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Research Article

Solubility Enhancement of Gliclazide by Surface Solid Dispersion Technique by Probe Sonication Method

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ABSTRACT

Many drug molecules are poorly water soluble so that unable to produce their desired effect. To solve this problem different approaches are used like physical modification which includes particle size reduction, solid dispersion, micro emulsion, complexation and chemical modifications. Among all techniques solid dispersion (SD) is promising technique to increase drug solubility, still very few SD are available in market because of stability issue of SD. So to overcome this issue new technique is applied known as Surface Solid Dispersion (SSD). SSD is a technique that provides deposition of the drug on the surface of certain materials (carriers) that can alter dissolution characteristics of drug. In SSD dissolution enhancement occurs because it reduces drug agglomeration and increases drug surface area. Drug release depends on nature of carrier so carrier should be porous, hydrophilic with fine particle size. Drug of choice in this study is Gliclazide (GLZ), BCS class II drug. SSD is prepared by probe sonicator to reduce particle size and solubility enhancement. The vibrations from sonicator are transferred into solution via tip of probe which induces cavities in solution. The solution in cavities becomes supercritical fluid because of large temperature and pressure difference between bulk solution and cavity solution. As per previous study compound shows high solubility in supercritical solvent, also cavitation cause micro streaming which leads turbulence of solid-liquid film which accelerates mass transfer process which leads solubility enhancements of drug. When formed cavities collapsed it releases tremendous energy which leads particle size reduction.

INTRODUCTION

There are many drug molecules having sufficient potency to produce pharmacokinetic and pharmacodynamic effects but because of their solubility issue, drug molecules become inefficient. Such poorly soluble drugs create many obstacles in *in-vitro* studies, in formulation studies and in *in-vivo* studies. This *in vivo* and *in vitro* characteristics and other parameters are very difficult to correlate each other because of the solubility issue [1].To solve this problem different approaches are used like physical modification which includes particle size reduction, solid dispersion, micro emulsion, complexation and chemical modifications [2].

In this all techniques Solid Dispersion (SD) is promising technique to increase drug solubility in which the dispersion of one or more active ingredients in an inert matrix at solid state prepared by melting method or solvent evaporation method or melting solvent method [3]. SD technology is generally used for BCS class II drugs. As per BCS classification BCS Class II drugs shows low solubility and high permeability [4]. So the SD is prominent technique to improve oral absorption and bioavailability of BCS Class II drugs [5]. Though SD showing good results for solubility, still few SDs are available in market because of stability issue of SD [6]. So to overcome this problem new technique is applied known as Surface Solid Dispersion (SSD). SSD is a technique that provides deposition of the drug on the surface of certain materials (carriers) that can alter dissolution characteristics of drug. Various hydrophilic carriers with high surface area are used for deposition of drugs which

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ultimately increases dissolution rate for hydrophobic drugs [7]. In SSD dissolution enhancement achieved because it reduces drug agglomeration and increases drug surface area. Drug release depends on nature of carrier, so carrier should be porous, hydrophilic with fine particle size which gives high surface area for adsorption of drug and it leads to high solubility of drug [8]. SSD is a sure technique for increasing the solubility, dissolution and bioavailability of insoluble or poorly soluble drugs like ibuprofen, pyroxicam, meloxicam, glimepride [9].

Drug of choice in this study is Gliclazide (GLZ), 1-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-[(4-methylphenyl) sulphonyl] urea, belonging to intermediate hypoglycemic agent category, it binds to sulphonyl urea receptors of β islets cells of pancreas to release insulin [10]. As GLZ is BCS class II drug, it is insoluble in water so it gives very low bioavailability, so SSD is the best way to solve this problem [11].

In previous study SSD of GLZ is prepared with Spray drying method which gives promising results to increase % Drug Dissolution (DD) [12]. In this study SSD of GLZ is prepared with probe sonicator which is used to reduce particle size and solubility enhancement. The vibrations from sonicator are transferred into solution via tip of probe which induces cavities in solution. The solution in cavities becomes supercritical fluid because of large temperature and pressure difference between bulk solution and cavity solution. As per previous study compound shows high solubility in supercritical solvent, also cavitation cause micro streaming which leads turbulence of solid-liquid film which accelerates mass transfer process. By this way solubility of drug increases [13].When formed cavities collapsed it releases tremendous energy which leads particle size reduction [14]. It is studied that probe sonication increases solubility of benzoic acid [15], ibuprofen [16]. This technique also show results in nitrendipine nanosuspension [17], fenofibrate nanocrystals [18] for dissolution enhancement.

SSDs of GLZ were prepared with super disintigrants like Sodium Starch Glycolate (SSG) and Cross Carmellose Sodium (CCS), separately as a hydrophilic carrier. It increases solubility of drug by swelling and wicking action respectively [19]. Aerosil is also used in SSD because it gives synergistic effect on solubility because of its silane group [20].

SSD were prepared with probe sonication method to compare drug dissolution with plain drug. Design expert software was used for optimization and response surface methodology was used to check effect of conc. of super disintegrant and aerosil on drug dissolution. After optimization of probe sonicated SSDs, it reveals that SSD with CCS gives higher drug dissolution than SSD of SSG. Plain GLZ and all optimized batches were studied for Scanning Electron Microscopy (SEM), Fourier Transform Infrared Spectroscopy (FT-IR), Differential Scanning Colorymetry (DSC), X- Ray Diffractometry (XRD). Dissolution studies also performed on plain GLZ and SSDs of GLZ.

EXPERIMENTAL

GLZ received as gift sample from BALPharma Pvt. Ltd, Banglore, India. SSG, CCS and Micro Crystalline Cellulose were obtained from JRS Pharma, Rosenberg, Germany. Lactose monohydrate received as a gift sample from Merck specialities, Pvt. Ltd., Mumbai, India. Aerosil 200, Magnesium stearate, Potassium chloride were purchased from SD fines, Mumbai, India. Other chemicals used were of analytical grade.

Preparation of SSD

One gram of drug was dissolved in 30 ml of ethanol and super disintegrant also dissolved in ethanol separately, both solutions were mixed properly and aerosil was added in final solution with the use of magnetic stirrer. Final solution was proceed for probe sonication with continuous mode in which solution was in contact with probe for continuous 2 minutes. Weight ratios (In grams) of GLZ, Super disintegrant, and Aerosil used to prepare SSD were 1:1:0.1, 1:2:0.2, 1:3:0.3. Volume of ethanol for drug dissolution is constant that is 30 ml, but volume ethanol for super disintigrant was 15ml, 30ml, 45ml respectively. After sonication, solvent evaporation was achieved by Buchi Rota evaporator, at 131 tore pressure and 60^0 C temperatures with speed of 90 rpm. Finally free flowing and dried product obtained which was stored in dried vials at cool and dried place.

Optimization by Design of Experiment

Different batches of SSDs were prepared with Design expert software, which generates different runs shows effect of independent variables or factors (X) on dependant variables(Y). Independent variables were conc. Of super disintegrant (X1) and conc. of aerosil

(X2), dependant variable was % DD (Y). Design generates total 9 runs with 2 factors varying on 3 levels, 3^2. All are indicated in table 1.

Table 1: Variables with different levels

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

ANOVA was used to establish statistical validation of the polynomial equation generated by design expert software. Fitting a quadratic model to a 3^2 factorial design gives a predictor equation incorporating interactive and polynomial term to evaluate the responses.

$$Y= b_0 + b_1X_1+ b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad \text{.....(1)}$$

Where Y is the response obtained from independent factors with different levels, b_0 an intercept obtained from arithmetic average of all nine runs, $b_i(b_1,b_2,b_{11},b_{12},b_{22})$ are regression coefficient calculated from values of Y, $X_1$and X_2 are independent variables, X_1X_2 represents interaction terms which shows changes in response with the change in this terms with different levels. A positive sign indicates synergistic effect of these terms on response while negative sign indicates antagonistic effect on response. With the use of Design Expert software best fitting model was selected for the response of highest % (DD).

Characterization of SSD

Scanning Electron Microscopy (SEM)

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

Fourier - Transform Infrared Spectroscopy (FTIR)

FTIR spectrometer (8400 S Shimadzu, Japan) was used to get spectra of GLZ, physical mixture and SSD. Samples were previously ground and mixed with potassium bromide in 1:100 (Sample: KBr) weight ratio. Scans were obtained at a resolution of 2 cm^{-1}, from 4000 to 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimeter (Mettler toledo) with a thermal analyzer was used to carry out this study on GLZ, Physical Mixture, and SSD. Parameters were set with nitrogen flow 25 ml/ min, scanning rate at 10^0c/ min from 35^0c to 400^0c. 2mg sample was placed in aluminum pan; another one aluminum pan was taken as a reference.

X- Ray Diffraction Studies (XRD)

GLZ, physical mixture and SSD were subjected to this study with the use of Philips Diffractometer (PW1140) and Cu-kα radiations. Diffractograms were obtained with scanning speed of 2^0/mm and chart speed of 2^0/2cm per 2θ.

***In Vitro* Dissolution Studies**

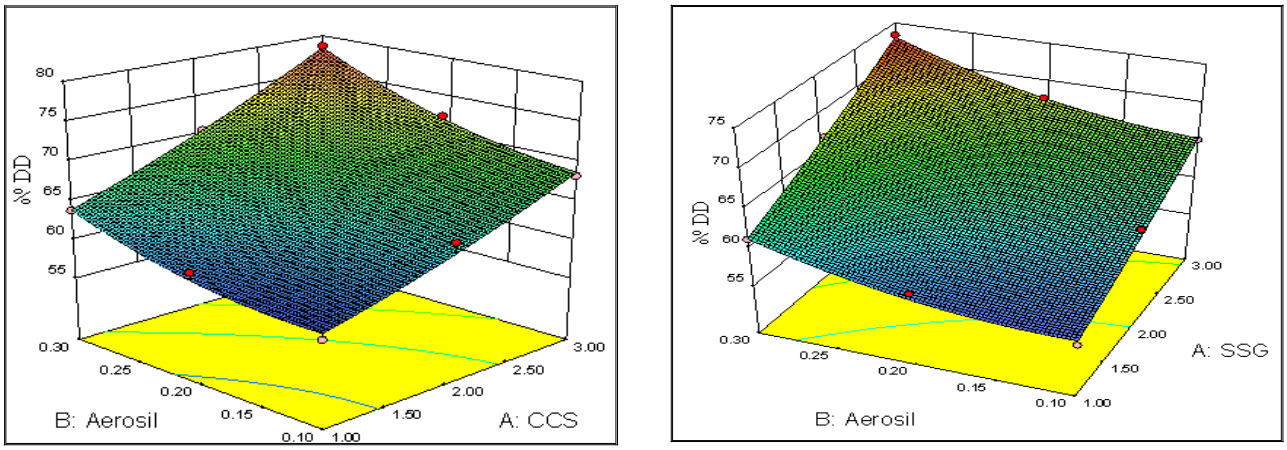
SSDs were subjected for dissolution studies with USP XXIV apparatus 2(Paddle) Method. Dissolution media was 1.2 pH buffer with 100 rpm paddle speed; temperature of bath was 37 ± 0.5 °C. SSD containing 10 mg equivalent drug was placed in muslin cloth and tied to paddle for dissolution studies. After 30 min 5 ml sample collected and proceed for UV analysis on UV-visible spectrophotometer (UV 1700 Shimadzu) at 227nm.

Dosage Form Development

From dissolution studies optimized batch was selected for development of immediate release tablet. Precompression parameters were performed and immediate release tablet prepared with component SSD with 40 mg equivalent dose of GLZ, lactose monohydrate as a diluent, Avicel 102 as a superdisintigrant and magnesium stearate as a lubricant. Prepared tablets were studied for post compression parameters like hardness, thickness, friability, weight variation, disintegration and dissolution test.

RESULTS AND DISCUSSION

As per design expert software total 9 runs generated for each superdisintigrant or carrier material by probe sonication method. 2designs were obtained for 2 carriers with 3 different levels; runs for each design are coated in table no.2& 3. All batches were studied for % DD and from its result optimized batch was isolated for each superdisintigrant from each design. It was observed that in every design, run having highest conc. of superdisintegrant and aerosil shows highest % DD.



(A) **(B)**

Figure 1: Response surface Plots for Probe sonicated batches, A- SSD of CCS, B- SSD of SSG

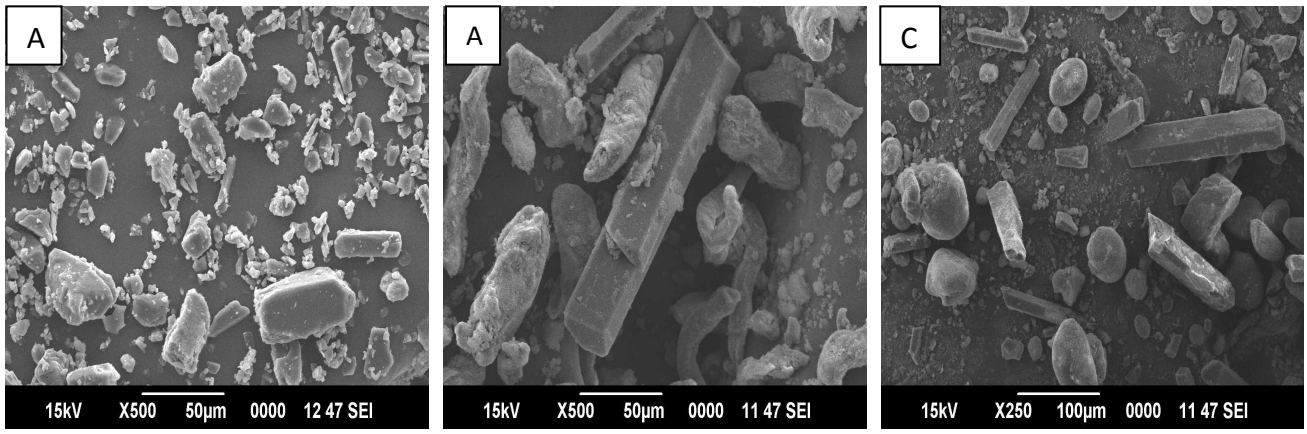


Figure 2: SEM images for A- Plain GLZ, B- Probe sonicated SSD of CCS A9 batch, C- Probe sonicated SSD of SSG- B9 batch.

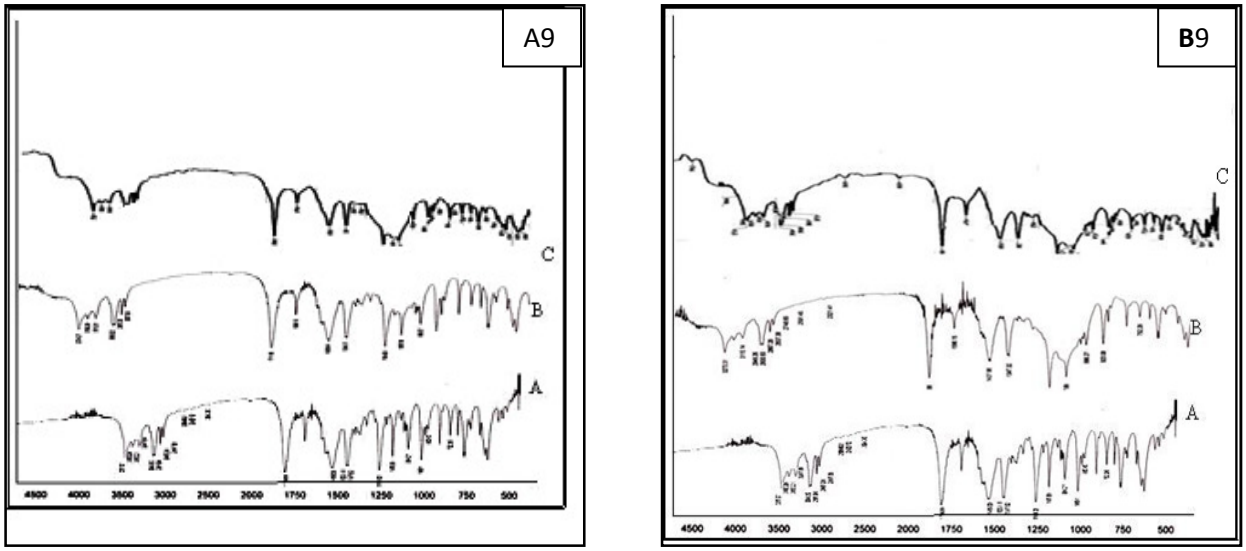


Figure 3: Fourier Transform Infrared Spectra for A9: A- Plain GLZ, B- Physical mixture with aerosil, C-Probe sonicated SSD of CCS-A9 batch ; B9: A- Plain GLZ, B- Physical mixture with aerosil, C-Probe sonicated SSD of SSG- B9 batch.

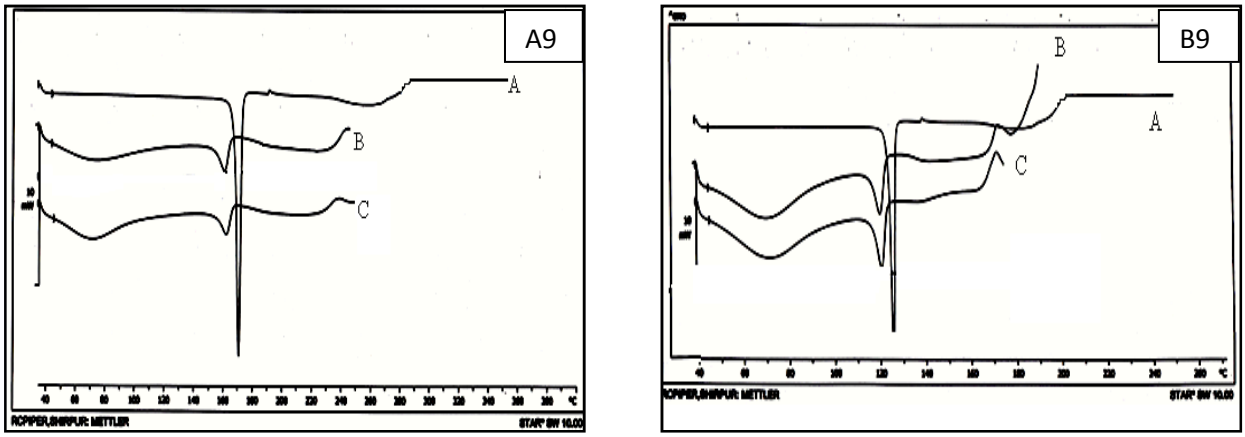


Figure 4: Differential Scanning Colorometric thermogram forA9: A- Plain GLZ, B- Physical mixture with aerosil, C- Probe sonicated SSD of CCS -A9 batch, B9: A- Plain GLZ, B- Physical mixture with aerosil, C- Probe sonicated SSD of SSG-B9 batch.

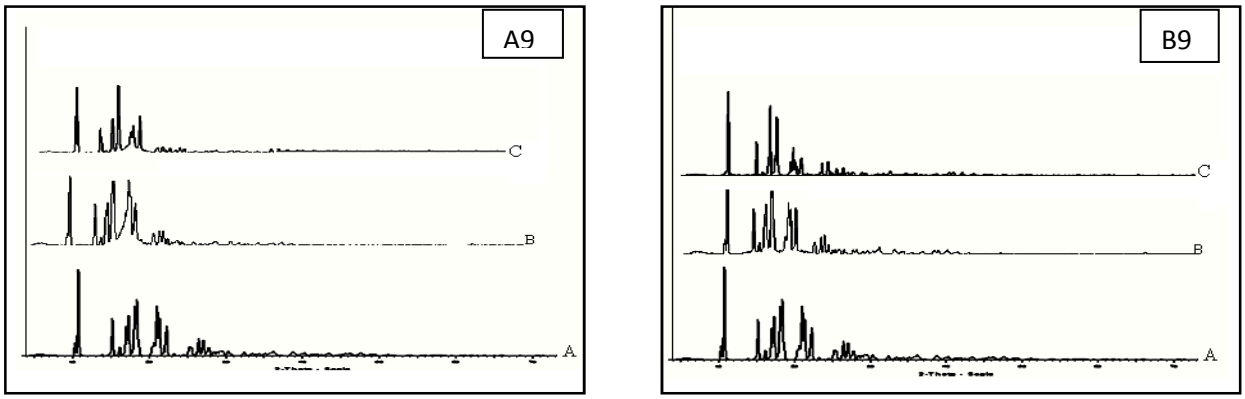


Figure 5: .X ray Diffractogram for A9: A- Plain GLZ , B- Physical mixture with aerosil, C- Probe sonicated SSD of CCSA9 batch, B9: A- Plain GLZ , B- Physical mixture with aerosil, C- Probe sonicated SSD of SSG B9 batch.

Table 2: Different runs for probe sonicated CCS SSD with predicted and observed values of %DD.

Batch code	CCS (gm)	Aerosil (gm)	Predicted Value (% DD)	Observed value (% DD)	Prediction error*(%)
A1	1	0.1	58.27	57.48	-1.35
A2	2	0.1	62.85	64.14	2.05
A3	3	0.1	68.7	68.22	-0.69
A4	1	0.2	59.52	60.44	1.54
A5	2	0.2	65.12	64.88	-0.36
A6	3	0.2	71.99	72.29	0.41
A7	1	0.3	63.89	63.77	-0.18
A8	2	0.3	70.51	70.44	-0.09
A9	3	0.3	78.4	78.59	0.24

So A9 and B9 batches are considered as optimized batches from their designs and proceed for further studies.

Optimization Data Analysis and Model Validation

2 factors and 3 levels designs were generated shown in table no. 2& 3. All responses observed for nine formulations of every design were fitted into models using design expert software, it generates quadratic model. Results of ANOVA and other values are quoted in table no. 4. It was observed that independent variable X_1 (Conc. of superdisintegrant) & X_2(Conc. of Aerosil) had a positive effect on dependant variable or response Y (% DD).

Table 3: Different runs for probe sonicated SSG SSD with predicted and observed values of % DD.

Batch code	SSG (gm)	Aerosil (gm)	Predicted value (% DD)	Observed value (% DD)	Prediction error*(%)
B1	1	0.1	55.87	55.25	-1.10
B2	2	0.1	60.3	61.18	1.45
B3	3	0.1	65.5	65.25	-0.38
B4	1	0.2	57.09	57.85	1.33
B5	2	0.2	62.07	61.92	-0.24
B6	3	0.2	67.83	67.85	0.02
B7	1	0.3	61.31	61.18	-0.21
B8	2	0.3	66.84	66.74	-0.14
B9	3	0.3	73.16	73.40	0.32

Regression equation of the quadratic fitted model,

For CCS

$$Y= 57.86+ 1.65\ X_1- 44.54X_2+10.20X_1X_2+0.63X_1^2 +156.03X_2^2 \quad \text{..... (2)}$$

For SSG,

$$Y= 54.56+ 2.70\ X_1- 38.33X_2+5.55X_1X_2+0.38X_1^2 +149.93X_2^2 \quad \text{..... (3)}$$

This equation reveals that relationship between factor and response is not always linear, when change in factor with different levels it leads different degrees of response. Positive sign indicates favorable effect of factors on response.

Table 4: Results of ANOVA for CCS & SSG probe sonicated SSD.

CCS PB	DF*	SS*	MS*	F*	Significance *p*
Model	5	336.88	67.38	124.17	<0.0001 significant
Residual	7	3.80	0.54	-	
Total	12	340.68	67.92	-	
SSG PB					
Model	5	247.73	49.55	172.90	<0.0001 significant
Residual	7	2.01	0.29	-	
Total	12	249.74	49.79	-	

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

Response Surface Plot Analysis

Three dimensional response surface plots were studied to observe response means % DD. Figure 1-A shows response surface plot of CCS conc. (X_1) and conc. of aerosil(X_2) on % DD(Y) & 1-B shows response surface plot of SSG conc. (X_1) and conc. of aerosil (X_2) on % DD(Y), both graphs shows that high the amount of superdisintegrant and aerosil shows higher % DD because of more surface area for drug adsorption.

Optimization and validation

This process optimizes to get best result for the response i.e. % DD. The formulation containing highest amount of super disintegrant and aerosil shows better response. So that batch A9 and B9 were selected as optimized batch as per their response.

Characterization of SSD

Scanning Electron Microscopy (SEM)

Plain GLZ shows irregular shape crystals with particle size more than 100 µm but SSD shows regular elongated and spherical crystal below 50 µm size. It proves that probe sonication causes size reduction and ultimately solubility enhancement. No any crystals were observed in SSD. Fig. 2-A, 2-B, 2-C shows images for plain GLZ, Probe sonicated A9 batch of CCS SSD, Probe sonicated B9 batch of SSG SSD.

Fourier Transform Infrared Spectroscopy (FTIR)

As shown in Fig.3 A9 & B9, all SSDs and GLZ shows characteristic peaks which confirms that there is no interaction of GLZ with CCS, SSG and Aerosilin SSDs. Peaks were observed at wave number 2950 (N-H stretching), 1709(C=O) stretching, 1164(S=O) stretching.

Differential Scanning Colorimetry (DSC)

GLZ shows sharp endothermic peak at 170 ^{0}C, while at physical mixture shows endothermic peak at 165^{0}C proves that there is no interaction of GLZ with superdisintegrants and aerosil. CCS containing SSD and SSG containing SSD also gives broad and less intense peak which due to molecular dispersion of drug in carrier as result of probe sonication, as reveals in fig.4 A9 & B9.

X-Ray Diffraction studies (XRD)

GLZ, physical mixture and SSDs were subjected for XRD studies, in that GLZ shows high intensity

peak at 10.67^0, 15.12^0, 22.21^0 because of crystalline nature of GLZ. No significant change in crystalline pattern of drug was observed in XRD studies, shown in fig. 5 A9 & B9.

Dosage Form Development

After in vitro characterization SSD batches were subjected for tablet formulation development by direct compression technique.

Tablet formulation evaluated for various parameters like weight variation (<0.5%), hardness 3-4kg/cm^2, thickness (<0.5%), friability (0.2-0.6%) and disintegration time (25-27 sec.). In dissolution studies A9 batch shows highest drug dissolution upto 80% while B9 shows 74%. It shows enhanced solubility compared with marketed tablet which shows 71 % DD.

CONCLUSION

The aim of improvement of % DD is achieved by using SSD technique with probe sonication method compared to marketed product. SSD prepared with superdisintegrant CCS gives better results than SSD with SSG. Optimized batches were subjected to SEM which gives fine particle size compared with plain GLZ while FTIR spectra also proves that there is no interaction of drug and excipients. DSC and XRD studies also give evidences that formation of SSD which is useful for solubility enhancement. The SSD were formulated as tablet dosage form with improved dissolution profile in comparison to marketed tablet formulation.

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