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FORMULATION AND EVALUATION OF GLIBENCLAMIDE SOLID DISPERSIONS USING KNEADING METHOD

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ABSTRACT

The objective of this research work was to formulate and evaluate Glibenclamide fast dissolving tablets with enhanced drug solubility by preparing solid dispersions using kneading method. Glibenclamide is an anti diabetic agent of the sulfonylureas drug class. It is a poorly water-soluble drug. Solid dispersions were made to enhance the solubility of the drug and increase drug absorption, further increasing the bioavailability. Glibenclamide tablets were prepared by direct compression technique using different polymers such as PEG 4000, PEG 6000 and Arginine along with Croscarmellose sodium, Sorbitol, Mannitol, Magnesium Stearate, and Talc. FTIR and DSC studies were performed to know the interaction of Glibenclamide with selected excipients. Glibenclamide tablets were developed in nine different formulations using various ratios of polymers. The formulations were evaluated for various physical parameters such as thickness, hardness, weight variation, friability, drug content and *in vitro* drug release. The formulation F9 showed maximum percentage of drug release. Hence, it was considered as the optimized formulation.

KEYWORDS: Glibenclamide, Solubility enhancement, Solid Dispersions, PEG, Arginine, Fast release tablets.

INTRODUCTION

Solubility is defined as a maximum quantity of solute dissolved in a quantity of solvent or quantity of solution at a specified temperature. To achieve desired concentration of drug in systemic circulation for pharmacological response solubility is one of the important parameter to be shown. Oral route of drug delivery is the most common, easiest and simplest way of administering dosage form. The drug must possess good solubility for oral administration. Oral bioavailability of a drug is found to be dependent on its solubility and/or dissolution rate. A low bioavailability will be seen if these drugs are not completely released in the gastrointestinal tract.[1-4] In Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility, slow dissolution rate, high dose and high permeability are categorized as class-II drugs. Particularly for drugs with low gastrointestinal solubility and high permeability, drug release is a crucial and limiting step for oral drug bioavailability. Thus, efforts are often required to increase dissolution of drugs with limited aqueous solubility.[5] Improvement of aqueous solubility of such drugs is one of the major concerning factors of the pharmaceutical industries.[6-8] Many methods are available to improve to overcome the low bioavailability either by salt formation, particle size reduction, floating granules, cryogenic technology, solid dispersions, nano-suspension, micronization etc.

One of the most successful strategies to improve drug release of poorly soluble drugs are Solid dispersions.[7,9,10] Solid dispersions are molecular mixtures of poorly aqueous soluble solid drug in an inert hydrophilic carrier. Drug release profile from such mixtures is driven by the polymer properties.[11] Diverse water-soluble carriers such as polyethylene glycols (PEG4000 and PEG 6000), polyglycolized fatty acid ester, polyvinylpyrollidone K25 (PVP), poloxamers, polyols (mannitol, sorbitol), organic acid (citric acid), hydrotopes (urea, nicotinamide), Arginine are used as carriers for solid dispersion.[12,13,14,15] There are various methods for preparing solid dispersion which includes the melting method, the solvent method, kneading method, fusion method, physical mixture, super critical fluid method, etc.[11]

Glibenclamide or glyburide is known as 5-chloro-*N*-(4- [*N*-(cyclohexylcarbamoyl) sulfamoyl]phenethyl)-2-methoxybenzamide chemically, is oral hypoglycaemic drug (sulphonyl urea's-second generation). It acts by inhibiting ATP-sensitive potassium channels in pancreatic beta cells which causes cell membrane depolarisation and in-turn voltage dependent calcium channels to open, with an increase in intracellular calcium in the beta cell

that stimulates insulin release. In treatment of type 2 diabetic patients after well establishing that this compound acts by increasing insulin release from the beta cells in the pancreas, it has been widely.

According to biopharmaceutical classification system (BCS) Glibenclamide is classified under class II and the solubility of drug depends on pH. At 37°C Glibenclamide exhibits very poor solubility (<0.004 mg/ml) in acidic and neutral aqueous media, solubility of drug is slightly increased to 0.02 mg/ml at pH > 7. An unpredictable bioavailability is observed due to this poor solubility leading to poor dissolution.

MATERIALS AND METHODS

The pure drug Glibenclamide was a gifted sample from Emco Labs. Arginine (25g) was bought from Premier Trading Company, Kothi, and Hyderabad. PEG4000, PEG6000, Sorbitol, Mannitol, Magnesium Stearate and Talc were bought from S.D.Fine Chemicals, Mumbai. All chemical and reagent used were of analytical grade.

Analytical Methods Used for the Estimation of Drug Either in BULK OR in Diffusion Samples: The U.V spectrophotometer analytical methods were developed for the above drug using U.V spectrophotometer of analytical technologies limited. The two steps involved are determining the lambda max of the drug (Glibenclamide) and establishment of standard graph or calibration curve.

Procedure for Estimating Lambda Max: Instruments and material: Instrument used was Pharma spec UV 1700 Schimadzu and AX200 analytical balance.

Stock I: 10mg of the drug was accurately weighed and transferred into the 100ml volumetric flask. It was dissolved in sufficient quantity of phosphate buffer and volume was made up to the mark with phosphate buffer to get a 100µg/ml solution. This solution containing 1 mg/ml of model drug was the standard stock (Stock I).

Estimation of Absorption Maxima (λ max) of Drug Sample in Phosphate Buffer 6.8 pH

Stock II: From the above solution one ml was then further diluted to 10 ml with phosphate buffer to get a stock solution of 10µg/ml. UV scanning was done for 10µg/ml drug solution from 200-400nm using phosphate buffer pH 6.8 as a blank in Schimadzu, UV spectrophotometer. The maximum wavelength was found to be at 238 nm. By repeating the procedure three times the value was confirmed.

Procedure for Establishing of the Calbration Curve

The required quantity of drug was dissolved in Phosphate buffer pH 6.8 to get a stock solution of 100µg /ml solution from which serial dilutions were made in order to get 2 to 32µg/ml of the final solution. Then the absorbance of these dilute solutions was measured at lambda max of 238 nm by using UV spectrophotometer against a blank of Phosphate buffer pH 6.8 solutions. The results obtained were tabulated and Standard curve preparation was performed. The absorbance was plotted against the concentrations and the graph with the straight-line equation and R^2 value were obtained obeying Beer Lamberts law.

Solubility Studies: The solubility of glibenclamide was determined in different solvents system (particularly phosphate buffer pH 6.8 and distilled water). An excess quantity of the drug was mixed separately with 10mL of each solvent in conical flasks and kept on shaker for 24 hours at room temperature. The solutions were analyzed spectrophotometrically at λmax 238 nm.

Preparation of Glibenclamide-PEG400 & 6000 and Glibenclamide-Arginine Solid Dispersion

a) Preparation of physical mixture: The physical mixture of drug (Glibenclamide) and carrier (PEG4000/PEG6000/Arginine) are mixed in the ratios of 1:1, 1:3 and 1:5 by accurately weighed amounts of drugs and various carriers with the help of a spatula in a glass mortar.

b) Preparation of solid dispersion by kneading method: The physical mixture is wetted with sufficient volume of methanol and kneaded thoroughly for 30 minutes in a glass mortar. The kneaded mixture so formed is passed through sieve no.60 and kept under an inverted funnel overnight and then dried in an oven at 40^0c in oven for 20 mins.[14]

Table No. 1: Physical Mixture Formulation.

Formulation	Drug: Polymer	Ratio
F1	Glibenclamide : PEG 4000	1:1
F2	Glibenclamide : PEG 4000	1:3
F3	Glibenclamide : PEG 4000	1:5
F4	Glibenclamide : PEG 6000	1:1
F5	Glibenclamide : PEG 6000	1:3
F6	Glibenclamide : PEG 6000	1:5
F7	Glibenclamide : Arginine	1:1
F8	Glibenclamide : Arginine	1:3
F9	Glibenclamide : Arginine	1:5

Preparation of Fast Release Tablets of Glibenclamide By Using Solid Dispersion Technique: The solid dispersion so obtained is then weighed and required quantity of SD is then mixed with croscarmellose sodium as a superdisintegrant, talc as lubricant, sorbitol as a sweetener, and mannitol as a diluent. This mixture is then subjected to direct compression in a tablet compression machine.

Tablet No. 2: Tablet Formulation.

Ingredients	Quantity (mg)
Solid Dispersion	8.5(equivalent to 5mg of drug)
Mannitol	50
Sorbitol	9.5
Croscarmellose Sodium	4
Magnesium Stearate	8
Talc	2
Total weight	80

Physical Characterization

Preformulation studies: Prior to compression, granules were evaluated for their characteristic precompression parameters, such as bulk density, tapped density, Hauser ratio, Carr's compressibility index and angle of repose.

Determination of Percent Yield: The percent yield of glibenclamide solid dispersions can be determined by using the following expression.[12]

Percent yield = (weight of prepared solid dispersion / weight of drug + carriers) X100

Determination of percent drug content: Weighed amount of solid dispersions, equivalent to 5 mg of glibenclamide were separately taken and added to 100 ml of phosphate buffer 6.8 in stopper conical flask. The sealed flasks were agitated on a sonicator. The solution was diluted with phosphate buffer 6.8 and was assayed by a UV-VIS spectrophotometer for drug content at 238 nm using the following expression: The actual drug content was calculated as follows.[13]

Percent Drug content = (practical glibenclamide content in weighed quantity of solid dispersions x 100)/Theoretical amount of glibenclamide in solid dispersion

Micromeritic Characterization: The powder mix was evaluated for flow properties i.e, bulk and tapped density, Angle of repose, Carr's compressibility index, and Hausner's ratio.

a) Determination of Bulk density: The pre-seived bulk powder blend was weighed. It was then placed in a graduated cylinder and the volume occupied by the powder wise noted without disturbing the cylinder and bulk density (g/ml) is calculated by the following equation: Bulk density = Weight of powder mix/volume of powder blend

b) Determination of Tapped density: The pre-weighed amount of powder blend was placed in a graduated cylinder and tapped for fixed number of taps (around 50) on mechanical tapping apparatus. From this the tapped volume was noted. Finally the tapped density was computed.

Tapped density = Weight of powder mix/tapped volume of powder blend.

c) Compressibility: Compressibility of the drug is found out using the following formula.

$$\% \text{ Compressibility} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

d) Hausner Ratio: Hausner of the drug is found out using the following formula.

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

e) Determination of Carr's Index: It was used to determine the compressibility of powder blends from the results of bulk density and tapped density.

Carr's index = (Tapped density - Apparent bulk density)/Tapped density

f) Determination of Angle of Repose: It was determined through funnel method. At a given height (H) glass funnel with its tip is fixed above a piece of graph paper on a horizontal surface. Powder was poured through the funnel specified the apex of the round shape pile touched the tip of the funnel. The angle of repose (θ) can be calculated using the formula:

$\tan \theta = H/R$ Where, H - Height of the pile, R- is the radius of the conical pile.

Evaluation of Glibenclamide Tablets

Weight variation: The procedure for weight variation test was performed as per I.P. The weight (mg) of every individual tablet for twenty tablets selected randomly from each batch was determined by dusting and placing them in an electronic balance. The percent deviation was determined by comparing individual weight with average weight.

Thickness: Six tablets were selected at random from each batch and thickness was measured by using vernier caliper.

Hardness: Tablets require a certain amount of hardness to withstand mechanical shocks of handling in manufacturing, packaging and shipping. Hardness was measured using Pfizer hardness tester. For each batch six tablets are tested.

Friability: Friability is the measure of tablet strength. Roche type friabilator was used for this purpose. Twenty tablets were weighed accurately and placed in tumbling equipment that revolves at 25 rpm dropping the tablets from a height of 6 inches in each revolution. The tablets were weighed after 4 minutes and the percentage loss was determined.

Drug content uniformity: Using methanol as the extracting solvent, the tablets were assayed for the drug content. Four tablets were weighed and crushed in a mortar then powder equivalent to 100 mg of drug was added to 100ml methanol. The solution was diluted appropriately and Glibenclamide was estimated spectrophotometrically at 238 nm.

***In vitro* disintegration time**

The disintegration test was performed using Electro lab disintegrating apparatus. Place one tablet in each of the six tubes of the basket and operate the apparatus using pH 6.8 phosphate buffer maintained at 37±0.5ºC as the immersion fluid, the time to complete disintegration of tablets was then noted.

***In vitro* dissolution study**

In vitro drug release studies of all the formulations were carried out using USP XXII type II dissolution test apparatus with phosphate buffer pH 6.8 at 50 rpm and temperature maintained at 37±1ºC. Samples were withdrawn at every 5 min intervals, diluted suitably and analyzed at 238 nm for cumulative drug release using an UV- spectrophotometer (Shimadzu-1700, Shimadzu Corporation, Japan). The study was done in triplicate. The calculated concentration was expressed as cumulative percent of the drug released.

RESULTS AND DISCUSSION

I) Preparation of Calibration Curve: The linearity of response of the drug was obtained at 0 to 32µg/ml concentrations. The calibration curve was obtained by plotting the absorbance versus the concentration data and was treated by linear regression analysis as shown in Figure 1.

Table No. 3: Standard Graph Values of Glibenclamide.

Concentration	Absorbance
0	0
4	0.128
8	0.284
12	0.381
16	0.489
20	0.592
24	0.732
28	0.863
32	0.978

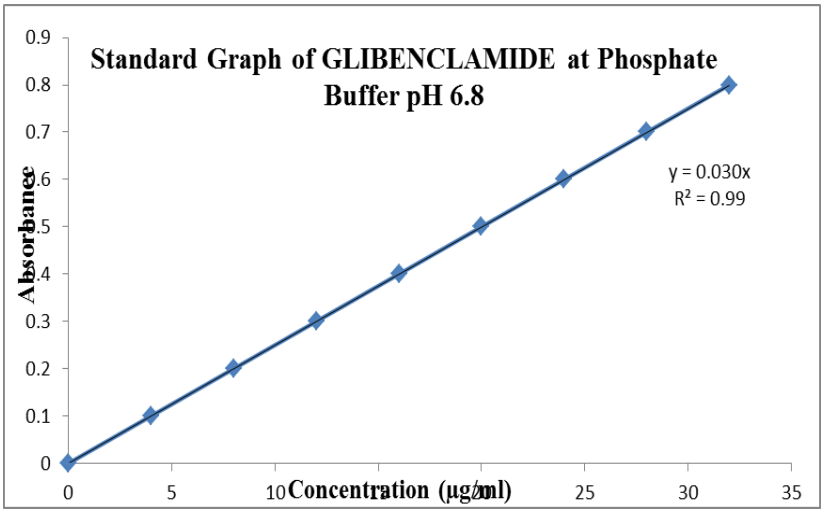


Figure No. 1: Standard Graph of Glibenclamide.

The linear regression analysis was done on absorbance data points and the results are as follows

The Slope= 0.030

The intercept= 0

The correlation coefficient= 0.99

A straight-line equation (y= mx + c) was generated to calculation for amount of drug. The equation is as follows: Absorbance = 0.03 X Concentration.

Fourier Transformed Infrared Spectroscopy

Fourier transformed infrared spectroscopy has been used to assess the interaction between carrier and drug molecule. FT-IR spectra were recorded from single average scans collected in the region 400-4000 cm^{-1} at spectral resolution of $2cm^{-2}$ and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu. In IR spectra of Glibenclamide and its solid dispersions are identical. The principal absorption of peaks of

Glibenclamide solid dispersion were found same that's mean there is not any interaction between drug and carriers used to preparation of solid dispersion of drug.

Table No. 4: Interpretation of FT-IR of Pure Glibenclamide

S. No.	Frequency (cm^{-1})	Vibration Mode
1	2361.58	S=O(cm^{-1})
2	1743.42	C=O(cm^{-1})
3	1516.46	C=C(cm^{-1})
4	1339.93	C-N Amines (cm^{-1})

Table No. 5: Interpretation of FT-IR of Glibenclamide Solid Dispersion.

S. No	Frequency (cm^{-1})	Vibration mode
1	3648.04	O-H ($cm^{-1)}$
2	2360.95	S=O ($cm^{-1)}$
3	1516.13	N-O ($cm^{-1)}$
4	1338.60	C-N Amines ($cm^{-1)}$

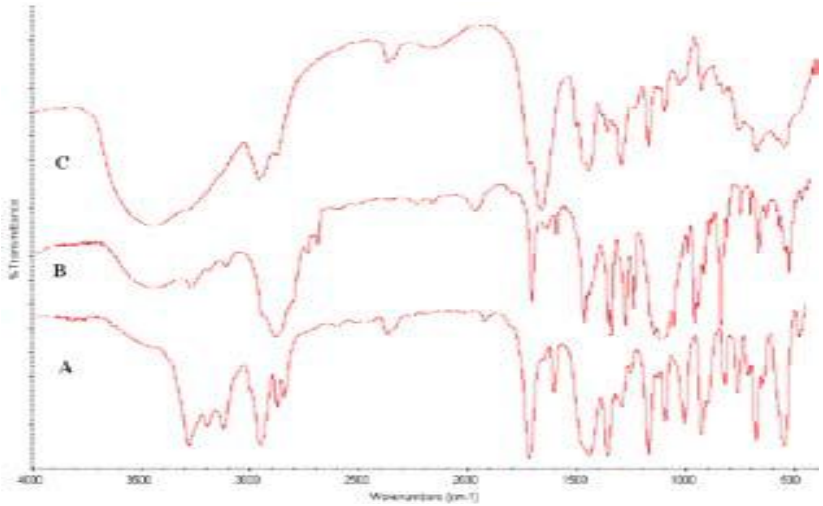


Figure No.2: (a) A – Glibenclamide, B-PEG 4000, C-Glibenclamide-PEG 4000 SDS.

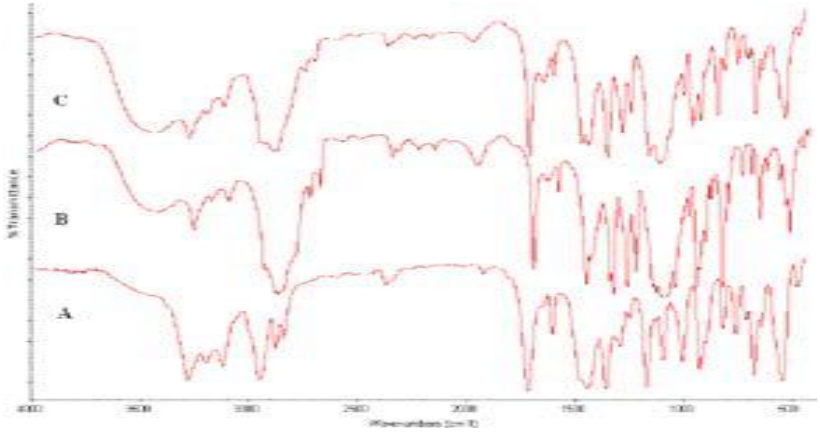


Figure No. 3: (b) A – Glibenclamide, B-PEG 6000, C-Glibenclamide-PEG 6000 SDS.

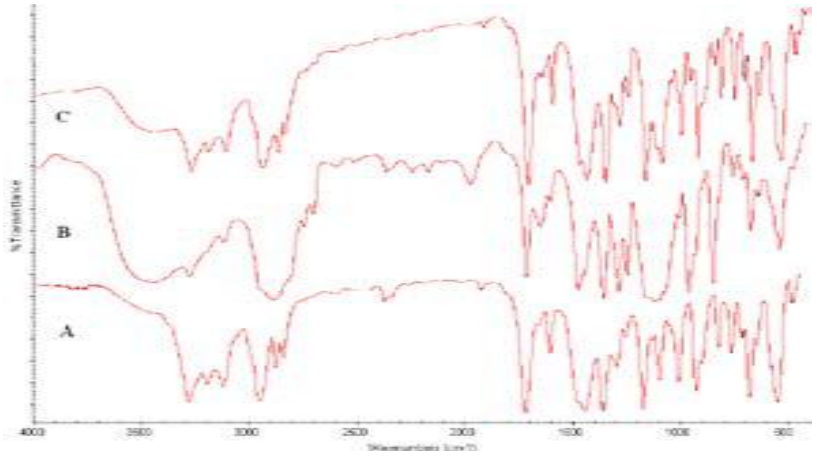


Figure No.4: (c) A – Glibenclamide, B-Arginine, C-Glibenclamide-Arginine SDS.

Differential Scanning Calorimetry: The DSC thermogram of GLIB indicates the onset of endothermic peak at around 168.61^{0}C, corresponding to the melting of drug, however, no distinctive endothermic peak appeared in the thermograms of GLIB-ARG and ARG formulations.

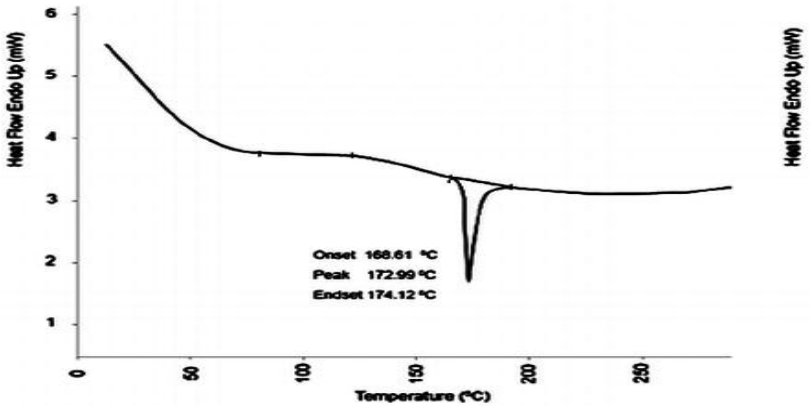
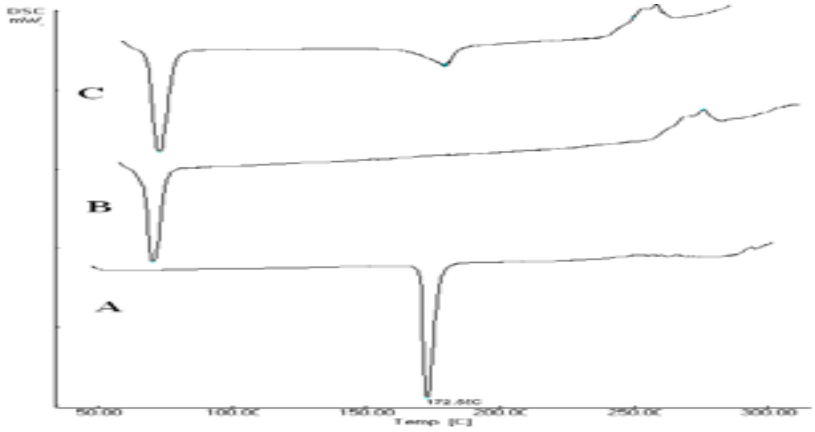


Figure No. 5: DSC thermogram of Pure Glibenclamide.



DSC Thermograms of (a) A – Pure Glibenclamide, B-PEG 4000, C-Glibenclamide-PEG 4000 SDS

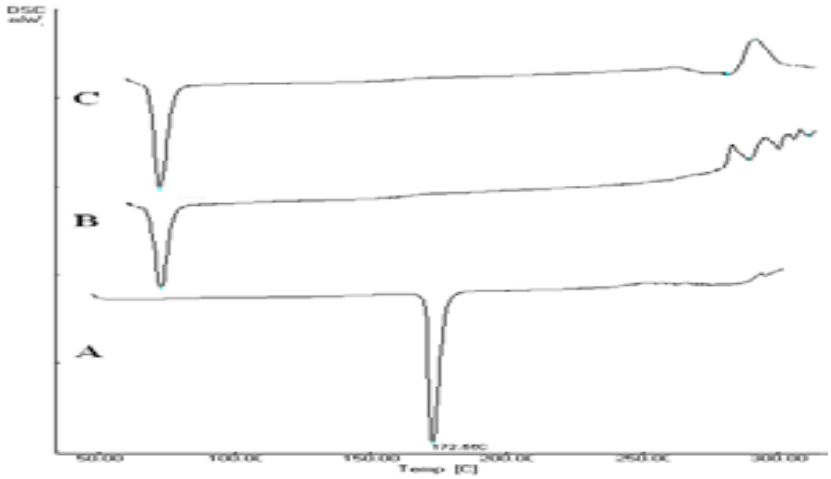


Figure No.6: (b) A – Pure Glibenclamide, B-PEG 6000, C-Glibenclamide-PEG 6000 SDS

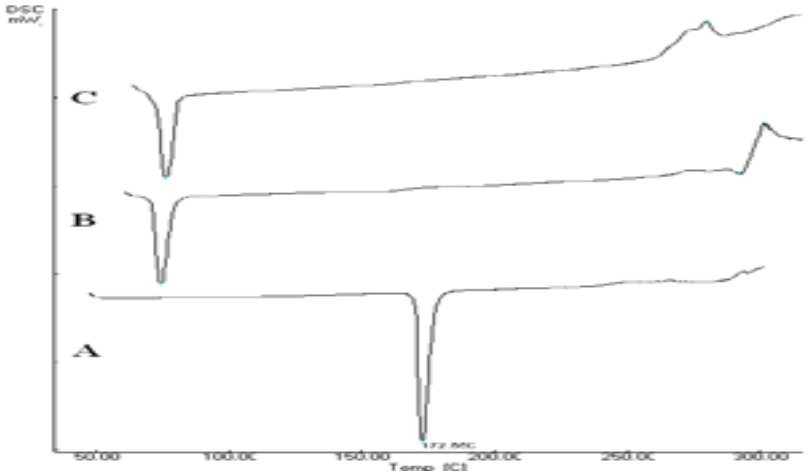


Figure No.7: (c) A – Pure Glibenclamide, B-Arginine, C-Glibenclamide-arginine SDS.

The solid dispersions and tablets were then characterized for various physio-chemical parameters.

II) Characterisation of Solid Dispersions: Solid dispersion of Glibenclamide was characterized for angle of repose, bulk density, tapped density, Carr's index (CI), Hausner's ratio. Result of the compressibility index, Hausner's ratio and angle of repose show that all materials have sufficient compressibility and flow properties and are shown in Table. 9.

Table No. 6: Precompression Parameters.

Properties	Range
Angle of Repose	20-30
Bulk Density	0.5938-0.6691
Tapped Density	0.708-0.784

From the bulk and tapped density, the values of carr's index and Hausner's ratio were calculated.

The values angle of repose were found good (<25°).

Carr's index was found to be 5-21.

The value of Hausner's ratio was found to be satisfactory (<1.27).

Solid dispersed powder showed good flow properties from the above values.

Also study % drug content ranges between 85.6 - 97.9 %.

Drug content: The drug content in solid dispersions was determined by UV- spectroscopy method. The maximum percent drug content for the all formulation was found to be 99.37 percent and minimum percent drug content from the all formulation was found to be 96.45%. Formulation F3 and F13 show 99.37 % and 98.54 % drug content respectively as shown in Table 9.

Table No. 7: Evaluation Parameters of Solid Dispersions.

Evaluation parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of Repose (θ)	24.44	23.21	24.52	23.11	24.68	24.17	22.22	22.43	23.10
Bulk Density (g/mL)	0.594	0.593	0.596	0.612	0.60	0.599	0.598	0.601	0.612
Tapped Density (g/mL)	0.680	0.691	0.690	0.698	0.68	0.699	0.70	0.748	0.751
Hausner's Ratio	1.012	1.028	1.019	1.124	1.156	1.138	1.221	1.236	1.241
Carr's Index	6.223	5.992	6.181	8.991	9.106	9.124	11.42	11.51	11.52
% Drug Content	85.6	86.8	86.9	89.1	90.2	92.7	94.6	96.2	97.9

Evaluation of Fast Release Tablets

In the present study, an attempt has been made to formulate and evaluate fast release tablets of Glibenclamide by using solid dispersion technique. Total 9 formulations were prepared with different polymers and complete composition of all batches is shown in tables.

Physiochemical evaluation of Glibenclamide tablet of different formulation were carried out, in that weight variation, hardness, friability, In-vitro disintegration time, Drug content study, Dissolution studies of tablet carried out.

The thickness was observed between 1.30-1.38mm respectively.

Drug content of all formulations was observed between and 91.2 - 96.9%.

Hardness test for all formulation was carried out and observations obtained were in the range of 5.8-6.2 Kg/cm^2.

Test for friability was conducted for all formulations. % friability was found to be in the range of 0.61-0.83%

In vitro disintegration time for all formulations was found to be in the range of 28-35 sec.

Table No.8: Evaluation Parameters of Fast Release Tablets.

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegra -tion Time (sec)	Weight Variation (mg)	Drug Content (%)
F1	1.30	5.8	0.81	34	79.1	91.2
F2	1.35	6.1	0.83	33	79.3	92
F3	1.33	5.9	0.79	32	79.1	90.9
F4	1.32	6.2	0.76	33	79.6	91.8
F5	1.36	6.0	0.72	31	79.8	92.6
F6	133	6.1	0.74	35	79.7	93.4
F7	1.35	5.9	0.65	31	80	94
F8	1.38	6.1	0.61	29	80.1	95.5
F9	1.39	6.1	0.63	28	80	96.9

Table No.9: Comparative Dissolution Data for F1-F9

Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	7.2	8.1	11.4	13.3	15.1	17.7	19.1	21.3	48.3
10	11.6	12.8	17.3	22.9	24.7	26.1	27.6	29.7	63.4
15	18.4	19.7	27.6	29.1	30.4	33.6	36.1	38.4	83.6
30	21.1	24.1	31.5	34.7	35.4	42.1	44.8	46.2	94.2
45	27.6	32.4	39.3	41.9	41.8	49.6	51.7	53.3	
60	34.1	41.7	48.7	51.3	52.1	58.8	59.3	61.7	
70	47.5	51.3	54.6	57.1	61.4	63.7	65.2	68.3	
80	51.3	60.6	62.8	65.4	69.2	73.2	76.7	78.1	
90	66.2	68.4	72.3	75	77.5	81.3	83.2	85.4	

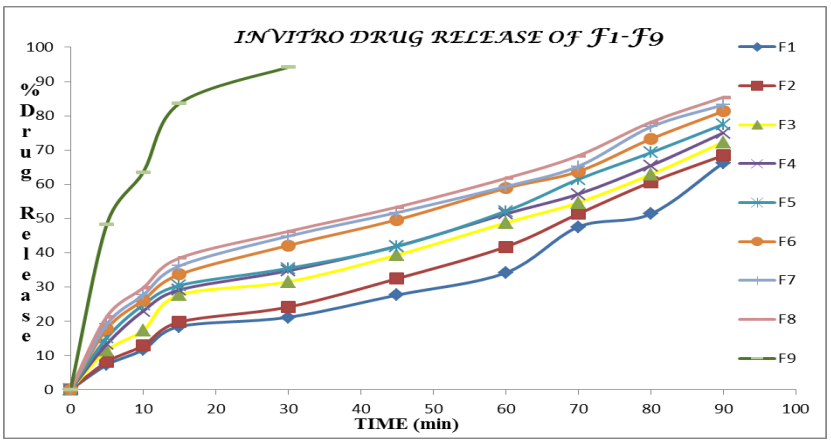


Figure No.8: *IN VITRO* Drug Release of Formulations F1-F9.

R^2	F1	F2	F3	F4	F5	F6	F7	F8	F9
First order	0.673	0.641	0.588	0.593	0.636	0.574	0.613	0.635	0.696
Higuchi's model	0.967	0.953	0.900	0.885	0.905	0.841	0.861	0.866	0.918
Peppa's model (n)	0.459	0.455	0.367	0.326	0.326	0.290	0.276	0.269	0.325
Zero order	0.856	0.823	0.736	0.717	0.740	0.657	0.693	0.698	0.690

Drug Release Kinetics

In vitro drug release data of all the fast dissolving was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in table. From the above data, it can be seen that all the formulations have displayed first order release kinetics ('r' values in the range of 0.657 to 0.856). From Higuchi and Peppas data, it is evident that the drug is released by fickian diffusion mechanism (n<0.5).

CONCLUSION

Glibenclamide is a hypoglycemic agent useful in the treatment of diabetes mellites. The half –life of drug is 10 hrs. In order to improve the bioavailability and efficacy, we have prepared fast release tablets of Glibenclamide by Solid dispersion technique using various polymers like PEG 4000, PEG 6000 and Arginine. From the results, formulation F9 evolved as the optimized formulation showing good mechanical properties and good drug release compared to other formulation, it releases more than 94.2% drug in 30 mins. IR spectroscopic studies indicated that there is no drug-excipient interaction in the optimized formulation. Success of the *In-vitro* drug release studies recommends the product for further in vivo studies, which may improve patient compliance. The optimized formulation F9 can be considered as a promising delivery system of Glibenclamide providing efficient drug release over a period of 30 mins.

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