Research Article

Formulation and Evaluation of High-Density Gastro Retentive Drug Delivery Systems of Norfloxacin

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ABSTRACT

The aim of the present investigation is to develop high-density gastro retentive drug delivery systems of norfloxacin. The main objective is to sustain the drug release for duration of 12 hours; hence different polymers are used in the investigation to achieve the desired objective. The polymers used in the present investigation include guar gum, HPMC K15 M and sodium alginate. For direct compression feasibility, the directly compressible vehicle micro crystalline cellulose has been used and as glidant, titanium dioxide has been used. The prepared powder mixture was analyzed for preformulation parameters and the tablets were characterized for tableting properties, drug release kinetics and mechanism.

1. Introduction

A controlled release GRDDS is the one which upon oral administration retains in the stomach. They are meant to release the drug slowly in a controlled manner which favours continuous absorption of drug in the upper gastrointestinal tract (GIT)[1–3]. GRDDS are known to offer better bioavailability for the drugs with specific absorption window in upper GIT with advantages in their pharmacokinetics and pharmacodynamics[4,5]. Among the different approaches for GRDDS, high density systems are having their own importance.

High density systems[6,7]

These are the systems that possess a density of 1.5-2.5 gm/cm³, which let them retain in the bottom of the stomach and hence not cross the pyloric region as shown in Figure 1 and are capable of withstanding its peristaltic movements. Such systems staying at the bottom shows a retention mechanism which offers an extension of GI transit time even up to 25 hours. World Health accumulation has verbalized mind-boggling polio syndrome as a Global Public Health Emergency of International Concern in May 2014 [4].

Figure 1: High density matrix system in stomach[8]

2. Materials and methods

Norfloxacin was obtained as a sample from. Polymers are purchased from Yarrow chemicals, Mumbai, India. All other chemicals used are of analytical grade.

Norfloxacin[9–11]

Norfloxacin (C₁₆H₁₈FN₃O₃) is a synthetic broad spectrum antibacterial fluoroquinolone active against gram-positive and gram-negative aerobic
bacteria. It is a white to pale yellow, order less crystalline powder with a bitter taste. IUPAC name of norfloxacin is 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4 di hydroquinoline-3-carboxylic acid. The daily dose of norfloxacin ranges from 400 mg to 800 mg in multiple doses. It comes under BCS class IV with poor solubility and poor permeability. Norfloxacin shows rapid absorption up to 40% and peak concentration is achieved in 1-2 hours. Norfloxacin has a half-life of 3 to 4 hours. Following oral administration 30 to 40% is rapidly absorbed from gastrointestinal tract.

**Analytical method for in vitro estimation of norfloxacin**[12]

Norfloxacin was estimated by using a reported UV spectrophotometric method by measuring the absorbance at 273 nm. 100 mg of norfloxacin was transferred to a volumetric flask of 100 mL, 5 mL of ethanol was added to solubilize the drug and the solution was made up to the mark with 0.1 N HCl to obtain a stock solution (Stock 1) of norfloxacin (1000 μg/mL). From this Stock 1, 10 mL was diluted to 100 mL with 0.1 N HCl to obtain the concentration of 100 μg/mL (Stock 2). From Stock 2 serial dilutions of 10, 20, 30, 40 and 50 μg/mL were prepared and absorption was measured at 273 nm by using ThermoFisher Scientific Genesys 180 UV-Visible spectrophotometer.

**Formulation of high-density gastroretentive tablets of norfloxacin**

Norfloxacin was used as model drug for optimizing the high-density gastroretentive tablets of abiraterone acetate. Initially norfloxacin tablets were prepared by using direct compression technique for optimizing the formula, and drug release characteristics over a period of 12 hours.

**Preparation of pre-compression blend**

The required quantities of drug and excipients for each formulation were weighed accurately according to the formulae shown in Table 1. All the ingredients required for a batch of 300 tablets were passed through sieve #40 (aperture 425 μm, ASTM). The ingredients were geometrically mixed except magnesium stearate until a homogenous blend was achieved using polyethene bag.

**Table 1: Formulae of norfloxacin high-density tablets**

<table>
<thead>
<tr>
<th>Contents (mg)</th>
<th>NH1</th>
<th>NH2</th>
<th>NH3</th>
<th>NH4</th>
<th>NH5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>30</td>
<td>95</td>
<td>65</td>
<td>20</td>
<td>55</td>
</tr>
<tr>
<td>Sodium algin</td>
<td>40</td>
<td>40</td>
<td>85</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Guar gum</td>
<td>60</td>
<td>40</td>
<td>30</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Talc</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>
</tr>
<tr>
<td>Micro crystalline cellulose</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td><strong>Total weight</strong></td>
<td>480</td>
<td>525</td>
<td>530</td>
<td>450</td>
<td>480</td>
</tr>
</tbody>
</table>

**Evaluation of flow properties of pre-compression blend**

The flow properties of the pre-compression blend were determined by angle of repose, bulk density, tapped density, Carr’s compressibility index and Hausner’s ratio.

**Angle of repose (θ)**[13]

It is used to measure the frictional forces in the loose powder. Angle of repose is a characteristic property that explains the flowability of a powder blend and is related to inter particulate friction or resistance to movement of particles. It is the maximum angle between the surface of powder pile and horizontal plane and fixed funnel method was followed in this investigation.

A clean and dry funnel was taken and attached to a burette stand. A white paper sheet was placed 5 cm below the funnel on a dry platform. The opening tip of the funnel was closed with a finger, gently the sample was poured into the funnel, and then the finger is removed to allow the fall of the powder, the height of the funnel was adjusted such that the tip of the funnel just touched the tip of the heap. Using a pencil, circle was drawn around the heap of the powder to estimate the diameter and then radius. The height of the heap was also measured. The same procedure was repeated 3 times to obtain average readings. Angle of repose was calculated by using the below formula.

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

where, \(\theta\) = Angle of repose, \(h\) = height of the heap and \(r\) = radius of the heap

**Bulk density**[13]

The bulk density of a powder blend depends primarily on several factors like particle size, particle shape and particle-size distribution, and the adherence tendency of the particles. 10 g of powder blend was weighed accurately and transferred into a 10 mL measuring cylinder and its volume was noted as bulk volume. Bulk density was determined by using the below formula.

\[
\text{Tapped density} = \frac{\text{Weight of the sample}}{\text{Tapped volume of the sample}}
\]

**Carr’s compressibility index**[14]

Compressibility is another important parameter that explains the flowability of a powder blend. Percentage compressibility of powder mix was determined by Carr’s compressibility of consolidation index. A high Carr’s index value means poor flow. Carr’s Compressibility Index was determined by using the below formula.

\[
\% \text{ CI} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100
\]

**Hausner’s ratio**[14]

It is a measure of compressibility of powder. Hausner’s ratio was determined by using the below formula.

\[
\text{Hausner’s Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

The relationship between flow properties and different parameters are shown in Table 2.

**Table 2: Scale of flowability for different methods**

<table>
<thead>
<tr>
<th>Flow Property</th>
<th>Angle of repose (*)</th>
<th>Carr’s index</th>
<th>Hausner’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>25-30</td>
<td>≤10</td>
<td>1.00-1.11</td>
</tr>
<tr>
<td>Good</td>
<td>31-35</td>
<td>11-15</td>
<td>1.12-1.18</td>
</tr>
<tr>
<td>Fair</td>
<td>36-40</td>
<td>16-20</td>
<td>1.19-1.25</td>
</tr>
<tr>
<td>Passable</td>
<td>41-45</td>
<td>21-25</td>
<td>1.26-1.34</td>
</tr>
<tr>
<td>Poor</td>
<td>46-55</td>
<td>26-31</td>
<td>1.35-1.45</td>
</tr>
<tr>
<td>Very Poor</td>
<td>56-65</td>
<td>32-37</td>
<td>1.46-1.59</td>
</tr>
<tr>
<td>Very, Very Poor</td>
<td>&gt;66</td>
<td>&gt;38</td>
<td>&gt;1.60</td>
</tr>
</tbody>
</table>

**Preparation of norfloxacin high-density matrix tablets**[15,16]

Tablet compression was done by using Natoli NP-RD10A tablet compression machine following direct compression technique using 12 mm, flat and round punch.
Evaluation of norfloxacin high-density matrix tablets[15,16]
The prepared norfloxacin high-density tablets were evaluated for different post compression parameters like thickness and diameter, density, hardness, friability, uniformity of weight and drug content uniformity.

**Thickness and diameter**
Thickness and diameter of tablets was measured by using Vernier calipers. All measurements were done for five times.

**Density**
The density of prepared tablets was calculated by using the below equation.

\[
\text{Density} = \frac{w}{(\pi r^2 h)}
\]
where, \(w\) = weight of a tablet, \(r\) = radius of a tablet, and \(h\) = thickness of a tablet

**Hardness**[17]
Tablets should be sufficiently hard enough to overcome the friction during handling, shipment, and packaging. Five tablets were randomly selected, and the hardness of individual tablets was measured using Optimal Inc. VK 200 hardness tester and average values are expressed in kg/cm².

**Friability**[18]
Friability is a measure of strength of granules and expressed in percentage. Friability test was done by using Vankel Industries Inc. VanderKamp-10801 friabilator where the tablets were placed in a friabilator chamber. They are subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm. Initially tablets equivalent to 6.5 g were weighed, noted their initial weight and subjected to 100 falls of 6 inches height (25 rpm for four minutes) and the tablets were dedusted by using hair brush, air blown to remove the separated particles, re-weighed and noted as final weight. The percent loss in weight or friability was calculated by using the below formula. As per Indian Pharmacopoeia the % friability should not be more than 1%.

\[
\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

**Uniformity of weight**[19]
Twenty tablets were selected at random, weighed individually and then together by using Mettler Toledo PL1502E electronic balance. The mean and percentage deviation were determined. Prepared tablets pass the uniformity test if not more than two of the tablets deviate from the average weight by more than the 5% none deviate more than twice that percentage. The allowed deviation of weight range for the prepared tablets (480-530 mg) should be in between ±24-26.5 mg.

**Drug content**[20]
From each batch, 10 tablets were randomly collected, powdered in a glass mortar and the powder equivalent to 100 mg of norfloxacin was placed in a 100 mL volumetric flask. The drug was extracted with 5 mL of ethanol with vigorous shaking on a mechanical shaker for 1 hour and filtered into a 50 mL volumetric flask through 0.45 µm Millipore nylon filter disc and the filtrate was made up to mark with 0.1N HCl. Further appropriate dilutions were made with 0.1N HCl and the absorbance was measured at 273 nm against blank prepared under same conditions without drug using Thermo Fisher Scientific Genesys 180 UV-Visible spectrophotometer. The drug content should be in the range of 90-110%. The drug content estimation was done in triplicate and average values are reported.

**In vitro drug release studies**[9]
In vitro drug release studies were carried out for the prepared formulations using USP type-II (paddle method) dissolution rate test apparatus Hansen Research SR8PLUS using 900 mL of 0.1N HCl as dissolution medium maintained at a temperature of 37°C±0.5°C. The shaft rotation speed was maintained at 75 rpm. The study was performed for 12 hours and 5 mL samples were withdrawn at fixed time intervals using a syringe fitted with prefilter. 5 mL of fresh medium maintained at 37°C±0.5°C was used for replacement at every time interval by washing the particles back to dissolution medium adhered to prefilter. The samples collected were analysed for norfloxacin content by measuring the absorbance at 273 nm using Thermo Fisher Scientific Genesys 180 UV-Visible spectrophotometer against blank of 0.1N HCl. The samples were diluted wherever necessary. All the in vitro drug release studies were performed in triplicate and average values are reported.

**Release kinetics and mechanisms**[21]
In vitro drug release data was fitted to different kinetic models like zero and first order to study the release pattern of the drug. The mechanism of the drug release from the dosage form was detected by fitting the dissolution data to mathematical models Higuchi (diffusion), Hixson-Crowell (erosion) and Korsmeyer-Peppas model (release from the matrix system). Based on the correlation coefficient value and linearity of plots, both order and mechanism were determined and reported.

### 3. Results and Discussion

**Calibration curve**
The experiment was performed in triplicate and average values are reported and the results are given in Table 3. Calibration curve was plotted between absorbance verses concentration as shown in Figure 2.

<table>
<thead>
<tr>
<th>Concentration (µg/ml)</th>
<th>Absorbance (mean±s.d., n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.172±0.45</td>
</tr>
<tr>
<td>20</td>
<td>0.263±0.65</td>
</tr>
<tr>
<td>30</td>
<td>0.388±0.34</td>
</tr>
<tr>
<td>40</td>
<td>0.557±0.53</td>
</tr>
<tr>
<td>50</td>
<td>0.676±0.47</td>
</tr>
</tbody>
</table>

**Figure 2:** Calibration curve of norfloxacin in 0.1 N HCl

A good linear relation was observed between absorbance and concentration of norfloxacin. The regression line equation was found to be \(y = 0.013x + 0.0206\) with a correlation coefficient value of 0.9954.

**Pre-compression studies**
The drug and excipient powder blends were prepared and evaluated for their flow characteristics of angle of repose, bulk density, tapped density, Carr’s index and Hausner’s ratio. The angle of repose of the powder blend was found to be in the range of 22.81°- 25.36° which indicated excellent flow property as shown in Table 4.

### Table 3: Absorbance values of norfloxacin in 0.1 N HCl

<table>
<thead>
<tr>
<th>Concentration (µg/ml)</th>
<th>Absorbance (mean±s.d., n=3)</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>0.172±0.45</td>
</tr>
<tr>
<td>20</td>
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<tr>
<td>30</td>
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<td>40</td>
<td>0.557±0.53</td>
</tr>
<tr>
<td>50</td>
<td>0.676±0.47</td>
</tr>
</tbody>
</table>
The Carr’s index values are in the range of 8.96 to 11.3 whereas the Hausner’s ratio values of all the formulations were in the range of 1.10 to 1.13. The results indicated good to excellent flow of the prepared powder blends confirming their suitability for direct compression.

Evaluation of norfloxacin high-density matrix tablets
Results of the post compression studies conducted for the prepared high-density tablets of norfloxacin are discussed below.

**Thickness and diameter**
The measured thickness and diameter of the tablets are shown in Table 5. The results showed a uniform thickness and diameter of the prepared tablets.

**Density**
By using the measured thickness and radius of tablets, the respective densities of the prepared high-density formulations were calculated. These results are shown in Table 5. It was found that the densities were in the range of 1.63-1.70 g/cm³, which was greater than the density of the gastric fluid and found optimum for the gastroretentive high-density system.

**Hardness**
The measured hardness of tablets ranged between 3.7 to 4.5 kg/cm². This ensures that prepared tablets are showing good handling characteristics. The results are shown in Table 5.

**Friability**
The values of friability test of prepared tablets ranged between 0.32 to 0.48%. The % friability was found to be showing less than 1% ensuring that the tablets were mechanically stable. The results are shown in Table 5.

**Uniformity of weight**
The prepared tablets passed uniformity of weigh test I.P. as the % uniformity of weigh was within the Pharmacopoeial limits of ±5% of the weight. The prepared tablets were found to be uniform with low standard deviation values as shown in Table 5.

**Drug content**
The drug content was found to be within the limits of 99 to 101% indicating that the test complies with the official compendia test for tablets. Results are shown in Table 5.

**In vitro drug release studies**
In vitro drug dissolution profiles are shown in Figure 3. As the prepared tablets were of high-density nature, the tablets sank to the bottom of the dissolution medium and observed to be in the bottom throughout the dissolution study. Formulation NH5 has shown better control over the drug release and hence the composition has been taken forward for further formulation with abiraterone acetate.

**Release kinetics and mechanisms**
The obtained dissolution data was fitted to different kinetic models for assessing the rate of release and mathematical models for assessing the mechanism of release. The respective correlation coefficient values, zero and first order release rate constants are shown in Table 6.
All the formulations, except NH2, were found to follow zero order drug release kinetics as the correlation coefficient (r) value of zero order plot is greater than that of first order plot. Formulations, NH1 and NH2 were found to follow erosion mechanism whereas NH3, NH4 and NH5 were found to follow diffusion mechanism of drug release based on the ‘r’ value. The optimized formulation, NH5 was further found to follow non-Fickian diffusion mechanism of drug release based on the ‘n’ value of Korsmeyer-Peppas plot.

4. Conclusion

The high-density gastroretentive tablets of norfloxacin were prepared by using HPMC K15M and gaur gum as release retardant polymers. The concentrations of the HPMC and gaur gum were changed. Sodium alginate was used as a gelling agent keeping its weight constant for all formulations. Complete drug release was not achieved for the high-density tablets prepared with higher amount of gaur gum due to its high swelling nature and retardation of drug from diffusion out of tablet (NH1). The amount of gaur gum was decreased in formulations NH2 and NH3 and HPMC K15M was increased. An improvement in the dissolution of the drug was observed in these two formulations compared to NH1. In case of NH4 with increase in the concentration of HPMC K15M drug release was completed in 10 hours due to less swelling of HPMC K15M and more diffusion of drug from the dosage form. By reducing the HPMC K15M in NH5 the drug release was completed in 12 hours and hence it was considered as optimized. Except NH1 formulation all other formulations released about 30-35% of drug during the first two hours which may act as loading dose. This may be due to lag time required for the swelling of the polymers. Once the polymers are swollen the drug release was controlled due to increase in diffusion path length and slow diffusion of the drug form the swollen matrix.

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Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

References