In-vitro Comparative Study Different Brands of Tenegliptin and Metformin HCl Prolonged Release Tablets by UV Spectroscopy

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Abstract
Evaluation of the quality control standards of different generic brands of Teneligliptin & Metformin HCl extended-release tablets has been compare with the innovator Glucophage XR®. The objective of this study is to determine the dissolution data by using f1 & f2.In this dissolution test following general method using 6.8 pH phosphate buffer volume 1000 ml at 100 rpm, USP I apparatus and also by using UV spectrum at 232nm. The uniformity of weight for the Six brands of this tablet with values that compiled with I.P specification and deviated less than 5% from the mean value. Using hardness tester, the strength of the tablets determined. Hardness of the tablets was in the range of 5.60±0.13 - 7.98±0.18kg/cm2 with all brands. The result of tablet friability test of all brands tested with friability values of 0.110% to 0.821% w/w. According to I.P. no batch having friability value > 1%w/w. This study concludes the physicochemical characteristic of six brands of this tablet complied with the official IP specification for hardness, friability, weight variation and dissolution. F1 and f2 factor provide uniformity in five brands of this tablet and analysis suggest that the Ingola M brand fails the test.

Keywords: *Dissolution, Teneligliptin and Metformin HCL, Glucophage XR, UV Spectroscopy.*

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INTRODUCTION

Both in terms of total population and the number of people living with diabetes, China tops the list as the world's most populated nation. [1] It is believed that more than 100 million people in China suffer from the condition known as diabetes. The dramatic growth in the incidence of diabetes in China over the course of the last 30 years has given rise to a number of issues and highlights the need of more strict policies for diabetes prevention and treatment. In addition to the conventional modifications in lifestyle and the initial first-line therapy with metformin for patients whose blood glucose levels are not sufficiently managed by lifestyle changes alone, the most recent management recommendations advocate intensifying treatment with alternative anti-hyperglycemic medications.[2,3] Metformin may no therapy may become less effective in preventing progression of disease with continued treatment and advancement of the fundamental condition [4].

The burden of long-term micro-vascular (such as nephropathy, neuropathy, and retinopathy), macro-vascular (such as atherosclerosis and peripheral

vascular disorders), and other consequences of type 2 diabetes is increasing [5, 6].

In addition, the therapies that are now considered conventional suffer from a number of drawbacks, including poor drug adherence, 7 hypoglycemia, weight gain, and treatment refractoriness. As a result of this, new types of anti-hyperglycemic medicines have been developed, such as dipeptidyl peptidase (DPP) 4 inhibitors. DPP-4 inhibitors have been found to be effective in improving glucose management. They reduce glycosylated haemoglobin (HbA1c) levels by lowering both fasting and postprandial glucose levels, and they do so without inducing weight gain, hypoglycemia, or any other significant adverse effects (AEs) [8-9].

Dipeptidyl peptidase-4 (DPP-4) inhibitors may be used as monotherapy as well as in conjunction with other medications that have complimentary modes of action, such as metformin. Because of this, the concentrations of active glucagon-like peptide 1 (GLP-1) increase, [10-11].

GLP-1 has an insulinotropic impact and glucagonostatic activities, both of which may accelerate postprandial insulin secretion, which has the effect of reducing glucose levels. [12, 13, 14]. Tenegliptin is a powerful third-generation dipeptidyl peptidase-4 (DPP-4) inhibitor that has lengthy action duration. As a consequence, glucose levels remain steady throughout the day [15, 16] and the inhibitory effects continue for 24 hours. 17 Even in patients with severe renal impairment or end-stage renal disease, the dosage of tenegliptin does not need to be adjusted since it is excreted by both the liver and the kidneys [17-18].

Additionally, it improves lipid profiles, left ventricular function, adiponectin levels, and it has a natriuretic impact. Previous studies of DPP-4 inhibitors in combination with metformin [19,20,21] as well as studies of tenegliptin added to metformin therapy [22,23] carried out in other locations demonstrated that the combination was generally well tolerated and resulted in improved glucose control without increasing the risk of hypoglycemia. In China, however, there have been no clinical studies of tenegliptin added to metformin treatment in individuals with type 2 diabetes whose diabetes is not well managed by metformin alone. In this trial, Chinese patients with type 2 diabetes that was poorly managed by metformin immunotherapy, diet, and exercise participated. The researchers compared the effectiveness and safety of Tenegliptin when added to Metformin treatment to a comparison group that received a placebo.

Metformin and tenegliptin are both medications used to treat diabetes. Together, they create the anti-diabetic medication known as Metformin & Tenegliptin.

Metformin is a kind of drug known as a biguanide that is used to treat diabetes. It does this by reducing the amount of glucose that is produced by the liver, slowing the rate at which glucose is absorbed from the intestines, and raising the sensitivity of the body to insulin.

Tenegliptin is a dipeptidyl peptidase-4 inhibitor, and its mechanism of action involves enhancing the release of insulin from the pancreas while lowering the production of hormones that cause an increase in blood sugar levels. This lowers the amount of sugar in the blood both before and after a meal. When combined, they provide improved regulation of blood sugar levels [24-25].

MATERIAL & METHOD:

The chemicals used were all of analysis purity. Double-distilled water was utilized through out the trials. The glassware used in the laboratory was soaked in a 10% v/v nitric acid solution overnight, rinsed with deionized water, and dried in a dust-free atmosphere. Sample Tenegliptin 20 mg and Metformin hydrochloride 1000 mg Extended-release tablets were purchased from seven different brands in Ghaziabad city. India. The different brand generic product are given below-

S. no	Batch no	Brand name	Manufacturer date	Expiry date
1	1203815	Tenglyn M	Oct/2022	Sep/2024
2	WS02004	Inogla M	Mar/2022	Feb/2024
3	22442717	Olymprix M	Sep/2022	Aug/2024
4	50220052	Ziten M	May/2022	April/2024
5	50220022	Afoglip M	Feb/2022	Jan/2024
6	TNC50015	Teneprid e M	May/2022	April/2024

Ziten M from Glenmark Pharmaceutical company, Inogla M from Wockhardt Pharmaceutical company, Olymprix M from Alkem Pharmaceutical company, Tenepride M from Micro Pharmaceutical company, Afoglip M from Torrent Pharmaceutical company, Tenglyn M from Zydus Pharmaceutical company.
Metformin hydrochloride powder (Working Standard) was gifted by the India pharma commission in Ghaziabad. Analytical grade reagent was utilized

throughout. The entire time, fresh distilled water was utilized. Sodium hydroxide was used to adjust to the pH 6.8 of a buffer. Potassium di hydrogen phosphate was used in preparinga6.8buffer solution.

RESULTS:

Description: Metformin hydrochloride is an oral anti-hyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (Biguanide hypoglycemic agent) (N, N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral anti-hyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of C4H11N5-HCL and a molecular weight of 165.63 g/mol. Tenegliptin is a recently developed oral dipeptidyl peptidase 4-inhibitor indicated for the management of type 2 diabetes mellitus (T2DM) in adults along with diet and exercise. [27-30]

Preformulation Study:

Organoleptic properties-

Table.1: Organoleptic properties

S. no	Drug	Order	Colour	Taste
1.	Metformin hydrochloride	Orderless	White to off-white crystalline	Tasteless
2.	Tenegliptin	Orderless	Pale yellow	Tasteless

Melting point:

Table.2: Melting Point Determination

S.No	Drug	Melting Point	Normal Range
1.	Metformin hydrochloride	198 ± 0.134	295–297°C
2.	Tenegliptin	208 ± 0.254	260–265°C

Solubility:

Table.3: Solubility Profile in wate

S.no	Drug	Solvents System	Solubility (mg/ml) at 37±2˚C
1	Metformin HCl	Distilled H$_2$O	2.0 g is soluble in 20 ml of water
2	Tenegliptine	Distilled H$_2$O	1.7mg/ml

Determination of λmax by UV-Spectrophotometer:

Table.4: Calibration curve data

S. no	Concentration (µg/ml)	Absorbance at 232nm
1	10	0.1602
2	20	0.3391
3	30	0.4334
4	40	0.6038
5	50	0.7647

Calibration curve Metformin Hcl

A U.V spectrophotometrically method based on the measurement of absorbance at λ max 232 nm in phosphate buffer of pH 6.8 was used for the estimation of Metformin hydrochloride. Before performing the dissolution test, ten serially diluted solutions of the reference standard (Metformin hydrochloride) and a standard solution curve were drawn. The curve was linear between the concentration range of 1-10µg/ml. Mean peak absorbance was plotted against the concentration to form the calibration curve [31-32].
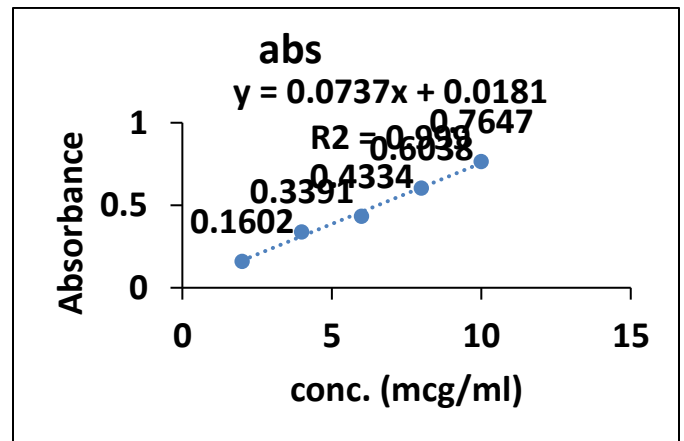
Calibration Curve of Metformin HCl

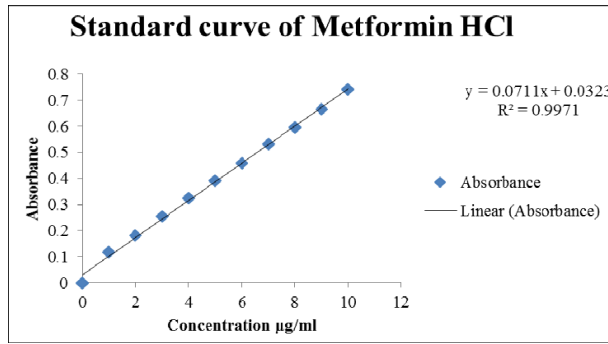**Fig.1:** Calibration curve of Metformin HCl

Fig 2: Standard calibration curve of Metformin HCl

FTIR Studies-
Method:
Weighed amount was added to KBr to form KBr pellet and subjected for scanning from $3000cm^{-1}$ to $3500cm^{-1}$ using FT-IR spectroscopy (Perkin Elmer Spectrum Rx, Serial No. 79225).
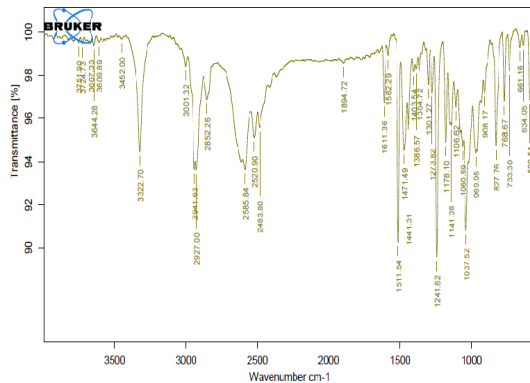
Fig.3: FTIR Spectrum of Metformin HCl

Table.5: FTIR Spectrum of Metformin HCl

S. No.	Functional Group	Range (cm-1)	Observed Frequency (cm-1)
2	N-H Stretching	3000-3500	3039
1	C-N Stretching	1060-1250	1226
3	C=O Stretching	1500-1750	1684
4	C=C stretching	1400-1750	1490.97
5	C=N Bending	1500-1650	1551
6	C-N-H Bending	1000-1400	1356
7	C-N-C Bending	410-550	430
8	C-C=N Bending	450-500	482
9	N-C=O Symmetric Bending	510-710	610

EVALUATION PARAMETER

Weight of uniformity:

This test's objective is to confirm every sample's uniformity and show the consistency of drug content throughout all batches of the formulation. The test was done in conformity with the official protocol The average weight, standard deviation, and percent difference of the 20 randomly chosen units were also determined.

Friability:

Ten tablets of each brand were taken and weight, these tablets were subjected to abrasion using Roche friability at 100 revolutions for 4 minutes. The tablets were deducted carefully and weighed accurately again then a percentage of weight loss was recorded. The friability of the tablets was calculated using the formula. *% Friability = [(Initial weight – Final weight)/Initial weight] × 100*

Hardness:

The hardness of different brands of tablets was determined by the Monsanto hardness tester and measured in terms ofkgcm2 Sample tablets (10) of each brand were taken; a tablet was placed between the spindle of the hardness tester machine until the tablet breaks, and the pressure required breaking.

Table.6: Different formulation data

Formulation Code(F)	Hardness (NMT 6.0 kg/cm2)	Thickness (3.20 ± 0.20 mm)	Friability (NMT 1.0%w/w)	Drug uniformity (NLT 80%)	Weight variation (250 ±3 %mg)
F1	6.5	3.20	0.15	99.6	249.2
F2	7.5	3.18	0.12	99.0	252.6
F3	6.9	3.14	0.13	99.0	250.9
F4	6.0	3.12	0.18	99.2	253.6
F5	7.4	3.10	0.15	99.3	247.1

In vitro release

The dissolution rate of each brand of tablets was determined using an 8-compartment Lab India dissolution test apparatus using a basket stirrer at 100 rpm and a temperature of $37\pm0.5^\circ$C. Phosphate buffer pH 6.8 (1000 ml) was used as dissolution fluid. One tablet (1000 mg) was used in each test. A sample of dissolution fluid (10ml) was withdrawn at intervals of 1, 3 and 10 minutes. A fresh 10 ml dissolution medium was replaced after each sampling to maintain sink condition. Each of the withdrawn samples was filtered

and the filtrate was diluted. The absorbance was measured at λ max 232nm using U.V. Visible double beam spectrophotometer (PERKIN ELMER). The concentration was determined against the standard solution of Metformin hydrochloride drug in the same medium. From the concentration, the percentage (%) of drug release was determined at a specified time interval. Each dissolution experiment was run in triplicate (n=3). Calculate the percentage of the labeled amount of metformin hydrochloride released at each time point [33-35].

Amount of drug = $[(A_u/A_s)*C_s*(V-V_s) + (C60*V_s) + (C180*V_s)]*100/L)$

A_u = absorbance of the sample solution.

A_s = absorbance of the standard solution.

C_s = concentration of the standard solution (mg/ml)

V = initial volume of Medium in the vessel (ml)

V_s = volume withdrawn from the vessel for previous sampling (ml)

C60 = concentration of Metformin hydrochloride in medium determined at 1HR (mg/ml)

C180 = concentration of Metformin hydrochloride in medium determined at 3h (mg/ml)

L = Label claim (mg/tab)

Table.7: Different brand data

Time hr	% Drug Released			
	Example 1	Example 2	Example 5	Glucophage XR (750 mg)
1	30	37	32	32
2	45	51	44	46
3	55	61	55	59
4	63	70	65	65
6	74	80	78	78
8	82	86	84	87
10	87	92	88	94
12	92	93	91	96

Initialization of the Dissolution by UV-Spectroscopy method:

Metformin HCL1000MG prolonged-release units were subjected to dissolve tests in line with USP44 NF39 general drug procedures. In vitro release of drugs investigations for marketed products were carried out utilizing a dissolving medium of 6.8 pH Phosphate buffer volume 1000 ml at 100 rpm, USP I apparatus.

Using a UV-spectrophotometer with wavelength to 232 nm

Table.8: Dissolution Parameters

Dissolution Parameter	For Metformin HCL PR Formulation
Apparatus	Basket
Media and Volume	1000 ml
RPM	100 rpm
Time (Min)	1,3and,10 h
Detector	232nm
Temperature	37ºC

Preparation of Dissolution Medium:

In purified water, dissolve 6.8gm potassium di-hydrogen phosphate. Make up to 1000ml of filtered water and adjust the pH to 6.8 with sodium hydroxide solution.

Preparation of Standard:

In a 20-ml volumetric flask, weigh precisely 20 mg of Metformin HCL Working Standard, add some dissolution media, and sonicated to dissolve before diluting to volume with dissolution media and mixing. To dilute further, pour 1 ml of this solution into a 100-ml volumetric flask, fill to the dissolving medium's capacity, and mix (concentration 10ppm).
Acceptances Criteria

Table 9: Preparation of standard

Time (h)	Amount dissolved 500mg tablet (%)	Amount dissolved 750mg tablet (%)
1HR	20-40	22-42
3HR	45-40	49-69
10HR	NLT 85	NLT 85

Every medication brand's dissolved quantity was determined by applying an 8-compartment Lab India dissolution test unit with a paddle stirrer at 100 rpm and 370.5 °C. Phosphate buffer pH 6.8 was used as a dissolving fluid. One tablet (1000 mg) was used in each test. At 1, 3, and 10hour intervals, a sample of dissolving fluid (10 ml) was obtained. Every drawn sample was filtered. The absorbance at 232 nm was quantified using UV spectroscopy. The concentration was determined by comparing it to a teneligliptin and metformin HCL reference solution in the same medium. Based on the concentration, the percentage (%) of drug release at a certain time interval was computed. Based on the specified amount, calculate the proportion of teneligliptin and metformin HCL released at each time point.

Table.10: Result for torrent

TEST READING	% ON1H+(22-42)	%ON3H+(49-69)	%ON10+(NLT85)
TEST-1	33.6	61.33	98.23
TEST-2	33.52	61.07	98.51
TEST-3	33.42	60.94	98.91
TEST-4	33.76	61.37	98.99
TEST-5	33.65	61.01	99.19
TEST-6	33.83	61.4	99.42
Content (Max)	33.83	61.4	99.42
Content (Min)	33.42	60.94	98.23
Average % Label Claim dissolved	33.63	61.18	98.88

Result for Torrent:

Table 11: Result for work hard

TEST READING	% ON1H+(22-42)	%ON3H+(49-69)	%ON10+(NLT85)
TEST-1	49.51	85.55	104.87
TEST-2	48.98	84.59	104.7
TEST-3	47.8	85.11	103.11
TEST-4	47.43	85.2	103.53
TEST-5	46.36	85.65	104.42
TEST-6	48.68	85.46	104.3

Result for work hard:

Table.12: Result for alkem

TEST READING	% ON1H+(22-42)	%ON3H+(49-69)	%ON10+(NLT85)
TEST-1	38.77	62.97	96.75
TEST-2	39.1	62.32	94.17
TEST-3	39.2	62.05	94.55
TEST-4	38.05	61.94	92.01
TEST-5	38.22	61.71	91.11
TEST-6	37.84	61.14	93.53
Content (Max)	39.2	62.97	96.75
Content (Min)	37.84	61.14	91.11
Average % Label Claim dissolved	38.53	62.02	93.69

Result for Alkem:

Table 13: Result for zydus

TEST READING	% ON1H+(22-42)	%ON3H+(49-69)	%ON10+(NLT85)
TEST-1	36.44	66.01	100.62
TEST-2	35.19	61.04	99.91
TEST-3	32.98	62.9	99.58
TEST-4	31.54	64.76	96.23
TEST-5	30.87	62.69	99.98
TEST-6	31.08	64.69	100.12
Content (Max)	36.44	66.01	100.62
Content (Min)	30.87	61.04	96.23
Average % Label Claim dissolved	33.02	63.68	99.41

Result for Zydus:

Table.14: Result for Glenmark

TEST READING	% ON1H+(22-42)	%ON3H+(49-69)	%ON10+(NLT85)
TEST-1	27.44	63.23	62.99
TEST-2	27.25	62.08	98.16
TEST-3	27.18	62.4	98.14
TEST-4	27.44	62.94	97.95
TEST-5	27.44	64.02	98.07
TEST-6	27.38	63.29	97.79
Content (Max)	27.44	64.02	98.43
Content (Min)	27.18	62.08	97.79
Average % Label Claim dissolved	27.35	62.99	98.09

Result for Glenmark:

Table.15: Result for micro

TEST READING	% ON1H+(22-42)	%ON3H+(49-69)	%ON10+(NLT85)
TEST-1	38.03	61.81	96.50
TEST-2	39.39	61.71	87.13
TEST-3	39.87	63.34	94.86
TEST-4	38.61	60.68	95.02
TEST-5	39.74	57.62	95.01
TEST-6	38.50	58.69	95.09
Content (Max)	39.87	63.34	96.50

Content (Min)	38.03	57.62	87.13
Average % Label Claim dissolved	39.02	60.64	93.94

Result for Micro:

Table 16: Results of Glucophage XR 750 MG (Bristol – Myer Squibb)

S.NO.	Time points (hrs)	Glucophage XR (750 MG) % Drug released
1	1	30
2	3	55
3	10	87

Result of glucophage 750mg:
Comparative dissolution profile of metformin HCl extended-release tablet with glucophage XR (BMS):

The dissolution profile of extended-release tablet of metformin carried out in PH 6.8 phosphate buffer as medium using USP-I Apparatus, @ 100 rpm speed.

Table 17: Comparative dissolution profile of metformin hcl extended-release tablet with glucophage XR (BMS)

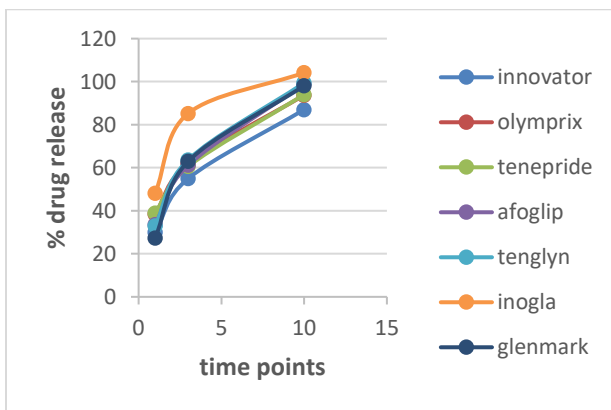| Time in hour	% Drug released						
	Ziten M	Inogla M	Tenglyn M	Afoglip M	Tenepride M	Olymprix M	Glucophage750 MG)
1	27.35	48.13	33.02	33.63	39.02	38.53	30
3	62.99	85.26	63.68	61.18	60.64	62.02	55
10	98.09	104.15	99.41	98.88	93.94	93.69	87

Fig.5: % drug release

Table.18: In-vitro cumulative drug Release of metformin HCl extended-release tablet

Time (min)	%CDR					
Code	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	15.62±0.01	17.42±0.76	13.68±0.74	16.29±0.61	17.33±1.41	14.23±0.75
60	36.90±1.22	33.073±0.4	30.69±0.86	32.71±0.42	34.83±0.26	31.68±0.97
90	47.89±2.31	42.54±2.31	44.58±1.21	45.35±0.41	46.75±0.26	42.13±0.34
120	56.60±1.43	52.24±1.02	51.437±1.25	52.042±0.71	58.137±1.13	52.042±0.75
150	65.72±0.14	62.01±1.15	62.107±0.32	59.42±0.25	66.68±0.86	59.42±0.24
180	74.53±1.26	71.89±0.56	75.94±0.37	69.91 ±0.19	76.12±0.64	68.21 ±0.15
210	80.610±0.84	78.23±1.31	82.15±0.44	79.89±0.22	86.52±0.05	76.99±0.11
240	90.41±0.75	88.26±0.13	94.12±0.07	90.79±0.75	97.14±1.22	94.29±0.34

In-vitro Drug Release of Metformin HCl extended-release Tablet:
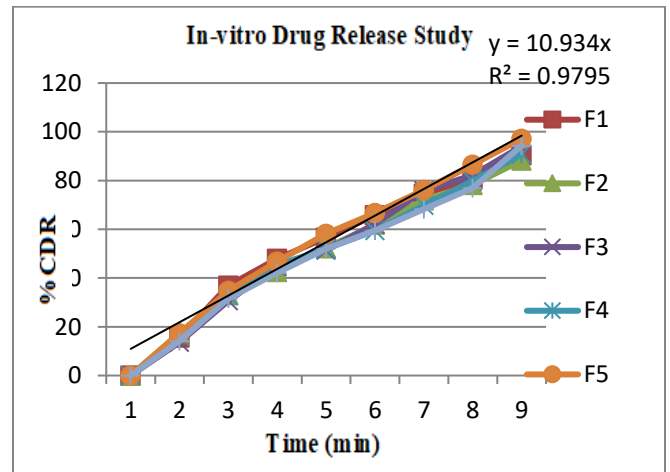

Fig.6: In-Vitro Drug Release Study F1-F6

Calculate of F1 and F2
The difference factor (f1) as defined by FDA as calculates the % difference between 2 curves at each time point and is a measurement of the relative error between 2 curves.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100$$

Where,
  n = number of time points
  Rt = % dissolved at time t of reference product
  Tt = % dissolved at time t of the product.

The similarity factor (f2) as defined by FDA is logarithmic reciprocal square root transformation of sum of square error and is a measurement of the similarity in the percentage (%) dissolution between the two curves.

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right)^{-0.5} \times 100 \right\}$$

Summary & Conclusion:

The current study compares release of several brands of Teneligliptin and Metformin HCL extended-release tablets in vitro using UV spectroscopy. Different oral anti-diabetic drugs include teneligliptin and metformin hydrochloride extended-release tablets. There are various brands of teneligliptin and Metformin units available on the market, which raises concerns regarding their quality and cost. The current study's purpose is to compare six different brands of teneligliptin and Metformin hydrochloride that are commercially available in market. They were subjected to a better of quality control tests in order to determine biopharmaceutical equivalence. They were subjected to a better of quality control tests in order to determine biopharmaceutical equivalence. The weight uniformity for the six brands of teneligliptin and Metformin hydrochloride delayed-release tablets produced results that complied with I.P specifications and differed by less than 5% from the mean value. A hardness tester was used to evaluate the strength of the tablets. The unit's hardness ranged from 5.600.13 to 7.980.18 kg/cm2 across all six brands. The results of the tablet friability test demonstrated that all of the brands tested had exceptional friability values ranging from 0.110% to 0.821% w/w. According to I.P., no batch shall have a friability rating more than 1% w/w. The study confirmed that the Six brands often Teneligliptin and metformin hydrochloride prolonged release tablets complied with According to IP official specification. To determine the interchangeability of generic and innovator brands, the model-independent approach of similarity and difference factors was utilized. The similarity factor should be between 50 and 100, with a difference factor less than 15. Accordingly, all of the brands can be used interchangeably with the innovator as they have a similarity factor of >50 and difference factor of <15. All of the brands satisfied the multiple-point USP pharmacopoeia criterion for drug substance release, according to the present research. Except for Inogla M, all of the brands may be used interchangeably with the innovator drug based on the fit factor criterion [35-40].

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