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FORMULATION AND DEVELOPMENT OF SUSTAINED RELEASED GLICLAZIDE TABLETS WITH THE DIFFERENT HYDROPHILIC POLYMER BY USING DIRECT COMPRESSION TECHNIQUE

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Abstract:

To effectively manage the diabetic mellitus type-II hyperglycemic problem, Gliclazide tablet is the sustained-release tablet that has been designed and fabricated for years. This research evaluated the effects of different grades of hydrophilic polymers in sustained release of Gliclazide tablets made with direct compression technique. HPC GF GRADE, HPMC K4M, and PARTECK® SRP 80 were used as the polymer, Avicel pH 101 (MCC) was used as the highly compressible diluent and Starch 1500 was used as insoluble tablet filler. Aerosil 300 and Magnesium Stearate was used as a Glidant and lubricant for improving the flow property of powder and to decrease the friction between dying wall and punches. Pre-compression characteristics were evaluated for angle of repose, bulk density, compressibility, tapped density, and Hausner's ratio and DSC, XRD, FT-IR. Tablets were prepared on a rotary tablet press machine (Eliza press) and after compression tablets were evaluated for weight variation, thickness, hardness, friability, drug content, and in-vitro drug release study. The physico-chemical properties of blends were estimated accelerated stability study was also developed formulations were kept for stability study for three months as per ICH guidelines and found to be stable. Advantages of formulating insoluble drugs such as Gliclazide is that if it is used in the preparation of capsules or tablets of the drug, its dose might be reduced which is economically beneficial.

Keyword: SR Gliclazide, HPC GF, HPMC K 4M, PARTECK SRP 80, Avicel pH 101, Starch 1500, Aerosil 300, Magnesium stearate, etc.

Introduction

Gliclazide is a potential oral hypoglycemic drug useful for the treatment of non-insulin-dependent diabetes (type 2) mellitus (NIDDM) [1-2] which is a growing global epidemic, especially in Asian populations. Gliclazide is a member of class sulphonylurea which involved insulin secretagogues, which perform by stimulating beta cells of the pancreas to release insulin[10,11]. Gliclazide which includes antiglycation effect on in-vitro AGE formulation was demonstrated[3]. Gliclazide is best known for reducing fasting plasma glucose, glycosylated hemoglobin (HbA1c) levels (reflective of the last 8-10 weeks of glucose control), and postprandial blood glucose[2]. Oral doses of 40 to 120 mg of Gliclazide results in a plasma concentration of 2.2 to 8.0 µg/ml within 2 to 8 hrs [2]. Gliclazide has a high protein binding affinity such as an albumin (85 to 97%) [2]and mainly binds to site II of the HSA (Human Serum Albumin) molecule with the involvement of the aromatic ring of Tyrosine [4] and high albumin (95%) binding affinity which helps to enhance its distribution in blood influencing its bio-availability and pharmacokinetics properties.

The half-life of the drug is 10.4 h, duration of action 10-24 hr and firstly extensively metabolized in the liver to form hydroxylated and oxidized derivatives, as well as glucuronic acid conjugates[5-6]. The drug reduced solubility in purified water by 0.19 mg/mL which is the problem for the biological effect as a result of reduced dissolution and bio-availability[5-6]. Gliclazide is characterized by considerable inter-individual variability in pharmacokinetics, clinical efficacy, and adverse effects, making the therapy more complicated also and which is helpful for the treatment of Type II Diabetes Mellitus with oral antidiabetes drugs [7]. Gliclazide exhibits variability in pharmacokinetics as its dissolution rate depends on gastric emptying time. Its dissolution varies 1) in the small intestine and stomach where it has a different degree of solubility 2) with extensive metabolism in the liver, and 3) with physiological and formulation characteristics [7]. The efficacy of Gliclazide as an oral dosage form is its very low aqueous solubility because hydrophobic. Gliclazide belongs to Class II of the Biopharmaceutical Classification System (BCS) in which the drug dissolution rate is the controlling step in drug absorption [7]. The slow dissolution of Gliclazide is due to poor wetting of its surface (powder form) by water [8]. Currently, Gliclazide formulation does not provide patient compliance since 2-3 tablets

per day are required to meet the daily therapeutic dose due to its poor solubility and bio-availability. Earlier research indicated that the formulation aimed to enhance the dissolution of Gliclazide, can increase its absorption in GI [8].

Evaluated the effect of mixing hydrophilic polymers on the release profile of Gliclazide from tablet used hydrophilic polymers HPC GF, HPMC K 4M, and PARTECK SR P-80 polymers which are known for their potential to prolong the release of the drug. In addition, HPC GF has a low water affinity and hence hydrates slowly preventing lumping during the preparation of the sample[13]. HPMC K4M (hypromellose) is a highly viscous polymer and thermally gel. Hypromellose provides the release of a drug in a controlled manner and effectively increases the release profile of a drug and prolongs its therapeutic effect[14]. Parteck SR P-80 is a new functional polymer based on polyvinyl alcohol (PVA) and has posed a matrix diffusion mechanism that helps to increase bio-availability. Parteck® SR P-80 is highly compatible with the direct compression technique[15]. This is aimed to develop Gliclazide tablet in such a way that a single dose can provide the required daily therapeutic dose, thereby increasing patient compliance and reducing cost of the treatment by reducing cost per dose as well as the number of doses.

In this study, tablets of Gliclazide were prepared by direct compression method, with an intention that the sustained release formulation will release the Gliclazide to combat the postprandial hyperglycemic surge followed by a steady-state plasma glucose level controlled by sustained release. The compatibility studies, pre-compression studies, post-compression studies, dissolution studies, and kinetic release profiles were performed[5].

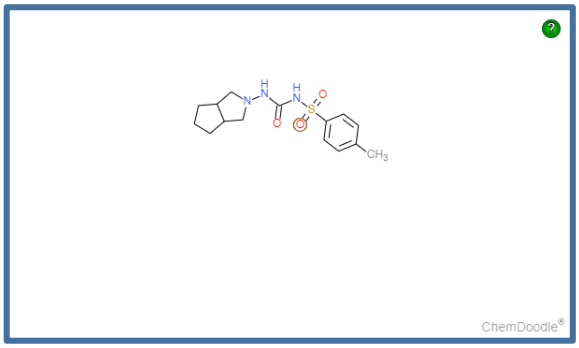

Fig. 1.: Structure of Gliclazide drug[9]

Experimental:

Material:

Gliclazide was obtained from Bajaj Healthcare; HPC GF grade polymer was obtained from Ashland (always solving) used for sustained the release of the drug; HPMC K4M was obtained from Dow used as a rate-limiting polymer; Parteck SRP 80 polymer has obtained from Merck well suited for direct compression processes and accelerates formulation; Avicel pH 101 FMC used as a diluent; Starch 1500 was obtained from Colorcon and; Magnesium stearate was obtained from SD Fine chemical Ltd and used as a lubricant and Aerosil 300 was obtained Evonik and used as Glidant. Acetonitrile and water employed for the preparation of mobile phases were of HPLC grade (Ranked). All the other chemicals and solvents etc., Triethylamine (TEA) and Trifluoroacetic (TFA) were ambient grade[s] [27].

Methods:

Direct Compression Technique:

The instrument which was used a Rotary press machine (Eliza press) and round shape punches of 8mm were used and tablet weight was 200 ± 7.5 mg Compressed with 10,30 KN for ejected from the die. Pure drug and diluents and binding agents were passed through 60 mesh sieve and glidant and lubricant were passed through 30 mesh sieve, to improve compressibility and flowability of the material. V-cone-shaped blender (Wintech pharmachem equipment Pvt. Ltd.) This was helpful for uniform mixing of the blend and blended for 10 min [16,19].

Characterization of Gliclazide drug and Polymers

Before compression have been taken, granules were examined for their parameters such as Angle of repose was determined by funnel method, Hausner's ratio and Carr's index, tapped density and bulk density was

calculated

$$\text{Angle of repose} = \tan^{-1}(h/r)$$

$$Cl = (TD - BD) \times 100/TD$$

Where TD is tapped density and BD is bulk density, H is Hausner's ratio, C is Compressibility[20].

- **Particle Size Distribution by Sieve analyzer:**

  The size distribution of the granules was determined by sieve analysis. A stack of sieves was arranged in reverse order (the top sieve has the largest screen opening). (20 gm) mass was poured on the top sieve. This stack of sieves was shaken for 15 min. After shaking the material retained on each sieve was weighed. The weight of a sample of each sieve is then expressed as a percentage retained in that particular sieve[28].

- **Particle size analysis by Malvern particle size analyzer:**

  Laser diffraction method Mastersizer equipped with 2000 MU. Drug powder was dispersed in 500 ml of DW.The amount of suspension required for the value of % obscuration (10-20%) of the equipment. Diffraction data was evaluated with respect to the diameter corresponding to 10% [d (0.1)], 50% [(0.5)], 90% [(0.9)], which means that 10%, 50%, and 90% (volume distribution) of the measured particle are below the given size. The measurement was performed in triplicate[22].

- **DSC (Differential Scanning Calorimetry):** Instruments used (Pyris-6, Perkin-Elmer), 3-5 mg of drug was placed on the aluminum pan and covered with a lid and crimped using DSC crimper. The crimped pans containing the drug were heated against blank crimped pans from 30°C to 300°C at the rate of 10°C/min under a nitrogen flow of 17 ml/min and endothermic peaks obtained were studied[23].

- **Fourier Transform Infrared spectroscopy (FT-IR):**

  Instruments used IR spectrophotometer (Shimadzu, Japan), The FT-IR spectrum of Gliclazide was recorded in the region of 4000 cm^{-1} to 700 cm^{-1}. Drug samples were identified for the functional groups present[21].

- **X-Ray Diffraction**

  Instrument used Shimadzu XRD 6100 (Japan). Cu K α X-Ray source was used with K = 1.54 A^0 with the filter of Ni. The 40 KV. Voltages with the current 2Θ Ma were set. The 40 KV voltages with a current of 2Θ Ma were set. Scanning rate 1^0/min for 2 Θ for 2-70°[21].

Initial studies of batches

Table 1 Formulation with different composition

Batch	GLICLAZIDE	HPC GF	AVICEL PH 101	HPMC K 4M	PARTECK SRP 80	STARCH 1500	MG. STEARATE	AEROSIL 300	TOTAL
G01	30	60	8	-	-		1	1	100
G02	30	15	53	-	-		1	1	100
G03	30	-	-	30	-	38	1	1	100
G04	30	-	-	60	-	8	1	1	100
G05	30	-	-	15	-	53	1	1	100
G06	30	-	-	-	60	8	1	1	100
G07	30	-	-	-	15	53	1	1	100
G08	30	-	-	-	30	38	1	1	100
G09	30	30	38	-	-	-	1	1	100
G10	30	-	-	60	-	8	1	1	100
G11	30	30	-	-	-	38	1	1	100
G12	30	60	-	-	-	8	1	1	100
G13	30	-	53	-	15	-	1	1	100

- ***In-Vitro* Dissolution study:**

An In-vitro drug release of Gliclazide tablets was studied by, using dissolution apparatus II-paddle (Electrolab Model TDT 08, India) as per the in-house developed method. 900 mL of pH 7.4 Phosphate buffer as the dissolution medium was placed in the dissolution vessels, and the temperature was maintained to 37 ± 0.5 °C. The rotation speed of the paddle was 75 rpm. At predetermined time intervals (2, 6, 12, 16, and 24 hours), 10 mL of dissolution medium was removed for determining a drug concentration and a fresh medium was replaced. The amount of Gliclazide released in the dissolution medium was measured using a UV Spectrophotometer at the wavelength of 226 nm. The dissolution study was performed using 6 tablets in triplicate [12,20].

Post compression parameter of tablets

The properties of compressed tablets, such as weight variation friability hardness, an assay of the tablets, and content uniformity were determined. Hardness was determined by using Monsanto hardness tester and it is expressed in (kg/cm2) or N. Friability was determined by using Roche friability testing apparatus tumbling that revolves at 25 pm. After 4 min. Weight variation and content uniformity of drug content was performed according to USP procedures[20].

Results and Discussion:

Characterization of the drug:

Table 2 Flow properties of polymer and Gliclazide Drug

Sr. No	Properties	HPC GF GRADE	HPMC K 4M	PARTECK SR P-80	Gliclazide Drug
1	Angle of Repose	18.24°C	20.21°C	17.94°C	14.41°C
2	Bulk density(g/ml)	0.4g/ml	0.50g/ml	0.5g/ml	0.555gm/ml
3	Tapped density	0.5g/ml	0.70g/ml	0.909g/ml	0.769gm/ml
4	Hausner's ratio	1.25	1.4	1.8	1.385
5	Compressibility Index	20%	28.57%	44.99%	27.82%
6	Moisture content (%)	5.545%	4.230%	4.710%	1.992%

The flow properties of Gliclazide drug exhibited bulk and tapped density 0.555 and 0.769 gm/ml. Angle of repose was found 14.41°C indicating very good flow and compatibility.Compressibility Index and Hausner's ratio, Moisture Content was found 27.82%, 1.385 and 1.992%. indicating the good flow properties and less moisture content. The flow properties of the polymer were presented in Table 2. The angle of repose of the polymers showed excellent flowability and compatibility range from (25 < angle of repose < 30). Bulk and tapped density was found in the range of 0.4 to 0.5gm/ml and 0.5 to 0.9gm/ml. Compressibility Index and Hausner's ratio of the polymers were exhibited that between 20.0% to 45 % and more than 1.25 respectively, confirming the poor flow of polymer and more moisture content [20].

Particle Size Distribution Analysis(Sieve Analysis)

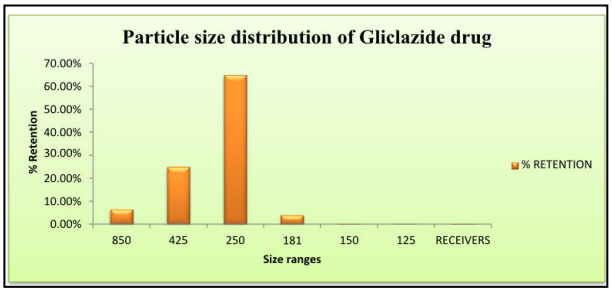

Fig. 2 Particle size distribution of Gliclazide drug by Sieve Analysis Instruments.

The flow properties of powders are dependent upon the particle size distribution as well as particle shape. The particle size of the drug was 250 micron[s] [28].

Particle Size Distribution Analysis (Mastersizer MU 2000)

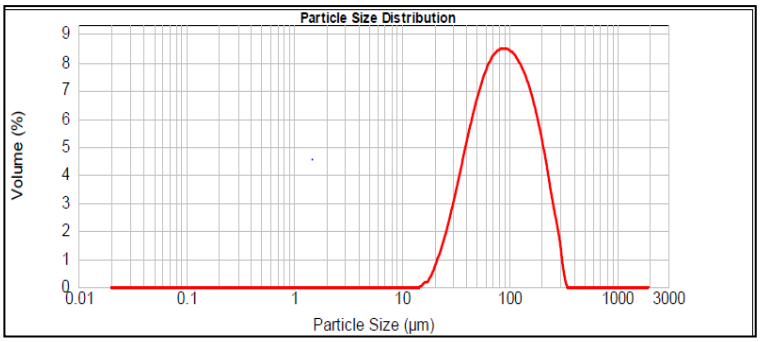

Fig. 3 Mastersizer MU 2000

The flow properties of powders are dependent upon the particle size distribution as well as particle shape. Asymmetric particles have poor flow characteristics and drug and other additives into particles of uniform size have good flow properties. Particle size of drug is d (0.9) = 196 µm, d (0.5) = 87.24 µm, d (0.1) = 36.71 µm[22].

Determination wavelength maximum absorbance (ƛmax) of Gliclazide in 7.4 pH phosphate buffer and methanol.

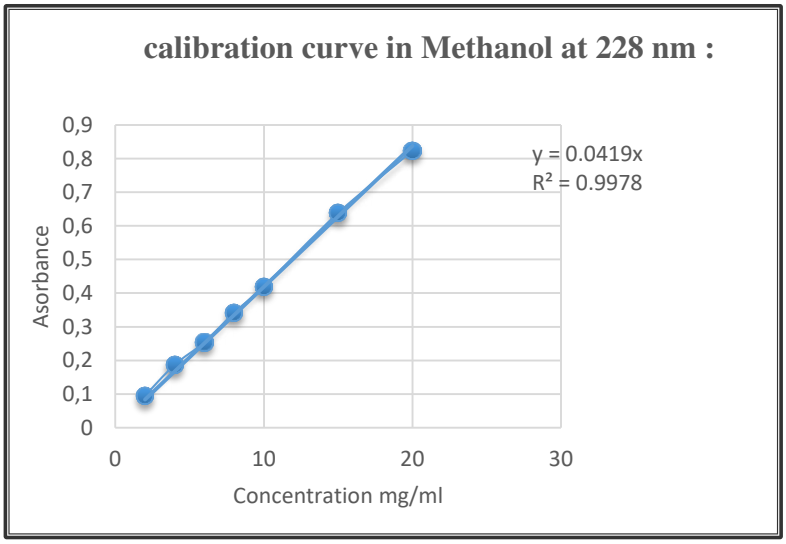

Fig.4 Linearity curve of 7.4 pH Methanol solution.

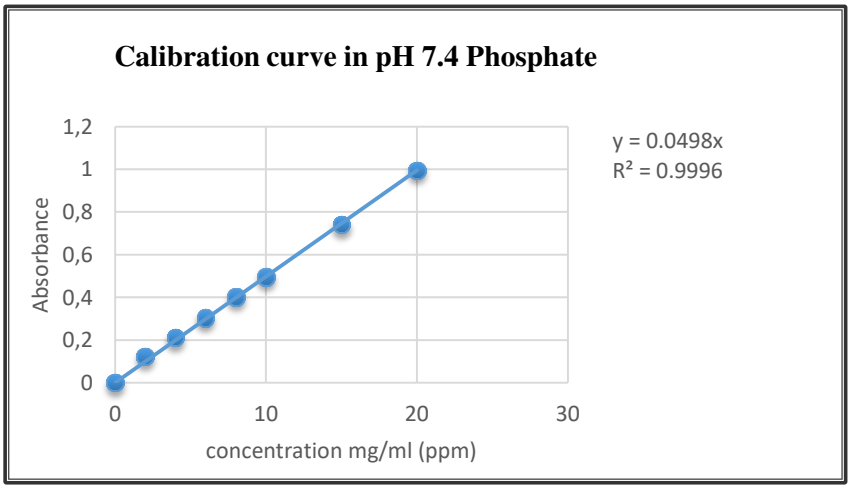

Fig. 5 Linearity curve of 7.4 pH phosphate buffer solution.

The Calibration curve of Gliclazide was obtained by using UV 2600 Shimadzu. Gliclazide has solubility in methanol and 7.4 pH phosphate buffer solution. According to ICH guidelines Q2 R1, the linearity was repeated in duplicate at 226 and 228 nm, and the linearity ranges were confirmed with an R^2 of 0.9996 and 0.9978. The linear regression equation was Y= 0.0498, Y=0.0419.

DSC (Differential Scanning Calorimetry)

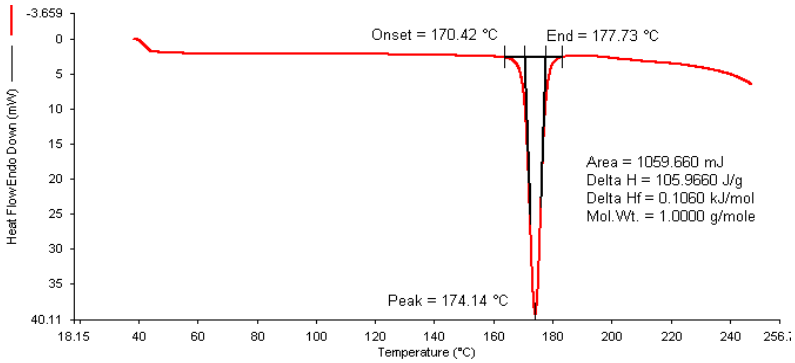

Fig.6 DSC (Differential scanning Calorimetry) Of Gliclazide drug

In DSC were used Perkin Elmer instrument for Gliclazide shows an endothermic process and its melting peak of crystalline Gliclazide is 174.14°C[23].

FTIR (Fourier –Transform Infrared Spectroscopy)

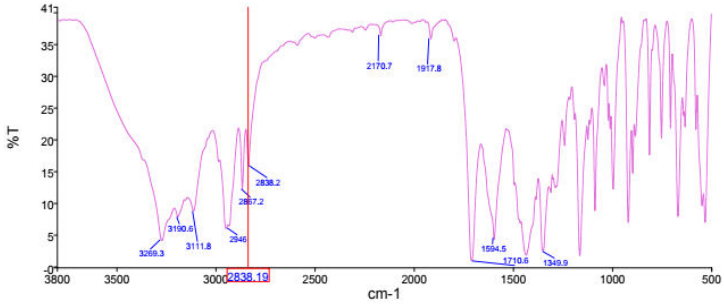

Fig.7 FTIR (Fourier-transform infrared spectroscopy) of Gliclazide drug

Perkin Elmer FT-IR-6600 instrument was used for the study. FTIR spectra of pure Gliclazide drug showed peaks at 1710.46 cm^{-1} (Carbonyl sulphonylurea group) and 3274.34 cm^{-1} (-NH Stretch) and 1349 cm^{-1} and 1162 cm^{-1} (Sulphonylurea group band) respectively[17, 21].

X-Ray Diffraction:

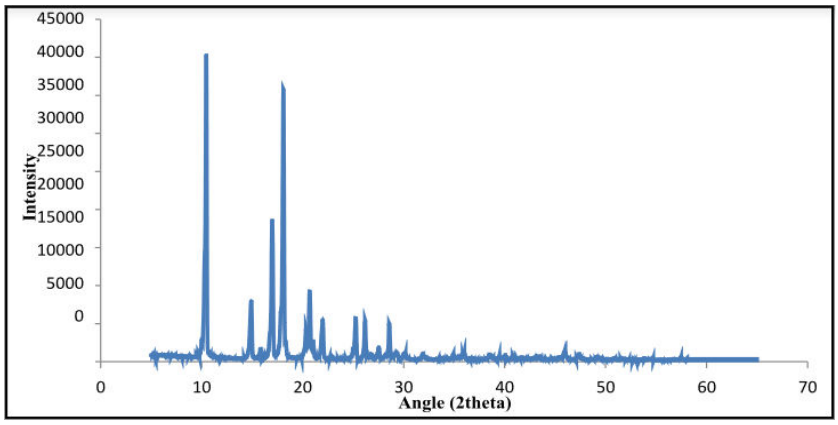

Fig.8 X- Ray Diffraction of pure Gliclazide

X-ray Diffraction was used Shimadzu Lab XRD-6100 instrument pattern of Gliclazide exhibited 10°C and 17°C while the sharp, highly intense, and less diffused peaks indicating the crystalline nature of the drug, while peaks at 15°C, 20°C, 25°C, and 26°C were short peak. The intensity of XRD peaks of the drug, physical mixtures, and solid dispersion was recorded[21].

- **Evaluation DSC (Differential scanning Calorimetry) of polymers**

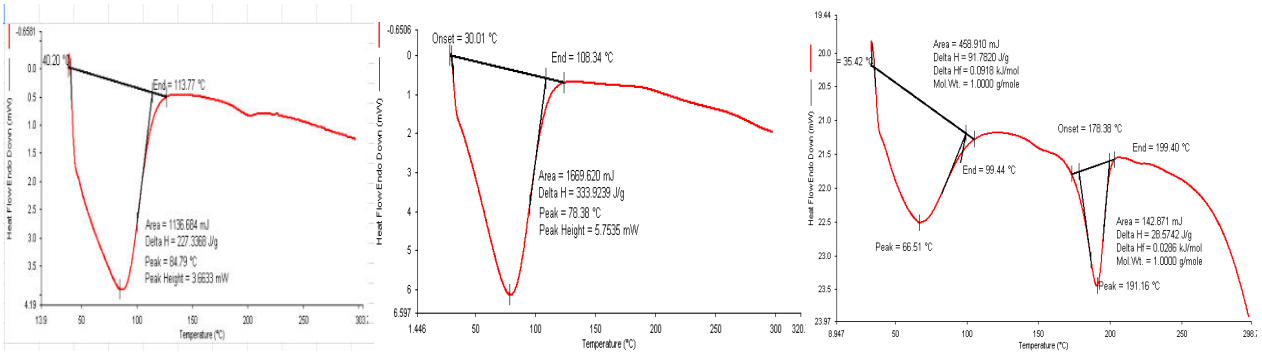

Fig.9 (Differential scanning Calorimetry) Of HPC GF GRADE AND HPMC K4M, PARTECK SR P -80 Polymer

Thermal stabilities and oxidative stabilities of the polymers were evaluated, using differential scanning calorimetry. PARTEK SR P-80 show Endothermic first peak at 66.51°C and 191.16°C thermal stability and oxidative stability of polymer.[23].

- **FTIR (Fourier-transform infrared spectroscopy) of polymers**

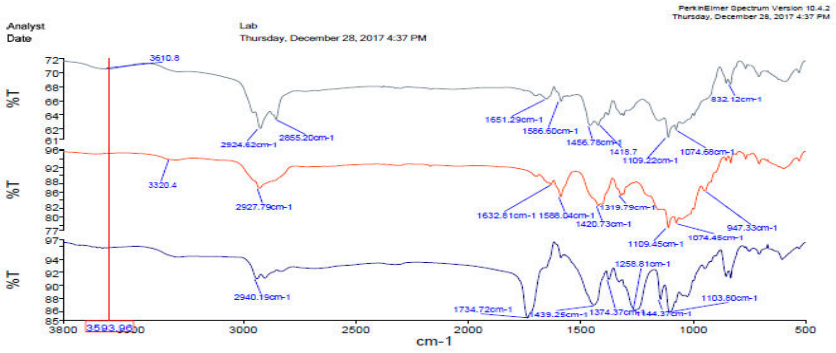

Fig.10 FT-IR OF HPC GF GRADE AND HPMC K4M, PARTECK SR P -80 POLYMERS

HPC GF GRADE POLYMER indicates that 2940.19 cm-1 is (C-H) stretch 1734.72cm-1 is carbonyl group present. HPMC k4M indicate 2927.79 is (C-H)

stretch and 1632.8cm-1 is (C=C) stretch. PARTECK SR P -80 is 2924.62 cm-1 is (C-H) and 1651.29cm-1 is (C=C) stretch[21,25].

Table 3 Post - Compression parameter

Sr. No.	Weight Variation	Thickness	Hardness	Friability
1	Range 200±7.5	3mm- 4 mm	7-12 kg/cm^2 .	Less than 1%

Weight variations of Gliclazide 30 mg tablet range 200±7.5 (8mm and concave round shape punch). Friability less than 1% and weight variation within acceptable limits and a tablet hardness range of 7-12 kg/cm^2, the thickness of tablets was between range of 3-4 mm. Overall, the tablet with the reduced weight and dimensions and with improved hardness and friability have been achievable by performing sustained released tablet by using various combinations of drug and polymer ratio[20].

DSC of Formulations of HPC GF, HPMC K4M, PARTECK SRP 80

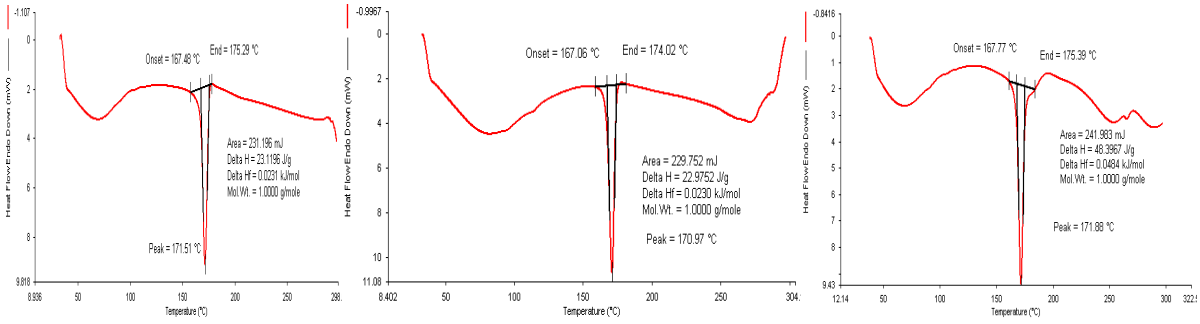

Fig.11 Differential scanning calorimetry of formulations of polymers

Results of DSC analysis of formulation batches of HPC GF, HPMC K4M, PARTECK SRP 80 batches found that the polymer and drug are compatible with each other and there is no reaction between the polymer and drug[23].

Fourier-transform infrared spectroscopy of drug and polymer

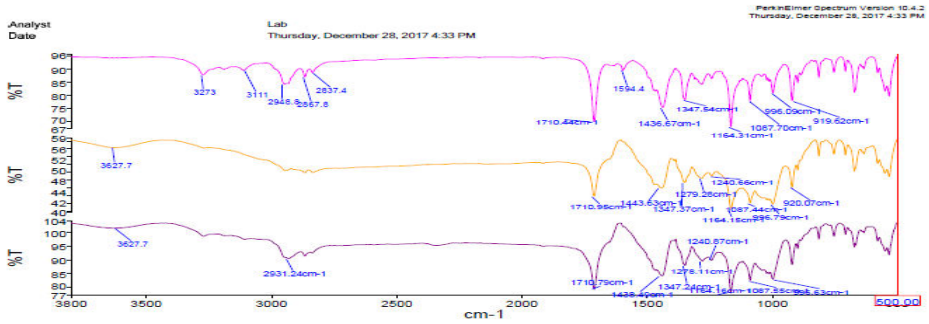

Fig. 12 Fourier-transform infrared spectroscopy of drug and polymers

The compatibility between the polymer and drug is evaluated using Infra-red Spectroscopy. IRS of the batch G1 formulation as shown in Figure indicates that 2931.24 cm-1 is (C-H) stretch 1710.79cm-1 is carbonyl group present. HPMC k4m indicate 2927.79 is (C-H) stretch and 1710.95 cm-1 is (C=C). Parteck SR P -80 is 2948.8 cm-1 is C-H stretch and 1710.44 cm-1 is (C=C) stretch[21,25].

% Drug Released of Formulations

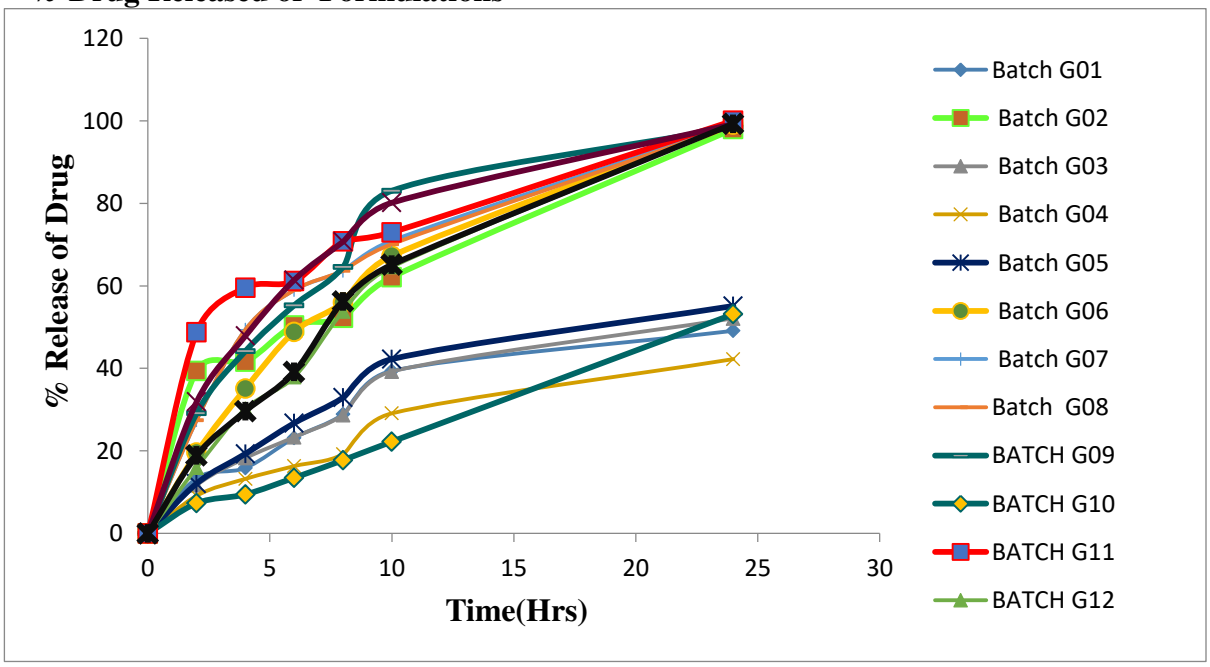

Fig. 13% Released of Drug Formulations

Ideally, Gliclazide tablets should be sustained the release of the drug to maintain an effective drug plasma concentration from *the in-vitro* drug dissolution profile of Gliclazide matrix tablets. It was found that after 2 hrs results of formulation batches G01, G02,G03,G04,G05,G06, G07,G08,G09,G10,G011,G12,G13 were 13.38%,39.4%,11.72%,9.14%,12.12%, 19.59%, 27.48%,27.48%, 29.14%, 7.33%, 48.77%,15.95%,31.9% of the drug was released till 2 hrs.from all batches[26]. During 1 to 2hrs, the marketed formulations percentage released was found to be 8 -25%. After the 2hrs more than 30% to 60% up to 8 hrs drug was released. After 8 hrs. the released rate increases slightly and a sustained released pattern was observed for 24 hrs. The formulation of G02, G06, G07, G08, G09, G012, observed. that the release profile was found to be biphasic with an initial burst effect in the first hour and then the release was slow and extended up to 24h.[18, 29]

In such an instance higuchi release is desirable, where the release rate is fast in initial conditions and the release rate will become slower as the time progress and concentration always be maintained within saturation level at the site of absorption and thus produces greater bio-availability [24,29]. The proposed method is simple and does not involve laborious time-consuming. Formulation G02, G06, G07, G08, G09, and G012 (containing 30 mg of Gliclazide had shown drug release over 24 hours. Formulation G08 is a better system for the once-daily therapy of Gliclazide. From the drug content, post-compression parameters, in-vitro drug release studies it was found that among the various formulations, Formulation G08 (Drug with Parteck SR P-80) was the found to be the best formulation. The formulation was further taken for pilot scale-up studies and stability studies.

Conclusion

The oral route of administration for sustained release drug delivery system increases the efficiency of the dose, more flexibility, reduced dose frequency, and better patient compliance. It depends upon the physic o-chemical properties of the drug, type of delivery system, the disease being treated, patient condition and treatment duration, presence of food, gastrointestinal motility, and administration of other drugs.

In the present study, we attempted to develop Gliclazide sustained-release tablet based on

HPMC K4M, HPC GF, PARTEK SRP 80 polymer. Since Gliclazide is having a long biological half-life duration of action is 10-24 hours. The tablets were prepared successfully by direct compression technique by using HPMC K4M, HPC GF, PARTEK SRP 80 polymer, The concentration of binder in the formulation was more effective for formulating tablets had acceptable characteristics[18]. Gliclazide having the maximum absorbance at 228nm, the drug content was analyzed by a sensitive and reproducible UV-Spectro-photometer method developed in our laboratory as explained in the experimental part. The drug content of the tablet was uniform and within acceptable limits. The physico-chemical parameters like thickness, hardness, friability, and weight variation of formulated tablets were within the standard limits of united States Pharmacopoeia[29] From the above discussion, we can conclude that Moreover; the reasonable cost of oral Sustained release drug delivery system has lead ease of market penetration as replacement of oral conventional drug delivery system.

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