Effect Of Hydrophilic and Hydrophobic Polymer Combinations in Vildagliptin Sustained Release Tablets: Fabrication and In Vitro Characterization

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Abstract

Vildagliptin is a dipeptidylpeptidase-4 (DPP-4) inhibitor class of anti-diabetic drug, which gets rapidly absorbed following oral administration and then required to administer twice a day. An attempt has been made to extend the release up to 24 h using various hydrophilic and hydrophobic polymers such as xanthan gum, guar gum (GG); hydroxypropyl methylcellulose and ethyl cellulose at different ratios were used. The wet granulation technique was employed for the preparation of tablets. The prepared tablets were characterized for pre- and post-compression parameters. The Fourier transform infrared study indicated no interaction between the drug and polymers. Formulation F10 having 30% GG and 10% ethyl cellulose showed better results. The drug release kinetic data confirmed that the optimized tablets best fit in to Higuchi model, which had shown a $R^2$ value of 0.988. The results of the in vitro release data were fitted to the Korsemeyer–Peppa’s equation to analyze the release pattern of the drug from the polymeric system. The value of “n” was found to be more than 0.89, indicating the drug release follows super case II transport. Optimized tablets showed no significant changes in the physical appearance, drug content, in vitro dissolution pattern after storage at 40°C/75% relative humidity for 3 months. It indicates good stability of vildagliptin extended release tablets.

Key words: Hydrophilic, hydrophobic, in vitro dissolution, modified release, release kinetics and vildagliptin

INTRODUCTION

In long-term therapy for the treatment of chronic disease conditions like diabetes mellitus type 2 conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.[1] Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintaining a steady drug plasma concentration.[2,3] The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Sustained release can be achieved by formulating drugs as matrix devices using hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose and other swellable polymer.[4-6] Furthermore, the matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behavior.[7] Hydrophilic polymers with high gelling capacity are of particular interest in the field of controlled release. On coming in contact with aqueous medium they hydrate at solid-liquid interface and form a viscous layer, which retards the release of the drug.[8,9] In this study, various hydrophilic polymers such as xanthan gum (XG) and guar gum (GG) were blended with hydrophobic and hydrophilic synthetic polymers to form an extended release (ER) matrix tablet. The aims of this study were to investigate the role of hydrophilic and hydrophobic polymers in sustaining the release of drugs in tablet dosage form, and the release kinetics and mechanism of drug release were also investigated by using various release kinetics model equations.

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MATERIALS AND METHODS

Vildagliptin was generously obtained as a gift sample from Apollo Life Sciences Pvt. Ltd., Mumbai, India. XG and GG were purchased from the Mohini Auxichem Private Limited, Gujarat, India. Micro crystalline cellulose was obtained from FMC Biopolymer; Mumbai, India, Ethyl cellulose 100 cps was obtained from Galaxy Chemicals Pvt. Ltd., Gujarat, India. Hydroxy propyl methyl cellulose was purchased from Colorcon Asia Pvt. Ltd., Mumbai, and India. Poly vinyl pyrrolidone was purchased from Glide Chem. Private Limited, Delhi, India. Isopropyl alcohol was obtained from Astron Chemicals Gujarat, India. Talc was purchased from Manek Minerals, Gujarat, India and magnesium stearate was purchased from Powder Pack Chem., Maharashtra, India.

Methods

Fourier transform infrared (FT-IR) was carried out to assess the interaction between drugs and tablet excipients. Prepared tablet mixture was taken in a ratio of 1:1 w/w and analyzed for functional groups by FT-IR. One milligram of substance in solid state was ground with 100 mg of dry potassium bromide and scanned from 400 to 4000 cm⁻¹ using Shimadzu FT-IR (IRAffinity1) spectrophotometer.  

Calibration curve of vildagliptin in pH 6.8 phosphate buffer

Preparation of standard stock solution

Accurately weighed 25 mg of the drug was dissolved in 25 ml pH 6.8 phosphate buffer in 25 ml volumetric flasks, which gives concentration of 1000 μg/ml. From the above solution, 1 ml was withdrawn and volume was fixed up to 100 ml with pH 6.8 phosphate buffer in the volumetric flask which gives concentration of 100 μg/ml. Preparation of calibration curve: From the above standard stock solution (100 μg/ml) appropriate aliquots of 2, 4, 6, 8, 10 ml were pipette out in 10 ml volumetric flasks and dilutions were made up to 10 ml with pH 6.8 phosphate buffer which gives concentrations of 2, 4, 6, 8, 10 μg/ml. The absorbance was noted using UV-visible spectrophotometer at 245 nm.

Preparation of vildagliptin extended release tablets

The tablets of vildagliptin modified release were prepared by the wet granulation method by utilizing different types of release retardant materials like natural gums and synthetic polymers in the ratio of 1:1, 1:2, 1:3. Microcrystalline cellulose was used as a diluent, polyvinyl pyrrolidone (PVP K-30) was used as a binder, magnesium stearate and talc were used as lubricants. The product was made according to the formulation ingredients given in Table 1. All the ingredients were passed through sieve no. 20 and were collected in amini octagonal blender (Shakti Pharmatech Pvt. Ltd., India), mixed well to make a uniform mixture. The paste of PVP K-30 in isopropyl alcohol was applied at a granulating medium. The prepared granules were dried in a tray dryer (Prism Pharma Machinerey, Ahmedabad, India) at 45°C, and dried granules were further passed through sieve no. 20. Magnesium stearate and talc were added as a lubricant, and the granules were compressed into tablets using a 16 station rotary tablet compression machine using 9.0 mm round standard concave punch (Mini Press II-8 Station Compression Machine, Karnavati, Gujarat, India).

Determination of precompression parameters

Angle of repose

The angle of repose of powder blends was determined by the funnel method. Accurately weighed powder blends were taken in a funnel. The top of the funnel was adjusted in such a manner that the grutuity of the funnel just touched the apex of the mound of the powder blends (2 cm). The powder blends were allowed to run through the funnel freely onto its surface the diameter of the powder cone was measured and angle of repose was calculated. Three determinations were performed.

Bulk density and tapped density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. Later the initial volume was regulated, the cylinder was allowed to flow under its own weight onto a hard surface from the elevation of 2.5 cm at 2 s intervals. The tapping was continued until no further alteration in volume was noted. LBD and TBD were calculated. The determination was carried out in triplicate.

Compressibility index and Hausner’s ratio

The compressibility index of the powder blends was determined by Carr’s compressibility index or Carr’s index (CI). Hausner ratio was also determined for each powder blend. Three determinations were done for each formula.

Evaluation of tablets

The prepared matrix tablets were characterized immediately after preparation for hardness, weight variation, thickness, friability and drug content. The weight variation of the tablets was evaluated (n = 20) tablets using an electronic balance (Sartorius GC 103, The Lab World Group, USA). The hardness of the tablets (n = 6) was tested using a Monsanto hardness tester (Campbell Electronics, India). Friability (n = 10) was determined in a Roche friabilator (Campbell Electronics, India) for 4 min at a speed of 25 rpm (Campbell Electronics, India). The thickness of the tablets was measured by Vernier caliper. Drug content was analyzed by measuring the absorbance of standard and samples at λ = 245 nm using UV/visible spectrophotometer (Shimadzu 1601, Kyoto, Japan).
In vitro dissolution of the ER tablets was studied in USP dissolution apparatus II (Electrolab, India) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37°C ± 0.5°C as a dissolution medium. One tablet was used in each trial. Aliquots of 5 ml each were drawn at specified time intervals (1, 2, 3, 4, 8, 16, 20 and 24 h) and replaced with an equal bulk of fresh medium. The withdrawn aliquots were analyzed for drug content spectrophotometrically at λmax 245 nm. Drug concentration was calculated and expressed as a cumulative percent of the drug released.[15,18]

Kinetic data analysis
The drug release kinetic studies of Vildagliptin Extended release tablets were evaluated by applying the linear regression method.
1. Zero order kinetic model – cumulative % of drug released versus T.[16]
2. First order kinetic model – Log cumulative percent drug remaining versus T.[17]
3. Higuchi model – cumulative percent drug released versus the square root of T.[22]

Accelerated stability study
In order to determine the change in evaluation parameters and in vitro release profile on storage, stability study of optimized batch was carried out on accelerated storage condition at temperature 40°C ± 2°C and 75% ± 5% relative humidity (RH) in a humidity chamber for 3 months. The samples were analyzed at 0, 1, 2 and 3 months for physical parameters (description, hardness, thickness and DT), physiochemical parameter (in vitro dissolution study) and chemical parameter (assay).[18,21]

RESULTS AND DISCUSSION

Drug-excipient compatibility
Fourier transform infrared spectroscopy study was carried out to check the compatibility between the drug and natural gums like GG, XG and synthetic polymers like ethyl cellulose used for the preparation of vildagliptin ER matrix tablets. The FT-IR was performed for drug and physical mixture of drug and other excipients. The spectra obtained from FT infrared spectroscopy studies at a wavelength from 4000 cm−1 to 400 cm−1 were shown in Figures 1 and 2 and the characteristic peaks obtained were presented in Tables 2 and 3.

Calibration curve of vildagliptin in pH 6.8 phosphate buffer
Standard graph of vildagliptin in pH 6.8 phosphate buffer was constructed. Concentrations and respective absorbances of vildagliptin were shown in Table 10. Figure 3 shows the calibration curve of vildagliptin in pH 6.8 phosphate buffer.

Preformulation studies
The preformulation studies of the vildagliptin were carried out using the methods that were mentioned in the above paragraph of materials and methods. The results for the formulations can be seen in Table 5.

Postcompression properties
After the compression of the tablets using desired size of punches the tablet properties were checked which were mentioned in the methods in the above paragraph. The results were given in Table 6.
In vitro dissolution studies

The in vitro release from Vildagliptin tablets (F1–F12) in pH 6.8 phosphate buffer for 24 h was presented in Table 7.4. The drug release percentage was calculated by using a formula

$$\text{Percentagedrug release} = \frac{\text{cumulative amount of drugin 900 ml}}{\text{dose of the drug}} \times 100$$

The total values for the release release kinetics of the formulations are given in the Tables 8 and 9.

Accelerated stability studies

The accelerated stability studies were carried out for the vildagliptin tablets for a period of 3 months. The in vitro dissolution studies for the optimized formulation at 40°C temperature and 75% RH was determined and the results were produced in the below Tables 10 and 11.

DISCUSSION

An FT-IR spectroscopy study was extended out to determine the compatibility between the drug and the synthetic polymers HPMC, ethyl cellulose, natural gums like GG, XG used for the preparation of vildagliptin ER matrix tablets. The characteristic peaks of the pure vildagliptin spectrum were present in both the spectra of pure drug and in the blend of tablet composition. The characteristic peak in 3345 cm⁻¹ due to N-H (amine) group present in vildagliptin structure. Elevation is shown at 2919 cm⁻¹ due to O-H (carboxylic acid) group present in vildagliptin and peak shown at 1691 cm⁻¹ was due to C=O (amide) group. No new peaks were observed in a physical mixture of drug and all excipients in spectrum compared to spectrum of pure vildagliptin. These phenomena suggest that in that location was an absence of any chemical interaction between the drug and excipients. The standard calibration curve of vildagliptin in pH 6.8 phosphate buffer was developed observed for their absorbance under UV-spectrophotometer at an absorption maximum of 245 nm. The standard graph of vildagliptin in pH 6.8 phosphate buffer showed a good linearity with $R^2$ of 0.997, and the equation of
the graph is \( y = 0.021x + 0.005 \). The Prepared granules were evaluated for angle of repose, bulk density, tapped density and compressibility index and Hausner’s ratio. The angle of repose was in the range of \( 27^\circ 21' - 35^\circ 13' \) CI was in the range of 10.19–25.88, Hausner’s ratio was in the range 1.09–1.22 for all the 12 formulations which indicates that the prepared granules have good precompression properties.

The weight variation for all the tablets used in this study showed compliance within the official specifications as none of the products deviated by up to 5% of their average weight. In addition, thicknesses of these tablets were found to be uniform. The outcomes of the hardness testing showed that hardness of all tablets was within the range between 5.58 and 6.91 kg/cm\(^2\). Hence, the consequences of the hardness testing for all these formulated tablets of vildagliptin were satisfactory. The friability (%) of all formulated tablets of vildagliptin was found within the range.
of 0.13–0.16 which shows compliance with the official specifications. The uniformity of drug (vildagliptin) present in tablet formulation was found to be between 95.1% and 102.5%. Hence, it was found that all the physicochemical parameters of prepared tablets comply with the standard specifications. In vitro release studies were carried out for all the 12 formulations and results were evaluated for 24 h. Drug release studies were performed using USP apparatus II at a 50 rpm paddle stirring rate. The dissolution media were HCl buffer at pH 1.2 for the first 2 h and phosphate buffer at pH 6.8 for the remaining 22 h maintained 35°C ± 0.5°C. Formulations F1 and F2 employing 20% of XG and GG alone as a rate retarding polymer. These two formulations were released 29% and 27% of the drug at the end of the 1st h, this is due to the presence of high concentration of polymers (20% of the tablet weight) than drug. The highly water soluble drug vildagliptin start dissolving as soon as the tablet comes into contact with the release medium. Hydration and swelling of XG and GG releases the drug up to 12 h; at the end of 12 h both the formulations were released 98% and 95% of the drug after that the drug release was decreased. Decreasing the drug release is due to lower concentration of drug remaining in the dosage form. Based on the above

![Image: In vitro dissolution profile of the optimized formulation at 40°C ± 2°C/75% relative humidity](image)

### Table 5: Micromeritic properties of prepared vildagliptin granules

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose (°)</th>
<th>Bulk density (g/cm³)</th>
<th>Tapped density (g/cm³)</th>
<th>CI (%)</th>
<th>HR</th>
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<tbody>
<tr>
<td>F1</td>
<td>32° 11′±0.23</td>
<td>0.401±0.01</td>
<td>0.453±0.12</td>
<td>11.47±0.21</td>
<td>1.13±0.23</td>
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<tr>
<td>F2</td>
<td>34° 28′±0.15</td>
<td>0.373±0.06</td>
<td>0.433±0.19</td>
<td>13.85±0.13</td>
<td>1.16±0.15</td>
</tr>
<tr>
<td>F3</td>
<td>31° 65′±0.19</td>
<td>0.376±0.02</td>
<td>0.447±0.18</td>
<td>15.88±0.14</td>
<td>1.19±0.13</td>
</tr>
<tr>
<td>F4</td>
<td>29° 45′±0.21</td>
<td>0.379±0.09</td>
<td>0.421±0.12</td>
<td>9.97±0.16</td>
<td>1.11±0.12</td>
</tr>
<tr>
<td>F5</td>
<td>33° 26′±0.26</td>
<td>0.567±0.15</td>
<td>0.681±0.10</td>
<td>16.74±0.22</td>
<td>1.20±0.08</td>
</tr>
<tr>
<td>F6</td>
<td>31° 43′±0.21</td>
<td>0.320±0.06</td>
<td>0.355±0.15</td>
<td>9.85±0.13</td>
<td>1.11±0.13</td>
</tr>
<tr>
<td>F7</td>
<td>35° 13′±0.19</td>
<td>0.354±0.11</td>
<td>0.422±0.11</td>
<td>16.11±0.12</td>
<td>1.19±0.19</td>
</tr>
<tr>
<td>F8</td>
<td>34° 17′±0.21</td>
<td>0.348±0.07</td>
<td>0.425±0.09</td>
<td>18.11±0.17</td>
<td>1.22±0.12</td>
</tr>
<tr>
<td>F9</td>
<td>30° 12′±0.13</td>
<td>0.450±0.03</td>
<td>0.513±0.13</td>
<td>12.28±0.14</td>
<td>1.14±0.13</td>
</tr>
<tr>
<td>F10</td>
<td>27° 43′±0.11</td>
<td>0.540±0.03</td>
<td>0.589±0.08</td>
<td>8.31±0.10</td>
<td>1.09±0.08</td>
</tr>
<tr>
<td>F11</td>
<td>34° 43′±0.23</td>
<td>0.401±0.04</td>
<td>0.453±0.12</td>
<td>11.23±0.15</td>
<td>1.13±0.21</td>
</tr>
<tr>
<td>F12</td>
<td>33° 26′±0.15</td>
<td>0.446±0.05</td>
<td>0.500±0.11</td>
<td>10.08±0.17</td>
<td>1.12±0.13</td>
</tr>
</tbody>
</table>

CI: Carr’s index, HR: Hausner’s ratio

### Table 6: Physicochemical properties of vildagliptin ER tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Weight (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Thickness (mm)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>400.54±1.28</td>
<td>5.63±0.42</td>
<td>0.13±0.37</td>
<td>5.45±0.02</td>
<td>95.6±2.45</td>
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<tr>
<td>F2</td>
<td>400.05±1.12</td>
<td>5.85±0.65</td>
<td>0.12±0.36</td>
<td>5.67±0.03</td>
<td>96.2±0.72</td>
</tr>
<tr>
<td>F3</td>
<td>400.15±1.10</td>
<td>6.91±0.34</td>
<td>0.14±0.25</td>
<td>5.01±0.08</td>
<td>98.4±3.4</td>
</tr>
<tr>
<td>F4</td>
<td>400.59±1.29</td>
<td>6.58±0.49</td>
<td>0.13±0.42</td>
<td>5.71±0.06</td>
<td>102.5±3.01</td>
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<tr>
<td>F5</td>
<td>400.00±0.92</td>
<td>6.11±0.36</td>
<td>0.16±0.23</td>
<td>5.13±0.10</td>
<td>96±3.51</td>
</tr>
<tr>
<td>F6</td>
<td>399.91±1.33</td>
<td>5.58±0.53</td>
<td>0.11±0.34</td>
<td>5.41±0.07</td>
<td>96.2±0.25</td>
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<tr>
<td>F7</td>
<td>399.61±1.47</td>
<td>6.45±0.49</td>
<td>0.12±0.64</td>
<td>5.50±0.06</td>
<td>95.1±3.03</td>
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<tr>
<td>F8</td>
<td>401.35±1.37</td>
<td>6.63±0.54</td>
<td>0.13±0.59</td>
<td>5.65±0.06</td>
<td>97.5±3.01</td>
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<tr>
<td>F9</td>
<td>399.57±1.30</td>
<td>6.63±0.48</td>
<td>0.15±0.32</td>
<td>5.35±0.08</td>
<td>99.4±1.42</td>
</tr>
<tr>
<td>F10</td>
<td>400.04±1.10</td>
<td>6.52±0.34</td>
<td>0.12±0.54</td>
<td>5.30±0.02</td>
<td>99.5±2.35</td>
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<tr>
<td>F11</td>
<td>400.05±1.17</td>
<td>6.29±0.52</td>
<td>0.15±0.35</td>
<td>5.03±0.12</td>
<td>94.3±3.01</td>
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<tr>
<td>F12</td>
<td>400.05±1.16</td>
<td>6.35±0.34</td>
<td>0.12±0.42</td>
<td>5.40±0.04</td>
<td>95.1±0.75</td>
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ER: Extended release

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result, we conclude these two gums alone were not suitable in controlling the release of the drug up to 24 h; the reason may be due to the rapid uptake of water by the hydrophilic gums for rapid release. Formulation F3 containing mixture of both the gums in the percentage of 10% of XG and 20% of GG and in the formulation F4, 15% of XG and 20% of GG. The combination of these two gums led the release further 4 h as compared with previous formulations (F1 and F2) at the end of 16 h both the formulations were released 98% and 96% of the drug. It has been reported earlier that guar and XGs have a synergistic effect when used together in a blend, which increases the viscosity of the medium may be the reason for extending the release further 4 h. In the present investigation, formulation F5 has (20% ethyl cellulose) 100cps alone as a release retarding polymer. It has been observed that higher viscosity grade of EC has affected drug release greatly in 0.1 N HCl (initial 2 h) only 30% drug released at the end of 2 h. However, in the phosphate buffer vildagliptin release was independent of viscosity of polymer. At the end of 12 h 92% of the drug were released and it has been reported earlier that 30% w/w of any viscosity grade EC have shown extended drug release over a longer period of time compared to tablets containing EC at lower content.\textsuperscript{[1,22]} This dissolution profile reveals that 20% of EC is not sufficient to extend the drug release up to 24 h. Formulations F6 HPMC K4M used as a ER polymer and it sustained the release of vildagliptin for over 12 h. It has been reported that a 20% w/w level of HPMC achieved the target sustained release profile, 35% \pm 15% in the first 2 h of the release study, for a water soluble drug.\textsuperscript{[2,23]} The formulation F6 has HPMC at 20% w/w in the tablet and it released 36%
of the drug at the end of the 2nd h. Up to 2nd h the drug release was similar to previous formulations this may be due to the thick gel structure of swollen polymer. The swelling of the polymer develops gel structure which makes a slower drug release. In the 4th h the gel was starting to erode and caused the tablet to break into pieces, which makes a faster release of drug finally at the end of 12 h 99% of the drug were released. Formulation batch F7 and F8 containing 10% of EC and 20% HPMC K4M vice versa. These two formulations extending the drug release up to 16 h indicating fair, uniform drug release throughout the dissolution study. Increasing and decreasing the concentration of ethyl cellulose and HPMC polymers does not influence of drug release pattern. Almost 95% of the drug were released at the end of 16 h from both the formulations. These 8 formulations (F1–F8) were extended the drug release 12–16 h only. Thus a combination of synthetic polymers and natural gums were used for further studies. Formation batch F9 employing 30% of XG and 10% of ethyl cellulose polymer blend for ER vildagliptin tablets. This formulation was released only 24% of the drug at the end of 2 h. When these two polymers were used separately (F1 and F5) release was extended up to 12 h but the blend of these two polymers extends the drug release up to 20 h the drug release rate depended on these two polymers. Incorporation of 10% ethyl cellulose into 30% of GG in F10 formulation extended drug release up to 24 h and 99% of the drug were released. This may be attributed to decreased the penetration of dissolution fluid in the presence of the hydrophobic ethyl cellulose into hydrophilic gum, leading to reduced diffusion of the drug from the matrix. Drug release from F11 and F12 batch tablets were controlled by blends of XG, HPMC and GG, HPMC respectively. When used separately all these three polymers controlled the drug release up to 12 h only (F1, F2 and F5) The faster release may be due to the low percentage of rate retarding polymers present in these formulations and the drug present at near the surface. The addition of GG with HPMC and XG with HPMC may create viscous thick gel structure around the drug this could be the reason to extend the release up to 20 h. Based on all the formulation dissolution studies, we concluded the combination of hydrophilic and hydrophobic polymers are best to extend the highly aqueous soluble drug like vildagliptin than the individual. Hence, formulation F10 with 30% GG and 10% ethyl cellulose was found to be most promising formulation and maintained excellent matrix integrity during the 24 h study period, thus selected as the optimized formulation. The drug release kinetic data of vildagliptin ER is shown in Table 5 and graphs are mapped in Figures 5-9. From the graphical representation it can be inferred that this is a best fit in to Higuchi model which had shown a Regression coefficient ($R^2$) of 0.988. The results of the in vitro release data of these were fitted to the Korsmeyer–Peppa’s equation to analyze the release pattern of the drug from the polymeric system. The value of “n” was found to be more than 0.89, indicating the drug release follows super case II transport. The optimized tablets from batch F10 were charged for stability studies at 40°C and 75% RH. There was no change in physical appearance, color. The formulations were analyzed for the period of 3 months for general tablet properties such as weight variation, thickness, hardness, friability, drug content and in vitro dissolution studies. Tablets have shown no much deviation in hardness, friability values. The average drug content of the tablets was found to be 99.5% ± 0.05%. The in vitro dissolution profile of optimized formulation has demonstrated no substantial change in the discharge rate of the drug in the period of 3 months. It indicates good stability of vildagliptin ER tablets (F10). This shows that the vildagliptin tablets are suitable for the manufacturing as a tablet without any problems as a sustained release formulation.

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<td>0.14</td>
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<tr>
<td>Drug content (%)</td>
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RH: Relative humidity
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REFERENCES


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