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FORMULATION AND EVALUATION OF GLIBENCLAMIDE TABLET USING SOLID DISPERSION WITH VARIOUS POLYMERS

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ABSTRACT

The aim of the present study is to enhance the solubility of water insoluble drug, Glibenclamide by preparing solid dispersion using various polymers and further formulating its tablet. Solid dispersion is an effective way of improving the dissolution rate of poorly water soluble drugs. Hence, Solvent evaporation technique is used for the improvement of the solubility of poorly water-soluble drug Glibenclamide. It is used an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II diabetes). Preformulation studies for Glibenclamide were done such as; determination of Melting point, partition coefficient, solubility studies and λmax. The melting point of procured sample was found to be 173-175°C. An absorption maximum (λmax) of the drug was observed to be at 245 nm. Drug-polymer compatibility studies were done by preparing physical mixture of drug with PEG 6000 and β-CD. Solid dispersion of Glibenclamide was prepared using drug: polymer (1:1 and 1:3) with sufficient amount of methanol in F1-F6 batches. From the resulted solid dispersion, tablet was compressed using MCC as binder, talc and magnesium stearate as lubricant. Evaluation of the prepared solid dispersion was done by determination of drug content, %yield, FT-IR, stability studies. Characterization of the compressed tablet was done by determining its hardness (2.5-4.1kg/cm^3), disintegration time was found 4.02-5.67 minutes, friability 0.25 and results, drug content was found to be 88.87±0.02 which was best observed in F2 batch. %yield was observed to be 96.18±0.34. Batch F2 gives the highest drug release 87.37 ± 0.11.

KEYWORDS: Glibenclamide, Solid Dispersion, PEG 6000, β-CD, MCC, Talc, magnesium Sterate.

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INTRODUCTION

The two main issues which are forced after administration of drugs into the body are poor solubility and bioavailability. Because of the solubility problems the bioavailability of the drug automatically effected. Due to the stated problems, 50% of the active pharmaceutical ingredients are rejected every year. Due to the solubility problems upto the 40% of the new drug molecules were tested and resulted in poor bioavailability and possible toxicity. Thus, solubility is a biggest challenge faced by the pharmaceutical industries. Instead of all these issues oral route is the most common route of administration that is cost-effective, high patient compliance as well as promotes flexibility. This route is also advantageous for both pediatrics and gastric patients. So to avoid all these issues of solubility, technique of solid dispersion was introduced. Solid dispersion is a technique we used to enhance the solubility of poorly drugs that helps in improvement of bioavailability.[1,2,3,4,5]

MATERIAL AND METHOD

Glibenclamide was obtained as a gift sample from Swiss Garnier Life Sciences Pvt. Ltd. Mehatpur. PEG 6000, β-CD, Methanol, Talc, Mannitol and Magnesium Sterate were obtained from Himedia Laboratories Pvt. Ltd., Mumbai**.**

METHOD

SOLID DISPERSION BY SOLVENT EVAPORATION

Solid dispersion with different ratios 1:1 and 1:3 of Glibenclamide and PEG 6000, Glibenclamide and β-CD were prepared using the Solvent evaporation method. Solvent was evaporated using hot plate. Small amount of methanol was added in the drug polymer mixture to mix them properly because the drug water insoluble. Methanol evaporated using hot plate after evaporation

incubate the mixture for 48 hours. Dried mixture pass through sieve and transferred into suitable container.[6,7,8]

PREPARATION OF GLIBENCLAMIDE TABLET USING DIRECT COMPRESSION METHOD

The amount of complex equivalent to 5mg of drug were taken and then mixed with directly compressible diluents and disintegrants in a plastic container. Magnesium stearate and talc were passed through sieve no.60, mixed and blended with the initial mixture in the plastic container followed by compression of the blend. Compression was performed on a Cadmach 16 station tablet compression machine using 8mm punches.

Table: 1 List of ingredients used in solid dispersion tablet.

S. No	Ingredients	1:1(mg)	1:3(mg)
1	Glibenclamide	5	5
2	PEG 6000/ β -CD	5	15
3	MCC	100	100
4	Mannitol	140	130
5	Magnesium stearate	50	50
6	Talc	50	50

CHARACTERIZATION OF SOLID DISPERSION OF GLIBENCLAMIDE

Solid Dispersion of Glibenclamide tablet was characterized for following parameters:

FT-IR Studies:

Physical appearance:

Table: 2 Physical appearance of the drug.

S No	Character	Observation
1	Physical state	Solid
2	Texture	Powder
3	Colour	White
4	Odour	Odourless
5	Taste	Slightly bitter

Melting point:

The melting point of Glibenclamide pure drug determined through capillary rise method was found to be 175-177^{o}C which coincides with the literature value ranges i.e., 173-175^{o}C.

Solubility Studies:
Solubility of Glibenclamide in different buffer solutions.

Table: 3 Solubility studies of Glibenclamide in different solvents.

S. No.	Buffers (pH)	Solubility (mg/ml)
1	0.1N HCl buffer	0.139±0.02
2	Phosphate buffer 6.8	0.221±0.01
3	Phosphate buffer 7.4	0.167±0.02
4	Methanol	0.152±0.03

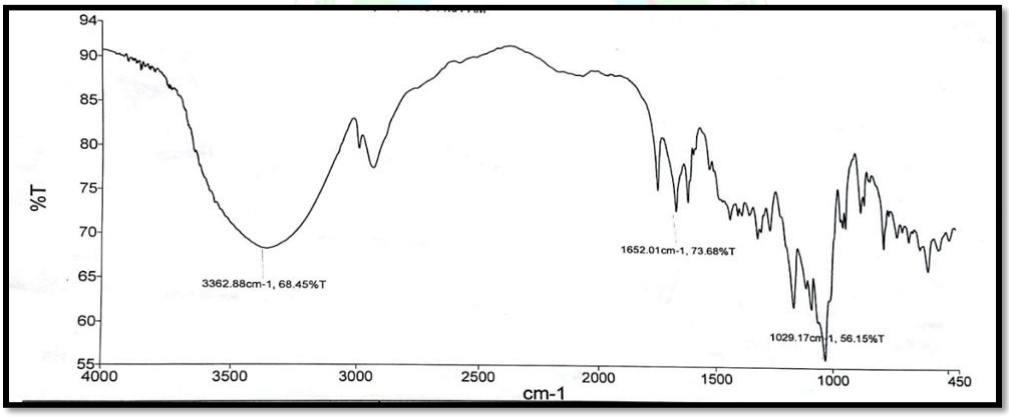

Figure: 1 FT-IR Spectra of Glibenclamide PEG 6000 solid dispersion of ratio(1:1)

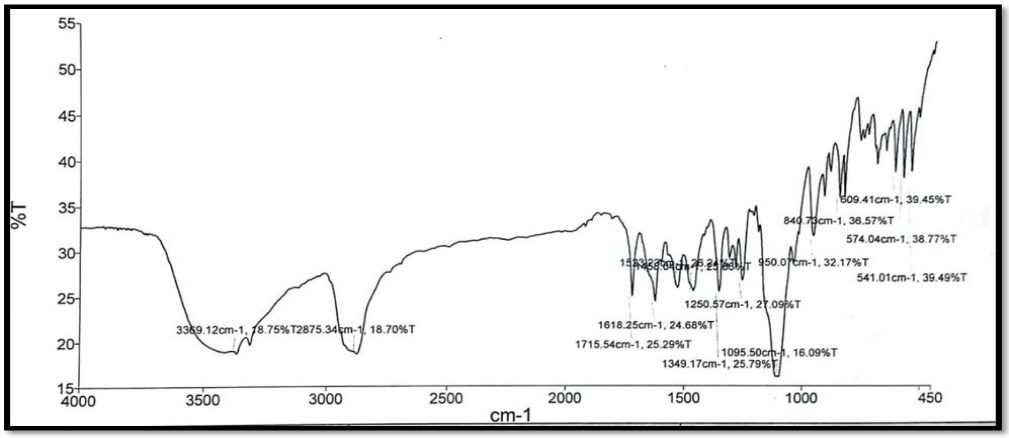

Figure: 2 FT-IR Spectra of Glibenclamide PEG 6000 solid dispersion of ratio(1:3)

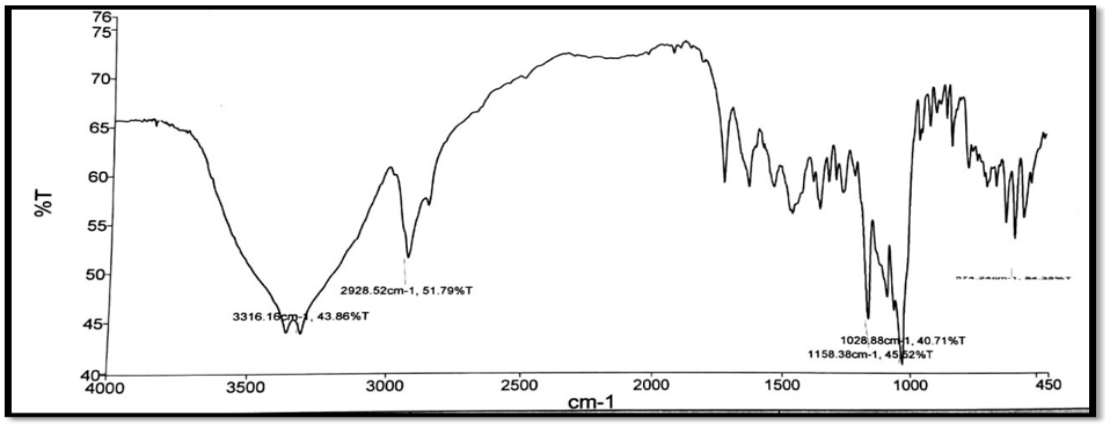

Figure: 3 FT-IR Spectra of Glibenclamide β--CD solid dispersion of ratio(1:1)

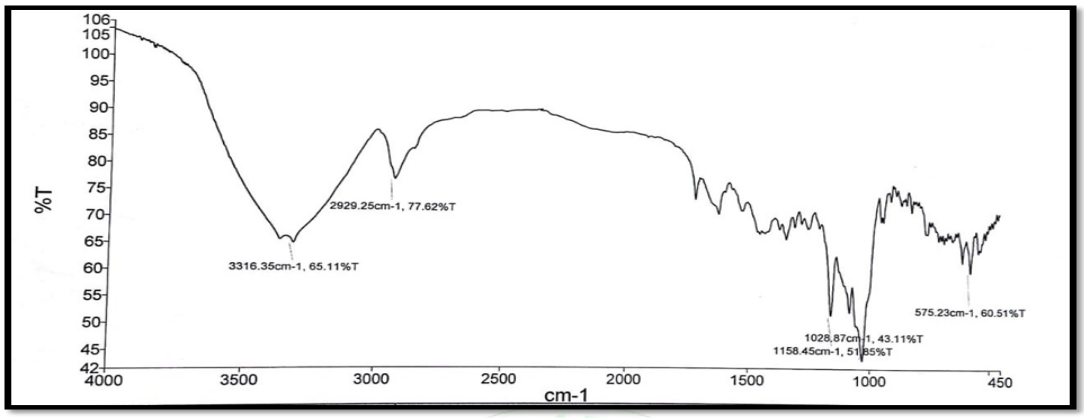

Figure: 4 FT-IR Spectra of Glibenclamide β--CD solid dispersion of ratio (1:3)

Formulation of Solid Dispersion tablet:

PRE-COMPRESSION PARAMETERS

Angle of repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane, it was measured by pouring the weighed powder mixture into the funnel which was fixed to stand at a definite height (h).

$$\Theta = \tan^{-1} h/r$$

The value for angle of repose for batches F1 to F6 lies between 23.12 to 34.12^{0}C. This implies good flow properties.

Bulk density(mg/ml): Bulk density is defined as the total mass of the powder to the total bulk of the powder. It is indicative of the packing of particle and as such is greatly influenced by the size of granules. Loose bulk density of tablets was determined by pouring gently 2g of the powder blend from each formula through a glass funnel into 10 ml measuring cylinder. The volume occupied by the samples were noted. Loose bulk density was expressed in (g/ml) and calculated by using following formula.

Bulk density = mass / bulk volume

Tapped density(mg/ml): Tapped density is defined as the total mass of the powder to the tapped volume of the powder. It was determined by pouring gently 2 g of the powder blend from each formula through a glass funnel into 10 ml of measuring cylinder. The cylinder was tapped gently on a hard surface from the height of 2 inches at second interval until a constant volume was obtained. Volume occupied by the sample after tapping was noted. The value for Tapped density for batches F1 to F6 lies between0.162 to 0.479. The value indicates good flow properties.

Carr's index(%): Carr's index is defined as the ratio of bulk density to tapped density. Carr's index was observed to be lies between 10.43 to 15.63 for F1 to F6 indicating good flow properties for compression which is suitable for content uniformity and less weight variation in final tablets.

Hausner's Ratio: It is calculated as Tapped density/Bulk density. The value for Hausner's Ratio for batches F1 to F6 lies between 0.66 to 1.54 indicating good flowability.[9,10,11,12,13]

Table: 4 Results of Pre compression parameters of all batches.

BATCHES	Angle of repose	Bulk density (mg/ml)	Tapped density (mg/ml)	Carr's index (%)	Hausner's Ration
F1 (D:PEG) (1:1)	23.12	0.542	0.162	10.43	0.72
F2 (D:PEG) (1:3)	26.78	0.423	0.234	12.79	0.66
F3 (D:β-CD) (1:1)	23.41	0.39	0.257	15.63	1.43
F4 (D:β-CD) (1:3)	24.73	0.431	0.369	13.54	0.64
F5 (D:PEG) PM_1	28.26	0.302	0.378	11.57	1.54
F6 (D:β-CD) PM_2	29.54	0.297	0.411	12.89	1.45

Table: 5 Results of drug content and disintegration time

Batches	Drug content (%)	Disintegration time (minutes)
F1 (D:PEG) (1:1)	87.12	5.34
F2 (D:PEG) (1:3)	88.87	4.02
F3 (D:β-CD) (1:1)	87.01	4.53
F4 (D:β-CD) (1:3)	87.13	4.46
F5(D:PEG) PM_1	87.01	5.56
F6 (D:β-CD) PM_2	86.23	5.32

IN-VITRO DISSOLUTION STUDIES

Dissolution studies were performed on the solid dispersions, tablet of Glibenclamide and simple conventional tablet batches (F1-F6). The *in vitro* release profile of conventional, all the formulations is shown in Table

Table: 6 *In vitro* cumulative % drug release of F1 to F6 batches.

Time (min)	F1 (D:PEG) (1:1)	F2 (D:PEG) (1:3)	F3 PM_1 (D:PEG)	F4 (D:βCD) (1:1)	F5 (D:βCD)(1:3)	F6 PM_2 (D:βCD)
0	0	0	0	0	0	0
10	36.58 ±0.23	42.42± 0.17	25.84 ±0.23	33.50 ± 0.17	39.61±0.29	25.96 ± 0.23
20	57.00± 0.23	53.89 ± 0.23	46.96 ±0.17	57.15± 0.17	58.54± 0.17	44.46 ± 0.17
30	66.35± 0.23	69.77 ± 0.29	50.04 ±0.23	61.58± 0.29	66.81±0.23	56.62 ±0.23
40	69.73± 0.24	76.96± 0.23	63.46 ±0.17	67.39 ± 0.11	72.42±0.23	69.85± 0.23
50	75.35± 0.23	84.77 ± 0.29	76.35 ±0.11	77.89 ± 0.23	78.73± 0.17	73.96 ± 0.17
60	79.0 ± 0.29	87.37± 0.23	82.08 ±0.23	84.73 ± 0.17	83.43± 0.23	81.08± 0.24

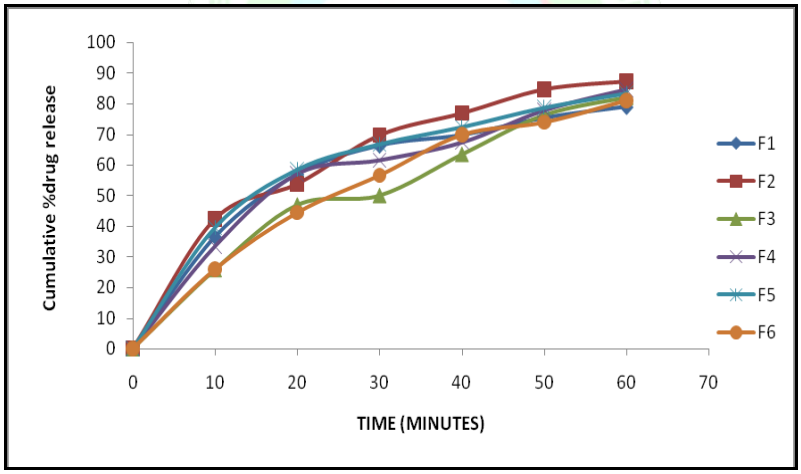

Figure: 5 *In vitro* drug release of F1 to F9 formulation Time v/s cumulative % drug release.

SELECTION AND EVALUATION OF BEST OPTIMIZED BATCH

Selection of Optimized batch

Total six batches (F1-F6) were prepared using different polymers. All these ratios were compatible with drug and show good results in increasing solubility and dissolution profile of Glibenclamide drug. F2 batch showed drug content 88.87 %yield was observed to be 96.18% and the highest drug release 87.37%

Evaluation of optimized batch

Optimized Solid dispersion batch was subjected to accelerated storage conditions, out by storing at 4°C - 8°C (refrigeration temperature), 25°C ±2°C and 40°C ±2°C for a period of 60 days as per ICH (International Conference on Harmonization) guidelines for Stability Testing of new Drug Substances and Products. At regular intervals the solid dispersions was characterized for physical appearance, drug content and in vitro drug release. There was no change in the physical appearance of solid dispersion during the study period and at the end of two months.

Table: 7 Stability data of the optimum batch (F2) solid dispersion at 4°C - 8°C

Formulation code	Time period (Days)	Physical appearance	Drug content (%)±SD*	Drug released at pH 6.8 at 2min (in %)*
F2	0	White color	88.87±0.02	87.37±0.11
	15	White color	88.87±0.02	87.37±0.11
	30	White color	88.86±0.02	87.35±0.11
	45	White color	88.84±0.02	87.33±0.11
	60	White color	88.83±0.05	87.29±0.13

Table: 8 Stability data of the optimum batch (F2) solid dispersion at 25^0C

Formulation code	Time period (Days)	Physical appearance	Drug content (%)±SD*	Drug released at pH 6.8 at 2 min (in%)*
F2	0	White color	88.87±0.02	87.37±0.11
	15	White color	88.85±0.02	87.35±0.11
	30	White color	88.84±0.02	87.34±0.11
	45	White color	88.83±0.02	87.32±0.11
	60	White color	88.81±0.05	87.30±0.13

Table: 9 Stability data of the optimum batch (F2) solid dispersion at 40^0C

Formulation code	Time period (Days)	Physical appearance	Drug content (%)±SD*	Drug released at pH 6.8 at 2 min (in %)*
F2	0	White color	88.87±0.02	87.37±0.11
	15	White color	88.86±0.02	87.36±0.11
	30	White color	88.85±0.02	87.35±0.11
	45	White color	88.83±0.02	87.34±0.11
	60	White color	88.80±0.05	87.33±0.13

The optimized batch was stored at 4°C-8°C (refrigeration temperature), 25°C ±2°C and 40^0C±2°C for a period of 60 days as per ICH (International Conference on Harmonization) guidelines for Stability Testing of new Drug Substances and Products. There is no change in physical appearance, FTIR spectra, given in figure no 6.

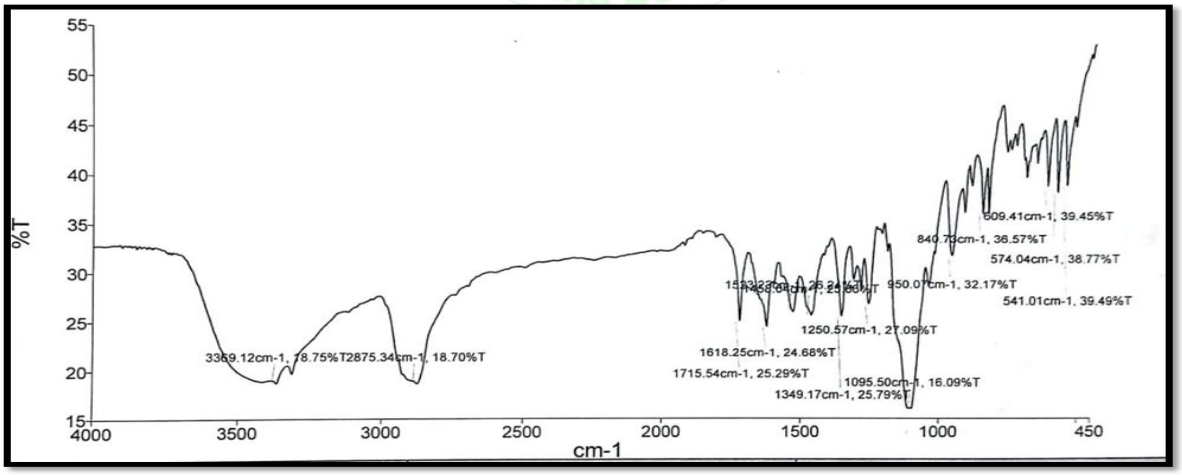

Figure: 6 FT-IR Spectra of optimized batch (F2) of Glibenclamide PEG 6000 solid dispersion of ratio (1:3)

CONCLUSION:

In the present work Glibenclamide, a poorly water soluble drug with high permeability was selected to form solid dispersions in order to enhance its aqueous solubility. PEG 6000 and β-CD were selected as the carrier to improve the dissolution characteristics of the drug. Solid dispersions of Glibenclamide were prepared

using Solvent evaporation method and using Methanol as solvent. The F2 batch was optimized batch and further kept under air tight container. The optimized formulation was stored at 4-8, 25 and 40° C ± 2°C and relative RH 75% ± 5% for two months. There is no change in physical appearance and FT-IR spectra.

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