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AMELIORATED SOLUBILITY AND DISSOLUTION RATE OF GLIMEPIRIDE BY CYCLODEXTRIN TERNARY COMPLEXES EMPLOYING AMINOACIDS

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ABSTRACT: The purpose of the current investigation was to ameliorate the aqueous solubility and dissolution rate of an anti diabetic drug Glimepiride by cyclodextrin ternary complexes employing aminoacids. Initially, Glimepiride (GMP) binary complexes with β -Cyclodextrin (β CD) and Hydroxy propyl β -Cyclodextrin (HP β CD) were formulated by physical mixing, kneading, solvent evaporation and spray drying techniques which was followed by ternary complex preparation of selected GMP-Cyclodextrin binary complex employing various aminoacids by kneading method. The kneading method was used in preparing ternary complexes of GMP, because it was proved to be the best method comparatively in yielding promising binary complexes of glimepiride in the initial stage of this study. GMP formed 1:1 M stoichiometric binary and ternary inclusion complexes as demonstrated by the A_L -type of phase solubility curve. An increment in the stability constant value (K_c) of GMP- β CD/HP β CD complex in the presence of aminoacids conceded higher complexation competency. FTIR and DSC studies evidenced the perfect inclusion complex formation. Ternary complexes ameliorated drug dissolution compared with GMP and GMP- β CD. The ternary complex containing 1:3:2 molar ratio of GMP:HP β CD:L-ARGININE exhibited 98.85% drug dissolution in 2 hours, which was significantly high in relation to ternary complexes containing other aminoacids and it was found to follow imperatively first order release mechanism in relation to Hixson-Crowell's cube root law. On aging studied complexes showed no significant change in physical appearance, drug content and drug dissolution attributes, which clearly shows high in-vitro stability of the complexes.

INTRODUCTION: Glimepiride (GMP) is the pioneer molecule among third generation oral blood glucose lowering sulfonylurea class and is used in the management of type 2 diabetes.

Chemically it is 3-ethyl-4-methyl-N-(4-(N-((1r, 4r)-4-methyl cyclohexylcarbamoyl) sulfamoyl) phenethyl)-2-oxo-2, 5- dihydro-1 H pyrrole -1-carboxamide, having the molecular formula $C_{24}H_{34}N_4O_5 S$ ^{1,2}. It is a basic drug with short half-life of (6-8 hours), exhibits very low water solubility ($< 0.004\text{mg/ml}$) ³. The poor water solubility and slow dissolution rate of drugs in biological fluids results in fluctuating bioavailability and unreproducible therapeutic response or therapeutic failure of the drug due to sub therapeutic plasma drug levels ^{4,5}.

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Cyclodextrins (CD's) are hydrophobic, cyclic, non-reducing oligosaccharide, compounds of 6-8 glucopyranose units and have been extensively utilized to ameliorate the aqueous solubility of numerous poorly soluble drug molecules. CD's have the ability to form inclusion complex with many drug molecules. In which the guest molecule is entrapped partially or completely within the cyclodextrin cavity thus resulting in an increase in the solubility of the drug. The inclusion complexes are shown to improve solubility and dissolution rate^{6, 7} chemical stability^{8, 9} and bioavailability^{10, 11} of drugs. Cyclodextrin complexation could reduce local irritation and side effects associated with some drugs¹².

Through the formation of ternary complexes with drug/CD/excipients it is feasible to improve the complexation efficiency (CE) of CDs and at the same time enhance bioavailability of drugs from CD containing drug formulations. Numerous investigations reported that, incorporation of small quantity of hydrophilic excipients such as organic acids, amino acids, basic compounds, and polymers to an aqueous complexation medium usually give rise to an enhancement in the CE of cyclodextrins and ultimately reduce their amounts in pharmaceutical formulations¹³. The purpose of the current study was to ameliorate the aqueous solubility, dissolution rate and thus bioavailability of glimepiride. This could be achieved by cyclodextrin ternary complexation of glimepiride employing aminoacids.

MATERIALS AND METHODS:

Materials: Glimepiride was obtained as agift sample from Dr Reddy's lab, Hyderabad, β CD, HP β CD, amino acids (L-lysine, L-isoleucine, L-valine and L-arginine) and all other reagents used were of analytical grade and were purchased from S.D Fine chem. Ltd Mumbai.

Methods:

Formulation of Glimepiride solid complexes:

Binary complexes of GMP with β CD and also with HP β CD at 1:1, 1:2, and 1:3 molar ratios respectively were prepared by the following methods.

(a) Physical mixture method (PM): The physical mixtures were formulated by triturating the

calculated quantity of GMP and cyclodextrins (CDs) in a glass mortar. The physical mixtures thus obtained were screened through 120-mesh screen and then stored in a dessicator until utilized for further investigations^{14, 15}.

(b) Kneading method (KM): The weighed quantity of GMP and CDs were transferred to a clean glass mortar and kneaded together with 2ml of dimethyl formamide. The damp mass thus obtained was passed through 60-mesh screen and the granules obtained were dried at 45 °C under vacuum, until a constant weight was obtained. The granules after drying sufficiently were stored in a dessicator until used for further studies^{14, 15}.

(c) Solvent evaporation method (SM): The calculated amount of GMP and CD's were dissolved in small volume of dimethyl formamide in a china dish and the solution was allowed to stand overnight. The solvent was removed at 60 °C under vacuum until binary complex was completely dried. The dried mass was crushed and screened through 120-mesh sieve and the powder obtained was stored in a dessicator until used in further studies^{14, 15}.

(d) Spray Drying Technique (SD): The calculated amount of GMP and CD's were dissolved in small volume of dimethyl formamide. Spray drying of this solution was performed using laboratory-scale spray dryer (SMST, tall type spray dryer, Kolkata, India) under the following set of conditions. Inlet temperature: 140 °C; Outlet temperature: 100 °C Feed pump rate: 5% (100% mean 1000ml/hour) Atomization air pressure: 2.5 kg/cm² and aspiration 1 m Bar. The complexes were subsequently desiccated under vacuum for 48 hrs¹⁶.

Selection of binary complex for ternary complex formulation: Based on high aqueous solubility and in-vitro drug release profile GMP: HP β CD (1:3 molar ratio) binary complex prepared by kneading method (Formulation code: GHK3) was selected to develop its ternary complexes employing various aminoacids.

Formulation of Glimepiride ternary complexes: Ternary complexes of GMP were prepared using GMP: HP β CD: different amino acids (L-Isoleucine, L-Arginine, L-Valine, L-Lysine) at 1:3:1 and 1:3:2

molar ratios respectively by kneading method (as described above).

Phase solubility study: Solubility determinations of GMP were conducted as per the reported method¹⁷. Surplus quantity of GMP (50 mg) was transferred to 20 ml aqueous CD's solutions of increasing concentration (3mM to 15mM) in 50 ml Stoppard conical flasks. After shaking the contents of the flask at 37 °C for 72 hours on a mechanical shaker, the undissolved GMP was filtered through a 0.45mm filter paper (Whatman Grade 2589a) and the solutions after appropriate dilutions were assayed for GMP content at 228nm spectrophotometrically. Phase solubility studies of GMP were also conducted with the incorporation of aminoacids at a concentration of 0.5% w/v to the solutions containing CD's. The blank trials were run simultaneously in the same concentrations of CD's in distilled water in order to cancel out any absorbance if showed by Cyclodextrin molecules. The above solubility experiments were repeated for two more times to get accuracy in the results. The apparent stability constants ($K_{1:1}$) were computed from phase solubility diagrams using the below equation:

$$K_{1:1} = \frac{\text{Slope}}{S_0(1 - \text{Slope})}$$

Where S_0 is the intrinsic solubility of pure glimepiride.

Drug content estimation: Each formulation equal to 100 mg of GMP was dissolved in 100ml of methanol in a volumetric flask separately. From these stock solutions 10µg/ml of GMP solutions were prepared using methanol and the contents were assayed for GMP by UV-visible spectroscopy at 228 nm using methanol as a blank.

FTIR Spectroscopy: Fourier transform IR spectra of GMP, Cyclodextrins, aminoacids and few selected solid complexes of GMP were obtained using FTIR-281-spectrophotometer by KBr pellet method.

Differential Scanning Calorimetry: The thermal analysis of GMP, Carriers and selected solid complexes of GMP were conducted with a Shimadzu DSC 60 (Japan). Accurately weighed

samples were carefully placed in an aluminium pans and sealed. The sealed samples were heated at a rate of 100 °C /min in the temperature range of 30-300°C under a nitrogen flow rate of 20 ml/min.

In vitro dissolution study: *In vitro* dissolution studies for Glimepiride and its solid binary and ternary complexes was carried out using USPXXI Type-1 dissolution test apparatus by the powder dispersion method¹⁸. Sample equal to 4 mg of GMP was used in each test. The dissolution tests were performed using 900 ml of distilled water (pH 7.0) at $37 \pm 0.5^\circ\text{C}$ with paddle rotation maintained at 50 rpm. The release of GMP from each sample was determined by withdrawing 5 ml samples at preset time intervals, and were filtered, appropriately diluted and analysed spectrophotometrically at 228nm. 5 ml of fresh medium was transferred to maintain sink conditions.

Stability Study: Stability Study for selected binary and ternary complexes of GMP was carried out by storing 1gm of each selected complex in an ambered coloured screw capped glass bottles at accelerated and controlled temperatures and relative humidities for a period of 3 months as per the reported method¹⁹. The complexes were evaluated for physical appearance, drug content and in-vitro dissolution at the end of three months.

RESULTS AND DISCUSSION:

Phase solubility study: Phase solubility studies for GMP and its complexes were carried out to get an information about the drug solubilization mechanism and the inclusion complex formation. Solubility graphs (**Fig. 1**) for solid inclusion complexes were A_L type as per the Higuchi and Connors classification, demonstrating a linear increase of drug solubility indicative of the formation of soluble complexes. The ratio between the slopes of the phase solubility curves of the ternary and binary complexes, assumed as an index of the relative solubilizing efficacy, it was 1.33 for GMP-HPβCD-ARG ternary complex asserting the higher effectiveness of the ternary complex in relation to binary complexes.

The stability constant values obtained for binary complexes of GMP are $156.2M^{-1}$, $193.2M^{-1}$,

188.5M⁻¹, 213.5M⁻¹, 225.9M⁻¹, and 286.6M⁻¹ for HPBCD, BCD, L-Lysine, L-Isoleucine, L-Valine and L-Arginine respectively. The higher constant that was observed with L-Arginine demonstrates GMP interacts more strongly with L-Arginine.

The stability constant values obtained for ternary complexes of GMP are 224.6M⁻¹, 296.2M⁻¹, 235.6M⁻¹, 227.9M⁻¹, 179.6M⁻¹, 203.5M⁻¹, 179.2M⁻¹, and 190.6M⁻¹ for HPβCD-L-Isoleucine, HPβCD-L-Arginine, HPβCD-L-Valine, HPβCD-L-Lysine,

βCD-L-Isoleucine, βCD-L-Arginine, βCD-L-Valine, and BCD-L-Lysine respectively. The higher constant that was observed with HPβCD-L-Arginine demonstrates GMP interacts more strongly with HPβCD in presence of L-Arginine; this could be because of synergistic effect of L-Arginine. Thus L-Arginine independently and in combination with HPβCD showed highest complex formation/phase solubilization of GMP among other complexing agents/solubilizers used in the study.

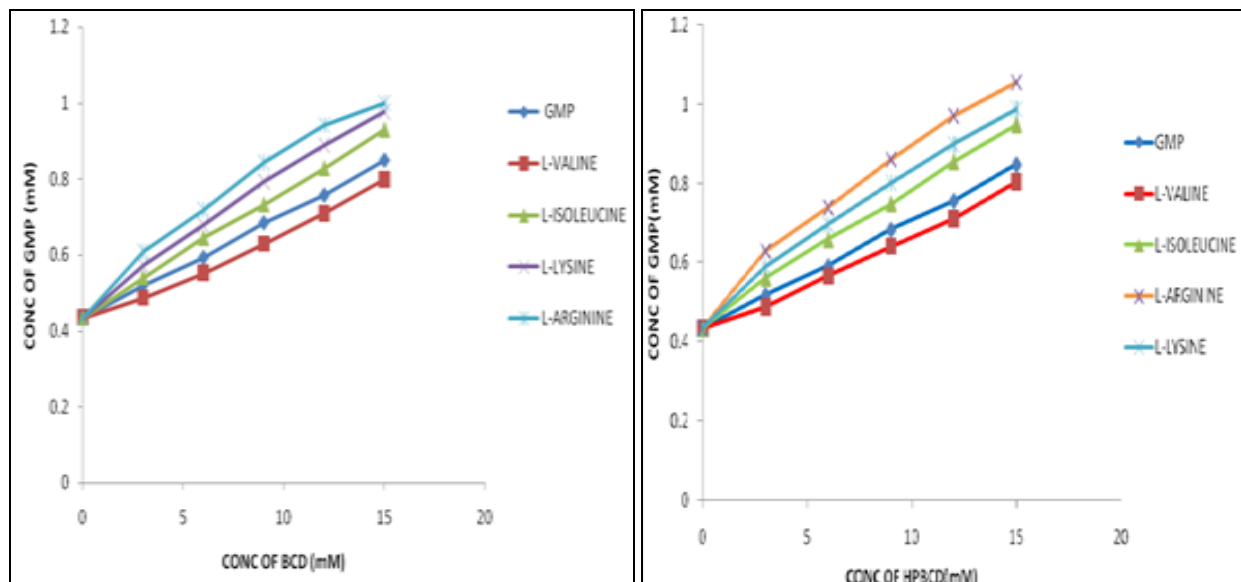


FIG. 1: PHASE SOLUBILITY GRAPHS OF GLIMPERIDE A) WITH βCD B) WITH HPβCD

Drug content estimation: The estimated drug content was in the range of 90.03%±1.692 to 97.78%±1.008 for binary complexes and 95.08%±0.494 to 98.66%±1.037 for ternary complexes with low SD and CV values. These values indicate that there was no significant loss of glimepiride through the formulation of its binary/ternary complexes. The coefficient of variation (CV) was found to be slightly higher than 1 in all the prepared complexes, which indicates that the methods employed in the preparation of glimepiride binary and ternary complexes were acceptable.

Fourier Transform Infrared Spectroscopy (FTIR): The IR spectrum of binary and ternary complex exhibited characteristic absorption band as given below. There is a significant change in the nature and positions of the peaks. Many of the peaks of IR spectrum of pure drug are missing in the spectrum of binary and ternary complexes.

The IR spectrum of pure GMP exhibited characteristic absorption band in the following IR region: 3369 cm⁻¹ and 3289 cm⁻¹, -NH groups 3860 cm⁻¹ and 3136 cm⁻¹-aromatic C-H stretching 2970 cm⁻¹ and 2862 cm⁻¹ C-H- stretching Of CH₃ both asymmetric and symmetric 2931 cm⁻¹ and 2843 cm⁻¹ C-H- stretching Of CH₂ both asymmetric and symmetric 1675 cm⁻¹ and 1704 cm⁻¹- C=O of CONH and ring C=O 1594 cm⁻¹, 1542 cm⁻¹ -C=C Ring stretching 1445 cm⁻¹, 1359 cm⁻¹ - C-H- bending Of CH₃ both asymmetric and symmetric 1407 cm⁻¹, 1346 cm⁻¹- C-H- bending Of CH₂ both asymmetric and symmetric 1317 cm⁻¹-C-N Stretching 1393 cm⁻¹ and 1542 cm⁻¹- O=S=O, 823 cm⁻¹, 4 disubstituted phenyl ring.

In both the spectra the peak for NH groups are appeared as broad bands. Similarly, the position of peaks for C-H stretching involving asymmetric and symmetric stretching for CH₃ and CH₂ groups are totally changed. The overall observation of the

spectra for binary and ternary complex revealed that there is a change in the position of peaks for functional groups as well as different types of

bonds. This type of changes in the nature and position of the peaks is possible only when inclusion complexes are formed (**Fig. 2**).

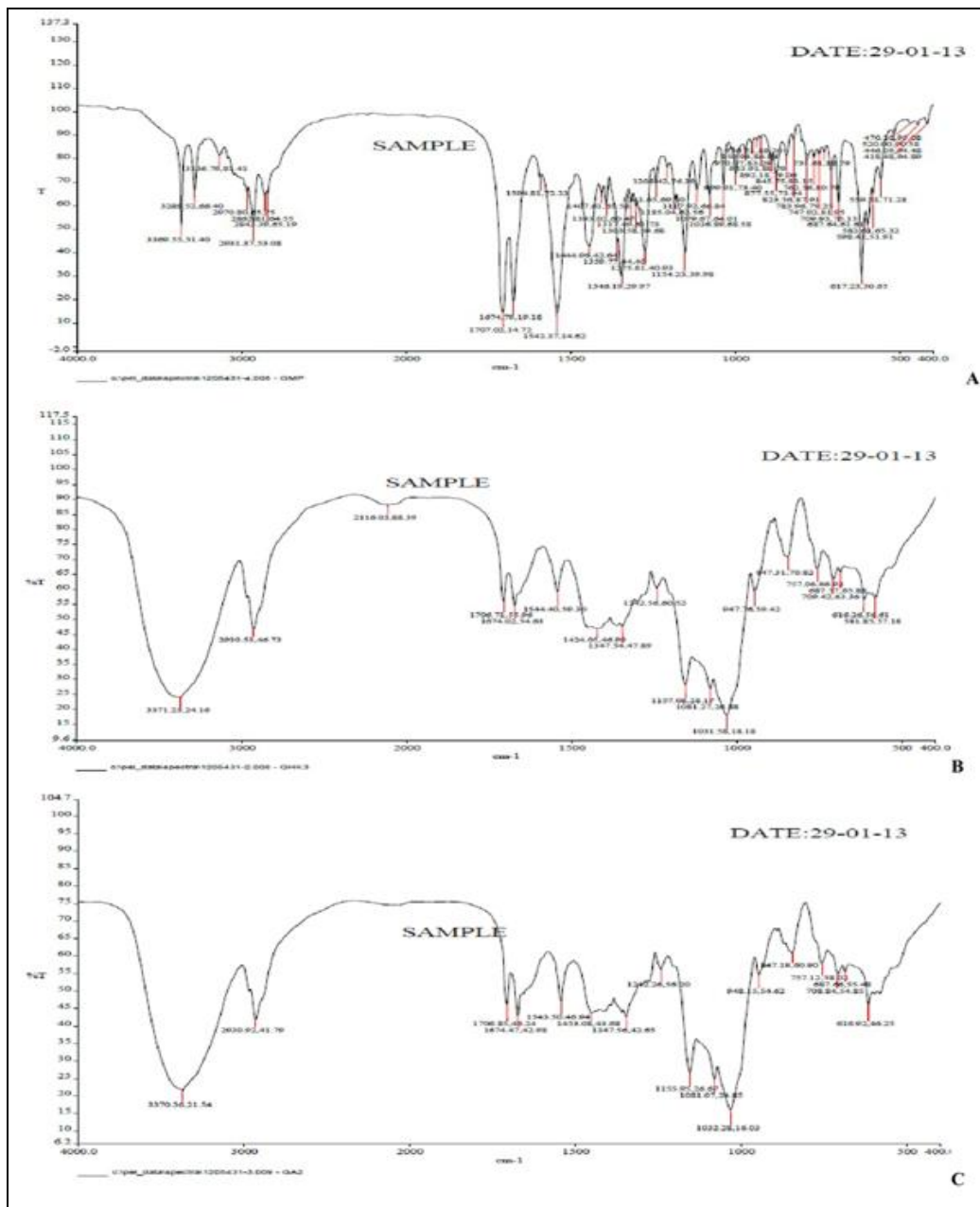


FIG. 2: FTIR SPECTRUM OF A) GLIMPERIDE B) GMP-HPβCD BINARY COMPLEX (GHK3) C) GMP-HPβCD-L-ARGININE TERNARY COMPLEX (GA2)

Differential Scanning Calorimetry (DSC): The thermal behaviour of the GMP and its complexes can be studied based on the type of the thermograms and nature of the peaks. The thermogram of pure GMP showed endothermic peaks at 200 °C. This corresponds to a melting point of the pure drug. This is almost in agreement with reported literature values of melting point 207 °C to 210 °C. In the thermogram of binary and

ternary complexes, the nature of peaks are totally changed, the peaks corresponding to pure drug 210 °C is shifted to 295 °C and 275 °C for binary and ternary complexes respectively (**Fig. 3**). The changes in the nature of thermograms of complexes indicate that inclusion complexes are formed. Hence it can be concluded from DSC studies that there is an interaction of drug with carrier and formation of complex like inclusion complexes.

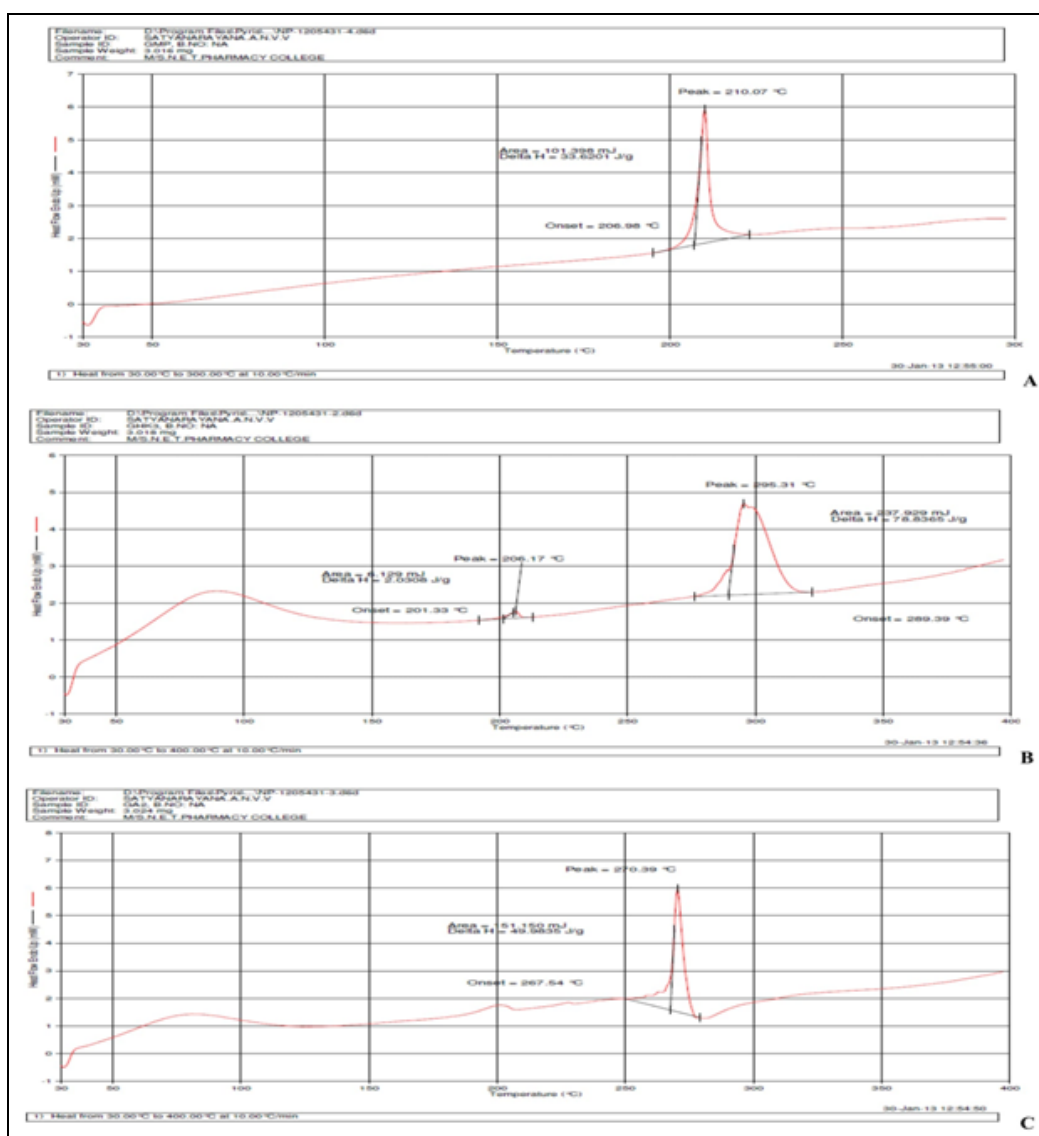


FIG. 3: DSC THERMOGRAM OF A) GLIMPERIDE B) GMP-HP β CD BINARY COMPLEX (GHK3) C) GMP-HP β CD-L-ARGININE TERNARY COMPLEX (GA2).

In vitro dissolution studies: All binary complexes of GMP and their corresponding physical mixtures (PM's) and also ternary complexes were evaluated for dissolution characteristics and compared with the pure GMP. The dissolution data obtained for GMP and its binary and ternary complexes was evaluated for statistical significance. The *in-vitro* dissolution results were assessed on the basis of cumulative percentage drug release, dissolution efficiency and correlation coefficient (r). The percentage of GMP dissolved at 30th min (DP₃₀) and dissolution efficiency at 10th min (DE₁₀), at 30th min (DE₃₀) and at 60th min (DE₆₀); and the characteristic time for 30% and 50% dissolution of GMP (T₃₀ & T₅₀ min respectively) were computed for all binary and ternary complexes. The

dissolution efficiency of all formulations was computed as per the method reported by Khan²⁰.

Binary complexes: All binary complexes demonstrated ameliorated rate and extent of drug dissolution and their dissolution efficiency values were higher than the PMs and pure GMP. The value of T₅₀ of all solid binary complexes was much smaller than pure GMP. Ameliorated drug dissolution rate and dissolution efficiency observed in the binary complexes was attributed to the formation of solid inclusion complexes with better interaction of GMP and CDs during the process. The rank order of dissolution rates was found in the following pattern, GMP:HP β CD > GMP: β CD > Pure GMP, with methods kneading > Solvent evaporation > Spray drying > Physical mixture.

The highest improvement in *in-vitro* dissolution performance was observed in GHK3 formulation containing 1:3 molar ratio of GMP:HP β CD (96.16% drug release in 120 minutes with DE₆₀ value 58.88% and T₅₀ value 26.88%). These results were in accordance with the phase solubility results.

Ternary complexes: *In vitro* dissolution data of GMP and its solid ternary complexes are depicted in Fig. 4. The percent drug dissolved from the solid ternary complexes prepared with L-Isoleucine after 120 minutes was 90.31 (GI 1), and 92.73 (GI 2), similarly, the percent drug dissolved from the solid ternary complexes prepared with L-Arginine after 120 minutes was 96.00 (GA-1), and 98.85 (GA-2). Also the percent drug dissolved from the solid ternary complexes prepared with L-Valine and L-Lysine after 120 minutes was 89.45 (GV-1), 92.08 (GV-2) and 91.17 (GL-1), 94.24 (GL-2) respectively. It was observed that the drug dissolution was constantly increased with increasing concentration of aminoacids in the ternary complexes.

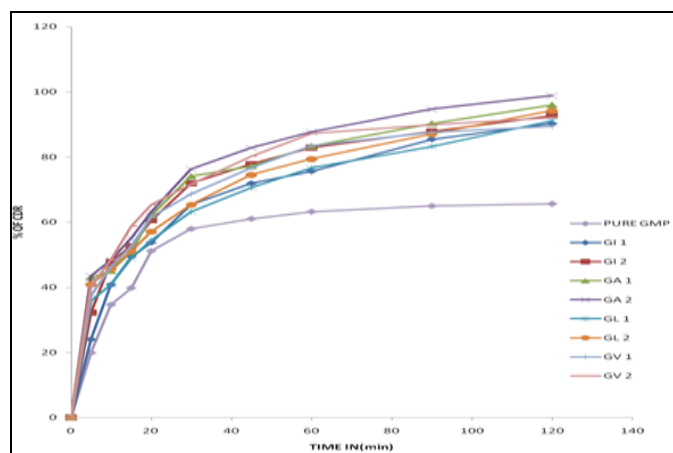


FIG. 4: CUMULATIVE % DRUG RELEASE VS TIME PROFILE OF PURE GLIMEPIRIDE, AND GLIMEPIRIDE SOLID TERNARY DISPERSION SYSTEMS

*GI= GMP: HP β CD: Isoleucine, GA= GMP: HP β CD: L-Arginine, GV=GMP: HP β CD: Valine, GL=GMP: HP β CD: Leucine

The various dissolution attributes and best model fitting curve values of GMP and solid ternary complexes are summarized in Table 1. *In vitro* dissolution profile of a highest drug releasing ternary complex formulation GA2 (a) Without model fitting curve and (b) With model fitting curve is illustrated in Fig. 5.

Dissolution profiles of pure GMP, and all its binary and ternary complexes were assessed in relation to Hixson-Crowell's cube root law and first order kinetics.

The correlation coefficient (*r*) values of the first order kinetics were found to be slightly higher to the '*r*' values of Hixson-Crowell's cube root model. Hence the release pattern in GMP and all its solid binary and ternary complexes were found to follow imperatively first order kinetics in relation to Hixson-Crowell's cube root law.

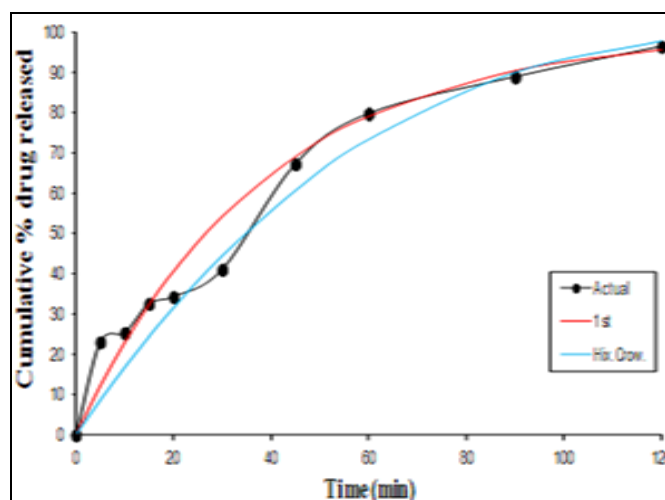
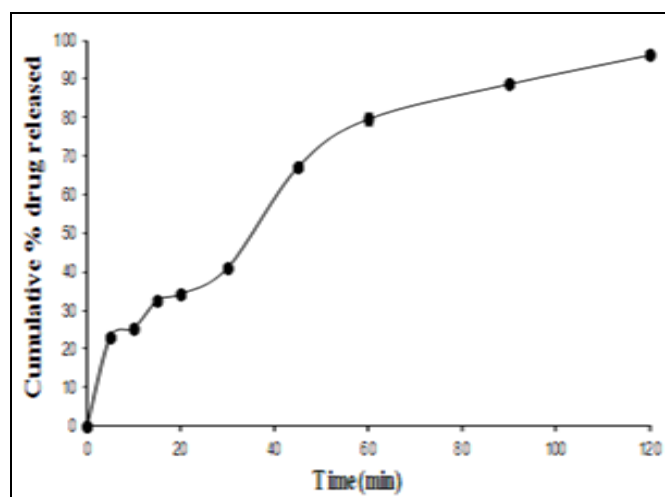


FIG. 5: IN VITRO DISSOLUTION PROFILE OF GA2 (A) WITHOUT MODEL FITTING CURVE AND (B) WITH MODEL FITTING CURVE

Stability Study: There was no significant change in the physical appearance, drug content and percent drug dissolution in the GMP complexes. Stability results clearly indicates that the complexes were sufficiently stable under accelerated and controlled conditions.

TABLE 1: VARIOUS DISSOLUTION PARAMETERS AND BEST MODEL FITTING CURVE VALUES OF GLIMEPIRIDE AND ITS SOLID TERNARY COMPLEXES

Ternary Complex	DP ₃₀			MDT ₃₀	First order rates $K_1 \times 10^2$ (min ⁻¹)		Hix.Crow $K_{HC} \times 10^2$ (mg ^{1/3} .min ⁻¹)				
	DE ₁₀ (%)	DE ₃₀ (%)	DE ₆₀ (%)		T ₃₀ (min)	T ₅₀ (min)	R	K ₁	R	K _{HC}	
GMP	15.41	32.24	42.90	49.682	10.45	19.85	7.43	0.8827	-0.0178	0.6012	-0.0050
GI1	23.01	44.14	58.03	66.054	14.88	26.88	9.95	0.9277	-0.0228	0.8141	-0.0056
GI2	28.85	49.98	64.13	72.572	14.75	27.75	9.34	0.9331	-0.0276	0.7883	-0.0064
GA1	33.56	51.77	65.19	74.744	14.72	28.72	9.22	0.9507	-0.0298	0.8072	-0.0067
GA2	34.59	53.70	68.38	76.918	10.78	21.78	9.05	0.9702	-0.0198	0.9432	-0.0091
GV1	31.07	50.32	63.71	69.332	12.78	26.78	8.22	0.9875	-0.0244	0.8511	-0.0060
GV2	33.02	53.59	67.06	72.378	11.00	23.25	7.79	0.9969	-0.0285	0.8903	-0.0066
GL1	28.96	45.86	58.44	63.904	14.91	30.81	8.47	0.9224	-0.0228	0.8911	-0.0056
GL2	32.64	48.86	61.51	66.084	14.97	31.99	7.82	0.9424	-0.0261	0.8056	-0.0061

*Where, DE= dissolution efficiency after 10, 30 and 60 min, DP= percent of drug dissolved after 30 min (DP), T₃₀T₅₀ = Time necessary to dissolve 30% and 50% of drug, R= coefficient of correlation; K₁, K_{HC} = release rate constants for First order and Hixon crowell's model respectively.

CONCLUSION: From the present study it is concluded that the formulated complexes revealed the key performance of HPβCD to ameliorate the solubility and dissolution rate of Glimepiride. Further, ternary complexes of GMP: HPβCD: L-ARG (1:3:2 molar ratio) prepared by Kneading method offers an improvement in the solid pharmaceutical formulations of the Glimiperide, which renders sufficiently the formulation aqueous soluble for clinical application. However further pharmacokinetic and pharmacodynamic evaluation of our promising GA2 formulation would yield much rewarding outcomes.

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CONFLICT OF INTEREST: None declared

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