Development and Optimization of Floating Multiparticulate Drug Delivery System of Norfloxacin

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ABSTRACT:

Objectives: Norfloxacin is a synthetic broad-spectrum antibacterial drug having poor bioavailability and pH-dependent solubility. The purpose of present study was to develop gastroretentive floating multiparticulate drug delivery system of Norfloxacin.

Materials and Method:

The Norfloxacin core pellets were prepared using microcrystalline cellulose (MCC) and polyvinylpyrrolidone K30 (PVP K30) by extrusion and spheronization technique. A 3-level, 3-factor, 17 run experimental box-behnken design was adopted to optimize levels of variables in the pellets formulations. The selected independent variables were amount of MCC, PVP K30, spheronizing speed and dependent variables were aspect ratio and hardness of pellets. Sodium bicarbonate and Hydroxyl Propyl Methyl Cellulose K15M in the ratio of 1:1, 1:2 and 2:1 (w/w) on a dry solid basis was incorporated into Norfloxacin pellets and was further coated with EudragitRL100 using fluidized bed processor to obtain weight gain of 5%, 10% and 15% w/w. Fourier Transform Infra-Red (FTIR) spectrum, scanning electron microscopy, physical characterization, particle size distribution analysis, floating studies and in vitro drug release studies of pellets were evaluated.

Result and Discussion:

Among the floating multiparticulate pellets batches, batch B-22 was found to be optimized based on the criteria of attaining minimum floating lag time (<10 minutes), and maximum value of drug released 82.11% in 8 hours. The percentage drug
release for batch B-21 and B-23 was found to be 91.12% in 5 hours and 60.67% in 8 hours respectively. The drug release studies indicated that as the Eudragit RL 100 polymer coat increases the drug release gets decreased produces sustained release of Norfloxacin. The floating studies reveal that 70–90% of pellets remained floating for up to 8 hrs. All the batches have excellent flow properties having angle of repose in the range 25.5±0.49° to 28.02±0.30°, Carr’s index and Hausner’s ratio in the range of 5% to 15% and 1.05±0.3 to 1.14±0.3 respectively.

**Conclusion:**

The significant outcome obtained with the study indicates that such an approach can be effectively employed for improvement of bioavailability of drugs having poor absorption in lower part of the gastrointestinal tract with enhanced therapeutic efficacy.

**Keywords:** Gastroretentive, Floating multiparticulate, Norfloxacin, Spheronization and Box-behnken design.

**INTRODUCTION:**

Oral route plays an important role in therapy as it is the most preferable and convenient route of drug delivery system.1 Gastroretentive drug delivery systems (GRDDSs) are one of the advanced approaches for the novel drug-delivery systems in which drug is retained in the stomach for a prolonged period of time.2,3 GRDDSs are particularly suitable for drugs having a narrow absorption window, drugs that act locally in a part of the gastrointestinal tract (GIT), drugs which are unstable in intestinal fluids and drugs that exhibit poor solubility in the intestinal tract.4 Floating drug delivery system (FDDSs) is one of the most prominent approaches of GRDDSs, characterized by the capacity of the formulation to float in and over the gastric contents. FDDSs are low density system which allows them to remain buoyant in the stomach for a prolonged period of time. In the development of FDDSs based on the mechanism of buoyancy widely employed technology is effervescent systems. In the effervescent systems, carbon dioxide gas production occurs due to the reaction of carbonates and bicarbonates present in the formulation with gastric fluid. The gas that forms is entrapped in the polymers, which allows the system to remain buoyant.
The FDDs are effectively used to design sustained drug delivery system and improvement in overall oral bioavailability of drugs.\textsuperscript{5-7} Norfloxacin is fluoroquinolone anti-infective antibacterial drug firstly used in the treatment of urinary tract infections, prostatitis, gonorrhea and genital tract infections.\textsuperscript{8} It has 30–40\% bioavailability with plasma half-life of 3 to 4 hours thus required multiple dosing to maintain adequate plasma concentration in the treatment.\textsuperscript{9} Norfloxacin is also poorly absorbed from the lower part of the gastrointestinal tract and it is well absorbed from the stomach. The solubility of norfloxacin in water is pH-dependent which increases sharply with decreasing pH below 5.\textsuperscript{10,11} The therapeutic dose of Norfloxacin is very high (400 mg orally twice daily) in the treatment of urinary tract infections.\textsuperscript{12} Many novel approaches have been reported which are used for bioavailability enhancement of norfloxacin, either directed towards development of single unit system or unable to produce significant effect on improvement of bioavailability. Thus it was decided to develop a floating multiparticulate drug delivery system of Norfloxacin that could produce sustained release so as to maintain drug plasma levels for improving bioavailability and therapeutic effects.

The floating multiparticulate has been developed in which Norfloxacin pellets containing different ratios of sodium bicarbonate (NaHCO\textsubscript{3}): Hydroxypropyl Methyl Cellulose (HPMC) K15M was prepared by extrusion spheronization process. The pellets are coated with Eudragit RL100 on fluidized bed processor by using bottom spray technique. The amount of the effervescent agent and coating level of Eudragit RL100 polymeric membrane were evaluated and optimized in terms of floating ability and drug release properties.

**MATERIALS AND METHODS**

**Materials:**

Norfloxacin was a kind gift provided from Aarti drugs ltd, Mumbai, India. Eudragit RL100 was provided by Evonik, Mumbai, India. As received all the other chemicals were used are of analytical reagent grade.
**Preparation method for Norfloxacin pellets:**

**Extrusion and spheronization:**

The Norfloxacin core pellets were prepared using wet granulation method by extrusion and spheronization technique. Powder mixture of Norfloxacin, microcrystalline cellulose, was mixed in mortar for 20 min. This was followed by addition of binding liquid consisting of 3% polyvinylpyrrolidone K30 in water. The obtained wet mass was passed through BSS sieve no.16 to get the extrudates. The prepared extrudates were then transferred to spheronizer (Shakti Pharmatech, Ahmedabad, India) and spheronized at different spheronizing speed to get pellets. The prepared core pellets were oven dried overnight at 60°C.

**Experimental Design:**

A 3-level, 3-factor, 17 run experimental box-behnken design was adopted to optimize levels of variables in the pellets formulations. The selected independent variables were amount of MCC i.e. microcrystalline cellulose (X1), PVP (K30) i.e. polyvinylpyrollidone (X2), and spheronizing speed (X3) as shown in (Table 1). The dependent variables were aspect ratio (Y1) so as to predict the sphericity and hardness (Y2). The generation of experimental runs, ANOVA study and optimization were carried out by Design-expert® software 10.

The optimized norfloxacin pellet batch in terms of sphericity and hardness was selected followed by incorporation of NaHCO₃ and HPMC K15M in the ratio of 1:1, 1:2 and 2:1 (w/w) on a dry solid basis as indicated in (Table 2b).

**Coating of Norfloxacin pellets containing NaHCO₃: HPMC K15M**

The Norfloxacin pellets containing NaHCO₃: HPMC K15M in the ratio of 1:1 was further coated with EudragitRL100 using fluidized bed processor (ACG, Miniquest-F, Mumbai, India), to obtain weight gain of 5%, 10% and 15% w/w as shown in (Table 2b). The coating solution was prepared by dissolving desired amount of EudragitRL100 in Isopropyl alcohol and stirred to obtain a clear solution.

The layering conditions were: batch size, 7.5 g; inlet temperature, 40°C; product temperature, 35°C; air flow, 0.8–1.0 bar; spray pressure, 0.5–0.9 bar; spray rate, 0.130 g/min and final drying at 40°C for 15 min.
### Table 1. Experimental design parameters

<table>
<thead>
<tr>
<th>Factors</th>
<th>Levels used (coded value)</th>
<th>Actual value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone K30</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Spheronizing speed (rpm)</td>
<td>-1</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 2 a. Composition of experimental formulations

<table>
<thead>
<tr>
<th>Batch Number</th>
<th>Microcrystalline Cellulose (%)</th>
<th>Polyvinylpyrrolidone K30 (%)</th>
<th>Spheronizing speed (rpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-1</td>
<td>25</td>
<td>4</td>
<td>850</td>
</tr>
<tr>
<td>B-2</td>
<td>35</td>
<td>6</td>
<td>750</td>
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<td>B-3</td>
<td>30</td>
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<td>850</td>
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<td>B-4</td>
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<td>6</td>
<td>950</td>
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<td>B-5</td>
<td>30</td>
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<td>850</td>
</tr>
<tr>
<td>B-6</td>
<td>35</td>
<td>8</td>
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<td>B-7</td>
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<td>850</td>
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<td>B-8</td>
<td>30</td>
<td>4</td>
<td>950</td>
</tr>
<tr>
<td>B-9</td>
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<td>4</td>
<td>850</td>
</tr>
<tr>
<td>B-10</td>
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</tr>
<tr>
<td>B-11</td>
<td>30</td>
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</tr>
<tr>
<td>B-12</td>
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<td>6</td>
<td>850</td>
</tr>
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<td>B-13</td>
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<td>B-14</td>
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<td>6</td>
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</tr>
<tr>
<td>B-15</td>
<td>25</td>
<td>6</td>
<td>950</td>
</tr>
<tr>
<td>B-16</td>
<td>30</td>
<td>4</td>
<td>750</td>
</tr>
<tr>
<td>B-17</td>
<td>30</td>
<td>8</td>
<td>950</td>
</tr>
</tbody>
</table>
Table 2 b. Composition of experimental formulations containing different ratios of NaHCO₃: HPMC K15M and Eudragit RL 100 coating

<table>
<thead>
<tr>
<th>Ingredients (gm)</th>
<th>Batch Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B-18</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>3.33</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>1.27</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone K30</td>
<td>0.3</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>1.25</td>
</tr>
<tr>
<td>Hydroxyl Propyl Methyl Cellulose K15</td>
<td>1.25</td>
</tr>
<tr>
<td>Eudragit RL100 (%weight gain)</td>
<td>-</td>
</tr>
</tbody>
</table>

Evaluation of Norfloxacin Floating Pellets:

Spectroscopic Studies:

Calibration curve of Norfloxacin in 0.1 N HCl:

10mg of Norfloxacin accurately weighed and was dissolved in 100 ml 0.1 N HCl in volumetric flask to get 100μg/ml stock solution. This solution was further diluted with 0.1 N HCl to get solutions in concentration range of 1 to 10μg/ml. Absorbance of these solutions were determined spectrophotometrically (Shimadzu 1700, Japan) at 273 nm.¹³,¹⁴

Fourier Transform Infra-Red (FTIR) spectrum:

The powder sample of Norfloxacin, Eudragit RL100 and physical mixture of Norfloxacin and polymer (Eudragit RL100) was kept in dryer to make moisture free. The dry sample of powders was separately mixed and triturated with dry potassium bromide. This mixture was placed in DRS assembly sample holder. The infrared spectrum was recorded and the spectral analysis was done (Shimadzu,8400S, Japan).¹⁵
**Drug Content:**

Norfloxacin pellets equivalent to 400 mg were grounded using mortar pestle and transferred into 50ml volumetric flask containing 0.1 N HCL and volume was made to 50 ml. The mixture was sonicated for 10 minute to ensure complete extraction of drug. The solution was filtered through whatmann filter paper and assayed spectrophotometrically (Shimadzu 1700, Japan) at 273nm to determine the percent drug content.\textsuperscript{16,17}

**In vitro drug release studies:**

Drug release studies of Norfloxacin pellets were performed by USP Dissolution Apparatus-I (Veego DA-8D, India). The dissolution studies were carried out with 900 ml 0.1N HCl as dissolution medium at 37±0.5°C on 50 rpm. Pellets equivalent to 400 mg of Norfloxacin were weighed and transferred to the dissolution apparatus. 10 ml aliquot was withdrawn and immediately replaced by the same volume of fresh medium to maintain sink condition. The aliquot was filtered through whatman filter paper and absorbance was measured at 273nm using UV spectrophotometer (Shimadzu 1700, Japan) to determine the drug release.\textsuperscript{16-18}

**In vitro buoyancy studies.\textsuperscript{19-21}**

The time required for the pellets to rise to the surface and float as floating lag time and total duration of time by which pellets remain buoyant i.e. total floating time was determined. The floating pellets (100) was kept in USP Type –I dissolution apparatus, the dissolution medium used was 0.1N HCl conditions were 37°C ± 5°C at 50 rpm. The percentage of floating was determined by following equation:

\[
\text{Floating pellets (\%)} = \frac{\text{no of floating pellets at measure time}}{\text{initial no of the pellets}} \times 100
\]

**Scanning electron microscopy (SEM):**

The surface morphology of optimized coated pellets was examined using the scanning electron microscope. SEM analysis was performed using Carl Zeiss Supra 5, Germany Scanning Electron Microscope. The pellets samples were mounted directly onto aluminium stages and were sputter coated with gold /Palladium mixture for 1 min under an argon atmosphere. The coated pellets were mounted onto stubs using double-sided adhesive tape.\textsuperscript{22}
**Particle Size distribution analysis:**

The size distribution of the gastroretentive pellets was determined using mechanical sieve shaker (Make-Kumar). A series of BSS standard stainless steel sieves no 8, 10, 22, 36, 44, 60, and 100 were arranged in order of decreasing aperture size. Accurately weighed amount of drug loaded gastroretentive pellets from each batch were placed on the upper most sieve. The sieves were shaken for a period of 10 minutes and the material retained on each sieve was weighed separately. Graph of mean size vs. % weight retained was plotted to analyse pellet size distribution.\(^{23,24}\)

**Physical characterization:**

The micromeritics properties (bulk density, tapped density, Carr’s index, Hausner’s ratio and angle of repose), of the floating pellets were determined. Friability of the pellets was determined by using USP friability test apparatus. Friability of the pellet formulations was determined as the percentage of weight loss after 200 revolutions of 6.5 g of the core pellets in a friabilator (Roche Friability Tester, India). The hardness of the pellets was determined using digital hardness tester (Veego, India).\(^{25-27}\)

**Pellets sphericity:**

Pellet sphericity was determined by measuring the feret diameter and perpendicular diameter of pellets by vernier calliper. From that aspect ratio (AR) is calculated i.e. (ratio of longest feret diameter and its longest perpendicular diameter).\(^{28}\)

**RESULT AND DISCUSSION**

**UV Spectrum of Norfloxacin in 0.1 N HCl:**

The λ\text{max} of Norfloxacin in 0.1 N HCl was found to be 273 nm. The calibration curve of Norfloxacin was obtained in 0.1 N HCl at the respective λ max value as indicated in (Figure 1).
Figure 1. Calibration curve of Norfloxacin in 0.1N HCL at 273nm.

Fourier Transform Infra-Red (FTIR) spectrum:

The IR spectrum of Norfloxacin, Eudragit RL100 and physical mixture of Norfloxacin and polymer (Eudragit RL100) was obtained by using FTIR (Figure 2). The interpretations of IR frequencies were done and absorption bands are consistent with structure of Norfloxacin and Eudragit RL100. The FTIR spectra of physical mixture indicated compatibility of Norfloxacin and Eudragit RL100. The FTIR spectra of pure drug showed functional peak at 3600 to 3250 1492.95 2524.46 1267.27 1614.47 cm\(^{-1}\). Eudragit RL100 IR spectra showed peak at 2920.32 1720.56 1072.46 while physical mixture shows peaks at 3491.27 3365.90 3012.91 2850.8 1745.64 1610.61 1456.30 1269.20 cm\(^{-1}\) with negligible shift in wave number.

![Calibration curve of Norfloxacin in 0.1N HCL at 273nm](image)
Figure 2. IR spectrum of (a) Norfloxacin (b) Eudragit RL100 and (c) physical mixture of Norfloxacin and polymer (Eudragit RL100).

**Drug Content:**
The drug content in all pellet formulation was determined by UV spectroscopy method and was found to be between 96.75±0.8% to 98.78±0.45% which indicated that the coating on the pellets also gives good reproducibility of drug content.

**Optimization of Norfloxacin pellets:**
To optimize the Pelletization process MCC, PVP K30, and Spheronizing speed was varied at different levels. 17 batches were prepared using box-behnken design, aspect ratio and hardness of pellets was determined as response as indicated in (Table 3).

Table 3. Aspect ratio and Hardness of experimental formulations

<table>
<thead>
<tr>
<th>Batch Number</th>
<th>Spheronizing speed (RPM)</th>
<th>Microcrystalline Cellulose (%)</th>
<th>Polyvinyl pyrrolidone K30 (%)</th>
<th>Aspect Ratio (mm)</th>
<th>Hardness (kg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-1</td>
<td>850</td>
<td>25</td>
<td>4</td>
<td>1.90</td>
<td>0.72</td>
</tr>
<tr>
<td>B-2</td>
<td>750</td>
<td>35</td>
<td>6</td>
<td>1.16</td>
<td>0.77</td>
</tr>
<tr>
<td>B-3</td>
<td>850</td>
<td>30</td>
<td>6</td>
<td>1.41</td>
<td>0.47</td>
</tr>
<tr>
<td>B-4</td>
<td>950</td>
<td>35</td>
<td>6</td>
<td>1.15</td>
<td>0.59</td>
</tr>
<tr>
<td>B-5</td>
<td>850</td>
<td>30</td>
<td>6</td>
<td>1.41</td>
<td>0.47</td>
</tr>
<tr>
<td>B-6</td>
<td>850</td>
<td>35</td>
<td>8</td>
<td>1.16</td>
<td>0.42</td>
</tr>
<tr>
<td>B-7</td>
<td>850</td>
<td>25</td>
<td>8</td>
<td>1.39</td>
<td>0.56</td>
</tr>
</tbody>
</table>
Sphericity and hardness of the pellets are essential properties to obtain effective coating. Spherical pellets provide uniform surface whereas sufficient hardened pellets can withstand the mechanical stress during subsequent coating process. The sphericity of pellets was determined in terms of aspect ratio. Aspect ratio value equal to unity indicates spherical shape of pellets. The response surface plots of aspect ratios obtained indicate that the increasing amount of MCC and spheronizing speed yields pellets having aspect ratio near to 1 which is desirable, whereas increasing the amount of PVP K30 yields pellets having aspect ratio greater than 1. The response surface plots of hardness obtained indicate that with increasing amount of PVP K30 hardness of pellets also increases as indicated in fig no.3. From the results of experimental design batch number (B-4) is selected having aspect ratio 1.1 and hardness 0.59, for incorporation of NaHCO3: HPMC K15M in different ratio and subsequent coating process.

Regression equations of the fitted quadratic model:

**Aspect ratio (Y1)**

\[ Y1 = +1.41 + 0.036 * A - 0.16 * B - 0.013 * C - 0.16 * A^2 - 0.030 * B^2 + 0.018 * C^2 - 0.030 * A * B - 0.038 * A * C + 0.13 * B * C. \]

**Hardness (Y2)**

\[ Y2 = 0.48 - 0.028 * A - 0.055 * B + 5.000E-003 * C + 0.068 * A^2 + 0.16 * B^2 - 0.081 * C^2 - 0.10 * A * B - 0.050 * A * C + 0.023 * B * C. \]

Where, A, B, C is spheronizing speed, MCC and PVP K30 respectively.
Figure 3. Response surface plot (a,b,c) Aspect Ratio (PVP vs SS, MCC vs SS, PVP vs MCC) respectively. (d,e,f) Hardness (MCC vs SS, PVP vs SS, PVP vs MCC) respectively.
It was observed from regression equation, that independent variable MCC has negative effect on aspect ratio (Y1). This proofs that increasing amount of MCC leads to decrease value of aspect ratio i.e. near to unity which is desirable. On hardness (Y2) positive effect of PVP K30 was observed. As the concentration of PVP K30 increases hardness of pellets also increases.

For further experiment NaHCO₃: HPMC K15M was incorporated in selected batch (B-4) in different ratios i.e. 1:1, 1:2, 2:1 to prepare additional three batches (B-18, B-19, B-20). Drug release and floating studies were conducted of the prepared batches. The batch (B-19) containing NaHCO₃ and HPMC K15M in the ratio of 1:2 yields irregular shape and size pellets due to higher amount of HPMC K15M, which was difficult to pass through sieve and affecting spheronization process was not studied for drug release and floating behaviour.

![Figure 4. Percentage Drug Release of Batch (B-4, B18, B-20) in 0.1 N HCl. Mean±S.D; n = 3.](image)

The plain Norfloxacin pellet batch (B-4) shows 87.43% drug release within 1 hour. The norfloxacin pellet batch containing NaHCO₃ and HPMC K15M in the ratio (1:1 and 2:1), exhibits 84.19% in 4 hours (B-18) and 92.42% in less than 2 hours (B-20).
respectively as shown in Figure 4). The drug release in batch (B-18) was sustained for 4 hours but batch (B-20) exhibits higher release in less than 2 hours, as it contains more amount of sodium bicarbonate and the generated CO₂ gas doesn’t get entrapped in polymer. The floating lag time for batch B-18 and B-20 was found to be 8 seconds and 3 seconds respectively in 0.1 N HCL. As the amount of sodium bicarbonate increases floating lag time gets decreased. The total floating time of batch B-18 and B-20 was quite short i.e. 4 hours and 2 hours respectively as shown in (Table 4). In batch B-18 the time requires to release above 80% of drug and total floating time was 4 hours. This type of behaviour could be attributed that once the HPMC gets dissolved there was no polymeric membrane which could entrap the generated CO₂ gas. Hence, batch B-18 containing NaHCO₃ and HPMC K15M in the ratio of 1:1 was further selected for coating with Eudragit RL 100 to design complete floating drug delivery system pellets. Eudragit RL 100 coating was given in order to increase the total floating time and to sustain the release of norfloxacin. Three batches (B-21, B-22, and B-23) were prepared with Eudragit RL 100 coating with weight gain of 5%, 10% and 15% by weight and evaluated for drug release and floating behaviour.

![Percentage Drug Release of Batch (B-21, B-22, B-23)](image)

**Figure 5.** Percentage Drug Release of Batch (B-21, B-22, B-23) in 0.1 N HCL. Mean±S.D; n = 3.

The percentage drug release for batch B-21, B-22, B-23 was found to be 91.12% in 5 hours, 82.11% and 60.67% in 8 hours respectively as shown in (Figure 5). The drug release studies indicated that as the Eudragit RL 100 polymer coat increases
the drug release gets decreased. The higher coat leads to thicker membrane over pellets which retarded dissolution medium penetration and hence sustained drug release obtained. The floating lag time for batch B-21, B-22, B-23 was found to be 290 seconds and 440 seconds and 795 seconds respectively in 0.1 N HCl. The total floating time of batch B-21, B-22, B-23 was found to be 5 hours and 8 hours respectively as shown in (table 4). Batch B-22 and B-23 performed satisfactory floating ability of which 70–90% of pellets remained floating for up to 8 hrs. The floating studies reveals that increasing level of polymeric membrane coating increase floating lag time as well as total floating time. Due to thicker polymer coat water penetration retarded which in turn delays CO₂gas generation leads to increased floating lag time. But once the CO₂gas generated the increasing amount of polymer coat inhibits the permeation of gas out of the floating pellets system and maintains the buoyancy for longer period of time.

Table 4. Floating studies of batch (B-18, B-20, B-21, B-22, B-23):

<table>
<thead>
<tr>
<th>Batch number</th>
<th>Floating lag time (sec)</th>
<th>Total floating time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-18</td>
<td>9±1</td>
<td>4.07±0.75</td>
</tr>
<tr>
<td>B-20</td>
<td>4±1</td>
<td>1.89±0.105</td>
</tr>
<tr>
<td>B-21</td>
<td>300±10</td>
<td>4.99±0.1</td>
</tr>
<tr>
<td>B-22</td>
<td>430±10</td>
<td>8±0.05</td>
</tr>
<tr>
<td>B-23</td>
<td>805±10</td>
<td>7.85±0.15</td>
</tr>
</tbody>
</table>

Mean±S.D, n = 3.

Among the three complete floating drug delivery system pellets batches B-21, B-22, and B-23, batch B-22 was found to be optimized based on the criteria of attaining minimum floating lag time (less than 10 minutes), maximum total floating time and maximum value of drug released in 8 hours.

**Scanning electron microscopy (SEM):**

The surface morphology of norfloxacin uncoated pellets batch (B-4) and coated pellets batch (B-22) was studied through SEM. The uncoated norfloxacin pellets
surface was wrinkled and rough whereas the polymer coated pellet showed smoother surface indicate in (Figure 6a and 6b).

![Figure 6](image)

*Figure 6.* Scanning electron microphotographs of (a) uncoated norfloxacin pellets and (b) Norfloxacin pellets coated with polymer at 100X magnification.

**Particle size distribution analysis of pellets:**

The particle size distribution analysis of pellets indicates narrow size distribution in which most of the pellets are in the size range of 1000µm to 1200 µm as shown in (Figure 7).

![Figure 7](image)

*Figure 7.* Particle size distribution curve

**Physical characterization of pellets:**

From the physical characterization of pellets, it was clearly observed that all the batches have excellent flow properties having angle of repose in the range 25.5±0.49° to 28.02±0.30°, Carr’s index and Hausner’s ratio in the range of 5% to 15% and 1.05±0.3 to 1.14± 0.3 respectively. The aspect ratio of pellets obtained
was near to unity. Hardness and friability obtained was in the range of 0.49± 0.01 to 0.61±0.01 Kg/cm² and 0.17±0.52% respectively.

Table 5. Physical characterization of pellets batch (B-4, B-18, B-20, B-21, B-22 and B-23)

<table>
<thead>
<tr>
<th>Batch number</th>
<th>Angle of Repose (°)</th>
<th>Carr's Index(%)</th>
<th>Hausner's Ratio</th>
<th>Aspect (mm)</th>
<th>Hardness(Kg/cm²)</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-04</td>
<td>27.07±0.6</td>
<td>14.85±0.65</td>
<td>1.12±0.02</td>
<td>1.17±0.02</td>
<td>0.59±0.005</td>
<td>0.30±0.1</td>
</tr>
<tr>
<td>B-18</td>
<td>27.85±0.3</td>
<td>9.23±0.66</td>
<td>1.05±0.3</td>
<td>1.14±0.02</td>
<td>0.49±0.01</td>
<td>0.48±0.2</td>
</tr>
<tr>
<td>B-20</td>
<td>26.19±0.5</td>
<td>12.13±0.63</td>
<td>1.08±0.07</td>
<td>1.13±0.01</td>
<td>0.57±0.02</td>
<td>0.52±0.09</td>
</tr>
<tr>
<td>B-21</td>
<td>23.16±0.3</td>
<td>7.51±0.37</td>
<td>10.6±0.01</td>
<td>1.14±0.03</td>
<td>0.61±0.01</td>
<td>0.35±0.02</td>
</tr>
<tr>
<td>B-22</td>
<td>25.5±0.49</td>
<td>5.62±0.42</td>
<td>1.03±0.01</td>
<td>1.18±0.00</td>
<td>0.54±0.025</td>
<td>0.16±0.01</td>
</tr>
<tr>
<td>B-23</td>
<td>28.02±0.3</td>
<td>11.62±0.36</td>
<td>1.01±0.00</td>
<td>1.09±0.06</td>
<td>0.56±0.015</td>
<td>0.21±0.1</td>
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</table>

Mean±S.D; n = 3.

CONCLUSION:
The gastroretentive multiparticulate drug delivery system of norfloxacin based on gas generation technique was successfully designed and developed. The identification and purity of drug was affirmed by conducting infrared and UV spectroscopy studies. A 3-level, 3-factor, 17 run experimental box-behnken design was employed to optimize norfloxacin pellets in terms of sphericity and hardness required to attain effective coating subsequently. The pellets batch obtained at spheronizing speed 950 rpm containing 35% MCC with 6% PVP K 30 produces pellets with desired sphericity and hardness. NaHCO₃ and HPMC K15M in the ratio of 1:1, 1:2 and 2:1 (w/w) on a dry solid basis was incorporated into Norfloxacin pellets and was further coated with Eudragit RL100 using fluidized bed processor to obtain weight gain of 5%, 10% and
15% w/w. The floating ability and in vitro drug release of the system was dependent on the ratio of NaHCO₃ to HPMC K15M and the percentage of Eudragit RL100 polymer coat. As the amount of sodium bicarbonate increases, floating lag time gets decreased. The drug release studies indicated that as the Eudragit RL100 polymer coat increases, the drug release gets decreased, producing sustained release of Norfloxacin. The floating multiparticulate pellets batch containing NaHCO₃ and HPMC K15M in the ratio of 1:1 with 10% Eudragit RL100 coating showed minimum floating lag time (<10 minutes), and 82.11% average drug release in 8 hours. The floating study reveals that 70–90% of pellets remained floating for up to 8 hrs. The significant result obtained with the study indicates that floating multiparticulate drug delivery system, based on effervescent mechanism can be effectively employed for improvement of bioavailability and therapeutic effect of drugs having poor absorption in lower part of the gastrointestinal tract.

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REFERENCES:


