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FORMULATION AND *IN VITRO* EVALUATION OF TABLET CONTAINING GLICLAZIDE NANOCRYSTALS FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT USING SOLUPLUS

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ABSTRACT: Poor aqueous solubility is the main problem in development of effective formulation which affects stability and bioavailability of drug formulation. So there is need of systematic formulation approach to make such poorly soluble drugs bioavailable. In the present investigation attempt has been made to investigate the effect of soluplus on solubility of gliclazide by preparing its nanocrystals. Nanocrystals of gliclazide with soluplus were prepared by using drug: carrier ratios of 1:0.5, 1:1, 1:2, 1:4, 1:6 and 1:8 by anti-solvent precipitation technique. Physicochemical analysis demonstrated the crystalline nature of particles and amongst all formulations 1:2 ratio provided the highest degree of gliclazide solubility *i.e.*, 2.5027 ± 0.77 mg/ml as compared to pure drug 0.4918 ± 0.51 mg/ml. This increase in solubility may due to increase in surface area and or characteristics of nanocrystals and soluplus. The prepared nanocrystals were characterized by Fourier Transformed Infrared Spectroscopy (FTIR), Differential Scanning Colorimetry (DSC), X-Ray Diffraction pattern (XRD), Scanning Electron Microscopy (SEM). The prepared nanocrystals with highest solubility was formulated into tablet and evaluated for hardness, friability, drug content, disintegration time and *in vitro* dissolution. The tablet containing nanocrystals found to possess more drug release (88.84%) as compared to tablet containing pure drug (63.03%) and marketed formulation (64.43%).

INTRODUCTION: Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose level caused by insulin deficiency and it is often combined with insulin resistance, called as hyperglycemia³. The rapid gastrointestinal tract (GIT) absorption is required for oral hypoglycemic drug, in order to prevent a sudden increase in blood glucose level after lunch of diabetes mellitus patients.

However, gliclazide GI absorption rate, in conventional dosage form like tablet, appears to be rather slow. Several clinical studies revealed that the time to reach peak serum gliclazide concentration ranges from 2 - 8 hours following oral administration of the gliclazide tablet. A slow absorption of drug originates from either poor dissolution of drug from the formulation or poor permeability of drug across the GI membrane⁴.

Nanocrystals are particles having size less than 1000 nm. As the particle size of crystals is decreased to about 100 nm there is a severe change in the properties of the material. There is increase in surface area and solubility with decreased size of drug and there is proportionate increase in the bioavailability of feebly water soluble drug (BCS

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class II and IV) ⁶. Nanocrystals may be able to reduce the dose to be administered, provide a sustained drug release and increase patient compliance ⁷.

Soluplus[®] is polymeric solubilizer with amphiphilic chemical structure, which was developed for solid solution. It is able to act as a matrix polymer for solid solutions and capable of solubilizing poorly soluble drugs in aqueous media due to bifunctional character. Soluplus[®] is a polyvinyl caprolactum polyvinyl acetate-polyethylene glycol graft copolymer (13% PEG 6000/57% vinyl caprolactum /30% vinyl acetate). It has a PEG 6000 Backbone with one or two side chains consisting of vinyl acetate randomly copolymerized with vinyl caprolactum ⁸.

MATERIAL AND METHOD: Gliclazide obtained as a gift sample from wallae Pharmaceuticals Pvt. Ltd. Goa and soluplus is obtained as a gift sample from BASF Mumbai. Microcrystalline cellulose obtained from shilpa medicare vishakhaptnam, Cross carmellose sodium and Lactose monohydrate obtained from Concept Pharmaceuticals, Auranagabad, Magnesium stearate and Talc obtained from S D Fine Chemicals, Mumbai, Dichloromethane, Sodium Hydroxide and Potassium dihydrogen phosphate used are of analytical grade.

Preparation of gliclazide nanocrystals: Nano crystals were prepared by anti-solvent precipitation technique. The solvent phase composed of 500 mg of drug dissolved in 10 mL of Dichloromethane. Anti-solvent phase prepared by using 100 ml of distilled water and soluplus 0.25 g, 0.5 g, 1 g, 2 g, 3 g. and 4 g so as to get drug and polymer ratio 1:0.5, 1:1, 1:2, 1:4, 1:6 and 1:8 respectively. Solvent phase added drop wise to anti-solvent phase at flow rate of 1ml per minute with stirring by magnetic stirrer at 1000 -1200 rpm. Resulting dispersion was stirred for 30 min and filtered by Whatman filter paper and kept overnight so as to dry completely. Resulting powder was triturated and pass through sieve no. #170 ⁹.

Characterization of nanocrystals:

Solubility of nanocrystals: The solubility was determined by adding excess amount of pure gliclazide and gliclazide nanocrystal formulations

to 10 ml distilled water in separate test tube and the mixture was magnetically stirred for 24 hours at 25°C temperature. The supernatant liquid was collected and filtered through Whatman filter paper and analyzed by UV Spectrophotometer at wavelength 226 nm¹⁰.

Drug content of nanocrystals: Accurately weighed 10 mg of gliclazide nanocrystals dissolved in 10 mL of distilled water. The resulting solution was sonicated for 3 min and filtered through Whatman filter paper. The filtrate was then diluted suitably with distilled water and gliclazide content was analyzed at 227 nm using UV Spectrophotometer. All the samples were analyzed in triplicate, and the data obtained was expressed as mean values \pm SD of three measurements ¹¹.

Fourier - Transform Infrared Spectroscopy: Fourier-transform infrared (FT-IR) spectra were obtained by using an FT-IR spectrometer-430 (Schimadzu, Japan). The samples (gliclazide or Nanocrystals) were previously ground and mixed thoroughly with potassium bromide as ratio of 1:100 (Sample/KBr) in motor and pestle. Resulting mixture placed in sample cell of FT-IR. Forty scans were obtained at a resolution of 4 cm⁻¹, from 4,600 to 300 cm⁻¹¹².

X-ray powder diffraction studies (XRPD): X-Ray powder diffraction patterns were obtained using a XRD-Bruker, AXS, D8 Advance, Germany diffractometer, with Cu K α radiation (λ = 1.54Å). The diffraction pattern was measured with a voltage of 30 kV and a current of 40mA in the range of 10°- 60° (2 θ) in a step scan mode ¹³.

Scanning electron microscopy (SEM): Surface characteristics of pure drug and prepared nanocrystals were observed using scanning electron microscope (JEOL, JSM- 6360 Tokyo, Japan). Samples were placed on a carbon specimen holder, and then coated with carbon in an auto fine coater (JEOL JFC 1600) ¹⁴.

Differential scanning calorimetry (DSC): DSC analysis was conducted to study the thermal behaviors of the samples. To this end, DSC 822e (Mettler Toledo, Switzerland) equipped with a refrigerated cooling system was used and the instrument was calibrated using indium standard. Samples of pure gliclazide and its nanocrystals

were placed in aluminum pans sealed with a lid. The crimped aluminum pans were placed inside the DSC and were scanned from 40 to 300 °C at a scanning rate of 10°C/min under nitro-gen gas at a flow rate of 80ml/min. To compare the thermal behavior of various samples their onset temperatures, melting points and endothermic and exothermic enthalpies were calculated using the software provided (STAR SW 10.00)¹⁵.

Tablet formulation of gliclazide nanocrystals:

The tablets were prepared by direct compression. Nanocrystals and the excipients required for tablet compression are passed through # 60 sieve. Quantities of the drug substance and the excipients are weighed accurately as mentioned in **Table 1**. The nanocrystal was mixed with the excipients by geometric dilution technique and then it was blended for 10 minutes in motor and pestles to get the uniformity in blend powder. From the above blend, a definite quantity which was equivalent to 40 mg of drug was weighed and compressed in to a tablet by using the single punch tablet compression machine (Karnavati).

TABLE 1: COMPOSITION OF TABLETS CONTAINING GLICLAZIDE AND GLICLAZIDE NANOCRYSTALS

Sr. No	Formulation composition	Batches (all ingredients were in mg)	
		F1	F2
1	Gliclazide	40	-
2	Gliclazide Nanocrystals	-	47
3	Lactose monohydrate	82	75
4	Microcrystalline cellulose	30	30
5	Cross-carmalose sodium	10	10
6	Magnesium stearate	08	08
7	Talc	10	10
	Total weight	180	180

Pre and post compression evaluation of tablet:

Precompression evaluation of tablet includes determination of angle of repose, Carr's index, Hausner's ratio of formulation mixture. Post compression evaluation includes determination of hardness, weight variation, friability, disintegration time and drug content. All these tests were performed according to USP 30 NF

In vitro dissolution studies: *In vitro* dissolution studies of the fabricated formulations and the marketed formulation was performed according to USP apparatus Type II (Electrolab). The 900 ml of

pH 7.4 phosphate buffer was used as dissolution media. The tablet containing 40mg (or equivalent to 40mg) of gliclazide was placed in dissolution media maintaining temperature at 37°C ± 0.5°C and rotation speed of paddle at 50 rpm. About 5ml of aliquot were withdrawn at 5, 10, 15, 20, 25 and 30 minutes and replaced with 5 ml of fresh dissolution medium to maintain the sink condition. Samples were filtered through whatmann filter paper and analyzed spectrophotometrically at 226 nm.¹⁶

Stability studies: Tablet formulation containing nanoparticles was subjected to accelerated stability studies according to ICH guidelines at 40 °C/75% RH in stability chamber (Photostability chamber S R Lab Instruments Pvt. Ltd. Mumbai)

RESULTS AND DISCUSSION:

Solubility study: Solubility studies were performed to determine the solubility enhancing properties of materials. Solubility studies give the basis for the selection of best ratio of nanocrystals that is to be used for tablet formulation. Nanoparticles of drug with soluplus in various ratios were analyzed for solubility determination. The results as shown in **Table 2** depicts that soluplus have very good solubility enhancing property may because of its good surfactant characteristics. Up to certain ratio (1:2) solubility goes increases constantly and further increase in polymer concentration solubility decreases. Studies revealed exponential increase in solubility which is an almost five times more (2.5027mg/ml) as compare to plain drug 0.4918mg/ml. Therefore 1:2 ratio of gliclazide nanocrystal was optimized and used for further formulation development.

TABLE 2: SOLUBILITY OF NANOCRYSTALS

S. no	Formulation		Water Solubility	
	Drug : polymer	Code	µg / ml	Increase (in folds)
1	1:0	Pure drug	0.4918 ± 0.51	1
2	1:0.5	GN1	2.2037 ± 0.47	4.4808
3	1:1	GN2	1.9863 ± 0.26	4.0388
4	1:2	GN3	2.5027 ± 0.77	5.0888
5	1:4	GN4	0.8179 ± 0.90	1.6630
6	1:6	GN5	2.3124 ± 0.58	4.7019
7	1:8	GN6	1.7690 ± 0.04	3.5969

Drug content of nanocrystals: Drug content of prepared gliclazide nanocrystals was found to be 85.2% showing uniform distribution of gliclazide in the nanocrystals.

FTIR-spectroscopy: The IR spectra of nanocrystals were compared with the standard spectrum of gliclazide **Fig. 1** shows that the principle peak values of drug remained unchanged in the soluplus treated nanoparticles indicating the compatibility between drug and polymer.

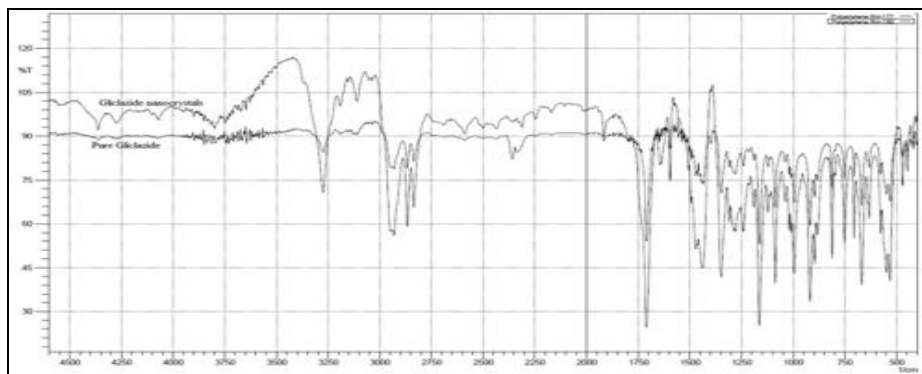


FIG. 1: FT-IR SPECTRA OF PURE DRUG AND NANOCRYSTALS

X-ray powder diffraction studies (XRPD):

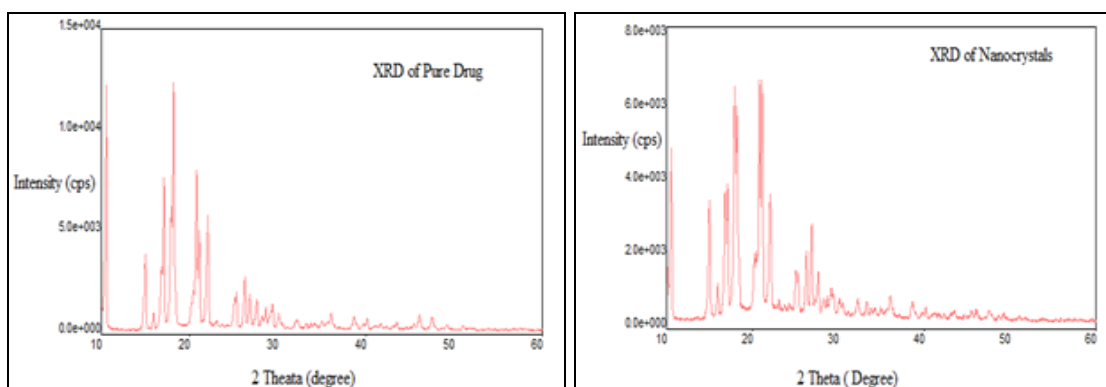


FIG. 2: XRPD PATTERN OF PURE GLICLAZIDE AND NANOCRYSTALS

XRD patterns obtained for untreated gliclazide exhibited sharp diffraction peaks at 2θ values of 10.52, 16.8, 17.06, 18.16, 20.76 and 22.04 and the nanocrystals shows sharp diffraction peaks at 2θ values of 10.5, 14.94, 16.78, 17.9, 20.76, 21.01, 22.04 and 26.28 indicating crystalline nature.

Scanning electron microscopy (SEM): Pure drug particles were found to be regular in shape with

smooth surface while optimized nanoparticles were found to be irregular in shape and size below 1000nm.

The SEM images **Fig. 3** clearly indicates that the shape of gliclazide completely changed in gliclazide nanocrystals showing complex form of gliclazide in soluplus.

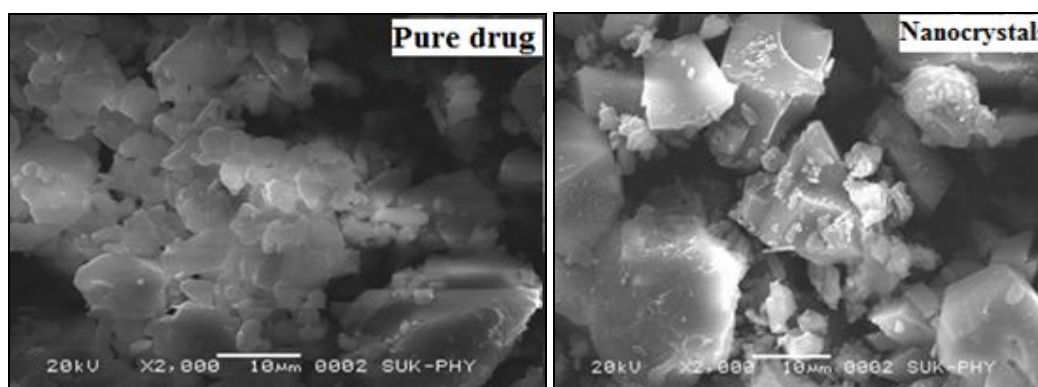
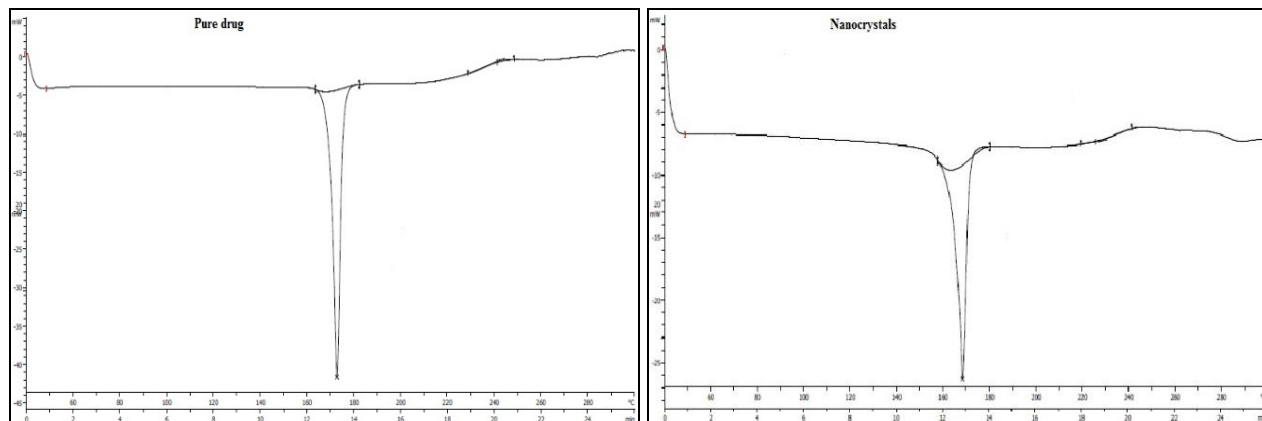


FIG. 3: SEM IMAGE OF PURE GLICLAZIDE AND NANOCRYSTALS

Differential scanning calorimetry (DSC):**FIG. 4: DSC TRACES OF PURE GLICLAZIDE AND NANOCRYSTALS**

DSC analysis was performed in order to investigate any interaction between gliclazide and soluplus or any changes in polymorphic form during the crystallization process. **Fig. 4** shows the DSC traces of gliclazide and obtained nanocrystals and their melting points and enthalpy of fusion. Pure gliclazide sample exhibited an endothermic peak around 170.82°C. The presence of soluplus

decreased the melting point of gliclazide 167.41°C. Small shift in melting point and broadening of peak indicate reduction/conversion of drug to nano crystalline form.

Pre and post compression evaluation of fast dissolving tablet: All the pre and post compression evaluation parameters are found to be within the limit as per USP 30 NF.

TABLE 3: PHYSICAL PARAMETERS OF THE TABLET

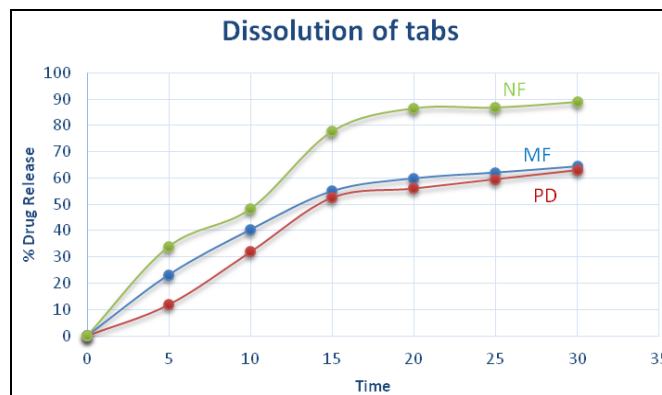
Formulation	Weight variation (%)	Friability (%)	Hardness (kg/cm ²)	Disintegration Time (second)	Drug Content (%)	Dissolution % CDR
PD	2.75	0.570	4.21 ±0.18	150 ± 9.5	97.23	63.03
MF	2.02	0.534	5.31 ±0.23	320 ± 8.0	97.89	64.43
NF	1.40	0.480	3.57 ±0.13	120 ± 5.7	98.92	88.84

PD- Pure drug, MF- Marketed formulation, NF- Nanocrystal formulation

In vitro dissolution of gliclazide nanocrystals fast dissolving tablet: The dissolution profiles of the different tablet formulations are depicted in **Fig. 5**. The tablet formulation prepared with pure drug (PD) exhibited very poor dissolution rate due to the hydrophobic and the crystalline nature of gliclazide. The formulation (PD) showed 52% drug release in 15 minutes and 63% release in 30 min, respectively. The formulation (MF) showed 55% drug release in 15 minutes and 64.43% release in 30 min, respectively. The formulation (NF) showed 77.67% drug release in 15 minutes and 88.84% release in 30 min, respectively.

Among all the formulations, NF had shown the highest drug release in the first 15min. Tablets prepared with nanocrystals showed higher drug release as compare to tablets prepared by pure drug and marketed tablet formulation. This increase may be due to decreased particle size, with increased

surface area and may also the micellar effect of soluplus.

**FIG. 5: PERCENT DRUG RELEASE OF PURE DRUG (PD), MARKETED FORMULATION (MF) AND NANO CRYSTALS FORMULATION (NF)**

Stability study: Fast dissolving tablet containing gliclazide nanocrystals subjected to stability studies (40°C/75%RH). It was found that no major change

in parameters such as color, odor, drug content and *in-vitro* drug release after 30 days of exposure. Hence it can be concluded from the stability data that prepared formulation is stable and not much affected by stress condition.

TABLE 3: STABILITY DATA OF TABLET FORMULATION

Time in days	% Drug content	% <i>In - vitro</i> drug release
0	98.92	88.84
30	98.12	87.94

CONCLUSION: Exponential increase in solubility of prepared gliclazide nanocrystals was observed as compared to pure drug. The percent drug release of tablet containing gliclazide nanocrystals was found to be rapid and more as compared to pure drug and marketed formulation. Also the tablet formulation was found to be stable under stress conditions. Thus it can be concluded that the present method can be used successfully for the preparation of nanocrystals and dosage form development with increased solubility and dissolution with proportionate increase in the bioavailability of feebly water soluble drug.

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CONFLICT OF INTEREST: The authors declare that there are no conflicts of interest.

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