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Research Article

Dissolution and Bioavailability Enhancement of Gliclazide by Surface Solid Dispersion Using Spray Drying Technique

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ABSTRACT

The objective of the present study was to formulate surface solid dispersions (SSD) of gliclazide to improve the aqueous solubility and dissolution rate. Gliclazide is a BCS Class II drug having low aqueous solubility and therefore low oral bioavailability. In the present study, SSDs of gliclazide with two different carriers in different drug–carrier ratios were prepared by a spray drying method. Surface solid dispersions were characterized by differential scanning calorimetry (DSC), x-ray diffractometry (XRD), scanning electron microscopy (SEM), and Fourier transform infrared spectroscopy (IR) and evaluated for in vitro dissolution, and relative bioavailability studies using rabbit models. Spray drying resulted in stable and uniformly sized spherical particles of SSDs in comparison to probe sonication as revealed from SEM study. DSC and XRD study demonstrated that there was a significant decrease in crystallinity of pure drug present in surface solid dispersions, which resulted in an increased dissolution rate of gliclazide. Surface solid dispersions showed increase in relative bioavailability than the plain gliclazide suspension. The spray drying would be suitable method for dissolution and bioavailability enhancement of gliclazide.

INTRODUCTION

About 40 % of New Chemical Entities, discovered by pharmaceutical industry, are lipophilic in nature or water insoluble. Hence problems may arise to correlate in *vivo* and *in vitro* characteristics of such drug [1]. As per BCS, class II drugs shows poor solubility and higher permeability, so for this class solubility enhancement is the promising way to increase the bioavailability of the drug [2]. There are various techniques to improve the solubility of drug such as particle size reduction, modification of crystal habit, drug dispersion in carrier, complexation and use of surfactants [3]. Among all techniques, solid dispersion (SD) is the most efficient technique from drug dispersion in carrier. More specifically, Chiou and Regelman [4], define this system as, the dispersion of one or more active ingredient in an inert matrix at solid state prepared by melting method, solvent evaporation method and melting solvent method.

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Though SD improves solubility, it has some problems related to stability of its dosage form, so not commercialized successfully [5]. To overcome this problem new technology is applied called as surface solid dispersion (SSD). SSD is the technique which provides deposition of drug on the carrier material which can alter the dissolution characteristic of the drug [6]. Deposition of the drug on carrier material gives more surface area to drug for solubility enhancement; SSD also prevents agglomeration of drug particles and increases wettability of drug molecule [7]. SSD technique has been extensively used to increase the solubility, dissolution and consequently the bioavailability of many practically insoluble or poorly water soluble drugs such as gliblenclamide, glimepride, piroxicam, celocoxib [8-10].

Gliclazide (GLZ),1-(hexahydrocyclopenta [c] pyrrol-2(1H)-yl)-3-[(4methylphenyl) sulphonyl] urea, belongs to the group of intermediate acting hypoglycaemic agents, which is useful for the treatment of non insulin dependent diabetes mellitus (NIDDS)[11].GLZ is class II drug of BCS classification system, which is insoluble in water hence showed slower dissolution rate and low

bioavailability because of poor absorption. Some results show that formation of amorphous form and reductions of particle size enhance the solubility [12].

SD with spray drying technique showed expected results with enhanced solubility, like in case of gliblenclamide, tolbutamide, indomethacin [13,14] Spray drying can evaporate the solvent in single step and yields small, spherical and amorphous product which can be easily solubilize because of such nature [15]. Hence present study was aimed to improve solubility with the technique SSD by use of spray drying technique.

SSDs of GLZ were prepared with superdisintegrant like croscarmellose sodium (CCS) and sodium starch glycolate (SSG) separately, as hydrophilic carrier. Aerosil was used as adsorbent and solubility enhancer due to presence of silane group on aerosil. SSDs prepared with spray drying method evaluated to assess the effect of carrier material and effect of method of preparation on % drug dissolved (% DD). Spray drying technique yields highly amorphous product.CCS containing SSDs showed high % DD as compare to SSG containing SSDs. All SSDs were characterized by scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FT-IR), differential scanning colorymetry (DSC), X- ray diffractometry (XRD). Dissolution studies were performed on plain GLZ, SSDs of GLZ. *In vivo* study was performed on rabbits (New Zealand White) to compare bioavailability of GLZ and solubility enhanced GLZ.

EXPERIMENTAL

Materials

Gliclazide was obtained as gift sample from Bal Pharma Pvt. Ltd., Banglore, India. SSG, CCS and microcrystalline cellulose were from JRS Pharma, Rosenberg, Germany. Aerosil 200, Magnesium stearate, Potassium chloride were purchased from SD Fine chemicals Mumbai, India. Ethanol and other chemicals used were of analytical grade.

Preparation of SSD

One gram of drug was dissolved in 40 ml of acetone and superdisintigrant was dissolved in ethanol, finally both solutions were mixed into each other. Aerosil was added into final solution and homogeneous solution was prepared with magnetic stirrer. This solution was spray dried using laboratory scale spray dryer (Labultima, Mumbai, India). The varying ratio of gliclazide, superdisintegrant, and aerosil (1:1:0.1 to 1:3:0.3) used to prepare SSDs. The processing parameters like inlet and outlet temperature were 80^0C and 60^0C, respectively. Aspirator speed was kept at 40% whereas feed pump speed was 6 ml /min.

Experimental designing

SSDs of GLZ were prepared with the use of Design expert software, which generates design of various runs or combinations to check the effect of independant variables(X) on the dependant variables (Y). In this design, amount of superdisintigrant (g) (X1) and aerosil(g) (X2) were taken as independent variables while % drug dissolved(%) (Y) was dependent variable. Design generated with two factors which varies on three levels that is 3^2. The variables as well as levels are indicated in Table 1.

Table 1: Variables with different levels

Levels	Factors	
	(X1)Superdisintegrant (gm)	**(X2) Aerosil (gm)**
Low	1	0.1
Medium	2	0.2
High	3	0.3

Statistical technique was used to establish the statistical validation of the polynomial equations generated by Design Expert® software (version 8.0.1, Stat-Ease Inc, Minneapolis, MN). On fitting a quadratic model to 3^2 factorial design, predictor equation generated incorporating interactive and polynomial term was used to evaluate the responses:

$$Y= b0 + b1X1 + b2X2 + b12X1X2 + b11X12 + b22X22 \quad \ldots\ldots (1)$$

Where Y is the measured response associated with each factor level combination; b0 is an intercept representing the arithmetic average of all quantitative outcomes of nine runs; bi (b1, b2, b11, b12and b22) are regression coefficients computed from the observed experimental values of Y (% drug dissolved) and X1 (amount of superdisintegrant) and X2 (amount of aerosol) are the coded levels of independent variables. The terms X1X2 represent the interaction terms. The main effects (X1 and X2) represent the average result of changing one factor from its low to high value. The interaction terms showed the response changes when two factors were changed simultaneously. The polynomial

equation was used to draw conclusions after considering the magnitude of coefficients and the mathematical sign it carries, i.e. positive or negative. A positive sign signifies a synergistic effect, whereas negative sign stands for an antagonistic effect.

This software was also used to generate the best model and to design a response surface model which showed the 3-D graph containing the effect of superdisintegrant and aerosil on the % DD for each SSD.

Characterization of SSD

Scanning Electron Microscopy (SEM)

The morphology of GLZ and SSDs were determined using SEM (JSM 5610 LV, Jeol Datum Ltd. Japan) operated at an accelerating voltage of 3 kV. Samples were prepared by mounting powder on to a brass stub using graphite glue and coated with gold under vacuum before use.

Fourier-transform infrared spectroscopy (FTIR)

FTIR spectra were obtained using FTIR spectrometer (8400 S, Shimadzu, Japan). Drug, SSDs were previously ground and mixed thoroughly with potassium bromide at 1:100 (sample: potassium bromide) weight ratio, separately. The potassium bromide discs were prepared by compressing the powders at pressure of 10 tons for 10 min in hydraulic press. Scans were obtained at a resolution of 2 cm^{-1}, from 4000 to 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

The DSC measurements of pure drug and SSDs were performed on a differential scanning calorimeter (Mettler Toledo) with a thermal analyzer. Under nitrogen flow of 25 ml/min, 2 mg of samples were placed in a sealed aluminium pan at 25 ml/min flow rate of N_2 gas and heated at a scanning rate of 10 ºC /min from 30 ºC to 300 ºC.

X-Ray Diffraction studies (XRD)

The powder X-ray diffraction patterns were determined for pure drug, and SSDs. X-ray diffractograms were obtained using the X-ray diffractometer Philips diffractometer (PW 1140) and Cu-kα radiation, diffractograms were run at scanning speed of 2°/mm and a chart speed of 2°/2 cm per 2θ.

***In Vitro* Dissolution Studies**

The dissolution of SSDs was carried out following the USP XXIV Apparatus 2 (paddle) method. The phosphate buffer (pH 1.2) used as media at 100 rpm, bath temperature was 37±0.5^0 C. SSD containing drug equivalents to 10 mg was placed in muslin cloth and then it was tied to paddle to avoid floating of SSD. Filter about 5 ml of aliquots collected at the end of 30 min and analyzed spectrophotometerically at 227 nm (UV 1700, Shimadzu).

Dosage form development

The SSDs that showed maximum dissolution was converted to tablet dosage form with direct compression method. Immediate release tablets were prepared by compressing SSDs equivalent to 40 mg of gliclazide, lactose monohydrate as filler, Avicel 102 as superdisintegrant and magnesium sterate as a glidant**.** The prepared tablets were evaluated for parameters viz weigh variation, hardness, friability, disintegration test, dissolution test.

***In- vivo* bioavailability study**

The animal experiment was carried out in compliance with the protocol of Institutional animal ethical committee (Registration No: 651/02/C/CPCSEA under CPCSEA, India). Six New Zealand white rabbits with mean weight of 2.5 ± 0.30 kg were used. The rabbits were accommodated to the dosing for one month before the study to prevent withdrawal and defense reaction that may lead to inaccurate dosing. The rabbits were kept in single cages and fasted for 12 h before the study with free access to water during the experiments. A cannula was inserted into the marginal ear vein for blood sampling and flushed with heparinized normal saline solution.

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 formulation containing solubility enhanced gliclazide (i.e. SSD) of same dose. Pure drug and SSD equivalent to dose were mixed in distilled water separately and this solution administered orally to the rabbits with the help of syringe. One mL of blood samples 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 ^{0}C until analysis [16].

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 (4 mL) 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).

$$\% \text{ relative bioavailability of test product (F)} = \frac{AUC\ TEST}{AUC\ STD} \times 100 \quad \ldots\ldots (2)$$

Stability study

To assess the effect of environmental condition or storage conditions on formulation. Optimized batch C9 was kept in environmental stability chamber (Remi Lab, Bombay) for accelerated stability condition at 40^{o}C ± 2^{o}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 [17].

RESULTS

Designs of SSDs were obtained with two different superdisintegrant or carrier prepared by spray drying technique, designs generated by Design expert software are shown in Table 2 and 3. All batches were subjected for dissolution studies to find out optimized batch from every design for each superdisintegrant and for each method. It was found that in every design, the batch containing highest amount of superdisintegrant and aerosil gives high % DD, so C9 and S9 batches considered as optimized batches from all designs and subjected for further studies and characterization.

Fitting of data to the model

The two factors with lower, middle and upper level are shown in Table 1. All the responses observed for nine formulations of every design were fitted into models using Design- Expert® software along with the regression equation generated for each batch. The results of ANOVA in Table 4, for the dependent variables demonstrate that the model was significant for the response variable.

It was observed that independent variables X_1 (amount of superdisintegrant) and X_2 (amount of aerosil) had a positive effect on response Y (%DD).

Regression equations of the fitted quadratic model:

For CCS,

$$Y= 44.85 + 9.57\ X_1 + 71.19\ X_2 - 8.35\ X_1\ X_2 + 1.26\ X_1^2 - 59.06\ X_2^2 \quad \ldots\ldots (3)$$

For SSG,

$$Y= 55.47 - 3.00\ X_1 + 34.43\ X_2 - 0.80\ X_1\ X_2 + 3.56\ X_1^2 - 20.82\ X_2^2 \quad \ldots\ldots (4)$$

The coefficients with more than one factor term in the regression equation represent interaction terms. It also showed that the relationship between factors and responses was not always linear. When more than one factor are changed simultaneously and used at different levels in a formulation, a factor can produce different degrees of response. The interaction effects of X_1 and X_2 were favorable (positive) for response Y.

Response surface plot analysis

Three dimensional response surface plots generated by the Design Expert® software are presented in following figures, for the studied response, i.e. % DD. Figures 1-A depicts response surface plot of CCS concentration (X_1) and aerosil

concentration (X_2) on % DD. which indicate that X_1 and X2 shows linear effect i.e. when increased from low to high the value of % DD was also increased. Figure 1-B represents response surface plot of the effect of SSG concentration (X1) and aerosil concentration (X2) on % DD which indicates a linear effect. Figure 1 show that an increase in % DD was observed, with increase in amount of superdisintegrant and aerosil, due to increase in surface area for drug adsorption.

Optimization and validation

A numerical optimization technique by the desirability approach was used to generate the optimum settings for the formulation. The process was optimized for the dependent variable such as % DD. The optimum formulations were selected based on the criteria of attaining the higher % DD. Formulations C9, S9, containing higher concentration of superdisintegrant as well as aerosil which showed high % DD, hence these formulations were considered as optimized batches from particular designs.

Characterization of SSDs

Scanning Electron Microscopy

Characteristic needle-shaped crystals of gliclazide were observed in the photomicrograph of pure drug GLZ (Fig. 2A). SEM of the SSD (Fig. 2B, 3C) reveals spherical shaped particles with small size which provide additional surface for deposition of the drug, it clears that spray drying can reduce particle size effectively which aids for solubility enhancement. There is no evidence of drug crystals in SSD.

Fourier-Transform Infrared spectroscopy (FTIR)

FTIR spectroscopy was used to study the possible interactions between GLZ, CCS, SSG and aerosil in the SSD. There is no significant difference in the FTIR spectra of pure drug, physical mixture, and SSD (Fig. 3 C-9, S-9). All characteristic peaks of GLZ observed at wave numbers at 2950 (N-H stretching), 1709 (C=O stretching), 1164 (S=O stretching) were also present in physical mixtures and SSDs, which clearly indicate that no interaction exists between pure drug, superdisintegrant and aerosil in SSD.

Differential Scanning Calorimetry

The DSC profiles of GLZ (A), physical mixture (B) and SSD containing CCS prepared by spray drying method are depicted in Fig. 4 (C9) DSC analysis of crystalline GLZ showed a single sharp fusion endotherm at 170 °C. It is revealed from DSC thermogram of physical mixture and SSD containing CCS there was decrease in sharpness and intensity of characteristic endothermic peak of drug which could be attributed to the conversion of most of the crystalline form of the drug to the amorphous. Fig 4 (S9) depicts DSC thermogram of gliclazide sharp endothermic peak at 170°C (A), while in physical mixture peak was observed at 165°C (B) suggesting no chemical interaction of drug and superdisintegrant. SSD containing sodium SSG showed only a little endothermic peak indicating conversion of crystalline drug into amorphous form(C), due to spray dying.

X-ray Diffraction Studies

The XRD pattern of Gliclazide, physical mixture and SD containing cross carmellose sodium and sodium starch glycolate was shown in Fig. 5 respectively. The diffraction pattern of gliclazide showed high intensity peaks at 2 theta values of 10.67°, 15.12°, and 22.21°, respectively. Sharp intense peaks might be due to presence of crystalline form of the drug. The diffraction pattern of physical mixture exhibited intensity peaks similar to drug, whereas SDs of gliclazide with cross carmellose sodium (C9) did not show characteristic drug peaks. The distinctive diffraction pattern for SD containing sodium starch glycolate (S9) was same as that of SD containing cross carmellose sodium. The absence of numerous distinctive peaks of the drug in solid dispersion demonstrated that high concentration of the drug was dissolved in the solid state carrier matrix in an amorphous structure suggesting the transformation of crystalline form of gliclazide to amorphous form in the solid dispersion. This polymorphic transformation contribute to faster dissolution rate of solid dispersions as the material in its amorphous form dissolves at a faster rate due to its higher internal energy and molecular motion when compared to crystalline forms.

Dissolution study of SSDs:

Surface solid dispersions with both carriers showed maximum drug release than drug; the SSD with CCS showed almost 92.47±1.98 % drug release, whereas SSD with SSG showed 86.05±2.47 % release within 30 min, indicating that SSD with CCS showed better dissolution profile than SSG.

Table 2: The predicted and observed response variables for SSDs containing cross carmellose sodium

Batch code	Superdisintegrant (gm)	Aerosil (gm)	% drug dissolved		Prediction error*(%)
			Predicted value	Observed value	
C1	1	0.1	61.08	60.81	-0.44
C2	2	0.1	73.91	74.51	0.81
C3	3	0.1	88.97	88.96	-0.01
C4	1	0.2	65.89	66.74	1.29
C5	2	0.2	77.52	77.48	-0.05
C6	3	0.2	91.82	91.55	-0.29
C7	1	0.3	69.22	68.96	-0.37
C8	2	0.3	80.09	80.07	-0.02
C9	3	0.3	93.48	93.77	0.31

Table 3: The predicted and observed response variables for SSDs containing sodium starch glycolate

Batch code	Superdisintegrant (gm)	Aerosil (gm)	% drug dissolved		Prediction error*(%)
			Predicted value	Observed value	
S1	1	0.1	59.19	58.96	58.96
S2	2	0.1	66.81	67.11	67.11
S3	3	0.1	81.56	81.55	81.55
S4	1	0.2	61.93	61.55	61.55
S5	2	0.2	69.47	69.70	69.70
S6	3	0.2	84.14	83.40	83.40
S7	1	0.3	64.25	64.88	64.88
S8	2	0.3	71.71	72.29	72.29
S9	3	0.3	86.3	87.11	87.11

Table 4: Results of analysis of variance for SSDs

CCS	DF*	SS*	MS*	F*	Significance *p*
Model	5	1063.89	212.78	1474.46	<0.0001significant
Residual	7	1.01	0.14	-	-
Total	12	1064.90	212.92	-	-
SSG	5	815.38	163.08	273.69	<0.0001 significant
Model	7	4.17	0.60	-	-
Residual	12	819.55	163.68	-	-
Total					

* DF indicates degrees of freedom; SS sum of square; MS mean sum of square and F is Fischer's ratio.

Table 5: Pharmacokinetic Parameters of gliclazide after oral administration of gliclazide suspension and SSD solution

Parameter	GLZ suspension	Formulation (SSD)
C_{max} (ng/ml)	112±10.14	130± 13.36
T_{max} (min)	120± 0.18	60± 0.14
AUC_{03}(ng/mL*min)	146.25±38.95	174.61±139.92
Fr (%)	--	119.39 ± 1.59

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

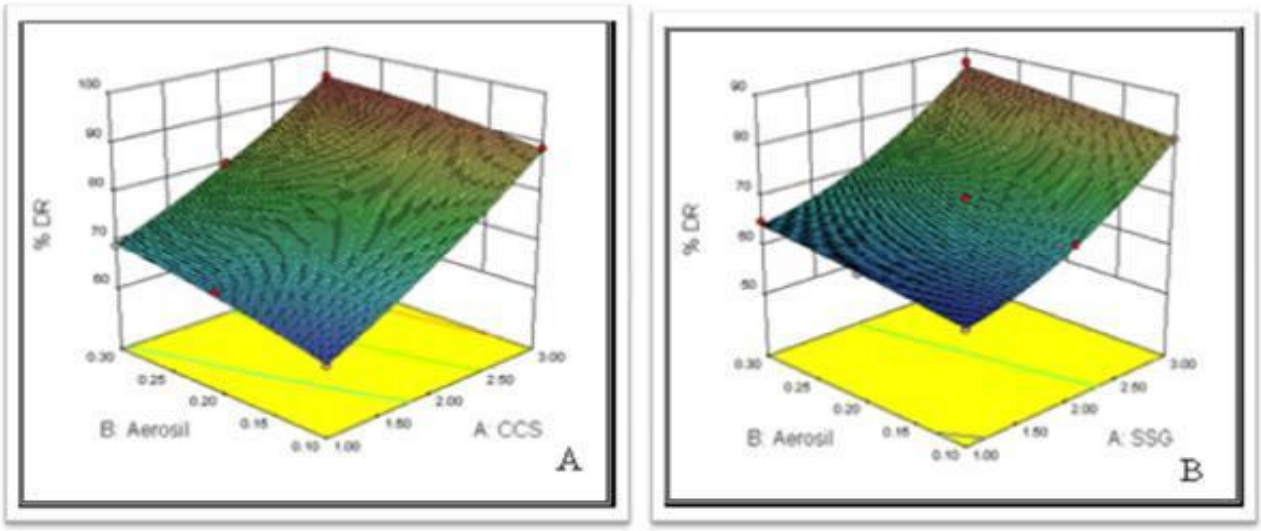


Figure 1: Response surface plots for spray dried batches, A- SSD containing cross carmellose sodium, B- SSD containing sodium starch glycolate.

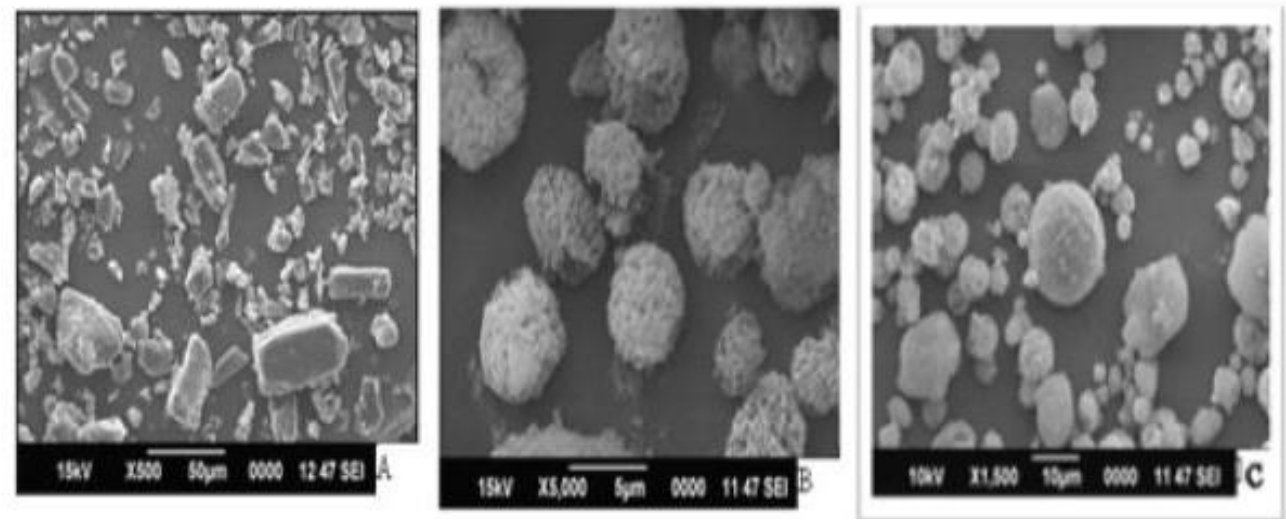


Figure 2: Scanning electron microscopic images of A- Gliclazide, B- SSD containing CSS (C9), C-SSD containing SSG (S9),

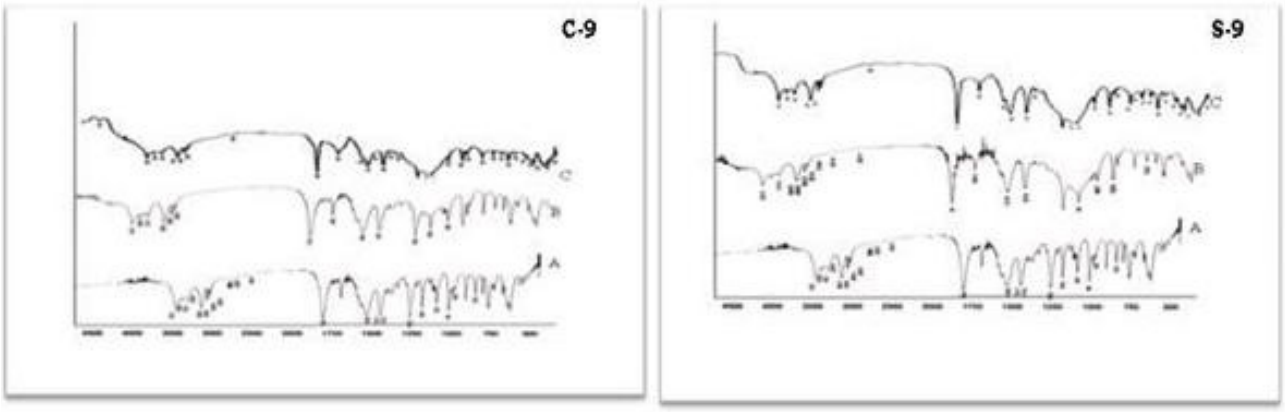


Figure 3: FT-IR spectra of (C-9: A- Gliclazide, B- Physical mixture of drug with CCS and aerosil, C- C9. S-9: A- Gliclazide, B- Physical mixture of drug with SSG and aerosil, C-S9)

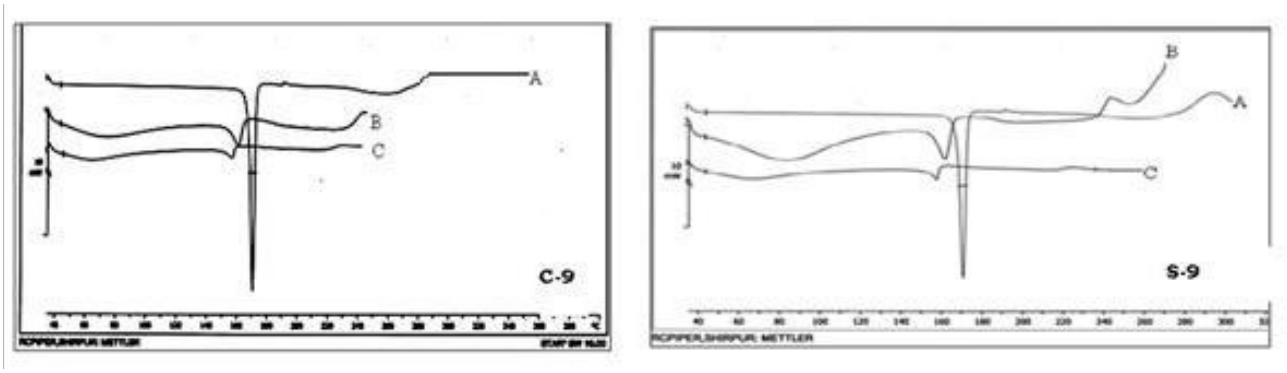


Figure 4: Differential scanning calorimetry thermograms (C-9: A- Gliclazide, B- Physical mixture of drug with CCS and aerosil, C- C9. S9: A- Gliclazide, B- Physical mixture of drug with SSG and aerosil, C-S9)

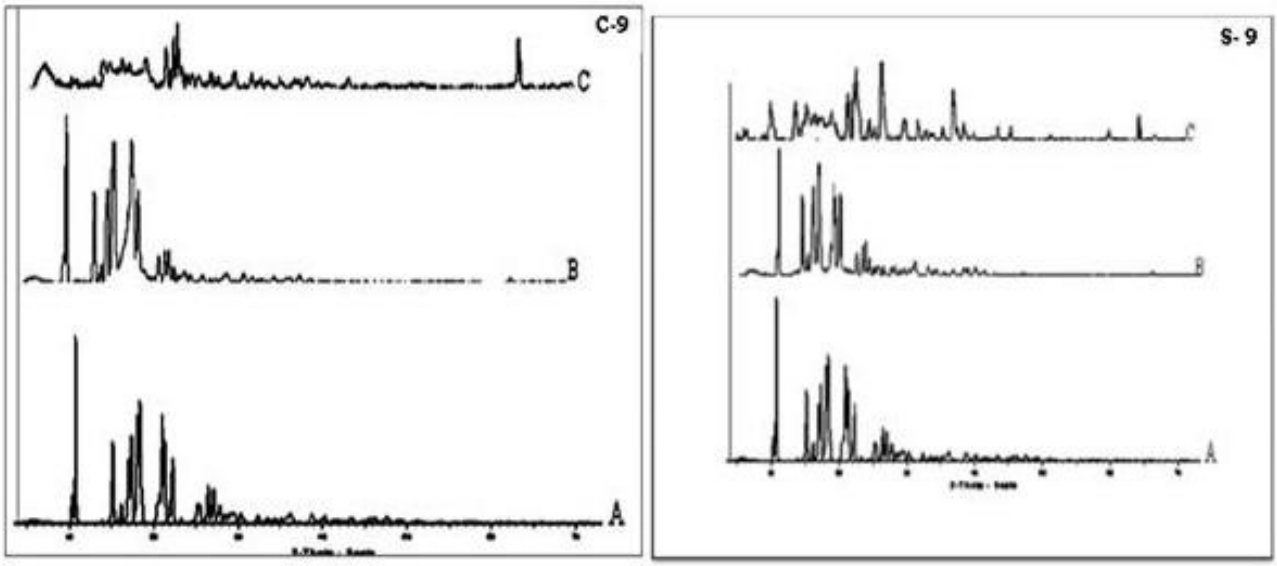


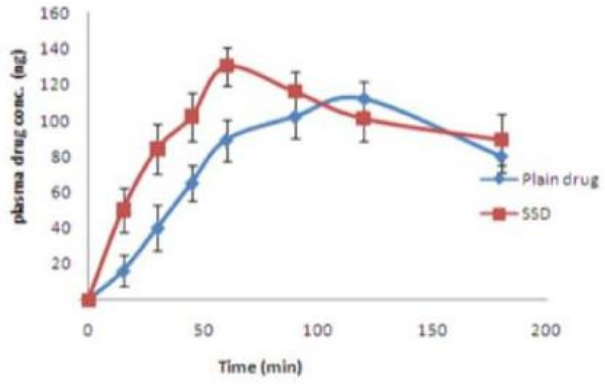
Figure 5 : X-Ray diffractograms (C-9: A- Gliclazide, B- Physical mixture of drug with CCS and aerosil, C- C9, S-9: A- Gliclazide, B- Physical mixture of drug with SSG and aerosil, C-S9).

Dosage Form Development

Tablets prepared from optimized formulations were evaluated for post compression parameters. The tablet dosage form showed weight variation (±4%), hardness (3.4-4kg/cm^2), friability (0.2-0.7%), and disintegration time (25-33sec). Dissolution study of formulation C9 showed highest % drug dissolution 95.95% ± 1.32 % where as formulation S9 showed 91.39 ± 1.62 %. Whereas conventional marketed tablet (Glizid- 40® Panacea Biotech,) showed only 66.22 ± 1.73 % drug dissolution.

***In- vivo* bioavailability study**

Plasma concentration vs time plots of GZ after oral administrations of GLZ suspension and SSD (C9) to rabbits are shown in Fig.6. In comparison to the reference drug, the blood level of test drug was higher throughout the period. The absorption of GLZ from test drug was very rapid, while the reference drug revealed relatively slower absorption. Pharmacokinetic parameters are listed in Table5. C_{max} of GLZ was 130± 13.36 ng/mL, which is higher than that of GLZ suspension. T_{max} was also shortened to 60 minutes in test drug, which is about half than the reference drug (120 min). The relative bioavailability of GLZ was increased to more than 119.39 ± 1.59% by the SD formulation.



Stability Study

Stability study of the formulated SSD was carried out as per ICH guidelines. In vitro drug release, drug content was studied. There was no colour change observed in formulation. From the stability studies of the optimized batches (C9) it was found that the SSDs remained stable even after exposing to stress conditions of temperature and moisture for three months.

DISCUSSION

Dispersion of poorly soluble drugs into hydrophilic carrier has been widely applied for increasing the dissolution and absorption. In this work SSD containing sodium starch glycolate and cross carmellose sodium has been successfully developed by spray drying technique.

The improved dissolution could be attributed to a conversion of crystalline drug to amorphous, its deposition on the surface of the carrier, and improved wettability. Moreover CCS and SSG have very fine particle sizes and hence large surface areas hence showed improvement in dissolution.

CONCLUSION

Surface solid dispersions of gliclazide (SSDs) have been successfully prepared with cross carmellose sodium or sodium starch glycolate as superdisintegrant and aerosil as a dispersing agent respectively, using spray drying technique, which can be scaled-up industrially. FTIR showed no evidence of interaction between the drug and carrier. DSC and XRD studies confirmed amorphism of drug after spray drying. SSDs showed significantly higher drug dissolution in comparison with pure drug. The improvement in bioavailability after administration of drug as SSDs containing CCS as superdisintegrant of over 119% was due to enhancement in rate and extent of drug dissolution. SSDs prepared by spray drying are promising approach for enhancing dissolution rate which increases oral bioavailability of poorly water soluble drugs.

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