

Fabrication and evaluation of levofloxacin hemihydrate floating tablet

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Abstract

The objective of this work was to develop and evaluate the levofloxacin hemihydrate floating formulations (F1-F9). Selection of optimized batch was done by model dependent approach and novel mathematical approach. F1-F9 batches were prepared by direct compression method using Gelucire 43/01 (hydrophobic) and hydroxypropylmethylcellulose (hydrophilic) polymer in different ratios. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and *in vitro* release studies. Various models were used to estimate kinetics of drug release. The criteria for selecting the most appropriate model were based on the goodness-of-fit test and lowest sum of square residual and Fischer's ratio. *In vitro* release study reveals that the release rate of drug was decreased by increasing the proportion of Gelucire 43/01, 5 to 40%. The release rate of levofloxacin hemihydrates from matrices was mainly controlled by the hydrophilic and hydrophobic polymer ratio. Matrix tablet containing 25% HPMC K4M and 15% Gelucire 43/01 (F4 batch) showed a release as target profile. Optimal batch (F4) was selected by regression analysis which followed Higuchi kinetic. Novel mathematical approach was applied to determine the deviation in area under the curve between predicated and observed dissolution data which found to be lowest in optimal batch. The drug release was found to be function of ratio of hydrophobic to hydrophilic matrixing agents.

Keywords: Levofloxacin hemihydrate; Floating tablet; Hydroxypropylmethyl cellulose; Gelucire

INTRODUCTION

In a relatively short time span, *Helicobacter pylori* (*H. pylori*) has been recognized as a major gastric pathogen with worldwide distribution (1). *H. pylori*, human-specific pathogen, is a causative organism in chronic active gastritis, duodenal ulcers and gastric adenocarcinoma (2,3). The pathogen is susceptible to many antibiotics *in vitro* but it is difficult to eradicate it *in vivo* (4). Extended resident time of the antimicrobial agents is desirable for effective eradication of *H. pylori* (1,5). In order to extend the gastric residence period, a number of approaches have been developed such as floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices (6-8).

Levofloxacin hemihydrate, a synthetic fluorinated quinolone derivative, is effective

for the treatment of *H. pylori* (9-12). The failure of the antibiotic therapy can be avoided by providing the effective concentration of drug at the site of action (13). In the present study, an attempt has been made to formulate levofloxacin floating tablets with the use of hydroxypropyl methyl cellulose (HPMC K4M) and release-retarding hydrophobic polymer Gelucire 43/01. Gelucire, chemically the mixtures of mono-, di- and tri-glycerides with polyethylene glycol (PEG) esters of fatty acids, was used in the combination with hydrophilic polymer, HPMC K4M, to control the release of highly water soluble levofloxacin hemihydrates. The change in composition of matrixing agents may influence the change in mechanism of drug release. It is therefore, very essential that the formulated products release the drug by the same mechanism for drawing meaningful conclusion in research. If the kinetics of drug release is known, it can also be advanced for the

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Table 1. Composition of tablet formulations of levofloxacin hemihydrates floating tablets.

| Sr. No | Ingredients | Fractions | | | | | | | | |
|--------|-------------------------------|-----------|----|----|----|----|----|----|----|----|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 1 | Levofloxacin hemihydrates (%) | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| 2 | Gelucire 43/01 (%) | - | 5 | 10 | 15 | 20 | 25 | 15 | 18 | 40 |
| 3 | Methocel HPMC* K4M (%) | 40 | 35 | 30 | 25 | 20 | 15 | 35 | 22 | - |
| 4 | Sodium bicarbonate (%) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

*HPMC indicates hydroxypropyl methylcellulose. 2% w/w talc, and 1% w/w magnesium stearate; the average weight of each tablet was 515 mg.

establishment of *in vivo* - *in vitro* correlation (IVIVC). Therefore, kinetic study forms an integral part in this study. The aim of the present investigation was to develop a site specific sustained dosage form of levofloxacin hemihydrates using a combination of hydrophilic and hydrophobic matrixing agents and to study kinetics of drug release.

MATERIALS AND METHODS

Levofloxacin hemihydrate was received as a gift sample from Pharmanza Pvt. Ltd. (Kheda, India). HPMC K4M was a gift from Colorcon Asia Pvt. Ltd. (Goa, India). Gelucire 43/01 (melting point 430 °C, HLB=1) was a gift from Gattefosse (St. Priest, Cedex, France). Sodium bicarbonate, talc and magnesium stearate (analytical grade) were purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). All the other ingredients were of analytical grade.

Preparation of levofloxacin hemihydrate floating tablet

HPMC K4M and Gelucire 43/01 were separately passed through sieve mesh No. 80. Levofloxacin hemihydrate was mixed with these matrixing agents. The other ingredients were sequentially mixed. The lubricated blend was compressed into tablets using 16 mm flat-face round tooling on a minirotary tablet press (Cadmach, Ahmadabad, India). The compression force was adjusted to obtain tablets with crushing strength in the range 5 to 6 kgf. Nine batches of tablets were prepared by direct compression technique according to formula depicted in Table 1.

Characterization of tablets

The formulated tablets were evaluated for

weight variation, crushing strength, friability and content uniformity.

Weight variation

Twenty tablets were selected at random and the average weight of the tablets was determined. The weight of individual tablets was compared with the average weight.

Crushing strength and friability

Crushing strength of levofloxacin tablet was determined by Strong Cobb's hardness tester (Tab-machine, T-SHT-17; Mumbai, India) Friability test was carried out using Roche friabilator (Erection instrument & engineering, Ahmedabad, India). Ten tablets were weighed and subjected to the combined effect of attrition and shock by utilizing a plastic chamber. The friabilator was operated for 100 revolutions (4 min, 25 rpm). The tablets were dedusted and re-weighed to calculate the percentage of friability.

Drug content uniformity

Prepared tablets were accurately weight and finely powdered by pestle in a mortar. A weighed portion of each powder equivalent to 1 mg/ml of prepared tablet was transferred in to a volumetric flask and the drug was extracted with methanol as the solvent. The contents of the flask were sonicated for 10 min and diluted with 0.1 N HCl as the solvent. The samples were analyzed spectrophotometrically at 293 nm.

Analytical method validation and preparation of calibration curve

Stock solution of levofloxacin (100 µg/ml) was prepared in 0.1 N HCl, repeated three consecutive days and each day in triplicate to find the inter- and intra-day variations. It was

further diluted to obtain the known standard solutions in range of 1-10 µg/ml. Absorbance was measured spectrophotometrically (Shimadzu UV/Visible spectrophotometer 2100; Tokyo, Japan) at 293 nm. The mean data (n=9) were used for the preparation of calibration curve. The concentration of the dissolved drug was calculated from regression equation obtained from calibration curve.

In vitro buoyancy studies

The *in vitro* buoyancy was determined by the method described by Rosa et al (14). The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface was determined as floating lag time.

Dissolution study of prepared formulations

Dissolution studies of the tablets were conducted using USP II apparatus (paddle). The dissolution medium was 900 ml of 0.1 N HCl at 37 ± 0.5 °C. The agitation rate of paddle was 50 rpm. Five ml sample aliquots were withdrawn up to 10 hr and an equal volume of the fresh medium was replaced. The drug content was determined spectrophotometrically at 293 nm.

Kinetic modeling of drug release

In vitro drug release data were fitted to kinetic models such as zero order (15), first order (16), Higuchi equation (17), Korsmeyer et al. equation (18) and Hixson Crowell equation (19). The regression analysis was performed. Q_t vs. t (zero order); log percentage remaining Q_t vs. t (first order), Q_t vs. square root of t (Higuchi), log $Q_t\%$ vs. log $t\%$ (Korsmeyer-Peppas), and Q_t vs. cube root of t (Hixson Crowell), where Q_t is the amount of levofloxacin released at time t . The criteria for selecting the most appropriate model were sum of square of residuals (SSR) and Fischer's ratio. SSR is the statistical tool which helps to find the discrepancy between the data and our estimation model. Fischer's ratio is the ratio of mean square between samples to mean square within samples (20).

Higuchi tried to co-relate the rate of drug release to physical constants, based on simple law of diffusion.

$$Q = [D (2C - C_s) C_s t]^{1/2} \quad \text{Eq. 1}$$

Where Q is the amount of the drug released in time (t) per unit area, C is the initial drug concentration, C_s is the drug solubility and D is the diffusivity of the drug molecules in the matrix. Eq. 2 is a simplified form of Eq. 1.

$$Q = k_H t^{1/2} \quad \text{Eq. 2}$$

Where k_H is the Higuchi dissolution constant. Eq. 2 was used to determine the Higuchi release rate constants of different formulations. Regression analysis was adopted to compute constants. Gohel et al. (2000) proposed mathematical approach for the determination of deviation in Higuchi release profile (21). The rationale behind this study was to select an optimized batch by evaluating the deviation of dissolution data using area under the curve (AUC) based on mathematical approach as well as goodness-of-fit to the kinetic models.

Mathematical approach

Novel approach of deviation from Higuchi model, proposed by Gohel et al., was used to evaluate deviation between predicted and observed dissolution profile of floating formulations (21). Predicted percentage of drug release versus square root of time was considered as a reference line. AUC at zero % deviation for the predicted and observed data were calculated by using Eq. 3. The dissolution profile was compared by taking the absolute difference (residual) between the predicted and observed AUC data.

$$AUC_{t \text{ hr}, 0\% \text{ deviation}} = \left[\frac{k_H \sqrt{t-n}}{2} \right] \times (\sqrt{t} - \sqrt{t-n})$$

$$AUC_{t \text{ hr}, 0\% \text{ deviation}} = \frac{k_H}{2} \times n \quad \text{Eq. 3}$$

Where k_H , t , and n are Higuchi dissolution constant, time and difference between two successive sampling time points, respectively. The predicted and observed data were used to calculate the sum of square of residuals as well as mean sum of square values for optimized batch among all the models.

Swelling studies

Radial swelling of the matrices was monitored by immersing the tablet in a beaker

Table 2. Physico-chemical characterization and floating lag time of levofloxacin hemihydrates floating tablets.

| Batch | Crushing strength (kgf) | Content uniformity (%) | Friability (%) | Floating lag time (s) |
|-------|-------------------------|------------------------|----------------|-----------------------|
| F1 | 4.2 ± 0.2 | 98.5 ± 1.0 | 0.45 | 258 ± 1.2 |
| F2 | 6.2 ± 0.4 | 98.6 ± 2.5 | 0.27 | 298 ± 2.2 |
| F3 | 4.0 ± 0.3 | 97.4 ± 2.7 | 0.42 | 312 ± 1.5 |
| F4 | 4.5 ± 0.2 | 97.3 ± 1.2 | 0.40 | 320 ± 2.2 |
| F5 | 5.1 ± 0.1 | 98.9 ± 1.4 | 0.27 | 385 ± 1.7 |
| F6 | 6.0 ± 0.2 | 99.0 ± 1.5 | 0.28 | 464 ± 1.0 |
| F7 | 4.3 ± 0.3 | 100.0 ± 0.3 | 0.41 | 375 ± 1.5 |
| F8 | 4.5 ± 0.4 | 98.0 ± 1.6 | 0.41 | 425 ± 1.9 |
| F9 | 4.0 ± 0.2 | 99.0 ± 1.1 | 0.48 | 465 ± 2.8 |

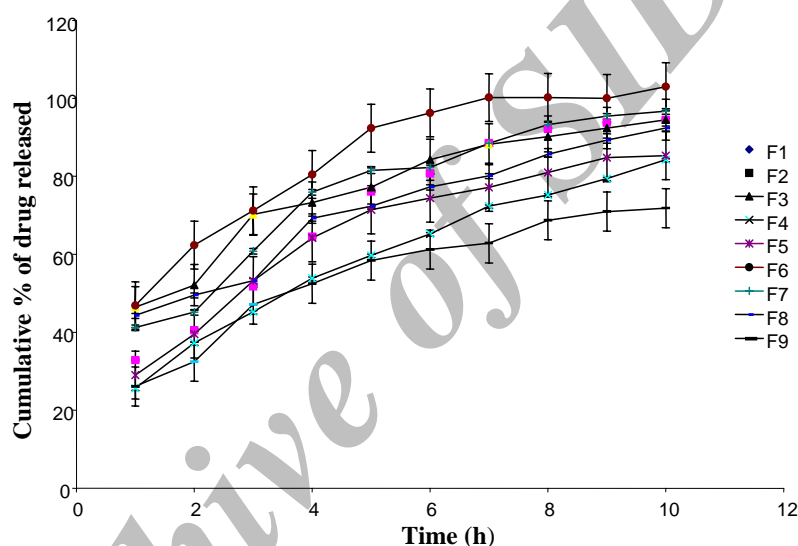


Fig. 1. Cumulative % of drug release vs. square root of time for F1 to F9 batches. The formulations containing HPMC K4 M showed early release. As the concentration of Gelucire 43/01 increased, the drug release was retarded. For example, the drug release profiles from the formulations, F5, F6, F7, F8 which contained higher concentrations of Gelucire 43/01 was retarded.

containing 250 ml of 0.1 N HCl (pH 1.2). The increase in the tablet diameter was measured at predefined times over a period of 24 h. The swelling index (SI), expressed as percentage, and was calculated from the following Eq. 4, similar to the study of Deshpande et al. (22):

$$SI = \frac{\text{Tablet diameter at time (t)} - \text{Initial diameter of tablet}}{\text{Initial diameter of tablet}} \times 100$$

RESULTS

The tablets of levofloxacin hemihydrates were prepared by direct compression using HPMC K4M, Gelucire 43/01 and sodium

bicarbonate. Magnesium stearate and talc were used as lubricant and glidant, respectively. The data of physical parameters like thickness, content uniformity, weight variation, length of the tablet and floating lag time, of all the formulations is enclosed in Table 2. All the parameters lie within the limits. The average weight of the tablets was 515 mg and the weight variation for every batch was less than ± 4%. The hardness was maintained as 4 to 6 kgf in all the formulations. The friability of all the formulations falls in the acceptable limit. The floating lag time ranged from 258 to 464 s. As the concentration of HPMC K4M

Table 3. Regression analysis (F1 to F9) of levofloxacin hemihydrate floating tablet in gastric fluid (pH 1.2).

| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|-------------------------|--------|--------|--------|--------|---------|--------|---------|---------|--------|
| Zero order | | | | | | | | | |
| b | 8.73 | 8.03 | 7.47 | 7.41 | 7.39 | 7.26 | 7.99 | 6.95 | 6.25 |
| a | 21.36 | 19.80 | 14.66 | 17.28 | 20.63 | 20.04 | 20.70 | 23.61 | 18.94 |
| r² | 0.89 | 0.90 | 0.94 | 0.91 | 0.83 | 0.86 | 0.86 | 0.83 | 0.85 |
| SSR | 991.48 | 715.78 | 369.78 | 528.10 | 1152.66 | 87.70 | 1058.29 | 1078.32 | 720.68 |
| F | 110.16 | 79.53 | 41.08 | 58.67 | 128.07 | 96.85 | 117.58 | 119.81 | 80.06 |
| First order | | | | | | | | | |
| b | -0.30 | -0.22 | -0.18 | -0.17 | -0.17 | -0.16 | -0.20 | -0.16 | -0.12 |
| a | 4.66 | 4.58 | 4.63 | 4.53 | 4.44 | 4.45 | 4.50 | 4.40 | 4.43 |
| r² | 0.98 | 0.98 | 0.90 | 0.99 | 0.96 | 0.97 | 0.98 | 0.96 | 0.95 |
| SSR | 217.52 | 236.93 | 526.09 | 84.65 | 389.09 | 234.53 | 169.58 | 420.50 | 340.88 |
| F | 24.16 | 26.32 | 58.45 | 9.40 | 43.23 | 26.05 | 18.84 | 46.72 | 37.87 |
| Higuchi | | | | | | | | | |
| b | 31.81 | 29.09 | 26.32 | 26.86 | 27.58 | 26.89 | 29.26 | 26.20 | 23.27 |
| a | -0.06 | 0.56 | -1.71 | -0.49 | 1.26 | 1.44 | 0.55 | 4.88 | 2.66 |
| r² | 0.98 | 0.98 | 0.96 | 0.99 | 0.96 | 0.98 | 0.97 | 0.97 | 0.98 |
| SSR | 123.21 | 107.35 | 206.65 | 4.96 | 230.61 | 90.28 | 161.86 | 146.37 | 83.67 |
| F | 13.69 | 11.92 | 22.96 | 0.55 | 25.62 | 10.03 | 17.98 | 16.26 | 9.29 |
| Hixson crowell | | | | | | | | | |
| b | 0.29 | 0.24 | 0.20 | 0.196 | 0.19 | 0.19 | 0.22 | 0.18 | 0.14 |
| a | 0.17 | 0.19 | 0.10 | 0.19 | 0.30 | 0.27 | 0.25 | 0.35 | 0.28 |
| r² | 0.98 | 0.98 | 0.94 | 0.98 | 0.92 | 0.94 | 0.96 | 0.93 | 0.92 |
| SSR | 173.04 | 273.62 | 343.29 | 190.79 | 594.07 | 401.97 | 407.03 | 607.44 | 445.41 |
| F | 19.22 | 30.40 | 38.14 | 21.19 | 66.00 | 44.66 | 45.22 | 67.49 | 49.49 |
| Korsmeyer et al. | | | | | | | | | |
| b | 0.50 | 0.46 | 0.48 | 0.51 | 0.55 | 0.50 | 0.54 | 0.42 | 0.46 |
| a | -0.50 | -0.50 | -0.58 | -0.58 | -0.59 | -0.56 | -0.56 | -0.49 | -0.58 |
| r² | 0.98 | 0.95 | 0.94 | 0.99 | 0.93 | 0.98 | 0.95 | 0.97 | 0.97 |
| SSR | 125.89 | 118.54 | 245.38 | 5.20 | 330.86 | 100.44 | 218.00 | 83.00 | 65.71 |
| F | 15.73 | 14.81 | 30.67 | 0.65 | 41.35 | 12.55 | 27.25 | 10.37 | 8.21 |

b = slope, a = intercept, r^2 = Square of correlation coefficient, F = Fischer's ratio

increased (15%, 20%, 25%, and 40% w/w of drug), the floating lag time decreased. The swelling characteristic of formulation F4 was examined in HCl (pH 1.2) for 10 h. The size of the tablet was found to increase 1.5 times compared to initial diameter after 10 h.

As shown in Fig. 1 the formulations containing HPMC K4 M showed early release. As the concentration of Gelucire 43/01 increased, the drug release was retarded.

Table 3 shows the result of regression analysis of F1-F9 batches on fitting various kinetic models. The next step in this investigation was batch selection. The Higuchi model showed lowest sum of square residual for F1 to F7 batches. The F8 and F9 batches showed insignificant difference between Korsmeyer-Peppas, and Higuchi models. Higuchi's square root model showed highest

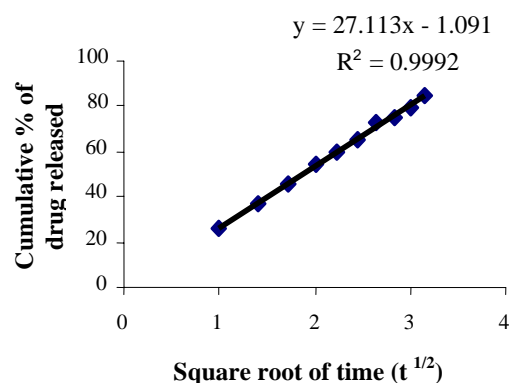


Fig. 2. Liner regression plot for F4 batch (Higuchi). When the cumulative percents of drug release were plotted as function of square root of time at which they were obtained, a nearly straight line plot was obtained. The coefficient of linear regression of the line was 0.9992 and it follows diffusion mechanism.

Table 4. Deviations for F4 batch from the ideal Higuchi release profile.

| Time (h) | Square root of time (hr) | Predicted Higuchi release profile | | Observed release profile | | error % between AUCs |
|----------|--------------------------|-----------------------------------|-------|--------------------------|-------|----------------------|
| | | CPR* | AUC | CPR | AUC | |
| 1 | 1.0 | 26.02 | 13.11 | 25.68 | 12.84 | 1.03 |
| 2 | 1.41 | 37.13 | 13.16 | 37.25 | 13.2 | 0.10 |
| 3 | 1.73 | 45.81 | 13.23 | 45.23 | 13.07 | 0.34 |
| 4 | 2.0 | 53.13 | 13.28 | 53.84 | 13.46 | 0.33 |
| 5 | 2.24 | 59.64 | 13.31 | 59.74 | 13.33 | 0.08 |
| 6 | 2.45 | 65.33 | 13.33 | 65.23 | 13.31 | 0.03 |
| 7 | 2.65 | 70.75 | 13.34 | 72.36 | 13.65 | 0.43 |
| 8 | 2.83 | 75.63 | 13.36 | 75.23 | 13.29 | 0.09 |
| 9 | 3.0 | 79.91 | 13.31 | 79.45 | 13.24 | 0.08 |
| 10 | 3.16 | 84.58 | 13.38 | 84.32 | 13.34 | 0.04 |

*CPR indicates cumulative percentage drug released; AUC indicating area under the curve.

correlation coefficient for F4 ($r^2 = 0.9992$).

Fig. 2 represents the liner regression plot for F4 batch. In general, the release pattern of levofloxacin from floating tablets was found to be diffusion.

Table 4 shows that the absolute difference between observed and calculated release profile was very small. Therefore, it can be concluded that the drug is released by diffusion mechanism. The result can be used for setting IVIVC. The swelling characteristic of formulation F4 was examined in HCl (pH 1.2) for 10 h. The size of the tablet was found to increase 1.5 times compared to initial diameter after 10 h. The increase in size may also prevent passage of non-disintegrating swollen tablet from stomach to intestine via pyloric sphincter and help to improve its gastric retention.

DISCUSSION

In this study, direct compression was adopted considering its advantages such as simple technology and saving of time. Crushing strength of the tablet was between 4 to 6 kgf and was maintained for all the batches in order to minimize the effect of crushing strength on the drug release. The acceptable results of crushing strength measurement also reveal that the drug and the excipients were possessing satisfactory compressibility. Drug content uniformity in all formulations was calculated and was found satisfactory.

Friability of all the formulations was found satisfactory (<1%) showing enough resistance to the mechanical shock and abrasion. Sodium bicarbonate in the acidic environment reacts with the acid and produces carbon dioxide. The evolved gas will get entrapped in the matrix leading to floating of the tablet. The formulations (F1 to F9) contained different ratios of HPMC K4M which showed different lag times. This may be due to variation in the mechanism of action of different swelling agents. HPMC K4M produced its action by both swelling and wicking in the presence of water, because of which the density of dosage form was reduced. Formulations F2, F3, F5, F6, and F8 showed high lag time due to higher preposition of Gelucire 43/01. Hydrophobic properties of Gelucire 43/01 retarded the swelling of matrix. Tablet formulation did not swell and float easily.

The results of *in vitro* dissolution studies are shown in Fig. 1. The higher initial drug dissolution was observed in tablets containing higher proportion of HPMC K4M (F1, F2, F3 and F4) as compared to F6, F8, F9. It showed that HPMC more rapidly release the drug compared to Gelucire 43/0. F7, F5 and F9 batches were exhibited very slow and had incomplete release after 10 h. F4 and F7 batches were selected for further data treatment.

In order to investigate the drug release kinetics, data were fitted to various kinetic models such as zero order, first order, Higuchi,

Korsemeier et al., and Hixson Crowell. The target profile design parameters of a SR product were as follows: after 2 h: $35 \pm 15\%$, after 4 h: $60 \pm 15\%$ and after 8 h: $90 \pm 15\%$ (23). It was decided to select a batch which showed less than 30% drug in first h. F1, F2, F3 and F8 batches failed to meet the stated criteria. The drug release from F5, F6, and F9 batches were very slow in terminal phase (3% between 8 to 10 h). The drug release from these batches may be incomplete. The final selection was done between F4 and F7 batches. The value of regression coefficient of F4 batch ($r^2 = 0.9992$) was higher than that of F7 batch ($r^2 = 0.9797$). Hence F4 batch was selected for final data treatment. The result revealed that mechanism of drug release was not changing by changing the formulation of F1-F9 batches. The next step in this investigation was batch selection. The Higuchi model showed lowest sum of square residual for F1 to F7 batches. F8 and F9 batches showed insignificant difference between Korsemeier-Peppas, and Higuchi models. Higuchi's square root model showed the highest correlation coefficient for F4 ($r^2 = 0.9992$).

The values of the release rate (k_H), being a direct function of matrix solubility, was found to decline by increasing the amount of Gelucire 43/01. The Higuchi slope ranged from 31.81 to 23.27 k_H ($h^{-1/2}$) for F1-F9 batches. As the concentration of HPMC K4M was increased in the formulation, the release rate was found to be increased.

CONCLUSION

The effervescent-based floating drug delivery is a promising approach to achieve *in vitro* buoyancy. The addition of gel-forming polymer (HPMC K4M), release retarding matrixing agent (Gelucire 43/01) and gas-generating agent (sodium bicarbonate) was essential to achieve *in vitro* buoyancy. Formulation F4 showed controlled drug release and adequate floating properties. The kinetics of drug release was best explained by Higuchi model. Further, it is concluded that AUC based mathematical approach can be used to quantify deviation in Higuchi model.

REFERENCES

- Warren JR, Marshall B. Unified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet*. 1983;321:1273-1275.
- Megraud F, Lamouliatte H. *Helicobacter pylori* and duodenal ulcers. *Dig Dis Sci*. 1992;37:769-772.
- Forman D, Webb P, Parsonnet J. *Helicobacter pylori* and gastric cancer. *Lancet*. 1994;343:243-244.
- Evans DG, Evans DJ, Graham DY. Adherence and internalization of *Helicobacter pylori* by Hep-2 cells. *Gastroenterology*. 1992;102:1557-1567.
- Shah S, Qaqish R, Patel V, Amiji M. Evaluation of the factors influencing stomach-specific delivery of antibacterial agents for *Helicobacter pylori* infection. *J Pharm Pharmacol*. 1999;51:667-672.
- Moes AJ. Gastroretentive dosage forms. *Crit Rev Ther Drug Carrier Syst*. 1993;10:143-195.
- Talukder R., Fassihi R. Gastroretentive delivery systems: a mini review. *Drug Dev Ind Pharm*. 2004;30:1019-1028.
- Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. *J Control Rel*. 1998;55:3-12.
- Di Caro S, Zocco AM, Cremonini F, Candelli M, Nista EC, Bartolozzi F, et al. Levofloxacin-based regimens for the eradication of *Helicobacter pylori*. *Eur J Gastroenterol Hepatol*. 2002;14:1309-1312.
- Cavallaro LG, Egan B, O'Morain C, Di Mario F. Treatment of *Helicobacter pylori* infection. *Eur Gastroenterol Rev*. 2005;1:56-59.
- Enrico CN, Marcello C, Maria AZ, Filippo C, Veronica O, Rosalba F, et al. Levofloxacin-based triple therapy in first-line treatment for *Helicobacter pylori* eradication. *Am J Gastroenterol*. 2006;9:1985-1990.
- Nista EC, Candelli M, Zocco MA, Cremonini F, Ojetti V, Finizio R, et al. Levofloxacin-based triple therapy in first-line treatment for *Helicobacter pylori* eradication. *Am J Gastroenterol* 2006;9:1985-1990.
- Majithiya RJ, Murthy RSR. Chitosan-based mucoadhesive microspheres of clarithromycin as a delivery system for antibiotic to stomach. *Curr Drug Deliv*. 2005;8:235-242.
- Rosa M, Zia H, Rhodes T. Design and testing *in vitro* of a bioadhesive and floating drug delivery system for oral application. *Int J Pharm*. 1994;105:65-70.
- Brazel CS, Peppas NA. Modeling of drug release from swellable polymers. *Eur J Pharm Biopharm*. 2000;49:47-58.
- Lapidus H, Lordi NG. Some factors affecting the release of a water soluble drug from a compressed hydrophilic matrix. *J Pharm Sci*. 1966;55:840-843.
- Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci*. 1963;52:1145-1148.

18. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. *Int J Pharm.* 1983;15:25-35.
19. Hixson AW, Crowell JH. Dependence of reaction velocity upon surface and agitation: theoretical considerations. *Ind Eng Chem.* 1931;23:923-931.
20. Bolton S, Bon C. *Pharmaceutical statistics: practical and clinical applications.* 2nd ed. New York: Marcel Dekker; 1990.
21. Gohel MC, Panchal MK, Jogani VV. Novel mathematical method for quantitative expression of deviation from the Higuchi model. *AAPS Pharm Sci Tech.* 2000;1:45-50.
22. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. *Pharm Res.* 1997;14:815-819.
23. Cohen JL, Hubert BB, Leeson LJ, Rhodes CT, Robinson JR, Roseman TJ, et al. The development of USP dissolution and drug release standards. *Pharm Res.* 1990;10:983-987.

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