VARIABLES FORMULATION VARIABLES EFFECTING FLOATATION BEHAVIOUR OF SINGLE UNIT GASTRORETTENTIVE CAPSULES OF OFLOXACIN

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INTRODUCTION
Among the various drug delivery routes, oral route has remained the most convenient route due to ease of administration of the dosage forms, patient acceptance and flexibility in formulation [1]. The success of an oral delivery depends on a number of factors like gastric emptying process, the gastrointestinal transit time of the dosage form, drug release from the dosage form and the site of absorption of drugs [2]. There are many limitations of most of the orally administered dosage forms such as rapid and inconsistent gastrointestinal transit time [3], incomplete drug release from the device and too short residence time in the absorption region of the gastrointestinal tract, which may lead to lower bioavailability of the dosage form [4, 5]. Even if sustained release of the drug is attained, the drug may be released after the dosage form has passed the absorption site, thus lowering the efficacy of the drug. To solve these problems, oral controlled release gastro-retentive drug delivery system (GRDDS) has been developed. GRDDS prolongs the retention time of dosage forms in the stomach so that there is improved solubility, bioavailability and reduces drug waste [6]; thereby increases the therapeutic efficacy of the drugs.

In the last few decades various techniques have been developed for gastric retention which is based on the mechanisms of sedimentation [7, 8], expansion [9, 10] mucoadhesion [11], modified shape systems [12, 13], flotation [14], or simultaneous administration of pharmacological agents that delay gastric emptying [15]. These mechanisms are nowadays applied for the preparation of various single and multiple unit dosage forms for large scale manufacture.

Rationale of the study
Ofloxacin, a second-generation fluoroquinolone, is a synthetic chemotherapeutic broad spectrum antibiotic which acts by inhibiting DNA gyrase, an enzyme necessary to separate replicated DNA, thereby inhibiting bacterial cell division. Ofloxacin is a drug with its absorption window in the upper region of GIT. Ofloxacin is soluble in aqueous solutions with pH between 2 and 5 i.e., at gastric pH. In the intestine due to the prevalence of neutral to slightly alkaline pH conditions, precipitation of ofloxacin occurs; this adversely affects its absorption in the lower sections of the intestine [16]. Thus acidic environment of the stomach provides a suitable site for the retention of ofloxacin as it is readily soluble in an acidic environment.

The objective of the present study was to study the effect of various polymers on matrix integrity and floating behaviour of the single unit gastro-retentive capsules of ofloxacin. Low-density single unit gastro-retentive systems remain buoyant above the gastric secretions for sufficient time to ensure sustained release of the drug[3]. Matrix integrity refers to a condition in which the dosage form does not disintegrate of the dosage form. If the dosage form does not maintain its physical integrity, it may be split into smaller fragments and will escape from the stomach to the lower parts of the gastrointestinal tract (GIT).

MATERIALS AND METHODS

Materials
Ofloxacin was obtained as a gift sample from Ranbaxy Laboratories Ltd., Sirmour, India; hydroxypropyl methylcellulose (HPMC) K15 and K15M used were found suitable for the purpose. HPMC levels of HPMC K15M and eudragit level should not exceed HPMC, while lactose a release rate enhancer decreased matrix integrity. Formulations containing zero level of HPMC were found buoyant for more than 12 h with all levels of eudragit S100 (i.e., -1, 0, +1 level). It was also observed that matrix integrity consequently buoyancy increased with increase in eudragit with all levels of HPMC.

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Delhi, India; Clear capsules were kindly sent by SKIMS, Srinagar and Eaton laboratories Ltd, Srinagar, India.

Methods

Preparation of single unit gastro-retentive capsules

Different formulation variables were used to prepare gastro-retentive capsules of ofloxacin. Each ingredient was carefully weighed using an electronic balance (AXIS-LCGC). The ingredients were homogeneously blended and filled in gelatin capsules in accordance with the method used by ‘Ali et al.’ for the preparation of single unit HBS capsules of metformin [17] (table 1).

In vitro buoyancy studies

Static volume beaker method

Static volume beaker method was initially used to have an idea of the floatation behaviour of the proposed dosage forms. In this method, capsules filled with different polymer blends and drug were taken and placed individually in separate beakers containing 900 ml of 0.1 N HCl[18]. The physical condition of the capsules was observed at regular time intervals. This method lacked simulation, so, it was decided to study the floatation capabilities in USP apparatus type II.

USP dissolution apparatus type II

In this method, the formulation was placed in 900 ml of 0.1N HCl as a dissolution medium maintained at 37±0.5 °C using USP dissolution apparatus type II (Bells India; PLC dissolution rate test apparatus). Eudragit S100 gave better results than eudragit L100, so only eudragit S100 was used for the study. It was observed that as the weight of contents of gastro-retentive capsules equal to 550 mg (table 2a). Initially, buoyancy studies were performed along with hydrophilic polymers. Eudragit S100 gave better results compared to eudragit L100 and was used for the study.

RESULTS AND DISCUSSION

Preformulation study for right selection of polymers

During this study different low-density hydrophilic polymers like carbopol, ethyl cellulose, hydroxypropyl methyl cellulose (HPMC) K15M and K1, methylcellulose, sodium carboxymethyl cellulose (Sod. CMC) in different combinations and ratios along with the drug were blended and subjected to buoyancy and matrix integrity study using static volume beaker method. These results showed the suitability of HPMC K15M and HPMC K1M for the study. The initial combinations [ratios] of HPMC K15M and the drug used in pre-formulation study are shown in table 1a. Matrix integrity and floatation behaviour is shown in table 1b. It was observed that buoyancy of the formulations containing lower quantities of HPMC (P 1 and P 2) was lost due to disruption of the capsules. If HPMC is not present in sufficient amounts, a complete gel layer may not form[21].

As there was stepped up HPMC ratio, there was an increase in matrix integrity and consequently buoyancy. This may be explained by an increase in thickness and strength of the colloidal gel barrier formed around the surface. Further studies were performed on combinations where both hydrophilic polymers mentioned above and hydrophilic polymers. Eudragit S100 and eudragit L100 were used as hydrophilic polymers. Eudragit S100 gave better results compared to eudragit L100 and was used for the study.

Effect of hydrophobic polymers on matrix integrity, buoyancy/ floating time

Effect of hydrophobic polymers (eudragit S100) on floatation behaviour was observed by blending them along with hydrophilic polymer (HPMC K15M) in the ratios 1:1, 1:2, 1:3, 2:1 and 3:1, and 200 mg of drug, keeping weight of contents of gastro-retentive capsules equal to 550 mg (table 2a). Initially, buoyancy studies were performed as per static volume beaker method followed by USP type II dissolution apparatus method. During the pre-formulation study, eudragit S 100 gave better results than eudragit L 100, so only eudragit S100 was used for the study. It was observed that as the amount of HPMC was decreased (ratio of hydrophobic polymers exceeded the hydrophilic), matrix integrity, consequently buoyancy was lost. Disruption in such cases (formulations F 4 and F 5) could be due to less quantity of HPMC K15 which was unable to form stable outer colloidal gel layer, consequently unable to hold the contents intact. If insoluble excipients are present in large amount, homogenous gel layer may not form.

Formulations F 1, F 2 and F 3 exhibited good matrix integrity and also buoyancy time of more than 12 h. F 2 and F 3 contained 2:1 and 3:1 ratio of HPMC K15; eudragit S100 respectively showed buoyancy for more than 16 h (table 2b, 2c). Thus it may be concluded that incorporation of eudragit S100 has increased matrix integrity which may be because eudragit forms insoluble mass with HPMC, longer residence of eudragit in gel layer and insoluble nature of eudragit S100 [22] but there might be sufficient amounts of hydrophilic polymer and also ratio of hydrophobic polymer (eudragit) should not exceed hydrophilic (HPMC), i.e., an appropriate ratio of the hydrophilic and hydrophobic polymers are required for such type of systems to show floatation behaviour for longer periods of time without losing their integrity.

Effect of release modifiers on matrix integrity, buoyancy/ floating time

Lactose was used as a release rate modifier [table 3a] which caused a decrease in matrix integrity and consequently buoyancy. A decrease of more than 3-6 h in floatation time was observed due to the addition of lactose to formulation F 1 and F 2 (table 3b) which may be attributed to high solubility of lactose which forms channels within dosage form, develops osmotic pressure inside the dosage due to hydration [23]; weakens the integrity of matrix[24].

Effect of formulation variables

To evaluate the effect of various levels of HPMC K15 and eudragit S100 on matrix integrity, floatation time and drug release, 3² factorial design was applied to F 3a. In this design two factors were evaluated, each at three levels, and experimental trials.

Table 1: (a): Showing composition (in milligrams) of preformulation gastro-retentive single unit capsules (b): flotation behaviour of the capsules using static volume beaker method

| Formulation code | Drug | HPMC K15M | P1 | P2 | P3 | P4 |
|------------------|------|-----------|----|----|----|----|
| P 1              | 200  | 250       | 200| 200| 200| 200|
| P 2              | 300  |           | 350| 350| 400| 400|

| Formulation code | Matrix integrity: n=3 | Floating/buoyancy time (h); n=3 |
|------------------|------------------------|-------------------------------|
| P 1              | +++                    | +                             |
| P 2              | ++                     | +                             |
| P 3              | ++++                   | +++                           |
| P 4              | ++++                   | +++                           |

+++ ≥ 12 h; ‘+++’ = 10-12h; ‘++’ = 7-10h and ‘+’ = 4-7 h (n=3; means all experiments were carried out three times)
were performed at all 9 possible combinations. Table 4a summarises independent and dependent variables along with their levels. Various formulations were prepared as per the compositions mentioned in table 4b. Total weight of the gastro-retentive capsules was 605 mg; results of responses are given in table 4c.

Table 2: (a): Composition of gastro-retentive capsules containing both hydrophilic and hydrophobic polymers (b): Floatation behaviour of the capsules using static volume beaker method (c): Floatation behaviour of the capsules using USP paddle type apparatus

| Formulation code | HPMC K15 | Eudragit S100 | Drug |
|------------------|----------|---------------|------|
| F 1              | 175.0 mg | 175.0 mg      | 200.0 mg |
| F 2              | 233.4 mg | 116.6 mg      | 200.0 mg |
| F 3              | 262.5 mg | 87.5 mg       | 200.0 mg |
| F 4              | 116.6 mg | 233.4 mg      | 200.0 mg |
| F 5              | 87.5 mg  | 262.5 mg      | 200.0 mg |

Matrix integrity, n=3

| Formulation code | Floating/buoyancy time (h), n=3 |
|------------------|--------------------------------|
| F 1              | ++++                           |
| F 2              | ++++                           |
| F 3              | ++++                           |
| F 4              | ++                             |
| F 5              | +                              |

('++++' ≥ 12 h; '++++' = 10-12h; '++' = 7-10h and '+' = 4-7 h)

Table 3: (a): Composition of Gastro-retentive capsules containing lactose (b): Floatation behaviour of the capsules using USP paddle type apparatus

| Formulation code | HPMC K15 | Eudragit S100 | Lactose | Drug |
|------------------|----------|---------------|---------|------|
| F 1              | 175 mg   | 175 mg        | 55 mg   | 200 mg |
| F 2              | 233.4 mg | 116.6 mg      | 55 mg   | 200 mg |
| F 3              | 262.5 mg | 87.5 mg       | 55 mg   | 200 mg |

Matrix integrity, n=3

| Formulation code | Floating/buoyancy time (h), n=3 |
|------------------|--------------------------------|
| F 1              | +                               |
| F 2              | ++                              |
| F 3              | ++++                            |

('++++' ≥ 12 h; '++++' = 10-12h; '++' = 7-10h and '+' = 4-7 h)

Out of nine formulations, F 3l, F 3l1, F 3l5 and F 3l15 remained intact and floated for more than 12 h. F 3u, F 3u1, F 3u5, F 3u and F 3u15 were intact and buoyant up to 9.0, 5.5, 11.0, 10.0 and 6.5 h respectively. These results showed that gastro-retentive capsules which contained 0 level (262.5 mg) of HPMC K15 showed greater matrix integrity and buoyancy with all levels of Eudragit S100 (F 3l, F 3l1, F 3l5 and F 3l15) than the capsules containing-1 (236.25 mg) and+1 (288.25 mg) levels of HPMC K15;+1 level was stable only with one level (+1) of Eudragit S100 (F 3l15). When+1 level of HPMC K15 was taken into consideration, an increase in floating time (from 6.5 to more than 12 h) was observed with increase in eudragit level from-1 to+1 level of HPMC K15. It may be interpreted that matrix integrity and floating time increased with increase in HPMC K15. A difference of one hour in floating times was observed between-1 and+1 levels of HPMC (containing the same level of eudragit S100). Thus it may be inferred that as time increases in matrix integrity and buoyancy time because of the formation of stable gel matrix layer which keeps the dosage form intact. In-1 HPMC level amount of HPMC may not be sufficient to form stable outer gel matrix layer; as a result, there is disruption of capsules into smaller fragments which may escape lower parts of GIT. If HPMC is not present in sufficient amounts, a complete gel layer may not form [21]. As there is an increase in HPMC content the gel matrix becomes stronger [25]. As the HPMC level increases [from 0 to+1 level], there is an increase in water imbibition, due to which there is an increase in density of the dosage form. At a point where density exceeds the density of the gastro fluid, the dosage form loses buoyancy (sinks). Increase in eudragit level has increased matrix integrity with all levels of HPMC (fig. 1). Eudragit S100 is an anionic methyl methacrylate copolymer insoluble in aqueous medium.

The combination of HPMC and polymethacrylates, most notably anionic polymers form an insoluble mass. Also, anionic polymers increase the gel strength and also show higher residence time within the matrix gel [22]. Because of these reasons, i.e. hydrophobic nature, the formation of solid mass with HPMC and higher residence time within matrix gel layer, there is enhanced matrix integrity/ buoyancy due to the addition of eudragit S100.
Table 4: (a): Factors (independent variables), factor levels and responses (dependent variables) used in 3² factorial experimental design
(b) composition of the gastro-retentive capsules (c): Floatation behaviour of the capsules

(a) Table 4: (a): Factors (independent variables), factor levels and responses (dependent variables) used in 3² factorial experimental design

| Factors          | Factor level | Response |
|------------------|--------------|----------|
| X1= Amount of HPMC K15M | 236.25       | 262.50   | 288.25   |
| X2= Amount of Eudragit S100 | 78.75        | 87.50    | 96.25    |

Y1 = Matrix integrity
Y2 = Floating time

(b) Table 4: (b) composition of the gastro-retentive capsules

| Formulation code | F 3L | F 3La | F 3Lb | F 3Lc | F 3Ld | F 3L e | F 3Lf | F 3Lg | F 3Lh |
|------------------|------|-------|-------|-------|-------|-------|-------|-------|-------|
| Drug             | 200.00 | 200.00 | 200.00 | 200.00 | 200.00 | 200.00 | 200.00 | 200.00 | 200.00 |
| HPMC K15M        | 262.50 | 262.50 | 262.50 | 236.25 | 236.25 | 236.25 | 236.25 | 288.25 | 288.25 |
| Eudragit S100    | 87.50  | 78.75  | 78.75  | 78.75  | 78.75  | 78.75  | 78.75  | 78.75  | 96.25  |
| Lactose          | 55.00  | 63.75  | 46.25  | 81.25  | 90.00  | 72.50  | 29.25  | 38.00  | 20.50  |

(c) Table 4: (c) formulation code with matrix integrity, n=3

| Formulation code | Matrix integrity, n=3 | Floating/buoyancy time (h), n=3 |
|------------------|------------------------|-------------------------------|
| F 3L             | ++++                   | ++++                          |
| F 3La            | ++++                   | ++++                          |
| F 3Lb            | ++++                   | ++++                          |
| F 3Lc            | ++                     | ++                            |
| F 3Ld            | +                      | +                             |
| F 3Le            | +++                    | +++                           |
| F 3Lf            | +++                    | +++                           |
| F 3Lg            | +                      | +                             |
| F 3Lh            | +++                    | +++                           |

*++++* ≥ 12 h; ‘+++’ = 10-12 h; ‘++’ = 7-10 h and ‘+’ = 4-7 h

CONCLUSION
Gastro-retentive capsules of ofloxacin were successfully formulated with the help of low-density polymers with desired floating time. Effect of various polymers including release rate modifier on matrix integrity and buoyancy were also studied; from which it was concluded that use of lower levels of HPMC K15M was unable to form stable outer colloidal gel layer thus unable to hold the contents intact. As the ratio of HPMC increased an increase in floating time was noted. Excessive amounts of HPMC decreased floating time because of increase in density of dosage forms. Eudragit L 100 and S 100 increased floating behaviour of gastro-retentive capsules, however, Eudragit S100 gave better results than Eudragit L 100. 3² Factorial design was used to study effect of independent variables (X1= amount of HPMC K15M, X2= amount of Eudragit S100) on matrix integrity and floating time (dependent variables): from which it was concluded that increase in eudragit level from -1 to 0 to +1 level increased floating time with all levels of HPMC, which was attributed to water insolubility of eudragit S100, formation of insoluble mass with HPMC, longer residence time of eudragit S100 within gel matrix layer; however eudragit S100 level should not surpass HPMC which causes a negative effect because of formation of incomplete and unstable gel matrix layer. Use of release rate modifier (lactose) caused a decrease in floating behaviour of the said formulations due to decrease in osmotic pressure within dosage form.

Thus to have gastric retention of such capsules over extended periods of time, an appropriate ratio of the drug and such ingredients is a need.

CONFLICT OF INTERESTS
Declared none

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