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DEVELOPMENT AND *IN-VITRO* CHARACTERISATION OF ORAL SUSTAINED RELEASE MATRIX TABLETS OF GEMIGLIPTIN

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ABSTRACT: This project involves in the development of sustained release matrix tablets of Gemigliptin. Which is an oral anti-hyperglycemic agent designed for the management of non insulin dependent diabetes mellitus (NIDDM). The basic goal of therapy is to achieve a steady sate blood level that is therapeutically effective and non toxic for an extended period of time. The objective in dosage form design is to optimise the delivery of medication to achieve the control of therapeutic effect in the face of uncertain fluctuation in the in-vivo environment in which drug release takes place. Eight formulations of Gemigliptin 50mg were formulated by admixing with HPMC K4M, Carbopol were used as rate controlling polymers in different concentrations, Micro crystalline cellulose, Lactose, Talc, Magnesium stearate. Pre-formulation and post-formulation studies were carried out and the values obtained, satisfies the pharmacopoeial specifications. Several kinetic models were applied to the dissolution profiles to determine the drug release kinetics. Of all the formulations F5 exhibited gradual and completion extended release for Gemigliptin. The F5 (carbopol) with 1:1 ratio produced 89% drug release at end of the hour.

INTRODUCTION: Tablets are solid oral dosage forms containing ingredients with or without filler material [1]. Sustained release dosage forms are the drug delivery systems that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The goal in designing oral sustained delivery system is to reduce the frequency of the dosing or to increase effectiveness of the drug by localizing at the site of action, reducing the dose required or provide uniform drug delivery, thereby also improving patient compliance [2].

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery [3].

Diabetes is an extremely common disorder which affects many people. It is defined as a heterogeneous metabolic syndrome characterised by chromic hyperglycaemia i.e. increase in blood levels with disturbances in carbohydrate, fat and protein metabolism. It is the most common occurring chronic endocrinal disorder which affects almost each and every cell of the human body. Gemigliptin is used in the management of non insulin dependent diabetes mellitus NDDM [4].

Gemigliptin is an oral anti- hyperglycaemic agent of the new dipeptidyl peptidase-4 inhibitor class of drugs. It is known that glucose lowering affects of DDP-4 inhibitors are mainly mediated by Glucagon

like peptide-1 and Gastric inhibitory polypeptide (GIP) incretin hormones which are inactivated by DDP-4 [5]. Gemigliptin was rapidly absorbed after single oral dosing and the compound was eliminated with a half-life of 3.6, 5.2, 5.4 and 30.8 hrs in the rat, dog, monkey and humans respectively. Bioavailability of gemigliptin in the rat, dog, monkey was species dependent with the values of 94%, 73%, 26% respectively. In clinical studies Gemigliptin monotherapy (50mg for 12 week) improved the $HbA_{1C,}$ FPG level, oral glucose tolerance test results, beta cell function and insulin sensitive measures and was well tolerated in subjects with type 2 diabetes [6].

Sustained release matrix tablets are relatively easy to fabricate by incorporating drug particles in slowly disintegrating or inert porous material. Hydroxypropyl methylcellulose is a hydrophilic polymer used to prolong the drug release pattern due to its gelling property, rapid hydration and robust mechanism, choice in viscosity grades, non-ionic nature, reproducible release profile and good compressibility property [7]. Carbopol is a hydrophilic polymer used as the matrix formers in oral controlled release dosage forms [8].

MATERIALS AND METHODS:

Materials: The various materials in our study include Gemigliptin, HPMC K4M, Carbopol, Microcrystalline cellulose, Lactose, Talc and Magnesium stearate. All other materials used were of analytical grade.

Methods:

Formulation of Gemigliptin sustained release matrix tablets: Sustained release matrix tablets Gemigliptin were prepared by Direct compression technique. Eight formulations of tablets each containing 50mg dose of Gemigliptin were prepared with different concentration of excipients as showed in the **Table 1**.

Gemigliptin and polymers such as HPMC K4M, Carbopol were accurately weighed, geometrically mixed and passed through #40 mesh and Lactose is used as diluents [9] and Microcrystalline cellulose as binder were accurately weighed and passed through #40 mesh [10]. Both mixtures were mixed for 5 minutes as a dry mixing and the mixture of talc and magnesium stearate 1:1 ratio was used as lubricant added to the mixture and mixed for 2 minutes [10]. Then the mixtures were compressed into tablets using 8 station rotary compressed machines with punch size of 9 mm with a hardness of 3 to 5 kg/cm^2.

TABLE 1: COMPOSITION OF DIFFERENT FORMULATIONS FROM F1 TO F8

Ingredients/formula code (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8
Gemiglipitin	50	50	50	50	50	50	50	50
HPMC K4M	50	75	100	150	-	-	-	-
Carbopol	-	-	-	-	50	75	100	150
Microcrystalline cellulose	97	84.5	72	47	97	84.5	72	47
Lactose	97	84.5	72	47	97	84.5	72	47
Talc	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3
Total weight of tablet (mg)	300	300	300	300	300	300	300	300

Evaluation of pre-compression blend:
Before compression the granules were evaluated for their flow and compressibility characteristics [11].

Angle of repose: The angle of repose of powder was determined by the funnel method. The accurately weighed granules were taken in a funnel .The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the powder. The granules were allowed to flow through the funnel freely onto the surface.

The diameter of the powder cone measured and angle of repose was calculated using the following equation:

$$\text{Tan } \Theta = h/r$$

Where h and r are the height and radius of the powder cone, Ѳ is the angle of repose.

Granules with angle of repose 31-35° show good flow property.

Determination of bulk Density and Tapped Density:

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and volume (Vo) was measured. Then the graduated cylinder was closed with the lid and set into the tap density tester (USP).The density apparatus was set for 100 taps and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and the tapped density were calculated using the following formula

$$\text{Bulk density} = W/V_o$$

$$\text{Tapped density} = W/V_f$$

Where,

W=Weight of the powder
V_O =Initial volume
V_f =final volume

% Compressibility or Carr's Index:

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is.

Carr's Index =
$$\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Granules with compressibility index value up to 16% show good flow property.

Hausner's Ratio:

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to inter-particle friction and, as such, could be used to predict powder flow properties. Generally a value ≤ 1.25 indicates good flow properties, which is equivalent to 20% of Carr's Index.

Hausner's ratio =Tapped density/Bulk density.

Evaluation of Gemigliptin matrix tablets:
Physical appearance:

The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, colour, presence or absence of odour, taste, surface texture and consistency of any identification marks. The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance.

Thickness:

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliperse. Average thickness was calculated.

Hardness:

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted.

Friability Test:

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4minutes and tablets were observed while rotating. The tablets were then taken, de-dusted and reweighed. The friability was calculated as the percentage weight loss. The acceptable limits of the weight loss should not be more than 1%. The percentage friability was calculated according to the following formula.

$$\% \text{ Friability} = (\text{initial weight} - \text{final weight})/\text{initial weight} \times 100$$

Weight Variation Test:

To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets were calculated.

$$\% \text{weight variation} = (W_A - W_I) \times 100/W_I$$

Where,
W_I= Individual weight of the tablets
W_A= Average weight of the tablets

According to IP 1996, out of twenty tablets for tablets weighing more than 250mg $\pm$5% weight variation can be allowed for not more than two tablets out of twenty tablets.

Content uniformity:

Tablets must comply with the requirements for uniformity of content specified in is calculated by doing assay for a particular drug. Over ten tablets were selected randomly and average weight was calculated. Tablets were crushed in a motor and accurately weighed amount of tablets triturate was taken for analysis and it was diluted with the phosphate buffer solution. The content was shaken well and sonicated for five minutes for dissolving the drug. Appropriate dilutions were made. The drug content was estimated by recording the absorbance at 257nm.

In-vitro dissolution studies:

Dissolution test is to provide critical in-vitro drug release information for quality control purpose i.e. to predict *in-vivo* drug release profiles [12]. Dissolution studies were carried out for all the formulations employing USP-II paddle method and 900 ml of phosphate buffer solution as the dissolution medium operated at 50rpm. The medium was allowed to equilibrate to temperature of 37 $\pm$ 0.5°C. The samples were collected after end of the hour at intervals of 1, 4, 8, 12, 16, 20, 24 hr, as per parameters showed in **Table 2**. The samples were analyzed spectrophotometrically at 257nm using UV-spectrophotometer.

TABLE 2: PARAMETERS OUTLINE INVOLVED IN IN-VITRO DISSOLUTION

Drug name	Dosage form	Dissolution apparatus	Speed (RPMs)	Medium	Medium volume (ml)	Sampling intervals (Hrs)
Gemigliptin	Tablets	USP II Paddle type	50 RPM	0.1N HCL	900	1, 4, 8, 12, 16, 20, 24 hrs

Kinetic Analysis of Dissolution Data:

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3).

$$C = K_o t \qquad \text{(1) Eq.}$$

Where,
K_o is zero-order rate constant expressed in units of concentration/time and t is a time.

$$\text{Log} C = \text{Log} C_o - K_1 t/2.303 \qquad \text{(2) Eq.}$$

Where,
C_o is the initial concentration of drug and K_1 is the first order constant.

$$Q = K_H t^{1/2} \qquad \text{(3) Eq.}$$

Where,
K_H is the constant reflecting the design variables of the system.

The following plots were made using the in-vitro drug release data

- Cumulative %drug release vs. time (Zero order kinetic model)

- Log cumulative of %drug remaining vs. time (First order kinetic model)

- Cumulative %drug release vs. square root of time (Higuchi model)

Mechanism of Drug Release:

Korsmeyer et al (1983) derived a simple relationship which described drug release from polymeric system to find out mechanism of drug release, first 60% drug release data was fitted in Korsmeyer-peppas model.

$$M_t/M_\infty = K t^n$$

Where M_t/M_∞ is a fraction of drug released at the time t, K is the exponent. The n value is used to characterize different release mechanisms.

RESULTS AND DISCUSSION:

The formulations prepared were subjected to various pre-formulation and post-formulation

evaluation studies. The results obtained were agreeing the pharmacopoeial standards.

Standard calibration curve of Gemigliptin:
Calibration curve of the pure drug Gemigliptin was prepared in the concentration range of 1 to 5 µg/ml

at the wavelength of 257nm using 6.8 pH phosphate buffer solution. The calibration curve showed good linearity and regression coefficient was 0.999 (r^2), showed in **Fig. 1.**
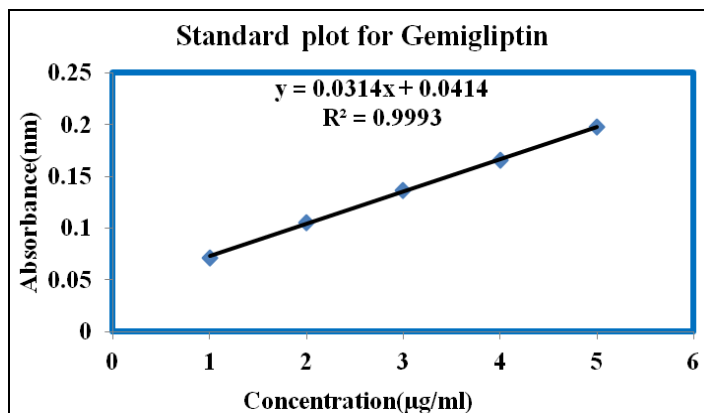

Standard plot for Gemigliptin

$y = 0.0314x + 0.0414$
$R^2 = 0.9993$

FIG. 1: STANDARD CURVE OF GEMIGLIPTIN IN pH 6.8 PHOSPHATE BUFFER SOLUTION

Pre-compression parameters:
The powder characteristics of various batches of sustained release Gemigliptin tablets were evaluated and the values obtained was mentioned in the **Table 3**. Various formulations shows good flow properties. Results of bulk density (0.362 to 0.539 gm/cc), tapped density (0.42 to 0.65gm/cc),

compressibility index (15.62% to 20.01%. 12-16 %), Hausner's ratio (1.18 to 1.25), angle of repose (27.74° to 30.07°) shows satisfactory results, Which are required for better bioavailability. Values of parameters obtained were figured in the **Fig. 2, 3, 4, 5, 6.**

TABLE 3: PHYSICAL EVALUATION PROFILE OF PRE-COMPRESSION BLEND

| Granulation blend	Bulk density (g/cc)	Tapped density (g/cc)	Hausner's Ratio	Compressibility Index (%)	Angle of repose (Θ)
F_1	0.4659	0.5824	1.2500	20.003	28.81°
F_2	0.4976	0.6108	1.2274	18.533	30.07°
F_3	0.5394	0.6593	1.2222	18.182	29.81°
F_4	0.5051	0.6114	1.2105	17.391	27.74°
F_5	0.4318	0.5299	1.2272	18.513	29.67°
F_6	0.4238	0.5159	1.2174	17.857	29.73°
F_7	0.4001	0.5001	1.2499	19.996	29.94°
F_8	0.3624	0.4295	1.1852	15.6250	30.02°
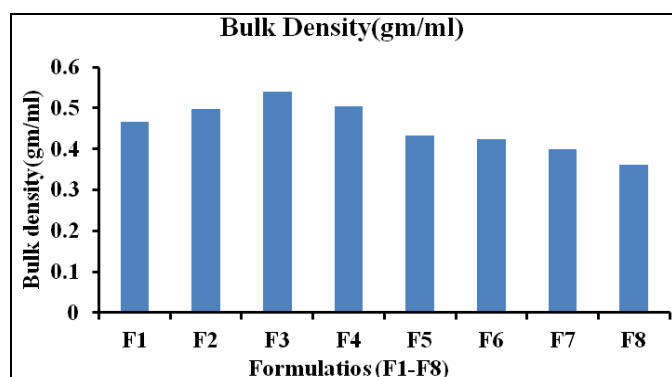
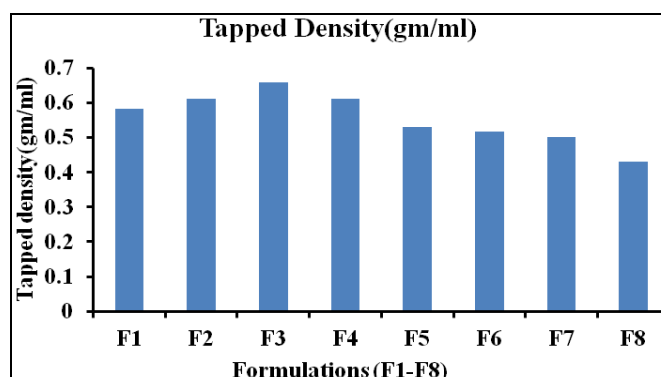**FIG. 2: COMPARISON OF BULK DENSITY OF GEMIGLIPTIN POWDER BLENDS FOR F1 TO F8 FORMULATIONS**

FIG 3: COMPARISON OF TAPPED DENSITY OF GEMIGLIPTIN POWDER BLENDS FOR F1 TO F8 FORMULATIONS
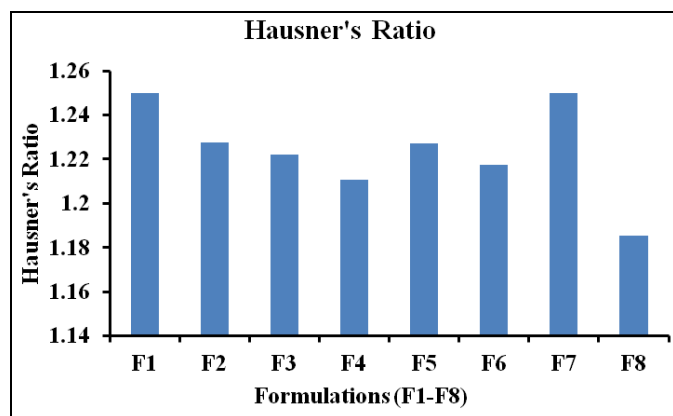
FIG 4: COMPARISON OF HAUSNER'S RATIO OF GEMIGLIPTIN POWDER BLENDS FOR F1 TO F8 FORMULATIONS
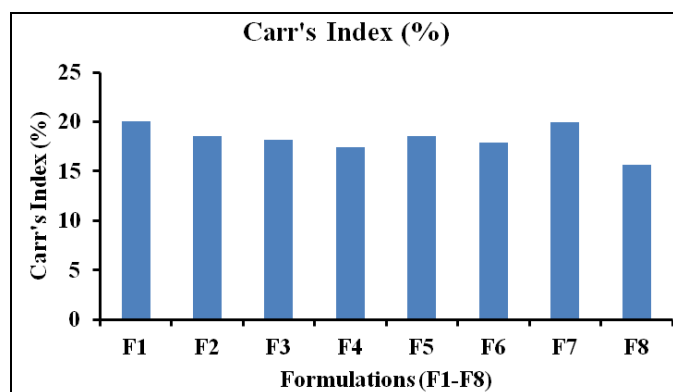

FIG 5: COMPARISON OF CARR'S INDEX OF GEMIGLIPTIN POWDER BLENDS FOR F1 TO F8 FORMULATIONS
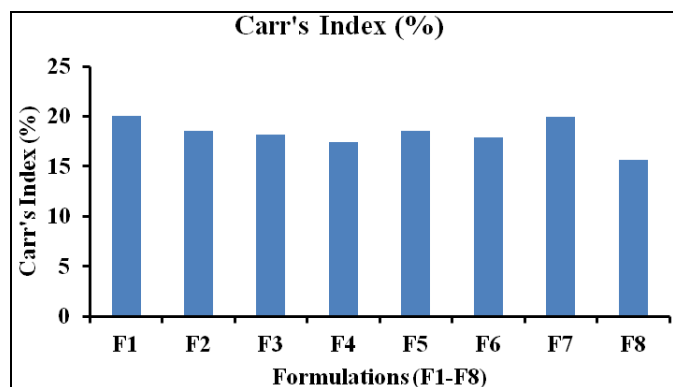

FIG. 6: COMPARISON OF ANGLE OF REPOSE OF GEMIGLIPTIN POWDER BLENDS FOR F1 TO F8 FORMULATIONS

Post-compression parameters:
In each batch, it was concluded that the tablets of all batches had desirable physical characteristics. Results of thickness (3.0 to 3.5 mm), Hardness (3.5 to 4.5 kg/cm^2), Friability (0.52 to 0.64%) as shown in the **Table 4 i**ndicate that the tablets having sufficient strength to withstand physical abrasion. Tablets of all batches passed the weight variation (296.35 to 302.77 mg) test and assay (97% to

100%) was as per the limits prescribed in IP. The values obtained were figured in **Fig. 7, 8, 9, 10, 11.**

TABLE 4: POST EVALUATION PARAMETERS PROFILE OF GEMIGLIPTIN SR MATRIX TABLETS

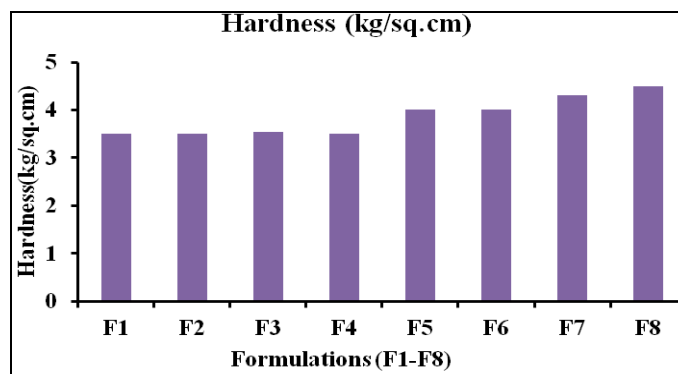| Formula Code	Hardness (kg/cm^2)	Thickness (mm)	Weight Variation (mg)	Friability (% loss)	Assay (%)
F1	3.5	3.0	298.72	0.52	99
F2	3.5	3.0	302.77	0.53	98
F3	3.55	3.0	302.13	0.64	97
F4	3.5	3.0	300.65	0.53	98
F5	4	3.1	296.35	0.55	100
F6	4	3.0	296.54	0.56	99
F7	4.3	3.1	298.85	0.59	98
F8	4.5	3.5	295.37	0.57	99

FIG. 7: COMPARISON OF HARDNESS (KG/CM^2) OF GEMIGLIPTIN TABLETS FOR F1 TO F8 FORMULATIONS
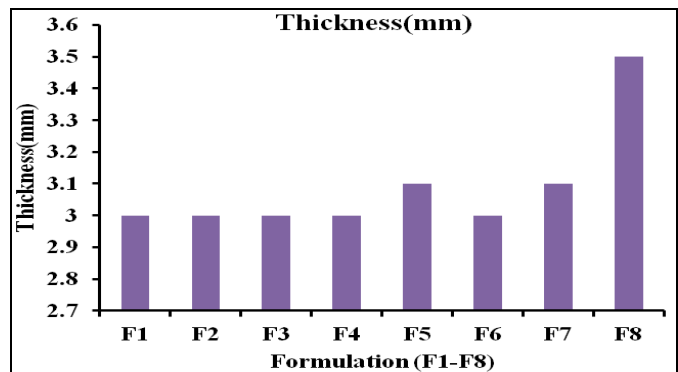

FIG. 8: COMPARISON OF THICKNESS (MM) OF GEMIGLIPTIN TABLETS FOR F1 TO F8 FORMULATION
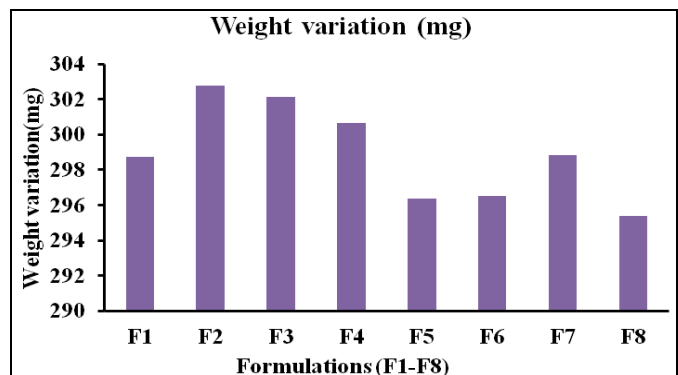

FIG 9: COMPARISON OF WEIGHT VARIATION (MG) OF GEMIGLIPTIN TABLETS FOR F1 TO F8 FORMULATIONS
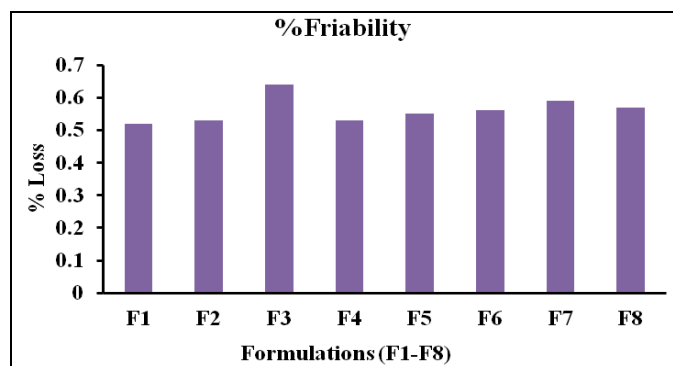
FIG. 10: COMPARISON OF % FRIABILITY OF GEMIGLIPTIN TABLETS FOR F1 TO F8 FORMULATIONS
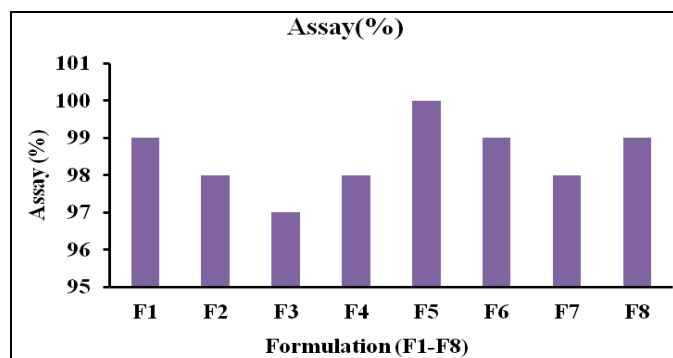

FIG. 11: COMPARISON OF ASSAY OF GEMIGLIPTIN TABLETS FOR F1 TO F8 FORMULATIONS

In-vitro drug release studies of Formulations (F1-F8):

The sustained release Gemigliptin matrix tablets containing drug, HPMC K4M, Carbopol, Microcrystalline cellulose, lactose, magnesium stearate, talc prepared by direct compression process, released the drug from sustain matrix release of time up to 24hrs as shown in the **Table 5**.

TABLE 5: *IN - VITRO* DRUG RELEASE DATA OF GEMIGLIPTIN FORMULATIONS (F1 TO F8)

Time(hrs)/ % Drug release	F1	F2	F3	F4	F5	F6	F7	F8
1	16	13	15	12	20	14	13	17
4	24	21	23	21	30	25	23	27
8	32	30	32	29	42	34	33	36
12	44	43	46	40	53	47	46	52
16	57	55	57	51	64	57	57	62
20	66	65	67	63	75	65	68	73
24	76	72	77	74	89	75	78	86

Among all the eight formulation F5 showed the 89% drug release at end of the time was determined by UV-visible spectrometer at 257nm. The results shown that the release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer decrease, the

kinetics of release increased. The comparative graphs of all the formulations for drug release were plotted shown in the **Fig. 12, 13, 14 15**.
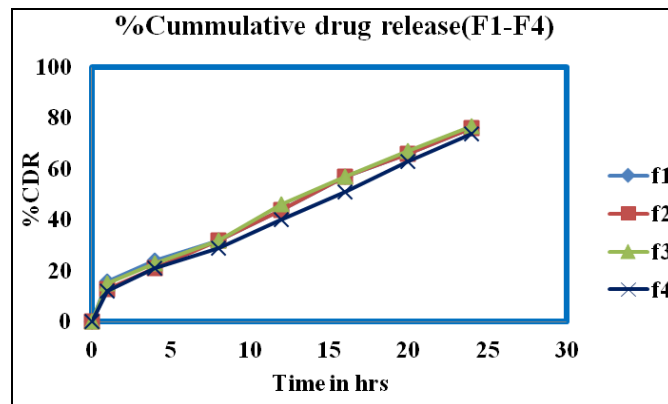

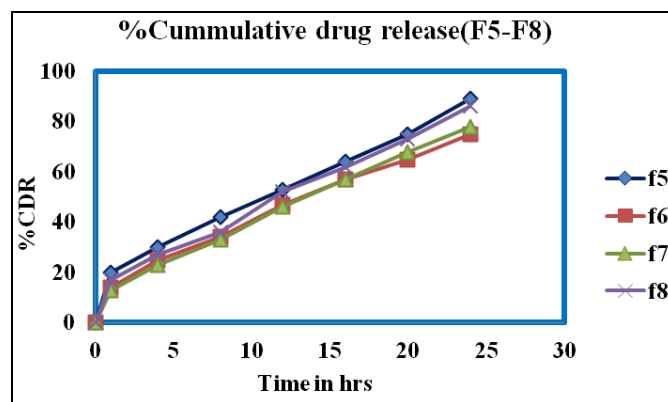**FIG. 12: DRUG RELEASE PROFILE OF GEMIGLIPTIN FORMULATIONS FROM F1 TO F4**

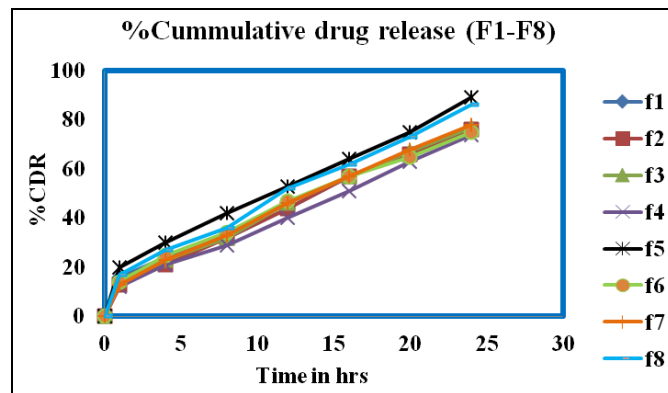**FIG. 13: DRUG RELEASE PROFILE OF GEMIGLIPTIN FORMULATIONS FROM F5 TO F8**

FIG. 14: DRUG RELEASE PROFILE OF SUSTAINED RELEASE GEMIGLIPTIN MATRIX TABLETS OF F1 TO F8

In-vitro drug release profile of pure drug Gemigliptin:

In-vitro dissolution studies of pure drug Gemigliptin were performed and the drug release profile obtained was compared with the drug release of optimized formulation as shown in the

Table 5. Comparison graph was plotted and showed in the **Fig. 15**.

TABLE 6: *IN-VITRO* DRUG RELEASE PROFILE OF OPTIMIZED FORMULATION (F5) OF GEMIGLIPTIN SUSTAINED RELEASE MATRIX TABLETS AND PURE DRUG GEMIGLIPTIN

Time in hrs	% Drug release in F5	% Drug release of pure drug Gemigliptin
1	20	23
4	30	36
8	42	48
12	53	56
16	64	69
20	75	78
24	89	94
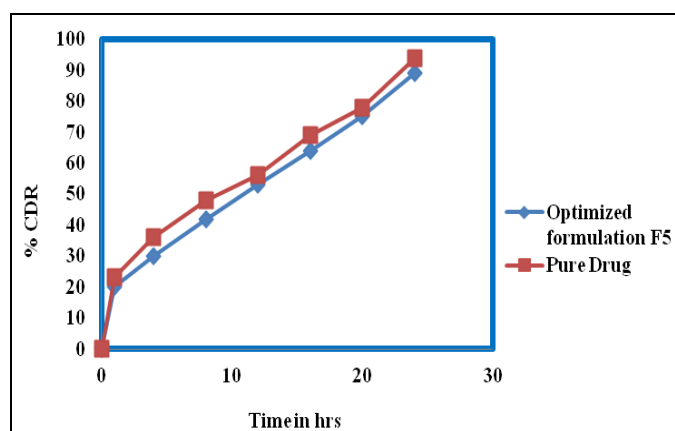
FIG. 15: *IN-VITRO* DRUG RELEASE PROFILE OF OPTIMIZED FORMULATION (F5) VERSUS PURE DRUG GEMIGLIPTIN

Study of Drug release kinetics:

For understanding the mechanism of drug release and release rate kinetcs of the drug release and rate kinetics of the drug from the dosage form, the in-vitro drug dissolution data obtained as showed in the **Table 7** was fitted to various mathematical models. The dissolution data of optimized formulation (F_5) tablets were subjected to various kinetic models such as Zero order kinetics (cummulative percentage amount of drug release versus time), First order kinetics (log cummulative percentage of drug remaining to release versus time), Higuchi (fraction of drug release versus square root of time) and Korsermeyer-peppas (log fraction of drug released versus log time) showed in the **Fig. 16, 17, 18, 19**.

Which were applied to assess the kinetics of drug release from prepared tablets. Most suited model for drug release was predicted on the basis of regression coefficient towards 1, greater the suitability of best fitted release mechanism. The kinetics shows that the release of drug followed zero order release in all the formulations. As the drug release was best fitted in Zero order kinetics, indicating that the rate of drug release is not dependent on the concentration of the drug.

TABLE 7: DISSOLUTION KINETICS DATA OF OPTIMIZED FORMULATION F5

Time (hrs)	Square root of time	Log time	% Drug release	Log% Drug release	% Drug remaining	Log % Drug remaining
1	1	0	20	1.301029	80	1.90309
4	2	0.60206	30	1.477121	70	1.84509
8	2.8284	0.90309	42	1.623249	58	1.76343
12	3.464	1.07918	53	1.724275	47	1.67209
16	4	1.20412	64	1.806179	36	1.55630
20	4.472	1.30102	75	1.875061	25	1.39794
24	4.8989	1.38021	89	1.949390	11	1.04139

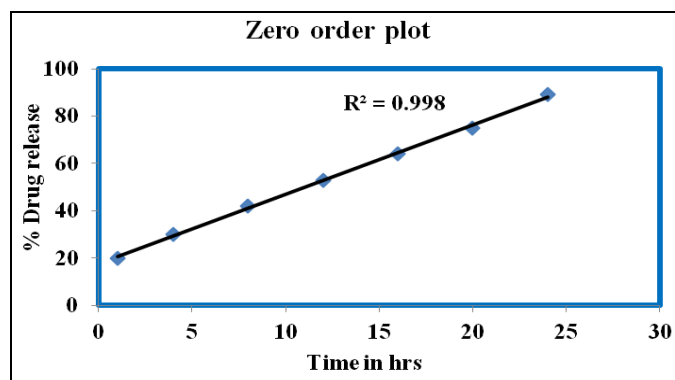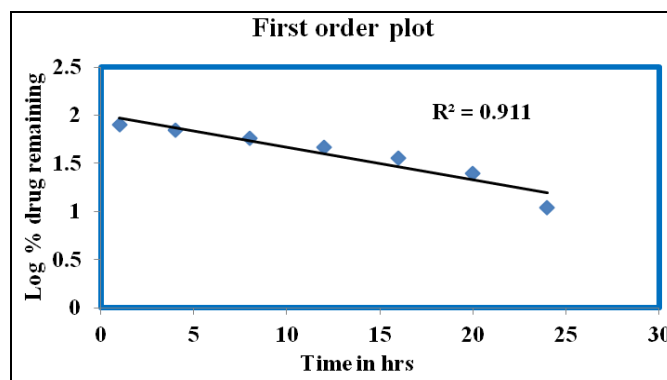**FIG. 16: ZERO ORDER KINETICS PLOT OF OPTIMIZED FORMULATION F5**

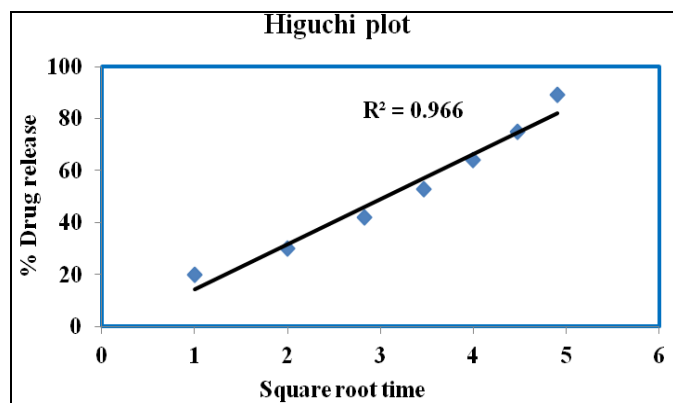**FIG. 17: FIRST ORDER KINETICS PLOT OF OPTIMIZED FORMULATION F5**

Higuchi plot

FIG. 18: HIGUCHI ORDER KINETICS PLOT OF OPTIMIZED FORMULATION F5
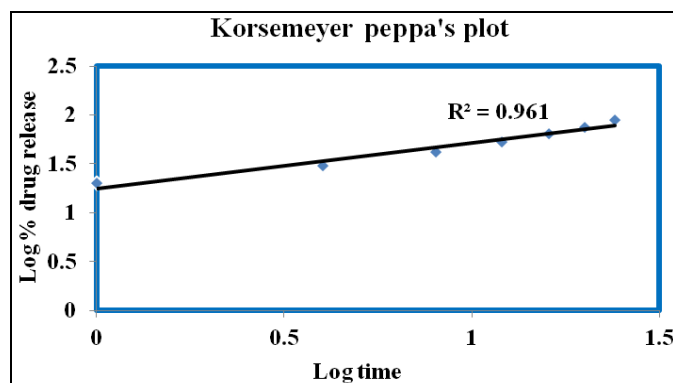
Korsemeyer peppa's plot

FIG. 19: KORSEMEYER PEPPA'S ORDER KINETICS PLOT OF OPTIMIZED FORMULATION F5

Comparison of release mechanism of Optimized formulation using kinetic study:
The release profile of Gemigliptin optimized formulation F5 was processed for comparison of different orders of drug release and to understand the linearity liaison, i.e., Kinetic principles. The data were processed for regression analysis. In vitro release data of time points between 1 to 24 hrs were considered and treated for following kinetic principles.

According to the regression values obtained showed in the **Table 8**, the formulation did not follows a first-order release pattern, when data plotted according to the zero-order equation shows a linearity, with regression value of 0.998. According to Higuchi plot the formulation shows a fair linearity with regression value 0.966.

In order to explore more precise mechanism of release of Gemigliptin from in domicile developed SR tablets, the dissolution data was fitted to the well-known exponential equation i.e., Korsemeyer-peppa's equation, which is often used to describe the drug release behaviour from polymeric systems.

After plotting the formulation showed $r^2 = 0.961$ and slope (n) value of 0.518. A value of n = < 0.45 indicates Fickian diffusion, $0.45 < n < 0.89$ indicates non-Fickian diffusion, n = 0.89 is case-II transport and n > 0.89 is Super case-II transport. The n value obtained is between $0.45 < n < 0.89$, hence the results concluded that non-Fickin mechanism for drug release. The relative complexity of this formulation and its components may indicate that the drug release is controlled by diffusion process and non-fickian mechanism.

TABLE 8: KINETIC PROFILE OF OPTIMIZED FORMULATION F5

Optimized formulation	Zero order	First order	Higuchi's	Peppa's	
	R^2	R^2	R^2	n	R^2
F5	0.998	0.911	0.966	0.518	0.961

Drug-polymer interaction/compatibility study using FTIR:
The different peaks of drug, polymer and their physical mixture indicate all groups and characteristics of the drug were not altered. There is no significant interaction in drug and polymer. Physical mixture of drug and polymer was characterised by FTIR spectral analysis for any physical as well as chemical alteration of drug characteristics. From results it was concluded that there was no interference in the functional group as the principal peaks of Gemigliptin were found to be un-altered in the drug polymer physical mixture as shown in the **Fig. 20, 21, 22, 23**.
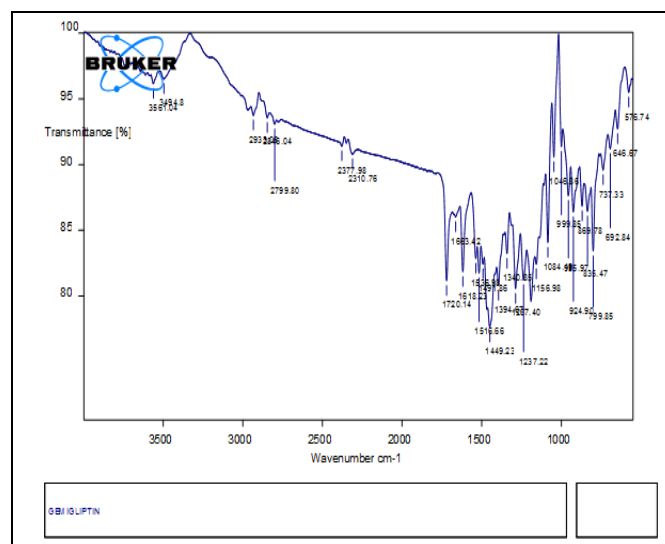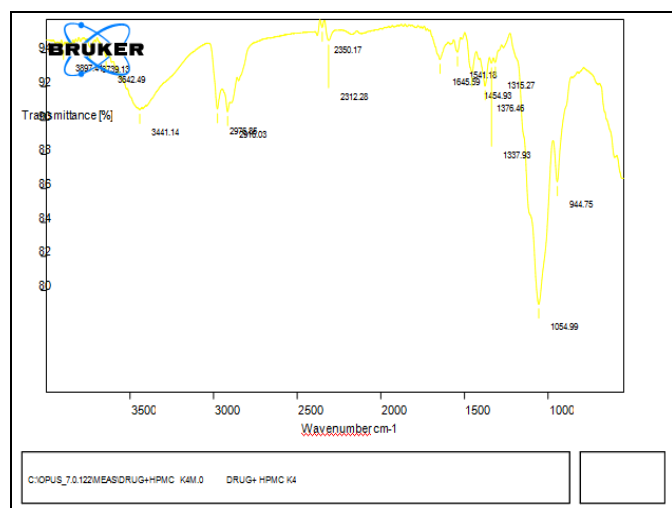

FIG. 20: FTIR CURVE OF PURE DRUG GEMIGLIPTIN
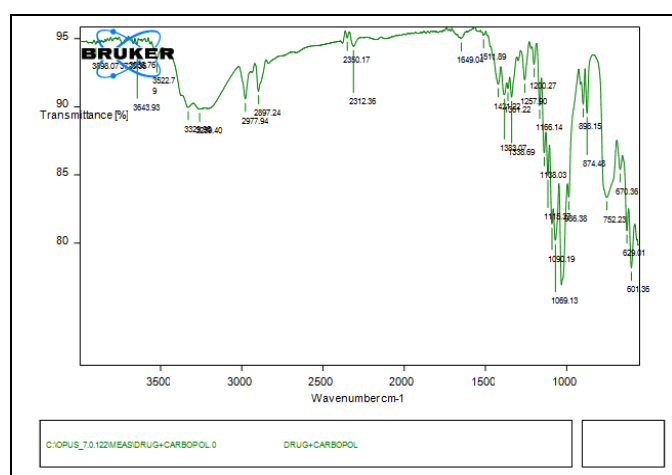
FIG.21: FTIR CURVE OF GEMIGLIPTIN + HPMC K4M

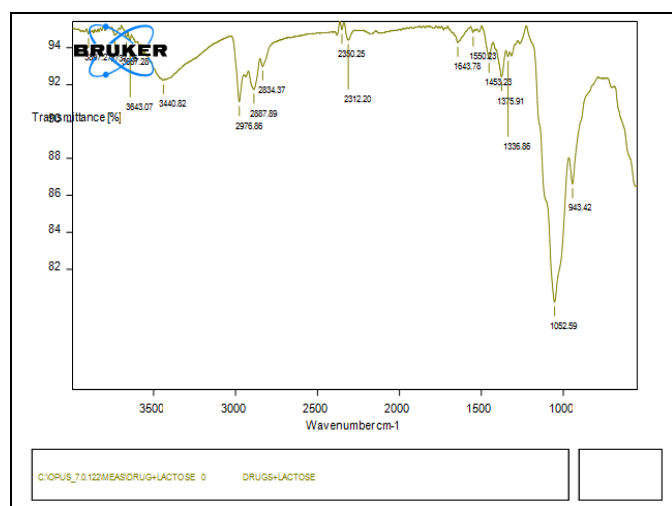**FIG. 22: FTIR CURVE OF GEMIGLIPTIN+CARBOPOL**

FIG. 23: FTIR CURVE OF GEMIGLIPTIN+LACTOSE

CONCLUSION: The drug release rate of the different formulation, among the hydrophilic matrix formers was in the subsequent order Carbopol, HPMC K4M. The results of *in-vitro* dissolution study indicated that the F5 as an optimized one since it successfully sustained the drug release at end of the hour and compared with pure drug and the drug release patterns obtained was within the pharmacopoeial limits. Direct compression is feasible for development of once a day controlled release tablet of Gemigliptin provided with careful selection of optimised concentration of Carbopol. The optimised formulation prepared with drug: polymer (carbopol) ratio 1:1 showed 89% drug release at end of the hour. The release kinetics shows that the release of drug followed Zero order release in all the formulation. From the Korsemeyer-peppas study, the n value of the formulations shows that the release profile obeys Fickian and Non-Fickian diffusion mechanism.

On the basis of result it was concluded that sustained release tablets of Gemigliptin prolong the time for absorption as well as bioavailability and thus better patient compliance can be achieved. The present study demonstrated the successful preparation of stable once daily sustained release matrix tablet of Gemigliptin thus the objectives envisaged in this work were achieved.

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