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SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT ANDMODIFIED RELEASE FORMULATION OF POORLY WATER SOLUBLE DRUG GLICAZIDE

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ABSTRACT

A drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through biomembrane and extensive presystemic metabolism. Glicazide is practically insoluble in water and having limited bioavalability. To enhance the dissolution rate and oral bioavailability. The present study was aimed Solubility and Bioavailability Enhancement and Modified release formulation of poorly water soluble drug Gliclazide by using β –Cyclodextrin as a water soluble polymer using different methods physical mixture(PF1 – PF3), spray drying(SF1- SF3) and kneading method(KF1-KF3). The interaction of a pure drug with polymer was studied by Fourier Transformation-Infrared Spectroscopy and Differential Scanning Calorimetry. Formulated batches were characterized for physicochemical properties like drug content, dissolution studies. Pharmacokinetic studies of optimized formulation (KF3) were compared with pure drug. Thedissolution rate of pure drug and tablet prepared by kneading method with ratio of polymer (1:3) showed 38.14% and 100.5% in the phosphate buffer pH 7.4 at 30 min. From above study it concluded that kneading method is an effective in increasing solubility and bioavailability of poorly water soluble drug.

KEYWORDS: Gliclazide, Enhancement, Bioavailability.

INTRODUCTION[1-13]

Diabetes mellitus is chronic metabolic disease caused by variable combination of insulin deficiency and insulin resistance. The result is disordered utilization and storage of the proximate nutrients and reduced production of ATP. Hyperglycemia is its most easily measured laboratory marker and the liability to chronic degenerative disease in almost all body tissues is its hallmark. **T**he etiology of DM is still obscure although it has a strong genetic basis. However, with proper management with diet, drugs and exercise a diabetic can enjoy an almost normal life.

Clinically diabetes mellitus is classified as

1. Type 1 DM: This is insulin dependent and the patient's survival depends uponuninterrupted insulin therapy.
2. Type 2 DM: This is not insulin dependent and the patient's survival does not depend upon insulin therapy.
3. Type 3 DM : Which is due to other hormonal disorders such as acromegaly, and drugs such as glucocorticoids; it may often respond to oral anti-diabetic agents
4. Type 4 DM: This must be treated with diet or without insulin.

Gliclazide binds to the β-cells sulfonyl urea receptor (SUR1). This binding subsequently blocks the ATP sensitive potassium channels. The binding result in the closure of channel leads to a resulting decrease in potassium efflux leads to depolarization of β-cells. This opens voltage-dependent calcium channel in the β-cell resulting in calmodulin activation, which in turn leads to exocytosis of insulin containing secretory granules.[1]

In recent years, the oral route is the most preferred of drug delivery for treatment of many number of disease, upto 40% of chemical entity discovered by the pharmaceutical industry. They leads the poor oral bioavailability.[2] Number of effective lipophilic drugs shows low oral bioavailability due to their poor aqueous solubility properties. For this class of compounds, gives the "lows solubility/ high permeability" class II, dissolution in environmental lumen.[3]

Various techniques have been used in attempt to improve solubility and dissolution rates of poorly water soluble

drugs which include as following: Particle Size Reduction, Nanonization, Cosolvency, Hydrotropy, pH Adjustment, Sonocrystallization, Supercritical Fluid (SCF) Process, Solid Dispersion, spray drying, kneading method, fusion method and self-emulsifying drug delivery system. These techniques are promising approach for oral delivery of poorly water-soluble compounds.[4-10] Some factors are also affects on solubility rate are Particle size, Temperature, pressure, nature of solid and polymorphism.[11-13] In the present work, physical mixture, kneading method and spray drying techniques were used to enhance solubility and bioavailability of glicazide. Polymer like β -Cyclodextrin were used to prepare tablet of glicazide with different ratios of drug with polymer. The pure drug and formulated batches were subjected to DSC and IR. The optimized formulation by kneading method was selected for further assessment of its pharmacokinetic evaluation.

MATERIAL

Gliclazide purshed from JIUZHOU Pharmaceutical, β – Cyclodextrin were purchased from Yarrow Chem Products, Mumbai. Starch, Mannitol were purchased from Research Lab Mumbai, Crosscarmellose sodium, Sodium starch glycolate were purchased from Fine Chemie Pvt. Ltd. Pune. Crosspovidone were purchased from Pallav Chem Pvt. Ltd.Boisar. Magnesium Stearate, Aerosil, Talcum Powder were purchased from Loba chemie Pvt.Ltd, Mumbai, Methanol and other solvents were used of analytical grade.

METHOD

Evaluation of pure drug Glicazide

a) Determination of solubility[14,15]

The solubility of glicazide was checked in water, ethanol, acetone, dichloromethane, phosphate buffer 7.4.

b) Determination of λ_{max}[14,16]

The UV absorption spectrum of pure drug was performed in phosphate buffer pH 7.4, Methanol, Methanol-Phosphate buffer pH 7.4.

c) FTIR of Drug and Polymer[14,16]

FTIR spectroscopy was carried out to study the interaction between drug and polymers used in the preparation for the test samples. FTIR spectrum of pure drug glicazide.

d) DSC study of Pure drug[14,16]

DSC was carried out to study how physical properties of drug change along with temperature against time by using Hitachi7020.

e) Phase solubility study of Gliclazide in water[17-19]

Phase solubility study was performed according to the method reported by Higuchi and Connors. The effect of concentration of β-CD on the equilibration solubilities of gliclazide in distilled water at 37±0.5^{0}C for 48 hrs. phase solubility study was carried out by adding an excess amount of drug into a screw-capped glass vials containing 20 ml of distilled water and various concentration of the carrier(0.5- 2.5 % w/v). The mixture were shaken for 48 hrs at room temperature on rotary flask shaker. After 48 hrs of shaking, an aliquotes of each solution was withdrawn and filtered through a 0.45µm Whatmann filter paper. The filtered samples were diluted suitably and drug content was assessed by U.V. Spectrophotometer method at 228 nm. The solubility experiment are calculated in triplicate.

f) Dissolution study of pure drug glicazide[20-21]

The dissolution study of pure drug was performed in USP basket dissolution apparatus (apparatus I) at a speed of 50 rpm in the dissolution medium 7.4 phosphate buffer system.

Preparation of inclusion complex[22-24]

Inclusion complex formation technique is used precisely to improve the aqueous solubility, dissolution rate and bioavailability of poorly water soluble drugs among all the solubility enhancement techniques. Inclusion complexs are prepared by the insertion of the non-polar molecule or the non-polar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. The complexes of gliclazide and β-CD were prepared at weight ratios of 1:1, 1:2, 1:3 using following techniques.

❖ **Physical Mixture**

The PM of Gliclazide and β-CD were obtained by mixing pulverizes powder together in mortor and pestle. Triturating for 1 hour then passed through sieve mesh no.100. These powdered physical mixture were then stored in the desicator until further use.

❖ **Kneading Method**

Gliclazide and β-CD was triturated in mortar and pestle with small volume of water: methanol (7:3) solution. The thick slurry was kneaded for 1 hr and then dried at room temperature for 24 Hrs. Dried mass was pulverized and sieved through sieve mesh no.100. The kneaded product was stored in desicator until further use.

❖ **Spray Drying Method**

In this method, β-CD is dissolved in water. The resulting solution is sonicated for about 1 hr then in this resulting solution drug is added and to get clear solution sufficient amount of ethanol is added. Water: Ethanol (1:1) is used in the solution and then solution is spray dried by observing air flow rate, atomizing air pressure, inlet-outlet temperature, flow rate of solution etc.

Accurately weighed amount of β-CD dissolved in water and gliclazide is added to this solution. To get a clear solution Ethanol is added. This solution is then spray dried using laboratory scale dryer.

Table 1: Spray Drying Method.

D:P	Temperature		Feed Rate	Aspirator Speed	Vacuum Pressure
	Inlet	Outlet			
1:1	100^{o}C ±1	60^{o}C±1	24	60±1	55±2
1:2	100^{o}C ±1	60^{o}C±1	24	60±1	55±2
1:3	100^{o}C ±1	60^{o}C±1	24	60±1	55±2

Formulation of Fast Dissolving Tablet [25-28]

Physical blending and kneading method complex was selected for the formulation of tablets. Tablet containing 120 mg of drug: β-CD kneading complex equivalent to 30 mg of drug wereprepared by wet granulation method.

Table 2: Formulation of Fast Dissolving Tablet.

Sr.no.	Component	Quantity for 1 tablet.
1	**Glicazide-β-CD Complex**	**120 mg**
2	Starch	24 mg
3	Crosscarmellose sodium	10 mg
4	Crosspovidone	10 mg
5	Sodium starch glycolate	10 mg
6	Mannitol	10 mg
7	Magnesium stearate	10 mg
8	Aerosil	6 mg
9	Talcum powder	10 mg
	Total	210 mg

Evaluation of Fast Dissolving Tablet

A. Post-compressional Parameters [28-31]

1. **Hardness -** Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers and the handle was pressed, the force of fracture was recorded.
2. **Thickness-** The thickness of 3 tablets were recorded during the process of compression using electronic vernier caliper. The average thickness was calculated.
3. **% Weight Variation:** The weight variation test is performed in order to ensure the uniformity in the weight of tablets in a batch. Weight variation test was performed as per IP 2014. Twenty tablets were selected randomly and weighed. Average weight of tablet was determined. Not more than the two of the individual weights deviates from the average weight by more than 5% deviation.

$$\%\ \boldsymbol{Weight\ variation} = (\boldsymbol{W_A} - \boldsymbol{W_I}) \times \frac{\boldsymbol{100}}{\boldsymbol{W_A}}$$

Where, W_A= Average weight of tablet W_I= Individual weight of tablet

Table 3: % Weight Variation.

Sr. No.	Average weight of tablet	% deviation
1	80 mg or less	±10
2	80 mg to 250 mg	±7.5
3	250 mg to more than 250 mg	±5

1. **Friability-** The Roche friability test apparatus was used to determine the friability of the tablets. Twenty tablets were accurately weighed and placed in the friabilator and operated for 100 revolutions. The tablets were de-dusted and reweighed. Percentage friability was calculated using the following formula.

$F = (1-W_0 / W) \times 100$

Where, W_0 is the weight of the tablets before the test and W is the weight ofthe tablet after the test.

2. **Drug Content Uniformity:** The gliclazide tablet were tested for their drug content. Five tablets were finely powdered; quantities of powder equivalent to 10mg of gliclazide were accurately and transferred to 100ml volumetric flask. The flask was filled with methanol solution and mixed thoroughly. 1ml of filtrate was further dilutedto 10ml of methanol and measure the absorbance of resulting solution at 227nm using UV-Visible double beam spectrophotometer. The linearity equation obtained from calibration curve as described previously was use for estimation of in the gliclazide tablet formulation.

3. **Disintegration Time:** The test was performed using Six tablets of different formulation were placed individually in each tube of basket of disintegration test apparatus and discs were placed. The basket was positioned in to beaker containing 900 ml Phosphate buffer solution of pH 7.4 which was maintained at a temperature of 37±2ºC and time taken for entire tablet to disintegrate completely was noted. Three trails were perform for each formulation of tablets.
4. **Wetting Time-** Five circular paper with 10 cm diameter were placed in Petri dish. 10 ml phosphate buffer pH 7.4 containing eosin 0.5%. Water soluble dye was added into Petri dish. Dye was used to identify complete wetting of tablet. Tablet were placed in separate Petri dish and record time required to complete wetting of tablet usingstopwatch.
5. **Water absorption Ratio:** Five circular paper with 10 cm diameter were placed in Petri dish. 10 ml phosphate buffer pH 7.4 containing eosin 0.5%. Water soluble dye was added into Petri dish. Dye was used to identify complete wetting of tablet. Wetted tablet were placed on the surface of tissue paper and time required to

complete wetting of tablet is recorded and tablet was again reweighted and calculate water absorption ratio by using following formula.

$$R = \frac{W_a - W_b}{W_b} X\ 100$$

Wa= weight of tablet after water absorption
W_b= weight of tablet before water absorption

6. In vitro Drug Release Study: The Dissolution study of Gliclazide from the fast disintegrating tablets were carried out using USP dissolution test apparatus type-II, Paddle type, using 900 ml of phosphate buffer pH 7.4 as the medium and the paddle rotating at 50 rpm for minute at 37±0.5ºC. 1ml of aliquot were withdrawn and filtered through Whatman filter paper at an interval of 5, 10, 15, 30 and 45 min with replacement of 1 ml fresh dissolution media. Solution were diluted up to 10 ml using same medium. The absorbance of the resultant solution was measured at 227nm using UV spectrophotometer.

B. Characterization of KF3

1. FT-IR Spectroscopy Study- FT-IR spectra of selected formulation and inclusion complex powder were recorded on FT-IR spectrophotometer using KBr discs. The instrument was operated under dry sir purge and the scans were collected at scanning speed 2mm/sec with resolution of $4cm^{-1}$ over the region 4000 - $400cm^{1}$. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due to cyclodextrin and appearance of new peaks due to complexation.

2. DSC Study- DSC was performed on Hitachi 7028 instrument. Thermographs were obtained by heating 1 mg sample in aluminium pans at heating rate 100/min, form 35c to 350c, in nitrogen atmosphere (flow rate 20ml/min). Data was analyzed, using PYRIS version-11.1.0.0488 software to obtained onset temperature (T end set) of endothermic peak

3. Stability study- Stability of active pharmaceutical ingredient is integral part of systemic approach to stability evaluation. The purpose of stability testing is to provide evidence on how quantity of drug substance or product varies with time under influence of various environmental factors. To establish a retest period for a product in recommended storage conditions. Stability is the event to which a product remains within specified limits throughout its period of storage and use.

The 45 days accelerated stability studies carried out for optimized formulation according to international conference on harmonization (ICH) guidelines. Optimized formulation were subjected to stability testing. The immediate release tablet formulation were filled in glass vials, closed with gray rubber closure and sealed with aluminium caps. The formulation vials kept in stability chamber at 40 ± 2^0c temperature and relative humidity 75± 5% for 45 days.

RESULT AND DISCCUSION

Pre-formulation of drug

1. **Solubility of Drug -** Solubility of Gliclazide was found to be insoluble in water. Slightly soluble in alcohol. Sparingly soluble in acetone. Freely soluble in dichloromethane. The maximum solubility of Gliclazide was found to be in phosphatebuffer 7.4
2. **Determination of λ max-** The UV absorption spectrum of pure drug in the phosphate buffer pH 7.4, Methanol, Methanol-Phosphate buffer pH 7.4 was found to be 227,228 and 227nm respectively.

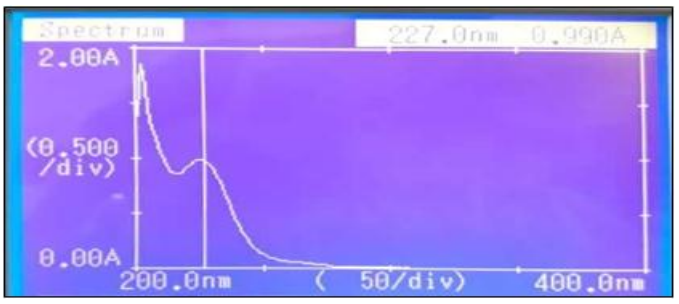

Fig. 1: λ max of Gliclazide in Methanol: Phosphate Buffer pH 7.4.

1. Infra-Red SpectroscopyFTIR Spectrum of Gliclazide

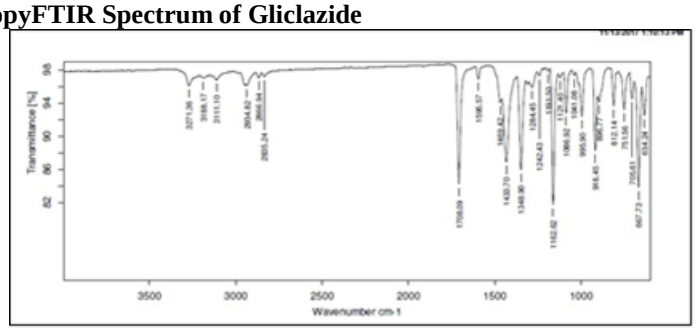

Fig. 2: FTIR Spectrum of Gliclazide.

In FTIR Spectrum of Gliclazide the characteristic peak are observed at the 667.13 due to CH bending, 1041.08 due to C-C stretching, 1121.40 due to C-O stretching alcohol, 1348.90 due to OH bending alcohol, 1284.45 due to CN Stretching amine, 1121.40 due to O=S=O stretching, 1708.09 due to C=O starching carboxylic acid, 3217.36 due to OH stretching alcohol, 3188.17 due to NH stretching amines and 2866.94 due to CH stretching alkanes.

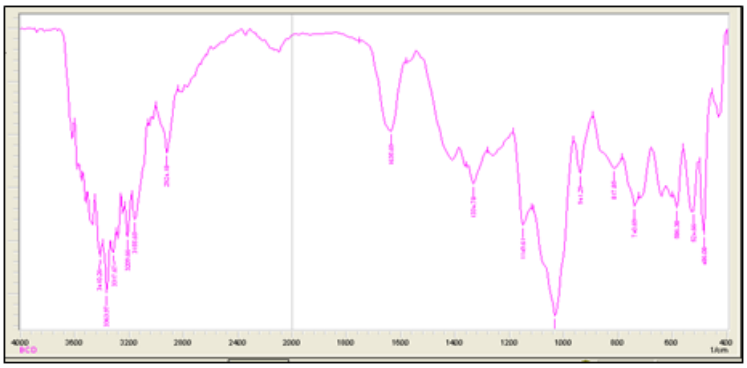

Fig. 3: FTIR spectra of β-Cyclodextrin.

2. DSC of Pure drug: DSC thermogram of given sample of Gliclazide was shown in figure. The thermogram shows small endothermic peak at 165.80°C and exothermic peak at 172.57°C. Sharp peak at 168.73°C which is near to the actual melting point of Gliclazide. From this it was confirms that the given drug sample was Gliclazide in crystalline nature at its exothermic peak.

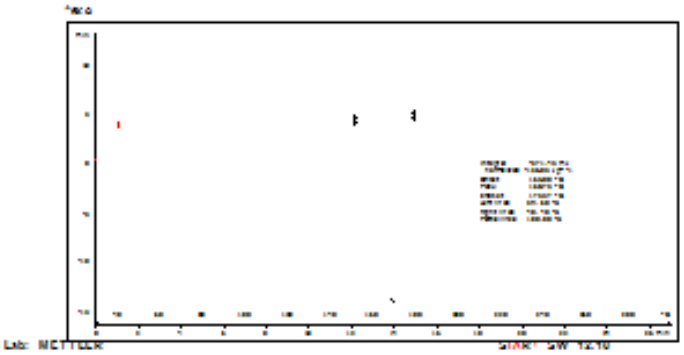

Fig. 4: DSC Spectrum of Gliclazide.

Compatibility Study of Drug-β-CD: Compatibility study was carried out by using FTIR Spectroscopy. Drug and polymer with equal proportions showed all characteristics peaks of their respective functional groups. As shown in fig. No. there is no significant shift observed in the positions of featured peaks of Gliclazide and β –Cyclodextrin. Hence, it can beconsidered that the drug and polymer are chemically compatible and can be together incorporated together in the formulation.

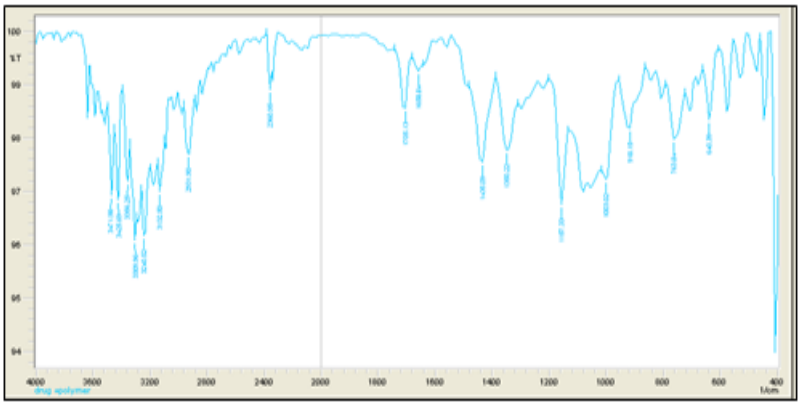

Fig. 4: DSC Spectrum of Gliclazide and β –Cyclodextrin.

3. Phase Solubility study of Gliclazide: β-CD in Distilled water

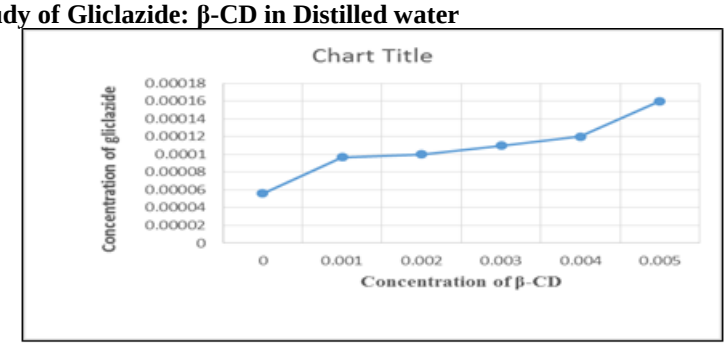

Fig. 5: Phase solubility study of Gliclazide: β-cyclodextrin.

4. Dissolution study of Pure Drug in phosphate buffer pH 7.4

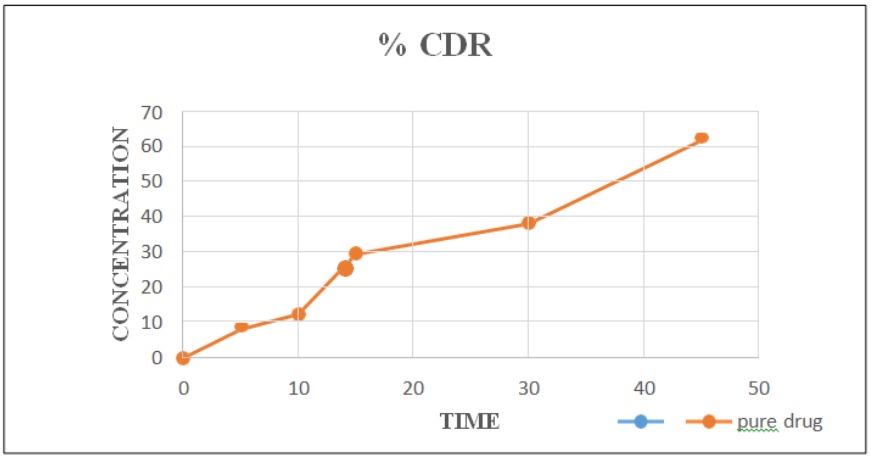

Fig. 6: Dissolution study of Pure Drug in phosphate buffer pH 7.4

Evaluation of Inclusion complex-

Table 4: Evaluation of Inclusion complex.

FC	Solubility (µg/ml)	% Yield	Drug content
Pure Drug	5.68	-	-
PF1	6.5	95.5%	89.4%
PF2	7.66	97.5%	93.84%
PF3	11.04	96.05%	99.6%
KF1	9.04	91.5%	93%
KF2	10.25	95.6%	84.08%
KF3	16.8	92.25%	100.8%
SF1	9.04	74.75%	82.8%
SF2	10.6	69.66%	74.44%
SF3	12.8	83.15%	89.66%

Post Compressional Parameter of Formulation

Table 5: Post Compressional Parameter of Formulation.

FormulationCode	Weight Variation ±SD (n=10)	Thickness ±SD (n=10)	Hardness ±SD (n=5)	Friability (%)
PF3	0.219 ± 0.009	3.546 ± 0.010	2.16 ± 0.240	0.60
KF3	0.216 ± 0.0015	3.529 ± 0.015	2.22 ± 0.192	0.55
SF3	0.212 ± 0.0015	3.417 ± 0.012	2.14 ± 0.230	0.56

Table 6: Post Compressional Parameter of Formulation.

FormulationCode	Drug Content (n=3)	DisintegrationTime (sec)	Wetting Time (sec)	Water absorptionratio
PF3	99.56 ± 1.552	130.66 ± 6.027	133.33 ± 6.110	37.46 ± 3.353
KF3	100.32 ± 0.814	122.66±4.509	122.66 ± 4.509	39.07 ± 2.249
SF3	97.24 ± 0.861	125.66±4.163	129 ± 3.605	38.54 ± 3.054

In Vitro Drug Release Study

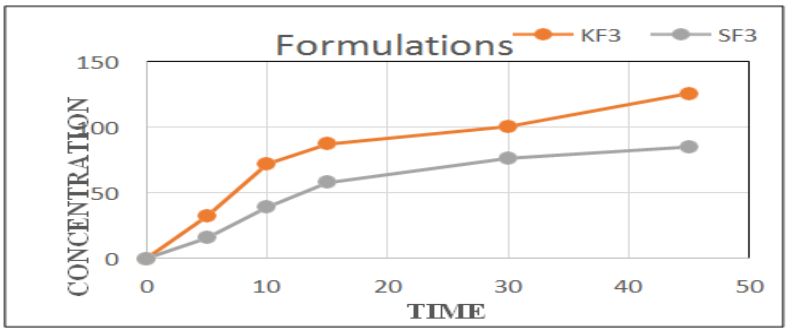

Fig. 7: In Vitro Drug Release Study of Fast Dissolving tablet gliclazide.

Characterization of Formulation

I. FT-IR Spectroscopy Study

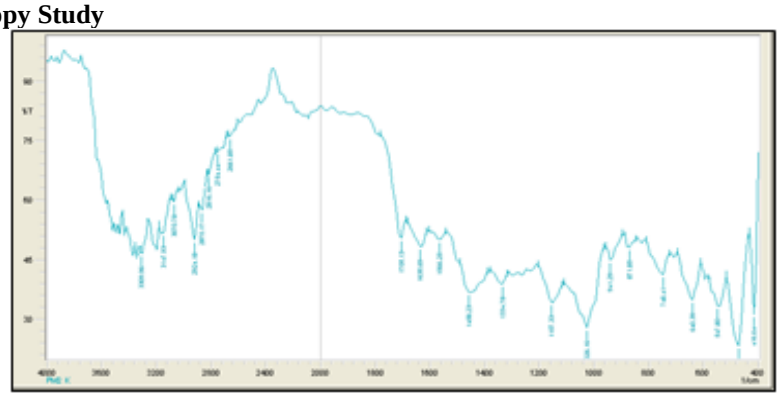

Fig. 8: FTIR Spectrum of Formulation KM3

II. DSC Study

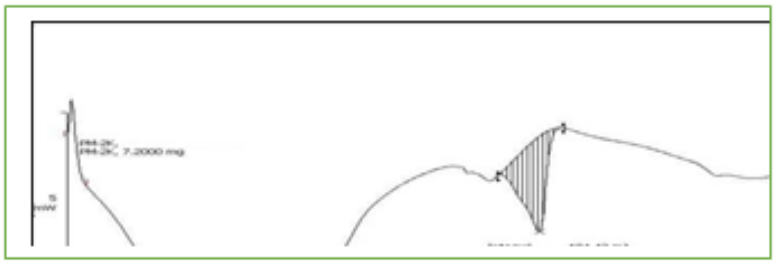

Fig. 9: 10 DSC of optimized formulation KM3.

III. Stability Study

Table 7 Stability study of gliclazide.

Batch	Physical appearance	Hardness	Content ofuniformity	In vitro % CDRafter 30 min
KF3	No change	2.22kg/cm^2	100.8%	95.59%

CONCLUSION AND SUMMARY

The objective of present work was to enhance the solubility of poorly water soluble drug glicazide. The dissolution rate of glicazide was successfully enhanced by cyclodextrin complexation techniques. Inclusion complexes of glicazide was produced by kneading method, physical mixture and spray drying method among this kneading method showed highest solubility (16.8µ/ml) and fast dissolution profile. In this present work fast dissolving tablet of glicazide were prepared by inclusion complex of kneading method, physical mixture and spray drying method by wet granulation compression method and evaluated for physiological parameters. Disintegration time of KM3 batch was found to be providing and displayed disintegration time 119 second. It shows faster drug release. Among the three methods kneading method was found to be superior method. Stability studies indicate that there were decrease in disintegration time, dissolution studies, hardness, friability.

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