FORMULATION, DEVELOPMENT AND IN VITRO EVALUATION OF IMMEDIATE RELEASE TABLET OF SITAGLIPTIN PHOSPHATE MONOHYDRATE.

Wale Kiran K*, Dr. Salunkhe K.S., Sayyed S.F., Dr. Chaudhari S.R., Santosh Bhujbal

1Amrutvahini College of Pharmacy Sangamner, Ahmednagar, Maharashtra, India.

ABSTRACT

The pivotal motif of the present research work is to develop immediate release tablet of sitagliptin phosphate monohydrate. The rate of dissolution and bioavailability of the sitagliptin phosphate monohydrate may be increased by using superdisintegrant in its immediate release tablets. This investigation is undertaken with an aim to develop pharmaceutically equivalent, stable, cost effective and quality improved formulation of sitagliptin phosphate monohydrate immediate release tablets. Wet granulation method was adapted to prepare the sitagliptin phosphate monohydrate immediate release tablets by using microcrystalline cellulose, lactose as diluents, crospovidone and sodium starch glycolate as superdisintegrant in different concentration (2-8%) to prepare (S1-S9) batches. Tablet where prepared and evaluated for hardness, friability, weight variation, content uniformity, disintegration time and in-vitro drug release. Among all the formulations S1 to S9, formulation S8 disintegrated in 303 sec. in-vitro dissolution study of immediate release tablet was done in USP type II along with UV spectrophotometer gave cumulative % drug release of sitagliptin phosphate 99.98% at 50 Min. From the study it was found that combination of high concentration crospovidone and low concentration of sodium starch glycolate good disintegration of sitagliptin phosphate tablet.

Keywords:- sitagliptin phosphate monohydrate, SSG, PVP K-30, superdisintegrant.
INTRODUCTION
In the present research and study novel drug delivery systems are developed for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. The development of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights. Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of ineffective therapy.

Sitagliptin phosphate monohydrate is used to treat type – II diabetes mellitus. Incretins, a gastrointestinal hormone, inhibits glucagon release from alpha cells and slow the absorption of nutrients into blood stream and further causes an increase in the amount of insulin release from beta cells. DPP4 is enzyme which inhibits incretins which lead to increase levels of glucose in the body. Sitagliptin phosphate monohydrate decrease blood glucose level by inhibiting the enzyme DPP4 so blood glucose level falls to normal.

In the present study an attempt has been made to prepare immediate release tablets of Sitagliptin phosphate monohydrate by using different superdisintegrants (crospovidone, sodium starch glycloate) to increase the rate of drug release from dosage form or the dissolution rate and hence its bioavailability.

MATERIALS AND METHODS
Sitagliptin phosphate monohydrate, crospovidone, sodium starch glycloate, was gifted from glenmark pharma nashik. Lactose anhydrous, Povidone K-30, Magnesium steate,
microcrystalline cellulose from Loba Chemie, Nashik. All other chemicals used in the formulation were of analytical grade.

**Evaluation of Powder Blend**

**Angle Of Repose (θ)**

The blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

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

Where, \( h \) = height of pile; \( r \) = radius of pile

**Bulk Density**

It is the ratio of total mass of powder to the bulk volume of powder. Bulk volume was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial volume was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by

\[ \text{Bulk density} = \frac{M}{V_b} \]

Where, \( M \) and \( V_b \) are mass of powder and bulk volume of the powder respectively.

**Tapped Density**

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 500 times and the tapped volume was noted. It is expressed in gm/ml and is given by

\[ \text{Tapped density} = \frac{M}{V_t} \]

Where, \( M \) and \( V_t \) are mass of powder and tapped volume of the powder respectively.

**Carr’s index (or) % compressibility**

It indicates powder flow properties. It is expressed in percentage and is given by

\[ \text{C.I.} = \left( \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \right) \times 100 \]
Hausner ratio
Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula.

Table 1: Composition of Formulation of Immediate Release Tablet of an Sitagliptin phosphate monohydrate.

<table>
<thead>
<tr>
<th>Ingredients (mg per tab.)</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
<th>S6</th>
<th>S7</th>
<th>S8</th>
<th>S9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin phosphate monohydrate</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>crospovidone</td>
<td>16</td>
<td>8</td>
<td>-</td>
<td>16</td>
<td>16</td>
<td>8</td>
<td>-</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>8</td>
<td>-</td>
<td>8</td>
<td>-</td>
<td>16</td>
<td>8</td>
<td>16</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>PVP k-30</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>lactose</td>
<td>70</td>
<td>86</td>
<td>86</td>
<td>77</td>
<td>61</td>
<td>77</td>
<td>77</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</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>

Hausner ratio = Tapped Density / Bulk Density

FTIR Spectroscopy Study
Sitagliptin phosphate, Excipient and their combination were analyzed by FTIR spectroscopy studies were conducted and the spectrum was recorded in the wavelength region of 4000 to 400 cm⁻¹ sample was placed in the light path and the spectrum was obtained. The peaks of pure drug are checked with drug-excipient combination graphs.

Preparation of immediate release tablets of Sitagliptin phosphate monohydrate
Sitagliptin immediate release tablets were prepared by wet Granulation method. Sitagliptin and other excipients like pre microcrystalline cellulose, crospovidone, sodium starch glycolate, polyvinyl pyrrolidone k 30 were sifted through sieve no 40 #. The wet granulate is prepared by adding the liquid binder–adhesive to the powder blend and mixing thoroughly. Screening the damp mass through a mesh to form pellets or granules. Drying the granulation. A conventional tray-dryer or fluid-bed dryer are most commonly used. After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size. Above mixture was lubricated for 2 min with magnesium stearate which was already passed through sieve 60. Finally collect the blend for compressing...
the tablet with 8.00mm concave shaped punches in a 8 Station Tablet Rotatory Machine (Jaguar- JM-D-4-8). The composition of each formulated tablets are shown in Table 1

Evaluation of immediate release tablets of sitagliptin phosphate

Uniformity of weight
Twenty tablets were taken and their weight was determined individually and collectively on digital weighing balance. The average weight of one tablet was determined from the collective weight.

Friability
The friability of sample of six tablets were measured using a Roche Friabilator. Six pre-weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fine's using 60 mesh screen and the percentage of weight loss was calculated.

\[
\% \text{ Friability} = \left( \frac{\text{Loss in weight}}{\text{Initial weight}} \right) \times 100
\]

Hardness
Hardness was determined by taking six tablets from each formulation, using a Monsanto Hardness Tester.

Wetting time
A piece of paper folded twice was kept in a Petri dish (internal diameter 5.5 cm) containing 6 ml of purified water. A tablet having a small amount of Rosaline dye powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded as the wetting time.

Disintegration time
Disintegration time was measured in distilled water according to the USP method at 37 ± 0.5oC temperature. The disintegration time of 6 individual tablets were recorded and the average was reported.

Content uniformity
To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. To perform the test, 10 tablets were crushed using mortar and pestle. Quantity equivalent to 100 mg of drug was dissolved in 100 ml 0.1N HCL, filtered and diluted up to 50µg/ml, and analyze spectrophotometrically at 267nm. The concentration of drug was determined using standard calibration curve.
Dissolution study

*In vitro* release of sitagliptin phosphate monohydrate from tablets was monitored by using 900 ml of 0.1 N HCL, at 37±0.5° and 50 rpm using programmable dissolution tester USP II. Aliquots of 10 ml were withdrawn from the dissolution apparatus at time intervals of 5, 10, 20, 30, 40, 50, 60…min and the samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 267 nm. The percent drug release was calculated using the calibration curve of the drug in 0.1 N Hydrochloric acid.

**RESULT AND DISCUSSION**

Immediate release drug delivery system is also conventional type of drug delivery system with several advantages such as release the drug immediately, more flexibility for adjusting the dose, no dose dumping problem, used in initial stage of disease, the drug is released at particular site from the system and shows its action. In present study, attempt was made to prepare such a tablet for reducing the sleep-wake disorders and the drug was selected for the study from the category of anti-diabetic on the basis of immediate action.

**Flow Properties of Blend**

Nine formulations was prepared by using wet granulation method, with different excipients like Lactose anhydrous, Povidone k-30, Croscarmellose sodium, sodium starch glycloate, Microcrystalline cellulose, and Magnesium steate. Blend of drug and excipients were evaluated for various parameters as follows.

**Angle of repose**

The angle of repose of six batches was found to be below 38, which indicated the blend having Excellent flow property. Angle of repose was found in the range of 30-38.37 (θ) the results was given in Table 2.

**Bulk density**

The bulk density of various granules blends were measured by graduated cylinder. The bulk density was found in the range 0.270-0.350 g/ml the results in Table 2.

**Tapped density**

The tapped density of various granules blends was determined by using measuring cylinder. The tapped density was found in the range of 0.0310-0.407 g/ml the results are given in Table 2.
Hausner’s ratio and Compressibility

The Hausner’s ratio and Compressibility of various granules blends was calculated by using bulk density and tapped density data. The compressibility index was found in the range 14.37–30.84%. The Hausner’s ratio was found in the range 1.224-1.418. The results are given in Table 2. The Compressibility and Hausner’s ratio of all batches were calculated. On the basis of batches S1-S9 will have to passable.

All flow properties of blend values indicated a fairly good flowability of powder mixture.

Flow properties of formulations(S1-S9)

Table no. 2 Flow properties of formulations(S1-S9)

<table>
<thead>
<tr>
<th>formulation</th>
<th>Angle of repose(θ)</th>
<th>Bulk density (gm/ml)</th>
<th>Tapped density (gm/ml)</th>
<th>% compressibility</th>
<th>Hausner’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>34.43</td>
<td>0.2955</td>
<td>0.344</td>
<td>19.917</td>
<td>1.36</td>
</tr>
<tr>
<td>S2</td>
<td>38.04</td>
<td>0.290</td>
<td>0.385</td>
<td>24.67</td>
<td>1.32</td>
</tr>
<tr>
<td>S3</td>
<td>33.69</td>
<td>0.314</td>
<td>0.407</td>
<td>29.61</td>
<td>1.292</td>
</tr>
<tr>
<td>S4</td>
<td>35.83</td>
<td>0.290</td>
<td>0.356</td>
<td>18.53</td>
<td>1.227</td>
</tr>
<tr>
<td>S5</td>
<td>40.85</td>
<td>0.272</td>
<td>0.33</td>
<td>10.41</td>
<td>1.224</td>
</tr>
<tr>
<td>S6</td>
<td>33.69</td>
<td>0.295</td>
<td>0.383</td>
<td>22.97</td>
<td>1.298</td>
</tr>
<tr>
<td>S7</td>
<td>35.83</td>
<td>0.282</td>
<td>0.400</td>
<td>29.9</td>
<td>1.418</td>
</tr>
<tr>
<td>S8</td>
<td>37.87</td>
<td>0.273</td>
<td>0.344</td>
<td>20.63</td>
<td>1.260</td>
</tr>
<tr>
<td>S9</td>
<td>33.34</td>
<td>0.274</td>
<td>0.320</td>
<td>14.37</td>
<td>1.347</td>
</tr>
</tbody>
</table>

FTIR Compatibility Studies:

Spectrum of Sitagliptin monohydrate phosphate

![Fig.no.1 Spectrum of Sitagliptin monohydrate phosphate](image)
Details of the peaks of sitagliptin IR spectrum

Table no.3 Details of the peaks of sitagliptin IR spectrum

<table>
<thead>
<tr>
<th>Functional group</th>
<th>Vibrational Frequencies cm⁻¹</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed peaks</td>
<td>Reported peaks</td>
</tr>
<tr>
<td>C-F str</td>
<td>1018.45 cm⁻¹</td>
<td>1016.34 cm⁻¹</td>
</tr>
<tr>
<td>C = O str</td>
<td>1637.62 cm⁻¹</td>
<td>1635.50 cm⁻¹</td>
</tr>
<tr>
<td>N tertiary amine str</td>
<td>1066.71 cm⁻¹</td>
<td>1068.45 cm⁻¹</td>
</tr>
<tr>
<td>AR – CH str</td>
<td>3050.52 cm⁻¹</td>
<td>3047.42 cm⁻¹</td>
</tr>
<tr>
<td>C =NH str</td>
<td>3323.46 cm⁻¹</td>
<td>3320.65 cm⁻¹</td>
</tr>
</tbody>
</table>

Spectrum of Sitagliptin and Excipients

Evaluation of sitagliptin phosphate monohydrate Immediate Release Tablets

The prepared tablets were subjected or evaluated to various parameters as follows.

Weight variation

All the formulation were varied from 198.5-201.5 mg with minimum standard deviation values indicate that the uniform distribution of excipients and drug in the tablets. The results are given in Table 4.
**Thickness**

The tablets from 3.4-3.5mm in thickness with minimum standard deviation values, it assumed that the tablets show uniformity in thickness. The results are given in Table 4

**Hardness**

The hardness of the tablets was found to be 2.5-3.2Kg/cm². The hardness of tablet varied although compression force was constant. This may be due to the increased concentration of the excipient in formulations. The results are given in Table 4

**Friability**

The friability of the tablets was found to be 0.1-1.09%. The results are given in Table 4

**Disintegration Time**

The disintegration time of the tablet was found to be 129-610. The results are given in Table 4

**Drug Content**

Drug content in the tablets was the limit of 97.5-101.5%. The results are given in Table 4

**Evaluation of Immediate release tablets (S1-S9) table no 4**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Average Weight variation mg (n=20)</th>
<th>Hardness Kg/cm² (n=3)</th>
<th>Thickness mm (n=3)</th>
<th>Friability % (n=20)</th>
<th>Disintegration Time (Sec.)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>199.6 ±0.2</td>
<td>2.8±0.1</td>
<td>3.4±0.02</td>
<td>0.3±0.011</td>
<td>129±1</td>
<td>97.5</td>
</tr>
<tr>
<td>S2</td>
<td>199±0.4</td>
<td>3.1±0.4</td>
<td>3.3±0.01</td>
<td>0.84±0.123</td>
<td>306±2</td>
<td>99.3</td>
</tr>
<tr>
<td>S3</td>
<td>198.5±0.1</td>
<td>3.3±0.2</td>
<td>3.5±0.03</td>
<td>1.09±0.11</td>
<td>258±1</td>
<td>98.7</td>
</tr>
<tr>
<td>S4</td>
<td>200.1±0.6</td>
<td>2.9±0.3</td>
<td>3.4±0.02</td>
<td>0.2±0.23</td>
<td>130±2</td>
<td>99.3</td>
</tr>
<tr>
<td>S5</td>
<td>198.8±0.4</td>
<td>2.8±0.2</td>
<td>3.5±0.01</td>
<td>0.15±0.129</td>
<td>176±1</td>
<td>97.9</td>
</tr>
<tr>
<td>S6</td>
<td>200±0.6</td>
<td>3.3±0.4</td>
<td>3.4±0.02</td>
<td>0.4±0.014</td>
<td>610±2</td>
<td>101.5</td>
</tr>
<tr>
<td>S7</td>
<td>198.6±0.4</td>
<td>2.7±0.2</td>
<td>3.3±0.02</td>
<td>0.1±0.012</td>
<td>416±3</td>
<td>98.6</td>
</tr>
<tr>
<td>S8</td>
<td>200.5±0.3</td>
<td>3.2±0.3</td>
<td>3.4±0.01</td>
<td>0.23±0.011</td>
<td>303±2</td>
<td>101.2</td>
</tr>
<tr>
<td>S9</td>
<td>201.5±0.5</td>
<td>2.6±0.4</td>
<td>3.3±0.04</td>
<td>0.10±0.023</td>
<td>281±1</td>
<td>99.27</td>
</tr>
</tbody>
</table>

**In-Vitro Drug Release**

The in-vitro drug release profile of batch S1 to S9 is displayed in Table 5 and figure 3,4 & 5.
Results indicate that batch S8 shows best results in terms of drug release. crospovidone & Sodium starch glycolate both combination proves to be better super disintegrant in comparison with singalsuperdisintegrant(crospovidone & Sodium starch glycoate)

Table no.5 % Drug Release

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Time</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
<th>S6</th>
<th>S7</th>
<th>S8</th>
<th>S9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>20.22</td>
<td>17.08</td>
<td>16.15</td>
<td>23.32</td>
<td>9.23</td>
<td>16.92</td>
<td>22.62</td>
<td>34.28</td>
<td>26.67</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>31.45</td>
<td>35.67</td>
<td>42.01</td>
<td>39.08</td>
<td>18.9</td>
<td>36.26</td>
<td>48.39</td>
<td>67.06</td>
<td>47.63</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>48.97</td>
<td>60.12</td>
<td>56.18</td>
<td>54.44</td>
<td>27.76</td>
<td>57.21</td>
<td>60.98</td>
<td>88.47</td>
<td>69.05</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>54.36</td>
<td>76.32</td>
<td>67.98</td>
<td>69.79</td>
<td>64.05</td>
<td>68.16</td>
<td>74.98</td>
<td>92.66</td>
<td>80.01</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>76.8</td>
<td>88.29</td>
<td>87.13</td>
<td>82.97</td>
<td>75.88</td>
<td>82.81</td>
<td>79.02</td>
<td>93.66</td>
<td>93.28</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>79.4</td>
<td>89.25</td>
<td>88.08</td>
<td>87.09</td>
<td>83.49</td>
<td>94.73</td>
<td>80.32</td>
<td>94.65</td>
<td>94.27</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>80.4</td>
<td>91.11</td>
<td>89.48</td>
<td>89.41</td>
<td>94.49</td>
<td>95.73</td>
<td>83.02</td>
<td>96.11</td>
<td>95.72</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>88.6</td>
<td>92.54</td>
<td>90.88</td>
<td>90.35</td>
<td>95.49</td>
<td>96.74</td>
<td>87.11</td>
<td>97.57</td>
<td>97.88</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>89.4</td>
<td>93.5</td>
<td>91.83</td>
<td>92.21</td>
<td>97.41</td>
<td>98.21</td>
<td>91.25</td>
<td>99.04</td>
<td>98.10</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>91.4</td>
<td>94.47</td>
<td>97.77</td>
<td>94.55</td>
<td>98.41</td>
<td>99.68</td>
<td>95.56</td>
<td>99.98</td>
<td>99.57</td>
</tr>
</tbody>
</table>

Figure No.3: In –Vitro Dissolution Profile For Immediate Release Sitagliptin Phosphate (S1-S3)
CONCLUSION
Immediate release tablet of sitagliptin phosphate monohydrate as promising approach to enhance the drug release profile using combination superdisintegrant. The result show That From Above Dissolution Study, The S8 Formulation Gives 99.98% Dr In 45 Min. And Also Shows Good Hardness, Thickness, And Friability, DT,Drug Contain So It Is Selected As
Optimized Formulation so immediate release tablet of sitagliptin phosphate monohydrate show better drug release profile as compare other formulation.

ACKNOWLEDGEMENT

The Authors Thankful To The Principal Dr S.R Chaudhari&Dr. Salunkhe K.S HOD Department Of Pharmaceutics, Amrutvahini College Of Pharmacy, Sangamner, Ahmednagar, Pune University, For Providing Required Facilities To Carry Out Research Work.

REFERENCES