DESIGN AND OPTIMIZATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM OF SITAGLIPTIN

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ABSTRACT: In the present study, Gastro retentive floating drug delivery systems (GFDDS) of sitagliptin, an anti diabetic drug, have been designed to increase the therapeutic efficacy & gastric residence time and to reduce frequency of administration. Therefore a sustained release medication was advantageous so as to achieve the prolonged therapeutic effect and to reduce peak and valley effect in plasma concentration. This can be achieved by formulating modified gastro retentive sustained release dosage forms which resides in the stomach for sufficient time to release the drug in vicinity of the absorption zone. The tablets were prepared by direct compression method, by employing polymers like HPMCK100, Poly vinyl pyrrolidine and polyacrylic acid respectively in various concentrations. The prepared granules were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner’s ratio and results obtained were satisfactory compressed formulations were further evaluated for thickness, friability, hardness, swelling index and in-vitro dissolution studies. All the formulations showed good results which were compliance with pharmacopoeial standards. In vitro dissolution study was carried out in pH 1.2 buffers. From in vitro dissolution studies, the cumulative % drug release of all formulations ranged from 92.96% – 99.28% at the end of 12 hrs. The in vitro drug release data was fitted into various mathematical model.

INTRODUCTION: High level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of the dosage form. A lot of advancements have been seen in oral sustained drug delivery system in the last few decades. But still oral sustained drug delivery system is complicated by limited gastric residence time. Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine. To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract like floating drug dosage systems (FDDS). Gastroretentive systems can remain in the gastric region for several hours and hence can significantly prolong the gastric residence time of drugs that offer numerous advantages; improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment of small intestine.

The main objective of the study is to formulate Gastroretentive dosage forms (GRDFs) of sitagliptin in order to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has
generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome. Gastroretentive dosage form (GRDFs) are designed on the basis of various approaches like, formulating high density (sinking) system that is retain in the bottom of the stomach, low density (floating) system that remain buoyant above gastric fluid, mucoadhesive system that cause bioadhesion to stomach mucosa, expandable, unflodable or swellable system which limits the emptying of dosage form through the pyloric sphincter of stomach, super porous hydrogels magnetic systems etc.

The gastroretentive tablets results in release of the drug in to the more absorptive regions of the GIT, in to the stomach and the small intestine rather than into the large intestine where drug absorption is poor or erratic. This is achieved by adjusting the time period of release for the drug so that it is about the same as or less than the retention time of the tablets at the site of absorption. Thus the system is not transported past the “absorption window” prior to releasing the entire drug, and the maximum bioavailability is attained. Sitagliptin is (R)-4-oxo-4-[3-(trifluromethyl)-5,6- dihydro [1,2,4] triazolo[4,3-a] pyrazin -7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine. Sitagliptin blocks dipeptidyl peptidase-4 (DPP-4) activity and it increasesincretin levels (GLP-1 and GIP) which inhibit glucagon release, in turn decreases blood glucose, but more significantly increases insulin secretion. Sitagliptin is for people with type-II diabetes (non-insulin-dependent) and sometimes used in combination with other diabetes medications, but is not for treating type-I diabetes.

In the present study Gastro retentive drug delivery system containing Sitagliptin was formulated which would remain in stomach for prolonged period of time in view to maximize bioavailability of the drug and increased patient compliance.

**MATERIALS AND METHODS:**

**Materials:**
Sitagliptin as gift sample from DR Reddy’s Laboratories, India, polymers from Hi Media Laboratories Pvt. Ltd, Mumbai, India, All the other materials used were of analytical grade.

**Pre-Compression Parameters:**
The various Pre-compression parameters are Angle of repose, Bulk density, Tapped density, compressibility index, Hausner’s ratio and Carr’s index were studied.

**Bulk Density (Db):**
It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in G/CC and is given by

\[
Db = \frac{\text{Mass powder}}{\text{Volume}}
\]

**Tapped density (Dt):**
It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in G/CC and is given by

\[
Dt = \frac{M}{V_t}
\]

Where, M - Mass of the powder

\[V_t = \text{Tapped volume of the powder}\]

**Angle of Repose:**
The accurately weighed quantities of granules were taken in to funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the granules. The granules were allowed to flowfreely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the formula.

\[
\tan(\theta) = \frac{h}{r}
\]

Where h and r are the height and radius of the powder cone.

**Carr’s index (I) & Hausner’s ratio:**
Carr’s index and Hausner’s ratio measure the propensity of granule to be compressed and the flow ability of granule. Carr’s index and Hausner’s ratio were calculated using following formula.

\[
C.I = \frac{(Dt – Db)100}{Dt}
\]

Where, \(Dt – \text{Tapped density of the powder}\)

\(Db – \text{Bulk density of the powder}\)
Preparation of Sitagliptin tablets by direct compression method:
All the ingredients were passed through sieves separately and weighed as per the formula given in Table 1. Weighed ingredients were transferred into polythene bag and mixed for 15 minutes. After mixing thoroughly the powder is subjected for compression. The powder was evaluated for various pre-compression parameters like bulk volume, tapped volume, bulk density, tapped density and angle of repose. After compression they were evaluated for appearance, diameter, tablet weight, thickness, hardness, and friability, uniformity of dispersion, weight variation, and content uniformity. The in vitro dissolution profile and stability studies were also carried out 4.

TABLE 1: FORMULATIONS CONTAINING & VARIOUS CONCENTRATIONS OF EXCIPIENTS

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC K100M</td>
<td>25</td>
<td>25</td>
<td>50</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Sodiumbicarbonate</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>MagnesiumStearate</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
</tr>
<tr>
<td>Talc</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
</tr>
<tr>
<td>Lactose</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

Evaluation of sitagliptin controlled release tablets:
The matrix tablets prepared were evaluated for the following parameters:

Weight Variation Test:
To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Hardness and Friability:
For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India) respectively.

Drug Content:
Five tablets were weighed and triturate, from that transfer an accurately weighed portion of the powder equivalent to about 100mg of sitagliptin in a 100ml volumetric flask containing buffer solution and then concentration is measured at λ max 271 nm.

In-Vitro Dissolution Studies:
The in-vitro dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm. The dissolution medium consisted of 900ml of phosphate buffer pH 6.8, maintained at 37±0.50C. An aliquot (5ml) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrometer at 271nm. The study was performed in triplicate.

Kinetic Analysis
The results of in-vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

Zero- order Kinetic model – Cumulative % drug released versus Time.
First- order Kinetic model – Log cumulative % drug remaining versus Time.
Higuchi’s model- Cumulative percent drug released versus square root of time.
Korsmeyer equation / Peppa’s model- Log cumulative percent drug released versus log time.

Stability Studies:
Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications throughout its shelf life.
**Method:**
The optimized formulation was subjected for two month stability study according to ICH guidelines. The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were then stored at 40°C / 75% RH for 2 months. Then samples were evaluated for their content and *in vitro* dissolution studies.

**RESULTS AND DISCUSSIONS:**

**FT-IR Analysis:**
The compatibility studies revealed both drugs and excipients were compatible after FT IR studies, the results shown in Fig. 1.

![FTIR Studies of Drug and Excipients](image1)

**Pre-compression evaluation parameters:**
For each type of formulation the active pharmaceutical ingredients and excipients was formulated and evaluated for various pre-compression parameter as explained earlier. The Bulk density was found in the range of 0.286 to 0.439 G/CC and the tapped density was found to be in the range of 0.338 to 0.514 G/CC. Using the above two density data, the Carr’s compressibility index were calculated, the compressibility index was found to be in the range of 11.69 to 21.09%. The compressibility and flow ability data indicated good flow properties for all the blended formulation. The better flow property of all powder blends was also evident from angle of repose. The angle of repose was range of 16.04 to 21.04°. Angle of repose below 30° indicates good flow property. In the present study all powder blends showed good flow property. The results are shown in the Table 2.
TABLE 2: PRE-COMPRESSION PARAMETERS

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk Density G/CC</th>
<th>Tapped Density G/CC</th>
<th>Compressibility Index %</th>
<th>Angle of Repose °</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.31±0.094</td>
<td>0.408±0.120</td>
<td>14.64±0.03</td>
<td>20.96±0.04</td>
</tr>
<tr>
<td>F2</td>
<td>0.28±0.011</td>
<td>0.341±0.034</td>
<td>12.14±0.094</td>
<td>17.64±0.067</td>
</tr>
<tr>
<td>F3</td>
<td>0.338±0.074</td>
<td>0.392±0.069</td>
<td>17.89±0.065</td>
<td>16.93±0.051</td>
</tr>
<tr>
<td>F4</td>
<td>0.29±0.089</td>
<td>0.338±0.091</td>
<td>16.72±0.074</td>
<td>18.14±0.079</td>
</tr>
<tr>
<td>F5</td>
<td>0.30±0.093</td>
<td>0.416±0.113</td>
<td>14.51±0.093</td>
<td>21.04±0.084</td>
</tr>
<tr>
<td>F6</td>
<td>0.41±0.112</td>
<td>0.495±0.108</td>
<td>11.69±0.034</td>
<td>20.19±0.099</td>
</tr>
<tr>
<td>F7</td>
<td>0.43±0.107</td>
<td>0.514±0.072</td>
<td>19.47±0.107</td>
<td>17.59±0.021</td>
</tr>
<tr>
<td>F8</td>
<td>0.326±0.099</td>
<td>0.396±0.074</td>
<td>20.14±0.099</td>
<td>18.69±0.044</td>
</tr>
<tr>
<td>F9</td>
<td>0.319±0.094</td>
<td>0.372±0.043</td>
<td>21.09±0.102</td>
<td>16.04±0.042</td>
</tr>
</tbody>
</table>

Post-Compression evaluation parameters:

Weight Variation:
All the formulations were evaluated for their uniformity of weight according to the procedure and they show maximum weight of 200.8 mg in F5 and the minimum weight of 199.4 mg in F9 formulations were observed. The maximum allowed percentage weight variation for tablets 200 mg by Indian pharmacopoeia is 7.5%, and no formulations were exceeded the limit. Thus all the formulations were found to be complying with the given standards, and the results are shown in Table 3.

Hardness:
All the tablet formulations were evaluated for their hardness as per procedure and all the formulations have an average hardness in the range 5.5±0.07 Kgm/cm² and 5.3±0.009 Kgm/cm². Which was found to be acceptable and the results are shown in the Table 3.

Friability:
The Gastro retentive tablets were evaluated for their percentage friability as per the standards the average percentage friability for all the formulations were found to be 0.299% to 0.899%, which is observed to be within the limit as per the standard and the results were tabulated in the Table 3.

Drug Content:
All the formulations were evaluated for their uniformity of drug content according to the procedure to determine the amount of drug in all the formulation. The percentage of drug was found to be in the range of 91.09 to 98.07% w/w. The maximum drug content of 98.07% w/w for F4 and the minimum of 91.09% w/w for F2 formulations was observed. The results are tabulated in the Table 3.

TABLE 3: POST COMPRESSION PARAMETERS

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight Variation (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>199.5±0.046</td>
<td>5.5±0.07</td>
<td>0.299±0.014</td>
<td>94.24±0.069</td>
</tr>
<tr>
<td>F2</td>
<td>199.6±0.074</td>
<td>5.0±0.143</td>
<td>0.461±0.079</td>
<td>91.09±0.014</td>
</tr>
<tr>
<td>F3</td>
<td>200.4±0.084</td>
<td>5.4±0.074</td>
<td>0.341±0.096</td>
<td>93.08±0.056</td>
</tr>
<tr>
<td>F4</td>
<td>200.1±0.104</td>
<td>5.9±0.007</td>
<td>0.286±0.0074</td>
<td>98.07±0.074</td>
</tr>
<tr>
<td>F5</td>
<td>200.8±0.096</td>
<td>5.1±0.139</td>
<td>0.490±0.0014</td>
<td>98.48±0.089</td>
</tr>
<tr>
<td>F6</td>
<td>199.9±0.034</td>
<td>5.4±0.079</td>
<td>0.578±0.0019</td>
<td>94.57±0.015</td>
</tr>
<tr>
<td>F7</td>
<td>200.6±0.097</td>
<td>5.6±0.094</td>
<td>0.699±0.034</td>
<td>98.07±0.045</td>
</tr>
<tr>
<td>F8</td>
<td>199.8±0.067</td>
<td>5.1±0.047</td>
<td>0.786±0.047</td>
<td>92.94±0.036</td>
</tr>
<tr>
<td>F9</td>
<td>199.4±0.024</td>
<td>5.3±0.009</td>
<td>0.899±0.0014</td>
<td>98.06±0.047</td>
</tr>
</tbody>
</table>

In-vitro drug release studies:
The drug release pattern was studied for all the formulations for 12 hours by using paddle type dissolution apparatus in both simulated gastric fluid and intestinal fluid of pH (1.2) & (6.8) respectively. The percentage cumulative drug release profile was found to be in the range of 92.9% to 99.28%. The maximum release was found to be 99.28% from F9 and minimum release of 92.9% in F5 formulation. From the above studies it was concluded that the formulation F5 & F9 containing HPMC K100M, poly vinyl pyrrolidone and Polyacrylic acid with increasing concentration has shown maximum release when compared to
other formulation. The results are shown in the Fig.2.

![Graph showing release kinetics](image)

**FIG. 2: IN-VITRO RELEASE STUDIES**

Release kinetics:
The examination of the correlation coefficient ‘r’ indicated that the drug release followed dissolution controlled mechanism from the cumulative drug release, as the values of ‘r’ for first order (ranged from 0.9591 to 0.9842) found to be more in comparison to zero order (ranged from 0.9282 to 0.9438) and Higuchi’s square root of time (ranged from 0.9390 to 0.9770). It was understood to be predominant first order release pattern. Further, to understand the drug release mechanism, the data were fitted into Peppas exponential model $M_t/M_\infty = Kt^n$, where $M_t/M_\infty$ is the fraction of drug released after time ‘t’ and ‘K’ is kinetic constant and ‘n’ is release exponent which characterizes the drug transport mechanism.

The values ‘n’ were in the range of 0.2951 to 1.7016. The formulation F2 indicating fickian release mechanism (‘n’ values are less than 0.45) and the other formulations like F1, F3, F4, F5, F6, F7, F8 and F9 is following super II release (‘n’ values are more than 0.89).

Stability study:
The selected formulation F5 and F9 were subjected to accelerated stability studies for 60 days at 25ºC / 60% RH, 30ºC / 65% RH, 40ºC / 75% RH, in-vitro release study was performed on every 30 days and showed negligible change in release profile. The formulation subjected for stability studies was found to have no change in the physical appearance and drug content. The result is shown in the Table 4.

<table>
<thead>
<tr>
<th>Sl No.</th>
<th>Time</th>
<th>Drug content (%)</th>
<th>Cumulative drug release (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$F_3$</td>
<td>$F_4$</td>
</tr>
<tr>
<td>1</td>
<td>1 Month</td>
<td>98.01</td>
<td>97.89</td>
</tr>
<tr>
<td>2</td>
<td>2 Month</td>
<td>97.79</td>
<td>97.02</td>
</tr>
<tr>
<td>3</td>
<td>3 Month</td>
<td>97.12</td>
<td>96.99</td>
</tr>
</tbody>
</table>

**TABLE 4: STABILITY STUDIES**

CONCLUSION: From the above study it can be concluded that the polymer plays a major role in the design of oral controlled release of gastro retentive tablet. The study reveals that the release of drug was good when the gastro retentive tablet contained polymers of Poly vinyl pyrolidone and Poly acrylic acid and also shows anomalous diffusion kinetics. Hence it clearly manifestates the necessity of combining different classes of polymer to get an acceptable pharmacokinetic profile in the fluctuating in-vivo environment.

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