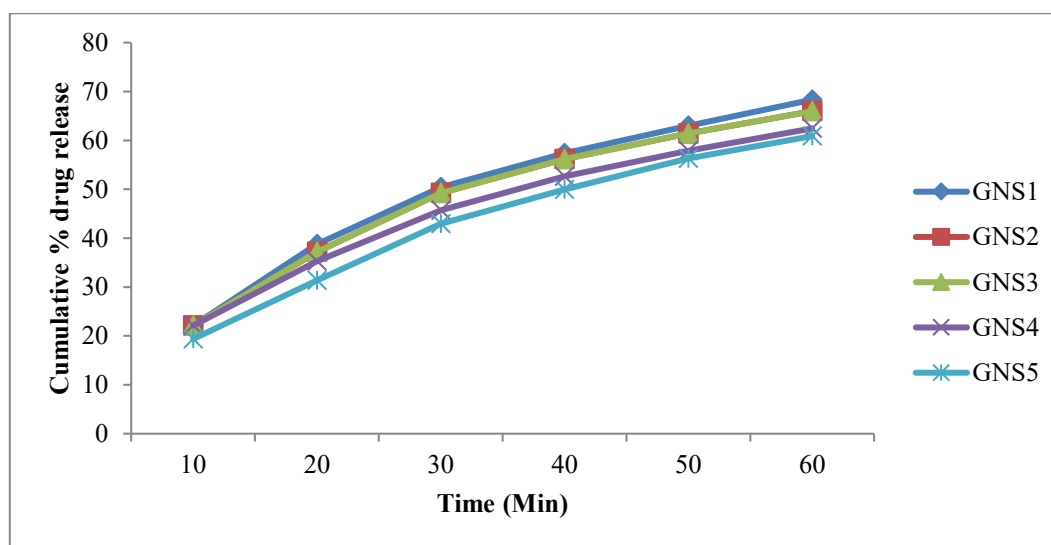


Figure 2: In vitro release of drug (glimepiride) from these nanosuspensions

IV. CONCLUSION

In this research work, it was clearly stated that the formulation of glimepiride nanosuspension prepared by antisolvent precipitation method with addition of suitable polymeric mixture, namely PEG 400 and PVP K30 with SLS as a suspending agent and help to improve the solubility as well as sustain release the drug within therapeutic range for producing action. The different evaluated properties like their particle size and size distribution, zeta potential, solubility, drug entrapment efficiency, drug content uniformity prove that improve the stability and developed the suspension. Also the in vitro release of drug in all formulation

showing High first 30 minutes (50%) after that it will release sustainly over long time. Formulation GNS1 having high in vitro sustain release as compare to GNS2 than GNS3 than GNS4 and finally GNS5 because the increase the amount of polymeric composition. Also the rate of drug entrapment and drug content is high in GNS1 formulation as compare the other due to the same reason of polymer concentration ratio increase which also influences the saturation solubility in purified water as well as phosphate buffer (pH-7.4). So this type of nanosuspensions will be very useful in the future to other suitable characterized drugs which help to improve solubility and sustain release the drug over prolong periods of time.

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