INTRODUCTION

There are different types of dosage forms, which are being administered through different routes. However oral route is the most preferred because of its better patient compliance. Majority of the drugs are having site-specific absorption in the G.I. tract and parameters like pH dependent solubility, stability and ionization of the drug in different portions of the G.I. tract influence the absorption. Gastric retention time is one of the important factors, which adversely affect the performance of these drugs when administered simply by an oral controlled drug delivery system (Chandel et al., 2012).

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the G.I. tract is to increase the gastric residence time (GRT). Dosage forms with prolonged GRT are gastro retentive drug delivery systems which will provide prolonged release thereby allowing the drug to retain for a long time in the gastric region for increasing the bioavailability. This application is effective in delivery of soluble sparingly soluble and insoluble drugs. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability (Sanjay and Sharma, 2003).

Norfloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class. It is a second-generation fluoroquinolone antibacterial. It kills bacteria by interfering with the enzymes that cause DNA to rewind after being copied, which stops DNA and protein synthesis. It is a potential drug in treating various serious G.I. diseases like gastritis,
urinary tract infections, prostatitis and gonorrhea etc. The half-life is 4 hrs (Nelson et al., 2007).

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape system or by the simultaneous administration of pharmacological agent that delay gastric emptying (Shweta et al., 2005).

**MATERIALS AND METHODS**

**Materials**

Norfloxacin (Gift sample of M/s. Micro Labs, Bangalore) is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. Guar gum, HPMC 15 KM (gift sample of Ontop pharmaceuticals, Bangalore) occurs as odorless or nearly odorless, white to yellowish-white powder with a bland taste used as suspending agent; tablet binder; tablet disintegrant; viscosity increasing agent, sustained-release matrix tablets. Hypromellose used as coating agent; film former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent. Sodium carboxy methyl cellulose acts as coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent. Sodium bicarbonate, Lactose, PVP K30, Magnesium stearate, talc were purchased from S.D fine chemicals, Mumbai, used as effervescent, channeling agent, binder, lubricant and glidant respectively. Hydrochloric acid was purchased from Qualigens Fine Chemicals.

**Method**

All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 min, then PVP K30, lactose and sodium bicarbonate, talc and magnesium stearate were mixed in polythene bag. After thoroughly mixing these ingredients, the powder blend was passed through #44 mesh. Tablets were compressed on a single punch tablet machine (Cadmach, India) using 8mm flat round punches. Total weight of the tablet is 670 mg, containing 400mg of norfloxacin in each tablet as given in Table 1.

**Pre-compression Parameters**

Tablets are evaluated for pre-compression parameters like angle of repose, bulk density, tapped density, Carr's index and values are tabulated in Table 2.

Angle of Repose: Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane and was
performed to determine the flow rate of powder (Banker et al., 1991 and Jain et al., 2012). The method used is the funnel method. The powder mass was allowed to flow through the funnel orifice kept vertically to a plane paper kept on the horizontal surface, giving a heap angle of powder on paper. The angle of repose was calculated by substituting the values of the base radius 'r' and pile height 'h' in the following equation:

\[
\theta = \tan^{-1}\left(\frac{h}{r}\right)
\]

Bulk Density: Bulk density was obtained by dividing the mass of powder by the bulk volume in cm\(^3\). The sample of about 50 cm\(^3\) of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped on to hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm\(^3\) of the sample contained in the cylinder. It was calculated by using equation given below:

\[
LBD = \frac{\text{weight of the powder}}{\text{volume of the packing}}
\]

Tapped density: The tapped density was obtained by dividing the mass of powder by tapped volume in cm\(^3\). The sample of about 50 cm\(^3\) of powder, previously been passed through a standard sieve no. 20, is carefully introduced in to a 100 ml graduated cylinder. The cylinder was dropped on to hard wood surface hundred times from a height of 1 inch. The tapped density of each formulation was then obtained by dividing the weight of sample in grams by the final tapped volume in cm\(^3\) of the sample contained in the cylinder. It was calculated by using equation given below:

\[
TBD = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}}
\]

Carr's index: Carr’s index is an indirect method of measuring powder flow from bulk densities (Martin et al., 1994). The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr’s index of each formulation was calculated to equation given below

\[
l_{a-CI} (%) = \left[\left(\frac{TBD}{LBD}\right)\right] \times 100
\]

Post compression parameters: Post compression quality control tests like tablet thickness, diameter, hardness, friability, uniformity of weight, content uniformity of drug (IP, 1996; Lachman et al., 1991) as

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight(^a)(mg)</th>
<th>Drug content(^a)(%)</th>
<th>Hardness(^a)(Kg/cm(^2))</th>
<th>Friability(^b)(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketed</td>
<td>515.00±1.36</td>
<td>98.62±0.18</td>
<td>10.2±0.32</td>
<td>0.06</td>
</tr>
<tr>
<td>FG1</td>
<td>670.00±1.46</td>
<td>99.24±1.54</td>
<td>5.82±0.49</td>
<td>0.45</td>
</tr>
<tr>
<td>FG2</td>
<td>670.00±1.28</td>
<td>99.74±0.97</td>
<td>5.14±0.24</td>
<td>0.32</td>
</tr>
<tr>
<td>FG3</td>
<td>670.00±1.37</td>
<td>99.94±0.48</td>
<td>5.06±0.56</td>
<td>0.26</td>
</tr>
<tr>
<td>FS1</td>
<td>670.00±0.56</td>
<td>99.34±0.54</td>
<td>6.02±0.49</td>
<td>0.38</td>
</tr>
<tr>
<td>FS2</td>
<td>670.00±0.18</td>
<td>99.66±0.86</td>
<td>5.94±0.24</td>
<td>0.30</td>
</tr>
<tr>
<td>FS3</td>
<td>670.00±0.47</td>
<td>98.25±0.68</td>
<td>5.30±0.56</td>
<td>0.27</td>
</tr>
<tr>
<td>FH1</td>
<td>670.00±1.46</td>
<td>98.67±0.54</td>
<td>6.82±0.49</td>
<td>0.22</td>
</tr>
<tr>
<td>FH2</td>
<td>670.00±1.28</td>
<td>99.65±0.97</td>
<td>5.14±0.54</td>
<td>0.26</td>
</tr>
<tr>
<td>FH3</td>
<td>670.00±1.37</td>
<td>98.25±0.58</td>
<td>6.06±0.36</td>
<td>0.31</td>
</tr>
</tbody>
</table>

\(^a\) Mean ±S.D., n=10 tablets, \(^b\) n=10 tablets

Table 3: Evaluation of Norfloxacin GFDDS with guar gum, sodium CMC, HPMC 15 KM.

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>% Cumulative drug released ±(S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Marketed</td>
</tr>
<tr>
<td>1</td>
<td>19.02±0.48</td>
</tr>
<tr>
<td>2</td>
<td>39.23±1.62</td>
</tr>
<tr>
<td>3</td>
<td>52.80±0.07</td>
</tr>
<tr>
<td>4</td>
<td>65.92±1.67</td>
</tr>
<tr>
<td>5</td>
<td>83.71±1.86</td>
</tr>
<tr>
<td>6</td>
<td>99.12±0.87</td>
</tr>
<tr>
<td>7</td>
<td>89.92±2.40</td>
</tr>
<tr>
<td>8</td>
<td>97.41±0.52</td>
</tr>
<tr>
<td>9</td>
<td>94.13±1.19</td>
</tr>
<tr>
<td>10</td>
<td>100.12±2.75</td>
</tr>
<tr>
<td>11</td>
<td>--</td>
</tr>
<tr>
<td>12</td>
<td>--</td>
</tr>
</tbody>
</table>

Table 4: % Cumulative drug released from GFDDS containing varying concentrations of Guar gum.
well as other specific evaluation tests for GFDDS like floating lag time and total floating time & release rate of drug are evaluated. Result is given in Table 3.

Table thickness and Diameter: Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier calipers.

Hardness: This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this five tablets were selected at random and the hardness of each tablet was measure with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm².

Friability: The friability test was carried out in Roche friabilator to evaluate the hardness and stability instantly. Twenty tablets were weighed (Wo) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, the tablets were again weighed (w). The percent loss in weight or friability (f) was calculated by the formula given below:

\[
Percent\ friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100
\]

Uniformity of weight: This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage show in the Table 3 and none deviate by more than twice the percentage The mean and standard deviation were determined.

Content Uniformity: This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range according to the Indian Pharmacopoeia .The content uniformity test is mandatory for tablets whose average weight is below 50mg. This test is performed by taking twenty tablets were selected randomly, weighed and powdered. A quantity of powdered tablet equal to 100mg of norfloxacin was dissolved in 0.1N HCl in 100 ml volumetric flask. The so formed sample was diluted and the absorbance was measured at 278nm using 0.1N HCl as blank and the % drug content were estimated using the following formula.

\[
In\ vitro\ buoyancy\ determination: \text{The}\ floating\ characteristics\ of\ the\ GFDDS\ are\ essential,\ since\ they influence\ the\ in\ vitro\ behaviors\ of\ the\ drug\ delivery\ system.\ However\ there\ seemed\ to\ be\ no\ threshold\ value\ for\ the\ floating\ system\ to\ remain\ afloat\ under\ a\ physiological\ condition\ due\ to\ the\ latter's\ complication.}
\]

Floating Lag Time: The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium simulated gastric fluid without pepsin, at pH 1.2, temperature 37±0.5°C, paddle rotation at 50 rpm and 900ml as volume, it is measured using stopwatch.
Total Floating Time: The time taken by the tablet to float constantly on the surface of the gastric fluid without pepsin, at pH 1.2, temperature 37±0.5°C, paddle rotation at 50 rpm it is measured using stopwatch.

In vitro dissolution studies: Dissolution test was carried out using USP XXIV (model DISSO, M/s. Labindia) rotating paddle method (apparatus 2). The stirring rate was 50rpm. 0.1 N hydrochloric acid was used as dissolution medium 900 ml and was maintained at 37±0.5°C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the norfloxacin at 278 nm by using a double beam UV spectrophotometer (Shimadzu-2000). Each dissolution study was performed for three times and the mean values were taken tabulated and shown in Table 4-6 and Figure 2-4.

Drug release kinetics: The analysis of drug release mechanism from the pharmaceutical dosage form is an important but complicated process and it is practically evident in case of matrix systems. As model-dependent approach, the dissolution data are fitted to four popular release models such as a zero-order, first order, Higuchi and peppas equations (Higuchi, 1963; Peppas, 1985; Ritger, 1987), which have been described in the literature. The order of drug release from matrix systems was studied by using Higuchi equation and Erosion equation. The value of n indicates the drug release mechanism. For a slab the value n = 0.5 indicates fickian diffusion and values of n between 0.5 and 1.0 or n=1.0 indicate non-fickian mechanism. In case of a cylinder n=0.45 instead of 0.5, and 0.89 instead of 1.0. This model is used to analyze the release from polymeric dosage forms, when the release mechanism is not well known or when there is a possibility of more than one type of release phenomenon being involved.

Stability studies: Adequate stability data of the drug and its dosage form is essential to ensure the strength, safety, identity, quality, purity and in vitro release rates that they claim to have at the time of use (Nash and Waltes, 2000). A controlled release product should release a predetermined amount of the drug at specified time intervals, which should not change on storage. Any considerable deviation from the appropriate release would render the controlled release product useless. The in vitro and in vivo release rates of controlled release product may be altered by atmospheric or accelerated conditions such as temperature and humidity.

RESULTS AND DISCUSSION

In the present study, GFDDS of norfloxacin were prepared by using different polymers like guar gum, sodium CMC, HPMC 15KM as natural polymer, using sodium bicarbonate as gas generating agent, PVPK30 is used as a binding agent and lactose is used as diluent. GFDDS tablets were prepared by direct compression technique. Formulation was optimized by using different ratios of polymers, gas generating agent and diluents. The hardness of the prepared GFDDS of norfloxacin was found to be in the range of 4.8 to 6.82 kg/cm². The
Figure 1: FTIR spectra of (a) Norfloxacin (b) Norfloxacin with guar gum (c) Norfloxacin with HPMC 15 KM (d) Norfloxacin with sodium CMC.

Figure 2: *In vitro* release profile of norfloxacin formulation FG1, FG2 & FG3, with marketed product.

Figure 3: *In vitro* release profile of norfloxacin formulation FS1, FS2 & FS3, with marketed product.
Figure 4: *In vitro* release profile of Norfloxacin formulation FH1, FH2 & FH3, with marketed product.

Figure 5: Linear regression plots for the dissolution profiles of norfloxacin formulations by (i) Zero order release (ii) First order release (iii) Higuchi plot (iv) Peppas plot for FG1, FG2 & FG3 with marketed product.
Friability of all the tablets was to be less than 1% i.e. in the range of 0.22 to 0.56%. All the prepared GFDDS tablets were evaluated for weight variation. Percent deviation from the average weight was found to be within the prescribed official limits. The drug content uniformity was examined as per I.P specification. All the batches of tablets were found to comply with uniformity of content test. FTIR spectras of pure norfloxacin, blend of polymers with drug were determined. Norfloxacin showed that the principle IR peaks 2832.92, 2360.44, 1730.8, 1622.81, 1483.96, 1270.86, 1145.51, 1031.73 Cm⁻¹. Norfloxacin with guar gum has shown 2833.24, 2360.48, 1627.81, 1479.30, 1271, 1149.50, 1033.77 Cm⁻¹. Norfloxacin with HPMC K15M has shown 1032.9, 1279.79, 2364.77, 2831.55 Cm⁻¹. Minor shifts were observed in between the pure drug and polymers (Figure 10-12). Floating lag time was observed that the range of 55 to 540 seconds and the tablet floats up to 24 hours for all the formulations. The results are given in Table 1.

Formulations FG1, FG2 and FG3 with guar gum exhibited 97.41, 100.12 and 99.87% of drug release in 8, 10 and 12 hours respectively and the data is given in Table 4 and drug release profiles are shown in Figure 2. Formulations FS1, FS2 and FS3 with Sodium CMC exhibited 98.34, 98.95 and 99.56% of drug release in 7, 9 and 10 hours respectively and the data is given in Table 5 and drug release profiles are shown in Figure 3. Formulations FH1, FH2 and FH3 with HPMC K15M exhibited 100.02, 99.65 and 89.25% of drug release in 8, 10 and 12 hours respectively and the data is given in Table 6 and drug

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**Figure 6**: Linear regression plots for the dissolution profiles of norfloxacin formulations by (i) Zero order release (ii) First order release (iii) Higuchi plot (iv) Peppas plot for FS1, FS2 & FS3 with marketed product.
release profiles are shown in Figure 4. The amount of drug released for a particular drug polymer ratio was found to be in the order of SODIUM CMC > HPMCK15M> GUAR GUM.

The marketed product has shown release of 99.12 at the end of 6th hour and the data is given in Table 4-6 and Figure 2-4. Formulation FG3 releases 99.87% of drug at the end of 12 hrs. The results of linear regression analysis of data including regression coefficient are summarized in Table 7 and Figure 5-7. When the regression coefficient ‘r’ value of zero order and first order plots were compared, it was observed that the ‘r’ values of zero order were in the range of 0.97 to 0.99 whereas the ‘r’ values of first order plots were found to be in the range of 0.70 to 0.93 indicating drug release from all the formulations were found to follow zero order kinetics. The good fit of the Higuchi model to the dissolution profiles of all the formulations suggested that diffusion is the predominant mechanism limiting drug release since the ‘r’ values of Higuchis plots were nearer to unity. The in vitro dissolution data as log cum percent drug release versus log time were fitted to Korsmeyer equation (Krosmeyer et al., 1983), values of the exponent ‘n’ was found to be in the range of 0.678 to 0.900 indicating that the drug release is by non-fickian diffusion mechanism.

Figure 7: Linear regression plots for the dissolution profiles of norfloxacin formulations by (i) Zero order release (ii) First order release (iii) Higuchi plot (iv) Peppas plot for FH1, FH2 & FH3 with marketed product.
CONCLUSION

Gastric Floating Drug Delivery (GFDD) systems of norfloxacin with shorter lag time can be prepared by direct compression method using guar gum, sodium CMC, and HPMC 15KM, NaHCO₃ as gas generating agent and were found to extend the drug release over a period of 7 to 12 hrs and the drug release decreased with decrease in polymer concentration. FG3 was considered as an ideal formulation which exhibited 99.87% of drug release in 12 hrs, and floating lag time of 130 seconds with a floating time of 24 hrs and no drug-excipient interaction in the prepared formulations was confirmed by FTIR studies.

REFERENCES


