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FORMULATION AND EVALUATION OF VILDAGLIPTIN EFFERVESCENT TABLETS

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Abstract:

Vildagliptin is an orally active dipeptidyl peptidase-4 inhibitor used in the management of type 2 diabetes mellitus. Eight formulations (F1–F8) were prepared by the direct compression method using different concentrations of citric acid or tartaric acid as effervescent acids with sodium bicarbonate as the gas-generating agent. The prepared tablets were evaluated for weight variation, thickness, hardness, friability, drug content, effervescence time, dispersion time, pH and in-vitro drug release. All formulations exhibited acceptable physical characteristics, with friability values ranging from 0.45 to 0.75%. Effervescence time ranged from 63 to 91 seconds, while dispersion time ranged from 52 to 91 seconds. Among the formulations F8 demonstrated the shortest effervescence time (63 seconds) and dispersion time (52 seconds) with a drug content of 98.88%. In-vitro dissolution studies using 0.1 N hydrochloric acid showed progressive and rapid drug release from all formulations with F8 exhibiting the highest release of 99.62% within 60 minutes. The release kinetics of the optimized formulation showed the highest correlation with the Higuchi model (R^2 = 0.909). Stability studies of F8 conducted for three months under different temperature and relative humidity conditions showed only a minor reduction in drug release with drug release remaining above 96%. Overall formulation F8 exhibited satisfactory physicochemical properties, rapid effervescence and dispersion, high drug release and acceptable short-term stability, indicating its potential as a rapidly dispersible effervescent dosage form of Vildagliptin.

Keywords: *Vildagliptin, Direct compression method, In vitro drug release studies*

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INTRODUCTION:

Effervescent drug delivery systems offer several potential advantages over conventional tablets. Since the dosage form is administered after dissolution or dispersion in water the need to swallow an intact tablet is eliminated. This characteristic may improve convenience for patients who have difficulty swallowing. Effervescence can also provide rapid and uniform dispersion of the drug, improve palatability through appropriate sweeteners and flavoring agents and potentially promote faster availability of the drug for gastrointestinal absorption compared with dosage forms that require tablet disintegration after administration.[1,2] Conventional oral tablets are among the most widely used pharmaceutical dosage forms because of their accurate dosing, good stability, economical manufacturing and convenience of administration. Effervescent tablets are uncoated tablets containing substances that react rapidly in the presence of water to release carbon dioxide.[3] They generally contain an acid component such as citric acid or tartaric acid together with a carbonate or bicarbonate, commonly sodium bicarbonate. When the tablet is placed in water the acid-base reaction produces carbon dioxide, resulting in rapid disintegration and dissolution or dispersion of the formulation.[4] The prepared solution or dispersion can then be consumed orally. The successful development of an effervescent tablet depends on careful selection and optimization of formulation components.[5] The concentrations and ratio of acid and bicarbonate components significantly influence effervescence time, tablet characteristics, solution pH and overall product performance.[6] Excipients such as binders, diluents, sweetening agents, lubricants and flavoring agents should be compatible with the drug and the effervescent system.[7] Particular attention must also be given to moisture control because premature exposure to moisture can initiate the acid-base reaction, adversely affecting the stability and quality of the finished product.[8] Vildagliptin is therefore an appropriate candidate for investigation in an effervescent oral dosage form intended to provide a convenient method of administration for patients requiring antidiabetic therapy. Formulation of vildagliptin as an effervescent tablet may combine the therapeutic utility of the DPP-4 inhibitor with the patient-friendly characteristics of an effervescent drug delivery system.[9] Vildagliptin is an oral antidiabetic drug belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class and is used in the management of type 2 diabetes mellitus. In the present study, vildagliptin effervescent tablets were formulated and evaluated using suitable effervescent agents and pharmaceutical excipients.[10] Different formulations were prepared by varying selected formulation components to identify an optimized composition. The prepared tablets were evaluated for physicochemical and pharmaceutical parameters.[11] The study was designed to develop an effervescent formulation of vildagliptin with acceptable tablet characteristics, rapid effervescence, satisfactory drug release and suitable overall performance for oral administration.

MATERIALS:

Vildagliptin was procured from Hetero Labs, Hyderabad. Citric acid, Tartaric acid, Lactose monohydrate PVPk30 and Sodium bicarbonate were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Formulation development

Table-1: Composition of Vildagliptin effervescent tablets

Ingredient	Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
Vildagliptin	50	50	50	50	50	50	50	50
Citric acid	50	100	150	200				
Tartaric acid	-	-	-	-	50	100	150	200
Lactose monohydrate	180	130	80	30	180	130	80	30
PVPk30	10	10	10	10	10	10	10	10
Sodium bicarbonate	100	100	100	100	100	100	100	100
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
Saccharin	5	5	5	5	5	5	5	5
Total wt	400	400	400	400	400	400	400	400

Preparation of Formulation:[12]

The required quantities of vildagliptin, citric acid, tartaric acid, sodium bicarbonate, Lactose PVP K30, Saccharin and Talc were accurately weighed according to the formulation composition. All ingredients were separately passed through a suitable #40 mesh sieve to ensure uniform particle size and remove lumps. Vildagliptin was initially mixed with a small quantity of lactose monohydrate by geometric dilution to ensure uniform distribution of the low-dose drug. Citric acid, tartaric acid and sodium bicarbonate were then carefully blended under dry conditions. The drug-containing mixture was gradually incorporated into the effervescent mixture and blended uniformly with the remaining lactose and PVP K30. Saccharin were subsequently added and mixed thoroughly to improve the palatability of the formulation. Finally magnesium stearate was added as a lubricant and blended gently for 2–3 minutes. The resulting powder blend was evaluated for pre-compression parameters and then compressed using a suitable tablet compression machine with appropriate punches.

Evaluation of tablets[13,14,15]

Physical Appearance:

The prepared Vildagliptin effervescent tablets were visually inspected for their colour, shape, surface texture and overall appearance. Tablets were examined under normal daylight for the presence of any visible defects such as cracks, chipping, mottling, capping, lamination or sticking. The appearance of all tablets was recorded to ensure uniformity in colour, size and shape.

Weight variation test

The weight variation test was performed according to the Indian Pharmacopoeia (IP)/United States Pharmacopeia (USP) guidelines. Twenty tablets were selected randomly from each formulation batch and individually weighed using a calibrated digital analytical balance. The average tablet weight was calculated, and the individual weights were compared with the average weight. The percentage deviation of each tablet from the average weight was calculated using the following formula:

% Weight Variation = [(Individual tablet weight − Average tablet weight) / Average tablet weight] × 100

The tablets were considered to comply with the pharmacopeial specifications if the percentage weight variation was within the prescribed limits.

Content Uniformity

Twenty tablets were randomly selected, and one tablet was finely powdered. A quantity of powder equivalent to 120 mg of Vildagliptin was accurately weighed and transferred into a 100 mL volumetric flask containing a suitable solvent (e.g., methanol or the solvent used for analytical method development). The solution was sonicated for 15–20 minutes to ensure complete dissolution of the drug and then made up to volume with the same solvent. The resulting solution was filtered through Whatman No. 1 filter paper or a 0.45 µm membrane filter. An appropriate aliquot was further diluted with the selected dissolution medium or solvent and analyzed using a UV–Visible spectrophotometer at the predetermined λmax of Vildagliptin . The drug content was calculated from the calibration curve and expressed as the percentage of the labeled amount. The tablets were considered to pass the test if the drug content was within the pharmacopeial acceptance limits (generally 95–105% of the labeled claim).

Friability

The friability of the effervescent tablets was determined using a Roche friabilator. Ten tablets were accurately weighed (initial weight, W_1) and placed in the friabilator. The apparatus was operated at 25 rpm for 4 minutes (100 revolutions). After completion of the test, the tablets were removed, dedusted carefully and reweighed (final weight, W_2). The percentage friability was calculated using the following equation:

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

Effervescence Time

One tablet was placed in a beaker containing a specified volume of water, generally 200 mL, maintained at room temperature. The time required for the tablet to completely react and stop producing visible effervescence was recorded using a stopwatch. The test was repeated for individual tablets, and the mean effervescence time was calculated.

Dispersion/Dissolution Time

One tablet was introduced into a beaker containing 200 mL of purified water at room temperature. The time required for complete effervescence and dispersion or dissolution of the tablet was recorded. The test was repeated for a suitable number of tablets and the mean time was reported.

pH of Effervescent Solution

After complete effervescence, the resulting solution was allowed to equilibrate briefly at room temperature. The pH was measured using a previously calibrated digital pH meter. The pH electrode was immersed in the solution without touching the sides or bottom of the container and the stable reading was recorded.

Drug release studies

The in-vitro drug release study of Vildagliptin Effervescent tablets was performed using the USP Dissolution Apparatus II (Paddle Method). The dissolution medium consisted of 900 mL of 0.1 N hydrochloric acid (pH 1.2) maintained at 37 ± 0.5°C, and the paddle speed was adjusted to 50 rpm.

One tablet from each formulation was placed in the dissolution vessel. At predetermined time intervals. 5 mL of the dissolution medium was withdrawn and immediately replaced with an equal volume of fresh medium maintained at the same temperature to maintain sink conditions. The withdrawn samples were filtered through Whatman No. 1 filter paper or a 0.45 µm membrane filter, suitably diluted if necessary, and analyzed using a UV–Visible spectrophotometer at the predetermined λmax of Vildagliptin . The cumulative percentage of drug released was calculated using the calibration curve and the drug release profile of each formulation was plotted as cumulative percentage drug release versus time

Drug release kinetics

The dissolution data obtained from the in-vitro drug release study were fitted into various mathematical kinetic models to determine the mechanism of drug release from the effervescent tablets. The cumulative drug release data were analyzed using the following kinetic models:

- **Zero-order model:** Cumulative percentage drug released versus time.
- **First-order model:** Log cumulative percentage drug remaining versus time.
- **Higuchi model:** Cumulative percentage drug released versus square root of time.
- **Korsmeyer–Peppas model:** Log cumulative percentage drug released versus log time.

The regression coefficient (**R^2**) was calculated for each model. The model exhibiting the highest **R^2** value was considered the best fit for describing the drug release kinetics. The release exponent (**n**) obtained from the Korsmeyer–Peppas equation was used to determine the mechanism of drug release, such as Fickian diffusion, anomalous (non-Fickian) transport, Case II transport or Super Case II transport.

Stability studies

The optimized formulation of Vildagliptin effervescent tablets was subjected to accelerated stability studies according to the International Council for Harmonisation (ICH) Guideline Q1A(R2). The tablets were packed in aluminum foil or high-density polyethylene (HDPE) containers and stored in a stability chamber at 40 ± 2°C and 75 ± 5% relative humidity (RH) for a period of 3 months.

Samples were withdrawn initially (0 month) and after 1, 2, and 3 months of storage.

RESULTS AND DISCUSSION:

Evaluation Parameters

Table-2: Evaluation parameters of Vildagliptin effervescent tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8
Weight variation (%)	1.03	1.07	0.95	0.75	1.12	0.98	0.82	0.73
Thickness (mm)	3.76	3.91	3.87	3.88	3.69	3.89	3.99	4.10
Hardness (kg/cm^2)	3.8	4.1	4.3	3.9	4.2	4.5	4.7	4.9
Friability (%)	0.75	0.69	0.71	0.73	0.53	0.51	0.49	0.45
Content uniformity	90.12	89.68	92.25	93.58	95.86	96.82	97.88	98.88
Effervescence time (Sec)	91	86	77	67	71	83	79	63
Dispersion Time	91	86	80	74	70	68	63	52
pH	5.91	5.66	5.70	5.66	5.71	5.69	5.66	5.50

Discussion

The weight variation of the formulations ranged from 0.73 to 1.12%. The relatively low percentage variation indicated good uniformity of the powder blend and consistent die filling during compression. F8 showed the lowest weight variation (0.73%) whereas F5 showed the highest (1.12%).

The thickness of the tablets ranged from 3.69 to 4.10 mm. The relatively small variation in thickness among the formulations indicated uniform compression and satisfactory filling of the die cavity. F8 exhibited the highest thickness of 4.10 mm while F5 showed the lowest thickness of 3.69 mm.

The hardness values ranged from 3.8 to 4.9 kg/cm². The hardness increased progressively in the later formulations, with F8 showing the highest hardness (4.9 kg/cm²). The observed hardness values indicated adequate mechanical strength to withstand handling, packaging and transportation while still allowing the tablets to undergo rapid effervescence and dispersion.

The friability values ranged from 0.45 to 0.75%. All formulations showed friability below 1%, indicating satisfactory resistance to abrasion and mechanical stress. F8 exhibited the lowest friability (0.45%), suggesting better mechanical integrity whereas F1 showed the highest value (0.75%).

The content uniformity ranged from 89.68 to 98.88%. The drug content increased from the initial formulations toward the later formulations, with F8 showing the highest value of 98.88%. The relatively higher drug content observed in F5–F8 suggests better uniformity of Vildagliptin distribution in these formulations. However, the lower values observed in F1–F4 indicate that further optimization of the blending and manufacturing process may be required if these are intended to meet a specific pharmacopoeial assay specification.

The effervescence time ranged from 63 to 91 seconds. F8 showed the shortest effervescence time (63 sec) followed by F4 (67 sec) whereas F1 required the longest time (91 sec). The reduction in effervescence time in some formulations can be attributed to differences in the acid composition and the interaction between the acidic components and sodium bicarbonate. Rapid effervescence is desirable for an effervescent dosage form because it facilitates quick formation of the drug-containing solution.

The dispersion time ranged from 52 to 91 seconds. F8 demonstrated the shortest dispersion time of 52 sec while F1 showed the longest dispersion time of 91 sec. The lower dispersion time observed with F8 indicates rapid breakup and dispersion of the tablet in the aqueous medium which is a desirable characteristic for an effervescent formulation.

The pH of the resulting solutions ranged from 5.50 to 5.91. The formulations produced mildly acidic solutions after effervescence. F8 showed the lowest pH (5.50) whereas F1 showed the highest pH (5.91).

In vitro Dissolution studies

Table-3: In vitro drug release of Vildagliptin effervescent tablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	24.97	25.19	27.52	25.21	22.84	26.31	28.45	29.26
10	35.26	39.48	43.65	48.32	37.84	42.16	46.75	52.48
15	51.74	56.82	61.35	66.28	54.63	59.74	64.82	70.36
20	66.38	71.45	76.28	81.46	69.52	74.83	77.64	85.72
30	80.25	84.68	88.54	92.37	82.16	87.35	82.12	93.50
45	89.64	92.35	94.72	96.48	91.26	93.85	97.12	97.84
60	95.16	96.50	96.29	97.15	95.63	97.28	98.02	99.62

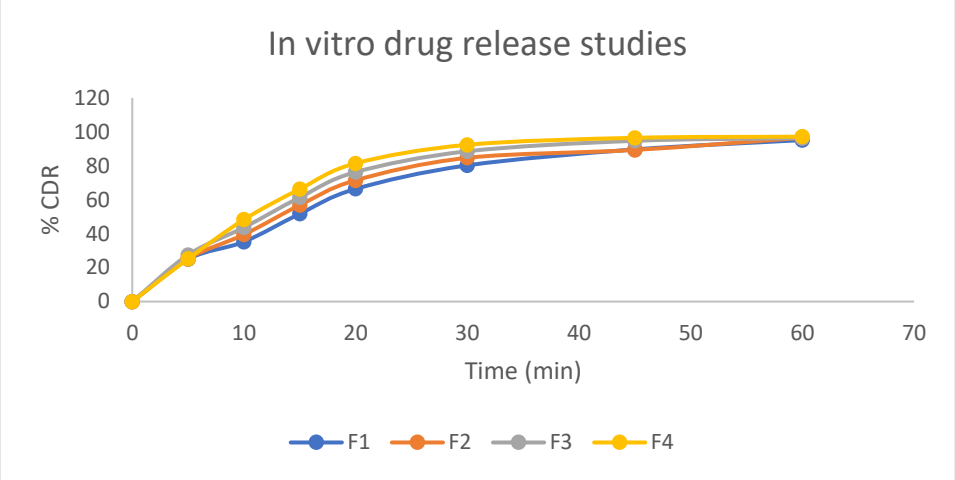

Fig-1: In vitro drug release for (F1-F4) formulations

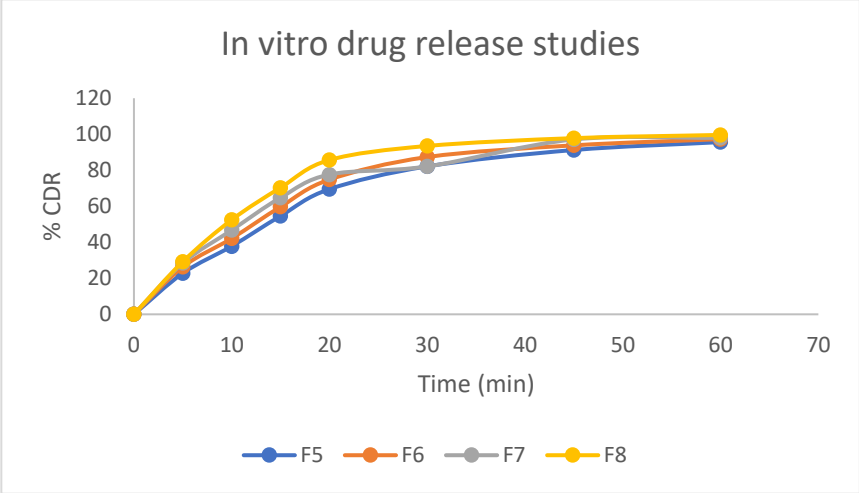

Fig-2: In vitro drug release for (F5-F8) formulations

Discussion

At 5 min, the drug release ranged from 22.84% to 29.26%. F8 showed the highest initial drug release (29.26%) whereas F5 showed the lowest release (22.84%). The relatively rapid initial release may be attributed to the rapid wetting, effervescence and dispersion of the tablet in the dissolution medium.

At 10 min, drug release increased to 35.26–52.48%. F8 showed the highest release (52.48%), followed by F4 (48.32%) and F7 (46.75%). This indicates that the effervescent reaction facilitated rapid disintegration and enhanced exposure of the drug particles to the dissolution medium.

At 15 min, the formulations showed drug release ranging from 51.74% to 70.36%. F8 exhibited the highest release of 70.36% while F1 showed the lowest release of 51.74%. The differences among formulations may be related to variations in the concentrations and proportions of citric acid and tartaric acid which influence effervescence and dispersion characteristics.

At 20 min, the drug release increased further to 66.38–85.72%. F8 showed the maximum release (85.72%) followed by F4 (81.46%) whereas F1 showed 66.38% release. The rapid release observed with F8 is consistent with its shorter effervescence time and dispersion time.

At 30 min, drug release ranged from 80.25% to 93.50%. F8 demonstrated 93.50% release, followed by F4 (92.37%) and F3 (88.54%). Most formulations had released more than 80% of the drug by this stage demonstrating the rapid-release characteristics of the effervescent formulations.

At 45 min, the cumulative drug release ranged from 89.64% to 97.84%. F8 exhibited the highest release (97.84%),followed by F7 (97.12%) and F4 (96.48%). At 60 min, the formulations showed cumulative drug release between 95.16% and 99.62%. F8 showed the highest release of 99.62%, whereas F1 showed the lowest release of 95.16%.

Drug release kinetic profile
Zero order kinetics

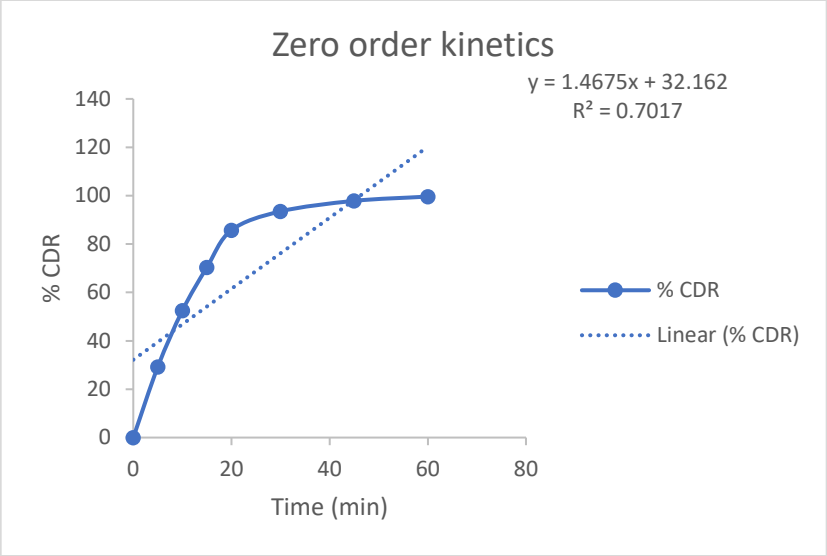

Fig-3: Drug release kinetics of zero order kinetics

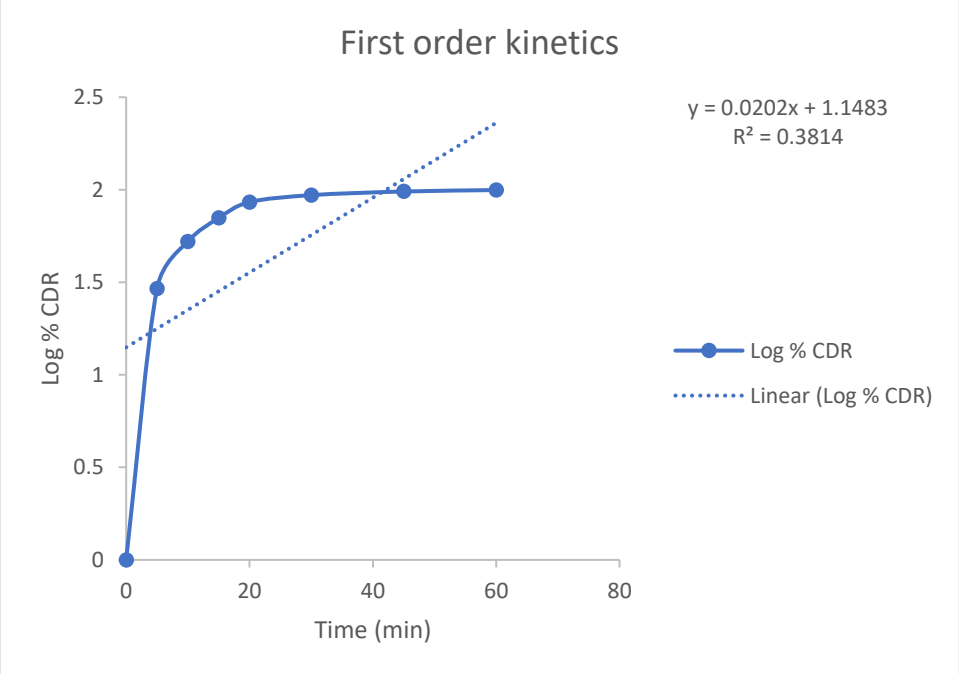

Fig-4: Drug release kinetics of First order kinetics

Higuchi model

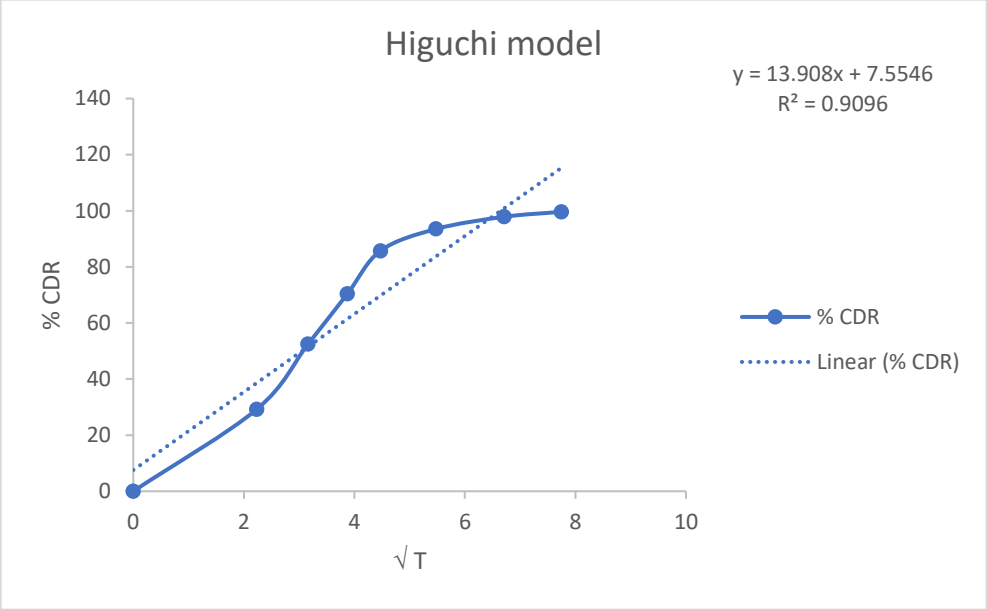

Fig-5: Drug release kinetics of Higuchi plot

Korsmeyer peppas

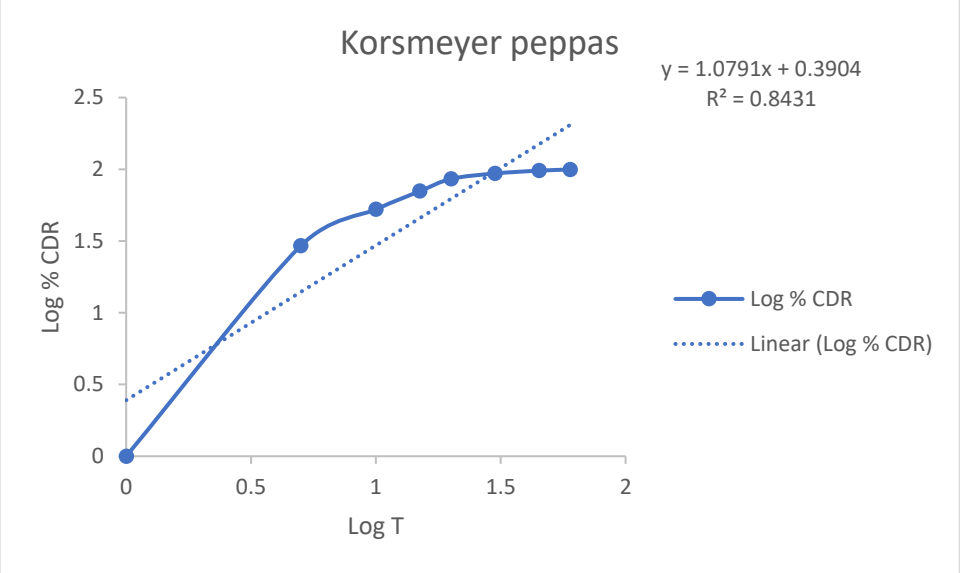

Fig-6: Drug release kinetics of Korsmeyer peppas

Discussion

Among the models studied, the Higuchi model showed the highest R^2 value (0.909), followed by the Korsmeyer–Peppas model (0.843), zero-order model (0.701), and first-order model (0.381). Therefore the dissolution data of F8 showed the best mathematical fit to the Higuchi model suggesting that diffusion was an important contributor to Vildagliptin release.

Stability Results

Table-4: Stability study for optimized formulation

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-8	**25^{0}C/60%RH % Release**	99.62	98.63	97.55	96.36	**Not less than 85 %**
F-8	**30^{0}C/75% RH % Release**	99.62	98.52	97.52	96.22	**Not less than 85 %**
F-8	**40^{0}C/75% RH % Release**	99.62	98.26	97.16	96.10	**Not less than 85 %**

DISCUSSION:

Overall, the results showed only a minor decrease in drug-release performance during the 3-month stability period under all tested conditions. Even under the highest temperature and humidity condition of 40°C/75% RH the formulation maintained 96.10% drug release which was considerably higher than the specified minimum requirement of 85%. Therefore the optimized F8 formulation demonstrated satisfactory in-vitro drug-release stability over the three-month study period with no substantial deterioration in performance observed. Further long-term stability studies would be required to establish the complete shelf life of the formulation.

CONCLUSION:

The present investigation successfully demonstrated the feasibility of developing Vildagliptin effervescent tablets by the direct compression method. The developed formulations exhibited satisfactory powder-flow characteristics and acceptable physical properties. Among the formulations studied, F8 demonstrated the most favorable overall performance, including the lowest effervescence time, shortest dispersion time, highest drug content, and highest cumulative drug release. The optimized F8 formulation exhibited rapid effervescence and dispersion, followed by rapid and efficient drug release, reaching 99.62% cumulative drug release within 60 minutes. The kinetic analysis showed the highest correlation with the Higuchi model suggesting that diffusion was an important contributor to drug release. The stability study further demonstrated that F8 maintained its drug-release performance under long-term and accelerated storage conditions investigated for three months, with drug release remaining above the predefined specification of 85%. These findings indicate that the developed Vildagliptin effervescent tablet formulation has potential as a convenient oral dosage form capable of providing rapid drug availability and improved administration convenience. However, further investigations including comprehensive assay/content-uniformity assessment according to the applicable pharmacopoeial requirements, moisture-protection studies, longer-term stability studies and comparative evaluation against a marketed Vildagliptin product would be useful before drawing conclusions regarding product equivalence and clinical performance. Overall, F8 was identified as the optimized formulation based on the investigated formulation and evaluation parameters and demonstrated satisfactory pharmaceutical characteristics, rapid effervescence, efficient drug release and acceptable short-term stability.

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