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Research Article

Liquisolid Compact of Gliclazide for Enhanced Dissolution and Oral Bioavailability

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ABSTRACT

Drug actions can be improved by developing new drug delivery systems; one such Liquisolid compact of gliclazide was prepared with the intension of improving the dissolution properties of gliclazide. Polyethylene glycol (PEG), Propylene glycol (PG) and mixture of both were used as non volatile liquid. The dissolution studies of the liquisolid compacts were performed *in vitro*, and the results obtained showed that the dissolution rate of gliclazide was considerably improved when formulated in liquisolid compact with PG and PEG as compared to original drug, and the increased dissolution rate favorable for further oral absorption. In the comparative pharmacokinetic study with gliclazide suspension, a reference drug product, liquisolid system (LS1-A3) showed improved bioavailability with higher Cmax and faster Tmax. We conclude that liquisolid system (LS1-A3) is a good candidate for the development of oral solid dosage forms.

INTRODUCTION

About 40% of the drug candidates identified via combinatorial screening programmes are poorly water soluble [1]. The dissolution rate is the rate-limiting factor in drug absorption for class II (low solubility and high permeability) and class IV (low solubility and low permeability) drugs as defined in the Biopharmaceutics classification system, BCS [2]. Poorly water-soluble drugs are difficult to formulate using conventional techniques. Different techniques have been reported in the literature to achieve better drug dissolution rates. For example, (a) reduce the particle size via micronisation or nanonisation to increase the surface area; (b) use of surfactants; (c) inclusion with cyclodextrins; (d) use of pro-drug and drug derivatisation; (e) formation of solid solutions or amorphous solids and (f) microencapsulation and inclusion of drugs into softgel or specially sealed hard gelatin capsules. Drawback of all these techniques is their poor scale-up for the purposes of commercial manufacturing.

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Among various techniques to overcome the solubility issue, several researchers reported that the formulation of liquisolid tablets is one of the promising techniques for promoting drug dissolution. The concept of ‘‘liquisolid tablets” was evolved from ‘‘powdered solution technology” that can be used to formulate ‘‘liquid medication”. The term ‘‘liquid medication” refers to solid drugs dispersed in suitable non-volatile liquid vehicles. By simple mixing of such ‘‘liquid medication” with selected carriers and coating materials, dry-looking, non-adherent, free-flowing and readily compatible powder admixtures can be produced that makes liquisolid technique advanced to others [3]. The prepared liquisolid powder system has acceptable flowability and compressibility which is advantageous to others methods. Gliclazide is a second-generation sulfonylurea that can lower the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat type II diabetes (non-insulin dependent diabetes mellitus.

EXPERIMENTAL

MATERIAL AND METHODS

Gliclazide was obtained from Bal Pharmaceutical, Banglore, India, Microcrystalline Cellulose 102 (Avicel PH 102) and Sodium Starch Glycolate

(Explotab) both were obtained from JRS Pharma, (Rosenberg, Germany), Colloidal Silicon Dioxide-Aerosil 200 (SD-Fine, India), Propylene Glycol (PG), Polyethylene Glycol 400 (PEG 400) all were obtained from Merck Germany, All other reagents and chemicals were of analytical grade.

Solubility Studies

Solubility studies of gliclazide were carried out in different non-volatile solvents, i.e. PG, PEG 400 & their admixture. Also distilled water and SGF were used to study solubility behavior of gliclazide. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the orbital incubating shaker (Remi International, India) for 24 hours at 25^{0}C under constant vibration of speed 50 rpm. After this period the solutions were filtered through a 0.45 µm Millipore filter, diluted with distilled water and analyzed by UV-spectrophotometer (Shimadzu-1700, Japan) at a wavelength of 228.5 nm against blank sample (blank sample contained the same concentration of specific solvent used without drug). Three determinations were carried out for each sample to calculate the solubility of gliclazide.

Calculation of the Loading Factor (Lf)

To calculate the loading factor, drug was dissolved in the PG, PEG 400 and PG-PEG 400 mixtures. Each of the above system was added to microcrystalline cellulose (MCC) as a carrier material and blended for 10 min using double cone blender (Karnavati, India). By using *L*f =*W*/*Q* formula (*W*: amount of liquid medication and *Q*: amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. The preliminary results showed that if the viscosity of the carrier was higher, lower amounts of microcrystalline cellulose powder are needed to produce flowable powder.

Pre Compression Parameters of Liquisolid Powders

Flow properties of the powders were evaluated by determining the angle of repose. Static angle of repose was measured according to the fixed funnel and freestanding cone method. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip 10 cm height, *H*, above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reaches the tip of the funnel. The mean diameter, 2 *R*, of *H*, base of the powder cone, was determined and the tangent of the angle of repose was given by: $\tan \alpha = H/R$ Where α is the repose angle.

Liquisolid powder admixtures were characterized for their physical parameters such as density, compressibility and Hausner's ratio.

Drug Excipients Compatibility Studies

Physical mixtures of drug and polymer were filled in the prewashed ampoules and sealed. The sealed ampoules were kept at 37 ± 0.5^{o}C for 28 days in stability chamber (Remi Lab, Mumbai). At the end of 28 days ampoules were removed from stability chamber and proceed for drug-excipients compatibility study. It was carried out by using Infrared spectroscopy and TLC.

Formulation of Gliclazide Liquisolid Tablets

In order to attain optimal gliclazide solubility in the liquisolid formulations, the concentration of the drug in the non-volatile solvent is 40 % W/W. The outline of the constituents of each of the formulae prepared is given in Table 1.

Drug and liquid vehicle were mixed and heated to 80–90^{0}C with constant stirring, the solution was then sonicated for 15 min, and until a homogenous drug solution was obtained. Then, the calculated weights of the resulting liquid medications were incorporated into the calculated quantities of the carrier material MCC (Avicel PH 102), after mixing, the resulting wet mixture was then blended with the calculated amount of the coating material (Aerosil 200) using a standard mixing process that was previously described by [9,10] to form simple admixture. The liquisolid mixture was blended with 4% of the disintegrant, explotab® (sodium starch glycolate). The prepared liquisolid systems that were proven to have simultaneous acceptable flowability and compressibility were compressed into cylindrical tablets of desired weight using a multi-station tablet press machine (Rimek, India). The required quantities of excipients incorporated were calculated from the application of 'new formulation mathematical model of liquisolid systems.

Characterization

***In vitro* Dissolution Studies**

In vitro dissolution studies were carried out by using USP XXIV type II apparatus. Liquisolid compact was added to 900mL of phosphate buffer (pH 1.2) maintained at 37±0.5^{o}C and agitated at 50rpm. An aliquot of 5mL was

withdrawn at predetermined time intervals 15, 30, 45, 60, 90, and 120 min with a syringe filter. The withdrawn volume was replaced immediately with same volume of dissolution medium to maintain total volume constant. The filtered samples were assayed spectrophotometrically at 228.5 nm. The mean of at least three determinations were used to calculate the drug dissolved.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) was performed on gliclazide, physical mixture, and liquisolid tablets. DSC measurement performed on DSC60 Shimadzu, Japan. Thermal behavior of the samples was investigated under a scanning rate of 10°C/min, covering a temperature range of 50 to 300°C under inert atmosphere flushed with nitrogen at a rate of 100C/min.

X-ray Diffractometry (XRD)

The crystallinities of gliclazide was evaluated by XRD measurement recorded for gliclazide, liquisolid formulation, physical mixture of gliclazide and excipients using x-ray diffractometer (PW3710, Philips diffractometer) and Cu-Kα line as a source of radiation which was operated at the voltage 40 kV and the current 30 mA. All samples were measured in the 2θ angle range between 00 and 1000 with a scanning rate of 30 /min and a step size of 0.020.

***In vivo* Bioavailability Study**

All animal experiments were approved and performed in accordance with the guidelines of Institutional Animal Ethics Committee (Registration No: 651/02/C/CPCSEA under CPCSEA, India).

Study Design

The New Zealand white rabbits were selected as an experimental model because it provides a well controlled animal model for bioavailability studies of formulations. In a crossover study with one week apart as wash out period, one group received pure drug (gliclazide) whereas the other group received liquisolid powders (LS1-A3). Pure drug and liquisolid compact equivalent to dose were mixed in distilled water separately and this solution administered orally to the rabbits with the help of syringe. Blood samples (1mL) were collected using 27 gauge needle from the marginal ear vein into heparinized tubes at time intervals of 0, 0.25, 0.5, 0.75, 1, 1.5, 2, and 3 hours after administration of the drug. The blood was immediately centrifuged at 6000 rpm for 10 minutes to separate the plasma and stored at -20 0C until analysis [11].

Sample Processing

Stock solution of drug was made in methanol and five dilutions were prepared with conc. 100ng/50µL, 200ng/50µL, 300ng/50µL, 400ng/50µL, 500ng/50µL.These solutions were spiked into plasma to get spiked plasma solutions. Acetonitrile (0.5mL) was added to 0.5 mL of spiked plasma solutions and vortexed for 10 sec., chloroform (4mL) was added and shaken for 1 min. Then the mixture was centrifuged at 3000 rpm, organic layer obtained was transferred to a clean glass test tube and air dried overnight. The residue obtained was redissolved in 0.5mL of methanol. About 50 µL of samples were filled in micro well UV plate and analyzed using micro titer plate spectrophotometer (USA Biotek) at 227 nm, against the blank (linearity range 100-500 ng/ml, r^2=0.992,Y=0.01X+0.005).

Same procedure was applied for the plasma samples obtained after administration of dose to animals at particular time interval were proceed as per same procedure.

Data Analysis

The maximum plasma concentration (C_{max}) and time of its occurrence (T_{max}) were directly computed from the plasma concentration Vs time plot. The area under curve (AUC) was determined from the software of Thermo Kinetica 5 (Thermo Fisher Scientific).

% relative bioavailability of test product (F) = $AUC_{test}/AUC_{std} \times 100$

Stability Study

To assess the effect of environmental condition or storage conditions on formulation. Optimized batch LS1-A3 was kept in environmental stability chamber (Remi Lab, Bombay) for accelerated stability condition at 40°C ± 2°C temperature and 75 ± 5% relative humidity for a period of 3 months. The samples were withdrawn at 1, 2 and 3 months interval and evaluated for drug content and *in vitro* drug dissolved [12].

RESULT AND DISCUSSION

Solubility Studies of Drug with Different Solvents

The solubility of gliclazide in various solvents is given in Table 2, shows that the solubility of gliclazide was increased by the presence of non-

Table 1: The composition of different gliclazide liquisolid formulations

Formulation Code	Batches	Gliclazide Concentration in liquid vehicle (W) (%W/W)	L_f	R	Avicel PH-102 (Q) (in mg)	Aerosil 200 (q) (in mg)	Unit dose Weight (in mg)
LS-1	A1	40	0.33	5	303.03	60.60	482.63
	A2	40	0.28	10	357.14	35.71	502.85
	A3	40	0.26	15	384.61	25.64	530.25
LS-2	B1	40	0.37	5	270.27	54.05	442.32
	B2	40	0.30	10	333.33	33.33	485.66
	B3	40	0.28	15	357.14	23.80	500.00
LS-3	C1	40	0.35	5	285.71	57.14	460.85
	C2	40	0.29	10	344.82	34.48	499.31
	C3	40	0.27	15	370.37	24.69	515.06

LS-1: Propylene glycol, L-2: Polyethylene glycol, LS-3: Propylene glycol and polyethylene glycol admixture. A1- R= 5, A2- R= 10, A3-R= 15

L_f: Liquid load factor; R: Ratio of carrier material (Q) to coating material (q) [R=Q/q]; carrier material (Q); coating material (q).

Table 3: Precompression parameters of and liquisolid powder admixtures

Physical mixture	Angle of repose (θ)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausner's Ratio (HR)	Compressibility Index (%)
A1	32.26±1.4	0.15±.031	0.18±.036	1.25±0.05	20
A2	34.58±1.5	0.16±.037	0.19±.078	1.18±0.03	18.75
A3	33.34±1.8	0.21±0.05	0.24±0.04	1.14±0.05	14.28
B1	32.67±1.6	0.19±.048	0.23±.042	1.21±0.03	21.05
B2	34.45±1.3	0.18±.057	0.21±.031	1.16±0.04	16.66
B3	31.86±1.6	0.2±0.065	0.23±0.03	1.15±0.07	15.45
C1	31.47±1.4	0.16±.032	0.19±.063	1.18±0.02	18.75
C2	32.89±1.2	0.18±.056	0.22±.052	1.22±0.03	22.22
C3	32.13±1.4	0.17±0.05	0.20±0.45	1.17±0.08	17.64

All values are mean ± SD, (n = 3)

volatile solvents (PG, PEG400 and their admixture). The solubility increases in order as PG > PG: PEG400 > PEG400.

Table 2: Solubility of gliclazide in different solvents

Solvent	Solubility (mg/ml)
Distilled water	0.370
PG	0.928
PEG 400	0.315
PG + PEG400	0.517

The liquisolid technique seems to be a suitable method for solubility enhancement of poorly soluble gliclazide. Liquisolid technique suggests that when the drug dissolved in the liquid vehicle, it incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e., the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.

Pre Compression Parameters Evaluation

The drug excipients physical mixture shows acceptable flow and compressibility suitable for direct compression (Table 3).

Drug Excipients Compatibility Studies

Characteristic absorption peaks due specific groups present in gliclazide were also found in the drug-polymer mixture and there was no change in the R_f value of drug reveals there was no interaction between drugs and excipients.

In-vitro Dissolution Studies of Liquisolid Tablets

Dissolution profiles of gliclazide liquisolid compacts are depicted in Fig.1. In all cases; dissolution was gradually increased up to 20 min. Since in liquisolid formulation all excipients used has particle size less than 150 µm (e.g. MCC used therein has particle size of less than 75 µm). The faster dissolution was observed due to significantly increased wetting properties and increased surface area available for dissolution [15, 16]. During dissolution of liquisolid tablet, after disintegration process is completed, the drug solution or liquid drug, carried on the thoroughly agitated primary particles, is dispersed throughout the volume of the dissolution medium. Hence more drug surface is exposed to the dissolving medium, the liquisolid systems exhibit enhanced drug release.

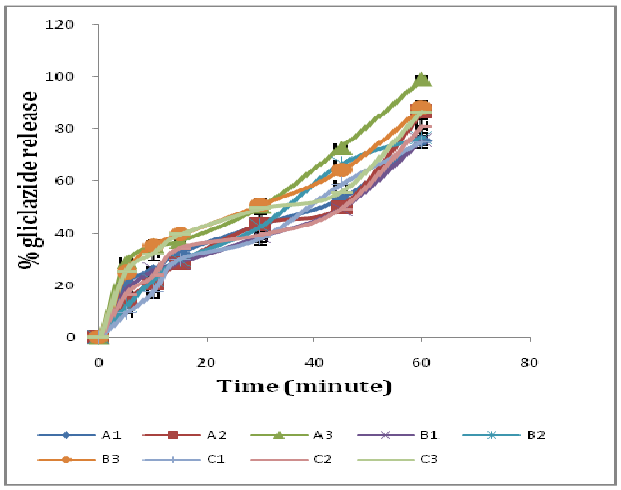

Figure 1: Dissolution profile of Gliclazide liquisolid formulations in phosphate buffer (pH1.2)

Liquisolid system LS1-A3 has desired pre compression properties like angle of repose, density, Hausner's Ratio, compressibility index indicating excellent flowability and showed significant enhancement in drug release as compared to gliclazide (less than 20% within 30 min) hence selected for further studies.

Differential Scanning Calorimetry (DSC)

Gliclazide showed the sharp characteristic endothermic peak at 175.04^{0}C corresponding to its melting temperature (T_m) signifies that gliclazide used was in pure crystalline state. The liquisolid formulations (Fig.2) showed the peak with less intensity, which indicates that molecular dispersion of the drug in carrier material during the formulation process. The endothermic peak obtained in liquisolid system is with decreased intensity indicates the conversion of drug in amorphous on dispersion with carriers.

X-Ray Diffractometry (XRD)

It has been shown that polymorphic changes of the drug are important factors that may affect the dissolution rate and bioavailability [19-20]. Therefore, it is important to study polymorphic changes of gliclazide in liquisolid compacts. The X-RD characteristics of gliclazide, physical mixture, liquisolid systems were given in Fig 3. The characteristic peaks appeared in the XRD of gliclazide at different angle of 13.53^0, 17.32^0, 22.65^0, 26.92^0 and 29.30^0 was observed in drug and excipients physical mixture. Absence of these characteristic peaks in liquisolid system reveals conversion of drug to amorphous state.

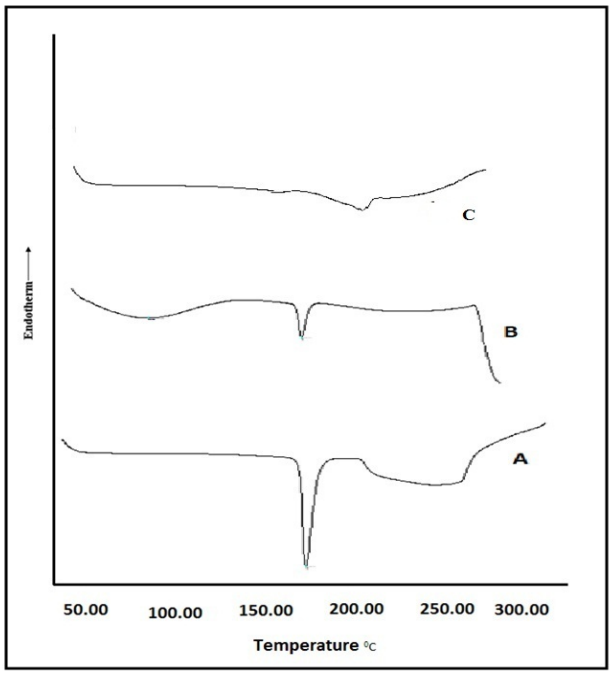

Figure 2: DSC thermogram of A) Gliclazide B) Physical mixture of gliclazide, Avicel pH102 and aerosil C) liquisolid system (LS 1-A3).

In- vivo Bioavailability Study

Pharmacokinetic parameters after oral administrations of gliclazide suspension and liquisolid powders (LS1-A3) to rabbits are shown in Table 3. In comparison to the reference drug, the blood level of test drug was higher throughout the period. The absorption of gliclazide from test formulation was very rapid, while the reference formulation revealed relatively slower absorption. Pharmacokinetic parameters are C_{max} of gliclazide was 171.30± 30.50ng/mL, which is higher than that of

gliclazide suspension. T_{max} was also shortened to 60 minutes in test drug, which is about half than the reference drug (120 min).

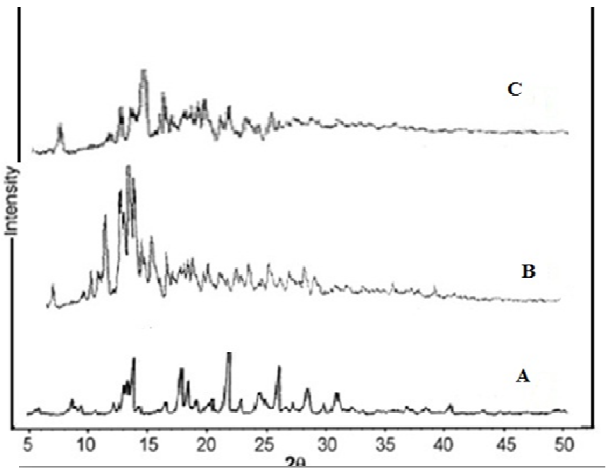

Figure 3: X-Ray Diffraction patterns of A) Pure Gliclazide; B) Physical Mixture of drug, Avicel pH 102 and aerosil; C) liquisolid system (LS 1-A3).

The relative bioavailability of gliclazide was increased to more than 121.08 ± 11.90% by the liquisolid compact formulation (Table 4). According to the biopharmaceutical classification system (BCS), gliclazide is a class II drug which has poor solubility and high permeability. Therefore, solubility or dissolution is the rate limiting step for drug absorption. In the comparative pharmacokinetic study with a reference drug product, liquisolid system showed (LS1-A3) improved bioavailability with higher C_{max} and faster T_{max}. This might be due to the fact that reduced particle size of gliclazide brought an increased surface area for dissolution, and followed by increased drug absorption in gastrointestinal tract [17].

Table 4: Pharmacokinetic Parameters of gliclazide after oral administration of gliclazide suspension and liquisolid formulation

Pharmacokinetic Parameter	Gliclazide suspension	Liquisolid Formulation (LS1-A3)
C_{max} (ng/ml)	112.02 ±10.14	121.30 ± 15.60
T_{max} (min)	120	60
AUC_{03}(ng/mL*min)	141.30±30.50	171.10±60.32
Fr (%)	--	121.08 ± 11.90

Data are expressed as the mean ± S.D. (n = 3).

Stability Study

Stability study of the formulated liquisolid compact was carried out as per ICH guidelines. Drug content was estimated at beginning (99.24 ± 0.83) and end of three months (99.02 ± 1.8) indicate stability of drug on storage under stress. There was no color change observed in formulation. From the stability studies of the optimized batch (LS1-A3) it was found that the liquisolid compact remained stable even after exposing to stress conditions of temperature and moisture for three months.

CONCLUSION

Liquisolid compact of gliclazide have been successfully prepared with polyethylene glycol as non volatile liquid vehicle and microcrystalline cellulose as carrier material. Aerosil is used as coating material. Based on the solubility and *in vitro* dissolution studies batch (LS1-A3) was considered as optimized formulations, resulting in enhanced dissolution rate. Liquisolid compact is a good candidate for the development of oral solid dosage forms due to improved bioavailability of over 121 %, compared to a reference drug product.

ACKNOWLEDGMENTS

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