International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com

Research Article

Solubility and Dissolution Enhancement of Gliclazide by Solid Dispersion Technique

More C.G*, Dabhade P.S, Jain N.P, Aher B.O

Department of Quality Assurance, S.N.D. College of Pharmacy, Yeola. (MS) India
*Corresponding author

Abstract

The solubility behavior of drugs remains one of the most challenging aspects in formulation development. Most NCE are poorly water soluble drugs, not well-absorbed after oral administration. Solid dispersion is an increasingly important approach to enhance dissolution rate and solubility of poorly water soluble drug. Gliclazide is a second generation hypoglycemic sulfonylurea which is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM). It exhibits slow GI absorption rate and inter individual variations of its bioavailability. Oral bioavailability of drug is 59%. Half-life of drug is about 10hr. Thus solubility enhancement and dissolution enhancement of Gliclazide from its dosage form is an important issue for its in vivo bioavailability and therapeutic efficacy. Therefore it was planned in this investigation to improve the solubility and bioavailability of drug by using different hydrophilic polymers. Also, it was planned to evaluate such solid dispersion formulations for their various pre-compression and compression characteristics, *in vitro* drug release kinetics and stability of the dosage forms.

Keywords: Non-insulin Dependent diabetes mellitus (NIDDM)**,** New chemical Entities(NCE), Solid dispersion's (SD's)

Introduction

The poor aqueous solubility and dissolution rate of API is one of the biggest challenges in pharmaceutical development and is becoming more common among new drug candidates over the past two decades[1]. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms offers many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form originating an effective and reproducible in vivo plasma concentration profile after oral administration[2.] The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability rather than the limited permeation through the epithelia and the formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in the industries[3].Moreover, most promising NCEs, instead of their high permeability, are usually only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, therefore, that there is a small absorption window. Consequently, the incomplete release of these drugs in the gastrointestinal area will show low bioavailability problems[4.] Drug release is a crucial and rate limiting step for oral bioavailability, particularly for drugs with low solubility and high permeability i.e. BCS class II drugs. By improving the drug release profile of BCS class II drugs, it is possible to enhance their bioavailability and reduce side effects[3]. Solid dispersions are one of the most promising strategies to improve drug release of poorly soluble drugs. Solid dispersion's (SD's) can be defined as homogeneous molecular mixtures of poorly water soluble drugs in hydrophilic carriers, presenting a drug release profile driven by the polymer properties.

Chemically Gliclazide is [1-(3-azabicyclo (3,3,0) oct-3-yl)-3-p-tolylsulfonylurea]. It is a second generation

hypoglycemic sulfonylurea which is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM).

Gliclazide is a white crystalline powder, relatively insoluble in water. The pKa of Gliclazide is 5.8. It exhibits slow GI absorption rate and inter individual variations of its bioavailability. Oral bioavailability of drug in rang of 79 to 81 percent. Half-life of drug is about 10hr. Thus solubility enhancement and dissolution enhancement of Gliclazide from its dosage form is an important issue for its in vivo bioavailability and therapeutic efficacy.

Materials and Equipments/Instruments:

1. Materials:

Table 1: List of Materials.

Sr. No.	Materials	Manufacturer
1.	Gliclazide	Indoco, Mumbai.
2.	Gelucire 50/13	Gattefosse, Mumbai.
3.	Polyethylene glycol 6000	LobaCheme, Mumbai.
4.	Glizid 40, Gliclazide tablet 40 mg.	Panacea biotech ltd. Mumbai.

2. Chemicals:

Table 2: List of Chemicals.

Sr. No.	Name of chemicals	Manufacturer
1.	Methanol	Loba chem.
2.	Acetone	Research-LAB-FineChemical Industries, Mumbai.
4.	Sodium phosphate monobasic	Research-LAB-Fine Chemical Industries, Mumbai.
5.	Sodium phosphate dibasic	Molychem, Mumbai.

3. Equipment's/Instruments:

Table 3: List of Equipment's/Instruments.

Sr. No.	Equipment/Instruments	Manufacturer
1.	UV-visible spectrophotometer V-630	Jasco, Japan.
2.	Electronic analytical balance AY.220	Shimadzu, Japan.
4.	Tablet Dissolution Test Apparatus TDT 08L	Electrolab.
5.	IR Spectrophotometer 8400S	Shimadzu, Japan.
7.	Water distillation assembly 3361	Borocil- D.A.P.S. controller.
8.	Melting point apparatus	Analab scientific instrument pvt.Ltd.
9.	Digital pH meter 335	Systronics, Ahmedabad.
10.	Stability chamber	Lab. made assembly.
11.	Water Bath	Classic Scientific, Mumbai.
12.	Differential Scanning Calorimeter DSC60	Shimadzu, Japan.
14.	Powder X-Ray DiffractometerD8	Brukar AXS D8 Advance.
15.	Hot Air Oven	Classic Scientific, Mumbai.
16.	Orbital Shaking Incubator.	Mack Auraa.

Experimental work:

Preformulation testing is important for rational development of dosage forms of a drug substance. Preformulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the dosage form. Hence, Preformulation studies were performed for the obtained sample of drug for identification and compatibility studies.

1. Preformulation study of drug

1. Organoleptic Property:

Drug sample was evaluated for color and odour.

2. Melting Point:

Melting point of Gliclazide was determined by taking a small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The melting point was noted in triplicate.

3. Solubility:

The solubility of Gliclazide was checked in different solvents like Methanol, Ethanol, 0.1 N HCl, 0.1N NaOH & PBS pH 7.4 etc.

4. UV-Visible Spectroscopy:

a) Determination of λ_{max} in Methanol, methanol-water &PBS pH 7.4:

The UV spectrum of Gliclazide was obtained using UV Jasco V630. Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of Methanol, Methanol- water, & PBS pH 7.4 and volume made up to 10 ml. The stock solution was diluted to obtain a concentration of 100 µg/ml. 1 ml of aliquot was withdrawn and volume was made up to 10 ml using methanol to obtain the concentration of 10 µg/ml. The resultant solution was scanned from 400 to 200 nm and the spectrum was recorded to obtain the value of maximum wavelength in respective solvents.

b) Preparation of Calibration curve in Methanol, Methanol-Water &PBS pH 7.4:

Stock solution of drug 100µg/ml was prepared in different solvents like Methanol, Methanol-water, & PBS pH 7.4. The stock solution of 100µg/ml was used to prepare different dilutions in the range of 5-25 µg/ml in respective solvents. The absorbance's of resulting solutions were measured at 227nm, 226nm, 225nm, using respective blank solvents by UV-visible spectrophotometry.

5. Infra-Red Spectrum

The infrared absorption spectrum of Gliclazide was recorded with a KBr disc over the wave number 4000 to 400 cm^{-1} by using Fourier transform infrared spectrophotometer (Shimadzu 8400s).

2. Compatibility Study:

1. Fourier Transform Infra-Red spectroscopy .

Compatibility study was carried out by using Fourier transform infrared spectrophotometer (Shimadzu 8400s). FTIR study was carried on pure drug. Physical mixture of drug and polymers were prepared and samples kept for 1 month at 40^0C. The infrared absorption spectrum of Gliclazide and physical mixture of drug and polymers was recorded using KBR disc over the wave number 4000 to 400 cm^{-1}.

3. Phase solubility study:

40 milligrams of Gliclazide was added into glass-stopper flasks containing 50 ml of polymers solutions of increasing concentrations (20, 40, 60, 80, 100, 120 mg) as in ratio 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, 1:3. The flasks were sealed and shaken at 25±0.5°C. After equilibration for 72 h, the solutions were filtered through Whatman filter paper. Then the filtrates were suitably diluted and the concentration of Gliclazide was estimated by UV spectroscopy at 226 nm.

4. Solid Dispersion:

The solid dispersion prepared by solvent evaporation and fusion method. The physical mixture and solid dispersion prepared by w/w ratio.

1 Preparation of Physical Mixture

The physical mixture of Gliclazide with carriers was prepared by mixing the required amount of Gliclazide and carriers for 15 min in a mortar with pestle until a homogeneous mixture was obtained. This resulting mixture was sieved through a 100 mesh screen. The powder was stored in a screw cap container at room temperature which is given in Table 7.1.

Table 1: Composition of various formulations of physical mixtures

Sr. no	Drug	Polymer	Molar ratios and coding	
1	Gliclazide	PEG6000	1:1 (PP1)	1:2 (PP2)
2	Gliclazide	Gelucire 50/13	1:1 (PG1)	1:2 (PG2)
3	Gliclazide	PEG6000+Gelucire 50/13	1:1:1 (PM1)	1:2:2 (PM2)

2. Preparation of solid dispersion:

Different polymers were employed in order to formulate Solid Dispersions of drug. Different drug: polymer w/w ratios were employed as 1:1, 1:2, 1:1:1, 1:2:2 & SD's were prepared by two methods as Solvent evaporation & Melt method. Polymers employed were PEG 6000 and Gelucire 50/13 in combination and individually.

A. Solvent evaporation method

Solid dispersions of Gliclazide were prepared by Solvent Evaporation method using PEG 6000 and Gelucire 50/13, as carrier in combination and individually, in various w/w ratios. Drug & polymers were dissolved in minimum volume of mixture of Methanol and acetone solvent system (1:1) v/v in the ratio 1:1, 1:2, 1:1:1, 1:2:2 and the solution were made homogeneous by continuous stirring and solvent was evaporated by subjecting the solution with constant stirring at room temperature till complete evaporation of solvent. The obtained SD's were dried and subsequently pulverized by triturating in pestle-mortar & screened through 80 mesh sieve. The prepared solid dispersion was then filled in glass bottles, sealed and stored in a desiccator until further use.

B. Melt method/Fusion method :

Solid dispersions of Gliclazide were prepared by Melt/ Fusion method using PEG 6000 and Gelucire 50/13, as carrier in combination and individually, in various w/w ratio. PEG 6000 or Gelucire 50/13 or in combination was placed in a porcelain dish and allowed to melt by heating 10^0C above the melting point of each carrier for 5 minutes with continuous stirring until homogenous dispersion was obtained. For rapid solidification, the resultant solution was cooled in ice bath and stored in dessicator for 24 hr. It was then scrapped, pulverized and passed through sieve. The prepared solid dispersion was then filled in glass bottles, sealed and stored in a dessicator until further use.

3. Composition of SD's:

Table 2: Composition of various solid dispersion's

Sr. No.	Drug	Polymer	Ratio and coding	Method of preparation
1.	Gliclazide	PEG 6000	1:1 (SP1) 1:2 (SP2)	Solvent Evaporation Method.
2.	Gliclazide	PEG 6000	1:1 (FP1) 1:2 (FP2)	Fusion Method.
3.	Gliclazide	Gelucire 50/13	1:1 (SG1) 1:2 (SG2)	Solvent Evaporation Method.
4.	Gliclazide	Gelucire 50/13	1:1 (FG1) 1:2 (FG2)	Fusion Method.
5.	Gliclazide	PEG 6000+Gelucire 50/13	1:1 (SM1) 1:2 (SM2)	Solvent Evaporation Method.
6.	Gliclazide	PEG6000+Gelucire50/13	1:1 (FM1) 1:2 (FM2)	Fusion Method.

5. Physical Characterization of Solid dispersion:

1. Angle of repose:

Funnel method:

Funnel with a sound stem of 20 to 30 mm diameter was attached to the burette stand the height of which was adjusted such that its tip just touches the apex of powder. The graph paper sheet was placed below the funnel. The powder was allowed to flow through the funnel freely onto the surface of the graph paper sheet. Circle was marked around the heap covering approximately 90% of total powder bed. Procedure was repeated thrice to obtain the average reading & average diameter.

$$tan\theta = \frac{h}{r} \quad \text{---------- (1)}$$

Where h is height if the powder pile and r is radius of heap.

Table 7.3: Relationship between angle of repose and powder flow.

Angle of repose °θ (degree)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

7.5.2. Compressibility index/ Carr's index:

It is also one of the simple method to evaluate flow property of a powder by comparing the bulk density and tapped density. Compressibility index was determined by placing the powder in a measuring cylinder, the volume (V0) was noted before tapping and after 100 tappings again volume (V) was noticed. Average of three compressibility indices of powder/granule readings were taken and tabulated (n = 3).

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

3. Hausner's ratio:

It provides an indication of the degree of densification that could result from vibration of feed hopper. Lower the Hausner's ratio better is the flowability.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Grading of the powder for their flow properties according to carrs index:

Table .4: Relationship between compressibility index and flow property.

Compressibility Index. (carr's %)	Flow
5-15	Excellent
12-16	Good
18-21	Fair to pass
23-35	Poor
33-38	Very poor
>40	Very very poor

4 Bulk density:

Bulk density of solid dispersion granules were determined by pouring gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. The powder was carefully leveled without compacting it and the apparent volume was measured (V_o). Bulk density was calculated as below**:**

Bulk density (g/ml) = M/Vo
Where,

M = mass of powder

V_o = apparent unstirred volume

5. Tapped density:

The tapped density was determined by pouring 25 gm sample (solid dispersion) through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume obtained. Volume occupied by the sample after tapping was recorded and tapped density was calculated.
Tapped density (g/ml) = M/V_f
Where,

M = weight of sample powder

V_f = tapped volume.

6. Percentage yield :

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus it help in selection of appropriate method production. Solid dispersion was collect and weighs to determine percentage yield from the following equation.

$$\text{Percent yield} = \frac{\text{Wt. of prepared solid dispersion}}{\text{Wt. of drug + wt. of carriers}} \times 100$$

7. Percentage drug content:

An accurate weight of solid dispersion equivalent to 40 mg of Gliclazide was dissolved in 20 mL of methanol in 100 mL volumetric flask, the volume was made to the mark with phosphate buffer solution pH 7.4 and the solution was filtered through Whatman filter paper No. 40. The above solution was further diluted with phosphate buffer solution pH 7.4.

7.8. Solubility studies

The solubility of Gliclazide, physical mixture and solid dispersion was determined in distilled water. The solubility of drug and solid dispersion were determined by taking 10 mg drug, equivalent quantity of solid dispersion and added them in 20 ml of distilled water, in 25 ml vials. The samples were kept at equilibrium for a period of 72 hrs. in incubator at 37 ± 0.5^0C with occasional shaking. The supernatant collected from vials was filtered through Whatman filter paper and analyzed by UV-Visible spectrophotometer (V630, Jasco) at the wavelength of 226 nm.

All experiments were conducted in triplicate (n=3) and tabulated.

9. Fourier Transform-Infra Red Spectroscopy:

FT-IR spectra of plane Gliclazide and solid dispersions with various carriers by using Fourier transform infrared spectrophotometer (8400S Shimadzu, Japan). Solid dispersions were mixed with potassium bromide (KBR) of IR grade in the ratio of 1:100 and compressed using motorized pellet press at 15 tones pressure. The pellets were then scanned using FT-IR spectra of mixtures were compared with that of plane drug for change or shift in any principle peak of spectra of plane drug.

10. Differential Scanning Calorimetry

The powdered sample (5-10 mg) was hermetically sealed in aluminum pans and heated at a constant rate of 10 °C/min, over a temperature range of 60-250°C with nitrogen flow rate of 30 ml/min. Thermograms of the samples were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale.

11 Powder X-Ray Diffraction:

PXRD analysis was done by irradiating the samples with monochromatized Cu Kα radiation (1.506 Å) and analyzed between 5° to 60° (2θ) employing a Bruker

AXS D8 Advance Diffractometer with Lynx Eye Detector. The step was at rate of 0.020^0 with step time of 32.8 sec. The diffractogram was produced by using Diffrac plus Software.

12. Dissolution Study:

The powder dissolution test of Drug, Physical mixture, Solid dispersion, Marketed formulation was carried out using the USP dissolution test apparatus type II. The dissolution media, paddle speed, bath temperature and UV analysis was done as per the information given in table 7.5. 5 ml aliquots were withdrawn at particular interval of time and replaced by 5 ml of fresh dissolution media. The collected samples were analyzed after filtration at wavelength of 226 nm using UV-visible spectrophotometer against the blank. *In vitro* drug release data of the best solid dispersion prepared was fitted to various release kinetic model viz. zero-order, first-order, and Higuchi matrix and Korsmeyers-peppas model.

Table .5: Dissolution test parameters for powder dissolution test of solid dispersions

SD (Drug)	Dissolution Media (900 ml)	Paddle Speed (RPM)	Bath Temperature (^oC)	UV analysis (wavelength) (nm)	Sampling Interval (min)
Gliclazide	pH 7.4	50	37±0.5	226 nm	5,10,15,30,60,90, 120.

13. Kinetic Models:

To study the release kinetics, data obtained form in vitro drug release study were tested with the following mathematical model.

1. Zero order equation:

The equation assumes that the cumulative amount of drug release is directly related to time. The equation may be as follows:

$$C = K_0 t \text{---------- (1)}$$

Where, K_0 is the zero order rate constant expressed in unit concentration/time and t is time. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

2. First order equation:

The release behaviour of first order equation is expressed as log cumulative percentage of drug remaining vs time. The equation may be as follows

$$\text{Log } C = \text{Log } C_0 - kt / 2.303 \text{ ---------- (2)}$$

Where,

C = the amount of drug un-dissolved at t time,
C_0 = Drug concentration at t = 0,
k = Corresponding release rate constant.

3. Higuchi square root law:

The Higuchi release model describes the cumulative percentage of drug release vs square root of time. The equation may be as follows

(Higuchi, 1961):

$$Q = K\sqrt{t} \text{ ---------- (3)}$$

Where, Q = the amount of drug dissolved at time t. K is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

4. Korsmeyers-peppas Equation:

Korsmeyers-peppas developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$Q_t / Q\infty = K_k t^n \text{ ---------- (4)}$$

Where, K_k is the constant incorporating structural and geometric characteristics of the drug dosage form and n is the release exponent, indicative of drug release mechanism. The release exponent can be obtained from the slope and the constant K is obtained from the intercept of the graphical relation between logarithmic versions of left side of equation verses log t.

Table 6: Release exponents and respective drug release mechanism

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$T^{-0.5}$
$0.5 \leq n \leq 1.0$	Anamalous transport	t^{n-1}
1.0	Case- II transport	Zero order release
	Super case-II transport	tn-1

14. Stability studies:

After determining the drug content and release studies, the optimized formulation was charged for the accelerated stability studies according to ICH guidelines (40 ± 2ºC and 75 ± 5% RH) for a period of 3 months in a stability chamber. The optimized formulations were placed in vials and hermetically closed with bromobutyl rubber plugs and sealed with aluminum caps. The samples were withdrawn at 15, 30, 60 and 90 days and evaluated for the drug content and *in vitro* drug release.

Results

The enhancement of the oral bioavailability is currently one of the greatest challenges in the development of poorly water soluble drugs.In this project we had discussed about fundamentals of solubility enhancement which ultimately leads to improvement in dissolution and bioavailability. There are numerous ways of solubility enhancement, each having its own advantages and disadvantages. Hence there is a need of such a reliable method that will fulfil the requirement of formulation and development. Here we have selected a novel method of solubility enhancement which forms solid dispersion by use of various water soluble carriers. To prove the applicability of the method we have selected drugs belonging to BCS class II.

Chemically gliclazide is [1-(3-azabicyclo (3,3,0) oct-3-yl)-3-p-tolylsulfonylurea]. It is a second generation hypoglycemic sulfonylurea which is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM).
Gliclazide is a white crystalline powder, relatively insoluble in water. The pKa of Gliclazide is 5.8. It exhibits slow GI absorption rate and inter individual variations of its bioavailability. Oral bioavailability of drug is 59 %. Half-life of drug is about 10 hr. Thus solubility enhancement and dissolution enhancement of Gliclazide from its dosage form is an important issue for its in vivo bioavailability and therapeutic efficacy.

Literature review revealed that various natural and synthetic polymers can be utilized as the carriers for the solubility and dissolution enhancement.Thus to enhance the solubility and dissolution rate of Gliclazide by solid dispersion with hydrophilic polymers, such as PEG 6000 and Gelucire 50/13 were prepared by solvent evaporation method and fusion method. Solid dispersions were prepared with PEG 6000 and Gelucire 50/13 in combination or individual polymer in various ratios. After comparing the solubility and dissolution profile of various solid dispersions, it was observed that solid dispeon prepared by Solvent Evaporation method using PEG 6000-Gelucire 50/13 in combination of polymers shows better dissolution profile as compared to PEG 6000 and Gelucire 50/13 individual polymer. In the characterizations of solid dispersion, FTIR shows from the peaks of solid dispersion namely SP_2, SG_2 and SM_2 it can be concluded that principle peak values of drugs remain unchanged in the solid dispersion.DSC study indicates that in solid dispersion formulation drug goes into amorphous state from crystalline state. *In vitro* study indicates that all solid dispersions shows better dissolution than pure drug and also when selected formulation compared with marketed formulations (Glizid 40) it shows better dissolutions than marketed formulations. Combination of polymers shows synergistic effect than individual polymers. In kinetics study Higuchi model shows better and Korseymeres-Peppas model shows fickian diffusion which indicates that drug release with diffusion and erosion pattern. Stability studies were conducted according to ICH guidelines region IV at 40ºC / 75 % RH indicates that there is no significant change in drug content for a period of 3 months which shows formulations was stable.

Conclusion

Above studies successfully demonstrated the use of PEG 6000 and Gelucire 50/13individually and in combination as carrier for formation of Solid dispersions in solubility and dissolution enhancement by solvent evaporation and fusion method.The solid disperseon Gliclazide: PEG 6000: Gelucire 50/13 (1:2:2 w/w ratio) show best result as compared to Gliclazide: PEG 6000 and Gliclazide: Gelucire 50/13 in solubility and dissolution enhancement. The PXRD and DSC studies indicated the transformation of crystalline Gliclazide to amorphous form by solid dispersion technology. The aqueous solubility and dissolution study shows a remarkable improvement in both solubility as well as drug dissolution of this new Gliclazide solid dispersion in combination polymer than individually. The dissolution of Gliclazide was found to follow Higuchi model. The stability studies state that, Solid dispersion containing formulations are stable. Finally from overall studies we can conclude that Solid dispersion can be successfully used for the solubility, dissolution and bioavailability enhancement.

- The value of U.V. absorbance maxima 226 nm obtained during this study corroborates with literature value.
- Melting point was found to 180-183ºC which was within the literature range 181ºC.
- Solubility of Gliclazide was found to be 0.0700 mg/mL in distilled water, 1.558 mg/mL in methanol and 0.319 mg/mL in pH 7.4 phosphate buffer and 0.155mg/mL in pH 1.2 Acetate buffer.
- In case of compatabity study FTIR of all physical mixture shows no interaction between drug and polymers.
- In case of physical property, most of the formulation shows good angle of repose which indicates flow of powder was good.
- From the results of Compressibility (Carr's) index and Hausner's ratio it can be clearly concluded that the drug and its different formulations are having good or passable, fair to good compressibility which shows poor flowing property i.e. greater interparticulate interaction was observed.
- Percentage yield of all selected solid dispersion formulations is for SP2 formulation 94.43% for SG2 formulation 91.25% and for SM2 formulation 97.55% which help in the selection of appropriate method.
- Percentage drug content of all selected solid dispersion formulation is for SP2 formulation 98.65±0.92, for SG2 formulation 98.98±0.43 and for SM2 formulation 100.02±1.17 which shows uniform distribution of drug in formulations.
- The aqueous solubility of Gliclazide was found to be 0.700 mg/ml. the aqueous solubility of selected formulations as SP2, SG2 and SM2 was 0.1210±0.005, 0.4674±0.007 and 0.7280±0.008 respectively.
- As compared the aqueous solubility of formulations with pure drug we found that increase the aqueous solubility of formulations SP2, SG2 and SM2 by 1.72 folds, 6.67 folds and 10 folds respectively with solvent evaporation method.
- FTIR shows from the peaks of solid dispersion namely SP_2, SG_2 and SM_2 it can be concluded that principle peak values of drugs remain unchanged in the solid dispersion. Thus it can also conclude that there was no chemical interaction between the drug and polymers and the polymers and their combinations we used for preparations of solid dispersion are compatible with the drug.
- In case of DSC, pure Gliclazide shows an apparent sharp endothermic peak at 170.56°C corresponding to its melting point, indicating its crystalline nature. In case of solid dispersions namely SP2, SG2 and SM2 shows DSC peak at 63.01°C, 61.74°C and 50.88°C which indicate that formulations is in amorphous state.
- *In vitro* study indicates that all solid dispersions shows better dissolution than pure drug and also when selected formulation compared with marketed formulations (Glizid 40) it shows better dissolutions than marketed formulations.
- When we apply kinetic models we found that Higuchi model with the best fit correlation coefficient value (R^2 value of SP2, SG2 and SM2 formulation was 0.9613, 0.9409 and 0.9693 respectively)and Korseymeres- Peppas model shows fickian diffusion.
- Stability studies were conducted according to ICH guidelines region IV at 40ºC / 75 % RH indicates that there is no significant change in drug content for a period of 3 months which shows formulations was stable.

References

1. Vo CL, ParkC, Lee BJ.Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics. 2013;85: 799–813.
2. Vasconcelos T, Sarmento B, Costa P. Dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discovery Today. 2007;12(23/24):1069-1075.
3. Horter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in gastrointestinal tract: Advance Drug Delivery Review. 1997; 25:3-14.
4. Sridhar I, Doshi A, Joshi B, Wankhede V, Doshi J. Influence of physicochemical properties on dissolution of drugs in gastrointestinal tract Review. Advance Drug Delivery Review. 2013; 2 (3): 685-694.
5. Amidon GL, Lennernas H, Shah VP,Crison JR. A theoretical basis for a biopharmaceutics drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical Research. 1995; 12(3): 413–420.
6. FDA, (2000) Guidance for Industry, Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Available at:
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf (Last accessed August 2013).
7. Artursson P, Palm K, Luthman K. Caco-2 monolayers in experimental and theoretical predictions of drug transport. Advanced Drug Delivery Reviews. 2012; 64: 27–43.
8. EMEA,(2010) Guideline on the investigation of bioequivalence. Available at: http://www.ema.europa.eu/docs/enGB/documentlibrary/Scientificguideline/2010/01/WC500070039.pdf.
9. WHO, 2006. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Annex. 7, WHO Technical Report Series 937. Available at: http://whqlibdoc.who.int/trs/ WHO TRS 937 eng.pdf.
10. Cook J, Addicks W, Wu YH. Application of the biopharmaceutical classification system in clinical drug development—an industrial view. The AAPS Journal. 2008; 10(2): 306–310.
11. Lobenberg R,Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international requlatory standers. European Journal of Pharmaceutics and Biopharmaceutics. (2000); 50: 3-12.
12. Kawabata Y,Wada K, Nakatan M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. International journal of pharmaceutics. (2001); 420: 1-10.
13. Horter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Advanced Drug Delivery Reviews. 2011; 46: 75–87.
14. Text book of physical pharmaceutics: CVS Subramanyam., 2nd edition, vallabhprakashan; 1995, p.180-234.
15. Mohd. Y, Mohd A, Kumar A, Aggarval A. Biopharmaceutical classification system: an account. International Journal of Pharmatech Research. 2010 July-Sept; 2(3):1681-1690.
16. Fasano A. Innovative strategies for the oral delivery of drugs and peptides. Trends in Biotechnology. 1998;16: 152–157.
17. Controlled release medication. In: Brahmankar DM, Jaiswal SB, editors. Biopharmaceutics and Pharmacokinetics a treatise. Vallabh Prakashan; 1995. p. 337- 356.