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# Formulation and evaluation of effervescent floating tablet of levofloxacin

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## ABSTRACT

*Levofloxacin effervescent sustained release tablets were developed in eight different formulations (F1 to F8) by employing different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid. The formulations were evaluated for various physical parameters, dissolution parameters and drug released mechanisms. F8 formulation showed maximum floating time of 12 hours and gave slow and maximum drug release of Levofloxacin spread over 12 hours and whereas Levofloxacin released from marketed tablet was rapid and maximum within 8 hours.*

**Key Words:** Levofloxacin, Effervescent sustained release tablet.

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## INTRODUCTION

The concept of floating drug delivery system offers experiencing engaging or choking by some person while swallowing medicinal pills. The researcher suggested that difficulty could overcome by providing pills having a density of less than 1.0g/ml. So that pill will float on water surface since then several approaches have been proposed for ideal floating delivery system. This buoyant delivery system includes hollow microspheres powder granules, tablet, capsules and laminated films.[1]

Effervescent floating drug delivery systems generate gas (CO2), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate. Depending on the mechanism of buoyancy two distinctly different menthods viz. effervescent and non effervescent system have been used in the development of floating drug delivery systems (FDDS).[2,3,4]

Levofloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class[5,6] and is used to treat severe or life-threatening bacterial infections or bacterial infections that have failed to respond to other antibiotic classes.[7,8] It is sold under various brand names, such

as Levaquin and Tavanic, the most common. In form of ophthalmic solutions it is known as Oftaquix, Quixin and Iquix. Levofloxacin is a chiral fluorinated carboxyquinolone. Investigation of ofloxacin, an older drug that is the racemic mixture, found that the l form [the (–)-(*S*) enantiomer] is more active. This specific component is levofloxacin.[9,10]

In present work, effervescent floating tablets of different formulation were developed with an objective of achieving above 12 hrs floating and drug release time and the effervescent floating tablet was compared with marketed formulation of Amlodipine besylate for drug released time.

## MATERIALS AND METHODS

### Materials

Levofloxacin was supplied from Ranbaxy lab., Devas, INDIA. Citric Acid and Sodium Bicarbonate was a kind gift from Rankem lab. Mumbai, INDIA. HPMC and EC was a kind gift from Sulab lab. Barodara. Ethanol and methanol was purchased from Sigma Lab, New Delhi, INDIA. All other Excipients used in our work were of analytical grade.

### Preparation of Floating Tablets of levofloxacin

Effervescent Floating tablets containing levofloxacin were prepared by direct compression technique using varying concentrations of different grades of polymers with Sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, Magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation. The formulation are shown in table I.

### Evaluation of effervescent floating tablet formulations

### Evaluation of Levofloxacin Granules

The flow properties of granules (before compression) were characterized in terms of angle of repose[11], tapped density, bulk density [12], Carr's index [13] and Hausner ratio. Physical evaluation of famotidine floating tablets Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for uniformity of weight using 20 tablets [14], hardness (Monsanto tester)[15], friability using 10 tablets (Roche type friabilator)[15].

### Determination of Swelling Index[14]

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 h. The swelling index (SI), expressed as a percentage, and was calculated from the following equation

$$SI = \frac{\text{Weight of Swollen tablet-Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

### *In vitro* buoyancy studies

In vitro buoyancy studies were performed for all the twelve formulations as per the method described by Rosa et al[16]. The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

### Drug Content Estimation

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 265nm using 0.1 N hydrochloric acid as blank. In vitro dissolution studies The release rate of famotidine from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 265 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

### Stability studies

The promising formulation was tested for a period of 4 weeks at $40^0$C with 75% RH, for their drug content and other parameters.

## RESULTS AND DISCUSSION

Floating tablets levofloxacin were developed to increase the gastric residence time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug to minimum 12 h. The tablets were made using different gel forming polymers such as HPMC along with effervescing agent sodium bicarbonate and citric acid to optimize the drug content, in vitro buoyancy, swelling index and in vitro drug dissolution studies. The selection of viscosity grade of a polymer is an important consideration in the formulation of tablet[17]. All the formulations were prepared by direct compression method. When a combination of gas entrapping as well as controlled release system is there, the use of disintegrating agent is important which does not quickly break the matrix and allows slow disintegration of the swollen matrix. PVP K30 in an optimized concentration (15mg/tablet) was employed for such unique disintegration properties[18-19]. Talc and magnesium stearate were employed for their glidant and lubricant property. The prepared tablets of all the formulations were evaluated for precompression parameters like angle of repose, bulk and tapped density and compressibility index and physical characters like tablet hardness, friability, weight variation buoyancy lag time, total floating time, assay, in-vitro drug release. The main aim was to optimize the formulation for 14 hours in-vitro release and total floating time to more than 12 hours.

### Precompression parameters of Levofloxacin granules

The formulations showed good flow property and compressibility index (Table 2). Angle of repose ranged from 26.35 to 28.46, Hausner ratio ranged from 0.718 to 0.730 and the

compressibility index ranged from 27.30 to 38.23. The bulk density and tapped density of the prepared granules ranged from 0.576±0.002 to 0.593±0.008 and 0.728±0.005 to 0.790±0.008 respectively. The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the flow property.

**Post compression parameters of levofloxacin tablets**

The shape of the tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks.The thickness of tablets was measured by vernier calipers and was ranged between 3.53 ± 0.05 to 4.05± 0.05 mm. The hardness of the tablets was measured by Monsanto tester (Monsanto hardness tester) and was in between 4.5 to 5.3 kg/cm$^2$. The friability was measured by Friabilator (Electrinics India, Himachal Pradesh) and was found to be 0.16± 0.04 to 0.58± 0.10 %, which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of 97.20 ± 0.34 to 99.60 ± 1.39% which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation testas the % weight variation was within the Pharmacopoeial limits of ±5% of the weight. The results are shown in table 3.

All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

**Buoyancy lag time (BLT) and total floating time (TFT)**

Effervescent floating tablet of different formulations were noted, where F1 BLT of 25 sec and TFT of >8 hours, F2 BLT of 35 sec and TFT of >10 hours, BLT of 56 sec and TFT of >12 hours, F4 BLT of 75 sec and TFT of >12 hours, F5 BLT of 60 sec and TFT of >12 hours, F6 BLT of 80 sec and TFT of >12 hours, F7 BLT of 110 sec and TFT of >12 hours, F8 BLT of 125 sec and TFT of >12 hours, With reference to buoyancy studies results it can be concluded that the batch containing HPMC polymers showed good buoyancy lag time (BLT) and total floating time (TFT). Formulation F8 containing Ethyl cellulose showed good BLT of 110 sec and TFT of more than 24 hrs. The results are shown in table no 4.

***In vitro* dissolution studies**

In vitro dissolution studies of all the formulations are shown in Table 5 and figure 1. It was observed that the type of polymer influences the drug release pattern. A significantly higher rate and extent of drug release was observed from the batches based on EC. Drug release from HPMC was lesser owing to its high viscosity and also due to less permeability of water to HPMC.

Moreover the HPMC containing tablets F7-F8 could not bear their matrix shape until 14 h and drug released before 14 h. As expected, the drug release rate was dependent on the viscosity grade and the concentration of the polymer used. This controlled release of drug from F8 could be attributed to the formation of a thick gel structure that delays drug release from the tablet matrix.

Thus a formulation F7 was selected as the promising formulation, containing combination of sodium bicarbonate (15 mg) and citric acid (30 mg) with EC (50 mg), as it achieved optimum in vitro buoyancy, floatability of more than 12 hrs as well as controlled and sustained in vitro drug release.

## Stability study of optimized formulation (F7)

The optimized floating tablets (F7) were selected for stability study on the basis of in vitro drug dissolution studies. The tablets were investigated at 40°C/75% RH for 3 months. From the data, the formulation is found to be stable under the conditions mentioned above since there was minimum significant change in the percentage amount of drug release (Table 6). Thus, it was found that the floating tablets of Levofloxacin (F7) were stable under these storage conditions for at least 3 months.

**Table I. Various formulation of levofloxacin Effervescent sustained release tablets**

| Excipients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| Levofloxacin | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| HPMC | 50 | 50 | 50 | 50 | - | - | - | - |
| Ethyl cellulose | - | - | - | - | 50 | 50 | 50 | 50 |
| PVP K30 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Citric acid | 25 | 20 | 30 | 20 | 25 | 20 | 30 | 20 |
| Sodium bicarbonate | 20 | 25 | 15 | 20 | 20 | 25 | 15 | 20 |
| Magnesium stearate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 20 | 15 | 25 | 25 | 20 | 15 | 25 | 25 |
| PEG | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**Table II : Result of study of physical parameters of Levofloxacin and formulation F1-F8**

| Material | Angle of repose (Degree) | Bulk density (gm/ml) | Tapped density (gm/ml) | Compressibility index | Hausner ratio |
|---|---|---|---|---|---|
| F1 | 28.31 | 0.582±0.002 | 0.732±0.007 | 27.33±0.73 | 0.721±0.01 |
| F2 | 26.35 | 0.581±0.008 | 0.730±0.006 | 28.33±0.72 | 0.723±0.01 |
| F3 | 27.82 | 0.576±0.002 | 0.728±0.005 | 27.30±0.68 | 0.720±0.01 |
| F4 | 27.69 | 0.570±0.007 | 0.729±0.003 | 29.30±0.65 | 0.726±0.03 |
| F5 | 28.30 | 0.580±0.003 | 0.735±0.004 | 30.30±0.61 | 0.730±0.04 |
| F6 | 29.28 | 0.585±0.003 | 0.732±0.006 | 32.80±0.64 | 0.728±0.06 |
| F7 | 28.46 | 0.582±0.004 | 0.742±0.003 | 36.24±0.70 | 0.720±0.03 |
| F8 | 28.04 | 0.582±0.006 | 0.740±0.008 | 38.23±0.61 | 0.718±0.01 |

**Table III : Results of Post Compression Properties of Levofloxacin effervescent Tablets**

| Formulation code | Thickness (mm) | Hardness /cm2) | Weight variation (mg) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 3.53±0.05 | 4.8 | 328.19± 2.94 | 0.58 ± 0.10 | 98.33± 0.92 |
| F2 | 3.94± 0.10 | 4.4 | 332.18 ± 3.77 | 0.51 ± 0.08 | 97.20 ± 0.34 |
| F3 | 3.96± 0.05 | 4.5 | 335.33 ± 1.50 | 0.38 ± 0.12 | 99.60 ± 1.39 |
| F4 | 3.95± 0.05 | 4.7 | 336.30 ± 3.30 | 0.16 ± 0.04 | 98.14 ± 1.69 |
| F5 | 3.93± 0.10 | 5.2 | 327.13 ± 2.83 | 0.31 ± 0.07 | 99.21 ± 1.07 |
| F6 | 4.03± 0.06 | 5.3 | 332.16 ± 2.33 | 0.27 ± 0.05 | 99.50± 1.81 |
| F7 | 4.05± 0.05 | 4.8 | 338.18 ± 3.11 | 0.29 ± 0.08 | 99.34 ± 0.37 |
| F8 | 3.98± 0.05 | 4.5 | 327.04 ± 2.56 | 0.34 ± 0.12 | 98.31± 0.91 |

**Table IV : Results of In vitro buoyancy study of levofloxacin floating time**

| Formulation Code | Buoyancy lag times (sec) | Total Floating Time (hrs) |
|---|---|---|
| F1 | 25s | >8 |
| F2 | 35s | >10 |
| F3 | 56s | >12 |
| F4 | 75s | >12 |
| F5 | 60s | >12 |
| F6 | 80s | >12 |
| F7 | 110s | >12 |
| F8 | 125s | >12 |

**Table V. *In vitro* drug release study of floating tablet**

| Time | % of Drug Release | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (hr) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| **1** | 08.23 | 07.14 | 07.24 | 08.23 | 07.23 | 07.45 | 08.32 | 07.26 |
| **2** | 12.32 | 10.23 | 11.45 | 10.45 | 10.45 | 11.23 | 12.23 | 11.87 |
| **4** | 26.23 | 22.42 | 24.23 | 23.76 | 31.23 | 38.23 | 32.13 | 26.28 |
| **8** | 42.45 | 40.32 | 45.23 | 44.23 | 48.23 | 46.32 | 47.14 | 38.21 |
| **10** | 76.34 | 66.11 | 72.21 | 65.71 | 68.34 | 67.02 | 71.13 | 68.24 |
| **12** | 82.23 | 77.33 | 81.11 | 82.34 | 84.23 | 88.13 | 91.23 | 89.12 |
| **14** | 98.32 | 97.13 | 95.13 | 98.35 | 99.12 | 99.13 | 99.56 | 99.25 |

**Figure I. In vitro Dissolution profile of batches F1-F4**

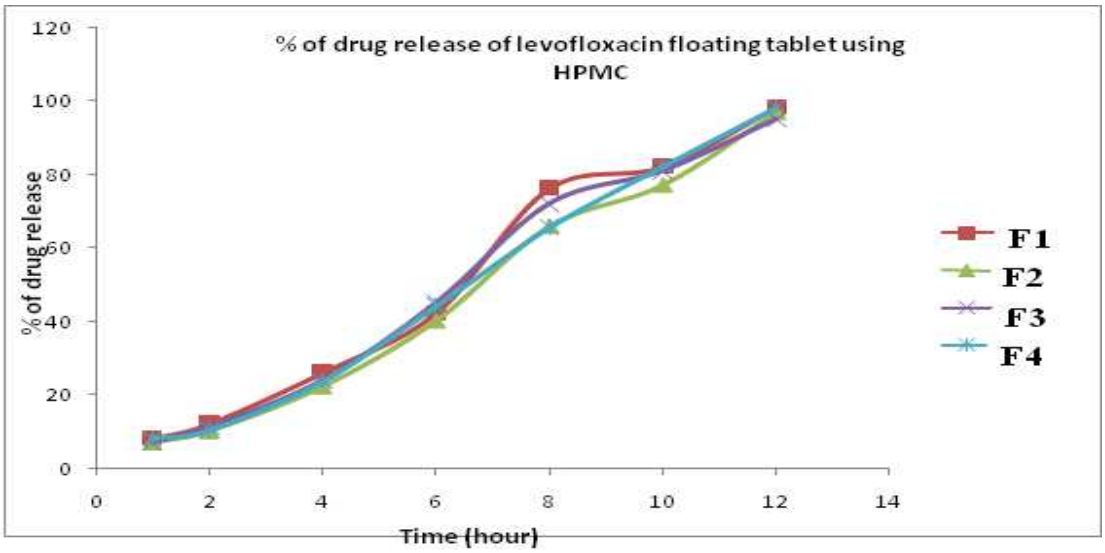


**Figure II. In vitro Dissolution profile of batches F5-F8**

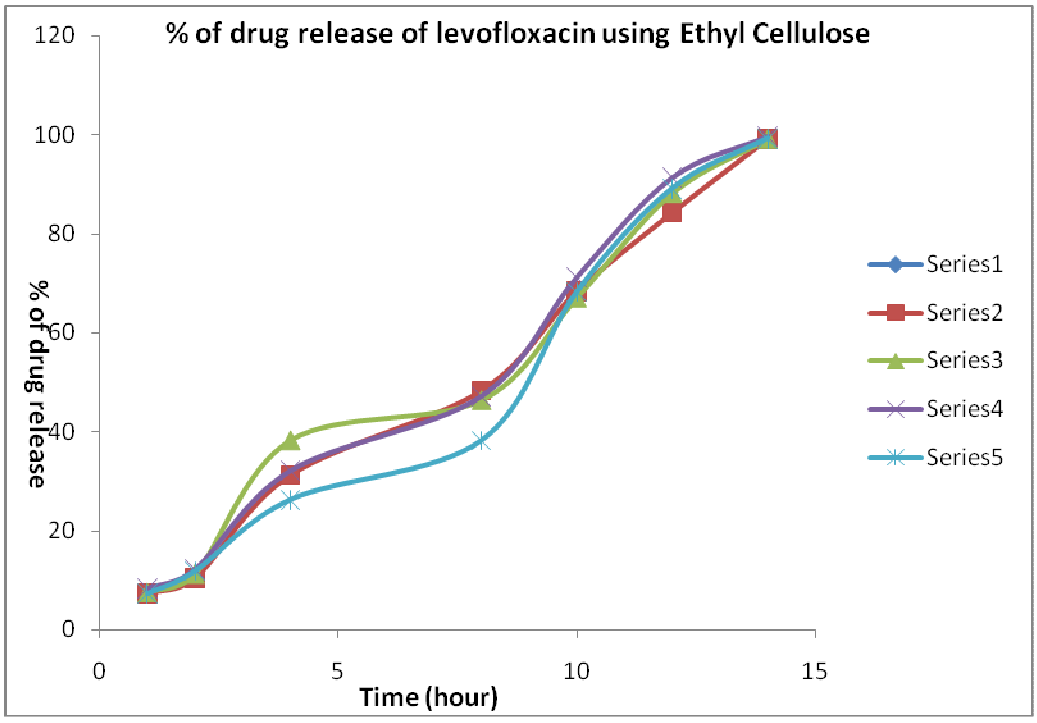

**Table VI. Change in In-vitro Drug Release Profile of Optimized Formulation During Stability Study**

| Product code | Temperature | In-vitro % Drug release profile | | |
|---|---|---|---|---|
| | | At 2 weeks | At 3weeks | At 4 weeks |
| F7 | $4^0$c | 97.7 | 97.04 | 97.43 |
| | $25^0$c | 98.63 | 98.34 | 98.14 |
| | $40^0$c | 98.67 | 98.34 | 98.23 |
| | $50^0$c | 98.69 | 98.47 | 98.03 |

## CONCLUSION

This study discusses the preparation of floating tablets of levofloxacine. The effervescent-based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of polymer HPMC, EC and gas-generating agent sodium bicarbonate was essential to achieve in vitro buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release. The type of polymer affects the drug release rate and the mechanism. Polymer swelling is crucial in determining the drug release rate and is also important for flotation. A lesser FLT and a prolonged floating duration could be achieved by varying the amount of effervescent and using different polymer combinations. The in vitro drug release profiles obtained for tablets (F7) showed a prolonged floating duration (> 12hrs) which was a controlled release characteristic ( 99.58%) for 14 h. Good stability was observed for 3 months during stability studies. Since the formulation showed sufficient release for prolonged period, the dose can be reduced and possible incomplete absorption of the drug can be avoided.

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