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Comparison of Dissolution and Pharmacokinetics of Vildagliptin Modified Release Tablets

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Abstract : The main aim of proposed work was to develop vildagliptin matrix tablets (Modified release dosage form) for the treatment of the Type 2 diabetes. Modified release formulation is the drug delivery system that is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. One of the biggest drawbacks of using vildagliptin is its biological half-life of ~2 hours, so it is rapidly eliminated from the body. Owing to the shorter half-lives of vildagliptin, it is suggested that patients need to be adhered rigorously to the dosing interval and that it should be administered in two doses of 50mg per day. Since vildagliptin follows a linear pharmacokinetics across 25mg -200mg (25mg,50mg, 100mg, 200mg). Here an attempt has been made to kinetically calculate the effective dissolution profile (*in vitro*) for the above mentioned four strengths that will be equally effective *in vivo* based on the severity of the subject. Calculation part consists of Loading dose and maintenance dose calculation concept. To support the data for the *in vivo* behavior, comparison has been done with a patented osmotic tablet of the same.

Key words : Loading Dose, Maintenance Dose, Volume of Distribution, Clearance, Plasma concentration, Linear Kinetics.

Introduction

Diabetes is increasing rapidly in every part of the world; the prevalence of the disease is predicted to reach 380 million people being affected by 2025 [1, 2]. Approximately 25% of the population has been identified with diabetes and a rise between 40-50% by 2020 is expected [3]. Some oral anti-diabetic drugs show poor tolerability during chronic treatment, which contributes to the relatively huge proportion of type 2 diabetes mellitus (T2DM) patients that remain inadequately managed. The currently available oral anti-diabetic agents lack the efficacy to directly restore the complex secretory function of the islet cells and are also limited by side effects. Hence, there has been much interest in identifying newer agents, capable of restoring the complex secretory dysfunction of patients with T2DM. The basis of the therapeutic efficacy of DPP-4 inhibitors lies in their ability to increase circulating levels of the intact, biologically active form of the incretin hormones,

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glucagon- like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which have several metabolically advantageous effects. With regard to mechanism(s) of action, vildagliptin is a DPP-4 inhibitor studied most thoroughly in clinical trials, and considerable progress has also been made towards understanding the molecular interaction between vildagliptin and the DPP-4 enzyme[4].One of the biggest drawbacks of using vildagliptin is its short biological half-life which eliminates rapidly. Owing to the shorter half-lives of vildagliptin, it is suggested that patients need to be adhered rigorously to the dosing interval and that it should be administered in two doses of 50mg per day[5, 6].

Materials and methods

Loading dose and maintenance dose of Vidagliptin & its modified release tablets are calculated using formulas at the dose of 25, 50, 100 and 200 mg. Dissolution profile and % release of vidagliptin at all strength were studied and compared.

Pharmacokinetic Calculations

Loading Dose (L_D):

Loading dose is dose required to achieve a specific plasma drug concentration level with a single administration.

$$\text{Loading dose} = \frac{\text{Volume of Distribution (Vd) X Desired Plasma Concentration (Cp)}}{\text{Bioavailability (F)}}$$

Volume of Distribution (V_d): V_d for Vildagliptin is ≥ 71 L[7].

Oral Bio-availability (F): Oral bio availability of Vildagliptin is 85%[7].

Plasma Concentration (C_p):

According to literature Cmax of Vildagliptin ranges from 245 ng/ml for 50 mg to 467 ng/ml for 100 mg[8]. Plasma concentration is linearly related to the administered dose in the range of 25 to 200 mg. Cmax for different doses of vidagliptin can be theoretically calculated as shown in Table 1.

Table 1: Different strength and C_{max} of Vidagliptin in different strength

Strength	**C_{max}**		
25 mg	123 ng/ml	0.123mg/L	Calculated
50 mg	245 ng/ml	0.245mg/L	Literature[8]
100 mg	467 ng/ml	0.467mg/L	Literature[9]
200 mg	980 ng/ml	0.980mg/L	Calculated

Maintenance Dose (M_D):

Maintenance dose is dose required to maintain a target plasma drug concentration level.

$$\text{Maintenance Dose } (M_{D)} = \frac{\text{Clearance (Cl) X Steady state Plasma Concentration(Css)}}{\text{Bioavailability (F)}}$$

Clearance (Cl): Average clearance of Vildagliptin is 40 L/hr[10].

Steady state concentration (C_{ss}):

Plasma concentration is linearly related to the administered dose, mean steady state concentration for respective strength will be calculated as shown in Table 2.

Table 2: Steady state concentration along with diverse strength

Strength	Css		Comment
25 mg	12.5ng/ml	0.0125mg/L	Calculated
50 mg	25 ng/ml	0.025mg/L	Calculated
100 mg	50 ng/ml	0.050mg/L	Literature
200 mg	100 ng/ml	0.100mg/L	Calculated

Result and Discussion:

Loading and maintenance dose of all four strengths of Vidagliptin modified release tablets were calculated and tabulated in Table 3.

Table 3: Loading and maintenance dose of all strengths of Vidagliptin

Vidagliptin Tablet	25mgMR Tablet	50mgMR Tablet	100mgMR Tablet	200mgMR Tablet
Loading Dose (L_D) in mg	10.3	20.5	39	82
Maintenance Dose (M_D) in mg/h	0.588	1.20	2.50	4.70

Table 4: Comparative dissolution profile of all the 4 strengths of vidalgliptin modified release tablets

Time (h)	25mgMR Tablet (% drug release)	50mg MR Tablet (% drug release)	100mg MR Tablet (% drug release)	200mg MR Tablet (% drug release)
1	41.20	41.00	39.00	41.00
2	43.55	43.40	41.50	43.35
3	45.90	45.80	44.00	45.70
4	48.26	48.20	46.50	48.05
5	50.61	50.60	49.00	50.40
6	52.96	53.00	51.50	52.75
7	55.31	55.40	54.00	55.10
8	57.66	57.80	56.50	57.45
9	60.02	60.20	59.00	59.80
10	62.37	62.60	61.50	62.15
11	64.72	65.00	64.00	64.50
12	67.07	67.40	66.50	66.85
13	69.42	69.80	69.00	69.20
14	71.78	72.20	71.50	71.55
15	74.13	74.60	74.00	73.90
16	76.48	77.00	76.50	76.25
17	78.83	79.40	79.00	78.60
18	81.18	81.80	81.50	80.95
19	83.54	84.20	84.00	83.30
20	85.89	86.60	86.50	85.65
21	88.24	89.00	89.00	88.00
22	90.59	91.40	91.50	90.35

23	92.94	93.80	94.00	92.70
24	95.30	96.20	96.50	95.05

Dissolution profile of all four strengths of Vidagliptin modified release tablets was studied and compared as shown in Table 4 and figure 1.

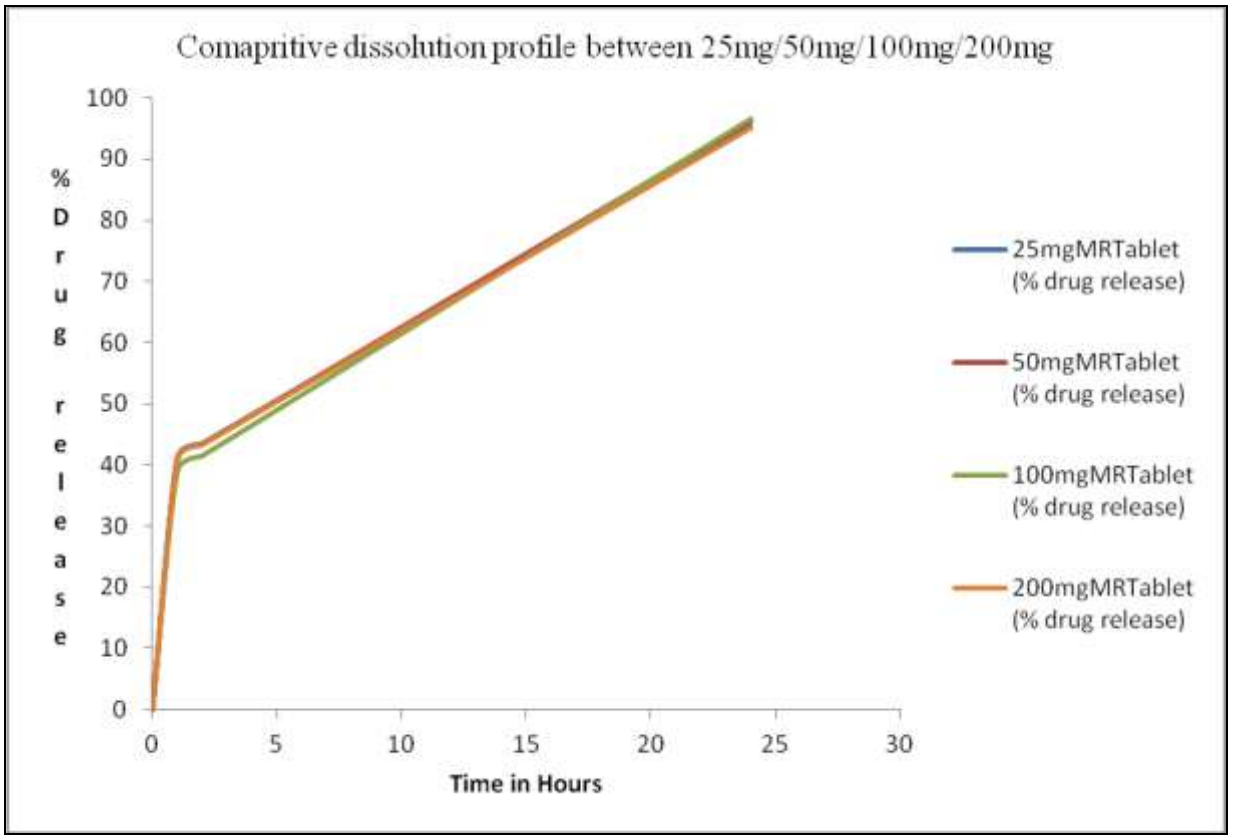

Figure 1. Graphical representation of the dissolution of all the 4 strengths of Vidagliptin

Almost similar percentage drug release is derived for all the doses considering linear pharmacokinetics. In order to prove that the above dissolution profile will be effective in the *in vivo* study, the data was compared to a study reported in the patent, wherein an oral osmotic tablet of vildagliptin was prepared. In this study 25mg vildagliptin was made as immediate release part (loading dose) and 75mg was made as sustained release part (Maintenance dose) and their dissolution profile obtained is showed in Table 5.

Table 5: Comparison of drug release between osmotic tablet and proposed matrix tablet of Vidagliptin

Time (h)	**% release of osmotic tablet**	**% release matrix tablet**
Acid stage 2	28.0	41.5
Buffer stage		-
3	32.0	44.0
4	35.0	46.5
6	42.0	51.5
10	59.0	61.5
14	78.0	71.5
20	87.0	86.5
24	91.0	96.5

Preclinical studies were carried out to evaluate the PK/PD profile Plasma drug concentrations and DPP-IV enzyme activity were assessed and compared to Galvus (Innovator IR Tablet)[11]. The study was carried out in the fasted animals. The animals were treated with two doses of Galvus and one osmotic tablet. Galvus showed more than 80% DPP-IV inhibition from 0.5-6 hour during first dose and 10.5-16 hour during second dose. Overall, Galvus maintained more than 80% DPP-IV for 6 hours after each dose. After 6 Hours Galvus showed DPP-IV Inhibition below 80% this correlated with the plasma drug concentration and after that there was a drastic drop.

The similar and consistent PK/PD outcomes can be anticipated in human volunteers in view of drug half-life and clearance correlations between humans and dog. As the *in vitro* dissolution profile of the kinetically calculated doses of vildagliptin across all the strengths matches with the dissolution profile of the osmotic tablet as mentioned in the patent, this further substantiates the current topic of interest. Further, the work will be equally effective in terms of the cost.

Conflict of Interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References:

1. Kikuchi M., Haneda M., Koya D., Tobe K., Onishi Y., Couturier A., Mimori N., Inaba Y., Goodman M., Efficacy and tolerability of vildagliptin as an add-on to glimepiride in Japanese patients with Type 2 diabetes mellitus, Diabetes Res Clin Pract, 2010, 89, 216-223.
2. Dong H. Q., Li M., Zhu F., Liu F. L., Huang J. B., Inhibitory potential of trilobatin from Lithocarpus polystachyus Rehd against I±-glucosidase and I±-amylase linked to type 2 diabetes, Food Chem, 2011, 130, 261-266.
3. Datamonitor, Summary of the "Stakeholder Opinions: Type 2 Diabetes in the UAE & Saudi Arabia Growth opportunities in fragmented markets" report, 2008, 12, 241-250.
4. Ahren B., Schweizer A., Dejager S., Villhauer E. B., Dunning B. E., Foley J. E., Mechanisms of action of the dipeptidyl peptidase-4 inhibitor vildagliptin in humans, Diabetes Obes Metab, 2011, 13, 775-783.
5. Doherty R., Vildagliptin successful in treating type 2 diabetes, Nat Clin Pract End Met, 2006, 2, 6-6.
6. Sunkara G., Sabo R., Wang Y., He Y. L., Campestrini J., Rosenberg M., Howard D., Dole W., Dose Proportionality and the Effect of Food on Vildagliptin, a Novel Dipeptidyl Peptidase IV Inhibitor, in Healthy Volunteers, J Clin Pharmacol, 2007, 47, 1152-1158.
7. He Y. L., Clinical pharmacokinetics and pharmacodynamics of vildagliptin, clin Pharmacokinet, 2012, 51(3), 147-62.
8. Sekar R., Chow B. K. C., Pharmacological Actions of Glucagon-Like Peptide-1, Gastric Inhibitory Polypeptide, and Glucagon, International Review of cell and Molecular Biology, 2016, 326, 279-341.
9. He Y. L., Sabo R., Study of the pharmacokinetic interaction of vildagliptin and metformin in patients with type 2 diabetes, Current medical research and opinion, 2009, 25(5), 1265-1272.
10. He Y. L., The absolute oral bioavailability and population based pharmacokinetic modelling of a novel dipeptidylpeptidase-IV inhibitor, vildagliptin, in healthy volunteers, Clin Pharmacokinet, 2007, 46(9), 787-802.
11. Kodgule M. M., Bansal A., An oral osmotic pharmaceutical composition of Vildagliptin, Indian Patent WO2017115252A1, 2016, Asignee: Wockhardt Limited

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