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DEVELOPMENT AND CHARACTERIZATION OF GLICLAZIDE SOLID DISPERSION USING MIXED SOLVENCY CONCEPT

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Abstract:

The present study focuses on the development and characterization of gliclazide solid dispersions employing the mixed solvency concept to enhance solubility and dissolution rate of the drug. Gliclazide, a second-generation sulfonylurea used in the management of type 2 diabetes mellitus, suffers from poor aqueous solubility, which limits its bioavailability. Solid dispersions of gliclazide were prepared using a combination of hydrotropic agents, cosolvents, and solubilizers to exploit the synergistic effect of mixed solvency. Various formulations were developed and evaluated for drug content, solubility enhancement, dissolution behavior, and physicochemical properties. Characterization techniques such as Fourier Transform Infrared Spectroscopy (FTIR), were employed to assess drug–excipient compatibility, crystallinity changes, and thermal behavior. The mixed solvency approach significantly improved the solubility of gliclazide compared to pure drug and conventional solid dispersions. Optimized formulations demonstrated enhanced dissolution rates, reduced crystallinity, and stable drug–excipient interactions. Stability studies confirmed that the solid dispersions maintained their physicochemical integrity under accelerated conditions. These approaches potentially enhance oral bioavailability and therapeutic efficacy, offering a cost-effective and industrially feasible solution for formulation scientists.

Keyword: *Gliclazide, Solid dispersions, Mixed solvency concept, Enhance solubility*

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INTRODUCTION:

The solid dosage forms (E.g., tablets, capsules) release drug instantly which are utmost used drug delivery systems (DDS). These dosage forms disintegrate and dissolve gastric fluid[1]. Dissolution of the drug(s) under physiological conditions is vital for its systemic absorption. Dissolution characterization is done for solid orals and to decide the agreement with dissolution necessities when stated in the discrete monograph[2]. In this drug is distributes as fine particles which enhance solubility. According to the classical Noyes-Whitney equation, this will hike drug solubility[3]. SDs elevates the solubility elevation of poorly soluble drugs, and established dissolution of drug at the absorption spot and thus mends the systemic availability[4]. The common method of administering SDs is in the form of tablets or capsules. The drug available in SDs in solid state is helpful in stabilizing unstable drugs. They have rapid dissolution rate. They are thermodynamically more active form of a drug and directly influences diffusion and release rate. The dose of the drug that is given in SDs could be decreased[5].

Gliclazide attaches itself to the sulfonyl urea receptor (SUR1) on β cells. Subsequently, the ATP-sensitive potassium channels are blocked by this binding. The channels close as a result of the binding. This causes a subsequent drop in potassium efflux, which causes the β cells to depolarize. This causes the β cell's voltage-dependent calcium channels to open, activating calmodulin and triggering the exocytosis of insulin-containing secretory granules[6].

Aim of enhancing solubility, dissolution rate and oral bioavailability of a poorly soluble BCS class II drug, Gliclazide was to be achieved through, the selected solid dispersion formulation.

MATERIALS AND METHODS

Preparations of Solid Dispersions Solid dispersions were prepared by solvent method. Gliclazide and PEG 6000 were dissolved respectively in 96% ethanol, and then mixed and stirred with a magnetic stirrer. The solution formed was evaporated and dried over water bath to obtain dried dispersion. Solid dispersion that formed was collected and stored in desiccators before use. Solid dispersion formulated into tablets using direct compression method. Crosspovidone (5,10, 15), microcrystalline cellulose, talc, and magnesium stearate added as disintegrants and lubricants (Table 4). Powder blends mixed in a container and compressed into tablets using a double punch tablet machine.

Table No. 4: Formulation of Inclusion Complex Tablet

S. No.	Content	F1	F2	F3	F4	F5
1	Solid Dispersion of Gliclazide and PEG 6000	10	10	10	10	10
2	Crospovidone	2	4	6	8	10
3	PVP K 30	10	10	10	10	10
4	Talc (TC)	10	10	10	10	10
5	Magnesium Stearate (MGS)	20	20	20	20	20
6	Microcrystalline Cellulose (MCC)	48	46	44	42	40
Total Weight (mg)		100	100	100	100	100

RESULTS AND DISCUSSION:

Preformulation Studies

Table No. 5: Organoleptic characterization of drug

Characters	Observations
Colour	White to off-white
Texture	Crystalline powder
Taste	Tasteless
Odour	Odourless
pH	Weak base

Table No. 5: Solubility check of drug

Solvents	Solubility
Water	Sparingly soluble
Ethanol	Freely soluble
Methanol	Freely soluble
Acetone	Soluble

Melting Point Determination: Melting point determination is another essential technique used to assess the purity and identification of a medication. The melting point range of a solid substance can be found by

measuring its temperature, and its identity can be verified by comparing the resultant value with known values. Gliclazide is a crystalline solid that exhibits a melting point of about 168.95 ± 0.969 ^{O}C.

Loss on Drying: The loss on drying was found to be 0.47% w/W.

Partition Coefficient: The partition coefficient of Gliclazide is found to be 2.10, indicating that gliclazide is moderately lipophilic and has good permeability across membranes; this value suggests a relatively high ability to distribute between an oily phase (octanol) and water.

Determination of Maxima Absorbance of Gliclazide

For identification of drug, first of all drug 50 mg dissolved in 100 ml of water and then we took 3 ml of solution in 25 ml volumetric flask and volume make up to 25 ml PBS (pH: 6.8) after that rinse the cuvette with methanol subsequently. Then after absorption maxima recorded by the U.V. spectrophotometry and wavelength range were selected between 200-400 nm. The λmax of Gliclazide in PBS (pH: 6.8) was measured in Shimadzu 1800 UV/visible spectrophotometer was found to be 229 nm (Figure 3).

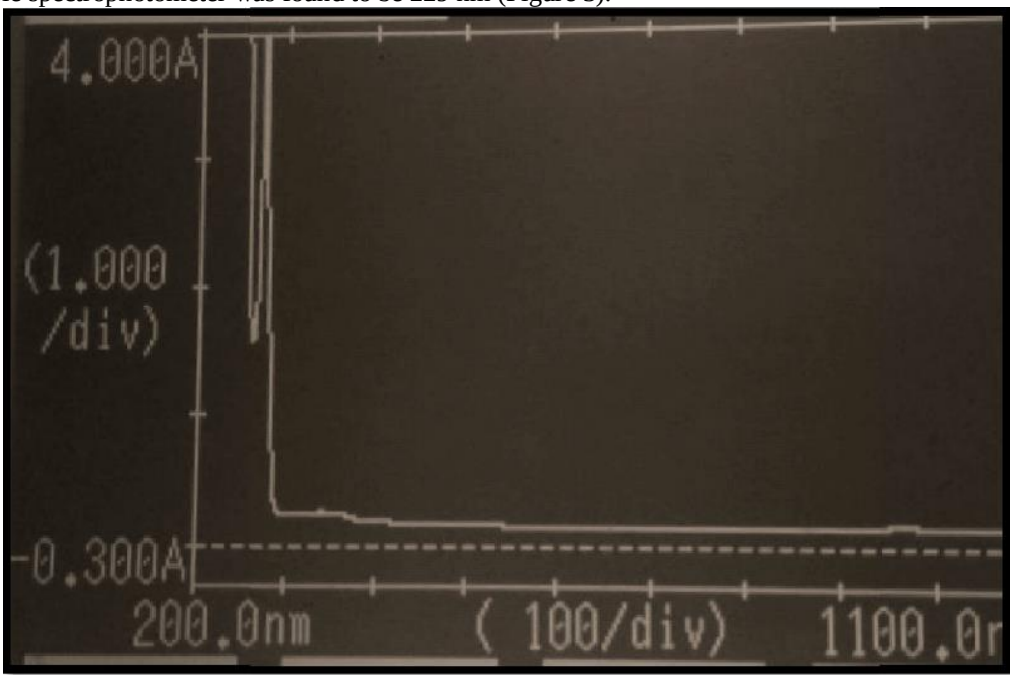

Figure 3: Determination of Maxima Absorbance of Gliclazide

Calibration curve of Gliclazide: The scan of Gliclazide solution in UV region (200-400) was performed to check the wavelength of maximum absorption (λ max). The λmax was found to be at 330 nm. Hence calibration curve of Mesalamine was constructed at 229 nm in pH 6.8 phosphate buffer by taking concentration on x-axis and absorbance on y-axis. The calibration curve showed the regression coefficient of 0.996 and found to be linear in the concentration range of 2 to 10 µg/ml.

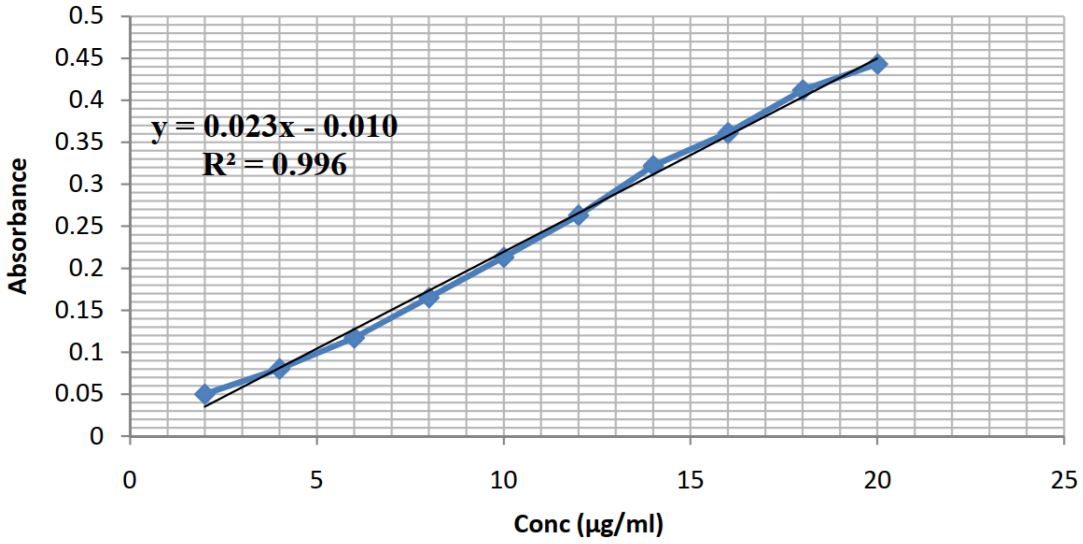

Figure 4: Calibration curve of Gliclazide in pH 6.8 phosphate buffer

FTIR Spectra of Gliclazide: The FTIR spectrum of gliclazide typically displays characteristic peaks corresponding to various functional groups present in the molecule. For example, the presence of a strong absorption peak around 1700 cm-1 is indicative of the carbonyl group present in the drug's chemical structure. Other peaks at specific wavenumbers can provide information about the presence of aromatic rings, aliphatic chains, and other structural features. By comparing the FTIR spectrum of gliclazide with reference spectra or theoretical predictions, researchers can confirm its identity and purity. Furthermore, changes in the FTIR spectrum may indicate potential interactions with other compounds or degradation processes that could affect the drug's stability or efficacy.

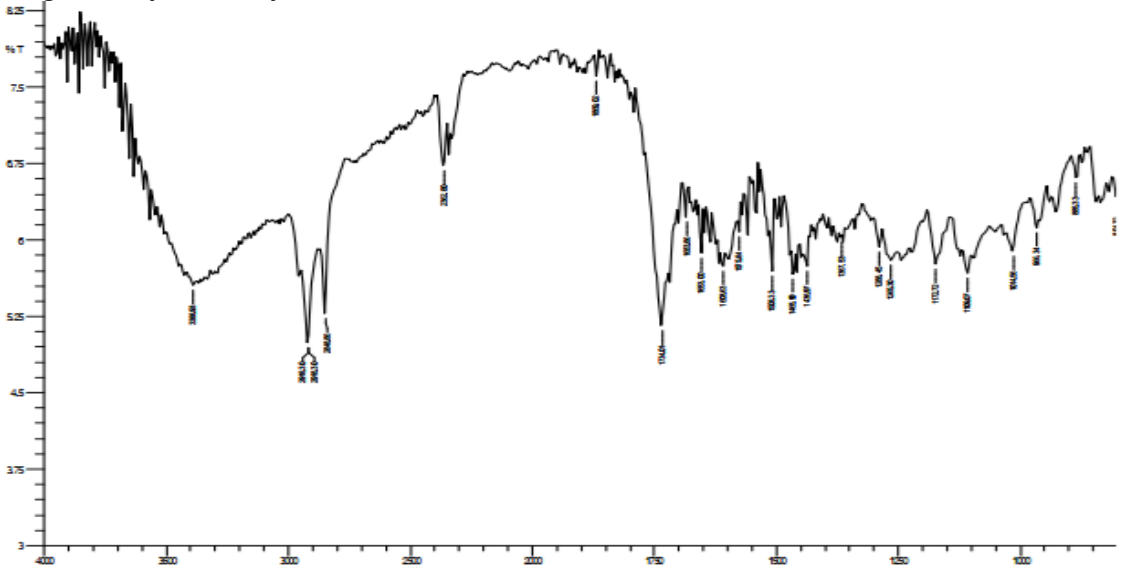

Figure 5: FTIR Spectra of Gliclazide

Evaluation Parameters:

Precompression Evaluation of powder blended characteristics of tablet formulation

Table No. 6: Physical properties of powder blends of single unit tablet formulations

Formulation	Angle of repose	Bulked Density	Compressibility index	Hausner's Ratio	Tapped Density
F1	29.6 ± 0.055	0.399 ± 0.545	17.7 ± 0.044	1.02 ± 0.856	0.491 ± 0.216
F2	29.5 ± 0.452	0.399 ± 0.056	18.9 ± 0.140	1.04 ± 0.044	0.495 ± 2.123
F3	30.5 ± 0.245	0.398 ± 0.056	20.9 ± 0.141	1.26 ± 0.056	0.499 ± 1.056
F4	29.2 ± 0.542	0.403 ± 1.556	18.1 ± 0.145	1.29 ± 0.245	0.495 ± 1.056
F5	31.8 ± 0.575	0.401 ± 0.185	17.3 ± 0.142	1.03 ± 2.056	0.491 ± 0.216

Post-compression Evaluation of Tablet formulation

Table No. 7: Postcompression Evaluation of Tablet formulation

Formulations	Drug Content Assay (%)	Disintegration Time (sec)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Weight Variation (mg)
F1	99.45 ± 0.076	42 ± 0.106	5.98 ± 0.056	0.32 ± 0.666	3.015 ± 0.460	98.24 ± 1.254
F2	99.65 ± 0.056	45 ± 0.486	6.15 ± 0.156	0.32 ± 0.106	2.214 ± 0.116	99.23 ± 1.256
F3	99.55 ± 0.996	47 ± 0.886	6.01 ± 0.106	0.33 ± 0.666	2.145 ± 0.416	100.54 ± 1.056
F4	99.55 ± 0.006	44 ± 0.926	5.98 ± 0.046	0.33 ± 0.126	3.152 ± 0.106	100.48 ± 2.551
F5	99.45 ± 0.106	38 ± 0.916	6.01 ± 0.116	0.29 ± 0.116	2.153 ± 0.456	100.69 ± 1.554

***In vitro* drug release studies:**

All the formulations batches were subjected to in-vitro dissolution studies using pH 6.8 phosphate buffer. The present drug release of all formulation was determined in pH 6.8 phosphate buffer at the interval of 2,4,8,6,10,15,20 minutes. Data of present drug release in phosphate buffer is shown in table 6.8 and plot for

dissolution profile of all the formulations. Among all formulations, F5 formulation containing highest concentration of superdisintegrant and sublimating agent showed fastest drug release within 10 minutes compared to other formulations.

Table No. 8: *In-vitro* drug release studies

Time Slots (minutes)	F1	F2	F3	F4	F5
2	5.54 ±0.606	32.41 ±1.756	36.26 ±0.356	35.45 ±0.476	41.15 ±0.325
4	11.65 ± 0.126	40.25 ±0.756	46.21 ± 0.116	45.54 ± 0.906	55.54 ± 1.206
6	29.25 ± 0.246	51.26 ± 0.006	56.95 ± 0.116	51.26 ± 0.325	63.55 ± 0.777
8	39.25 ± 0.216	59.35 ± 0.756	63.55 ± 0.756	69.35 ± 0.255	71.26 ± 0.245
10	49.25 ± 0.226	68.25 ± 0.756	70.26 ± 0.446	78.25 ± 0.222	83.26 ± 0.333
12	55.26 ± 0.176	76.14 ± 0.256	80.26 ± 0.126	86.14 ± 0.106	98.12 ± 0.112
15	63.25 ± 0.700	85.65 ± 0.516	95.12 ± 0.125	99.65 ± 0.756	-
20	74.25 ± 0.525	96.21 ± 0.745	99.91 ± 0.786	-	-

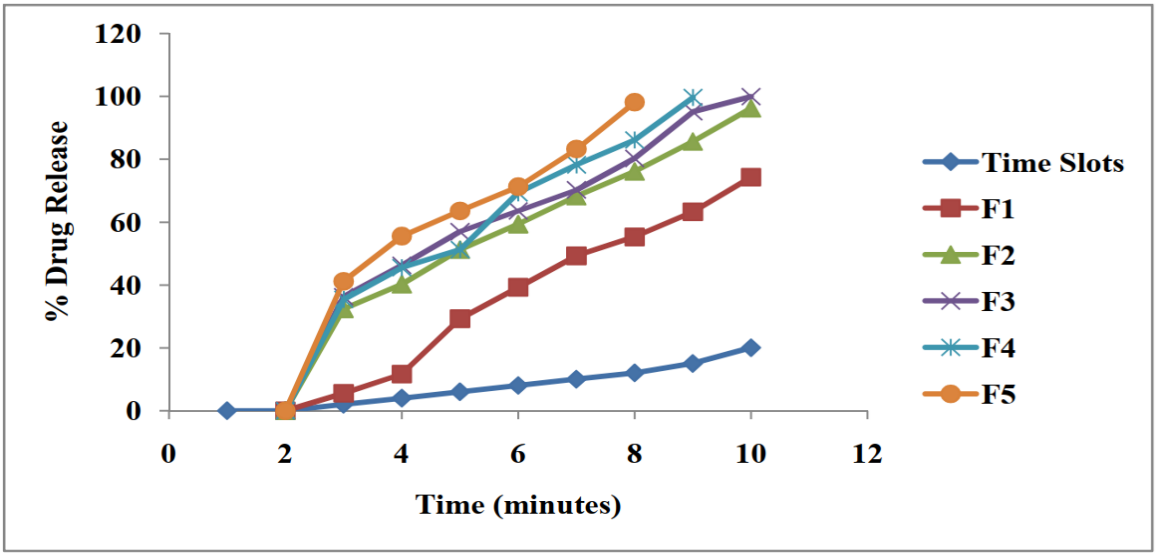

Figure 6: *In-vitro* drug release studies

Stability Studies

Stability Study of Optimized Batch (F5) is shown in Table 9. As per the data, it was concluded that tablet dosage form was stable enough till 6 months under the accelerated conditions as per the ICH.

Table No. 9: Stability Study of Optimized Batch (F5) under accelerated Conditions as per ICH guideline

Test parameters	Specifications	Initials	1st Month	3rd Month	6th Month
Description	Buff coloured coated spherical Tablets	Buff coloured spherical Tablets	No change	No change	No change
Moisture content	NMT 2.5	2.09	2.01	2.35	2.29
Assay (Drug Content)	NLT 90% and NMT 110% of label claim	93.90 ±0.23	98.56 ±1.73	99.56 ±0.73	98.06 ±1.33
% CDR at 5th hrs	NLT 90% and NMT 110% of label claim	97.98 ± 1.214	97.08 ± 0.514	97.88 ± 0.864	97.99 ±0.214
Friability	Not greater than 1 %	0.85	0.95	0.91	0.81
Microbial limit test	Total count < 102 CFU (As per USP)	Complies	Complies	Complies	Complies

CONCLUSIONS:

The oral administration is the most common and preferred route of drug delivery, due to benefits like, patient compliance and ease of administration. As for every drug to be taken through oral route, the solubility of the drug in the aqueous physiological fluids is the primary requisite to be taken to the task otherwise the drug having poor solubility will precipitate out without forming solution, thereby fails to elicit the particular pharmacological/therapeutic effect. The number of new drug entities with low aqueous solubility and dissolution rate has grown increasingly in the pharmaceutical arena over the decades due to high throughput screening and combinatorial chemistry techniques during the selection phase in the drug discovery. This has led to the tremendous increase in the number of new drugs with high molecular weight and lipophillicity, which is obviously beneficial for pharmacological action of the said drug molecule but simultaneously, renders the same drug entity poorly soluble. Almost, 70% of the new drug molecules discovered nowadays has solubility problems and 40% of the already developed drugs existing in the market as conventionally formulated commercial products face low bioavaliability issues due to erratic solubility behaviour of such drugs in physiological aqueous fluids and consequently many pharmaceutical companies have stopped formulating such drug candidates. So, to tackle the issue of low bioavailability of poorly soluble BCS Class II drug candidates, formulation scientists were pressed to come up with strategies to develop such compounds into therapeutically effective, orally bioavailable drugs. Among different solubility enhancing strategies explored over the years by various pharmaceutical researchers, solid dispersion technology is considered to be better than other strategies in terms of use of carriers having wide spread availability, safety and other outstanding properties like being in solid form provide the solid dispersion formulation stability over the extended period of time as compared to other solubility enhancing strategies. The majority of drugs are of poor water soluble and such compounds may exhibit insufficient dissolution throughout the gastrointestinal tract results in failing to achieve systemic acquaintance after oral administration. Fading bioavailability is the major cause for leaving inventive oral dosage forms. The applicability of the solid dispersion technique as an approach for improving the gastric absorption of drugs has been discovered in order to attain better dissolution characteristics and better bioavailability for poorly soluble drugs.

So, in the present study potential of the solid dispersion technology towards dissolution rate and oral bioavailability enhancement of Gliclazide was investigated.

The development and characterization of Gliclazide solid dispersion tablets is a crucial area of research in pharmaceutical science. Gliclazide is a widely used oral hypoglycemic agent for the treatment of type 2 diabetes. However, its poor solubility and bioavailability pose challenges for its effective delivery. Solid dispersion technology offers a promising solution to enhance the dissolution rate and bioavailability of poorly water-soluble drugs like gliclazide. In the formulation of gliclazide solid dispersion tablets, various techniques such as solvent evaporation, melting method, and kneading method are employed to improve drug solubility and stability. The physical characteristics, such as particle size, shape, and surface morphology, play a significant role in determining the drug release profile and overall performance of the tablets. Characterization studies including Fourier-transform infrared spectroscopy (FTIR) was conducted to evaluate the physicochemical properties of gliclazide solid dispersion tablets. These studies provide valuable insights into the molecular interactions between drug molecules and excipients in the formulation. The development of gliclazide solid dispersion tablets holds great potential for improving the therapeutic efficacy and patient compliance of this important antidiabetic medication. Further research into optimizing formulation parameters, such as excipient selection, drug loading capacity, and manufacturing process optimization, will contribute to advancing this innovative drug delivery system in clinical practice.

Further, solid dispersion technology is gaining huge potential to redress the low bioavailability problems of vast majority of the poorly soluble BCS Class II drugs due to continuous efforts of researchers globally to develop newer methods of manufacturing and search for most advanced hydrophilic carriers etc.

CONFLICTS OF INTERESTS

There are no any conflicts of interests

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