INTRODUCTION

Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficiency of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine [1]. To overcome these limitations, several controlled oral drug delivery systems with prolonged gastric residence times have been reported recently such as: floating systems [2, 3], mucoadhesive systems [4, 5], swelling and expanding systems [6], high density systems [7, 8], ion exchange resins [9], osmotic regulated systems [10] which delay gastric emptying. Both single unit systems (tablets or capsules) [11, 12] and multiple unit systems (multi particulate systems) have been reported in the literature. A gastric drug delivery system (GFDDS) is particularly useful for drugs have narrow absorption window in the upper part of gastrointestinal tract that are primarily absorbed in the duodenum and upper jejunum segments [13]. It retains the dosage form at the site of absorption and thus enhances the bioavailability [14].

Metformin is a biguanide hypoglycemic agent used in the treatment of non-insulin dependent diabetes mellitus not responding to dietary modification. The drug is stable, does not bind to plasma protein and is excreted unchanged in urine. It has been reported that the absolute bioavailability of Metformin hydrochloride when given orally is 50-60% only because of its narrow absorption window. The biological half-life of Metformin hydrochloride is 1.7 hrs and the main site of its absorption is proximal small intestines [3, 4]. Recently, research has been carried out using Metformin hydrochloride in effervescent-type drug delivery system by using different grades of low density polymer [15]. The GFDDS was planned for Metformin hydrochloride as such a system when administered would remain buoyant on the gastric fluid for a prolonged period of time and release the drug in sustained manner, thus providing the drug continuously to its absorption sites and increasing the magnitude of drug effect. In this way it stands an advantage over conventional dosage form, which needs to be administered twice or thrice a day.

MATERIALS AND METHODS

Materials

Metformin hydrochloride was obtained as a gift sample (Grandix pharma Ltd, Chennai, India). HPMC K4M, HPMC K100LV, CP934P and Carbopol-934P were procured as a gift sample from Ranbaxy India Pvt. Ltd., Gurgaon, India. Talc, Magnesium Stearate, Hydrochloric acid and PVP K30 were purchased from S.D fine chemicals, Mumbai, India. All the materials received have been used as such in the formulations without any further modification.

Tablet preparation

Floating matrix tablets containing Metformin hydrochloride were prepared by wet granulation method using variable concentrations of HPMC K4M and HPMC K100LV, CP934P with sodium bicarbonate (Table 1) [16]. All the ingredients except magnesium stearate and talc were passed through sieve no 60 and blended in glass mortar uniformly. Required quantity of ethanolic PVP K30 was added as a granulating agent to make a coherent mass. The coherent mass was passed through sieve no 16 and the granules were then dried in a hot air oven at a temperature of 60°C for 30 minutes. The dried granules were passed through sieve no 22, mixed with sodium bicarbonate as a gas-generating agent and lubricated with magnesium stearate and talc which previously screened through sieve no 100. The lubricated granules were compressed into tablets using 13mm Beveled edge punch in a Remach 10 station Rotary punching machine.

Compatibility Studies

Compatibility studies of drug with the excipients were determined by LR Spectroscopy (FTIR) using Perkin Elmer spectrum RXI FT-IR spectrometer model. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of drug and other ingredients in the formulations were compared with that of the original spectra.
Table 1: Formulation of floating tablets of Metformin hydrochloride

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin HCl</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>-</td>
<td>-</td>
<td>62.5</td>
<td>62.5</td>
<td>125</td>
<td>125</td>
</tr>
<tr>
<td>HPMC K100LV</td>
<td>125</td>
<td>125</td>
<td>62.5</td>
<td>62.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carboxol 934P</td>
<td>-</td>
<td>75</td>
<td>-</td>
<td>75</td>
<td>-</td>
<td>75</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Talc</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

HPMC = Hydroxy propyl methyl cellulose.
(All quantities are given in mg)

Characterization of granules
The characteristic parameters of the granules were evaluated. The angle of repose and flow rate were determined by the Fixed funnel method. The bulk density and tapped density were determined by the cylinder method. Compressibility Index and Hausner’s ratio was calculated to evaluate the micromeritics of the powder.

Characterization of tablets
Drug content and physical evaluation
The drug content of the tablets was determined by weighing powdered tablet equivalent to 100 mg Metformin and dissolved in 0.1 mol/l HCL as solvent and the samples were analyzed spectrophotometrically at 233 nm. Tablets were also examined with...
regard to their weight variation (n=10), friability (n=10) and hardness (n=6) [17].

Buoyancy lag-time & Total Floating Time studies

The buoyancy lag-time of the tablets was studied in 100 ml 0.1 mol/l HCL (pH 1.2) at 37±0.5°C. The time required for the tablet to rise to the surface for float was taken as the buoyancy lag-time and the time extend of floating was recorded as Total Floating Time [18, 22].

Dissolution studies

The release rate of Metformin hydrochloride from floating tablets was determined using USP dissolution testing apparatus - II (Labindia, Paddle type). The test was performed using 900 ml 0.1 mol/l HCL at 37±0.5°C and 100 rpm. A sample(1ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these aliquots was measured at 233 nm.

Swelling characteristics

The swelling properties of HPMC, CP934P matrix containing drug were determined by placing the tablet in the dissolution test apparatus, in 900 ml 0.1 mol/l HCL at 37±0.5°C. The tablets were removed periodically, removed the excess free water and the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU%) according to the equation [19].

\[
WU\% = \frac{W_t - W_i}{W_i} \times 100
\]

Wt = weight of dosage form at time t.
wi = initial weight of dosage form.

Stability studies

Short-term stability studies were performed at a temperature of 45±1°C/75±5%RH over a period of three months (Sameeksha Pvt.Ltd,) on the promising HBS tablet formulation (F6). The samples were analyzed at weekly intervals for any qualitative and quantitative changes. At the end of three months, in vitro release and in vitro floating studies were performed [20, 21].

RESULTS AND DISCUSSION

In the present work efforts have been made to develop floating drug delivery system for Metformin hydrochloride containing HPMC of different viscosity grades (HPMC K4M and HPMC K100LV) and CP934P. Drug-Excipients compatibility study was done initially and results directed the further course of formulation. The characteristic drug peak at 3375 cm⁻¹, 3296 cm⁻¹, 1628 cm⁻¹, 1572 cm⁻¹ and 1058 cm⁻¹ responsible for Aliphatic Primary amine, Aliphatic Secondary amine NH Stretch, Aliphatic Secondary amine NH bend, Primary amine NH bend and Primary amine CN Stretch respectively confirms the availability of Metformin Hydrochloride as unchanged with the excipients. The formation of new peaks at 2934 cm⁻¹ and 2103 cm⁻¹ are responsible for Functional groups of HPMC. Hence the Drug is compatible with the polymers used in the formulations.

The results of micromeritics evaluation were shown in Table 2. The angle of repose value ranged between 28°-61°±0.15 to 29°-58°±0.19. The Bulk Density and Tapped Density ranged between 0.32±0.044 to 0.37±0.045 and 0.32±0.07 to 0.43±0.08 respectively. The Carr's index (%) ranged between 05.90±0.6 to 12.94±0.2. The Hausner’s ratio ranged between 1.13±0.04 to 1.19±0.06. The result of Angle of repose indicated the powder blend has acceptable flow properties and the result of Carr’s Index, Hausner’s ratios indicates the fine flowing and compressible properties of the granules.

The weight variation, friability, hardness and content uniformity were found to be within acceptable limits (Table 2). Thus, all the physical properties of these tablets were satisfactory as specified in the Indian Pharmacopoeia.

Invitro buoyancy studies

The results of in vitro buoyancy studies was shown in table-3, supports that the Floating tablet containing HPMC K100LV/HPMC K4M, CP934P polymer shows acceptable buoyancy lag time (BLT) and good total floating time (TFT). Among the formulations, F4 containing HPMC K100LV / HPMC K4M, CP934P showed good BLT of 70 sec, while the other formulations have little higher BLT. This may be due to the difference in concentration of polymers and gas generating agent.

Swelling characteristics

The results of swelling study were illustrated in Fig-3. The swelling of tablets increased as the time passes because the polymer gradually absorbs water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, this maintaining the integrity of the dosage form. In the present study, the higher swelling index was found for tablets of batch F1 containing CP934P having nominal viscosity of 39,400 cps. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability.

Table 2: Characterization of granules and tablets of Metformin hydrochloride

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose (θ)°</td>
<td>29±0.31</td>
<td>28±0.15</td>
<td>28±0.11</td>
<td>28±0.13</td>
<td>29±0.41</td>
<td>29±0.34</td>
</tr>
<tr>
<td>Bulk density (g/cc)*</td>
<td>0.35±0.04</td>
<td>0.32±0.04</td>
<td>0.32±0.04</td>
<td>0.37±0.05</td>
<td>0.33±0.04</td>
<td>0.38±0.04</td>
</tr>
<tr>
<td>Tap density (g/cc)*</td>
<td>0.39±0.09</td>
<td>0.34±0.07</td>
<td>0.32±0.09</td>
<td>0.37±0.04</td>
<td>0.37±0.04</td>
<td>0.43±0.08</td>
</tr>
<tr>
<td>Carr’s index*</td>
<td>10.01±0.2</td>
<td>0.99±0.06</td>
<td>0.91±0.08</td>
<td>1.03±0.1</td>
<td>10.95±0.4</td>
<td>12.40±0.2</td>
</tr>
<tr>
<td>Hausner’s ratio*</td>
<td>1.16±0.2</td>
<td>1.13±0.04</td>
<td>1.14±0.08</td>
<td>1.19±0.06</td>
<td>1.13±0.04</td>
<td>1.13±0.04</td>
</tr>
<tr>
<td>Weight variation (%)***</td>
<td>694.6±2.29</td>
<td>769.5±1.73</td>
<td>10.95±0.18</td>
<td>768.5±1.49</td>
<td>694.5±1.18</td>
<td>768.6±1.29</td>
</tr>
<tr>
<td>Friability (%)***</td>
<td>0.90±0.14</td>
<td>0.72±0.26</td>
<td>0.91±0.11</td>
<td>0.86±0.19</td>
<td>0.79±0.21</td>
<td>0.79±0.21</td>
</tr>
<tr>
<td>Hardness (kg/cm)**</td>
<td>5.5±0.47</td>
<td>6.0±0.32</td>
<td>6.0±0.54</td>
<td>5.5±0.42</td>
<td>7.0±0.35</td>
<td>7.0±0.35</td>
</tr>
<tr>
<td>Content uniformity (%)***</td>
<td>99±0.56</td>
<td>98.0±0.41</td>
<td>98.0±0.72</td>
<td>97.19±0.35</td>
<td>98.08±0.19</td>
<td>99.05±0.56</td>
</tr>
</tbody>
</table>

Results are presented as mean±standard deviation (n=3), “(n=6), “(n=10)

Table 3: Invitro buoyancy studies of Metformin hydrochloride floating tablet

<table>
<thead>
<tr>
<th>Batch</th>
<th>Tablet Density (gm/cc)</th>
<th>Buoyancy Lag Time (Sec.)</th>
<th>Total Floating Time (Hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.84</td>
<td>76</td>
<td>&gt;8</td>
</tr>
<tr>
<td>F2</td>
<td>0.73</td>
<td>74</td>
<td>&gt;8</td>
</tr>
<tr>
<td>F3</td>
<td>0.87</td>
<td>83</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F4</td>
<td>0.94</td>
<td>70</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F5</td>
<td>0.96</td>
<td>86</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F6</td>
<td>0.92</td>
<td>89</td>
<td>&gt;12</td>
</tr>
</tbody>
</table>
In vitro dissolution studies

The tablets are subjected to in vitro dissolution study and in vitro release kinetic study. All formulations showed that considerable interest in using different grades of HPMC in controlled release drug delivery system due to their hydrophilic nature and fast hydration. It has been reported that polymers of different viscosity grades can yield different drug release. The release profiles of formulation F1-F6 were shown in Fig. 4. The release profiles appear to be biphasic, with initial burst effect followed by a polymer controlled slower release in the second phase. Polymeric system with low viscosity polymer (HPMC K100LV) yielded a faster initial burst effect and incorporation of CP934P decreased the release of Metformin hydrochloride from the GFDDS. Likely due to the fact that CP934P is a cross-linked polymer with high molecular weight and viscosity, and, when contacted with water, it would swell and hold water inside its micro gel network. This particular property may partially be responsible for the retarded release of Metformin hydrochloride from the GFDDS.

![Fig. 3: Comparative Swelling index results of Floating tablets](image)

![Fig. 4: Comparative in-vitro release data for Metformin hydrochloride Floating tablets formulation (F1-F6) and marketed product](image)

From results of in vitro drug release studies using USP dissolution apparatus, it concludes that F6 had better sustained release than the other formulation [Fig. 4]. To analyze the Metformin release mechanism, the in vitro release data were fitted into various release equations and kinetic models (first order, zero order, Higuchi, Korsemeyer-peppa's plot) [Table 4], as indicated by the value of R²; the Higuchi model was found to be efficient in describing the diffusion mechanism. To explore the release pattern, results of the in vitro release data of all formulations were fitted to the Korsemeyer-peppa’s equation that suggested that the release governed by non-fickian diffusion.

![Table 4: Drug release kinetics of Metformin hydrochloride](image)
Comparison with marketed product

From the result the optimized formulation F6 had better control over release rate when compared with the marketed product (Gluformin XL-500mg) (Figure 5). The results indicate that gas generated intra gastric buoyant tablets of Metformin hydrochloride containing HPMC K4M (125mg) and CP934P (75mg) provides a better option for sustained release, results drug available in the dissolved form at its absorption window (i.e., proximal small intestine) thus leads to improve its bioavailability. The drug release rate was sustained for formulation F6 when compared with the marketed product.

Stability study

Short-term stability study was performed on the promising formulation F6 by storing the sample at 45±1°C/75±5%RH for three months. Analysis was performed on the drug content, buoyancy lag-time, buoyancy time and drug release parameters. The results indicated that there were no significant changes in drug content, buoyancy lag-time, buoyancy time (Table 5) and dissolution profile of formulation F6 during storage at 45±1°C/75±5%RH for three months (Figure 6).

Table 5: Drug Content and Floating behavior of optimized F6 formulation during Short term stability study

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Drug Content (%)</th>
<th>Buoyancy lag-time (sec)</th>
<th>Buoyancy Time (H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>99.05±0.56</td>
<td>89</td>
<td>&gt;12</td>
</tr>
<tr>
<td>01</td>
<td>98.76±1.06</td>
<td>90</td>
<td>&gt;12</td>
</tr>
<tr>
<td>02</td>
<td>99.00±0.25</td>
<td>89</td>
<td>&gt;12</td>
</tr>
<tr>
<td>03</td>
<td>98.84±1.2</td>
<td>88</td>
<td>&gt;12</td>
</tr>
</tbody>
</table>

CONCLUSION

Overall this study concludes that viscosity is a major factor affecting the release and floating properties of the GFDDS. The higher viscosity seems to inhibit the initial burst effect of Metformin hydrochloride release from the GFDDS. It was concluded on the basis of buoyancy and drug release kinetics that optimized formulation containing 500mg of Metformin hydrochloride granulated with 125mg of HPMC K4M and 75mg of CP934P gave the best in vitro release of 97.83% in 12 hrs in 0.1 mol/l HCl at 1.2 pH. The release of Metformin hydrochloride from the formulation followed zero order release kinetics. Thus, the result of the current study clearly indicate, a promising potential of the Metformin hydrochloride floating system as an alternative to the conventional dosage form. However, further clinical studies needed to assess the utility of this system for patient suffering from non insulin dependent diabetes mellitus.

ACKNOWLEDGEMENT

The authors are very thankful to Grandix Pharma Ltd., Chennai, India; Ranbaxy India Pvt. Ltd., Gurgaon, India; for providing gift samples and all other supporters who helped to carryout this research work successfully.
REFERENCES