Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF GLIPIZIDE BY LIQUISOLID TECHNIQUE

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ABSTRACT:

Liqui-solid technique are novel approach for enhancement of dissolution rate of BCS class II drugs. Liqui-solid compact converts a liquid drug or drug solution into a free flowing powder with enhanced dissolution rate. In the present study, Liqui-solid compacts is applied to enhance the dissolution of the Glipizide Twenty two formulations of Glipizide were prepared by liqui-solid technique using micro crystalline cellulose as carrier material and Aerosil and Crosspovidone ascoating material. Water, poly ethylene glycol-600 and Tween-80 were used as solvent system . Tablets were subjected to evaluation of various physical and chemical characteristics. Dissolution profiles of tablets prepared by the novel techniques were compared with marketed conventional tablets. Model independent techniques including similarity factor, dissimilarity factor and dissolution efficiency were applied for comparison of dissolution profiles. The results obtained indicated that liqui-solid compact formulations were more effective in enhancing the dissolution rate. The liqui-solid compacts improved the dissolution rate

KEYWORDS: Liquisolid compacts, Glipizide Dissolution, BCS Class 2 , Dissolution rate

INTRODUCTION

Bioavailability is the most important property of a dosage form[1]. It is the ability ofthe dosage form to deliver the active ingredient to its site of action in an amount sufficient to elicit the desired pharmacological response[2]. It is well known that the drug bioavailability and efficacy is severely limited by its poor aqueous solubility and dissolution rate[3]. The drug in a solid dosage form must undergo dissolution before it is available for absorption in the gastrointestinal tract. Dissolution forms the rate limiting step in the absorption of drug from solid dosage forms especially when the drug is poorly soluble[4]. Many of the modem drugs belong to the Class II category under Biopharmaceutical Classification System1 (BCS), which are characterized by low solubility and high permeability. These drugs are insoluble in water and aqueous fluids in the pH range of 1.0 - 7.5 and exhibit low and variable dissolution and bioavailability. There is a great need to develop technologies for these 'BCS' Class II drugs for enhancing their dissolution rate and bioavailability[5]. The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug product development. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and. greatest challenges to formulation scientists in the pharmaceutical industry[6]. One of the major current challenges of the pharmaceutical industry is related to strategies that improve the aqueous solubility of drugs. Briefly, solubility is defined as the concentration of solute in a saturated solution at a defined temperature and pressure[7]. Solubility is closed related to dissolution which is a kinetic process that involves the detachment of the molecules from the solid surface and subsequent diffusion across the diffusion layer surrounding the solid surface.[8]

Materials

Glipizide.:API , Tween-80: Non volatile solvent, PEG-600:, Non volatile solvent PEG-6000:Solubilizer, Urea: Solubilizer, PVPK30: Solubilizer, MCC: Carrier, Aerosil:Coating materaial, Crosspovidone: Coating materaial, SSG:Superdisintegrant.

Instruments Electric balance :shimadzu , FTIR :Clp drug testing lab, DSC :Q10v24.11build 124 , UV: thermoscientific, Hardness tester:, Secor india, friability tester :Secor india, Ph meter :Data instruments, Dissolution apparatus: Labinidia DS 8000, Disintegration apparatus : Secor india

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Methodology

Pre formulation

By the determination of Preformulation parameters the powder Micromeritic parameters were found to be very poor the melting point was found to be 205-211

Table I : Preformulation parameters

s.no	Micromertic parameters	Result
1	Colour	whitish powder
2	Odour	odourless
3	Soluble in	0.1 *N* NaOH , dimethylformamide
4	Insoluble in	water and alcohols
5	Melting Point	205-211˚C
6	Angle of repose	54.19˚
7	Bulk density	0.511 g/cc
8	Tapped density	0.628 g/cc
9	Carr`s index	20 %
10	Hausner`s ratio	1.22

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Compatability studies

The compatability of Glipizide and excipients was evaluated by FTIR spectral studies the pure drug and proposed polymers are found there was no interaction between drug and polymers

The FTIR spectra of pure drug and optimized formulation are shown in figure. From the figure, it is clear that the characteristic peaks at 3325 & 3371 cm^{-1} (N-H stretching), 2930 & 2922 cm^{-1} (C-H stretching), 1688 & 1693 cm^{-1} (C=O stretching), 1552 & 1553 cm^{-1} (C=C stretching), 1601 & 1599 cm^{-1} (C=N stretching), are seen in both pure Glipizide and its formulation respectively without any change in their position, indicating no chemical interaction between Glipizide and excipients present in formulation.

FIGURE I FTIR range for pure drug

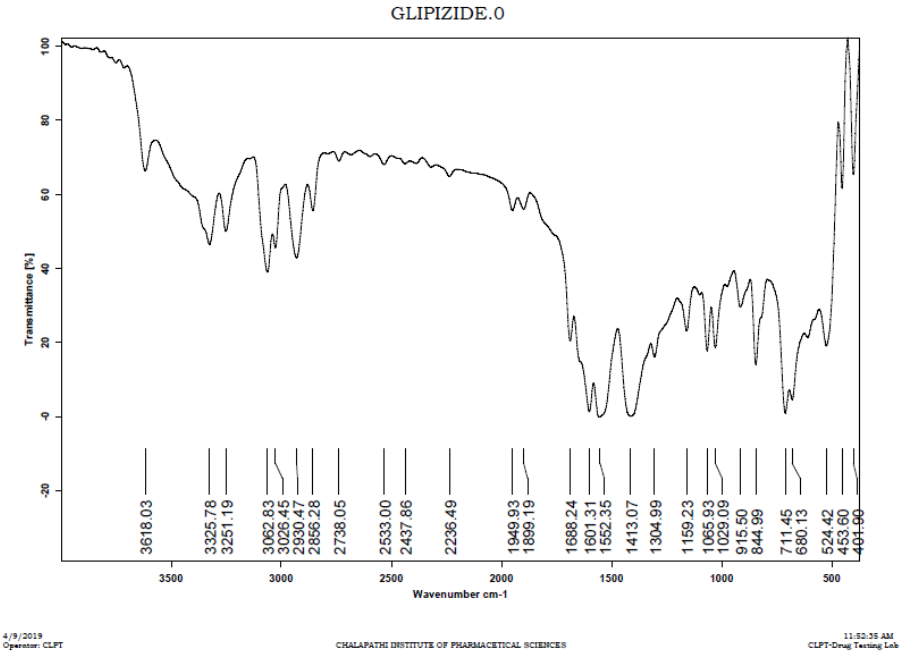

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FIGURE II FTIR for pure drug and polymer mixture

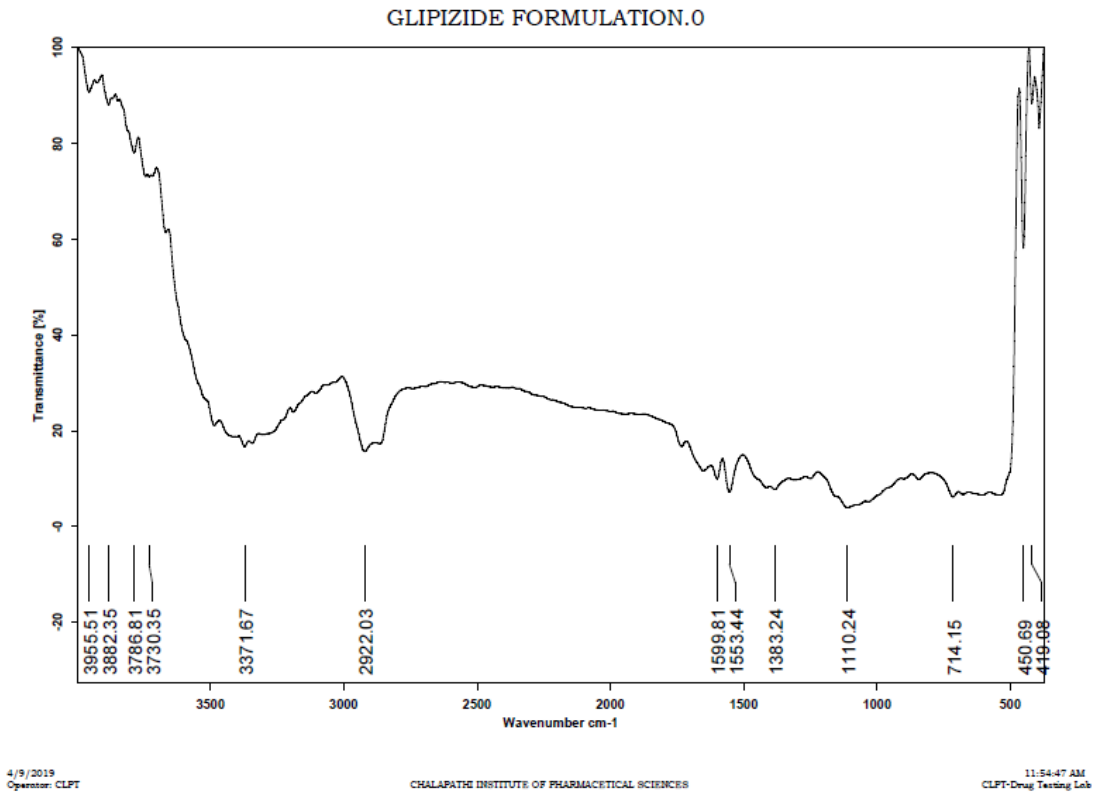

Table II**: Absorbance values of Glipizide Analytical study:** Calibration curve of Glipizide (Ph 7.4) λ_{max} at 264 nm:

S. NO	Concentration (ug /ml)	Absorbance				Standard Deviation
		Trial 1	Trial 2	Trial 3	Average	
1	2	0.494	0.494	0.493	0.49	0.001
2	3	0.597	0.6	0.597	0.60	0.002
3	4	0.67	0.68	0.65	0.67	0.015
4	5	0.765	0.766	0.764	0.77	0.001
5	6	0.828	0.85	0.85	0.84	0.013
6	7	0.96	0.961	0.96	0.96	0.001
7	8	1.064	1.06	1.061	1.06	0.002
8	10	1.25	1.26	1.173	1.23	0.048

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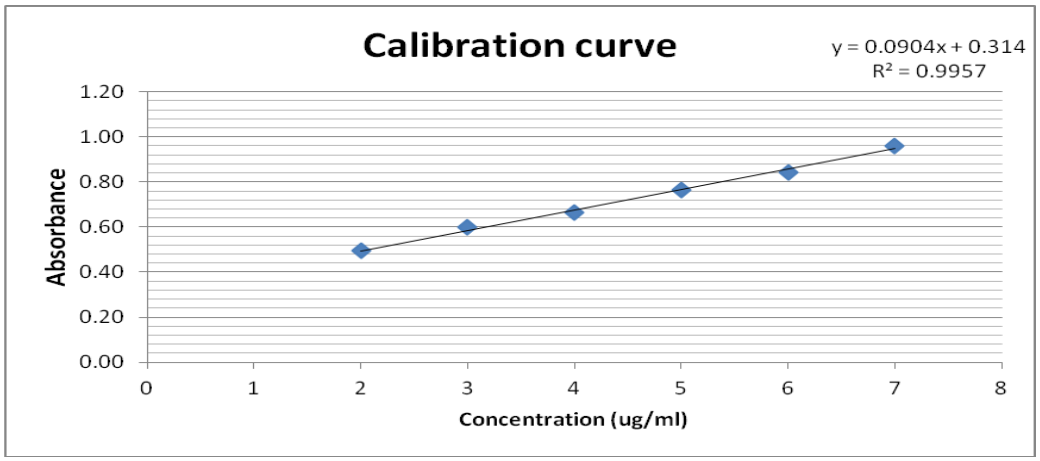
FigureIII: Calibration curve of Glipizide in 7.4 pH Phosphate buffer.

The calibration curve was linear in the concentration range of 2-7 µg/ml with the Regression coefficient 0.9957 at 264nm.



Formulation Design

The liquisolid compacts were prepared in accordance to method described by Spireas et al. Glipizide was dissolved in non-volatile solvent i.e., PEG 600 (based on results of solubility test) to prepare the drug solution. The mixture of carrier-coating materials was added to the liquid medication and blended in a porcelain mortar avoiding excessive triturating and particle size reduction. The mixing was done in three stages; first stage the system was mixed slowly to allow uniform distribution of liquid medication. In second stage the mixture was spread as a uniform layer on the surface of the mortar and left standing for few minutes. In the final stage 5% of disintegrant (Crosspovidone) was added to the powder and mixed thoroughly. The final mixture was compressed into tablets with 8 mm round flat punches using 16 station rotary tablet machine

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Table III **Formulation Design**

	GLP	TWEEN 80	PEG 600	PEG 6000	UREA	PVP K30	MCC (Q)	AER (q)	CP (q)	SSG (-5%)	Total Weight (mg)
GLS 01	5	10	0	5	0	0	180	9	0	11	220
GLS 02	5	10	0	5	0	0	180	0	9	11	220
GLS 03	5	10	0	5	0	0	190	0	0	11	221
GLS 04	5	0	10	5	0	0	180	9	0	11	220
GLS 05	5	0	10	5	0	0	180	0	9	11	220
GLS 06	5	0	10	5	0	0	180	9	0	11	220
GLS 07	5	10	0	0	5	0	190	0	0	11	221
GLS 08	5	10	0	0	5	0	180	0	9	11	220
GLS 09	5	10	0	0	5	0	180	9	0	11	220
GLS 10	5	0	10	0	5	0	190	0	0	11	221
GLS 11	5	0	10	0	5	0	180	0	9	11	220
GLS 12	5	0	10	0	5	0	180	9	0	11	220
GLS 13	5	10	0	0	0	5	190	0	0	11	221
GLS 14	5	10	0	0	0	5	180	0	9	11	220
GLS 15	5	10	0	0	0	5	180	9	0	11	220
GLS 16	5	0	10	0	0	5	190	0	0	11	221
GLS 17	5	0	10	0	0	5	180	0	9	11	220
GLS 18	5	0	10	0	0	5	190	0	0	11	221
GLS 19	5	10	0	5	0	0	180	0	9	11	220
GLS 20	5	0	10	5	0	0	190	0	0	11	221
GLS 21	5	0	10	0	5	0	180	9	0	11	220
GLS 22	5	10	0	0	0	5	190	0	0	11	221

Pre compression Parameters

Flow properties of the liquisolid system:

The flow properties of the liquisolid systems were estimated by determining the angle of repose, Carr's index, and Hausner's ratio. The angle of repose was measured by the fixed funnel and freestanding cone method. The Bulk density and Tap densities were determined for the calculation of Hausner's ratio and Carr's Index. (5) The powder mixtures of different formulations were evaluated for angle of repose and Carr's index and their values were shown in table. The results of angle of repose <40 and compressibility index <22 indicates fair to passable flow properties of the powder mixture

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Table IV

Formulation code	Angle of repose(⁰) (±sd), n=3	Bulk Density(gm/cc)	Tapped Density(gm/cc)	Hausner ratio(±sd)	carr's index %
GLS 01	20.32±0.22	0.52±0.032	0.625±0.02	1.20	16.80
GLS 02	22.96±0.34	0.52±0.031	0.66±0.052	1.27	21.05
GLS 03	25.33±0.32	0.51±0.042	0.65±0.055	1.29	22.45
GLS 04	22.69±0.38	0.48±0.032	0.62±0.073	1.26	20.39
GLS 05	23.65±0.26	0.49±0.021	0.62±0.026	1.28	21.57
GLS 06	25.32±0.79	0.48±0.028	0.62±0.081	1.29	21.33
GLS 07	24.32±0.15	0.49±0.016	0.62±0.039	1.28	21.57
GLS 08	23.19±0.21	0.49±0.019	0.58±0.085	1.28	21.57
GLS 09	16.98±0.41	0.51±0.023	0.56±0.098	1.18	15.00
GLS 10	16.23±0.47	0.48±0.026	0.66±0.071	1.17	14.56
GLS 11	30.47±0.31	0.53±0.014	0.60±0.059	1.33	21.90
GLS 12	20.68±0.19	0.58±0.019	0.55±0.041	1.22	18.00
GLS 13	10.32±0.41	0.54±0.025	0.62±0.053	1.11	10.00
GLS 14	22.34±0.81	0.51±0.016	0.64±0.023	1.25	20.00
GLS 15	28.54±0.28	0.49±0.018	0.62±0.041	1.31	21.53
GLS 16	22.31±0.28	0.57±0.021	0.62±0.047	1.25	20.00
GLS 17	22.36±0.47	0.59±0.027	0.62±0.021	1.25	20.00
GLS 18	19.23±0.26	0.52±0.022	0.62±0.043	1.19	15.79
GLS 19	12.65±0.54	0.51±0.019	0.55±0.078	1.11	10.00
GLS 20	22.95±0.38	0.53±0.022	0.63±0.083	1.27	21.00
GLS 21	21.32±0.58	0.51±0.011	0.62±0.081	1.23	18.37
GLS 22	22.58±0.37	0.55±0.017	0.62±0.079	1.25	20.00

FIGURE IV Solubility study:

Excess amounts Glipizide of Formulations were mixed with solvent. The mixtures were shaken on a shaker for 48 h. Then solutions were filtered through a 0.45 μm membrane filter, diluted suitably and analyzed ultraviolet (UV) spectrophotometrically at 276 nm for their drug content. Three determinations were carried out for each sample to calculate the solubility of Glipizide.

The tablets were found to contain 95-102% of the labeled amount indicating uniformity of drug content and 92.23 to

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99.72 % of the practical yield.

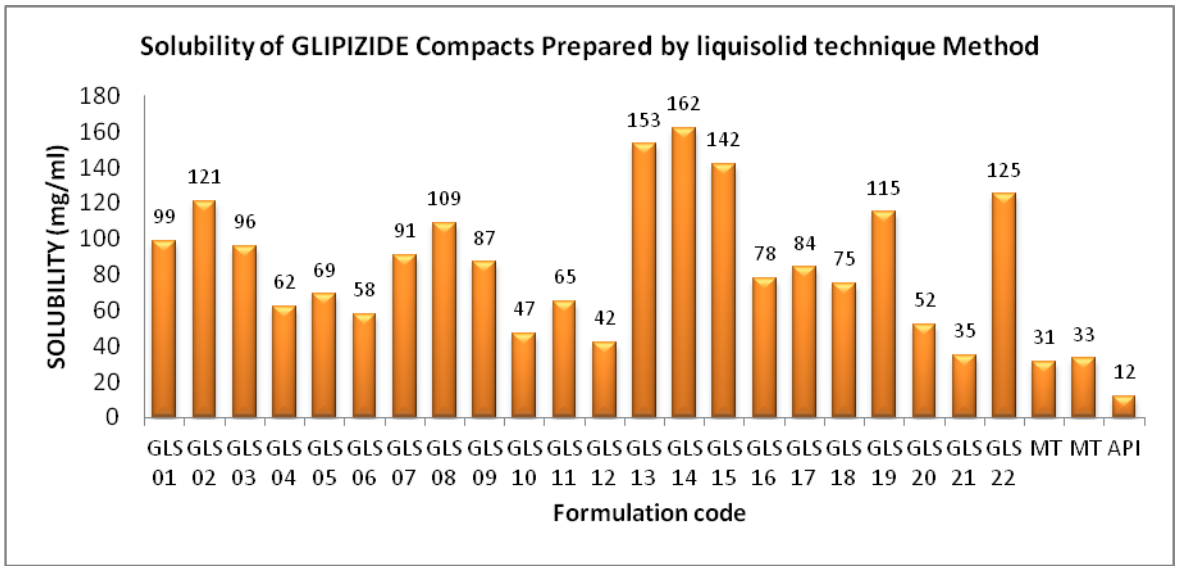
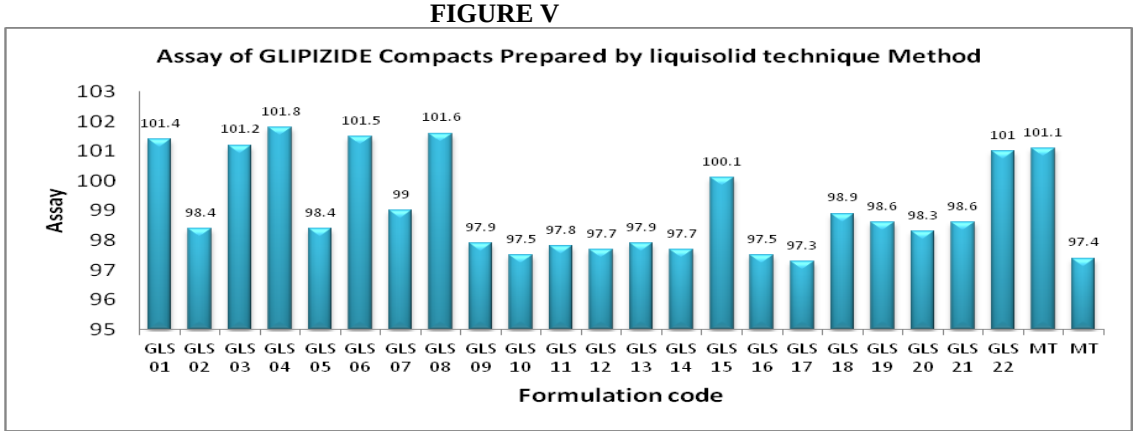


FIGURE V



Evaluation of liquisolid tablets (Post compression parameters):

The physical properties of Glipizide tablets were given in Table. In weight variation test, the pharmacopoeia limit for the tablets of not more than 7.5% of the average weight. The hardness of the tablets was found to be in the range of 3-5 kg/cm2. Another measure of tablets strength is friability. Conventional compressed tablets that loss less than 1% of their weight are generally considered acceptable. The percentage friability for all formulations was below 1%, indicating that the friability is within the prescribed limits.

Table v

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Formulation code	Average weight Of Tablet n=10	Thickness(mm) n=10	Diameter (mm)	Hardness test (kg/cm²)(±SD) n=3	Disintegration (Sec)	% of friability n=10
GLS 01	211.0±1.92	4.22±0.012	8.64±0.012	3.2±0.024	22	0.65
GLS 02	208.1±1.22	4.35±0.035	8.63±0.006	3.2±0.034	3	0.68
GLS 03	207.97±1.77	4.26±0.075	8.62±0.023	4.9±0.035	5	0.67
GLS 04	211.83±2.17	4.22±0.017	8.63±0.012	4.6±0.204	23	0.53
GLS 05	210.4±1.82	4.28±0.081	8.64±0.017	3.9±0.100	3	0.58
GLS 06	208.5±2.24	4.25±0.023	8.62±0.013	3.2±0.201	24	0.6
GLS 07	211.1±2.20	4.27±0.035	8.65±0.021	4.3±0.078	6	0.69
GLS 08	208.29±1.72	4.19±0.017	8.62±0.023	4.9±0.012	4	0.49
GLS 09	214.6±2.14	4.17±0.023	8.64±0.024	4.9±0.025	30	0.61
GLS 10	213.2±2.47	4.15±0.029	8.68±0.026	4.1±0.211	7	0.53
GLS 11	217.4±2.68	4.21±0.006	8.67±0.028	3.5±0.205	4	0.54
GLS 12	212.9±2.69	4.15±0.012	8.64±0.023	3.7±0.211	34	0.42
GLS 13	214.1±1.78	4.19±0.023	8.68±0.031	3.2±0.217	10	0.67
GLS 14	207.8±1.92	4.20±0.006	8.65±0.033	4.2±0.178	4	0.62
GLS 15	215.4±1.33	4.15±0.029	8.65±0.035	4.9±0.236	44	0.52
GLS 16	212.8±2.41	4.24±0.006	8.68±0.036	4.3±0.213	12	0.58
GLS 17	218.4±1.17	4.23±0.046	8.65±0.038	4.9±0.422	5	0.47
GLS 18	219.9±2.34	4.18±0.035	8.64±0.040	3.9±0.204	12	0.65
GLS 19	212.5±2.15	4.16±0.012	8.66±0.042	3.1±0.207	5	0.58
GLS 20	217.4±2.34	4.19±0.052	8.64±0.043	3.3±0.234	15	0.68
GLS 21	210.1±2.31	4.17±0.000	8.65±0.045	4.9±0.047	45	0.42
GLS 22	212.6±2.17	4.22±0.035	8.65±0.047	4.8±0.178	20	0.44

Dissolution studies:

The percent of GLP release from liquisolid tablets varying amounts of carrier and coating material (From GLS1 to GLS22) was found vary from 5.4 % to 64.4 % in 30 min. This indicates that fast release of GLP is observed from GLS 14 formulation. The optimized formulations GLS14 shows the release 64.4% in 30 min where as the marketed formulations showed 42.31% in 30 min. Thus the formulation GLS 14 was decided best compare to other formulations to faster release of the GLP. All the dissolution results were shown in the table.

FIGURE VI

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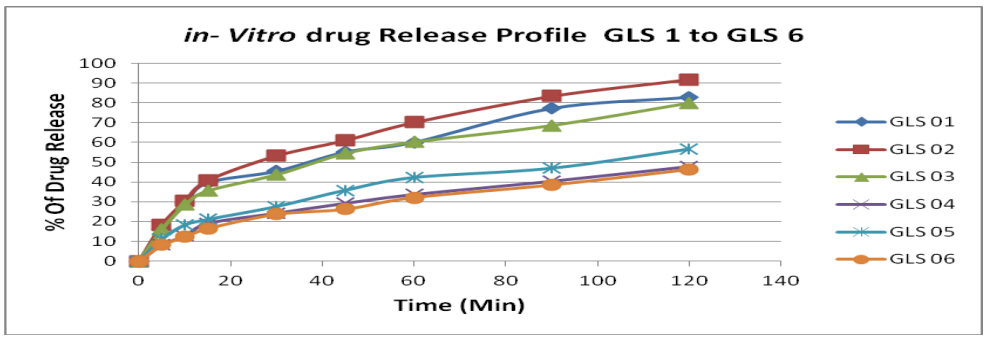

FIGURE VII

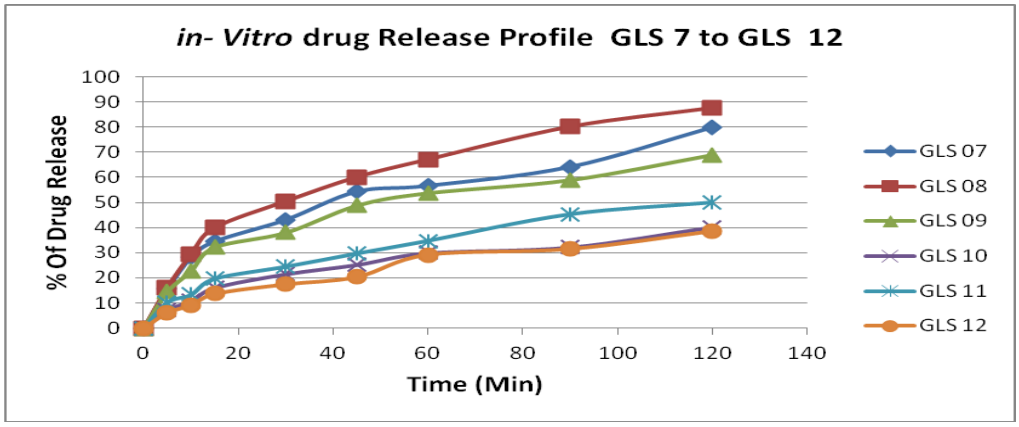

FIGURE VIII

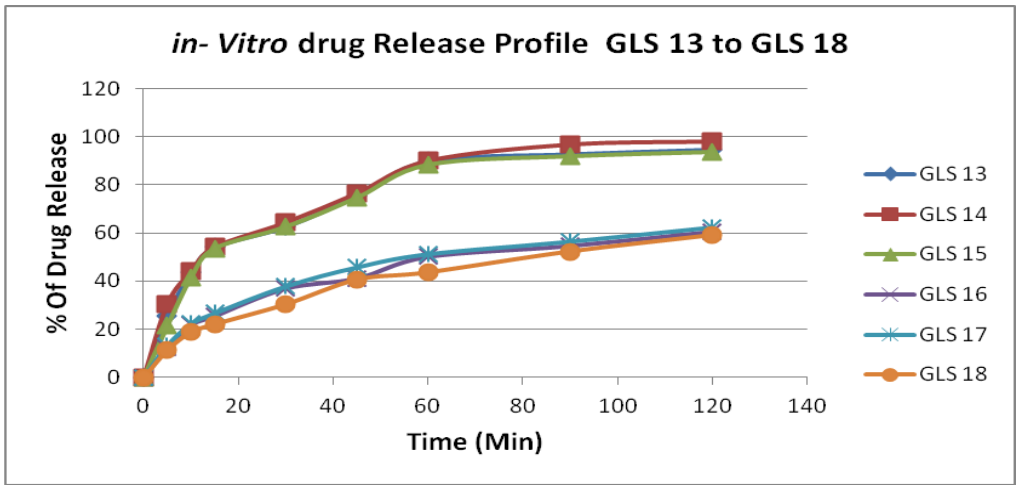

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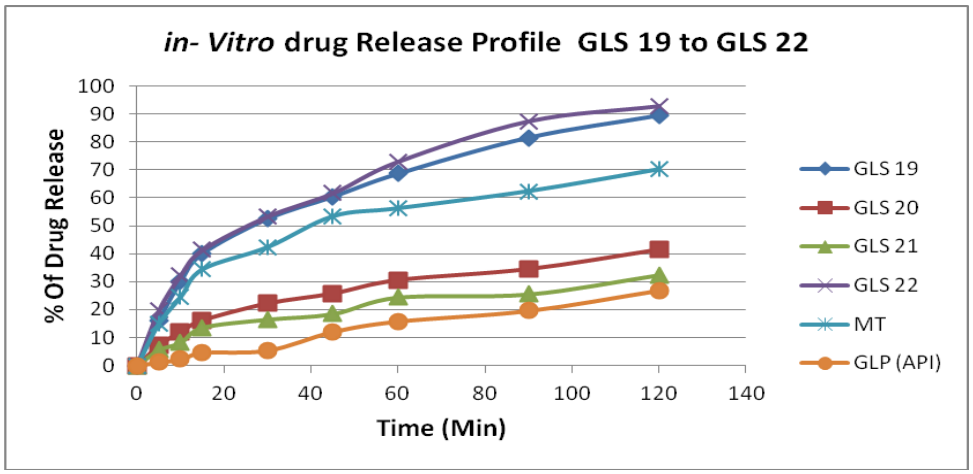
FIGURE IX



DSC Thermogram:

DSC thermogram of optimized formulation GLS-14 was compared with the DSC theromogram of pure drug sample. The pure Glipizide displayed a single sharp endothermic peak at 216^{o}C corresponding to the melting point of the drug, and a similar peak was also observed at 215^{o}C in optimized formulation. The DSC thermogram, thus, confirms that there is no interaction between the polymer and drug Glipizide.

FIGURE X

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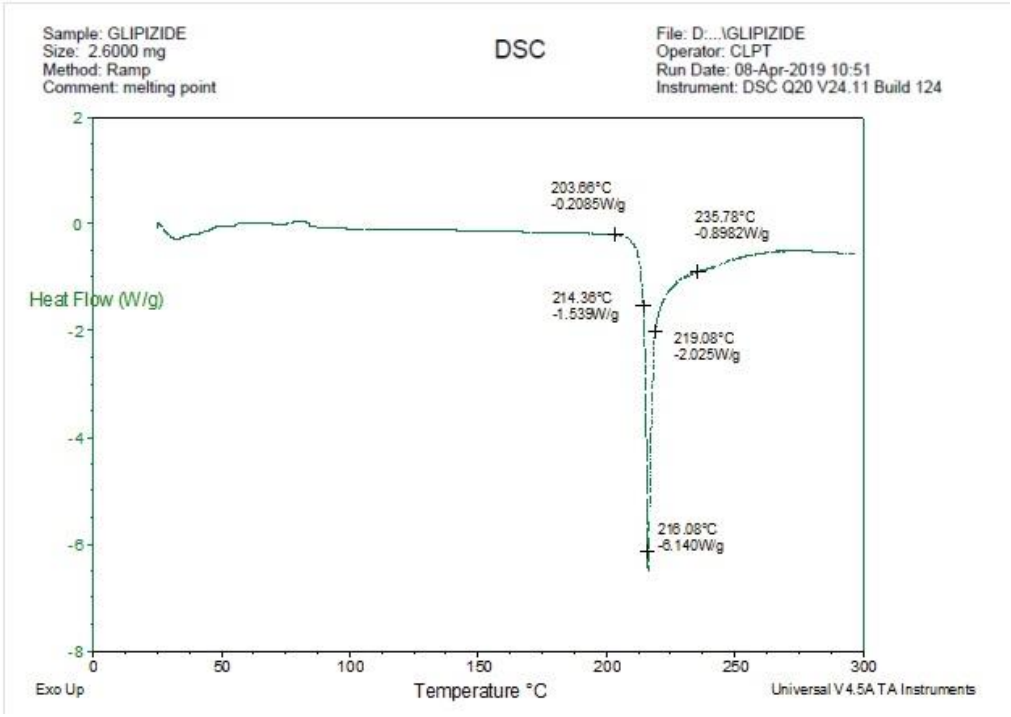
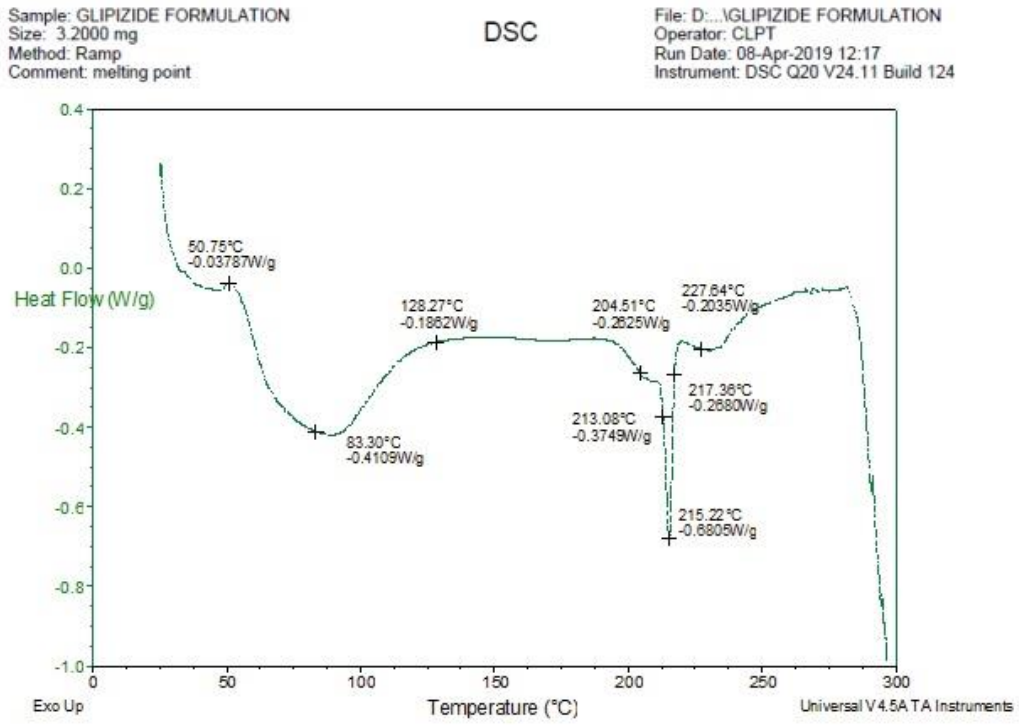


FIGURE XI



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