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# Studies on Gemifloxacin Mesylate Floating Matrix Tablets

**Ramji Anil Kumar Arza[1,2*], B. Vijaya Kumar[1]**
*1.Jangaon Institute of Pharmaceutical Sciences, Yeshwanthapur, Jangaon-506167, T S, India.*

## ABSTRACT

The aim of the present work was to develop and optimize gastroretentive floating system of Gemifloxacin mesylate using HPMC polymers, Gelucire 50/13 and Polyox WSR 301 to improve oral bioavailability of Gemifloxacin mesylate floating tablets by increasing gastric residence time. The tablets were prepared by direct compression method. The effect of polymers concentration and viscosity grades of HPMC on drug release profile was evaluated. The result of *in vitro* dissolution study showed that the drug release profile could be sustained by increasing the concentration of HPMC and Polyox WSR 301. The optimized formulation (F12) containing HPMC K100M, Gelucire 50/13 and Polyox WSR301 showed 99.12% drug release at the end of 12h. The optimized formulations (F12) containing showed desired buoyancy (floating lag time of about 35 seconds and total floating time of >12h). Optimized formulation (F12) followed diffusion controlled zero order kinetics and non-fickian transport of the drug. FTIR studies revealed the absence of any chemical interaction between drug and polymers used.

**Keywords:** Gemifloxacin mesylate**,** floating drug delivery system, HPMC, WSR 301, floating lag time

*Corresponding Author Email: ramjianil@gmail.com
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## INTRODUCTION

Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Controlled/sustained release preparations using alternating routes have also been formulated but oral route still remains preferable[1,2]. In recent years, peroral dosage forms for gastric retention have attracted more attention for their theoretical advantage in gaining control over time and the site of drug release. This would be particularly valuable for drugs that exhibit an absorption window in the upper part of the small intestine. Various approaches have been used to prepare dosage forms for gastric retention[3]. These systems mainly consist of swelling and expanding systems[4, 5], floating capsules[6, 7, 8], floating pellets[9], and floating granules[10]. Gastric retention of the drugs provides such advantages as better delivery of the drugs with narrow absorption windows in the small intestinal region and longer residence time in the stomach, which could be advantageous for local action in the upper part of small intestine.

One of the novel approaches in the area of oral sustained release drug delivery is gastro retentive drug delivery system (GRDDS)[11]**.** Gastric retention devices are designed to prolong the gastric residence time of oral controlled release dosage forms. Thus result in increased contact time for drugs that act locally, increased absorption of drugs that have absorption windows in upper part of gastrointestinal tract (GIT), and better absorption for drugs less soluble in the intestinal fluid[12]. Gastro retentive drug delivery systems (GRDDS) can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability[13]. Extended-release dosage forms with prolonged residence time in the stomach are highly desirable for drugs with i) narrow absorption windows, ii) stability problems in the intestinal or colonic environment, iii) local action in the stomach, and iv) low solubility at high pH values[14]. Floating matrix tablets are designed to prolong the gastric residence time after oral administration at a particular site. It is useful for achieving controlled plasma level as well as improving bioavailability[15].

Gemifloxacin mesylate is an oral broad-spectrum quinolone antibacterial agent used in the treatment of acute bacterial exacerbation of chronic bronchitis and mild-to-moderate pneumonia. It has low bioavailability of 71% and half life of 7h[16].

The aim of present work is to design and in vitro evaluation of Gemifloxacin mesylate gastro retentive floating tablet using different polymers to release the drug in stomach and upper part of

GIT in a controlled manner which enhance its bioavailability and prolonged drug release in the body.

## MATERIALS AND METHOD

**Materials:**

Gemifloxacin mesylate pure drug was generous gift from Hetero Drugs Ltd**,** Hyderabad, India. HPMC K 4M, K 15M and K100M were obtained from Rubicon labs, Mumbai, India, POLYOX WSR 301 was obtained from Dow chemical's, New York. Gelucire 43/01 and PVP K 30 were gifted from MSN Labs Ltd, Hyderabad. All other excipients and chemicals used were of analytical grade.

**Preparation of Gemifloxacin mesylate floating tablet**

The tablets were prepared by direct compression method. All the ingredients except Gemifloxacin mesylate were passed through # 80 mesh prior to mixing. The ingredients were weighed separately and mixed to get a uniform polymer mixture. The drug was then mixed with the polymer mixture for a period of 30 minutes to ensure uniform mixing of the drug using mortar and pestle. These powder mixtures were lubricated with magnesium stearate and compressed to obtain tablets. The composition of Gemifloxacin mesylate floating tablets was shown in Table 1.

**Table 1: Composition of Gemifloxacin mesylate floating tablets**

| Formulation code | Gemifloxacin mesylate (mg) | HPMC K 4M (mg) | HPMCK 15M (mg) | HPMC K 100M (mg) | WSR* 301 (mg) | $NaHCO_3$ (mg) | Gelucire 50/13 (mg) | Magnesium stearate (mg) | Talc (mg) |
|---|---|---|---|---|---|---|---|---|---|
| F1 | 320 | 80 | --- | --- | 25 | 42 | 30 | 1.5 | 1.5 |
| F2 | 320 | 85 | --- | --- | 20 | 47 | 25 | 1.5 | 1.5 |
| F3 | 320 | 90 | --- | --- | 15 | 52 | 20 | 1.5 | 1.5 |
| F4 | 320 | 95 | --- | --- | 12 | 55 | 15 | 1.5 | 1.5 |
| F5 | 320 | --- | 80 | --- | 25 | 42 | 30 | 1.5 | 1.5 |
| F6 | 320 | --- | 85 | --- | 20 | 47 | 25 | 1.5 | 1.5 |
| F7 | 320 | --- | 90 | --- | 15 | 52 | 20 | 1.5 | 1.5 |
| F8 | 320 | --- | 95 | --- | 12 | 55 | 15 | 1.5 | 1.5 |
| F9 | 320 | --- | --- | 80 | 25 | 42 | 30 | 1.5 | 1.5 |
| F10 | 320 | --- | --- | 85 | 20 | 47 | 25 | 1.5 | 1.5 |
| F11 | 320 | --- | --- | 90 | 15 | 52 | 20 | 1.5 | 1.5 |
| F12 | 320 | --- | --- | 95 | 12 | 55 | 15 | 1.5 | 1.5 |

*WSR= Water soluble resin

**Evaluation of floating tablets**

**a) Thickness**

The thickness of the prepared tablets was tested using vernier calipers. The test was done in triplicate and average was determined.

**b) Hardness**

Hardness of prepared tablets was determined using Monsanto hardness tester and measured in terms of $kg/cm^2$.

**c) Weight variation**

The weight variation test was performed as per the I.P. guidelines. Twenty randomly taken tablets were weighed together and the average weight was determined. Each tablet was then weighed individually and deviation from average weight was calculated.

**d) Friability**

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche friabilator. It was operated for 4min at a speed of 25 rpm, and then the tablets were removed, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,

%Friability= (Loss in weight/ Initial weight) x 100.

**e) Drug content**

Ten tablets for each batch was taken and triturated. Powder equivalent to 100mg of drug was weighed and was transferred to breaker and 0.1N HCl was added and it was then shaken for 5 minutes and finally 0.1N HCl was added to make the volume up to 100ml and solution was then sonicated for 15 minutes and filtered through Whatman filter paper. Finally a solution was diluted suitably and the absorbance of resultant solution was measured to determine the drug content spectrophotometrically at 271nm using UV/Visible spectrophotometer Shimadzu 1800 against 0.1N HCl blank.

**f) Swelling studies**

The extent of swelling was measured in terms of % of weight gained by the tablet. One tablet from each formulation was weighed and kept in petridish containing 50 ml of 0.1N HCl buffer solution. At the end of specified time intervals tablets were withdrawn from petri dish and excess buffer blotted with tissue paper and weighed. The % of weight gained by the tablet was calculated by using the following formula:

Swelling Index (%) = $M_t$-$M_0$/$M_0$ X 100[17].

**Buoyancy lag time determination & total floating time**

The in vitro buoyancy was determined by the floating lag time. The tablet was placed in a 250 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the buoyancy lag time and further total floating time of all tablets was determined by visual observation[18].

**In vitro dissolution studies**

In vitro drug release studies for the prepared immediate release tablets were conducted for a period of 12 hrs using USP XXIV type-II (Paddle) dissolution apparatus at 37±0.5oC at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. At predetermined interval of time, 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium. After filtration and appropriate dilution, the samples were analyzed for cumulative percentage drug release of Gemifloxacin mesylate by UV/Visible spectrophotometer Shimadzu 1800 at 271 nm.

**Kinetic modeling of drug release**

To analyze the mechanism of drug release from the tablets the in vitro dissolution data was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas model.

**Zero order equation**

This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fitted into zero order equation.

$Q=Q_{\circ}K_{\circ}t,$

Where

Q=Amount of drug released at time t

$Q_{\circ}$= Amount of drug release initially

$K_{\circ}$ t =Zero order rate constant

A graph of concentration vs. time would yield a straight line with a slope equal to $K_{\circ}$ and the intercept at the origin of the axes. The zero order plot is derived from plotting the cumulative percent drug dissolved Vs time.

**First order Equation**

The first order equation describes the release from systems where dissolution rate is dependent upon the concentration of the dissolving species release behavior

Generally follows the following first order release equation.

In M= In M0-K1t

Where

M is the amount of drug dissolved at time t,

M0 is the amount of drug dissolved at t=0 and

M1 is the first order rate constant.

A graph of log concentration of drug release Vs time yields line.

**Higuchi Square Root law**

A form of the Higuchi Square Root Law is given by equation

$Q=KS\sqrt{t}$

Where

Q= Amount of drug dissolved at time t,

Ks=Higuchi rate constant

The Higuchi square root law equation describes the release from system where the solid drug is dispersed in a insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

**Korsmeyer and Peppas release model**

The release rate data were fitted to the following equation

$Mt/M\alpha = K.t^n$

Where

$Mt/M\alpha$= the fraction of drug released,

K=the release constant't' is the release time.

'n' is diffusion exponent, if n is equal to 0.89, the release is Zero order. If n is equal to 0.45 the release is best explained by Fukien diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non fickian diffusions (Swellable & Cylindrical Matrix)

In this model, a plot of log ($Mt/M\alpha$) vs. log time was plotted and slope was noted to explain release pattern.

**Drug excipient compatibility studies**

**Fourier Transform Infrared Spectroscopy (FTIR)**

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons.

**Differential Scanning Calorimetry (DSC)**

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5ºC /min, over a temperature range of 0 to 250ºC.

**Stability studies**

The stability studies were carried out as per ICH guidelines. The best formulation F15 was subjected to accelerated stability test by storing at $40\pm2^0$C/75±5% relative humidity in an accelerated stability chamber (Remi, Mumbai). After specified period of time (1, 2, 4 & 6 months) samples were withdrawn and floating lag time, total floating time and in vitro dissolution studies were conducted[19].

# RESULTS AND DISCUSSION

**Evaluation of physicochemical parameters**

All the formulations were tested for physicochemical parameters like weight variation, hardness, thickness, friability and % drug content and found to be within the limits. The results are tabulated in **Table 2.** All the studies indicated that all the prepared formulation were good. The results were tabulated.

**Table 2: Physical properties of prepared formulations**

| Formulation code | Weight variation (mg) | Hardness ($kg/cm^2$) | Thickness (mm) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 501±5 | 5.2±0.4 | 5.3 | 0.13 | 97.8 |
| F2 | 504±2 | 4.5±0.2 | 5.5 | 0.12 | 98.2 |
| F3 | 501±1 | 4.8±0.3 | 5.4 | 0.10 | 98.6 |
| F4 | 502±4 | 5.2±0.2 | 5.2 | 0.12 | 97.2 |
| F5 | 502±5 | 5.4±0.3 | 5.1 | 0.14 | 98.7 |
| F6 | 500±5 | 5.1±0.5 | 5.5 | 0.16 | 97.4 |
| F7 | 501±3 | 5.3±0.2 | 5.4 | 0.12 | 98.1 |
| F8 | 504±4 | 4.8±0.4 | 5,1 | 0.13 | 97.2 |
| F9 | 501±5 | 4.7±0.2 | 5.3 | 0.11 | 97.3 |
| F10 | 498±3 | 5.3±0.3 | 5.2 | 0.12 | 96.4 |
| F11 | 499±1 | 5.3±0.4 | 5.2 | 0.16 | 98.3 |
| F12 | 500±6 | 5.0±0.6 | 5.3 | 0.12 | 99.2 |

**Floating properties for the prepared formulations:**

All the formulations were evaluated for in vitro buoyancy lag time and total floating period. The time required for the tablet to rise to the surface (when the tablets were placed in a beaker containing 0.1 N HCl) for floating was described as the buoyancy lag time. $NaHCO_3$ induces $CO_2$ generation in the presence of HCl. All the formulations had buoyancy lag time in the range of 35 to 51 sec. The total floating period for all the formulations was found to be more than 12 hrs, which indicates a stable gel layer formation by all polymers and that $NaHCO_3$ remains for a longer time. Formulation F12 was found to be less floating lag time i.e. 35 sec when compared with other formulations and the results are depicted in Table 3 & Figure 1.

**Table 3: Floating properties of Gemifloxacin mesylate floating tablets**

| Formulation code | Floating lag time (sec) | Total floating time (h) |
|---|---|---|
| F1 | 51 | >12hrs |
| F2 | 47 | >12hrs |
| F3 | 44 | >12hrs |
| F4 | 40 | >12hrs |
| F5 | 50 | >12hrs |
| F6 | 48 | >12hrs |
| F7 | 44 | >12hrs |

| | | |
|---|---|---|
| F8 | 41 | >12hrs |
| F9 | 48 | >12hrs |
| F10 | 45 | >12hrs |
| F11 | 42 | >12hrs |
| F12 | 35 | > 12hrs |

**At time 0**

**after 35 sec**

**Figure 1: In vitro buoyancy lag time of the optimized formulation (F12)**

**Study of swelling characteristics of Gemifloxacin mesylate floating tablets**

**Table 4: Swelling Index of Gemifloxacin mesylate floating tablets**

| Formula code | % Swelling (h) | | | | | |
|---|---|---|---|---|---|---|
| | **2** | **4** | **6** | **8** | **10** | **12** |
| F1 | 35 | 59 | 71 | 90 | 100 | 108 |
| F2 | 37.5 | 62 | 75 | 94 | 101 | 110 |
| F3 | 39.6 | 64 | 78 | 97 | 104 | 112 |
| F4 | 38 | 61 | 72 | 95 | 106 | 114 |
| F5 | 36 | 59.5 | 72 | 91.5 | 100 | 110 |
| F6 | 34 | 56 | 74 | 85.7 | 102 | 112 |
| F7 | 33 | 54 | 76 | 85.8 | 104 | 114 |
| F8 | 31 | 52.8 | 78 | 84.6 | 101 | 116 |
| F9 | 30 | 51.5 | 73 | 82 | 100 | 110 |
| F10 | 31 | 52.2 | 76 | 84 | 101 | 115 |
| F11 | 30 | 51 | 82 | 90 | 104 | 118 |
| F12 | 40 | 50.5 | 85 | 92 | 108 | 125 |

The purpose of swelling study is to determine the water uptake capability of the polymer. Swelling study was performed on all the batches of floating tablet for 12 hours. All the floating tablets swelled but remained intact without breaking throughout the period of swelling in 0.1 N HCl. The order of swelling index observed with the polymers was HPMC K100 M > HPMC K15M > HPMC K15M. Formulation F12 prepared with HPMC K 100M was found to have highest swelling property and the results are summarized in Table 4.

***In vitro* drug release studies**

**Table 5: In vitro cumulative % drug Gemifloxacin mesylate release formulations F1 to F6**

| Time(h) | F1 | F2 | F3 | F4 | F5 | F6 | Innovator Genex SR 400mg |
|---|---|---|---|---|---|---|---|
| 0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 |
| 1 | 15.01±0.44 | 16.04±0.87 | 16.71±0.23 | 19.05±0.11 | 21.15±0.11 | 18.95±0.87 | 25.12±0.12 |
| 2 | 24.51±0.32 | 26.16±0.98 | 25.29±0.18 | 29.60±0.43 | 31.86±0.22 | 23.93±0.76 | 36.23±0.22 |
| 3 | 34.49±0.18 | 35.05±0.21 | 34.24±0.18 | 42.30±0.76 | 42.18±0.43 | 38.09±0.11 | 45.34±0.43 |
| 4 | 43.32±0.19 | 47.06±0.99 | 49.8±0.98 | 51.40±0.87 | 46.81±0.54 | 47.72±0.98 | 56.12±0.54 |
| 6 | 52.83±0.32 | 54.94±0.97 | 57.50±0.32 | 65.50±0.32 | 57.496±0.59 | 69.77±0.87 | 68.72±0.55 |
| 8 | 60.49±0.11 | 61.88±0.18 | 64.69±0.23 | 68.76±0.87 | 66.574±0.87 | 76.36±0.76 | 72.45±0.76 |
| 10 | 72.28±0.43 | 75.74±0.33 | 78.69±0.17 | 76.27±0.43 | 79.21±0.55 | 87.23±0.44 | 84.56±0.79 |
| 12 | 83.15±0.11 | 87.50±0.23 | 89.81±0.19 | 86.68±0.11 | 90.40±0.33 | 94.14±0.32 | 94.23±0.98 |

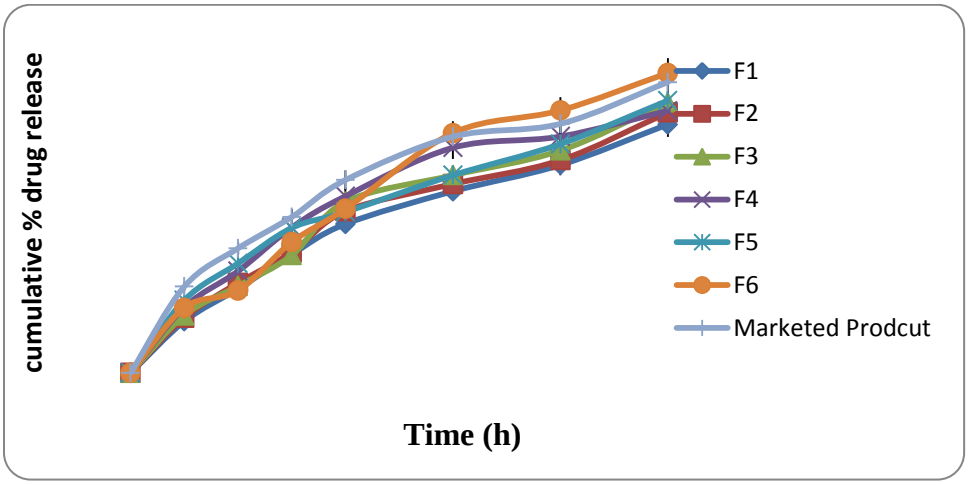


**Figure 2: Percentage drug release of Gemifloxacin mesylate formulations F1-F6**

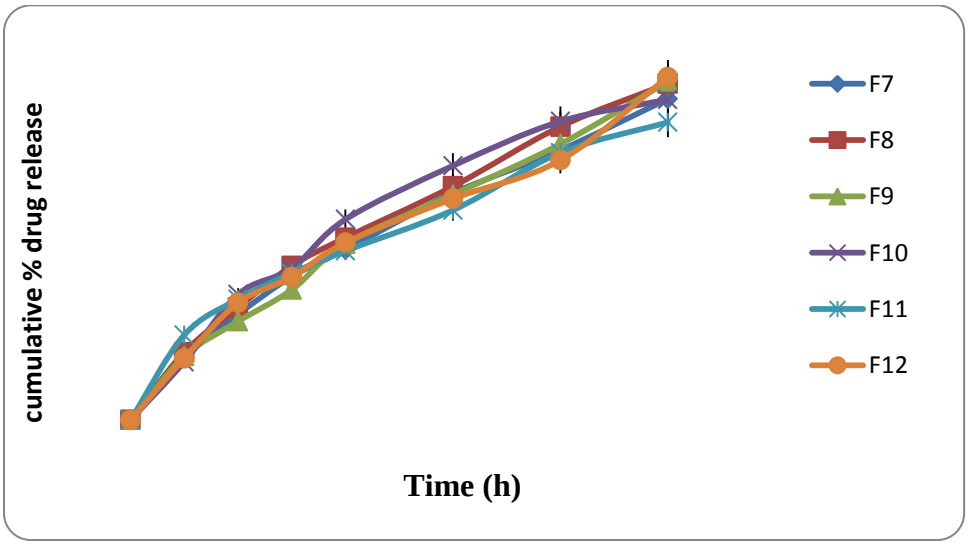


**Figure 3: Percentage drug release of Gemifloxacin mesylate formulations F7 to F12**

All the formulations (F1-F12) were prepared with polymers like HPMC with different grades, POLYOX WSR 301 and lipid excipient Gelucire 50/13. The release of Gemifloxacin mesylate from different formulations was carried out in 0.1N HCl**.** The highest drug release was found in the formulation F12 i.e. 99.12% within 12h when compared with other formulations. F12 was found to be optimized formulation based on the dissolution and other evaluation parameters. The comparison of marketed product Genex SR tablet and optimized formulation F12 was shown in Figure 2. The drug release from marketed product was 94.23.

**Mathematical modeling of optimized formula of Gemifloxacin mesylate tablets (F12):**

**Table 6: Release kinetics of optimized formulation of Gemifloxacin mesylate floating tablets:**

| **Formulation** | **Zero Order** | | **First Order** | | **Higuchi** | | **Korsmeyer-Peppas** | |
|---|---|---|---|---|---|---|---|---|
| **Code** | $R^2$ | K | $R^2$ | K | $R^2$ | K | $R^2$ | N |
| F12 | 0.997 | 8.003 | 0.762 | 0.131 | 0.981 | 35.20 | 0.549 | 2.184 |

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.997 indicates that the drug release follows a zero order mechanism. This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics.

Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer plots. The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one i.e. 0.549 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 2.184 suggest that the drug release from floating tablet was anomalous Non fickian diffusion.

**Drug- excipient compatibility studies**

**Fourier Transform Infrared (FTIR) spectroscopy**

Drug polymer interaction was checked by comparing the functional groups using IR spectrum of the pure drug (Figure 4), physical mixture (Figure 5) and optimized formulation (F12) (Figure 6) & Table 7, and it was found that the same peaks of the drug are available and there was no possible interation takes place between drug and polymers used in the formulation. Since it proves that there is no incompatibility with the polymers.

**Table 7: Results of Fourier Transform Infrared (FTIR) Spectroscopy**

| Material | Wave number ($cm^{-1}$) | Functional group |
|---|---|---|
| | 1036.51 | C–F Stretching |
| | 1454.25 | O–CH3 Bending |
| | 1159.51 | R–COOH Stretching |
| | 1628.26 | N–H Scissoring |
| Pure API | 1713.74 | Aromatic–C=O Stretching |
| | 730.79 | C–H Rocking |
| | 1040.76 | C–F Stretching |
| | 1455.25 | O–CH3 Bending |
| | 1153.16 | R–COOH Stretching |
| | 1630.54 | N–H Scissoring |
| API + Physical | 1711.92 | Aromatic–C=O Stretching |
| mixture | 768.93 | C–H Rocking |

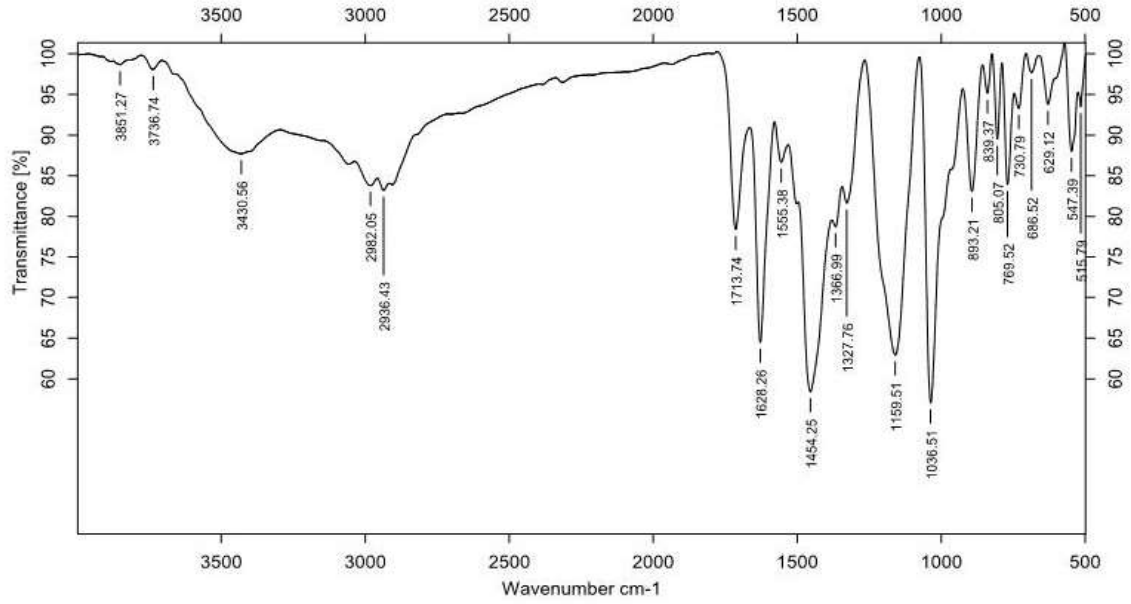


**Figure 4: Gemifloxacin pure drug**

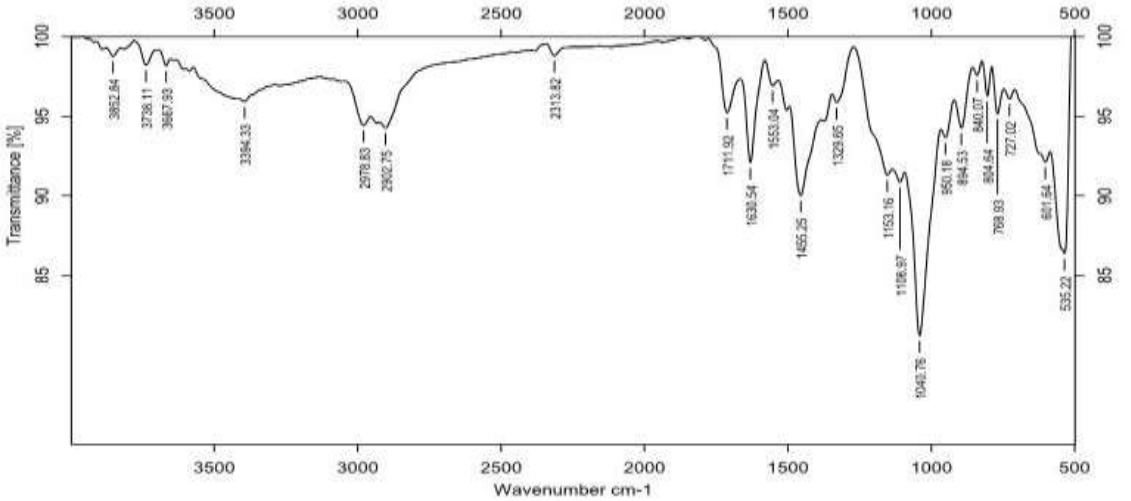


**Figure 5: Physical mixture**

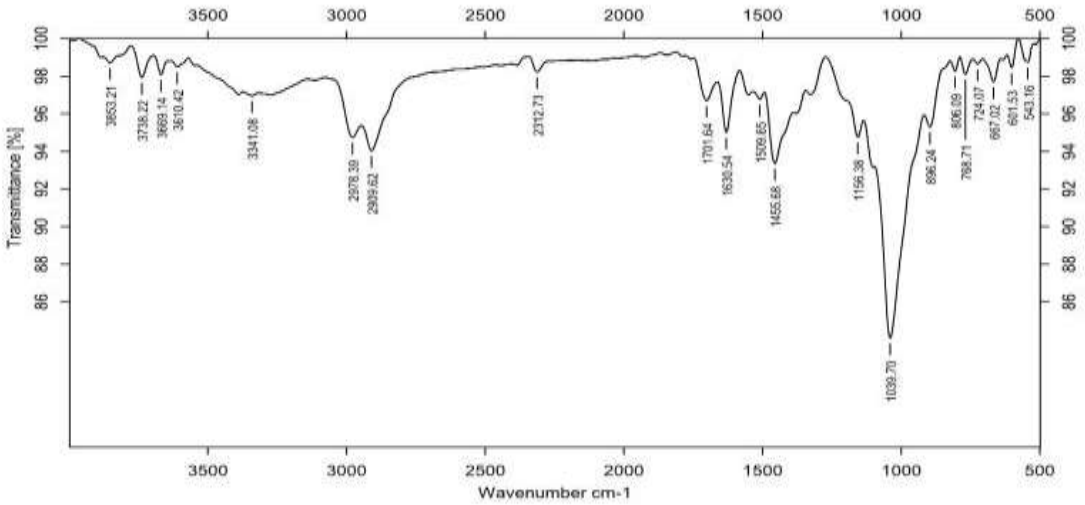


**Figure 6: Gemifloxacin mesylate optimized formulation (F12)**

**Stability studies:**

Optimized formulation (F12) was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for In vitro % drug release and floating lag time for 6 months according to ICH guidelines and retained the same properties. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences which depicted in **Table 8.**

**Table 8: Stability studies of optimized formulation (F12):**

| **Retest time for optimized formulation(F12)** | ***In-vitro* (%) drug release** | **Floating lag time (sec)** |
|---|---|---|
| 0 days | 99.12 | 35 |
| 30 days | 98.56 | 35 |
| 60 days | 97.12 | 33 |
| 120 days | 94.92 | 32 |
| 180 days | 93.68 | 32 |

## CONCLUSION

In conclusion, the effervescent based FDDS is a promising approach to achieve *in vitro* buoyancy by using gel forming polymers such as HPMC K4M, HPMC K15M, employing sodium bicarbonate as gas generating agent. Among the various FDDS formulations studied, the formulation prepared with HPMC K100, WSR 301 and Gelucire 50/13 showed the best result in terms of the required lag time (35sec), total floating time of 12 hrs and cumulative % drug release was 99.12% within 12hrs and is considered as the ideal formulation**.** The compatibility study (FT-IR) showed that the drug has no interactions with polymers and other excipients. Thus the objective of formulating a floating dosage form with controlled release of Gemifloxacin mesylate has been achieved.

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