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Formulation and Evaluation of Glimepiride Nanosuspension Using Simple High Shear Homogenizer at Lab Scale

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ABSTRACT

The aim of the present research work is to develop nanosuspension using Glimepiride for the treatment of diabetes mellitus. Glimepiride faces solubility and subsequently bioavailability problems, which we are aims to solve by preparing there nanosuspension using simple high shear homogenization technique. Nanosuspension technique has been successfully employed to improve the dissolution rate of poorly soluble compounds. In this technique drug mixed with polymer & SLS solution. And the solution is stirred for 4-5 hr. at 7000 rpm. So that due to high homogenization the drug particle size gets reduced to nanosized in range of 200 – 600 nm. The reduction of particle size get directly increases the surface area of drug & indirectly rapid dissolution of the drug. The prepared nanosuspension were analyzed for all the parameters like Appearance, Particle size distribution and polydispersity index, Zeta potential, % Drug content & Saturation studies. From this research work, it is evident that the *In-vitro* dissolution of homogenized Glimepiride nanosuspension and its pure drug was shown maximum drug release as compared to pure drug.

INTRODUCTION

Glimepiride is a sulfonylurea antidiabetic drug. It is used to treat type 2 diabetes. It reduces the blood sugar by stimulating the release of the insulin by pancreatic beta cells and by inducing increased activity of intracellular insulin receptors[1]. The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often causes insufficient bioavailability. It is a common problem for those drugs belonging to the biopharmaceutical classification system (BCS) classes II and IV. As for BCS class II drugs rate-limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility, in turn, increases the bioavailability for BCS class II drugs. For increasing solubility of poorly water-soluble drugs, various techniques are employed. Solubility improvement techniques can be categorized into physical modification, chemical modifications of the drug substance, and other techniques. Physical Modifications Particle size reduction like micronization and nanonisation, modification of the crystal habit like polymorphs, amorphous form, and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions, and cryogenic techniques. Chemical Modifications Change of PH, use of buffer, derivatization, complexation, and salt formation. Miscellaneous methods supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.[2, 3]

Nanosuspensions found to be a promising methodology that can be used for enhancing the dissolution of poorly water-soluble compounds. Nano-suspensions play an important role in drug delivery system associated with water-insoluble and both water and lipid-insoluble drugs. These suspensions keep pharmaceutical active ingredient at the submicron levels in a liquid phase stabilized by added stabilizers.[4]innanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability.[5]

Preparation of nanosuspensions in lab scale was reported to be a more cost-effective and technically simple alternative and yield physically more stable nanosuspension.

The main objective of the present study was to develop simple, lab scale preparation of nanosuspension with the improvement of solubility and dissolution of poorly water-soluble drugs.

MATERIALS AND METHODS:

Glimepiride as gift sample from Zim laboratory, Nagpur, HPMC E15 & sodium dodecyl sulfate from Zim laboratory, Nagpur, Maharashtra.

PREPARATION OF NANOSUSPENSION

Glimepiride nanosuspension was prepared by homogenization method (Top-down). HPMC E15 solution was prepared by dissolving the weighed quantity of HPMC E15 in distilled water. To the HPMC E15 solution, a weighed amount of SDS was added and stirred for 15 min to obtain a clear solution. To this solution, the weighed quantity of API was added stirred for 30 min at 5000 rpm to obtain a coarse suspension and then the speed and time for homogenization were gradually increased as given in **Table No.1**. The resulting nanosuspension then settled for overnight. After that, the resulting nanosuspension were evaluated for various parameters.

Table 1: The composition of formulation batches of Glimepiride nanosuspension

Formulation codes	Glimepiride (%w/v)	HPMC (%w/v)	SDS (%w/v)	Water (ml)	Speed (rpm)	Time (min)	Temperature (^{o}C)
G1	0.4	1	12	100	7000	150	R.T
G2	**0.4**	**1**	**12**	**100**	**8000**	**180**	**R.T.**
G3	0.5	1	11	100	7000	150	R.T.
G4	0.5	1	11	100	8000	180	R.T.
G5	0.6	1	10	100	7000	150	R.T.
G6	0.6	1	10	100	8000	180	R.T.
G7	0.7	1.5	9	100	7000	150	R.T
G8	0.7	0.5	9	100	8000	180	R.T

R.T=Room Temperature

Evaluations of prepared nanosuspensions

a) Appearance

Nanosuspensions are generally transparent in appearance because the suspended particle is in nanosize range. Therefore all the formulations were visually observed whether those are opaque or transparent.

b) Particle size distribution and polydispersity index (PDI)[6]

Particle size was determined by photon correlation spectroscopy (PCS) using Horiba Nanoparticle Analyzer. This analysis yields the mean diameter (z-average) at 25^0 C, and at an angle of 90 degrees. The PCS analysis yields the mean diameter (z-average) as a light intensity – weighed the size of the bulk population.

PDI is an index of width or spread or variation within the particle size distribution. the monodisperse system has a lower PDI value, whereas the higher value of PDI indicates a wider particle size distribution and the polydisperse nature of the sample. The PCS analysis yields the polydispersity index as a measurement for a width of a particle size distribution. the polydispersity index (dimensionless measure for the broadness of a particle size distribution) of the prepared formulation was determined by instrument software. The usual range of PDI value is 0-0.05 (monodisperse standard), 0.05-0.08 (nearly monodisperse). 0.08-0.7(mid rangepolydispersity), >0.7 (very polydisperse).

c) Zeta potential[7]

Zeta potential of a nanosuspension is essential as it gives an idea about the physical stability of nanosuspension. Zeta potential was determined by photon correlation spectroscopy using "Horiba Nanoparticle Analyzer". The minimum zeta potential of ±30mV is required for stability of nanosuspension.

d) Drug content[8]

An aliquot (1ml) of nanosuspension was diluted to 10 ml with methanol. 1ml of the solution was further diluted with methanol and filtered through a 0.45 µm filter paper. The solution was further diluted and analyzed using UV- spectrophotometer (Shimadzu -1700)at 233nm methanol as blank for Glimepiride. Each sample was prepared and analyzed in triplicate.

e) Saturation solubility studies[3]

The saturation solubility studies were carried out for both the pure drug and different batches of nanosuspension. 10 mg of pure drug and nanosuspension equivalent to 10 mg of Glimepiride was weighed and separately introduced into 250 ml stopper conical flask containing 10 ml distilled water. The flask was sealed and placed on a rotary shaker for 24 hr at room temperature. The sample was collected and filtered. The filtered sample was analyzed using Shimadzu UV- visible spectrophotometer at 265nm and 233nm, against distilled water as a blank. Each sample was prepared and analyzed in triplicate.

f) *In – vitro* dissolution studies[9]

In-vitro drug release studies were performed in USP- Type I Basket apparatus at 75 rpm. Dissolution of the prefilled capsules with nanosuspension (0.5ml) and pure drug equivalent to the concentration of the drug present in 0.5 ml nanosuspension was carried out in 500 ml pH 7.8 buffer at $37^0C \pm 2^0C$ and 900ml pH 1.2 buffer at $37^0C \pm 0.5^0C$, respectively. 10ml of the sample was withdrawn periodically and replaced with an equal quantity of fresh dissolution fluid. The sample was filtered through 0.45µm Whatman filter paper, and analyzed spectrophotometrically at λ_{max} 228nm, against pH7.8 phosphate buffer as blank and at λ_{max}230 nm, against pH1.2 acidic buffer as blank. The *in-vitro* dissolution testing studies were performed in triplicate for all the batches.

RESULT AND DISCUSSION:

Table 2: Preliminary evaluation parameters of Glimepiride nanosuspension formulation

FORMULATION	APPEARANCE	DRUG CONTENT (%)
F1	Clear	95.86±2.61
F2	Clear	96.48±4.1

Fig. 1: Image of Glimepiride nanosuspension formulation

The results obtained from the preliminary evaluations indicate that the formulations F1and F2 were clear, transparent, stable in appearance as shown in **Table No. 2 and Fig No. 1**and were selected for further evaluations. Drug and excipients were in nano size, therefore, prepared nanosuspension was clear and transparent.

a) Particle size distribution and polydispersity index (PDI)

Particle size and size distribution are very important parameters. Since reducing particle size help in the improvement of solubility of pure drug thereby increasing the dissolution and bioavailability.

PDI gives the degree of particle size distribution. The higher value of PDI indicates broad particle distribution. Narrow size distribution is essential to prevent particle growth due to Ostwald ripening and maintaining the stability of nanosuspension. Particle size data and PDI results for nanosuspension formulation are tabulated in **Table No. 3.**

The mean particle sizes of Glimepiride nanosuspension for varying time are given below.

- **Stirring time –** generally decreasing the particle size and PDI was found due to increasing stirring time. Longer the stirring time result in fine nanosuspension with smaller and more uniform particle size. The decrease of PDI was observed with time, which confirmed that with prolonged stirring time, a remaining larger particle size in nanosuspension was broken down into smaller particle size.

a) Zeta potential -The determination of the zeta potential of a nanosuspension is essential as it gives an idea about the physical stability of the nanosuspension. The zeta potential of a

nanosuspension is governed by both the stabilizer and the drug itself. In order to obtain a nanosuspension exhibiting good stability, for an electrostatically stabilized nanosuspension.

The minimum zeta potential of ±30mV is required whereas, in the case of a combined electrostatic and steric stabilization, a minimum zeta potential of ±20mV is desirable. Zeta potential of Glimepiride nanosuspensions was found to be indicating a stable system. In the nanosuspension, SDS is used as a stabilizer, which provides steric stabilization to the nanoparticles. Therefore negative zeta potential is achieved to the drug particle.[10]

Table 3: Physicochemical Characterization of Glimepiride Nanosuspension Formulations

Sr. No.	Mean particle size (nm)	Polydispersity Index	Zeta Potential (mV)
F1	38.7±2.2	0.562	-10.9

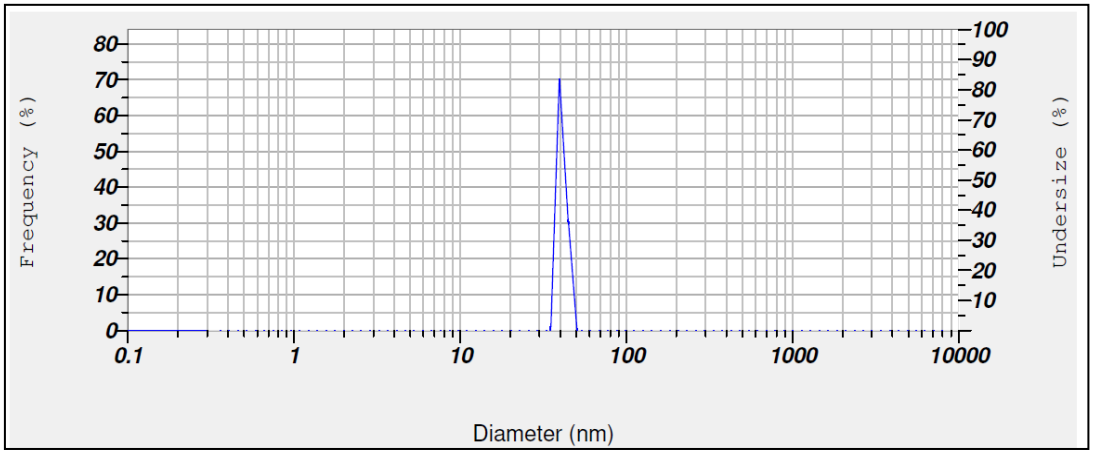

Fig. 2: Particle Size Distribution of Glimepiride Nanosuspension.

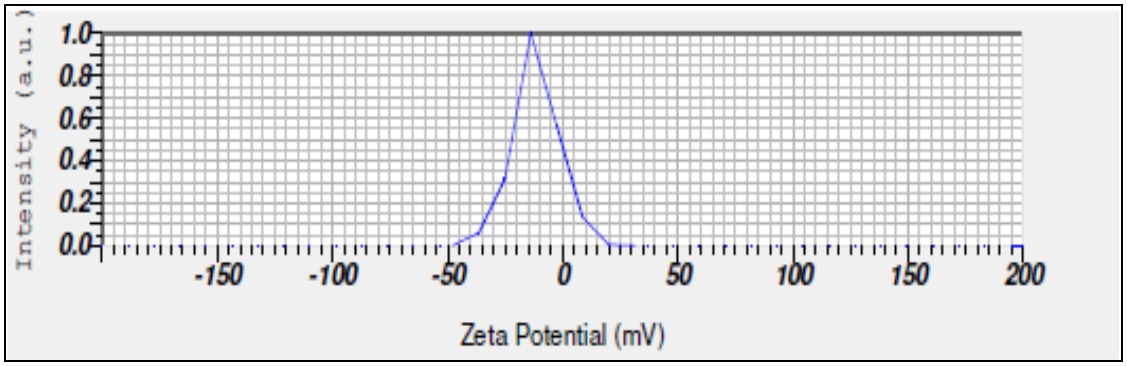

Fig. 3: Zeta Potential of Glimepiride Nanosuspension

c) Drug content

The drug content was determined by UV-visible spectrophotometer method. The results of Glimepiride drug content was tabulated in **Table 4**. in the nanosuspension formulation, the drug particle were reduced to nano size.

d) Saturation solubility studies

The solubility data of Glimepiride nanosuspension and pure drug shown in **Table 4**.The result indicates that nanosuspension showed maximum solubility compared to pure drug. In these studies, the aqueous solubility of nanosizedGlimepiride was greater than their respective pure drugs. The reduction of the homogenized drug to the nano range increased the surface area and enhanced hydrophilicity was responsible to enhance the saturation solubility.[11]

Table 4: Drug content and Saturation solubility of Glimepiride nanosuspension

Formulation code	formulation	Drug Content (%)	Saturation solubility Mg /10ml
F1	nanosuspension	94.39	7.43
	Pure drug	-	1.01

e) *In-vitro* dissolution Studies

In-vitro dissolution of homogenized Glimepiride nanosuspension and its pure drug are shown in **Fig 4 and 5** in pH 1.2 and pH 7.8 buffer, respectively.

Formulation F1 showed maximum release of drug 90.73% and77.68% within 10min in pH 7.8 buffers and pH 1.2 buffers, respectively. And for the pure drug showed the 22.53% and 27.87% drug released within 10min in pH 7.8 buffer and pH 1.2 buffer, respectively. The dissolution of the Glimepiride nanosuspension increased due to the reduction of particle size.

The dissolution of nanosuspension was shown maximum drug release as compared to pure drug. The reason for increased the dissolution was due to increase the stirring time of preparation of nanosuspension due to which smaller the particle size of the drug. As the size decreases, increases the surface area of the drug result in an increase in dissolution according to "Nernst Brunner- Noyes Whitney equation".[12]

Compared to the pure drug, the nanosuspension displayed a significant increase in dissolution rate. Due to large surface area and large apparent volume and surface wetting by the surfactants in the nanosuspension formulation results in an increase in dissolution of nanosuspension as compared to pure drug particles.[13]

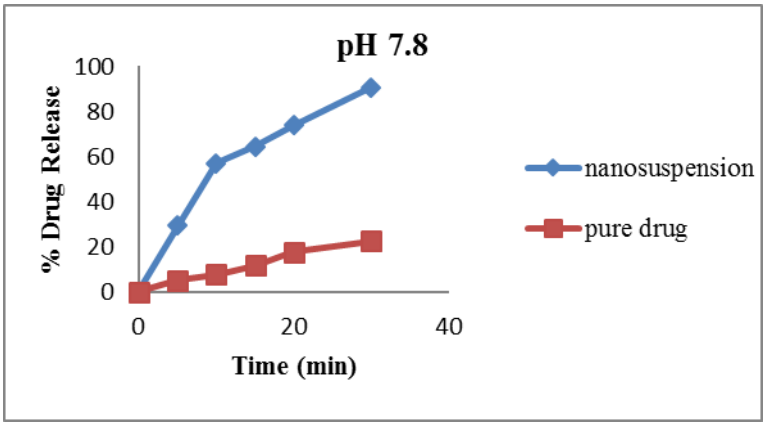

Fig. 4: *In-vitro* dissolution profiles of Glimepiride nanosuspensions and pure drug in pH 7.8 buffer

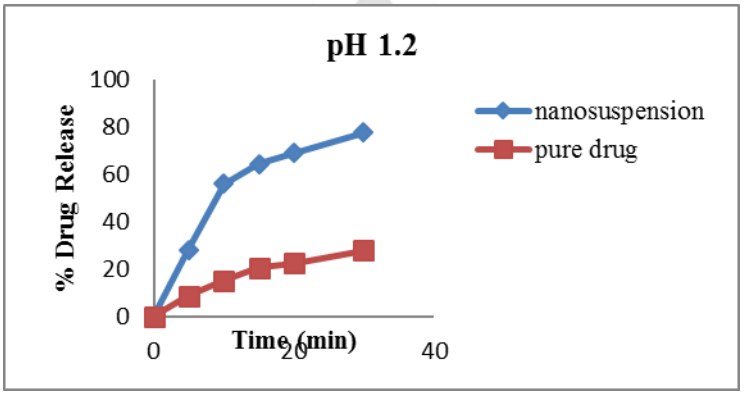

Fig. 5: *In-vitro* dissolution studies of Glimepiride nanosuspension and pure drug in pH 1.2

CONCLUSION

From the above studies, we concluded that high shear homogenization technique has been successfully utilized for the preparation of nanosuspensions at lab scale of poorly water-soluble drugs using the stabilizers - HPMC E15 (polymer) and Sodium dodecyl sulfate (surfactant). Glimepiride nanosuspension the particle size was in nano size and maximum loading was obtained.

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