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IN-VIVO EVALUATION OF GLICLAZIDE SOLID DISPERSIONS INCORPORATED TABLETS FOR CONTROLLED DRUG RELEASE

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Keywords:

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ABSTRACT: Gliclazide is an anti-diabetic medication used to treat diabetes mellitus type 2.It suffers from deprived solubility, reduced drug dissolution, and bioavailability. The current paper is aimed to formulate and evaluate gliclazide solid dispersion with HP β Cyclodextrin for enhanced solubility and incorporate into controlled-release tablet formulation. Gliclazide solid dispersion (SD) was prepared using varying ratios of HP β Cyclodextrin and evaluated. The optimized SD formulation was incorporated into the tablet by using hydroxypropyl cellulose and HPMC K 100M. The formulation SD 3 was chosen based on solubility and evaluation parameters, hence formulated into a controlled release matrix tablet formulation. Around 15 formulations of controlled release tablet blends evaluated for micrometric properties demonstrate that all the formulations posses good flow properties. The controlled release tablet formulation F15 with maximum drug content of 99.99% and drug dissolution of 99.96 % over 16h was chosen optimal and characterized. *In-vivo* bioavailability studies of optimized formulation (F15) and marketed products are performed on rabbits. The C_{max} of the optimized formulation (132.56 ± 0.08ng/ml) was higher than the marketed product (98.73±0.063ng/ml), T_{max} of F15 and marketed product were found to be 6 and 4 h, respectively. $AUC_{0-\infty}$ infinity for F15 formulation was higher (464.21 ± 1.47ng.h/ml) than the gliclazide marketed formulation (353.8±0.82ng.h/ml). Statistically, AUC_{0-t} of the controlled release solid dispersion formulation was significantly higher ($p<0.05$) as compared to the Gliclazide marketed product formulation. The combination of SD and controlled release formulations of Gliclazide can facilitate prolonged action with better solubility, bioavailability, and greater patient acceptance.

INTRODUCTION: The extent of drug absorption from any drug delivery formulation largely depends on its rate of dissolution, solubility and bioavailability. For sparingly water-soluble drugs, the drug dissolution rate is the rate-limiting step that depends on the extent of drug solubility.

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The improvement of drug solubility is a challenging aspect of drug development process especially for oral-drug delivery system. There are various approaches reported in literature to enhance the solubility of poorly water-soluble drugs.

The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form [1]. The solid dispersions along with water insoluble and swell able polymer in developing of controlled release formulations is of great attention in recent past for

enhancing drug solubility and bioavailability. The controlled-release formulations are designed to achieve a therapeutically effective drug concentration. They can also be cost-effective, posses higher efficacy and reduce adverse effects [2]. In most cases, these formulations release initial large amounts of drug known as 'burst release'. Burst release leads to high initial drug concentration and reduces the delivery system's effective lifetime. Among various approaches for controlled drug release, the matrices prepared in insoluble polymers using the SD technique are proven effective. The controlled release SD formulations can bypass the risk of burst release as the drug is homogeneously dispersed in the SD formulation. The drug dissolution is also controlled by a matrix that comprises hydrophilic or hydrophobic polymeric excipients [3, 4]. Gliclazide is antihyperglycemic agent employed for the treatment of type -2 diabetics. It belongs to the oral hypoglycemics class used to control blood sugar in people suffering from type 2 diabetics [5, 6, 7]. Even though the drug displays 96% protein binding capacity, its deprived water solubility makes it difficult to attain the required therapeutic effect [8-13]. The current paper deals with the formulation and *in-vivo* bioavailability studies of controlled release matrix tablets of gliclazide SD (SDCR) for enhanced solubility and bioavailability.

MATERIALS AND METHODS:

Materials: The drug gliclazide was procured from Zhejiang Jiuzhou Pharmaceutical co. Ltd., China. The hydroxypropyl cellulose was purchased from Ashland, colloidal silicon dioxide from Evonik industries limited, HB β-Cyclodextrin was purchased from Cydex pharmaceuticals, microcrystalline cellulose (Avicel PH 101) was purchased from FMC International Health and Nutrition, polyvinylpyrrolidone (povidone K-30) from BASF and magnesium stearate from Nitika Pharmaceutical Specialties Pvt. Ltd.

Preliminary Solubility Studies: A little excess drug was transferred into a 50ml flask containing various concentrations of carriers *i.e* (1: 1, 1: 2, 1: 3) in distilled water. All flasks were sealed with a stopper and covered with a cellophane membrane to prevent solvent loss. The flasks were kept in the incubator shaker for 72 h.

After 72 h the content was filtered through Whatman filter paper, filtrate diluted and analyzed spectrophotometrically for gliclazide content at 230 nm [14].

Preparation of Gliclazide Solid Dispersions (SD): In this method, accurately weighed quantities of HP β Cyclodextrin in the stated proportions were carefully transferred into boiling test tubes and dissolved in acetone. To these solutions, accurately weighed quantities of Gliclazide were added and allowed to dissolve. The solution was transferred to a petridish, the solvent was allowed to evaporate at room temperature, and dispersions were dried at room temperature for 1 h, followed by drying at 65°C for 6h in a hot air oven. The mass obtained in each case was crushed, pulverized, and sifted through 100 mesh [14] **Table 1.**

TABLE 1: PREPARATION OF GLICLAZIDE SD

Formulation code	Gliclazide (mg)	HP β Cyclodextrin (mg)	Acetone (mg)
SD1	30	10	80
SD2	30	20	70
SD3	30	30	60

Evaluation of Gliclazide SD:

Solubility Studies*:* Solubility studies carried out by preparing suspensions of SD and agitating for 48 h, followed by filtration. The filtrate was estimated for Gliclazide at 230 nm using UV visible spectrophotometer [15].

Percentage Practical Yield (PPY) Estimation [16], % Drug Content Determination [17]: These studies were performed with reported methods.

In-vitro **Dissolution of Gliclazide SD:** The dissolution of Gliclazide from SDs prepared was investigated in 900 ml phosphate buffer of pH 6.8 in USP apparatus type II (paddle type) dissolution test maintained at stirring speed of 50 rpm, temperature of 37±0.5 °C. 5 ml aliquots of dissolution medium were drawn at an interval of 5 minutes and filtered through 0.45 µm filter. The equal volume of dissolution medium was replaced.

The collected sample solution is suitably diluted and assayed at 230 nm [18, 19].

Formulation of Gliclazide SD Incorporated Controlled-Release Tablets:

Pre-compression Parameters: The lubricated blend was evaluated for angle of repose, Carr's index, bulk and tapped density, Hausner's ratio [20-22] as per the referred procedures.

Preparation of Gliclazide SD Controlled-Release Tablets: The gliclazide SD controlled-release tablets were prepared by wet granulation method **Table 2** [23]. Gliclazide SD equivalent to 40 mg of gliclazide in weight was chosen for formulation. This hydroxypropyl cellulose and HPMC K100 M were used as rate controlling polymers. Microcrystalline cellulose was used as the diluent; colloidal silicon dioxide was used as glidant with magnesium stearate was used as a lubricant. Accurate quantity of the Gliclazide, microcrystalline cellulose, hydroxypropyl cellulose (klucel EXF), hydroxypropyl methylcellulose (HPMC K-100M), colloidal silicon dioxide, magnesium stearate were weighed, and sieved through #40 separately. The mixture was then granulated with purified water in which povidone was dissolved. The wet mass dies in a hot air oven, and then it is lubricated with colloidal silicon dioxide, and magnesium stearate, and the lubricated blend is compressed into tablets.

TABLE 2: FORMULATION TABLE OF GLICLAZIDE CONTROLLED RELEASE TABLETS

Code	Gliclazide+HP β Cyclodextrin complex (mg)	Avicel PH 101 (mg)	Klucel EXF (mg)	HPMC K100M (mg)	Povidone K-30 (mg)	Purified Water	silicon dioxide (mg)	Magnesium Stearate (mg)	Tablet weight in mg
F1	120	111	5	4	5	Qs	3	2	250
F2	120	107	5	8	5	Qs	3	2	250
F3	120	103	5	12	5	Qs	3	2	250
F4	120	94	10	16	5	Qs	3	2	250
F5	120	90	10	20	5	Qs	3	2	250
F6	120	86	10	24	5	Qs	3	2	250
F7	120	77	15	28	5	Qs	3	2	250
F8	120	73	15	32	5	Qs	3	2	250
F9	120	69	15	36	5	Qs	3	2	250
F10	120	60	20	40	5	Qs	3	2	250
F11	120	56	20	44	5	Qs	3	2	250
F12	120	52	20	48	5	Qs	3	2	250
F13	120	43	25	52	5	Qs	3	2	250
F14	120	39	25	56	5	Qs	3	2	250
F15	120	34	25	60	5	Qs	3	2	250

Evaluation of gliclazide SD incorporated controlled-release tablets: Average weight, hardness, thickness, weight variation, and friability were recorded as per the referred procedures [24, 25].

***In-vitro* Drug Dissolution:** The dissolution study of all tablets was carried out using USP apparatus II with 900 ml phosphate buffer (pH 6.8) as dissolution medium at 37±0.5ºC and 50 rpm. Aliquots of the dissolution medium were withdrawn at an interval of 5 minutes and filtered through 0.45 µm filter. The equal volume withdrawn was replaced with a fresh dissolution medium. The collected sample solution is suitably diluted and assayed against a suitable blank using a UV-visible spectrophotometer (T60 PG Instruments) at 243 nm and the drug release was compared with the pure drug [19].

Pharmacokinetic Study of Gliclazide:

Animal Preparation*:* Twelve New Zealand white rabbits of either sex (2–3 kg) were chosen for study and ensured that the animals remained healthy throughout the experiment. The rabbits were kept at 25°C, 45% relative humidity, and 12 h of light and dark cycles with 100% fresh air exchange and an uninterrupted power, and water supply. The animals were fed with a standard diet and water ad libitum. An in vivo pharmacokinetic study was conducted according to Animal Ethics Committee bearing no: 1722/RO/Ere/S/13/CPCSEA.

Study Design: All the 12 animals were divided into 2 equal groups. Group A was fed with gliclazide optimized formulation, and Group B was fed with a marketed product with a dosage equivalent to the weight of the animal body [26].

Blood sampling: About 0.5 ml of blood was drawn with a syringe from a marginal ear vein at regular intervals 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20, and 24 h post doses. The samples mixed with heparin to hamper blood clotting.

The plasma was separated by centrifugation of samples at 7500 rpm for 20 min, stored at −20°C for analysis.

Determination of Gliclazide in Rabbit Plasma by HPLC:

HPLC Analysis: HPLC analysis was performed on C18 column (250 mm X 4.6 mm X 5 µm). The mobile phase comprises of ACN and phosphate buffer (pH 6.8) in 50:50 v/v ratio.

A flow rate of 1 mL/min, column pressure of 150-200 Kg/cm^2 and column temperature of 35°C was maintained. The injection volume was 20 µL over a run time of 10 min. The eluents were analyzed at 230nm by PDA detector [27].

Determination of Pharmacokinetic Parameters: Pharmacokinetic parameters such as peak plasma concentration (C_{max}), time at which C_{max} occurred (T_{max}), area under the curve (AUC), biological half-life ($t_{½}$), and bioavailability were calculated using the plasma drug concentration data [28].

The pharmacokinetic parameters were performed by non-compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean ±SD.

Statistical Analysis: Statistical analysis was performed with Graph Pad In-Stat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. The difference with $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION:

Preliminary Solubility Studies of Gliclazide: The pure Gliclazide exhibits maximum solubility in 6.8 pH phosphate buffer (1.68 mg/ml). The solubility of Gliclazide and HP β Cyclodextrin physical mixture show that 1:3 ratio of the mixture exhibited higher solubility (1.16 mg/ml), which was almost 16-fold increase than that of pure drug **Table 3.**

TABLE 3: PHASE SOLUBILITY STUDIES

Polymer	Drug: Polymer Ratio	Solubility (mg/ml)
Pure drug		0.07±0.87
Xanthan gum	1:1	0.8±1.75
Xanthan gum	1:2	0.84±1.24
Xanthan gum	1:3	0.92±0.89
Hupu gum	1:1	0.85±1.27
Hupu gum	1:2	0.94±1.94
Hupu gum	1:3	1.04±0.37
Methyl cellulose	1:1	0.84±1.83
Methyl cellulose	1:2	0.95±1.88
Methyl cellulose	1:3	1.03±1.26
HP β Cyclodextrin	1:1	0.84±1.14
HP β Cyclodextrin	1:2	0.94±1.85
HP β Cyclodextrin	1:3	1.16±1.62
Povidone	1:1	0.632±1.51
Povidone	1:2	0.84±1.47
Povidone	1:3	1.01±1.52
HPC	1:1	0.448±1.89
HPC	1:2	0.52±1.72
HPC	1:3	0.62±1.26
Captisol	1:1	0.79±1.26
Captisol	1:2	0.85±1.15
Captisol	1:3	0.94±0.63

Preparation of Gliclazide SD: The Gliclazide SDs prepared by adopting the solvent evaporation method by employing varying amounts of polymers **Table 2**. The gliclazide SD comprising HP β Cyclodextrin (SD3) exhibited greater solubility of 3.01±0.16 mg/ml which was almost 43-fold increase when compared to pure drug solubility (0.07±0.87 mg/ml) **Table 4.**

TABLE 4: SOLUBILITY STUDIES OF GLICLAZIDE SOLID DISPERSIONS (SD1-SD3)

Gliclazide solid dispersion	Solubility (mg/ml)
Pure drug	0.07±0.87
SD1	2.68±0.29
SD2	2.82±0.20
SD3	3.01±0.16

Percentage Practical Yield (PPY) and Drug Content of Gliclazide SD: The PPY for all gliclazide SD's found to be within 94.98±0.21%-98.61±0.21%. A maximum yield of 98.61±0.21% observed for formulation SD 3. The drug content in all gliclazide SD's lie within 95.63±0.26-99.33±0.26% with SD 3 exhibiting maximum drug content.

***In-vitro* Drug Dissolution Studies of Gliclazide SD:** A significant increase in drug dissolution rate is observed in all the formulated SDs of Gliclazide in comparison to pure drugs.

The formulation SD3 exhibiting highest dissolution rate of 99.82±1.41% **Fig. 1**. Hence 1: 3 ratio of Gliclazide and HP β Cyclodextrin solid dispersion (SD3) was further chosen for characterization.

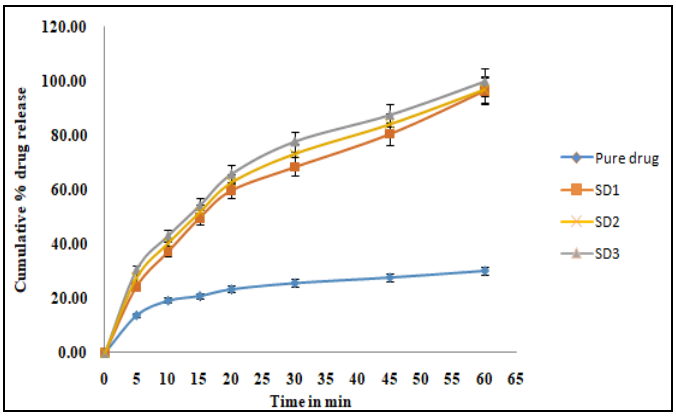

FIG. 1: *IN-VITRO* DRUG DISSOLUTION OF PURE GLICLAZIDE AND SD1-SD3

Preparation of Gliclazide SD Incorporated Controlled-Release Tablets: All the fifteen formulations of Gliclazide controlled-release tablets (F1-F15) were round in shape, white in color with smooth appearance **Table 2.**

Evaluation of Gliclazide SD Incorporated Controlled-Release Tablets: The bulk densities of F1 to F15 were measured and ranged between 0.445±0.72g/cc³ to 0.518±0.48g/cc³.

The tapped density ranged from 0.512±0.31g/cc³ to 0.608±0.39g/cc³. The angle of repose of F1-F15 was good, with F15 displaying an optimal value of 24.85 ± 0.82^0 having excellent flow property. The compressibility index ranged between 8 to 15 %. These findings show that all the formulation blends possessed desirable flow properties.

Physical Evaluation of Gliclazide SD Incorporated Controlled-Release Tablets: The results of the physical tests of the prepared blends were within limits. The weight variation of all the formulations is within limits.

The hardness of formulations F1 to F15 ranged between 9.0 to 11.0 kg/cm^2. The thickness of all tablet formulations is uniform with values ranging between 3.3-3.5 mm.

The friability value ranged between 0.13-0.22. The drug content of all formulations varied between 96.1-99.99%, with the highest value exhibited by F15 formulation.

***In-vitro* Drug Dissolution Study:** Due to the high viscosity of rate-controlling polymers (HPMC K 100 M and klucel EXF) used in the formulation, sustained release of Gliclazide was achieved. Formulation F15 containing a higher amount of rate-controlling polymers, exhibited the highest drug release of 99.96% up to 16h, whereas the marketed product released 98.12% up to 12 h. Hence, out of all formulations F15 is selected as the best optimized formulation and further studied for its characterization **Fig. 2, 3.**

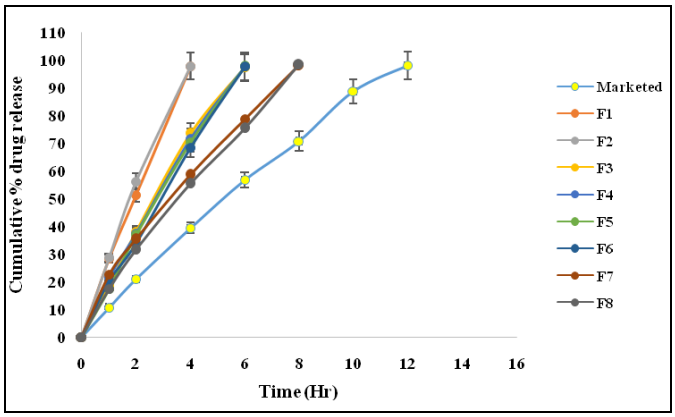

FIG. 2: % DRUG RELEASE OF GLICLAZIDE TABLET FORMULATION (F1 TO F8) AND MARKETED PRODUCT. Above parameters are communicated as average ± standard deviation; (n=3).

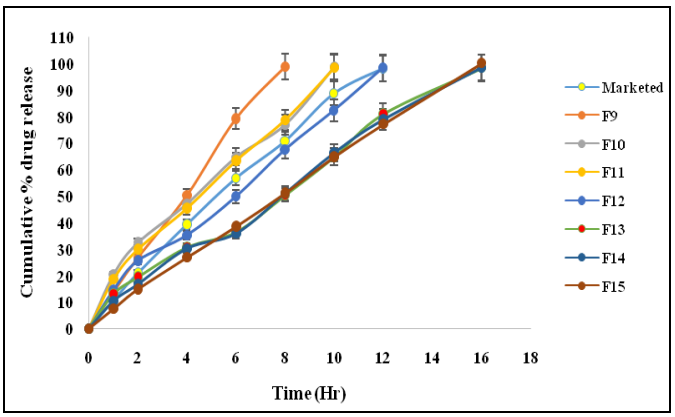

FIG. 3: % DRUG RELEASE OF GLICLAZIDE TABLET FORMULATIONS F9 TO F15 AND MARKETED PRODUCT. Above parameters are communicated as Average ± Standard Deviation; (n=3).

***In-vivo* Bioavailability Studies:** The Gliclazide and internal standard (glipizide) were observed at 7.4 and 4.5 min RT respectively, without any intrusion of endogenous compounds in the plasma **Fig. 4.**

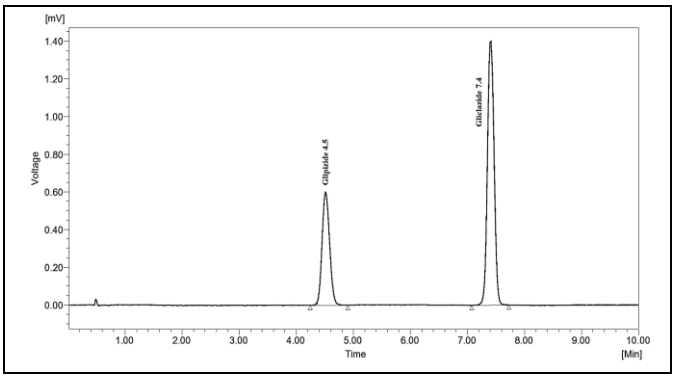

FIG. 4: STANDARD HPLC CHROMATOGRAM OF GLICLAZIDE AND GLICLAZIDE IN RABBIT PLASMA

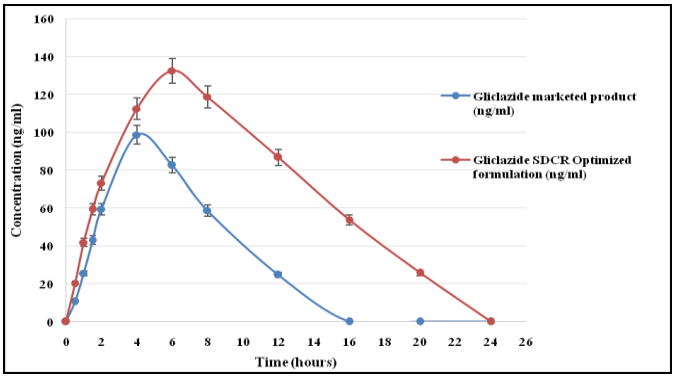

FIG. 5: PLASMA CONCENTRATION PROFILES OF GLICLAZIDE SDCR AND MARKETED PRODUCT IN RABBIT PLASMA

Gliclazide concentrations in plasma following oral administration of Gliclazide marketed product and optimized gliclazide SDCR administered oral route and respective plasma concentration-time curves are shown in **Fig. 5**. From *in-vivo* bioavailability studies the C_{max} of the optimized formulation F15 was (132.56±0.08ng/ml) significant ($p<0.05$) as compared to the Gliclazide marketed product formulation (98.73±0.063ng/ml). T_{max} of both F15 and Gliclazide marketed products was 6.0±0.07h and 4.0±0.04h, respectively. $AUC_{0-\infty}$ infinity for the F15 formulation was higher (464.21±1.47ng.h/ml) than the Gliclazide marketed product formulation 353.8±0.82ng.h/ml. Statistically, AUC_{0-t} of the F15 formulation was significantly higher ($p<0.05$) than Gliclazide marketed product formulation. A higher amount of drug concentration in blood indicated better systemic absorption of Gliclazide from F15 formulation when compared to the gliclazide marketed product, and also *in-vivo* pharmacokinetic studies in rabbits confirmed the prolonged-release by showing an increase in bioavailability for Gliclazide from F15 formulation as compared to the Gliclazide marketed product formulation **Table 5.**

TABLE 5: PHARMACOKINETIC PARAMETERS

Pharmacokinetic parameters	Gliclazide marketed product	Gliclazide– SDCR Optimized Formulation (F15)
C_{max} (ng/ml)	98.73±0.063	132.56±0.08
AUC_{0-t} (ng. h/ml)	232.3±1.04	352.4±1.74
AUC_{0-inf} (ng. h/ml)	353.8±0.42	464.21±1.37
T_{max} (h)	4.0±0.03	6.0±0.06
$t_{1/2}$ (h)	4.20±0.02	7.692±0.04

CONCLUSION: In the current research, the SD tablets of Gliclazide were formulated using hydrophilic polymer and hydrophobic polymer for controlled drug release. The gliclazide SD was prepared using HP β Cyclodextrin (1:3) and evaluated for percentage yield, drug content, and drug release. The formulation SD3 with higher values of drug content and drug release of 99% was chosen optimally for incorporating into tablet formulation by wet granulation technique. The controlled release tablet blend was initially evaluated for pre-compression parameters, and results show that formulation F15 exhibited excellent flow properties. The post-compression parameters were also found within acceptable limits. The drug release of F15 was found to be 99% extended over a period of 16h, while the marketed formulation released about 98% of the drug in 12h. In-vivo bioavailability studies of optimized formulation (F15) and marketed products are performed on rabbits. From *in-vivo* bioavailability studies, the C_{max} of optimized formulation (132.56±0.08ng/ml) is higher than the marketed product (98.73±0.063ng/ml), T_{max} of F15 and marketed product of Gliclazide was found to be 6 and 4 h respectively. $AUC_{0-\infty}$ infinity for the F15 formulation was higher (464.21±1.47ng.h/ml) than the Gliclazide marketed product formulation (353.8±0.82ng.h/ml). Statistically, the AUC_{0-t} of the SDCR formulation was significantly higher ($p<0.05$) as compared to Gliclazide marketed product formulation. The combination of solid dispersion and application of hydrophilic and hydrophobic polymers in matrix tablets of

Gliclazide can facilitate prolonged action with better solubility, bioavailability and greater patient compliance.

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CONFLICTS OF INTEREST: Nil

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